

Bevacizumab Plus Chemotherapy as First-Line Treatment for Patients with Metastatic Colorectal Cancer: Results from a Spanish Observational Study

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Abstract: *Background:* This observational study evaluated the efficacy and safety of treatment with bevacizumab plus chemotherapy until disease progression (PD) in Spanish patients with metastatic colorectal cancer (mCRC).

Methods: This multicentre, retrospective, observational analysis included patients receiving bevacizumab plus fluoropyrimidine-based chemotherapy as first-line treatment for mCRC who then developed PD. All patients received treatment in hospital oncology departments and none received bevacizumab as part of a clinical trial. Patients discontinuing treatment with bevacizumab for reasons other than PD were excluded. The primary endpoint was PFS; secondary endpoints were overall response rate (ORR) and safety.

Results: Overall, 165 patients were evaluable for analysis: median age 63.0 years; male/female 62%/38%; ECOG performance status 0/1/2 55%/43%/2%. Median duration of bevacizumab treatment was 8.7 months. ORR was 48.5% (6 complete and 74 partial responses) and disease control rate was 74%. Median progression-free survival (PFS) was 8.4 months (95% CI 7.2–9.6). Patients receiving oxaliplatin- or irinotecan-based regimens had median PFS of 9.2 and 7.7 months, respectively; those receiving treatment not containing either oxaliplatin or irinotecan had a median PFS of 6.1 months. KRAS status did not have a statistically significant effect on PFS (9.5 vs. 7.8 months for KRAS wild-type vs. mutant tumours, respectively; $p=0.647$) or ORR (44.8% vs. 52.6%, respectively; $p=0.391$). The most common grade 3/4 adverse events were: diarrhoea (7%), paraesthesia (7%), neutropenia (3%), cutaneous toxicity (2%), and thrombocytopenia (2%).

Conclusions: Treatment with bevacizumab plus standard chemotherapy is an effective and well-tolerated option for patients with mCRC who continue treatment until PD.

Keywords: Bevacizumab, mCRC, observational, clinical practice, disease progression.

INTRODUCTION

The assimilation of oxaliplatin, irinotecan and targeted agents such as bevacizumab and cetuximab into treatment regimens for metastatic colorectal

cancer (mCRC) has resulted in improved survival for many patients. This extended survival has called into question the optimal duration of treatment with some of these agents. Bevacizumab is an anti-vascular endothelial growth factor (VEGF) antibody that has several postulated modes of action, including regression of existing tumour vasculature, inhibition of tumour vessel growth, and reduction of tumour vessel

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permeability [1, 2]. Preclinical models suggest that continued administration of bevacizumab may be necessary to maximize its effect on tumour growth [3-5].

Bevacizumab has been shown to improve outcomes when combined with chemotherapy for the treatment of patients with mCRC [6, 7]. In the NO16966 (XELOX1) study, adding bevacizumab to chemotherapy prolonged progression-free survival (PFS), but not overall survival (OS), compared with placebo [8]. Notably, only 29% of bevacizumab and 47% of placebo recipients were treated until disease progression. A more pronounced clinical benefit was observed for bevacizumab in the predefined on-treatment PFS analysis (hazard ratio [HR] 0.63) than in the primary analysis (HR 0.83). This led the authors to state that continuation of bevacizumab, and probably the fluoropyrimidine component as well, until disease progression was critical with regards to the magnitude of effect of bevacizumab.

The efficacy and tolerability of bevacizumab have also been assessed outside of the clinical trial setting. Several observational studies in patients with mCRC have demonstrated that the addition of bevacizumab to a variety of chemotherapy regimens is well tolerated and effective [9-14]. In the US BRiTE observational study, patients who continued bevacizumab treatment after disease progression had a median OS of 31.8 months compared with 12.6 months for those who received no bevacizumab treatment after disease progression [15].

In routine clinical practice, treatment is often discontinued before disease progression because the emergence of toxicity caused by one of the components leads to the cessation of all agents in the treatment regimen. This can compromise the efficacy of treatments such as bevacizumab, which are believed to be more effective when administered continuously.

The present observational study evaluated the efficacy and safety of optimal treatment with bevacizumab plus chemotherapy in Spanish patients with mCRC and included only those patients who continued treatment until disease progression.

PATIENTS AND METHODS

Design and Patient Selection

This was a multicentre, retrospective, observational national study. Patients were included if they were

aged ≥ 18 years with histologically confirmed metastatic adenocarcinoma of the colon or rectum and treated in hospital oncology departments in Spain. Patients were treated with bevacizumab plus fluoropyrimidine-based chemotherapy according to standard clinical practice at their treatment centre. Patients were only included if they received bevacizumab treatment until disease progression, which was defined as radiological evidence of tumour progression.

The study was approved by local ethics committees, conducted in accordance with the Declaration of Helsinki and adhered to Good Clinical Practice Guidelines. All patients provided written consent or gave oral consent before witnesses independent of the research team.

Patients were excluded if they had received first-line bevacizumab as part of a clinical trial or if they discontinued treatment for any reason other than disease progression.

Treatment

All patients received bevacizumab as part of their first-line treatment regimen. The choice of chemotherapy was at the discretion of the physician.

Objectives and Assessments

Primary Study Objective

To evaluate PFS in mCRC patients receiving first-line treatment with a combination of bevacizumab plus fluoropyrimidine-based chemotherapy when bevacizumab was maintained until disease progression.

Secondary Study Objectives

To determine the response rate, evaluate the safety profile of bevacizumab and to describe the chemotherapy combinations used in conjunction with bevacizumab.

Data on the time to progressive disease and the response rate were collected retrospectively. Adverse events of interest with bevacizumab therapy were also collected retrospectively.

Statistical Analysis

An estimated 311 patients were initially to be recruited, based on a precision of ± 0.5 months and variance of 4.5 months, with 95% confidence (alpha

error 0.0). However, following slow enrolment and after extending the recruitment period foreseen in the protocol, the study was closed prior to obtaining the complete sample size; the sample obtained at the end of the study was 201 patients.

The primary endpoint was PFS, which was defined as the time from the start of treatment to progression or death. Secondary endpoints included response rate and safety. Survival curves were estimated using the Kaplan–Meier method; median, mean and 95% confidence intervals (CIs) were calculated. As the secondary objective of describing the chemotherapy combinations used in conjunction with bevacizumab was descriptive and the study was not powered to compare the different treatment regimens, these PFS curves will be presented as separate graphs.

RESULTS

Patients and Treatment

Between January 2009 and December 2010, 201 patients were recruited at 43 centres in Spain; this was fewer than the planned sample size of 311 patients. Of

these, 36 patients were excluded from the study, 32 of whom did not fulfil the entry criteria and four of whom had incomplete data. After extending the recruitment period foreseen in the protocol, it was decided to close the study without achieving the planned sample size.

Patients' baseline characteristics are shown in Table 1; patients' mean age was 63 years and 62% of patients were male. KRAS mutation status was evaluated in 136 patients (82.5% of those analysed): 58 patients (35%) had KRAS wild-type tumours and 78 patients (47%) had mutant-type tumours.

The median number of bevacizumab cycles administered was 13 (range 3–46). The median duration of bevacizumab treatment was 8.7 months (range 0.5–23.9 months) and the mean ($\pm$ standard deviation) bevacizumab dose was 6.7 mg/kg ($\pm$ 1.7 mg/kg). The most common chemotherapy regimen administered with bevacizumab was capecitabine/oxaliplatin (n=55; 33%), followed by 5-fluorouracil/leucovorin (5-FU/LV) plus irinotecan (n=39; 24%), 5-FU/LV plus oxaliplatin (n=25; 15%), capecitabine (n=16; 10%) and other regimens (n=30; 18%).

Table 1: Patient Characteristics at Baseline (n=165)

Characteristic	Variable	
	n	%
Median age, years (range)	62.8 (36.6–86.5)	
Sex:		
Male	103	62
Female	62	38
ECOG performance status:		
0	90	54.5
1	71	43
2	4	2.5
Primary tumour type:		
Colon	125	76
Rectum	40	24
Surgical resection of primary tumour	122	74
Neo/adjuvant therapy:		
Chemotherapy	50	30
Radiotherapy	12	7
No. of metastatic sites:		
1	90	54.5
2	61	37
>2	14	8.5
Metastatic site:		
Liver	130	79
Lung	55	33
Peritoneum	38	23
Other location	29	18

ECOG, Eastern Cooperative Oncology Group.

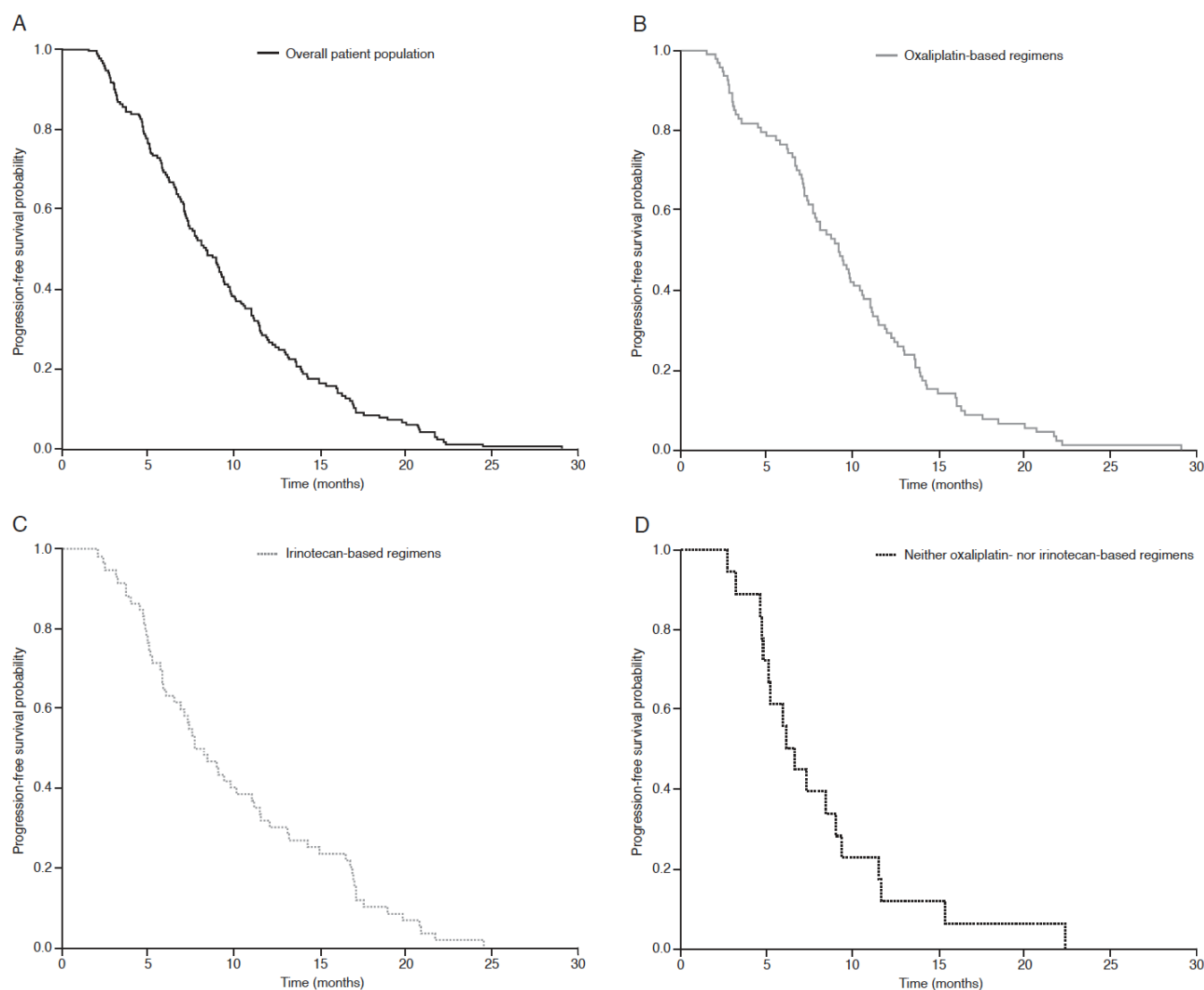


Figure 1: Progression-free survival in in: (A) the overall population; (B) oxaliplatin-based regimens; (C) irinotecan-based regimens; and (D) neither oxaliplatin- nor irinotecan-based regimens in patients with mCRC.

At baseline, 40 patients (24%) had hypertension that required treatment and two patients (1%) were receiving anticoagulant therapy. During the study, 43 patients (26%) received antihypertensive agents and seven patients (4%) had anticoagulant therapy.

Efficacy

The median PFS was 8.4 months (95% CI 7.2–9.6 months) in the overall patient population (Figure 1A). Patients who received oxaliplatin-based regimens had a median PFS of 9.2 months (95% CI 7.7–10.7 months) (Figure 1B), while those who received an irinotecan-based regimen had a median PFS of 7.7 months (95% CI 5.6–9.8 months) (Figure 1C). In patients who received treatment that did not contain either oxaliplatin or irinotecan, the median PFS was 6.1 months (95% CI 4.6–7.6 months) (Figure 1D). Median

PFS values of the different treatment regimens were not compared statistically as the study was not powered to do this.

Patients with KRAS wild-type tumours had a median PFS of 9.5 months (95% CI 7.2–11.8 months), while those with KRAS mutant-type tumours had a median PFS of 7.8 months (95% CI 6.6–9.0 months) (Figure 2). The difference between these groups in median PFS was not statistically significant (log-rank $p=0.647$).

The overall response rate in the total population was 48.5% (95% CI 40.7–56.4%), with six patients (3.5%) having a complete response and 74 patients (45%) having a partial response (Table 2). Stable disease was observed in a further 42 patients (25.5%), resulting in a disease control rate of 74% (95% CI 66.4–80.3%). There was no statistically significant

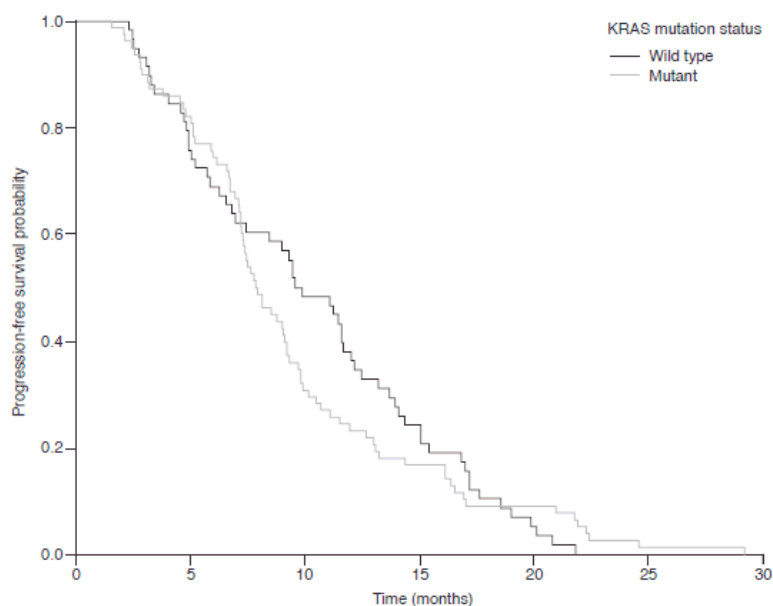


Figure 2: Progression-free survival according to tumour KRAS status.

Table 2: Response Rates in Patients Receiving Bevacizumab Plus Chemotherapy According to Chemotherapy Regimen (n=165)

Outcome, n (%)	Overall (n=165)	Capecitabine + oxaliplatin (n=55)	Capecitabine + irinotecan (n=13)	5-FU/LV + oxaliplatin (n=25)	5-FU/LV + irinotecan (n=39)	Capecitabine (n=16)	Other regimens (n=17)
Complete response	6 (4)	2 (4)	0	0	3 (8)	0	0
Partial response	74 (45)	34 (62)	6 (46)	10 (40)	15 (38.5)	1 (6)	4 (23.5)
Stable disease	42 (25.5)	6 (11)	4 (31)	7 (28)	9 (23)	9 (56)	11 (65)
Progressive disease	43 (26)	13 (24)	3 (23)	8 (32)	12 (31)	6 (37.5)	2 (12)

difference in response rates according to KRAS status (45% vs. 52.5% for KRAS wild-type vs. mutant-type tumours, respectively; $p=0.391$). Overall response rate varied according to chemotherapy regimen administered, ranging from 65.5% with capecitabine/oxaliplatin to 6% for single-agent capecitabine (Table 2), while disease control rate ranged from 77% with capecitabine/irinotecan to 62.5% with single-agent capecitabine.

Nineteen patients (12%) underwent surgery during bevacizumab treatment (liver $n=10$, peritoneum $n=3$, colon $n=2$ and other sites $n=7$).

Safety

Capecitabine doses were reduced in 25 of 97 patients (26%) receiving capecitabine. The most common reasons for capecitabine dose reductions were skin toxicity ($n=11$), diarrhoea ($n=8$) and haematological toxicity ($n=3$). Capecitabine was

discontinued in eight patients because of skin toxicity ($n=4$), haematological toxicity ($n=2$), investigator's decision ($n=2$) and intestinal toxicity ($n=1$).

The dose of 5-FU was reduced in 19 of 78 patients (24%), primarily because of stomatitis ($n=4$), diarrhoea ($n=4$) or haematological toxicity ($n=5$). 5-FU was discontinued in eight patients with diarrhoea ($n=3$) and haematological toxicity ($n=3$) being the most common reasons for discontinuation.

Oxaliplatin doses were reduced in 27 of 93 patients (29%); the most common causes of which were neurotoxicity ($n=17$), haematological toxicity ($n=6$), and diarrhoea ($n=3$). Oxaliplatin was discontinued in 26 patients (28%), primarily because of neurotoxicity ($n=16$).

Irinotecan doses were reduced in 20 of 60 patients (33%) with the most common reasons being haematological toxicity ($n=9$), and diarrhoea ($n=8$).

Irinotecan was discontinued in 7 patients (12%), primarily because of diarrhoea (n=4).

Adverse events were reported in 99 patients (60%). The most common grade 3/4 events are summarised in Table 3. Only six grade 4 events were recorded, comprising three cases of neutropenia and one case each of intestinal obstruction, osteomyelitis and bowel perforation. Adverse events thought to be related to bevacizumab treatment occurred in 32 patients (19%). The most common of these were low-grade epistaxis (grade 1 in 12 patients and grade 2 in 1 patient) and hypertension (grade 1 in 4 patients and grade 2 in 3 patients). One patient had bowel perforation that was considered treatment-related.

Table 3: Most Common Grade 3/4 Adverse Events (n=165)

Adverse event	No. of patients with event (%)	
	Grade 3	Grade 4
Paraesthesia	12 (7)	0
Diarrhoea	11 (7)	0
Thrombocytopenia	4 (2)	0
Cutaneous toxicity	3 (2)	0
Neutropenia	2 (1)	3 (2)
Neurotoxicity	2 (1)	0
Vomiting	2 (1)	0
Hypersensitivity	2 (1)	0
Epistaxis	1 (<1)	0
Arterial hypertension	1 (<1)	0
Digestive haemorrhage	1 (<1)	0
Deep vein thrombosis	1 (<1)	0
Bowel perforation	0	1 (<1)

DISCUSSION

Given the availability of a variety of chemotherapy and biological agents, treatment decisions in mCRC are no longer straightforward for the physician. Extended survival means that patients are potentially going to receive treatment for longer periods of time than previously, which calls into question not only the optimum combination of agents but also the duration of treatment. The AVAMAX study investigated the effect of continued bevacizumab plus chemotherapy treatment until disease progression on PFS and ORR.

In this study, a median PFS of 8.4 months for the overall population was similar to median PFS of 9.9

and 11.3 months reported in the BEAT and BRITe observational studies, respectively [11, 14]. Analysis of PFS by treatment regimen found that PFS was longest in patients who received oxaliplatin-based regimens, followed by irinotecan; PFS in patients who did not receive either of these agents in combination with bevacizumab was considerably shorter.

A similar pattern was observed for ORR; patients treated with combined chemotherapy regimens had numerically higher response rates than those who received single-agent chemotherapy. The highest rate (65.5%) observed was in patients who received capecitabine/oxaliplatin plus bevacizumab. Notably, only one partial response was observed in 19 patients (5%) who received single-agent capecitabine plus bevacizumab.

This study has demonstrated that the combination of bevacizumab with a range of commonly used chemotherapy backbones is effective and well tolerated. However, the efficacy was variable across the different regimens, with bevacizumab combined with capecitabine plus oxaliplatin (XELOX), 5-FU/LV plus oxaliplatin (FOLFOX) and 5-FU/LV plus irinotecan (FOLFIRI)-type regimens providing the longest PFS and ORR.

In this group of patients with mCRC, KRAS status did not appear to be predictive for response to bevacizumab. Response rates were numerically but not statistically significantly higher in patients with KRAS mutant-type tumours compared with those in patients with KRAS wild-type tumours, and PFS was numerically but not statistically significantly higher in patients with KRAS wild-type tumours. These findings are in line with those of previous studies, which suggest that KRAS mutations are prognostic of poor survival rather than predictive of outcome with bevacizumab in patients with mCRC [16-18].

Caution is required when interpreting the findings of this study as there are several limitations associated with it. The study is retrospective rather than prospective in its design and analysis; patients were excluded if they prematurely discontinued treatment prior to disease progression, and while this was important within the confines of the analysis and evaluation of the impact of continuing bevacizumab therapy until disease progression it is not very representative of the general clinical population.

In conclusion, the AVAMAX study has shown that treatment with bevacizumab plus standard

chemotherapy is an effective and well-tolerated option for patients with mCRC who continue treatment until disease progression. The availability of bevacizumab and a variety of chemotherapy regimens expands the range of treatment options open to the physician and patient and careful consideration of the patient's physical condition, previous therapies and treatment goals is essential in the selection of appropriate treatment for each patient.

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