Role of Kras Status in Patients with Metastatic Colorectal Cancer Receiving First-Line Chemotherapy plus Bevacizumab: A TTD Group Cooperative Study

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Abstract

Background: In the MACRO study, patients with metastatic colorectal cancer (mCRC) were randomised to first-line treatment with 6 cycles of capcitabine and oxaliplatin (XELOX) plus bevacizumab followed by either single-agent bevacizumab or XELOX plus bevacizumab until disease progression. An additional retrospective analysis was performed to define the prognostic value of tumour KRAS status on progression-free survival (PFS), overall survival (OS) and response rates.

Methodology/Principal Findings: KRAS data (tumour KRAS status and type of mutation) were collected by questionnaire from participating centres that performed KRAS analyses. These data were then cross-referenced with efficacy data for relevant patients in the MACRO study database. KRAS status was analysed in 394 of the 480 patients (82.1%) in the MACRO study. Wild-type (WT) KRAS tumours were found in 219 patients (56%) and mutant (MT) KRAS in 175 patients (44%). Median PFS was 10.9 months for patients with WT KRAS and 9.4 months for patients with MT KRAS tumours (p = 0.0038; HR: 1.40; 95% CI:1.12–1.77). The difference in OS was also significant: 26.7 months versus 18.0 months for WT versus MT KRAS, respectively (p = 0.0002; HR: 1.55; 95% CI: 1.23–1.96). Univariate and multivariate analyses showed that KRAS was an independent variable for both PFS and OS. Responses were observed in 126 patients (57.5%) with WT KRAS tumours and 76 patients (43.4%) with MT KRAS tumours (p = 0.0054; OR: 1.77; 95% CI: 1.18–2.64).

Conclusions/Significance: This analysis of the MACRO study suggests a prognostic role for tumour KRAS status in patients with mCRC treated with XELOX plus bevacizumab. For both PFS and OS, KRAS status was an independent factor in univariate and multivariate analyses.

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Introduction

At present, standard first-line treatment for patients with metastatic colorectal cancer (mCRC) includes combination chemotherapy in conjunction with either an anti-epidermal growth factor receptor (EGFR) agent such as cetuximab [1,2] or panitumumab [3], or an antiangiogenic agent, such as bevacizumab [4–6]. One critical issue is the selection of patients who will benefit from treatment with these biological agents. In the case of anti-EGFR therapies, the presence of a KRAS mutation is a negative predictive factor for response to treatment [7–9] and determination of KRAS status is now required by American and European authorities before these agents can be administered [10–13].

The prognostic value of tumour KRAS status has been extensively evaluated in patients with advanced and localised CRC, although results have been conflicting. Some studies have demonstrated a prognostic effect [14–19], while others have failed to show any significant prognostic effect [20–24].

Recent studies of chemotherapy regimens, with or without cetuximab, in the first-line treatment of patients with mCRC have sparked new interest in this issue [7,25–27].

The interaction of EGFR and vascular endothelial growth factor (VEGF) is well known [28,29], although the potential role of KRAS mutation status in patients undergoing treatment with bevacizumab remains of great interest. Retrospective analyses have shown that bevacizumab in combination with irinotecan/5-fluorouracil (5-FU)/leucovorin chemotherapy provides a significant clinical benefit for patients with mutant (MT) and wild-type (WT) KRAS tumours [30,31]. The authors also noted that the benefit of treatment was greater in patients with WT compared with MT KRAS tumours. Other studies have shown no prognostic effect of tumour KRAS status on survival in patients receiving combination chemotherapy with bevacizumab [32–35].

We undertook an analysis of data from the MACRO study to evaluate the prognostic value of tumour KRAS status in patients receiving combination therapy with capecitabine plus oxaliplatin (XELOX) and bevacizumab. Correlations between KRAS status and response rate, progression-free survival (PFS) and overall survival (OS) were analysed.

Methods

Ethics Statement

The Institutional Review Board and Ethic Committee of Hospital Clínico San Carlos, Madrid as Reference Ethics Committee, as well as the Spanish Medicine Agency, approved the study protocol (Study TTD-05-02; EudraCT: 2005-003325-67; clinicaltrials.gov identifier NCT00335595). Study procedures were carried out in accordance with the Declaration of Helsinki and its subsequent amendments and Good Clinical Practice guidelines. Written informed consent was obtained from all patients before enrolment.

Patients and Study Design

The design of the MACRO study has been reported previously [36]. In brief, patients aged ≥18 years, with histologically confirmed mCRC, Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 2, measurable disease, no previous chemotherapy for advanced disease, adequate hepatic and renal function, and no contraindications to bevacizumab therapy were included.

The primary endpoint of the MACRO study was PFS; secondary endpoints included OS, objective response rate (ORR), toxicity and several translational research assessments. Between July 2006 and September 2008, 480 patients were entered into the study; 239 were randomized to maintenance XELOX plus bevacizumab after induction XELOX plus bevacizumab and 241 were randomized to single-agent bevacizumab after induction XELOX plus bevacizumab. Induction XELOX consisted of 6 cycles of bevacizumab (7.5 mg/kg intravenously [iv] d1), capecitabine (1000 mg/m² orally bid d1–14) and oxaliplatin (130 mg/m² iv d1) every 3 weeks followed by XELOX plus bev or bev alone until progression.

KRAS Mutation Analysis

Evaluation of KRAS status was performed retrospectively. As KRAS analysis is standard practice in Spain, sample analysis was performed either at the treating centre or centrally using existing platforms. Participating centres sent KRAS findings to the data collection centre. Data were obtained on KRAS status (WT or MT), the type of mutation found (12 Ala, 12 Arg, 12 Asp, 12 Cys, 12 Ser, 12 Val or 13 Asp) and the methodology used (methodology DxS, StripAssay and sequencing). These findings were correlated with patient’s existing data, including response rate, PFS, OS, rescue surgery and second-line therapy.

Statistical Analysis

The primary objective of this ancillary analysis of the MACRO study was to evaluate the utility of tumour KRAS status as a prognostic factor in patients with mCRC who were treated with chemotherapy and bevacizumab. The MACRO study demonstrated that single-agent bevacizumab was not statistically significantly inferior to XELOX plus bevacizumab as maintenance therapy [36]; therefore tumour KRAS mutation data from patients in the two treatment groups were combined for the purposes of the present analysis. PFS and OS curves were calculated according to KRAS tumour mutation status using the Kaplan–Meier method. The prognostic value of the biological marker was determined using the log-rank test. Univariate and multivariate Cox proportional hazards models were built with the following variables: ECOG PS 0–1 versus 2; age <70 versus ≥70 years; number of metastatic sites 1 versus ≥2; lactate dehydrogenase (LDH) high levels versus within the normal range; alkaline phosphatase high levels versus within the normal range; male versus female sex; KRAS MT versus WT status; maintenance treatment (XELOX–bev vs bev), prior adjuvant chemotherapy and radiotherapy and surgical removal of metastases prior to the study entry.

Results

Patient Characteristics

The intent-to-treat (ITT) population of the MACRO study comprised 480 patients, 394 (82.1%) of whom had information on KRAS status and were included in this biomarker sub-study (Figure 1).

Patient characteristics according to KRAS status are shown in Table 1. Significant differences were observed between the two groups in prior adjuvant chemotherapy, prior radiotherapy and surgical removal of metastases prior to entry into the study.

KRAS Analysis

Questionnaires were completed by 171 (43.4%) of Spanish reference centres and 185 (47.0%) of other centres participating in the study. The most common technique for KRAS determination was DxS (76.4% of cases), followed by sequencing (13.3%),
StripAssay (10.0%) and pyrosequencing (0.3%). In total, 219 of the 394 patients (55.6%) had WT KRAS tumours, while 175 patients (44.4%) had some type of mutation. The most frequent mutations were G12D (33.3%), G12V (26.9%), G13D (21.8%), G12C (8.3%), G12S (1.9%), G12A (3.9%) and G12R (2.6%). This information was not available in 19 (10.9%) cases.

Prognostic Value of KRAS

The confirmed ORR was 57.5% in patients with WT KRAS tumours compared with 43.4% in patients with MT KRAS tumours (p = 0.0054; OR: 1.77, 95% CI 1.18–2.64). Median PFS was significantly longer in patients with WT versus MT KRAS tumours, 10.9 months versus 9.4 months (p = 0.0038; HR: 1.40; 95% CI: 1.12–1.77) (Figure 2A). A statistically significant difference was observed in OS (Figure 2B): patients with WT KRAS tumours had a median OS of 26.7 months versus 18.0 months for patients with MT KRAS tumours (p = 0.0002; HR: 1.55; 95% CI: 1.23–1.96).

When patients were analysed for PFS according to treatment received, a similar pattern was observed in the KRAS MT and WT groups. In the XELOX plus bevacizumab maintenance group, median PFS was 12.6 months versus 10.0 months in patients with WT and MT KRAS tumours, respectively (p = 0.0560; HR: 1.39; 95% CI: 0.99–1.95). In the single-agent bevacizumab group, median PFS was 10.8 versus 8.7 months in patients with WT and MT KRAS tumours, respectively (p = 0.0492; HR: 1.38; 95% CI: 1.00–1.89).

A total of 47 patients (11.9%) underwent salvage surgery of metastases, 28 of whom had WT KRAS tumours and 19 had MT KRAS tumours (p = 0.0064; OR: 4.1, 95% CI 1.7–9.6). Median PFS was 16.2 months versus 12.7 months in patients who underwent salvage surgery of metastases versus 18.0 months in patients with WT and MT KRAS tumours (p = 0.0002; HR: 1.55; 95% CI: 1.23–1.96).

When patients were analysed for PFS according to treatment received, a similar pattern was observed in the KRAS MT and WT groups. In the XELOX plus bevacizumab maintenance group, median PFS was 12.6 months versus 10.0 months in patients with WT and MT KRAS tumours, respectively (p = 0.0560; HR: 1.39; 95% CI: 0.99–1.95). In the single-agent bevacizumab group, median PFS was 10.8 versus 8.7 months in patients with WT and MT KRAS tumours, respectively (p = 0.0492; HR: 1.38; 95% CI: 1.00–1.89).

Reasons for withdrawal from the study were similar in patients with WT and MT KRAS. The most common reasons for withdrawal were: disease progression (WT KRAS n = 104 [48.4%]; MT KRAS n = 102 [58.6%]), toxicity, adverse events or intercurrent disease (WT KRAS n = 52 [24.2%]; MT KRAS n = 39 [22.4%]), surgery (WT KRAS n = 36 [16.7%]; MT KRAS n = 17 [9.8%]) and death (WT KRAS n = 6 [2.8%]; MT KRAS n = 5 [2.9%]). There were no statistically significant differences between the two groups in this respect (p = 0.1815).

Subsequent therapy just after the study discontinuation is described in more detail in Table 2.

Median OS was 28.0 months in patients with WT KRAS tumours who received post-study anti-EGFR therapy versus 20.2 months in those with MT KRAS tumours (HR: 1.68; 95% CI: 1.25–2.26; p = 0.0006). OS was longer in patients with WT KRAS tumours who did not receive anti-EGFR therapy than in patients with MT KRAS tumours (26.9 months versus 20.2 months; HR: 1.48; 95% CI: 1.02–2.16; p = 0.0379). There was no difference in OS between patients with WT KRAS tumours who did not receive anti-EGFR therapy and those who did (28.0 versus 26.9 months; HR: 1.13, 95% CI: 0.77–1.67; p = 0.5373) (Figure 3).

Figure 1. Patient flow. doi:10.1371/journal.pone.0047345.g001

Figure 2. OS by KRAS status. doi:10.1371/journal.pone.0047345.g002

Figure 3. OS in patients who received post-study anti-EGFR therapy. doi:10.1371/journal.pone.0047345.g003

Figure 4. OS in patients who received no further therapy. doi:10.1371/journal.pone.0047345.g004

Figure 5. OS in patients who received chemotherapy with bevacizumab. doi:10.1371/journal.pone.0047345.g005

Figure 6. OS in patients who received chemotherapy alone. doi:10.1371/journal.pone.0047345.g006

Figure 7. OS in patients who received no anti-EGFR therapy. doi:10.1371/journal.pone.0047345.g007

Figure 8. OS in patients who received anti-EGFR therapy. doi:10.1371/journal.pone.0047345.g008
Results of the univariate and multivariate analyses for PFS are shown in Table 3. For the univariate analysis, variables independently associated with PFS were: age (HR: 1.32; 95% CI: 1.02–1.70; p = 0.032); LDH level (HR: 2.02; 95% CI: 1.57–2.60; p < 0.0001), alkaline phosphatase level (HR: 1.30; 95% CI: 1.03–1.64; p = 0.0264), KRAS status (HR: 1.40; 95% CI: 1.12–1.77; p = 0.0040) and surgical removal of metastases prior to the study entry (HR: 1.61; 95% CI: 1.01–2.57; p = 0.0457). In the multivariate analysis, significant predictors of PFS were: age (HR: 1.34; 95% CI: 1.01–1.76; p = 0.0422), the number of organs involved (HR: 1.39; 95% CI: 1.07–1.81; p = 0.0142), LDH level (HR: 2.24; 95% CI: 1.68–3.01; p < 0.0001), KRAS status (HR: 1.47; 95% CI: 1.14–1.91; p = 0.0031) and surgical removal of metastases prior to the study entry (HR: 1.75; 95% CI: 1.04–2.94; p = 0.0367).

Predictors of OS in the univariate analysis were: number of organs involved (HR: 1.45; 95% CI: 1.14–1.83; p = 0.0023), LDH level (HR: 2.13; 95% CI: 1.65–2.75; p < 0.0001), alkaline phosphatase level (HR: 1.47; 95% CI: 1.16–1.86; p = 0.0012) and KRAS status (HR: 1.55; 95% CI: 1.23–1.96; p = 0.0002). Significant factors in the multivariate analysis were the number of organs involved (HR: 1.58; 95% CI: 1.22–2.06; p = 0.0006); LDH (HR: 2.27; 95% CI: 1.71–3.01; p < 0.0001) and KRAS status (HR: 1.60; 95% CI: 1.24–2.08; p = 0.0004) (Table 4).

### Discussion

The present analysis of the MACRO study indicates that tumour KRAS status is a prognostic factor in patients with mCRC receiving bevacizumab in combination with capecitabine plus oxaliplatin. Patients with WT KRAS tumours had a significantly greater clinical benefit than those with MT KRAS tumours in terms of ORR (57.5% versus 43.4%), PFS (10.9 versus 9.4 months) and OS (26.7 versus 18.0 months). The same trend was observed when both treatment arms were combined and when analysed separately. Univariate and multivariate analyses showed the independent role of KRAS status for both PFS and OS. This indicates that in the MACRO study, KRAS was a prognostic factor in patients with mCRC receiving bevacizumab in combination with chemotherapy.

The prognostic value of KRAS was initially suggested by the RASCAL I study, which included 2721 patients [16]. Multivariate analysis established that the effect of KRAS was independent of other variable factors such as sex, tumour site or Dukes stage. The

### Table 1. Baseline characteristics of patients included in the KRAS analysis according to tumour KRAS status (n = 394).

| Characteristic | WT KRAS (n = 219) | MT KRAS (n = 175) | p-value |
|---------------|------------------|------------------|---------|
| Median age, years (range) | 63 (40–82) | 64 (30–80) |        |
| Sex, %         |                  |                  |         |
| Male           | 64.8             | 62.3             |        |
| Female         | 35.2             | 37.7             |        |
| ECOG PS, %     |                  |                  |         |
| 0              | 61.5             | 50.6             |        |
| 1              | 37.2             | 47.1             |        |
| 2              | 1.4              | 2.3              |        |
| Primary tumour location, % |            |                  |         |
| Colon          | 28.3             | 23.4             |        |
| Rectum         | 60.3             | 64.0             |        |
| Both           | 11.4             | 12.6             |        |
| Metastases, %  |                  |                  |         |
| Liver only     | 40.2             | 31.4             |        |
| Locoregional   | 16.4             | 16.6             |        |
| Lung           | 39.3             | 42.9             |        |
| Other          | 27.4             | 29.7             |        |
| Prior adjuvant therapy, % |          |                  |         |
| Chemotherapy   | 11.4             | 20.0             | <0.05<sup>a</sup> |
| Radiotherapy   | 5.5              | 11.4             | <0.05<sup>a</sup> |
| Median no. of organs affected (range) | 2 (1–5)    | 2 (1–6)          |         |
| Median no. of metastatic sites (range) | 4 (1–20)    | 3 (1–11)         |         |
| Resection of primary tumour, % | 71.2        | 78.3             |         |
| Surgery for metastatic disease prior to study entry, % | 5.5         | 11.4             | <0.05<sup>b</sup> |
| Median LDH, U/L (range) | 423 (150–5386) | 393.5 (95.4–5313) |       |
| Median CEA, ng/mL (range) | 36.7 (0.5–14280) | 42.1 (0.8–8527)   |   |

Abbreviations: CEA, carcinoembryonic antigen; LDH, lactate dehydrogenase; ECOG PS, Eastern Cooperative Oncology Group performance status; MT, mutant; WT, wild type.

<sup>a</sup>Chi-Square Test.

<sup>b</sup>Fisher’s Exact Test.

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Figure 2. Progression-free survival (A) and overall survival (B) according to KRAS status.
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Table 2. Subsequent therapy according to tumour KRAS status.

| Regimen, n (%)                                  | WT KRAS (n = 219) | MT KRAS (n = 175) |
|------------------------------------------------|-------------------|------------------|
| Anti-EGFR alone                                | 1 (<1%)           | 1 (<1%)          |
| Anti-EGFR + irinotecan-based chemotherapy      | 39 (17.8%)        | 7 (4.0%)         |
| Anti-EGFR + capecitabine- or 5-FU-based chemotherapy | 1 (<1%)           |                  |
| Anti-EGFR + oxaliplatin based chemotherapy     | 2 (0.9%)          | 1 (<1%)          |
| Bevacizumab alonea                            | 7 (3.2%)          | 1 (<1%)          |
| Bevacizumab + irinotecan-based chemotherapy   | 16 (7.3%)         | 27 (15.4%)       |
| Bevacizumab + capecitabine- or 5-FU-based chemotherapy | 10 (4.6%)         | 9 (5.1%)         |
| Bevacizumab + oxaliplatin-based chemotherapy  | 19 (8.7%)         | 17 (9.7%)        |
| Bevacizumab + anti-EGFR + irinotecan          | 1 (<1%)           |                  |
| Irinotecan alone or irinotecan-based chemotherapy | 42 (19.2%)        | 55 (31.4%)       |
| Capecitabine or 5-FU alone or oxaliplatin-based chemotherapyb | 27 (12.3%)        | 20 (11.4%)       |
| No treatment                                  | 54 (24.7%)        | 37 (21.1%)       |

Abbreviation: EGFR: epidermal growth factor receptor.

aPatient discontinued chemotherapy and continuous bevacizumab after the study withdrawal.

bOne patient received additional gemcitabine.

cIncludes one patient who received methotrexate.

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Figure 3. Effect of post-progression anti-EGFR therapy on survival. Abbreviations: EGFR, epidermal growth factor receptor; HR, hazard ratio; MT, mutant; WT, wild type.

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RASCAL study suggested that KRAS was important not only for carcinogenesis of CRC but also for prognosis in patients with all stages of the disease. Other studies have confirmed the prognostic value of KRAS status [14,15,17–19,25,26]. Several studies have evaluated the role of KRAS status in patients with mCRC receiving first-line treatment with bevacizumab (Table 5) [30–35]. In the study by Ince et al, no statistically significant difference was observed for OS in KRAS WT and MT bevacizumab-treated patients (27.7 versus 19.9 months for WT and MT KRAS, respectively; HR: 0.64; 95% CI 0.35–1.15) [30]. In the subsequent analysis by Hurwitz et al., response rates (60% versus 43%) and PFS (13.5 versus 9.3 months) were numerically greater for bevacizumab-treated patients with WT versus MT KRAS tumours, although the difference in PFS was not statistically significant (HR 0.66; p = 0.09) [31]. Other studies have also reported that KRAS mutation status is not a prognostic factor for patient outcome [32–35]. This variability in results could be a result of several factors, including the number of patients included in the different trials, the proportions of patients tested for KRAS mutation status and the technology used, the chemotherapy regime under investigation, and subsequent second- and third-line therapies.

Our study did not aim to determine whether KRAS status was predictive in patients receiving bevacizumab, as all patients were treated with bevacizumab. Results from the studies by Hurwitz et al. [31] and Ince et al. [30] appear to show that KRAS status is not predictive and that all patients can benefit from bevacizumab treatment. Our study did not include a bevacizumab-free control arm and therefore we cannot state with certainty that patients with MT KRAS tumours benefit from bevacizumab treatment;

| Parameter                        | Univariate analysis | Multivariate analysis |
|----------------------------------|---------------------|-----------------------|
|                                  | p-value  | HR       | 95% CI     | p-value  | HR       | 95% CI     |
| ECOG PS (2 vs 0–1)               | 0.1773   | 1.748    | 0.777–3.932| 0.7731   | 1.144    | 0.458–2.861|
| Age (≥70 vs <70 years)           | 0.0320   | 1.318    | 1.024–1.696| 0.0422   | 1.335    | 1.010–1.763|
| No. affected organs (≥2 vs 1)    | 0.1908   | 1.168    | 0.926–1.474| 0.0142   | 1.392    | 1.069–1.814|
| LDH (elevated vs normal)         | <0.0001  | 2.018    | 1.566–2.600| <0.0001  | 2.244    | 1.675–3.007|
| AP (elevated vs normal)          | 0.0264   | 1.300    | 1.031–1.639| 0.4705   | 0.901    | 0.680–1.195|
| Sex (female vs male)             | 0.6592   | 1.056    | 0.829–1.346| 0.9184   | 1.014    | 0.775–1.326|
| KRAS status (MT vs WT)           | 0.0040   | 1.404    | 1.115–1.769| 0.0031   | 1.473    | 1.139–1.905|
| Maintenance treatment (XELOX-bev vs bev) | 0.3017 | 1.129    | 0.896–1.423| 0.4513   | 1.104    | 0.854–1.428|
| Prior chemotherapy (no vs yes)   | 0.7756   | 0.956    | 0.703–1.301| 0.4418   | 0.845    | 0.550–1.299|
| Prior radiotherapy (no vs yes)   | 0.7988   | 0.951    | 0.643–1.404| 0.5954   | 1.159    | 0.672–2.000|
| Surgical removal of metastases prior to the0.0457 study entry(no vs yes) | 1.610    | 1.009–2.568| 0.0367   | 1.746    | 1.035–2.944|

Abbreviations: AP, alkaline phosphatase; bev, bevacizumab; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; MT, mutant type; WT, wild type; XELOX, capecitabine + oxaliplatin.

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Table 4. Univariate and multivariate analyses of overall survival.

| Parameter                        | Univariate analysis | Multivariate analysis |
|----------------------------------|---------------------|-----------------------|
|                                  | p-value  | HR       | 95% CI     | p-value  | HR       | 95% CI     |
| ECOG PS (2 vs 0–1)               | 0.3518   | 1.469    | 0.654–3.302| 0.8815   | 0.933    | 0.376–2.314|
| Age (≥70 vs <70)                 | 0.1682   | 1.198    | 0.927–1.548| 0.3342   | 1.150    | 0.866–1.526|
| No. of affected organs (≥2 vs 1) | 0.0023   | 1.445    | 1.140–1.831| 0.0006   | 1.584    | 1.217–2.062|
| LDH (abnormal vs normal)         | <0.0001  | 2.130    | 1.647–2.754| <0.0001  | 2.266    | 1.706–3.011|
| AP (abnormal vs normal)          | 0.0012   | 1.472    | 1.164–1.861| 0.7607   | 1.044    | 0.792–1.377|
| Sex (female vs male)             | 0.7310   | 0.958    | 0.752–1.221| 0.3318   | 0.875    | 0.668–1.146|
| KRAS status (MT vs WT)           | 0.0002   | 1.552    | 1.228–1.962| 0.0004   | 1.604    | 1.236–2.083|
| Maintenance treatment (XELOX-bev vs bev) | 0.3503 | 1.117    | 0.886–1.409| 0.2184   | 1.175    | 0.909–1.518|
| Prior chemotherapy (no vs yes)   | 0.1665   | 1.266    | 0.906–1.769| 0.3616   | 1.244    | 0.778–1.989|
| Prior radiotherapy (no vs yes)   | 0.5676   | 1.135    | 0.735–1.755| 0.9887   | 1.004    | 0.542–1.861|
| Surgical removal of metastases prior to study entry(no vs yes) | 0.6795   | 1.098    | 0.704–1.714| 0.6656   | 1.118    | 0.674–1.855|

Abbreviations: AP, alkaline phosphatase; bev, bevacizumab; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; MT, mutant type; WT, wild type; XELOX, capecitabine + oxaliplatin.

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Table 5. Summary of KRAS data from larger studies of bevacizumab + chemotherapy in patients with metastatic colorectal cancer.

|                | Hurwitz (31) | CAIRO2 (35) | AGITG MAX (33) | PACCE (34) | MACRO       |
|----------------|--------------|--------------|-----------------|------------|-------------|
| Regimen        | IFL + Bev    | Cape + Ox + Bev | Cape+Bev+ MitC | CT (Iri, Ox) + Bev | Cape + Ox + Bev |
| No of patients tested/No. of patients in study | 129/402      | 264/368      | 212/314        | 425/525    | 394/480     |
| Patients with KRAS mutation, %     | 34           | 41           | 29             | 40         | 44          |
| Availability for KRAS analysis, %   | 32           | 72           | 67             | 82         | 82          |
| Response rate, %                      |              |              |                |            |             |
| WT                           | 60           | 50           | 41–45          | 48–56      | 58          |
| p = NA                       | P = 0.16     | p = NS        | 24–46%         | 38–44      | 43          |
| MT                           | 43           | 59           | 9.3            | 8.2        | 10.9        |
| p = 0.09                     | P = 0.80     | p = NS        | 11.0–11.9      | 9.4        | p = 0.0038  |
| OS, months                    |              |              |                |            |             |
| WT                           | 27.7         | 22.4         | 19.8           | 19.8–24.5  | 26.7        |
| p = NA                       | p = 0.82     | p = NS        | 19.3–20.5      | 18         | p = 0.0002  |
| MT                           | 19.9         | 24.9         | 17.6           | 18         |             |

Abbreviations: Bev, bevacizumab; Cape, capecitabine; CT, chemotherapy; Iri, irinotecan; MitC, mitomycin C, MT, mutant type; NA, not available; NS, not significant; Ox, oxaliplatin; WT, wild type.

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However, bevacizumab does not seem to have an adverse effect on survival, as has been seen in some studies of the anti-EGFR agents [3,35]. The benefit of treatment with bevacizumab appears to be survival, as has been seen in some studies of the anti-EGFR agents, however, bevacizumab does not seem to have an adverse effect on survival (28.0 versus 20.2 months; HR: 1.68; p = 0.0006), yet there was no significant difference in patients with WT KRAS tumours who were treated with an anti-EGFR versus those who were not (28.0 versus 26.9 months; HR: 1.13; p = 0.5373). Later lines of therapy might influence OS, but response rates and PFS, which are not influenced by second- and third-line therapy, were also better in patients with WT KRAS tumours and may be a more appropriate marker for the success of treatment than OS.

In conclusion, this analysis of the MACRO study highlights the prognostic role of tumour KRAS mutation status in patients receiving chemotherapy in combination with bevacizumab, which is consistent with some literature reports but not others. The reasons for the discrepancy between studies are not yet apparent, and sufficiently powered, prospective studies will be required to answer this question. The importance of KRAS mutation type, as suggested by the RASCAL studies [Andreyev et al 2001; Andreyev et al 1998] and the correlation of KRAS status with microsatellite instability suggested by the PETACC-3 study [24] and other biomarkers such as BRAF, PTEN and PIK3CA [38], remain to be explored.

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