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Discontinuation of first-line bevacizumab in metastatic colorectal cancer: the BEAWARE Italian Observational Study

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Abstract

Aims: BEAWARE investigated the pattern of first-line bevacizumab early interruption in the Italian real-world setting of metastatic colorectal cancer.

Methods: A total of 386 patients were followed for 15 months after first-line chemotherapy + bevacizumab start. The rate of bevacizumab interruption for progression or adverse drug reactions (ADRs) constituted the primary endpoint.

Results: A total of 78.2% of patients interrupted bevacizumab: 56.6% for progression, 7.3% for ADRs, and 36.1% for other reasons. Median treatment duration was 6.7, 2.5, and 4.6 months, respectively. Median progression-free survival was 10.3 months; however, 35.8% of patients were not progressed and were thus censored at the data cutoff of 15 months, while 21.8% were still receiving bevacizumab. Patients discontinuing for progression/ADRs more frequently had metastases in >1 site ($p = .0001$), and a shorter median progression-free survival (6.9 vs 13.9 months, $p < .0001$).

Conclusions: In Italy, first-line bevacizumab is interrupted mainly for progression, only 7.3% due to adverse events, and about one third of cases for other reasons. In clinical practice, the attitude to treat until progression as per guidelines might be implemented.

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Keywords

Metastatic colorectal cancer, bevacizumab, therapy interruption, clinical practice, progression-free survival

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Introduction

To date, colorectal cancer remains the second leading cause of cancer death in Europe.[1] Approximately 20%–25% of patients present metastases already at the time of diagnosis, and 50%–60% of the remainder will develop metastases later on.[2] Although the introduction of new chemotherapy and biologic agents, used alone or in combination, has led to significant improvement in clinical outcomes, patient prognosis remains dismal and the 5-year survival rate is about 10%.

Addition of bevacizumab has been shown to increase significantly the overall response rate (44.8% vs 34.8%, $p = .004$), overall survival (OS, 20.3 months vs 15.6 months, $p < .001$), and progression-free survival (PFS, 10.6 months vs 6.2 months, $p < .001$) in a randomized trial comparing the efficacy of 5-fluorouracil (5-FU)–based chemotherapy with or without monoclonal antibodies (mAbs).[3] Further studies then confirmed the significant improvement of OS and PFS provided by bevacizumab in combination with oxaliplatin- and 5-FU-based chemotherapy in first-line regimens.[4,5]

Since its first approval by the Food and Drug Administration in 2004, new targeted agents have been developed for metastatic colorectal cancer (mCRC) (e.g. anti–epidermal growth factor receptor and other anti–vascular endothelial growth factor [VEGF] mAbs), but their use is either limited to subgroups of patients, such as those with a RAS wild-type (wt) tumor,[6–8] or not recommended in first-line regimens.[9,10]

As VEGF is physiologically produced, interruption of bevacizumab likely causes neoangiogenesis restoration, and this mechanism constitutes the rationale to continue its administration in maintenance therapy: indeed, patients with mCRC interrupting bevacizumab together with chemotherapy have been reported to have a significantly shorter PFS than those continuing therapy until progression of disease (PD) or toxicity (7.9 vs 10.4 months, $p < .0001$).[7] A phase III trial showed a significant improvement in PFS in patients treated with capecitabine and bevacizumab after induction with capecitabine plus oxaliplatin (XELOX) bevacizumab versus those randomized to observation (11.7 vs 8.5 months, $p < .0001$), suggesting the efficacy of the bevacizumab-based maintenance strategy.[11] Yet the optimal maintenance regimen following induction therapy with chemotherapy plus bevacizumab remains controversial: recently, the AIO 0207 trial showed the noninferiority of bevacizumab alone compared to bevacizumab plus standard fluoropyrimidine in terms of time to failure of strategy (i.e. maintenance plus reinduction after first PD),[12] whereas the SAKK trial failed to demonstrate the noninferiority of treatment holidays versus maintenance with bevacizumab alone.[13] Analogously, 2 randomized phase III trials have recently shown that continuation or reintroduction of bevacizumab plus second-line chemotherapy beyond PD leads to a significant extension in OS (of up to 1.8 months) compared to chemotherapy alone,[14,15] supporting the idea of a benefit yielded by the prolongation of angiogenesis inhibition over time. However, despite this evidence and the fact that international guidelines by the National Comprehensive Cancer Network (NCCN) clearly suggest to continue bevacizumab until PD or unacceptable toxicity, data from clinical practice unveil a significant number of patients prematurely interrupting therapy for reasons other than PD.[16,17] Besides progression, other causes include toxicity, chemotherapy holiday, achievement of maximum benefit, and physician decision.[17] As a result, in US clinical practice, the median duration of first-line bevacizumab treatment was reported to be up to 5.4 months, although PD is expected >10 months after therapy initiation.[16,17] In line with these results, data on file show that Italian physicians prematurely stop bevacizumab in daily practice, but this trend remains underinvestigated.

Here, we report the results of the BEAWARE observational study, which is the first Italian study specifically designed to assess, in the real-world setting, the proportion of patients with mCRC treated first-line with chemotherapy plus bevacizumab who discontinued therapy because of PD, adverse drug reactions (ADRs), or other reasons. Furthermore, BEAWARE provides a comprehensive evaluation of the causes for earlier interruption, together with the effects on PFS and the type of treatment adopted by patients who discontinued first-line therapy.

Methods

Study design and patient population

BEAWARE is an Italian multicenter, retrospective/prospective observational cohort study (ClinicalTrials.gov Identifier: NCT01609075) that collected data on patients with mCRC given first-line fluoropyrimidine chemotherapy plus bevacizumab and consecutively enrolled depending on their KRAS exon 2 mutational status. In order to obtain a representative sample of the target population, a consecutive enrollment considering KRAS exon 2 mutational status (according to a proportion wt:mut of 6:4) was suggested by study protocol based on published data.[18] During the enrollment phase, this proportion was not satisfied in all centers, so the actual proportion was 49% wt and 51% mut KRAS. Enrollment was performed by 74 centers specialized in the treatment of mCRC across Italy, between June 2012 and June 2013. Patients were eligible for this study if ⩾18 years of age, diagnosed with mCRC, and if they started a first-line fluoropyrimidine-based chemotherapy plus bevacizumab between September 1, 2011, and February 29, 2012. Other inclusion criteria were previous execution of KRAS genotyping test and informed consent and privacy forms given (authorization from the Privacy Guarantor was obtained for deceased or

unreachable patients). Patients participating in clinical trials were excluded from the study. The total observational period was 15 months from the start of treatment with bevacizumab, thus the follow-up ended in June 2013. Patient inclusion was based on information present in medical records. Files from deceased patients meeting inclusion and exclusion criteria were allowed to participate in the study. For deceased subjects and for those starting bevacizumab greater than 15 months previously, all data were collected retrospectively. For alive patients starting bevacizumab less than 15 months previously, data were collected partly retrospectively, until the enrollment visit, and partly prospectively, until the 15-month follow-up visit.

All patients provided informed consent prior to any study-specific procedures. Study approval was obtained first by the ethics committee of the coordinator center (Università Campus Bio-Medico, Rome) and then by the independent ethics committees at every institution (the full list is provided in the Acknowledgements). The study was conducted in accordance with the Declaration of Helsinki.

Study endpoints

The primary objective of this study was to investigate, in routine clinical practice, the proportion of patients who interrupted bevacizumab administration due to PD or to an ADR that requires discontinuation of the treatment as defined in the summary of product characteristics (SPC). Patients who died during treatment with bevacizumab contributed to this analysis and were considered as patients who interrupted bevacizumab for PD.

Secondary endpoints included evaluation of the proportion of patients who interrupted bevacizumab due to reasons other than PD or ADRs (not requiring discontinuation of treatment according to the SPC) and to describe those. The 2 groups of patients (who discontinued bevacizumab due to PD or ADRs related to the treatment and who discontinued for other reasons) were compared in terms of demographic and clinical characteristics, along with PFS. The proportion of patients undergoing second-line therapy, together with the regimens given, was also reported.

KRAS *genotyping*

Genomic DNA was extracted from tumor tissue blocks and screened for the presence of mutations in codons 12 and 13 of *KRAS*, according to each site's clinical practice at the time of observation.

Data collection

Data were collected with reference to information present in the medical records. All data were reported in a detailed structured case report form (CRF) in an electronic format (e-CRF). Each study investigator was responsible for collecting and reporting all sociodemographic, adverse reactions, and treatments data on the e-CRF. Collected data were verified during data entry by automatic controls (edit check). Any correction to original data entry was documented by means of an audit trail. Entered data were checked by data management staff, using automatic validation routines and database listings. Raised discrepancies were referred to the site's personnel for resolution. The database was locked on September 30, 2014.

All serious and nonserious adverse reactions related to bevacizumab, reported during the observation period, were included in the e-CRF.

Clinical outcome assessment

PFS was defined as the time elapsed from the start of bevacizumab treatment to the first PD or death. Patients who experienced PD (including death) were considered as failed observations, while other patients were considered as censored and were included in the analysis as well.

Time to ADR onset was calculated as the difference between the event occurrence date and the start date of bevacizumab treatment. In the case where a patient experienced more than one event, only the first ADR was considered. ADRs were coded according to the MedDRA Dictionary v. 16.1.

Statistical analysis

Sample size was calculated on the basis of published data[4,5]; thus, 33.3% of patients were expected to interrupt bevacizumab because of PD or an adverse reaction related to the drug. Sample size was calculated to have a relative error of the estimate equal to 15%. A sample size of 420 enrolled subjects, corresponding to 336 evaluable patients assuming 20% as not evaluable, allowed to observe a 95% confidence interval (CI) of the expected proportion equal to $33.3 \pm 5.0\%$. All patients evaluable for inclusion/exclusion criteria were considered for analysis.

Results

Patients' characteristics

Out of 437 patients with mCRC enrolled, 88.3% (386/437) met inclusion criteria, while 11.7% (51/437) were excluded for protocol deviation or absence of privacy consent. At diagnosis, mean age was 63.6 ± 10.8 years. At the start of bevacizumab administration, 58.8% of all eligible patients were men and the mean age was 63.7 ± 10.8 years (Table 1). The Eastern Cooperative Oncology Group Performance Status (ECOG-PS) was <2 in 88.3% of patients. A total of 57% had metastases in one site (56.8% with synchronous

Table 1. Patient characteristics at the time of bevacizumab start.

Variable	Eligible patients ($n = 386$)
Age, y	63.7±10.8
Male	227 (58.8)
Concomitant diseases	
None	159 (41.2)
Hypertension	140 (36.3)
Diabetes	34 (8.8)
Heart disease	25 (6.5)
Dyslipidemia	20 (5.2)
COPD	13 (3.4)
Asthma	4 (1.0)
Hepatitis C	4 (1.0)
Hepatitis B	3 (0.8)
Renal failure	2 (0.5)
Cirrhosis of liver	1 (0.3)
Other	114 (29.5)
ECOG-PS	
0	254 (65.8)
1	87 (22.5)
2	8 (2.1)
3	1 (0.3)
NA	36 (9.3)
Primary tumor site	
Colon	270 (69.9)
Rectum	100 (25.9)
Colon-rectum	14 (3.6)
Other[a]	1 (0.3)
NA	1 (0.3)
Organs with metastases	
1	220 (57.0)
>1	166 (43.0)
KRAS mut	196 (50.8)
Concomitant chemotherapy regimen	
FOLFIRI	159 (41.2)
FOLFOX (4,6,7)	116 (30.1)
XELOX/CAPOX	63 (16.3)
XELIRI/CAPIRI	18 (4.7)
Capecitabine (monotherapy)	12 (3.1)
FOLFOXIRI/Flr-B/FOx	8 (2.1)
DeGramont	6 (1.6)
5-FU/FA (LV) bolus	4 (1.0)

Data are reported as mean ± standard deviation or *n* (%).
[a]Primary tumor localized in the intestine.
SD: standard deviation; COPD: chronic obstructive pulmonary disease; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; NA: not available; mut: mutated; FOLFIRI: folinic acid, 5-fluorouracil (5-FU), irinotecan; FOLFOX: folinic acid, 5-FU/oxaliplatin; XELOX/CAPOX: capecitabine, oxaliplatin; XELIRI/CAPIRI: capecitabine, irinotecan; FA: folinic acid; LV: leucoverin; FOLFOXIRI: folinic acid, 5-FU: oxaliplatin, irinotecan; Flr-B/FOx: triplet chemotherapy plus bevacizumab.

metastases, 36.4% with metachronous metastases, and 6.8% with type not available, data not shown), whereas the remaining 43% had more than one organ involved (56.6% with synchronous metastases, 38.6% with metachronous metastases, and 4.8% with type not available, data not shown). Metastases were most frequently found in liver (67.1%), lung (30.8%), abdominal lymph nodes (19.9%), and peritoneum (15.5%). *KRAS* exon 2 was mutated in 196 out of 386 patients (50.8%).

First-line treatment

Regimen characteristics. The median time from mCRC diagnosis to the beginning of bevacizumab was 1.5 months (range 0–21.6). A similar percentage of patients received the combination of oxaliplatin-based and irinotecan-based doublets (46.4% and 45.9%, respectively), but with different proportions of intravenous and oral fluoropyrimidine (FP): FOLFOX/XELOX 30.1% (116/386) and 16.3% (63/386), respectively, and FOLFIRI/XELIRI 41.2% (159/386) and 4.7% (18/386), respectively (Table 1). Only 5.7% of patients (22/386) received FP monotherapy in association with bevacizumab, and 2% (8/386) were treated with a triplet plus bevacizumab. The median number of cycles administered was 11 (range 1–37) for chemotherapy (independently of bevacizumab) and 12 (range 1–35) for bevacizumab; the median duration of mAb administration was 7.2 months (range 0–16.5).

Treatment interruption and response. At the end of the observational period, only 31 patients (8%) were still under treatment, while the majority of evaluable patients had interrupted chemotherapy (92%; 355/386). Bevacizumab was interrupted in 78.2% (302/386) of all cases (Table 2): due to PD occurrence in 44.3% (171/386) (including 74 deceased patients), to ADRs related to bevacizumab (requiring discontinuation of treatment according to the SPC) in 5.7% (22/386), and to other motivation in 28.2% (109/386). Considering only the subgroup of patients who discontinued ($n = 302$), the percentages were 56.6, 7.3, and 36.1, respectively. A detailed list of ADRs is provided in Table 3. Reasons other than PD or ADRs are heterogeneous (Table 4) and include toxicities related to bevacizumab that did not require interruption according to the SPC (grade 2 headache and grade 2 hemorrhage in 1 case each) and to chemotherapy (3 cases).

Overall, upon first-line therapy, PD occurred in 64.2% (248/386) of cases, with a median PFS of 10.3 months (95% CI 9.2–11.2 months); the best response was CR in 8.3% (32/186) of subjects, partial response in 32.4% (125/386), stable disease in 33.2% (128/386), and PD in 18.4% (71/386).

Comparisons between the subgroups of patients who interrupted bevacizumab. We next compared the main characteristics of patients subgrouped based on reasons for

Table 2. Proportion of patients with metastatic colorectal cancer who discontinued first-line bevacizumab and reasons for interruption.

Reason for bevacizumab interruption	Eligible patients ($n = 386$), *n* (%)	Patients interrupting therapy ($n = 302$), *n* (%)
Overall interruptions	302 (78.2)	302 (100.0)
PD[a] or ADRs[b] (primary endpoint)	193 (50.0)	193 (63.9)
PD	171 (44.3)	171 (56.6)
ADRs	22 (5.7)	22 (7.3)
Other reasons (secondary endpoint)	109 (28.2)	109 (36.1)

[a]PD as a motivation includes also deceased patients ($n = 74$).
[b]The primary endpoint of the study considers only the ADRs requiring discontinuation of treatment according to the summary of product characteristics (see Table 3). Additional ADRs ($n = 2$) are included among other reasons (secondary endpoint; see Table 4).
PD: progression of disease; ADRs: adverse events related to bevacizumab.

Table 3. Frequency and type of bevacizumab-related adverse events that led to treatment discontinuation (primary endpoint).

Adverse events related to bevacizumab	Patients who discontinued due to ADRs ($n = 22$), *n* (%)
Pulmonary embolism (grade 4)	3 (12.5)
Arterial thromboembolism	2 (8.33)
Pulmonary embolism and lung failure	2 (8.33
Hypertensive crisis/hypertensive encephalopathy	1 (4.16)
Hypertension	1 (4.16)
Healing complications	1 (4.16)
Grade 3–4 bleeding	1 (4.16)
Tracheo-esophageal fistula or any grade 4 fistula	1 (4.16)
Hypertension not adequately controlled with antihypertensive therapy	1 (4.16)
Gastrointestinal perforation	1 (4.16)
Rectal bleeding	1 (4.16)
Deep venous thrombosis (subclavian, internal jugular, axillary, humeral vein)	1 (4.16)
Severe lower limb venous thrombosis	1 (4.16)
Left leg thrombosis	1 (4.16)
Esophageal ulcer	1 (4.16)
Pulmonary embolism and lung failure (grade 3)	1 (4.16)
Deep venous thrombosis	1 (4.16)
Venous embolism	1 (4.16)

bevacizumab interruption (i.e. first group: for PD or adverse events [AEs] related to the drug requiring discontinuation of treatment according to SPC; second group: for other reasons) (Table 5). Demographic characteristics were similar across the 2 groups, whereas significant differences were observed with regard to PS (PS=0 in 68.9% and 74.2% of patients interrupting bevacizumab for PD/AEs and other reasons, respectively, PS=1 in 29.9% and 20.4% and PS=2 in 1.1% and 5.4%, respectively; $p = .036$), and the number of organs involved by metastases (1 in 47.7% vs 70.6% in the first and second group, respectively; >1 in 52.3% vs 29.4%, respectively, $p = .0001$).

The median duration of bevacizumab treatment was 6.7 months (range 0.03–15.4) in patients interrupting for PD, 2.5 months (range 0.03–10.1) for ADRs, and 4.6 months (range 0.03–14.7) for other reasons.

A total of 185 (95.9%) and 54 (49.5%) patients progressed, respectively, in the first and second group of subjects, with a median PFS of 6.9 months (95% CI 6–7.8) and 13.9 months (95% CI 10.7–NA, $p < .0001$) (Figure 1). In particular, patients interrupting for PD had a PFS of 6.7 months (95% CI 5.7–7.2), whereas those interrupting for ADRs experienced PD in 63.6% (14/22) of cases and had a median PFS of 9.5 months (95% CI 7.5–NA).

Second-line treatment

A total of 57.9% (175/302) of patients received a second-line treatment: chemotherapy and/or targeted therapy in 97.7% (171/175) of cases. The most common regimen administered was FOLFIRI in 18.9% (33/175) of cases, followed by FOLFOX in 16.0% (28/175). As for chemotherapy plus targeted therapy (given in 28.6% of cases, 50/175), FOLFIRI plus cetuximab was the most frequently used regimen (28.0%, 14/50). Targeted therapy alone was administered in 8.6% (15/175) of patients, whereas 5.7%

Table 4. Reasons (other than progression of disease and adverse drug reactions) leading to interruption of first-line bevacizumab (secondary endpoint).

Reasons	Eligible patients ($n = 386$), *n* (%)
Main reasons	
R0/R1 surgical resection (complete)	15 (3.9)
PS	11 (2.8)
Achievement of CR	8 (2.1)
Complications due to primary tumor site	8 (2.1)
Achievement of clinical response	7 (1.8)
chemotherapy interruption	6 (1.6)
Patient refusal	4 (1.0)
Patient compliance	3 (0.8)
chemotherapy toxicity	3 (0.8)
RT (in case of rectal cancer)	2 (0.5)
Bevacizumab-related toxicities that did not require interruption by SPC[a]	2 (0.5)
Other	40 (10.4)
Secondary reasons	
No other reasons	83 (21.5)
Disease progression	7 (1.8)
R0/R1 surgical resection	5 (1.3)
PS	2 (0.5)
chemotherapy tolerability–toxicity	2 (0.5)
Patient compliance	1 (0.3)
Other	7 (1.8)
NA/NR	5 (1.3)

Reasons were classified as main or secondary depending on the physician's judgment.
[a]Grade 2 headache ($n = 1$) and grade 2 hemorrhage ($n = 1$).
R0: complete resection with no microscopic residual tumor; R1: complete resection with no grossly visible tumor as defined by the surgeon, but microscopic cancer may be left behind; PS: performance status; CR: complete response; RT: radiotherapy; SPC: summary of product characteristics; NA: not available; NR: not reported.

(10/175) received palliative radiotherapy in the second-line setting.

Safety of bevacizumab administration

Out of 386 evaluable patients, 13.7% ($n = 53$) experienced at least one adverse reaction related to bevacizumab during the 15-month follow-up, for a total number of 66 ADRs, the majority (78.8%, 52/66) of which was resolved without consequences before study end. Furthermore, 22.6% (12/53) of these subjects presented at least one severe ADR to the mAb. As a consequence, 10 patients were hospitalized or required prolonged hospitalization (all resolved), whereas one patient presented a life-threatening drug-related event.

KRAS *mutational status*

To assess whether *KRAS* status affected the investigated endpoints including safety of bevacizumab, patients were subgrouped according to the presence of mutations. Overall, a *KRAS* exon 2 mutation was found in 50.8% (196/386) of cases: of these, 74.0% (145/196) harbored a mutation in codon 12 and 15.3% (30/196) in codon 13. No difference was observed between the 2 groups in terms of demographic and clinical characteristics and chemotherapy regimen administered (data not shown). Also, the median duration of treatment was similar between the 2 groups, being 7.3 months (range 0.03–16.4) and 7.0 months (range 0.03–16.5) in wt vs mut, respectively. Finally, both PD frequency and PFS were comparable between *KRAS* wt and mut patients undergoing bevacizumab in combination with chemotherapy (PD frequency: 62.6% vs 65.8%, respectively; PFS: 10.5 months [95% CI 8.7–12.1] vs 10.1 months [95% CI 9.0–11.5], respectively).

Patients classified according to *KRAS* status were further subgrouped based on the reasons for bevacizumab interruption and results reflected those obtained in the whole population. In fact, patients interrupting for PD or ADRs (46.6% with *KRAS* wt) vs other reasons (52.3% with *KRAS* wt) more frequently had >1 organ affected ($p = .0123$ in KRAS wt and $p = .0038$ in *KRAS* mut) and a shorter PFS (data not shown). However, only in the subgroup of patients with *KRAS* mut, subjects interrupting treatment for PD or ADRs had significantly more synchronous and less metachronous metastases than patients interrupting for other reasons (data not shown).

Discussion

BEAWARE is the first Italian observational study designed to assess, in the real-world setting, the proportion of patients with mCRC who interrupted first-line bevacizumab over a 15-month period, and to explore in detail the reasons (besides PD and ADRs) and consequences of early discontinuation. Indeed, despite the fact that NCCN guidelines suggest continuing treatment until PD or toxicity, in daily practice bevacizumab is often prematurely interrupted. Our findings show that 78.2% of eligible patients interrupted mAb administration in the 15 months of observation, due to PD in 56.6% of cases (44.3%), bevacizumab-related adverse reaction in 7.3% (requiring discontinuation of treatment according to SPC: 5.7%), or other causes in the remaining 36.1% (28.2%). Previous studies have reported an overall frequency of treatment discontinuation of ~60%[17] and 71%.[4] As for causes of interruption, the ARIES observational study indicated PD in 8.3% of cases, toxicity (AEs or serious AE [SAEs]) in ~30%, and other reasons, including chemotherapy holidays, maximum benefit achieved, planned surgery, and physician's decision, in the remaining.[17] Instead, in the

Table 5. Characteristics of patients subgrouped according to the main reason for bevacizumab discontinuation.

Variables	Patients discontinuing for PD or ADRs ($n = 193$)	Patients interrupting for other reasons ($n = 109$)	p Value
Age at diagnosis, y	62.8±11.3	63.7±10.2	.50
Age at the start of bevacizumab, y	63.0±11.3	63.9±10.3	.5
Time from diagnosis to start of bevacizumab, mo	1.9±2.0	2.0±2.5	.85
Duration of first-line bevacizumab, mo	6.3 (0.03–15.4)	4.6 (0.03–14.7)	
Male	116 (60.1)	69 (63.3)	.58
Concomitant diseases			
None	75 (38.9)	48 (44.0)	
Hypertension	69 (35.8)	37 (33.9)	
Diabetes	19 (9.8)	7 (6.4)	
Heart disease	12 (6.2)	8 (7.3)	
Dyslipidemia	10 (5.2)	7 (6.4)	
COPD	5 (2.6)	6 (5.5)	
Asthma	2 (1.0)	1 (0.9)	
Hepatitis B	0 (0.0)	2 (1.8)	
Hepatitis C	2 (1.0)	0 (0.0)	
Renal failure	2 (1.0)	0 (0.0)	
Cirrhosis of liver	1 (0.5)	0 (0.0)	
Other	61 (31.6)	31 (28.4)	
ECOG-PS			**.036**
0	122 (68.9)	69 (74.2)	
1	53 (29.9)	19 (20.4)	
2	2 (1.1)	5 (5.4)	
Organs with metastases, *n*			**.0001**
1	92 (47.7)	77 (70.6)	
>1	101 (52.3)	32 (29.4)	
Type of metastases			.23
Synchronous	118 (64.1)	58 (56.9)	
Metasynchronous	66 (35.9)	44 (43.1)	
PFS, months (median [95%CI])	6.9 (6.0–7.8)	13.9 (10.7–NA)	**<.0001**
KRAS mut	103 (53.4)	52 (47.7)	

Statistically significant (<.05) p values are reported in bold. For ECOG-PS and type of metastases, percentages are computed on evaluable patients with available data. For continuous variables, the t-test was performed, while for categorical ones, the chi-squared test is provided (Fisher exact test for ECOG-PS). Log-rank test is shown for PFS.

PD: progression of disease; ADR: adverse drug reaction; COPD: chronic obstructive pulmonary disease; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; PFS: progression-free survival; CI: confidence interval; mut: mutated; NA: not available.

phase III randomized trial conducted by Saltz and coworkers, therapy was discontinued for PD in 29% of cases and for AEs in approximately 5% of subjects.[4] These differences may be partly explained by the study duration, which was 15 months in the present report, 15.6 months in the randomized trial,[4] and 21 months in the ARIES study.[17] It is unlikely that the chemotherapy regimens associated with bevacizumab account for the differences observed, as data collected specifically regarded bevacizumab-related AEs. In addition, the sample size of the ARIES study ($n = 1550$) is larger than ours but similar to that of the trial by Saltz et al. ($n = 1401$).[4]

The median duration of bevacizumab treatment in our study was 7.2 months, whereas previous observational studies reported a duration of 4.7,[17] 5.4,[16] 5.5,[19] and 7 months.[20] This aspect is of particular interest as some studies suggested an association between the duration of bevacizumab administration and its efficacy, reporting an OS benefit for those patients who continued therapy beyond first PD.[14,15,21] However, the optimal strategy after first-line chemotherapy plus bevacizumab remains controversial, both in the maintenance[11–13] and the "beyond progression" setting.[14,15] While this topic was beyond the focus of the BEAWARE study, in the future it would be important to investigate what happens in Italian daily practice to patients who do not interrupt bevacizumab at PD, both in terms of survival and safety. Finally, median PFS was 10.3 months, in line with previous observational studies reporting a median time to progression between 9.9 and 11.5 months,[16,17,19,20,22] as well as with randomized

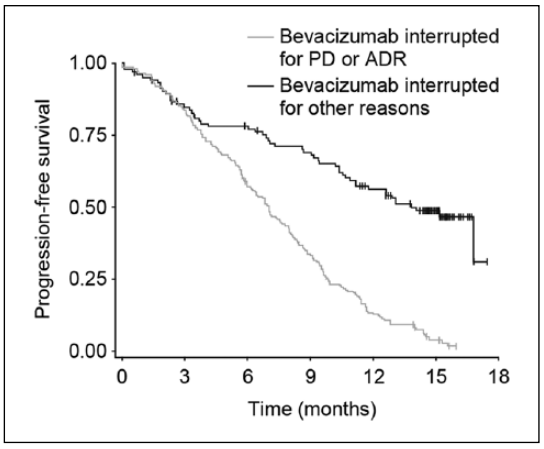

Figure 1. Progression-free survival of metastatic colorectal cancer patients subgrouped according to the reasons for bevacizumab discontinuation (progression of disease [PD], adverse drug reactions [ADR], or for other reasons).

trials showing a median PFS ranging from 8.5 to 12.1 months.[3,4,23–26] In addition, the short period of treatment of patients interrupting for ADR in our study confirms that bevacizumab toxicity, if present, occurs early during treatment.

When the characteristics of patients subgrouped according to reasons for bevacizumab discontinuation were compared, a single metastasis was found to be less common among subjects interrupting for PD or ADRs, compared to those interrupting for other reasons (47.7% and 70.6%, $p = .0001$). Accordingly, the median PFS was 6.9 months in the first group (6.7 months in case of PD and 9.5 in case of ADRs), vs 13.9 in the second one. Yet this is not surprising, as the first group included patients with progressive disease, while the second one comprised subjects who achieved the maximum clinical response or surgical resection.

Approximately 50% of patients enrolled in the BEAWARE study carried a *KRAS* exon 2 mutation. No difference was observed between wt and mut subjects in terms of patient characteristics, chemotherapy regimen, treatment duration, PD frequency, or PFS. It is worth noting that we found a median PFS of 10.5 and 10.1 months in wt and mut, respectively, which is in accordance with the median interval of 10 months reported in both *KRAS* groups in a recent retrospective study assessing the prognostic impact of these mutations in patients with mCRC (64% wt and 36% mut) receiving first-line bevacizumab.[27]

When patients classified by *KRAS* status were further subgrouped based on the reason for treatment discontinuation, few differences were found, which mostly reflected those of the whole cohort.

The BEAWARE study has several limitations, some intrinsic to observational studies, such as the lack of randomization. However, participating sites ($n = 74$) were well-distributed among geographic areas and types of institution. Also, patients were consecutively enrolled at each center, taking into account their mutational status, in a proportion of 1:1.

The period of observation of the present trial was 2012–2013; at that time, results of maintenance trials[11–13] were still not available, and decision on how long to prosecute treatment with bevacizumab in daily practice was made case by case by the physician. As a general message, maintenance trials showed a PFS benefit in continuing bevacizumab, preferably with a fluoropyrimidine, until progression, but a limited impact on survival. Up to now, the impact of those findings in Italian clinical practice is not clear, or if, according to that, the results of the BEAWARE Study are still reproducible after 5 years.

Any consideration on PFS should be taken with caution, due to the short period of observation. In fact, 21.8% of patients were still receiving bevacizumab and 35.8% were not progressed at 15 months. All those patients were thus censored for PFS at the last observation, resulting in a potentially immature PFS estimate.

In the BEAWARE study, the most frequent reason for treatment discontinuation was PD, rather than ADRs or other causes. Indeed, bevacizumab-related AEs and SAEs were reported in 13.7% and 3.1% of all eligible subjects, respectively, but only about half of them interrupted therapy because of these ($n = 24$), confirming an acceptable safety profile of this agent. In addition, a total of 23 (7.6%) of the patients interrupted bevacizumab due to tumor response (radical surgery or complete response). To avoid an improper interruption in the remaining 26% (not PD or ADRs, not complete response), a better knowledge on relative contraindications of antiangiogenic therapy that require only temporary withdrawal of the treatment and on the management of concomitant illness should be implemented.

Given the role of continuous VEGF inhibition in first-line treatment,[2] the attitude to continue bevacizumab until progression in patients with a good balance between benefit and risk might be implemented in Italian clinical practice.

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