Aflibercept Plus FOLFIRI for Second-line Treatment of Metastatic Colorectal Cancer: Observations from the Global Aflibercept Safety and Health-Related Quality-of-Life Program (ASQoP)

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Abstract

This study evaluated safety and quality of life in patients with metastatic colorectal cancer undergoing treatment with aflibercept and FOLFIRI (fluorouracil, leucovorin, irinotecan). Most patients treated with this combination experienced either improvement or stability in quality of life scores. Aflibercept plus FOLFIRI is tolerable in the treatment of patients with metastatic colorectal cancer with a safety profile similar to that seen in previous studies of these individual medications.

Background: The objectives of this study were to evaluate the safety profile of aflibercept and health-related quality of life (HRQL) in patients with metastatic colorectal cancer (mCRC) provided with aflibercept access before marketing authorization. **Patients and Methods:** Patients received aflibercept followed by FOLFIRI (fluorouracil, leucovorin, irinotecan) on day 1 of a 2-week cycle until disease progression, unacceptable toxicity, death, or patient/investigator decision to discontinue. Treatment-emergent adverse events (TEAEs) were evaluated, and HRQL was assessed at baseline, cycle 3, and every other cycle using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, EORTC QLQ-CR29, and EuroQol 5-Dimensions 3-Levels questionnaires (NCT01571284).

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Results: Overall, 779 adult patients with mCRC, who received ≥ 1 prior oxaliplatin-based regimen and had disease progression during or following their last administration of oxaliplatin-based chemotherapy, were enrolled. At data cutoff, all patients had discontinued treatment, mainly owing to disease progression (51.7%). The most common TEAEs of any grade were diarrhea (61.6%), hypertension (48.4%), and nausea (43.3%). The most common grade 3/4 TEAEs were hypertension (24.1%), neutropenia (23.1%), and diarrhea (15.3%). Clinically meaningful changes in HRQL were reported for all measures. Most patients either had an improvement in their HRQL scores or remained stable during the treatment period based on patient-reported outcomes. **Conclusion:** The data from this study support the tolerability of the combination of aflibercept and FOLFIRI in a setting that more closely approximates real life in patients with mCRC who failed to respond to oxaliplatin-based chemotherapy, and also suggest an improvement in HRQL.

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Introduction

Aflibercept (Zaltrap, known as ziv-aflibercept in the United States) is an anti-angiogenic protein approved in combination with fluorouracil (5-FU), leucovorin, and irinotecan (FOLFIRI) for patients with metastatic colorectal cancer (mCRC) that has progressed following an oxaliplatin-containing regimen, with or without previous bevacizumab.[1] Aflibercept consists of key domains from the human vascular endothelial growth factor (VEGF) receptors 1 and 2 fused with the Fc portion of human immunoglobulin G[1,2] and blocks all VEGF-A and VEGF-B isoforms plus placental growth factor from interacting with their receptors.[3]

In the phase III VELOUR study, aflibercept plus FOLFIRI improved survival outcomes and response rates in patients treated with prior oxaliplatin-based chemotherapy.[4] The median overall survival (OS) was 13.50 months with aflibercept plus FOLFIRI versus 12.06 months in the placebo and FOLFIRI arm (hazard ratio [HR], 0.82; 95.34% confidence interval [CI], 0.71−0.94; $P = .0032$).[4]

The Aflibercept Safety and health-related Quality-of-life Program (ASQoP) (NCT01571284) is a global, multicenter, single-arm, open-label study evaluating the safety and health-related quality of life (HRQL) of aflibercept plus FOLFIRI in patients with mCRC previously treated with an oxaliplatin-containing regimen. As efficacy was demonstrated in the VELOUR trial, the objective of this study was to provide patients with mCRC access to aflibercept before marketing authorization, to evaluate safety, and to document changes in HRQL in a setting that more closely approximates real life.

Materials and Methods

Study Design

Patients received aflibercept (4 mg/kg intravenous infusion over 1 hour) followed by FOLFIRI (DL-leucovorin [400 mg/m^2], irinotecan [180 mg/m^2], 5-FU [400 mg/m^2 bolus + 2400 mg/m^2 continuous infusion], or individualized dosing based on physician's clinical judgment) on day 1 of a 2-week cycle. Patients were treated until disease progression, unacceptable toxicity, death, or patient/investigator decision to discontinue. Patients were followed throughout treatment and for 30 days after their last treatment (aflibercept or FOLFIRI) administration (end of treatment [EOT]).

Dose adjustments or cycle delays owing to toxicity were permitted, based on investigator discretion; treatment was resumed after the toxicity resolved. Patients could permanently discontinue aflibercept, FOLFIRI, one component of FOLFIRI, or all treatment. Supportive treatment with granulocyte-colony stimulating factor was permitted at the first occurrence of grade ≥ 3 neutropenia and as secondary prophylaxis for subsequent cycles in patients at increased risk for neutropenic complications.

Patients

Eligible patients were aged ≥ 18 years; had metastatic histologically or cytologically confirmed adenocarcinoma of the colon or rectum; had European Cooperative Oncology Group performance status (ECOG PS) of 0/1; and had received at least one prior oxaliplatin-based regimen, with disease progression during or following the last administration of oxaliplatin-based chemotherapy. Patients with prior irinotecan therapy, inadequate bone marrow function (absolute neutrophil count < 1.5 × 10^9/L, platelet count < 100 × 10^9/L, hemoglobin < 9.0 g/dL), inadequate liver function tests (total bilirubin > 1.5 × upper limit of normal [ULN], transaminases > 3 × ULN, alkaline phosphatase > 3 × ULN), or uncontrolled hypertension were excluded.

Written informed consent was obtained from all patients. The study was conducted according to the principles of the International Conference on Harmonisation guidelines for Good Clinical Practice. The clinical trial protocol and subsequent amendments were approved by an independent ethics committee.

Study Objectives

The primary objective of ASQoP was to evaluate the safety of aflibercept plus FOLFIRI in patients with previously treated mCRC in a setting that more closely approximates real life. The secondary objective was to document the impact of aflibercept plus FOLFIRI on patient-reported HRQL. Moreover, this trial provided access to aflibercept to patients with mCRC and investigators before marketing authorization and commercial availability.

Safety Assessments

Treatment-emergent adverse events (TEAEs) were evaluated by clinical examination and reported using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03. TEAEs reflect adverse events (AEs) that occurred during treatment regardless of their relationship to the study drug. Laboratory parameters and vital signs were classified according to NCI-CTCAE version 4.0. Safety was also analyzed in subgroups.

HRQL Assessments

HRQL was assessed via patient-reported outcomes (PROs) before clinical examination at baseline, cycle 3 (week 6), every other cycle during treatment, and at EOT. The PROs included the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire core module (QLQ-C30 [C30]; version 3) and the EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) questionnaire. Sites also had the option to administer the EORTC 29-item colorectal cancer-specific module (CR29) as an exploratory endpoint.

For the C30, global health status (scoring of items 29 and 30) and 5 functional scales (Physical, Role, Emotional, Cognitive, and Social) were assessed. For the EQ-5D, a single health state utility value (HSUV) and visual analog scale (VAS) were analyzed. For the CR29, questions on body image, anxiety, weight concerns, and sexual interest for men/women were analyzed. Scale and single-item measures range from 0 to 100, except for the EQ-5D HSUV, which ranges from 0 to 1. Higher scores generally indicate better HRQL; however, higher scores for symptoms (anxiety, weight) indicate worse HRQL.

The percentage of patients experiencing a clinically meaningful change in HRQL (the within-person change needed to indicate a relevant treatment benefit representing the difference between 2 time points that can be considered clinically relevant)[5] was reported in terms of improvement, deterioration, or neither (stable HRQL). The clinically meaningful changes are $\geq \pm 7$ points for EQ-5D VAS,[6] $\geq \pm 0.074$ points for EQ-5D HSUV score,[7] and $\geq \pm 10$ points for C30 and CR29 summary and subscales.[8]

Statistical Analyses

The study planned to enroll approximately 900 patients from 150 sites worldwide, with patient recruitment ending when aflibercept became commercially available in each country.

The safety population included all patients who provided written informed consent and received ≥ 1 complete cycle of study treatment (aflibercept or FOLFIRI). The HRQL population included those patients from the safety population who completed the C30, EQ-5D, and CR29 (where available) questionnaires at baseline, had ≥ 1 post-baseline assessment, and completed the EOT survey.

No imputations of missing data were performed. If 1 of the 2 EQ-5D-5L items had missing data, the HSUV single index score was not calculated, and the patient was not included in the analysis. Missing values for subscales of the C30 and CR29 were calculated according to the EORTC scoring manual.[9] For a multi-item scale, a subscale score was calculated only if $\geq 50\%$ of the constituent items were completed, with the score for missing items assumed to be 0. Missing data were not imputed for single-item scales nor if an assessment was missed/not completed at a study visit.

Results

Of 798 patients screened at 151 sites in 23 countries, 781 were enrolled (June 6, 2012–January 3, 2015), and 779 received ≥ 1 complete cycle of study treatment. Overall, 1 to 28 sites and 1 to 200 patients were enrolled per country.

At data cutoff (March 20, 2017), all patients had discontinued treatment owing to disease progression (51.7%), TEAEs (26.8%), patient request (10.8%), lost to follow-up (0.4%), or other reasons (10.3%). Overall, 188 patients (24.1%) discontinued 1 component of treatment: 91 (11.7%) discontinued aflibercept only and 97 (12.5%) discontinued FOLFIRI only.

The median age was 61.0 years (range, 20-89 years), with 8.3% aged ≥ 75 years (Table 1). The colon was the primary tumor site in one-half (52.1%) of the patients, most (77.5%) patients had undergone prior surgery, and almost one-half (46.2%) of patients had previously received bevacizumab.

Patients received a median of 7.0 (interquartile range [IQR], 4.0-12.0) treatment cycles (aflibercept, 6.0 [IQR, 3.0-12.0]; 5-FU, 7.0 [IQR, 4.0-12.0]; irinotecan, 7.0 [IQR, 4.0-12.0]), and were treated for a median of 16.6 weeks (IQR, 9.3-32.1 weeks) (aflibercept, 15.0 weeks; 5-FU, 16.4 weeks; irinotecan, 16.0 weeks). Dose modifications of aflibercept, 5-FU, and irinotecan were required in 19%, 50%, and 50% of patients, respectively. The planned/actual weekly dose intensities were aflibercept 2.00/1.63 mg/kg, 5-FU 1400.00/1058.97 mg/m^2, and irinotecan 90.00/68.91 mg/m^2.

Safety

Overall, TEAEs were reported in 98.7% of patients (Table 2), including grade 3/4 TEAEs in 78.2% of patients and serious AEs in 34.9% of patients; 94.0% (732/779), 65.0% (506/779), and 20.4% (159/779) of these events, respectively, were considered treatment-related. TEAEs led to permanent treatment discontinuation in 208 (26.7%) patients, and premature discontinuation of aflibercept or FOLFIRI in 104 (13.4%) patients.

The most common TEAEs were diarrhea (61.6%) and hypertension (48.4%) (Table 2). Grade 3/4 hypertension was reported in 24.1% of patients and was possibly related to treatment in 43.3% of patients (grade 3/4, 22.7%). Hematologic laboratory abnormalities included anemia (535/744; 71.9%), leukopenia (532/745; 71.4%), and neutropenia (450/744; 60.5%). The incidence of grade 3/4 hematologic abnormalities was generally low; however, neutropenia was reported in 227 (30.5%) of 744 patients (febrile neutropenia, 15/779 [1.9%]). The most common non-hematologic laboratory abnormalities were elevated alkaline phosphatase (465/733; 63.4%), proteinuria (468/779; 60.1%), and elevated aspartate transaminase (342/727; 47.0%). Grade 3/4 proteinuria was observed in 7.6% of patients, mostly without clinical signs of edema. The most common TEAEs of specific interest (grouped term) were diarrhea (61.7%) and hypertension (50.2%) (see Supplemental Table 1 in the online version).

In total, 48 (6.2%) patients died on study; 36 died during the on-treatment phase owing to disease progression (n = 19; 2.4%),

Table 1 Demographics and Baseline Characteristics

Characteristic	Safety Population (N = 779), n (%)[a]
Age, y	
Median (range)	61.0 (20-89)
<65	475 (61.0)
65-74	239 (30.7)
≥75	65 (8.3)
Gender	
Male	465 (59.7)
Female	314 (40.3)
Median time from diagnosis, mos (range)	13.4 (3-142)
ECOG PS	
0	484 (62.1)
1	292 (37.5)
Missing	3 (0.4)
Prior bevacizumab	360 (46.2)
Prior anti-EGFR therapy[b]	59 (7.6)
Primary Site	
Colon	406 (52.1)
Rectosigmoid	171 (22.0)
Rectum	200 (25.7)
Other	2 (0.3)
Main Metastatic Site at Baseline	
Liver	574 (73.7)
Liver (only)	225 (28.9)
Liver + any other site	349 (44.8)
Lung	369 (47.4)
Distant lymph nodes	176 (22.6)
Organs With Metastases at Baseline	
1	358 (46.0)
>1	421 (54.0)
Prior Treatments	
Surgery	604 (77.5)
Radiotherapy	139 (17.8)
Prior advanced chemotherapy only	576 (73.9)

Abbreviations: ECOG PS = European Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor.
[a]Unless otherwise stated.
[b]Patients who have taken cetuximab and/or panitumumab as previous anti-cancer therapy.

Table 2 TEAEs Occurring in ≥ 20% of Patients (Safety Population)

TEAE, %	Aflibercept + FOLFIRI (N = 779)	
	All Grades, n (%)	Grade 3/4, n (%)
Most Frequent TEAEs		
Any TEAE	769 (98.7)	609 (78.2)
Diarrhea	480 (61.6)	119 (15.3)
Hypertension	377 (48.4)	188 (24.1)
Nausea	337 (43.3)	22 (2.8)
Stomatitis	334 (42.9)	82 (10.5)
Fatigue	287 (36.8)	53 (6.8)
Decreased appetite	207 (26.6)	15 (1.9)
Vomiting	196 (25.2)	24 (3.1)
Asthenia	194 (24.9)	57 (7.3)
Weight decreased	171 (22.0)	8 (1.0)
Laboratory Abnormalities		
Hematologic laboratory abnormalities		
Anemia	(n = 744) 35 (71.9)	(n = 744) 14 (1.9)
Leukopenia	(n = 745) 532 (71.4)	(n = 745) 72 (9.7)
Neutropenia	(n = 744) 450 (60.5)	(n = 744) 227 (30.5)
Thrombocytopenia	(n = 745) 293 (39.3)	(n = 745) 13 (1.7)
Non-hematologic laboratory abnormalities		
Elevated alkaline phosphatase	(n = 733) 465 (63.4)	(n = 733) 23 (3.1)
Proteinuria[a]	(n = 779) 468 (60.1)	(n = 779) 59 (7.6)
Elevated AST	(n = 727) 342 (47.0)	(n = 727) 12 (1.7)
Elevated ALT	(n = 736) 270 (36.7)	(n = 736) 10 (1.4)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate transaminase; TEAE = treatment-emergent adverse event.
[a]Proteinuria includes the number of incidents from the overall TEAE listing and incidents identified by a morning spot and/or 24-hour urinalysis and/or dipstick.

TEAEs (n = 15; 1.9%), or sudden death (n = 2; 0.3%). The TEAEs leading to death were infections (n = 6; 0.8%), general physical health deterioration, intestinal/large intestinal perforation (each n = 2; 0.3%), acute pulmonary edema, psychiatric disorders, cardiac arrest, pneumonia aspiration, and pulmonary hemorrhage (each n = 1; 0.1%). In addition, 12 deaths occurred ≥ 30 days after EOT; only 1 of these (stoma site hemorrhage) was considered treatment-related. One patient was included in the clinical trial but died owing to disease progression before receiving treatment.

The incidence of TEAEs was similar among patients with and without prior bevacizumab treatment (99.2% and 98.3%, respectively; grade 3/4 in 76.1% and 80.0%). Hypertension was reported in a similar number of patients in both groups (46.1% vs. 50.4% with and without prior bevacizumab treatment, respectively); however, the incidence of grade 3/4 hypertension was slightly lower in patients who had previously received bevacizumab compared with those who had not (19.7% vs. 27.9%, respectively). Proteinuria was reported in 11.4% of patients with prior bevacizumab exposure versus 15.0% in bevacizumab-naive patients (grade 3/4 in 2.2% and 3.8%, respectively). The incidences of all grades of diarrhea, neutropenia, fatigue, asthenia, and stomatitis were similar in both groups.

The incidence of TEAEs was also similar among patients aged < 65 and ≥ 65 years (98.9% and 98.4%, respectively); however, the incidence of grade 3/4 TEAEs was slightly lower among patients aged < 65 versus ≥ 65 years (76.2% vs. 81.3%, respectively).

Table 3 Baseline Characteristics

Baseline HRQL Scores	No. Patients (%)	Mean Score (SD)
EQ-5D-3L		
Visual analog scale	334 (42.9)	74.5 (17.8)
HSUV	353 (45.3)	0.78 (0.22)
C30		
Global health	356 (45.7)	70.1 (19.1)
Physical function	357 (45.8)	82.4 (19.3)
Role function	357 (45.8)	80.1 (26.4)
Emotional function	358 (46.0)	77.8 (21.6)
Cognitive function	358 (46.0)	85.6 (20.1)
Social function	358 (46.0)	80.9 (25.8)
CR29		
Body image	210 (27.0)	81.8 (23.0)
Anxiety	211 (27.1)	48.3 (28.4)
Weight concerns	210 (27.0)	81.7 (26.3)
Sexual interest (men)	110 (14.1)	37.6 (30.3)
Sexual interest (women)	76 (9.8)	17.1 (22.1)

The EQ-5D-3L HSUVs range from 0 to 1, and the VAS scores range from 0 to 100, with higher HSUV and VAS scores indicating better HRQL.[10-12] For the C30 and CR29, all scales and single-item measures range from 0 to 100. Higher scores for C30 and CR29 indicate better HRQL, whereas higher scores on the C30 and CR29 symptom scales indicate greater symptomatology/problems.[13]
Abbreviations: C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item core module; CR29 = European Organisation for Research and Treatment of Cancer 29-item colorectal cancer-specific module; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels; HRQL = health-related quality of life; HSUV = health state utility value; SD = standard deviation; VAS = visual analog scale.

Dehydration was more common in elderly than younger patients (4.3% vs. 1.7%, respectively). Hypertension was similar in both groups (all grades 48.4% each; grade 3/4 in 23.4% and 25.3% aged $<$ 65 and $\geq$ 65 years, respectively). Proteinuria was reported in 12.0% and 15.5% of patients, respectively (grade 3/4 in 2.7% and 3.6%).

Acute myocardial infarction was observed in 1 patient (grade 4) in the group aged $<$ 65 years and in 1 patient (grade 3) in the group aged $\geq$ 65 years. There were no grade 3/4 incidences of angina pectoris. Deep vein thrombosis was observed in 1.1% and 3.6% of patients, respectively (grade 3/4 in 0.4% and 2.0%). Pulmonary embolism was observed in 2.1% and 2.0% of patients, respectively; all cases were grade 3/4.

HRQL

Overall, 358 (50.0%), 358 (50.0%), and 212 (27.2%) patients completed the EQ-5D, C30, and CR29 questionnaires at baseline, EOT, and at least once during treatment (Table 3). Reasons for non-completion included failure to distribute the questionnaire (20%), followed by patient decision (10%), patient missed clinical visit (10%), death (4%), toxicity (3%), and other reasons (2%). Baseline demographics and disease characteristics in the HRQL population were consistent with the safety population. Clinically meaningful changes were observed in all scales/subscales of the HRQL PROs, with most patients demonstrating stable or clinically meaningful improvements in HRQL scores on all scales/subscales measured (Table 4).

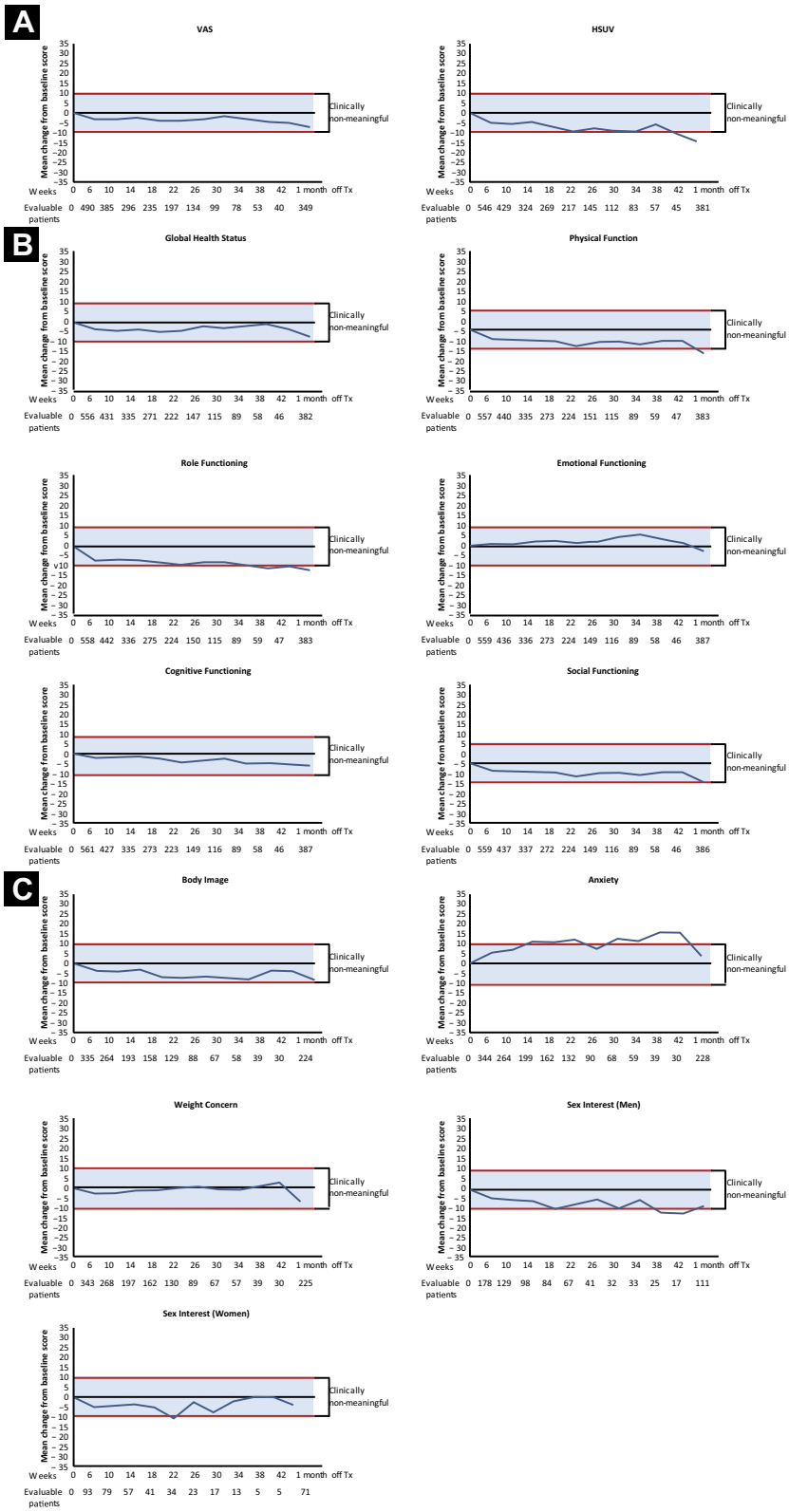
When HRQL scores were analyzed over time (change from baseline for each cycle), there was an initial drop in HRQL scores, but they were generally stable throughout the remainder of

Table 4 Responder Analyses: Changes in HRQL Scores

Scale	N	Patients, %		
		Improvement	Stable	Deterioration
EQ-5D-3L				
VAS	319	21	34	45
HSUV	349	18	38	44
C30				
Global health status/QoL	352	15	42	43
Physical functioning	353	9	50	41
Role functioning	353	16	38	46
Emotional functioning	357	23	52	25
Cognitive functioning	357	19	45	36
Social functioning	356	16	41	43
CR29				
Body image	206	18	38	44
Anxiety	209	33	47	20
Weight concerns	206	17	48	35
Sexual interest (men)	102	14	51	35
Sexual interest (women)	63	5	68	27

Mean change scores for HRQL parameters from baseline to end of treatment. Change scores were deemed clinically meaningful (improvement or deterioration) if there was a change of $\geq \pm 7$ points for the EQ-5D VAS,[6] $\geq \pm 0.074$ points for the EQ-5D HSUV score,[7] or $\geq \pm 10$ points for the C30 and CR29 summary and subscales.[8]
Scale and single-item measures range from 0 to 100, except for the EQ-5D HSUV, which ranges from 0 to 1. Higher scores generally indicate better HRQL; however higher scores for symptoms (anxiety, weight) indicate worse HRQL.[10-13]
Abbreviations: C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Quality of Life Questionnaire 30-item core module; CR29 = European Organisation for Research and Treatment of Cancer 29-item colorectal cancer-specific module; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels; HRQL = health-related quality of life; HSUV = health state utility value; QoL = quality of life; VAS = visual analog scale.

Figure 1 Mean Change in Health-related Quality of Life Scores Over Time (by Cycle/Week for EQ-5D-3L) (A), C30 (B), and CR29 (C) Questionnaires



Abbreviations: C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Quality of Life Questionnaire-30 items; CR29 = European Organisation for Research and Treatment of Cancer 29-item colorectal-specific module; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels; HSUV = health state utility value; Tx = treatment; VAS = visual analog scale.

treatment (Figure 1). Patients who completed the CR29 reported a statistically significant improvement in Anxiety score from baseline to EOT ($P = .005$), which was clinically meaningful at visits 7 to 11 and 15 to 21. A clinically meaningful decline in the Sexual Interest (men) subscale was also observed (visits 9, 15, and 19-21); all other CR29 measures demonstrated maintenance of HRQL from baseline to EOT (Figure 1).

Changes in HRQL from baseline to EOT were also examined in patients based on prior bevacizumab therapy (Table 5), patient demographics, and baseline characteristics (ECOG PS, age, and gender; see Supplemental Table 2 in the online version), and the presence of diarrhea as a TEAE (see Supplemental Table 3 in the online version). Overall, the greatest differences were observed in patients previously treated with bevacizumab (Table 5). A higher proportion of these patients had a clinically meaningful deterioration in HRQL score (except for Sexual Interest [women] and Anxiety parameters) compared with patients without prior bevacizumab. Conversely, a smaller proportion of patients who had received prior bevacizumab treatment had clinically meaningful improvements in HRQL score (except for Anxiety, Emotional Functioning, and EQ-5D VAS). Tables 5 and 6 also provide, respectively, summary results of HRQL by prior use of bevacizumab and the safety of ASQoP compared with VELOUR.

Discussion

The ASQoP study provided patients with mCRC access to aflibercept before marketing authorization. This setting more closely approximated real life than the VELOUR study, allowing evaluation of safety and assessment of patient HRQL throughout treatment.

The patient populations were similar between ASQoP and VELOUR, although patients with ECOG PS 2 were excluded from ASQoP. In addition, although the colon was the primary tumor site in only 52.1% of patients in the ASQoP study, this was similar to the rate of 47.2% to 49.2% of patients observed across the 2 arms in VELOUR. There were also minor differences in the protocols of these studies. In ASQoP, physicians could use lower starting doses of the irinotecan and/or 5-FU components of the FOLFIRI regimen after consideration of toxicities from prior therapies and patient baseline characteristics. In contrast, in VELOUR, initiation of FOLFIRI at lower doses was not permitted, regardless of prior dose modifications during first-line treatment.[4] In fact, the median actual dose intensity of aflibercept was lower than that of 5-FU and irinotecan because the dose could be augmented or skipped owing to the presence of AEs. Although it is known that there is a dose–response relationship with irinotecan, there is a plateau effect; thus, it was surmised that reducing the dose slightly would not affect efficacy.

Overall, the safety profile in ASQoP was consistent with the known safety profile of aflibercept and FOLFIRI,[1] and with that observed in the VELOUR study[4] (Table 6), with no new safety signals identified. The frequency of grade 3/4 AEs appeared slightly lower in ASQoP across the whole population (78.2% [ASQoP] vs. 83.4% [VELOUR]) and in the elderly subgroup (81.3% vs. 89.3%). The incidence of TEAEs commonly associated with FOLFIRI treatment and anti-VEGF therapy was largely similar between the 2 studies, although the incidence of grade 3/4 neutropenia was lower in ASQoP compared with VELOUR (24.8% vs. 36.7%). These differences may reflect the more flexible FOLFIRI dosing, as well as greater familiarity with the aflibercept toxicity profile, or routine TEAE management. The reduced treatment time (6 vs. 7 median cycles), differences in TEAE reporting (MedDRA version 19.0 vs. 13.1 and NCI-CTCAE version 4.03 vs. 3.0), and greater use of granulocyte-colony stimulating factor prophylaxis between ASQoP and VELOUR, respectively, may have also contributed.

The safety profile was also largely similar in the subgroups analyzed, although the incidence of hypertension appeared lower in patients who had received prior bevacizumab compared with those who had not. However, it is important to note that patients who developed uncontrolled hypertension during previous bevacizumab treatment were excluded from this study, which may, in part, account for this discrepancy. Furthermore, the overall incidence of hypertension was higher in ASQoP compared with VELOUR, although this was not believed to be clinically significant. This is possibly related to changes in the NCI-CTCAE criteria for hypertension between the 2 protocols. Alternatively, the higher proportion of patients who previously received bevacizumab therapy in this trial (46% vs. 30.4% in VELOUR) may have contributed to this difference.

In ASQoP, TEAEs leading to death during the on-treatment phase occurred in 15 (1.9%) of 779 patients. This was numerically higher than seen in VELOUR[14] (6/611 patients; 1.0%), in the TML study[15] (4/401 patients; 1.0%), and in the RAISE study[16] (8/536 patients; 1.5%). In all studies, gastrointestinal events, cardiovascular events, and infections were seen. The overall incidence of TEAEs leading to death during the on-treatment phase did not differ between studies.

Among the subset of patients who completed the HRQL instruments, the majority had either stable or improved HRQL on all scales and subscales of the 3 HRQL measures. Although some patients experienced clinically meaningful declines from baseline to EOT, it should be noted that the final HRQL assessment was conducted 30 days after the last treatment administration, by which time approximately 50% of patients had experienced disease progression and 25% had discontinued therapy owing to TEAEs. As the treatment cycles continued, fewer patients completed the surveys; therefore, scores toward the EOT may have artificially higher outcomes because the sickest patients had dropped out of the study. The high drop-out rate in this study is common in trials conducted in the metastatic setting, in particular after first- and second-line therapy when patients still have additional options to manage their disease.

When patients were separated by baseline characteristics or the presence/absence of TEAEs, the only characteristic that appeared to impact HRQL scores was prior bevacizumab use Tables 5. A higher proportion of patients who received prior bevacizumab experienced HRQL deterioration compared with those who had not. Conversely, a higher proportion of patients who had not received prior bevacizumab experienced HRQL improvements. One possible explanation is that there is a cumulative effect of prior exposure to bevacizumab treatment. This would also explain why a higher proportion of those without prior bevacizumab treatment experienced HRQL improvements. Further investigation is needed to explore the relationships between OS, progression-free survival, HRQL, and prior bevacizumab treatment.

Overall, the data available from ASQoP demonstrate that the combination of aflibercept and FOLFIRI in patients with mCRC

Table 5 Responder Analyses: Changes in HRQL Scores[a] by Prior Bevacizumab Therapy

	No Prior Bevacizumab Treatment				Prior Bevacizumab Treatment			
Scale	**N**	**Imp, %**	**Stable, %**	**Det, %**	**N**	**Imp, %**	**Stable, %**	**Det, %**
EQ-5D-3L								
VAS	180	21	36	43	139	21	33	46
HSUV	196	22	36	42	153	13	40	47
C30								
Global health status/QoL	200	17	41	42	152	13	42	45
Physical functioning	201	10	55	35	152	7	44	49
Role functioning	201	17	42	41	152	14	34	52
Emotional functioning	203	21	59	20	154	25	42	33
Cognitive functioning	203	22	44	34	154	16	44	40
Social functioning	203	17	43	40	153	15	37	48
CR29								
Body image	107	22	37	41	99	14	40	46
Anxiety	107	29	51	20	102	36	44	20
Weight concerns	105	20	50	30	101	14	44	42
Sexual interest (men)	56	16	50	34	46	11	52	37
Sexual interest (women)	31	10	61	29	32	0	75	25

Scale and single-item measures range from 0 to 100, except for the EQ-5D HSUV, which ranges from 0 to 1. Higher scores generally indicate better HRQL; however higher scores for symptoms (anxiety, weight) indicate worse HRQL.
Abbreviations: C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Quality of Life Questionnaire 30-item core module; CR29 = European Organisation for Research and Treatment of Cancer 29-item colorectal cancer-specific module; Det = deterioration; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels; HRQL = health-related quality of life; HSUV = health state utility value; Imp = improvement; VAS = visual analog scale.
[a]Mean change scores for HRQL parameters from baseline to end of treatment, by prior bevacizumab treatment.

Table 6 Safety Outcomes of VELOUR Compared With ASQoP

	VELOUR		ASQoP
TEAE, %	**Aflibercept (n = 605)**	**Placebo (n = 611)**	**Aflibercept (n = 779)**
Any TEAE	99.2	97.9	98.7
Grade 3/4 TEAE	83.5	62.5	78.2
Specific Grade 3/4 TEAEs			
Neutropenia	36.7	29.5	24.8
Diarrhea	19.3	7.8	15.3
Hypertension	19.1	1.5	24.5
Asthenic conditions	16.9	10.6	13.6
Stomatitis and ulceration	13.7	5.0	10.7
Infection	12.3	6.9	11.7
Proteinuria	7.9	1.2	3.6
Venous thromboembolic events	7.9	6.3	4.1
Thrombocytopenia	3.3	1.7	0.8
Hemorrhage	2.9	1.7	1.9
Palmar-plantar erythrodysesthesia	2.8	0.5	1.7
Arterial thromboembolic events	1.8	0.5	0.9
GI fistula, fistulae, or perforation	0.8	0.6	2.2
Drug reactions	0.5	0.5	1.2
TEAEs leading to discontinuation from study treatment	26.8	12.1	26.7

Abbreviations: ASQoP = The Aflibercept Safety and health-related Quality-of-life Program; GI = gastrointestinal; TEAE = treatment-emergent adverse event.

who have failed to respond to oxaliplatin-based chemotherapy is tolerable but with commonly associated toxicities. Furthermore, these data demonstrate clinically meaningful improvements and/or maintenance of HRQL in most patients. This study provides important and unprecedented safety and HRQL data from a global population of patients with mCRC treated with aflibercept in a setting that more closely approximates real life.

Clinical Practice Points

- Data from this study, conducted in a setting that more closely approximates real life, demonstrate that the combination of aflibercept and FOLFIRI is tolerable in patients with mCRC who have failed to respond to oxaliplatin-based chemotherapy, with commonly associated safety events.
- Clinicians can potentially see clinically meaningful improvements and/or maintenance of HRQL in most patients during their treatment.

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Supplemental Data

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Supplemental Data

Supplemental Table 1 TEAEs of Specific Interest Occurring in ≥ 2% of the Population (Safety Population)

TEAE, n (%)	Aflibercept + FOLFIRI (n = 779)	
	All Grades	Grade 3/4
Diarrhea	481 (61.7)	119 (15.3)
Hypertension	391 (50.2)	191 (24.5)
Hemorrhage	219 (28.1)	15 (1.9)
Respiratory, thoracic, and mediastinal disorders	155 (19.9)	4 (0.5)
Proteinuria	108 (13.9)	28 (3.6)
Skin and subcutaneous tissue disorders	84 (10.8)	2 (0.3)
Parodontopathy	75 (9.6)	7 (0.9)
Gastrointestinal disorders	65 (8.3)	9 (1.2)
Venous thromboembolic events	48 (6.2)	32 (4.1)
General disorders and administration-site conditions	36 (4.6)	1 (0.1)
Vascular disorders	31 (4.0)	15 (1.9)
Infections and infestations	27 (3.5)	4 (0.5)
Adverse drug reaction	22 (2.8)	5 (0.6)
Neutropenic complications	20 (2.6)	20 (2.6)
Arterial thromboembolic event	19 (2.4)	7 (0.9)

Abbreviation: TEAE = treatment-emergent adverse event.

Supplemental Table 2 HRQL Change Scores (Baseline to End of Treatment) by Demographics and Baseline Characteristics

	ECOG PS							Age, y							Gender						
	0			1				<60			≥60				Male			Female			
Scale	N	Mean (SD)	CMR D/I, %	N	Mean (SD)	CMR D/I, %	P[a]	N	Mean (SD)	CMR D/I, %	N	Mean (SD)	CMR D/I, %	P[a]	N	Mean (SD)	CMR D/I, %	N	Mean (SD)	CMR D/I, %	P[a]
EQ-5D																					
VAS	245	−6.7 (18.7)	47/21	74	−6.0 (16.1)	36/20	.77	154	−6.5 (17.7)	43/18	165	−6.5 (18.6)	46/23	.97	183	−4.4 (17.4)	39/25	136	−9.3 (18.8)	51/15	.02
HSUV	268	−0.12 (0.31)	45/19	81	−0.13 (0.32)	41/17	.70	166	−0.13 (0.31)	46/15	187	−0.11 (0.31)	43/21	.59	199	−0.12 (0.30)	44/16	150	−0.12 (0.33)	45/22	.97
C30																					
Global health status/QoL	271	−8.1 (23.9)	42/16	81	−10.0 (23.1)	44/14	.53	166	−8.4 (21.5)	43/14	186	−8.6 (25.6)	43/16	.95	204	−8.0 (22.3)	43/14	148	−9.2 (25.6)	43/17	.66
Physical functioning	273	−11.1 (22.5)	41/10	80	−12.5 (20.2)	41/6	.61	168	−10.5 (19.7)	40/8	185	−12.2 (23.9)	42/9	.44	205	−9.7 (21.2)	39/10	148	−13.7 (22.9)	44/7	.10
Role functioning	274	−13.5 (29.3)	46/14	79	−8.0 (27.8)	43/25	.14	169	−9.6 (26.9)	39/18	184	−14.8 (30.7)	52/14	.09	204	−10.9 (28.2)	45/17	149	−14.2 (30.0)	47/15	.29
Emotional function	276	−1.6 (21.3)	24/22	81	−4.8 (25.4)	31/23	.30	168	−1.6 (19.6)	24/24	189	−3.0 (24.5)	26/22	.57	205	−1.6 (20.8)	23/22	152	−3.3 (24.2)	28/23	.50
Cognitive functioning	276	−5.3 (22.6)	37/19	81	−6.6 (21.4)	36/20	.64	168	−4.4 (21.2)	33/18	189	−6.6 (23.3)	39/20	.34	205	−5.1 (20.9)	36/17	152	−6.1 (24.2)	38/23	.68
Social functioning	275	−9.2 (26.8)	43/17	81	−10.3 (25.9)	43/15	.73	168	−10.2 (25.5)	43/14	188	−8.7 (26.5)	44/19	.58	204	−8.3 (24.5)	41/16	152	−10.9 (27.9)	46/17	.37
CR29																					
Body image	167	−9.8 (25.1)	46/15	39	−3.0 (25.9)	36/33	.13	94	−8.2 (21.9)	43/15	112	−8.8 (28.0)	45/21	.86	123	−6.7 (23.6)	42/18	83	−4.2 (27.7)	46/19	.21
Anxiety	170	7.5 (30.1)	17/35	39	0.0 (34.2)	31/21	.18	95	5.3 (31.6)	20/34	114	6.7 (30.5)	19/32	.73	124	3.0 (30.1)	21/27	85	10.6 (31.8)	18/40	.08
Weight concern	167	−8.4 (33.3)	35/18	39	−10.3 (27.7)	36/13	.74	93	−7.9 (32.7)	34/18	113	−9.4 (32.0)	36/16	.73	123	−9.5 (30.0)	36/15	83	−7.6 (35.4)	35/20	.69
Sexual interest (men)	80	−10.4 (31.2)	38/13	22	−3.0 (22.8)	27/18	.30	43	−10.9 (33.1)	40/14	59	−7.3 (27.0)	32/14	.56	102	−8.8 (29.6)	35/14	—	—	—	—
Sexual interest (women)	54	−7.4 (17.9)	28/6	9	−11.1 (23.6)	22/0	.59	35	−8.6 (16.8)	29/3	28	−7.1 (21.0)	25/7	.77	—	—	—	63	−7.9 (18.7)	68/5	n/a

Abbreviations: C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Quality of Life Questionnaire 30-item core module; CMR = clinically meaningful response; CR29 = European Organisation for Research and Treatment of Cancer 29-item colorectal cancer-specific module; D = deterioration; ECOG PS = European Cooperative Oncology Group performance status; EQ-5D = EuroQol 5-Dimensions; I = improvement; HRQL = health-related quality of life; HSUV = health state utility value; n/a = not available; QoL = quality of life; SD = standard deviation; VAS = visual analog scale.

[a]Difference between mean change in HRQL score; paired *t* test. Scale and single-item measures range from 0 to 100, except for the EQ-5D HSUV, which ranges from 0 to 1. Higher scores generally indicate better HRQL, however higher scores for symptoms (anxiety, weight) indicate worse HRQL.[10-12]

Supplemental Table 3 HRQL Change Scores (Baseline to End of Treatment) by the Presence of Diarrhea as a Treatment-emergent Adverse Event

	Diarrhea						
	Absent			Present			
Scale	N	Mean (SD)	CMR D/I, %	N	Mean (SD)	CMR D/I, %	*P*[a]
EQ-5D							
VAS	110	−5.8 (18.5)	40/25	209	−6.9 (18.0)	47/19	.60
HSUV	119	−0.12 (0.34)	42/25	230	−.12 (.30)	45/15	.94
C30							
Global health status/QoL	117	−7.1 (21.7)	40/17	235	−9.3 (24.7)	44/14	.41
Physical functioning	121	−10.6 (22.1)	36/10	232	−11.8 (22.0)	44/8	.62
Role functioning	121	−8.8 (27.8)	41/19	232	−14.1 (29.5)	48/15	.11
Emotional functioning	121	−3.4 (23.4)	26/19	236	−1.8 (21.7)	25/25	.53
Cognitive functioning	121	−4.4 (23.4)	32/23	236	−6.1 (21.8)	39/17	.49
Social functioning	121	−9.6 (25.0)	46/17	235	−9.3 (26.6)	42/16	.90
CR29							
Body image	68	−8.3 (25.2)	40/21	138	−8.6 (25.5)	46/17	.92
Anxiety	68	6.4 (31.2)	21/31	141	5.9 (3.9)	19/21	.92
Weight concerns	67	−4.0 (33.6)	28/22	139	−11.0 (31.4)	39/14	.14
Sexual interest (men)	33	−8.1 (30.1)	30/12	69	−9.2 (29.6)	38/14	.86
Sexual interest (women)	21	−6.3 (17.1)	24/5	42	−8.7 (19.6)	29/5	.64

For the EQ-5D-3L, HSUVs range from 0 to 1 and VAS scores range from 0 to 100, with higher HSUV and VAS scores indicating better HRQL.[10-12]
For the C30 and CR29, all scales and single-item measures range from 0 to 100. Higher scores for C30 and CR29 indicate better HRQL, whereas higher scores on the C30 and CR29 symptom scales, indicate greater symptomatology/problems.[13]
Abbreviations: C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Quality of Life Questionnaire 30-item core module; CMR = clinically meaningful response; CR29 = European Organisation for Research and Treatment of Cancer 29-item colorectal cancer-specific module; D = deterioration; EQ-5D = EuroQol 5-Dimensions; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels; I = improvement; HRQL = health-related quality of life; HSUV = health state utility value; QoL = quality of life; SD = standard deviation; VAS = visual analog scale.
[a]Difference between mean change in HRQL score; paired *t* test.