Aflibercept Plus FOLFIRI in the Real-life Setting: Safety and Quality of Life Data From the Italian Patient Cohort of the Aflibercept Safety and Quality-of-Life Program Study

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Abstract

The Italian subset of the real-life Aflibercept Safety and Quality-of-Life Program study evaluated the safety and health-related quality of life (HRQL) of aflibercept plus FOLFIRI (folinic acid, 5-fluorouracil, irinotecan) in 200 patients with pretreated metastatic colorectal cancer (mCRC). No significant worsening of HRQL occurred, and the safety profile was consistent with the reported data. The combination was well tolerated as second-line treatment for patients with mCRC in a real-life setting.

Background: Aflibercept combined with FOLFIRI (folinic acid, 5-fluorouracil, irinotecan) as second-line treatment of metastatic colorectal cancer (mCRC) significantly improved survival compared with FOLFIRI alone in the pivotal VELOUR (aflibercept vs. placebo in combination with irinotecan and 5-fluorouracil in the treatment of patients with metastatic colorectal cancer after failure of an oxaliplatin-based regimen) trial. No quality-of-life assessment was performed in VELOUR; therefore, the ASQoP (Aflibercept Safety and Quality-of-Life Program) trial was designed to capture the safety and health-related quality of life (HRQL). **Patients and Methods:** ASQoP was an international, open-label, single-arm trial evaluating the safety and HRQL of aflibercept combined with FOLFIRI administered in a real-life setting to 781 patients with mCRC, pretreated with an oxaliplatin-based regimen with or without bevacizumab. The Italian subset of ASQoP enrolled 200 patients from 28 institutions. The primary endpoint was safety; HRQL was a secondary endpoint, assessed by validated questionnaires (European quality of life 5-dimension instrument 3-level; European Organization for Research and Treatment for Cancer Quality of Life Questionnaire Core 30, version 3; and EORTC-CR29) at baseline, during treatment, and at the end of treatment. **Results:** The median age of the Italian ASQoP population was 63 years; the median number of aflibercept and FOLFIRI cycles was 7. Treatment-emergent adverse events were reported in 97.5% of patients. Hypertension (28.5%), neutropenia (27.5%; from laboratory data), asthenic conditions (20.0%), diarrhea (17.0%), and stomatitis (13.0%) were the most frequent (incidence, $\geq$ 5%) grade 3/4 toxicities. One toxic death occurred during the study period due to sepsis, without neutropenic complications. No

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significant worsening of HRQL was shown during treatment. **Conclusion:** Aflibercept combined with FOLFIRI was well tolerated when administered as second-line treatment for patients with mCRC in a real-life setting. It did not affect HRQL and showed similar rates of treatment-emergent adverse events as those observed in the VELOUR trial. No new safety signals were identified.

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Introduction

Although first-line chemotherapy regimens for unresectable, metastatic colorectal cancer (mCRC) are well established,[1,2] the choice of the optimal treatment strategy for patients with failure of first-line therapy for mCRC remains challenging. Aflibercept (also known as VEGF [vascular endothelial growth factor]-Trap or ziv-aflibercept) is a recombinant fusion protein that blocks all human VEGF-A isoforms and other members of the VEGF family, such as VEGF-B and placenta growth factor,[3-6] thus inhibiting the growth of new blood vessels that supply oxygen and nutrients to tumors dependent on VEGF pathways.[7]

The efficacy of aflibercept combined with FOLFIRI (folinic acid, 5-fluorouracil, irinotecan) for second-line treatment of mCRC was demonstrated in the VELOUR (aflibercept vs. placebo in combination with irinotecan and 5-fluorouracil in the treatment of patients with metastatic colorectal cancer after failure of an oxaliplatin-based regimen) trial, a large, multinational, randomized controlled study (ClinicalTrials.gov identifier, NCT00561470). Aflibercept plus FOLFIRI improved overall survival (OS), progression-free survival (PFS), and overall response rate with respect to FOLFIRI plus placebo in patients previously treated with oxaliplatin-based chemotherapy for metastatic disease (median OS, 13.50 vs. 12.06 months; hazard ratio, 0.817, $P = .0032$; median PFS, 6.90 vs. 4.67 months; hazard ratio, 0.758; $P < .0001$; overall response rate, 19.8% vs. 11.1%; $P = .0001$).[8]

In mCRC, palliation is among the primary treatment aims.[1] Therefore, tolerability and health-related quality of life (HRQL) are of paramount importance. Considering that no assessment of HRQL was performed in VELOUR, the findings of the study prompted the Aflibercept Safety and Quality-of-Life Program (ASQoP; ClinicalTrials.gov identifier, NCT01571284) designed to capture utility values from HRQL instruments and to collect safety data from a patient population similar to that in VELOUR but treated in a real-life setting.

We report the safety and HRQL data from the Italian cohort of the ASQoP study (before reporting of the main study results).

Patients and Methods

ASQoP was a multicenter international, single-arm, open-label, phase IIIb/IV trial evaluating the safety and HRQL of aflibercept plus FOLFIRI in a real-life setting for second-line treatment of mCRC. ASQoP was conducted at 151 sites in 23 countries worldwide, with 781 patients enrolled overall. Of these 781 patients, 200 were enrolled in the 28 Italian participating centers.

The study was conducted in accordance with applicable laws and regulations, good clinical practices guidelines, and the 1964 Declaration of Helsinki. Each local institutional review board or independent ethics committee reviewed and approved the study protocol. All the subjects provided written informed consent before participation in the study. The trial was recorded in a public registry website before the beginning of enrollment (ClinicalTrials.gov identifier, NCT01571284).

Subjects

The inclusion criteria for ASQoP were similar to those for the VELOUR trial[8]: patient age $\geq$ 18 years, histologically or cytologically proven mCRC not suitable for curative treatment, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. In contrast, ~2% of patients in the VELOUR trial had an ECOG performance status of 2.

Eligible patients were also required to have been pretreated with an oxaliplatin-based regimen in the first line or to have documented progression of disease within 6 months of completion of oxaliplatin-based adjuvant chemotherapy. Previous treatment with bevacizumab was allowed. Eligible patients were required to have had no previous treatment with irinotecan, no other previous known malignancies in the previous 5 years, with the exception of basal cell carcinoma or squamous cell skin cancer or cervical carcinoma in situ. Patients with inadequate bone marrow, liver or renal function, known brain or meningeal metastases, major surgery within 28 days, uncontrolled hypertension in the previous 3 months, or deep vein thrombosis within the previous 4 weeks were excluded. At enrollment, no patient with grade $\geq$1 adverse events (AEs) from previous treatments using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, was allowed.

Treatment

The study design for ASQoP is presented in Supplemental Figure 1 (available in the online version). Patients received aflibercept (4 mg/kg) by a 1-hour infusion, followed by FOLFIRI every 14 days until disease progression, unacceptable toxicity, investigator or patient decision, or death (whichever came first). Dose adjustments for each study treatment component and/or cycle delays ($\leq$ 2 weeks) were permitted in the event of toxicity. Only 1 dose reduction for aflibercept was allowed. If FOLFIRI was permanently discontinued, patients could continue to receive aflibercept and vice versa.

The planned FOLFIRI schedule consisted of intravenous irinotecan 180 mg/m^2 over 90 minutes, with intravenous leucovorin 400

mg/m^2 over 2 hours, followed by 5-fluorouracil as a 400-mg/m^2 bolus and 5-fluorouracil 2400 mg/m^2 as a continuous infusion over 46 hours. In contrast to the VELOUR trial, starting with full-dose FOLFIRI was not mandatory, and either first-dose or subsequent modifications were decided according to the choice of the investigators. Moreover, the use of granulocyte colony-stimulating factors (GCSFs) was at the discretion of the investigator. However, in the VELOUR study, the use of GCSF was allowed only after the approval of an amendment to the protocol in the final month of study accrual and only for the high-risk population.

Safety Assessments

Safety was the primary endpoint of the study. Efficacy was not assessed. The safety population included patients who had received $\geq$ 1 cycle of aflibercept or FOLFIRI. AEs were collected from the time the patient signed the informed consent form until 30 days after the last administration of treatment (aflibercept or FOLFIRI). Treatment-emergent AEs (TEAEs) for patients who had received $\geq$ 1 dose of the study drug were reported using descriptive statistics. TEAEs were assessed and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03,[9] and summarized using the Medical Dictionary for Regulatory Activities, version 19.0, terminology.

Assessments were performed at baseline, after each cycle of treatment, and 30 days after the last drug administration. Physical examination and assessment of vital signs, including body weight, ECOG performance status, blood pressure, and routine laboratory tests, including complete blood count, clinical chemistry, and urinalysis, were undertaken by the investigator and reported in the electronic case report form. AEs and serious AEs were also collected and reported in the electronic case report form.

Quality of Life Assessments

The ASQoP trial assessed the changes from baseline HRQL using 3 validated instruments: European quality of life (EuroQOL) 5-dimension instrument 3-level (EQ-5D-3L); European Organization for Research and Treatment for Cancer Quality of Life (QoL) Questionnaire Core 30 (EORTC QLQ-C30), version 3; and EORTC QLQ-CR29.

EQ-5D-3L Questionnaire. The EQ-5D-3L questionnaire is a standardized self-reported HRQL assessment tool that provides a generic measure of health for clinical and economic appraisal and is widely used across a range of disease areas, including oncology.[10] The EQ-5D-3L index score measures a patient's general health status by a descriptive system comprising 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression within a particular EQ-5D dimension. Each dimension has 3 levels: no problems, some problems, and extreme problems. Evaluations were performed at baseline and every other treatment cycle. The 5-dimensional 3-level system can be converted into a single index utility score (health state utility value [HSUV]).

The values for the 243 theoretically possible health states defined by the EuroQOL classification were calculated using a regression model and weighted according to the social preferences of the UK population.[11] The possible values for the HSUV ranged from -0.594 (severe problems in all dimensions) to 1.0 (no problem in all dimensions) on a scale with 1 representing the best possible health state for the 5 dimensions. In addition, a visual analog scale was used to evaluate the respondent's self-rated health on a scale with the endpoints of 100 (best imaginable health state) at the top and 0 (worst imaginable health state) at the bottom. This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

EORTC QLQ-C30, Version 3. The EORTC QLQ-C30, version 3, is a cancer-specific, self-reported, 30-item, generic measure of HRQL that provides a multidimensional assessment of participant-reported outcome dimensions. The validity and reliability of the instrument has been established for various types of cancers.[12] The EORTC QLQ-C30 is a standard instrument for the evaluation of new cancer chemotherapy regimens and provides a comprehensive assessment of the principal participant-reported outcome dimensions identified as relevant by cancer subjects (physical functioning, emotional functioning, cognitive functioning, role functioning, social functioning, global QoL, and effect of symptoms and toxicities).

The first 28 questions use a 4-point scale (1, not at all; 2, a little; 3, quite a bit; 4, very much) to evaluate 5 functional scales (physical functioning, emotional functioning, cognitive functioning, role functioning, and social functioning), 3 symptom scales (fatigue, nausea/vomiting, and pain), and other single items. For each item, a higher score implies a greater level of symptoms or problems. The last 2 questions represent the participant's assessment of overall health and QoL, coded on a 7-point scale (from 1, very poor, to 7, excellent). The recall period is the preceding week.

The EORTC QLQ-C30—observed values and changes from baseline were analyzed for global health status (scoring of questions 29 and 30), 5 functional scales, 3 symptom scales, and other single items (scoring of questions 1 to 28). The raw scores were transformed into a linear grading scale ranging from 0 to 100. A high score represented a favorable outcome on the global health status/QoL and functioning scale, providing a measure of the best possible QoL for the participant. The clinically important difference was defined as a group-level mean change of $\geq \pm 10$.[13]

EORTC QLQ-CR29. The EORTC QLQ-CR29, optional in the present study, is a colorectal cancer disease-specific module supplement to the QLQ-C30.[14] The EORTC QLQ-CR29 includes 4 scales (urinary frequency, blood and mucus in stool, stool consistency, and body image) and 19 single items assessing other common problems during treatment of colorectal cancer.

Statistical Analysis

Both safety and QoL analyses were descriptive. No formal sample size calculation was conducted. The targeted overall sample size for the study was 900 patients. Standard demographic and baseline characteristics, medical and surgical history, cancer diagnosis, and previous anticancer therapy data were summarized at baseline, and the baseline safety variables were assessed, including vital signs and main laboratory parameters.

Table 1 Baseline Demographic and Clinical Characteristics of the Safety and Quality of Life Populations of the ASQoP Italian Cohort

Characteristic	Safety Population (n = 200), n (%)	EQ-5D-3L (n = 145), n (%)	EORTC QLQ-C30 (n = 149), n (%)
Age, y			
Median	63.0	62.0	63.0
Q1-Q3	53.0-68.0	53.0-68.0	53.0-68.0
Age group			
<65 y	113 (56.5)	87 (60.0)	89 (59.7)
≥65 but < 75 y	78 (39.0)	51 (35.2)	53 (35.6)
≥75 y	9 (4.5)	7 (4.8)	7 (4.7)
Sex			
Female	79 (39.5)	61 (42.1)	63 (42.3)
Male	121 (60.5)	84 (57.9)	86 (57.7)
ECOG PS			
0	162 (81.0)	123 (84.8)	125 (83.9)
1	38 (19.0)	22 (15.2)	24 (16.1)
Median blood pressure, mm Hg	120/80	125/80	125/80
Interval from initial histologic diagnosis to baseline visit, mo			
Median	12.3	12.3	12.3
Q1-Q3	9.1-18.6	8.9-18.8	9.1-19.2
Primary tumor location			
Colon	120 (60.0)	89 (61.4)	92 (61.7)
Rectosigmoid	46 (23.0)	32 (22.1)	33 (22.1)
Rectum	34 (17.0)	24 (16.6)	24 (16.1)
Organs with metastases			
1	89 (44.5)	66 (45.5)	68 (45.6)
>1	111 (55.5)	79 (54.5)	81 (54.4)
Metastatic sites			
Liver	149 (74.5)	109 (75.2)	112 (75.2)
Lung	96 (48.0)	68 (46.9)	70 (47.0)
Distant lymph nodes	45 (22.5)	34 (23.4)	35 (23.5)
Peritoneum	36 (18.0)	24 (16.6)	24 (16.1)
Other[a]	20 (10.0)	13 (8.9)	13 (8.7)

Abbreviations: ASQoP = Aflibercept Safety and Quality-of-Life Program; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organization for Research and Treatment for Cancer Quality of Life Questionnaire Core30; EQ-5D-3L = European Quality of Life 5-dimension Instrument 3-level; Q = quartile; PS = performance status.
[a]Included ovaries (2.0%) and bone (3.5%) in the safety population.

An analysis of the safety variables was performed by summarizing the AEs and laboratory data. The on-treatment period was defined as the period from the first dose of treatment to 30 days after the last day of treatment (either aflibercept or FOLFIRI). The safety variables included TEAEs, post-treatment AEs, discontinuation, and clinical and laboratory data. TEAEs were defined as AEs reported during the on-treatment period. Post-treatment AEs were defined as an AE that developed, worsened, or became serious > 30 days after the last dose of treatment. Discontinuation, including the reason for discontinuation, and discontinuation because of AEs, were recorded.

The HRQL variables were analyzed as follows. The EORTC QLQ-C30 instrument assessed the change from baseline for the global health status (scoring of items 29 and 30), 5 functional scales (physical, role, emotional, cognitive, and social), 3 symptom scales (fatigue, nausea/vomiting, and pain), and the other single items. The EQ-5D—observed values and changes from baseline on HRQL and HSUV.

For each scale and item, the median and mean values, with 95% confidence intervals, were recorded at every other cycle. In the absence of any predefined study hypothesis, no test of significance was performed. For each scale and item, the median and mean values and 95% confidence intervals at 30 days after the final treatment cycle were also analyzed, stratified by the cause of treatment stop.

Results

From June 2012 to September 2013, 201 patients were screened at 28 Italian centers, 200 of whom were enrolled and received ≥ 1 cycle of treatment and constituted the safety population. One of the 200 patients never started aflibercept and discontinued after 1 FOLFIRI cycle because of physician choice. The other 199 patients

Table 2 Previous Anticancer Therapies in Italian ASQoP Patients (n = 200)

Variable	Neoadjuvant Only (n = 19)	Advanced Only (n = 161)	Neoadjuvant and Advanced (n = 20)
Oxaliplatin-based regimen	19 (100.0)	161 (100.0)	NA
Oxaliplatin only	0 (0)	0 (0)	
Oxaliplatin/fluoropyrimidine[a]	18 (94.7)	41 (25.5)	
Oxaliplatin/fluoropyrimidine[a] plus any biologic agent[b]	1 (5.3)[c]	120 (74.5)	
Oxaliplatin/fluoropyrimidine[a] plus bevacizumab	1 (5.3)	104 (64.6)	
Maintenance bevacizumab only	0 (0)	7 (4.3)	
Neoadjuvant/adjuvant chemotherapy	NA	NA	20 (100)
No oxaliplatin			11 (55.0)
Oxaliplatin-based regimen			9 (45.0)
Advanced chemotherapy	NA	NA	20 (100)
No oxaliplatin			0 (0)
Oxaliplatin-based regimen			20 (100.0)
Oxaliplatin/fluoropyrimidine[a]			8 (40.0)
Oxaliplatin/fluoropyrimidine[a] plus any biologic agent[b]			12 (60.0)
Oxaliplatin/fluoropyrimidine[a] plus bevacizumab			12 (60.0)
Maintenance bevacizumab only			2 (10.0)

Abbreviations: ASQoP = Aflibercept Safety and Quality-of-Life Program; NA = not applicable.
[a]5-Fluorouracil or capecitabine.
[b]Bevacizumab, cetuximab, panitumumab, and/or regorafenib.

received aflibercept plus FOLFIRI. Of the 200 patients, 149 and 145, respectively, were included in the EORTC QLQ-C30 and EQ-5D-3L QoL populations (completing the questionnaires at baseline, ≥ 1 assessment thereafter, and receiving 1 dose of study treatment).

Patient Characteristics and Disposition

The key baseline demographics and clinical characteristics are summarized in Table 1. The median age of the patients was 63 years (vs. 61 years in the aflibercept plus FOLFIRI arm of VELOUR), with 43.5% of patients aged > 65 years and 4.5% aged > 75 years (vs. 33.5% and 5.4%, respectively, in the VELOUR trial).[15] The ECOG performance status was 0 for 81% of patients. Of the 200 patients, 19 (9.5%) were enrolled after progression of disease during neoadjuvant or adjuvant therapy, 20 (10.0%) started treatment after undergoing adjuvant therapy and first-line treatment, and 161 (80.5%) were enrolled after first-line chemotherapy without any previous curative chemotherapy (Table 2). The median interval from the initial histologic diagnosis to the first dose of study treatment was 12.3 months. Of the 200 patients, 117 (58.5%) had received bevacizumab before enrollment in the ASQoP trial. In contrast, previous bevacizumab use was reported for 30.4% of the aflibercept plus FOLFIRI arm of the VELOUR study.[8]

Patients received a median of 7 cycles (16.9 weeks) of the combination of aflibercept plus FOLFIRI for a total of 1978 cycles. The median relative dose intensity of the individual drugs was 81.0% for aflibercept, 80.3% for 5-fluorouracil, and 79.8% for irinotecan. At cycle 1, 27 patients (13.5%) received a lower than protocol dose of 5-fluorouracil and 24 (12.0%) received a reduced irinotecan dose.

Treatment delays were registered for 162 patients (81%) who received aflibercept plus FOLFIRI, with 19%, 55%, and 59% receiving dose modifications for aflibercept, 5-fluorouracil, and irinotecan, respectively. Overall, treatment with aflibercept plus FOLFIRI was permanently discontinued in 64% of patients for disease progression, 22% for AEs, 8.0% for patient decision, and 6.0% for unknown reasons. Twelve patients discontinued aflibercept because of AEs (6.0%), 3 patients (1.5%) decided not to continue aflibercept, and 3 patients (1.5%) discontinued aflibercept for other reasons (including 1 patient who never received aflibercept). Fifteen patients (7.5%) discontinued FOLFIRI because of AEs, 6 (3.0%) by patient decision, and 14 (7.0%) for other reasons.

During the study, GCSF support was used in 52 patients (26%; Supplemental Table 1; available in the online version). Seventeen patients (8.5%) received GCSF during cycle 1 (prophylactically in 5.0% and therapeutically in 3.5%). Thirty-five patients (17.5%) received GCSF support at any cycle other than cycle 1 (prophylactically in 10.0%, therapeutically in 4.5%, and prophylactically and therapeutically in 3.0%).

After second-line treatment with aflibercept and FOLFIRI, ≥ 28% of patients received a further line of treatment after discontinuation of the study treatment (Supplemental Table 2; available in the online version). The mean time ± standard deviation from the last administration of study treatment to the first further systemic anticancer therapy was 1.1 ± 0.7 months.

Safety

Overall, the incidence of TEAEs was similar to that reported in the VELOUR trial (Table 3). TEAEs of any grade were reported in 97.5% of patients in the Italian cohort of ASQoP, with grade 3 and 4 toxicities recorded in 68.0% and 9.5% of patients, respectively. The most frequent grade 3/4 toxicities were hypertension (28.5% in ASQoP vs. 19.3% in the VELOUR study), neutropenia (determined by laboratory abnormalities; 27.5% vs. 36.7%), diarrhea

Table 3 Summary of Selected Treatment-emergent Adverse Events in the Italian Cohort of the ASQoP and VELOUR Studies

	Aflibercept Plus FOLFIRI, %					
	ASQoP Italian Cohort Safety Population (n = 200)			VELOUR Safety Population (n = 611)		
Adverse Event	All Grades	Grade 3/4	Grade 4	All Grades	Grade 3/4	Grade 4
Any event	97.5	77.5	9.5	99.2	83.5	21.4
Diarrhea (PT)	53.5	17.0	0.0	69.2	19.3	0.3
Asthenic conditions[a] (HLT)	55.5	20.0	0.0	60.4	16.9	0.8
Stomatitis and ulceration (HLT)	41.5	13.0	0.5	54.8	13.7	0.2
Nausea (PT)	39.5	3.5	0.0	53.4	1.8	0.0
Infections and infestations (SOC)	25.0	6.5	0.5	46.2	12.3	1.3
Hypertension (grouped term)	49.0	28.5	0.0	41.4	19.3	0.2
Vomiting (PT)	19.5	1.5	0.0	32.9	2.8	0.2
Hemorrhage (grouped term)	30.5	2.0	0.5	37.8	2.9	0.2
Epistaxis (PT)	23.5	0.0	0.0	27.7	0.2	0.0
Other anti-VEGF–associated events (grouped terms)						
Arterial thromboembolic event	2.0	1.0	0.0	2.6	1.8	1.0
Venous thromboembolic event	4.0	2.5	0.9	9.3	7.9	4.7
GI fistula	1.5	0.5	0.0	1.1	0.3	0.0
Fistula (non-GI origin)	0.0	0.0	0.0	0.3	0.0	0.0
GI perforation	1.0	1.0	0.5	0.5	0.5	0.3
Biologic abnormalities						
Anemia[b]	64.6	2.1	0.0	82.3	3.8	0.5
Neutropenic complications (grouped term)	1.0	1.0	0.5	6.5	5.7	1.3
Neutropenia[b]	58.7	27.5	5.8	67.8	36.7	13.6
Proteinuria[c]	58.5	3.5	0.0	62.2	7.9	0.3

Adverse events reported using the Medical Dictionary for Regulatory Activities, version 19.0, terminology and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03 for ASQoP and version 3.0 for VELOUR; a cross-trial comparison was not appropriate, and data are for illustrative purposes only.
Abbreviations: ASQoP = Aflibercept Safety and Quality-of-Life Program; FOLFIRI = folinic acid, 5-fluorouracil, irinotecan; HLT = high-level term; PT = preferred term; SOC = system organ class; VEGF = vascular endothelial growth factor; VELOUR = aflibercept versus placebo in combination with irinotecan and 5-fluorouracil in the treatment of patients with metastatic colorectal cancer after failure of an oxaliplatin-based regimen (trial).
[a]Asthenia and fatigue.
[b]Included only laboratory data.
[c]Included grouped terms of proteinuria as an adverse event and proteinuria from laboratory data.

(17.0% vs. 19.3%), asthenic conditions (asthenia and fatigue; 20.0% vs. 16.9%), and stomatitis and ulceration (13.0% vs. 13.7%).

Most AEs in the Italian cohort of the ASQoP occurred in the early cycles of aflibercept plus FOLFIRI administration. The time course of the main AEs during the course of the study is presented in Figure 1. The incidence of worst-grade AEs was greatest in cycle 1 and decreased during the subsequent cycles. The worst-grade AEs consisted of grade 4 hemorrhage and grade 4 stomatitis and ulcerations, each in 1 patient (0.5%) and grade 3 diarrhea (n = 34; 17%), hypertension (n = 57; 28.5%) and proteinuria (n = 3; 1.5%).

In addition, 22.0% of patients discontinued because of TEAEs of any grade, with grade 3/4 toxicities in 15.0%. The most frequent TEAEs leading to permanent treatment discontinuation were gastrointestinal disorders in 6.0% of patients (grade 3/4 in 4.5%), including diarrhea in 1.0% (grade 3 in 0.5%) and grade 3/4 intestinal perforation in 0.5% of patients. Vascular disorders led to permanent discontinuation in 3.5% of patients (grade 3 in 3.0%), including grade 3 hypertension in 2.0% and grade 3 deep vein thrombosis in 0.5%. Although no grade 3/4 proteinuria was observed, 3.5% of patients permanently discontinued treatment because of proteinuria. In contrast, AEs led to permanent treatment discontinuation in 26.5% of patients in the aflibercept plus FOLFIRI arm of the VELOUR trial.

Overall, in the Italian cohort of the ASQoP, AEs led to premature or permanent aflibercept discontinuation in 27.5% of patients (grade 3/4 in 18.0%). The main reasons were gastrointestinal disorders in 6.5% of patients (grade 3 in 5.0%), proteinuria in 5.0% (grade 3 in 0.5%), and vascular disorders in 6.0% (grade 3/4 in 5.0%), including hypertension grade 3 in 4.0%. Grade 4 TEAEs leading to aflibercept discontinuation were uncommon, occurring in 2.5% of patients. 5-Fluorouracil and irinotecan were discontinued in 25% of patients, mostly because of gastrointestinal disorders (diarrhea, all grades, 2%) and general health disorder (including asthenia).

Of the 200 patients, 30.5% experienced all-grade hemorrhage during aflibercept treatment (grade 3/4 in only 2.0%), of which

Figure 1 Time Course of Selected Treatment-Emergent Adverse Events (Worst Grade) in the Italian Cohort of the Aflibercept Safety and Quality-Of-Life Program Study

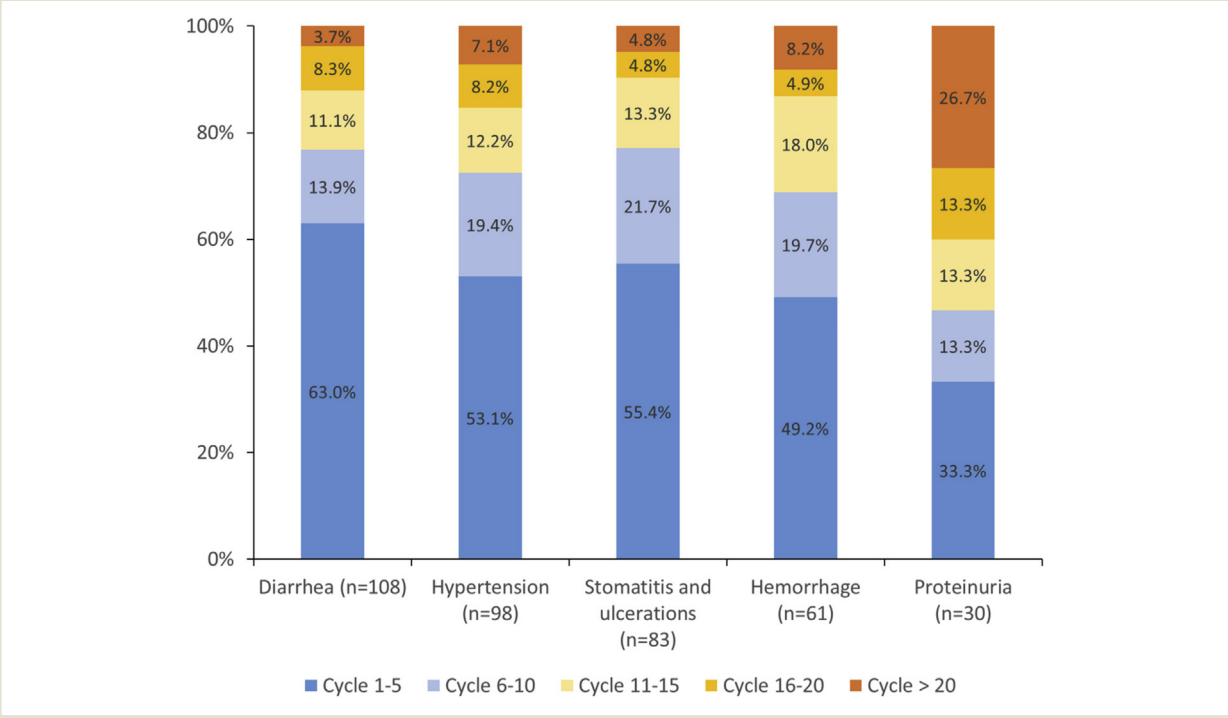


Figure 2 Single Index Utility Score Health Status Measure European Quality of Life 5-Dimension Instrument 3-Level (A) During Treatment and (B) Within 30 Days After Final Treatment. Error Bars Represent 95% Confidence Interval of the Mean

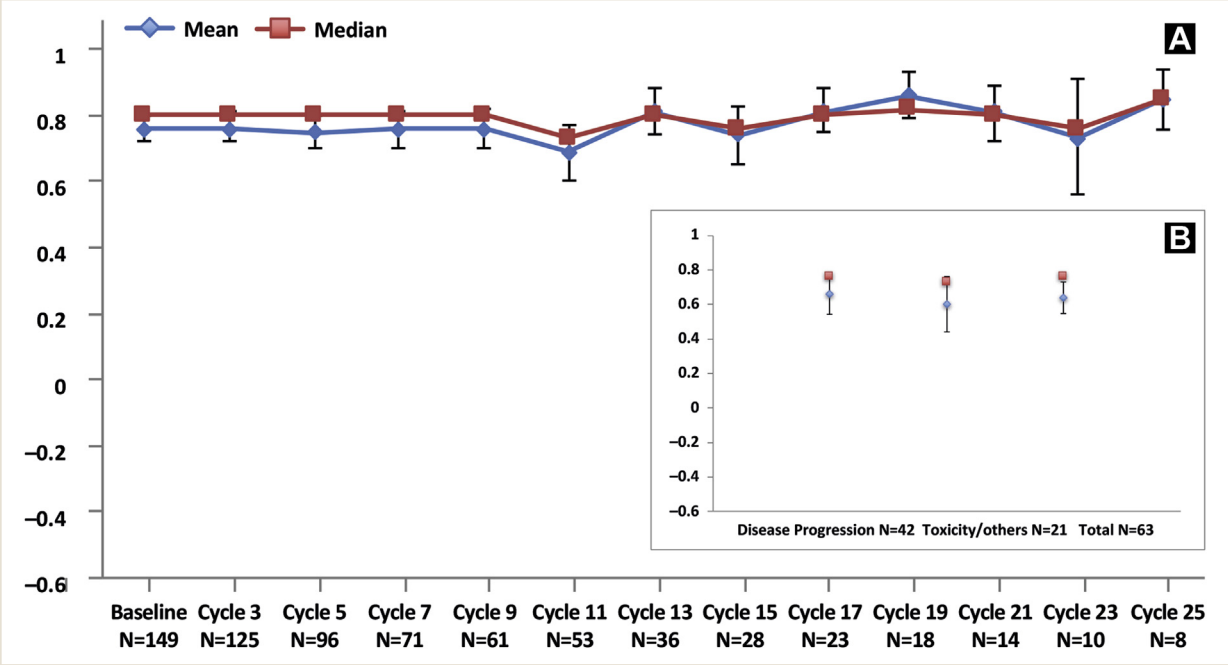
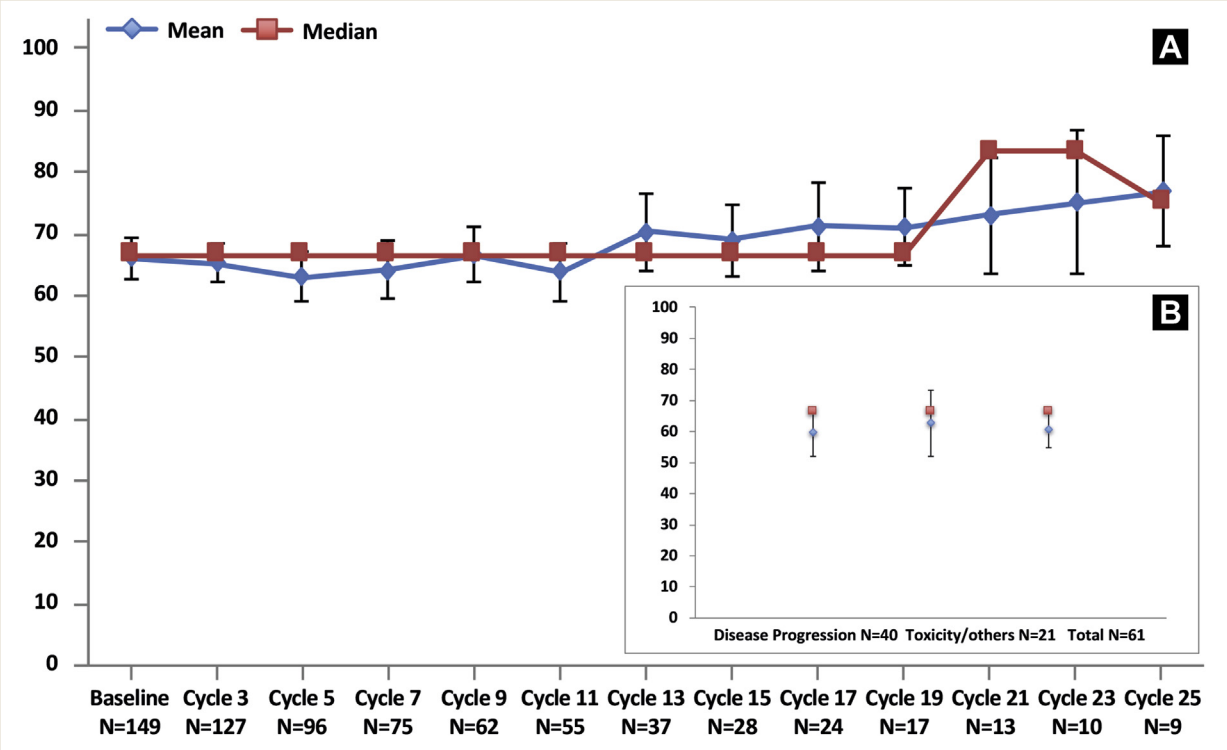
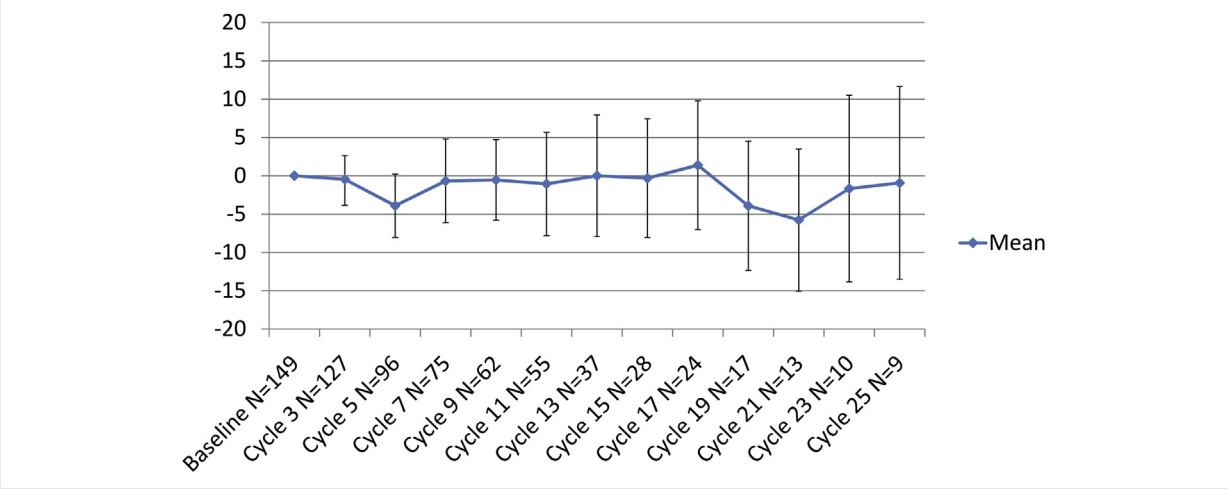


Figure 3 Global Health Status of the European Organization for Research and Treatment for Cancer Quality of Life Questionnaire Core 30 (A) During Treatment and (B) Within 30 Days After Final Treatment. Error Bars Represent 95% Confidence Interval of the Mean



23.5% was grade 1/2 epistaxis. Also, 15% of patients had proteinuria reported as a TEAE (1.5% grade 3 and no grade 4), 6.0% of patients experienced arterial or venous embolic events (no grade 4), and gastrointestinal fistula and gastrointestinal perforation occurred in 1.5% and 1.0%, respectively. Wound healing was not compromised in any patient. The incidence and severity of TEAEs

Figure 4 Change From Baseline Global Health Status of European Organization for Research and Treatment for Cancer Quality of Life Questionnaire Core 30 During Treatment. Error Bars Represent 95% Confidence Interval of the Mean. Clinically Important Difference Change Score Considered Clinically Meaningful at ≥ ±10



were similar in patients with and without previous exposure to bevacizumab and in patients aged < 65 years versus those aged ≥ 65 years (data not shown).

Overall, 10 deaths (5.0%) occurred during the study period: 7 (3.5%) due to disease progression and 2 (1.0%) for other reasons. One was a toxic death, caused by sepsis in the context of continuous diarrhea in the absence of neutropenic complications.

Health-related QoL

Of the 200 patients enrolled in the Italian ASQoP cohort, 145 (72.5%) completed the baseline and ≥ 1 subsequent (on-treatment) EQ-5D-3L questionnaire. The data were similar for the EORTC-QLQ-C30 questionnaire: 149 patients (74.5%) completed the EORTC-QLQ-C30 form, and 145 patients (72.5%) completed the EORTC-QLC-CR29 (145 patients; 72.5%). The key baseline demographics and clinical characteristics of the HRQL populations are listed in Table 1. In general, the characteristics of the HRQL populations closely reflected those of the overall Italian ASQoP cohort. Patients in the HRQL populations tended to be slightly younger and to have a slightly better ECOG performance status (Table 1).

The number of patients completing the QoL questionnaires decreased during the subsequent cycles because of treatment stops owing to progression or toxicity and noncompliance. After 25 cycles (≈1 year), it was too low (< 10) to allow for any reliable statistical analysis; that is, the small number of patients resulted in wide 95% confidence intervals. As a consequence, all analyses focused on the absolute values and changes during the first 25 cycles.

The mean and median values of the HSUV health measure (Figure 2A) showed remarkable stability at values of ~0.8 throughout the entire treatment period, without any detectable worsening in patients who were evaluated during the second part of the year. The decrease in HSUVs observed within 30 days after the final treatment scale was moderate (range, 0.1 to 0.2 points) and was similar in patients who stopped therapy because of progression or for other reasons (Figure 2B).

The global health status of the EORTC QLQ-C30 (Figure 3A) was basically stable at 60/100 to 70/100 up to cycle 19 (9 months), with a slightly increasing trend thereafter, although of little significance owing to the small numbers (wide confidence intervals) involved. Again, little change was observed after therapy was stopped (Figure 3B). The analyses of the change from baseline did not show any variation qualifying as a clinically important difference throughout the entire treatment period and only moderate and transient deteriorations in the mean group-level changes were seen at cycle 5, 19 and 20 (Figure 4).

The behavior of 3 symptoms during the 25 treatment cycles is shown in Supplemental Figures 2 to 4 (available in the online version). Fatigue (Supplemental Figure 2; available in the online version), potentially representing a specific side effect of the treatment regimen, failed to show any noteworthy worsening during the study period. No diarrhea (Supplemental Figure 3; available in the online version), another relevant TEAE, was reported by > 50% of the patients during all cycles but 2 and was seldom perceived as serious. Pain (Supplemental Figure 4; available in the online version) was moderate or absent in most patients at the start of treatment and did not show any remarkable modifications during the first 6 months of therapy. The patients still receiving treatment afterward showed similar or even lower pain levels during the second part of the year.

The results of visual analog scale and EORTC QLQ-CR29 (data not shown) resembled those reported for the other questionnaires.

Discussion

Achieving clinical benefit with antineoplastic treatment is a balance between efficacy and toxicity. The VELOUR trial[8,16] showed that the combination of aflibercept and FOLFIRI produced an incremental second-line survival gain of 1.4 months and a long-term 2-year 50% proportional increase and 10% absolute increase in survival compared with FOLFIRI alone. However, an increase in toxicity in the combination treatment arm was also found, with greater rates of diarrhea, hypertension, and asthenia. Real-life studies, such as the ASQoP study, are very important to refine the assessment of safety and, in particular, to investigate the HRQL effects of new therapies in unselected patients representative of the future populations who will be receiving the therapy.

For these reasons, Italian ASQoP data provide useful additional information about the safety and effects on HRQL of aflibercept in patients with mCRC in the real-life setting of a validated and effective regimen in combination with FOLFIRI. No new safety signals were observed. The Italian ASQoP data, when compared with those from VELOUR, showed a similar safety profile for aflibercept and FOLFIRI in a relevant number of patients (200 patients vs. 611 patients treated with aflibercept and FOLFIRI in VELOUR).[8] In particular, the Italian ASQoP trial enrolled a slightly older population than that enrolled in VELOUR (43% vs. 33% of patients aged ≥ 65 years), 10% of whom had early disease progression after oxaliplatin adjuvant or neoadjuvant treatment and 58.5% of whom had received previous bevacizumab treatment compared with 30.4% in VELOUR.

The number of grade 4 toxicities in ASQoP were relatively fewer than in VELOUR, and the AEs tended to occur in during the early treatment period. Similarly, lower toxicity rates were confirmed in the subgroup of elderly patients and in those pretreated with bevacizumab (more than one half of the ASQoP Italian cohort had received bevacizumab vs. 30% in VELOUR).[8]

These lower rates of toxicities can be explained in part by the percentage registered receiving a lower starting dose of FOLFIRI (13.5% and 12.0%, respectively, received a lower than protocol dose of 5-fluorouracil and irinotecan); the better patient selection in ASQoP resulting from the toxicity data from the VELOUR trial (mostly hypertension, diarrhea, asthenia); greater experience with aflibercept, leading to more careful use of premedication; and closer attention and monitoring for the early detection and mitigation of toxicity symptoms. Furthermore, the use of GCSF in almost 25% of patients enrolled can justify the lower rate of grade 3/4 neutropenia (27.5% vs. 36.7% in VELOUR).

The data on HRQL reported in the present study are relevant because no such data were collected in the VELOUR trial. Overall, a remarkable stability in all indexes of HRQL was recorded during the entire first year of therapy, although the data at the longer follow-up times were not reliable owing to the small number of patients still receiving treatment. The consistency of the results obtained with the 3 different HRQL assessment tools supports the

conclusion that the HRQL of patients with mCRC can be maintained during treatment with aflibercept plus FOLFIRI.

Three symptoms were more closely examined; 2 (fatigue and diarrhea) associated with treatment, and 1 (pain) because of its relationship with worsening of the underlying disease. However, none of these symptoms was reported by a significant proportion of patients as significantly affecting HRQL throughout the treatment period, and improvements were often reported.

Conclusion

Efficacy data on survival and response rates from the VELOUR study had a strong internal validity. However, the increased toxicity profile resulting from the addition of aflibercept to FOLFIRI might compromise the applicability of this regimen and/or reduce its clinical benefits. The results of the ASQoP trial, which enrolled a real-life less-fit patient population than VELOUR, suggest the applicability on a large scale of FOLFIRI combined with aflibercept as second-line treatment of mCRC. The safety profile from the ASQoP was consistent with the known safety profile of aflibercept plus FOLFIRI, and the incidence and severity of the AEs suggest a manageable and favorable safety profile in the real-life setting. The design of the ASQoP did not provide an assessment of outcomes; thus, we could not establish whether the conditions that resulted in a lower frequency and grade of toxicities, such as a lower starting dose and/or dose-modifications and/or use of GCSF, might have compromised the efficacy of the regimen. Of interest is whether the gains in OS and PFS obtained with the use of aflibercept plus FOLFIRI in the VELOUR will be sustained in the ASQoP, which demonstrated maintenance of HRQL during treatment with the combination.

Clinical Practice Points

- Aflibercept combined with FOLFIRI for second-line mCRC significantly improved survival and the overall response rate compared with FOLFIRI alone in the pivotal VELOUR trial; however, no QoL assessment was performed in VELOUR.
- Therefore, the ASQoP trial was designed to capture the safety and HRQL.
- The Italian subset of the ASQoP enrolled 200 patients with mCRC who were treated with aflibercept plus FOLFIRI administered in a real-life setting.
- The patients had been pretreated with an oxaliplatin-based regimen with or without bevacizumab.
- The primary endpoint was safety; HRQL was a secondary endpoint, assessed by validated questionnaires (EuroQOL EQ-5D-3L, EORTC-C30, and EORTC-CR29) at baseline, during treatment, and at the end of treatment.
- Treatment did not significantly affect HRQL.
- The incidence and severity of TEAEs were consistent with those observed in VELOUR, which was conducted in a similar patient population, and no new safety signals were identified.
- These data from the Italian cohort of the ASQoP have shown that aflibercept plus FOLFIRI is well tolerated, does not adversely affect QoL, and support its use as a second-line treatment for patients with mCRC in a real-life setting.

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Supplemental Data

The supplemental figures and tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.clcc.2018.03.002.

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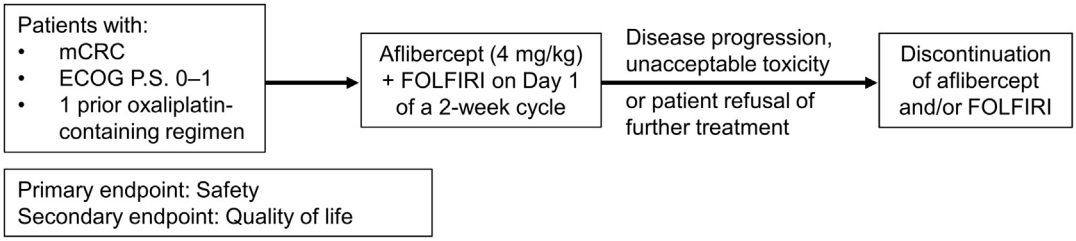
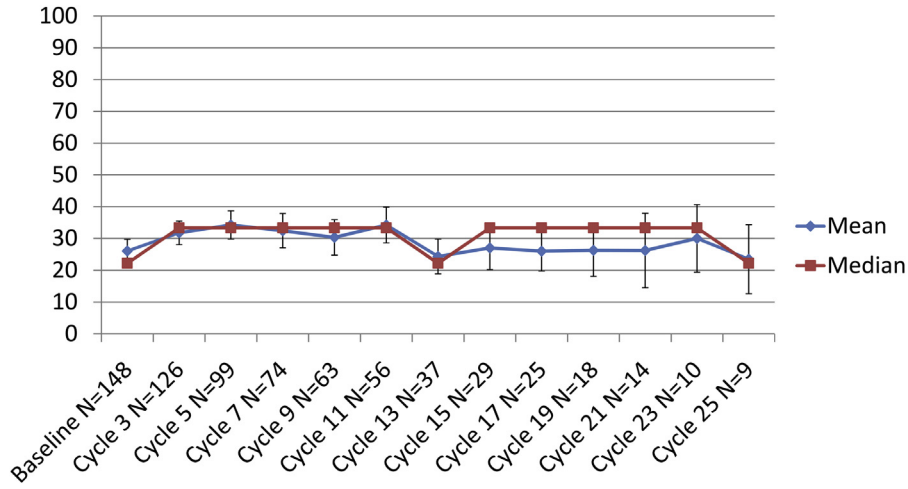
Supplemental Figure 1 Overall Study Design of Aflibercept Safety and Quality-Of-Life Program Study

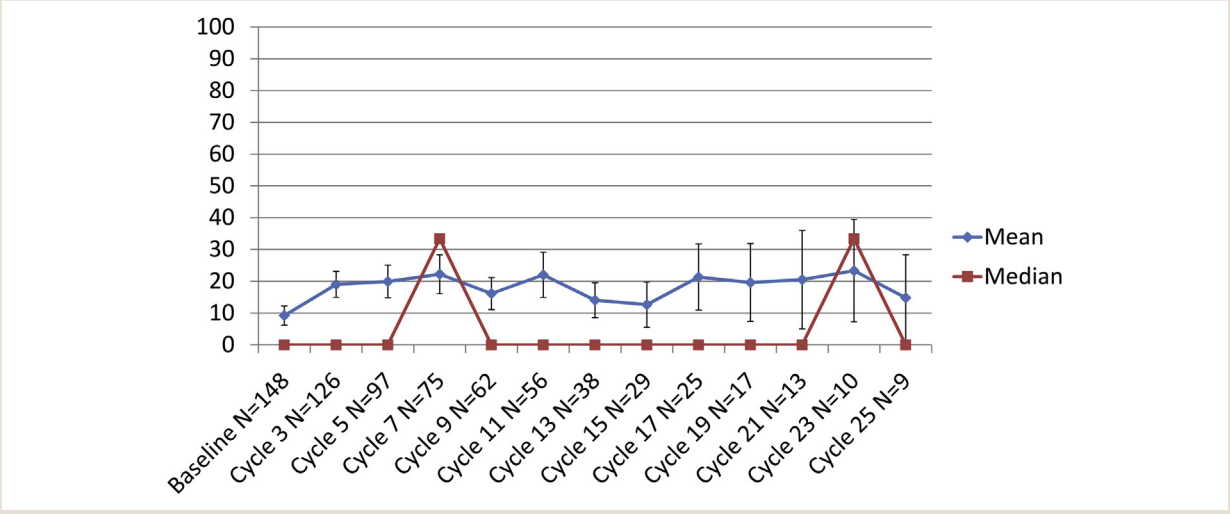


FOLFIRI, dl-leucovorin 400 mg/m^2, irinotecan: 180 mg/m^2, fluorouracil (5-FU) 400 mg/m^2 bolus + 2400 mg/m^2 continuous infusion, or individualized by the clinical judgment of the Physician.
Health-related quality of life assessments were administered at baseline (day 1 of cycle 1), at the beginning of every odd treatment cycle starting at cycle 3, and at the end of treatment visit.
Abbreviations: ASQoP, Aflibercept Safety and Quality-of-Life Program; ECOG PS, Eastern Cooperative Oncology Group performance status; mCRC, metastatic colorectal cancer.

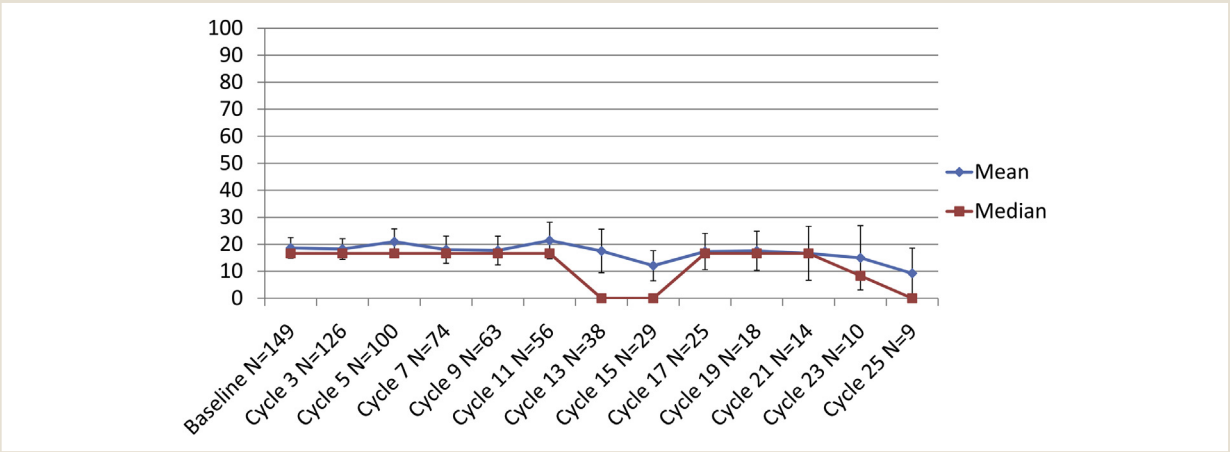
Supplemental Figure 2 Symptom Scales of the European Organization for Research and Treatment for Cancer Quality of Life Questionnaire Core 30 During Treatment for Fatigue. Error Bars Represent 95% Confidence Interval of the Mean



Supplemental Figure 3 Symptom Scales of the European Organization for Research and Treatment for Cancer Quality of Life Questionnaire Core 30 During Treatment for Diarrhea. Error Bars Represent 95% Confidence Interval of the Mean



Supplemental Figure 4 Symptom Scales of the European Organization for Research and Treatment for Cancer Quality of Life Questionnaire Core 30 During Treatment for Pain. Error Bars Represent 95% Confidence Interval of the Mean



Supplemental Table 1	Use of Granulocyte Colony-stimulating Factors per Cycle in the ASQoP Italian Cohort (n = 200)
Variable	**Safety Population, n (%)**
GCSF received at cycle 1	
No	182 (91.0)
Yes	17 (8.5)
Data missing	1 (0.5)
Prophylactic	10 (5.0)
Therapeutic	7 (3.5)
GCSF received at any cycle other than cycle 1	
No	150 (75.0)
Yes	35 (17.5)
Data missing	15 (7.5)
Prophylactic	20 (10.0)
Therapeutic	9 (4.5)
Prophylactic and therapeutic	6 (3.0)

Abbreviations: ASQoP = Aflibercept Safety and Quality-of-Life Program; GCSF = granulocyte colony-stimulating factor.

Supplemental Table 2	Further Anticancer Treatment After Second-line Aflibercept Plus FOLFIRI in ASQoP Italian Cohort (n = 200)
Variable	**n (%)**
Any further therapy[a]	56 (28.0)
Radiotherapy	0 (0)
Systemic therapy	56 (28.0)
Biologic agents/small molecules	20 (10)
Cetuximab	11 (5.5)
Panitumumab	7 (3.5)
Regorafenib	2 (1.0)
Chemotherapy	46 (23)
Fluoropyrimidine[b]	30 (15)
Irinotecan	21 (10.5)
Oxaliplatin	11 (5.5)
Folinic acid	12 (6.0)
Mitomycin	9 (4.5)
Other	6 (3.0)

Abbreviations: ASQoP = Aflibercept Safety and Quality-of-Life Program; FOLFIRI = folinic acid, 5-fluorouracil, irinotecan.
[a]Recorded if started within 30 days after the last study treatment; patients could be included in > 1 category.
[b]5-Fluouroacil, capecitabine, or tegafur/gimeracil/oteracil.