Role of RAS mutation status as a prognostic factor for patients with advanced colorectal cancer treated with first-line chemotherapy based on fluoropyrimidines and oxaliplatin, with or without bevacizumab: A retrospective analysis

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Abstract. The role of Kirsten rat sarcoma viral oncogene homolog (KRAS) and neuroblastoma RAS viral oncogene homolog (NRAS) mutations as negative predictors for anti-epidermal growth factor receptor (EGFR) therapies in metastatic colorectal cancer (CRC) has been firmly established. However, whether the RAS mutation status plays a role as a biomarker for anti-vascular endothelial growth factor (VEGF) treatment remains controversial. Data from 93 CRC patients who received first-line cytotoxic chemotherapy with fluoropyrimidines and oxaliplatin, with or without bevacizumab, were analyzed. We investigated the association between the RAS mutation status and clinical outcomes in terms of response rate, progression-free survival (PFS) and overall survival (OS). Mutations in RAS genes were observed in 47 (52.6%) patients (45 KRAS and 2 NRAS mutations). Patients with tumours harbouring RAS mutations were less suitable for primary tumour resection, were more likely to develop lung metastases, and received bevacizumab treatment for a shorter time period compared with those with wild-type tumours. The response rate to chemotherapy did not differ according to the RAS mutation status, and there were no significant differences in PFS [RAS mutation: 12 months, 95% confidence interval (CI): 8.7-15.2 vs. RAS wild-type: 12 months, 95% CI: 9.67-14.32; P=0.857] or OS (RAS mutation: 20 months, 95% CI: 14.3-25.6 vs. RAS wild-type: 24 months, 95% CI: 18.7-29.2; P=0.631). Patients with RAS mutation vs. those with RAS wild-type exhibited a favourable trend in PFS when treated with bevacizumab (13 months, 95% CI: 6.5-19.4 vs. 10 months, 95% CI: 4.2-15.7, respectively; P=0.07) and OS (27 months, 95% CI: 18.5-35.4 vs. 15 months, 95% CI: 12.4-17.5, respectively; P=0.22). In conclusion, RAS mutations are not a prognostic marker for PFS and OS in CRC patients receiving fluoropyrimidine-oxaliplatin treatment, with or without bevacizumab. RAS mutations are not predictive of the lack of efficacy of bevacizumab, and these patients appear to benefit from anti-angiogenic treatment.

Introduction

In Western countries, ~20% of patients with colorectal cancer (CRC) present with advanced disease stage at diagnosis (1-3). For >40 years, the standard treatment approach for advanced CRC with inoperable metastasis has been systemic chemotherapy. With the advances in systemic chemotherapy for metastatic CRC, survival has increased from 12 months with 5-fluorouracil monotherapy to ~2 years with the addition of oxaliplatin, irinotecan and targeted or biological agents (4-6). There is a need for identifying biomarkers for these biological agents that lead to a personalized approach to cancer treatment, ensuring maximum efficacy while simultaneously minimizing toxicity and treatment-related side effects.

Vascular endothelial growth factor (VEGF) and epithelial growth factor receptor (EGFR) are involved in molecular pathways related to the growth, survival, proliferation and metastasis of tumour cells. Targeted agents that are able to inhibit signal transduction through these proteins have been incorporated into the standard first-line treatment of advanced CRC (7,8). Anti-EGFR therapies with the monoclonal antibodies cetuximab and panitumumab improve chemotherapeutic efficacy, but this effect is restricted to patients with wild-type Kirsten
rat sarcoma viral oncogene homolog (KRAS) and neuroblas-
toma RAS viral oncogene homolog (NRAS) mutations (9,10). 
Thus, assessing the RAS status is currently a routine procedure 
worldwide to identify patients that would not benefit from such 
treatment in order to avoid unnecessary toxicity. However, 
bevacizumab, a monoclonal antibody against VEGF, was the 
first inhibitor of angiogenesis approved for the treatment of 
advanced CRC in combination with chemotherapy, based on 
the survival benefit observed in clinical trials. However, no 
biomarker able to identify patients who may benefit from this 
therapy has been established to date (7).

KRAS is a proto-oncogene encoding a small 21-kD guano-
sine triphosphate/guanosine diphosphate-binding protein 
involved in the regulation of cellular response to several 
eracelluar stimuli (11). Mutations within KRAS abrogating 
GTPase activity and resulting in activation of RAS/RAF signaling are found in 35-42% of CRCs and are considered to 
occur early during CRC carcinogenesis. Activating mutations in 
other members of the RAS oncogene family (HRAS and 
NRAS) have also been described, although they are significan-
tly less frequent. NRAS appears in ~2% of patients with 
advanced CRC (12). The presence of NRAS mutations has also 
recently been associated with a lack of benefit from anti-EGFR 
therapies (13), and has been incorporated in clinical practice as 
a predictive biomarker to select first-line treatment for patients 
with advanced CRC.

VEGF is an important regulator of physiological as well as 
pathological angiogenesis, and it is overexpressed in a number 
of different tumour types. It has been demonstrated that RAS 
pathway signaling increases VEGF expression and represses 
negative regulators of angiogenesis, suggesting that RAS aber-
trations may modulate the tumour response to anti-angiogenic 
therapies (14-16). It remains controversial whether KRAS 
mutation, independently of the use of anti-EGFR thera-
pies, has a prognostic role in CRC (17,18). Different studies 
published to date have not been conclusive, even several large 
studies (19,20), and the role of KRAS and NRAS mutation 
status as a predictor of outcome of oxaliplatin-based chemo-
therapy and bevacizumab remains uncertain.

The aim of this study was to evaluate the role of RAS 
mutation status as a predictive and prognostic factor in 
patients with advanced CRC treated with first-line standard 
chemotherapy with fluoropyrimidines and oxaliplatin, with or 
without bevacizumab.

Patients and methods

Study design and ethics. This was a multicenter and retro-
spective study of patients presenting with advanced CRC at 
diagnosis who were treated with fluoropyrimidine and oxali-
platin combination chemotherapy regimens, with or without 
bevacizumab, at four different hospitals in Valencia, Spain.

The study was performed following approval by the 
Independent Ethics Committees of the participating institu-
tions and in accordance with the Declaration of Helsinki, the 
Good Clinical Practices and local ethical and legal require-
ments (Spanish laws). Prior to study entry, all the patients (or 
their relatives) provided written informed consent according 
to the local ethics committee regulations. This study complied 
with all applicable regulations for human participant studies.

Patient characteristics. The medical records of patients diag-
nosed with advanced CRC were reviewed. The patients had 
pathologically confirmed advanced colorectal adenocarcinoma 
available for evaluation of KRAS and NRAS mutations, and 
had been treated between January, 2009 and December, 2012 
with a first-line chemotherapy regimen involving FOLFOX or 
XELOX, with or without bevacizumab.

Treatment and follow-up. All enrolled patients were treated 
with fluoropyrimidine and oxaliplatin combination chemo-
therapy regimens, with or without bevacizumab. A complete 
review of the medical history and baseline measures of the 
tumour prior to treatment initiation were performed to eval-
uate the patients. The diagnosis and treatment evaluation were 
performed with computed axial tomography.

The following data were collected from inpatient and 
outpatient records: Relevant clinical data, such as age, 
gender, presence of symptoms related to the tumour (weight 
loss, haemorrhage or bowel occlusion), comorbidities and 
Eastern Cooperative Oncology Group performance status.

RAS mutation analysis. The analysis of RAS mutations was 
performed using the TheraScreen®KRAS Pyro kit (for KRAS 
codons 12, 13 and 61), and the TheraScreen®RAS Extension 
Pyro kit (for KRAS codons 59, 117 and 146, and NRAS codons 
12, 13, 59, 61, 117 and 146) (Qiagen, Madrid, Spain), according 
to the manufacturer's instructions. Briefly, 5 µl of template 
DNA (10 ng of genomic DNA) were amplified by polymerase 
chain reaction (PCR) using, 12.5 µl of PyroMark®PCR 
Master Mix 2x, 2.5 µl of Coral Load Concentrate 10x, 4 µl of 
nuclease-free water, and 1 µl of the corresponding set of PCR 
primers (Qiagen). The reactions took place in a MasterCycler® 
thermocycler (Eppendorf, Hamburg, Germany) under the 
following cycling conditions: 94°C for 15 min; 42 cycles of 
denaturation at 95°C for 20 sec; annealing at 53°C for 30 sec, 
followed by extension at 72°C for 20 sec.

The amplicons were immobilised on Streptavidin Sepharose® High Performance beads (Qiagen) to prepare 
the single-stranded DNA and the sequencing primers were 
annealed to it using a PyroMark Q24 plate and a vacuum 
workstation (Qiagen). PyroMark Gold Q24 reagents (enzyme 
mixture, substrate mixture and nucleotideall from Qiagen) 
were then prepared and loaded into a cartridge so they could 
be dispensed during the sequencing process. Finally, the plate 
and the cartridge were loaded into the PyroMark Q24 System 
and the sequencing process was initiated. The sequences were
analysed using software provided by the manufacturer (Qiagen). In each run, two controls were included: Unmethylated control DNA, which worked as a positive control for PCR and sequencing reactions, and a negative control (without template DNA).

Statistical analysis. All statistical analyses were performed using the SPSS statistical package, version 16 (SPSS, Inc., Chicago, IL, USA). A descriptive statistics analysis, including measures of central tendencies and dispersions of quantitative variables, as well as absolute and relative frequencies for categorical variables, was also performed; t-test was used to compare two independent samples of continuous variables.

The Chi-square test was used to compare two or more independent groups of subjects with respect to a given categorical variable. PFS and OS according to KRAS status were analyzed using the Kaplan-Meier method to estimate the probability of survival and survival difference with the use of the log-rank test. All reported P-values were the result of two-sided tests, with P<0.05 considered statistically significant.

Results

Patient characteristics. A total of 93 patients with advanced CRC and available samples for NRAS and KRAS analysis, who were treated with fluoropyrimidine and oxaliplatin combination chemotherapy regimens (XELOX or FOLFOX), with or without bevacizumab, were identified. A total of 49 patients (52.6%) had tumours with RAS mutations, namely 47 KRAS and 2 NRAS mutations. The proportion of patients with KRAS mutations who underwent surgery for the primary tumour was significantly lower compared with that of patients with RAS wild-type tumours (P=0.019), and they exhibited a higher rate of lung metastases (34.6 vs. 15.9%, respectively; P=0.03). Furthermore, patients with RAS mutations were less likely to receive bevacizumab in the first-line treatment setting compared with the wild-type population (29.5 vs. 44.8%, respectively; P=0.09).

Treatment efficacy. The overall response rate (ORR) with first-line chemotherapy treatment was 53.8%, and the disease control rate (DCR) was 81.2%. There were no significant differences in ORR according to the RAS mutation status (mutation vs. wild-type, 48.9 vs. 58.9%, respectively; P=0.129), as shown in Table II.

The median PFS for the global population was 12 months, without significant differences between groups [RAS mutation: 12 months, 95% confidence interval (CI): 8.7-15.2 vs. RAS wild-type: 12 months, 95% CI: 9.67-14.32; P=0.857]. The median OS was 22 months, without a significant difference according to the RAS status (RAS mutation: 20 months, 95% CI: 14.3-25.6 vs. RAS wild-type: 24 months, 95% CI: 18.7-29.2; P=0.631), as shown in Fig. 1.

Patients treated with bevacizumab exhibited a median PFS of 12 vs. 11 months for those treated with chemotherapy alone (P=0.055). Significant differences in OS according to the use of bevacizumab in the overall population were not observed, although there was a favourable trend for patients treated with the combination of chemotherapy and bevacizumab (patients receiving bevacizumab reached an OS of 27 months (95% CI: 21.9-32), whereas patients without bevacizumab reached an OS of 20 months (95% CI: 13.8-26.1; P=0.25). Patients with RAS mutations also exhibited a non-significant favourable trend in PFS when treated with bevacizumab (13 months, 95% CI: 6.5-19.4) compared with those treated with chemotherapy alone (10 months, 95% CI: 4.2-15.7; P=0.07). The median OS was longer in patients with RAS mutations who received bevacizumab, but this difference did not reach statistical significance (27 months, 95% CI: 18.5-35.4 vs. 15 months, 95% CI: 12.4-17.5, respectively; P=0.22) as shown in Fig. 2. Furthermore, the median OS of patients treated with bevacizumab was similar between the RAS mutation and wild-type groups (27.0 vs. 27.0 months, respectively; P=0.562).

Discussion

This retrospective study was designed to analyze the prognostic role of RAS mutations in patients with advanced CRC treated with fluoropyrimidine and oxaliplatin chemotherapy, with or without bevacizumab. We also assessed whether patients with RAS mutations obtain any benefit from bevacizumab treatment.

The predictive and prognostic value of KRAS mutations in patients with advanced CRC treated with first-line chemotherapy and anti-EGFR therapy has been confirmed by retrospective analysis of phase III trials with cetuximab and panitumumab (9,10). Amado et al (9) published data from a randomized trial comparing panitumumab monotherapy with best supportive care (BSC) in patients with chemotherapy-refractory advanced CRC they detected KRAS mutations in 43% of the patients, and observed that the efficacy of panitumumab was significantly higher in the wild-type group in terms of PFS (12.3 vs. 7.3 weeks, respectively; P<0.001), response rate (17 vs. 0%, respectively) and OS [hazard ratio (HR)=0.67; 95% CI: 0.55-0.82]. Similarly, Karapetis et al (10) reported results from 394 patients included in a phase III trial that compared cetuximab with BSC in chemotherapy-refractory advanced CRC they detected KRAS mutations in 42.3% of the patients, and the presence of this molecular aberration was associated with a lack of benefit from cetuximab treatment in terms of OS (4.8 vs. 9.5 months, respectively; HR=0.55; 95% CI: 0.41-0.74; P<0.001) and PFS (1.9 vs. 3.78 months, HR=0.40; 95% CI: 0.30-0.54; P<0.001). They also observed that the mutation status of the KRAS gene did not affect survival among patients treated with BSC alone. More recently, mutations in NRAS, another member of the RAS oncogene family, that appear in 2-5% of patients with advanced CRC, have also been found to predict lack of response to anti-EGFR treatment (22). Doudillard et al retrospectively analyzed the efficacy and safety of panitumumab plus FOLFOX chemotherapy according to the RAS (KRAS and NRAS) mutation status (22); they detected NRAS mutations in 3.4% of the patients, and their association with...
The data reported by our study suggest that RAS status does not have a prognostic value for PFS or OS in patients with advanced CRC treated with optimal first-line chemotherapy. Our study, similar to other studies published to date investigating this issue, has a retrospective nature and may yield conflicting results. Our findings are in accordance with data from other small retrospective studies that did not identify an association between RAS mutation status and patient

Table I. Clinicopathological factors.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (n=93)</th>
<th>RAS wild-type (n=44)</th>
<th>RAS mutation (n=49)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (range)</td>
<td>65 (39-83)</td>
<td>68.5 (46-80)</td>
<td>68 (39-83)</td>
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<td>Gender</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>56 (60.2)</td>
<td>30 (68.1)</td>
<td>26 (53.0)</td>
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</tr>
<tr>
<td>Female</td>
<td>37 (39.8)</td>
<td>14 (31.9)</td>
<td>23 (47.0)</td>
<td></td>
</tr>
<tr>
<td>Performance status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.402</td>
</tr>
<tr>
<td>0-1</td>
<td>76 (81.1)</td>
<td>35 (79.5)</td>
<td>41 (83.7)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>17 (19.9)</td>
<td>9 (20.1)</td>
<td>8 (16.3)</td>
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<td>Tumour-related symptoms, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss &gt;10%</td>
<td>17 (18.3)</td>
<td>10 (22.7)</td>
<td>7 (17.0)</td>
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</tr>
<tr>
<td>Bleeding</td>
<td>30 (32.3)</td>
<td>16 (47.0)</td>
<td>7 (17.0)</td>
<td>0.184</td>
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<td>Occlusion</td>
<td>8 (8.6)</td>
<td>1 (3.0)</td>
<td>14 (34.1)</td>
<td>0.056</td>
</tr>
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<td>Surgery of primary tumour, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.019a</td>
</tr>
<tr>
<td>Yes</td>
<td>49 (52.6)</td>
<td>18 (41.0)</td>
<td>16 (32.6)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>42 (47.4)</td>
<td>26 (59.0)</td>
<td>33 (67.3)</td>
<td></td>
</tr>
<tr>
<td>Location of metastases, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>75 (80.6)</td>
<td>38 (86.3)</td>
<td>37 (75.5)</td>
<td>0.145</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>19 (20.4)</td>
<td>10 (22.7)</td>
<td>9 (18.3)</td>
<td>0.396</td>
</tr>
<tr>
<td>Lung</td>
<td>24 (25.8)</td>
<td>7 (15.9)</td>
<td>17 (34.6)</td>
<td>0.033a</td>
</tr>
<tr>
<td>Bone</td>
<td>3 (3.2)</td>
<td>0 (0.0)</td>
<td>3 (6.1)</td>
<td>0.142</td>
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<td>Lymph node</td>
<td>22 (23.7)</td>
<td>10 (22.7)</td>
<td>12 (24.4)</td>
<td>0.519</td>
</tr>
<tr>
<td>Number of metastatic locations, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>52 (55.9)</td>
<td>25 (56.8)</td>
<td>27 (20.4)</td>
<td>0.517</td>
</tr>
<tr>
<td>≥2</td>
<td>48 (44.1)</td>
<td>19 (43.1)</td>
<td>22 (44.9)</td>
<td></td>
</tr>
<tr>
<td>Operable metastases after chemotherapy, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17 (19.8)</td>
<td>10 (25.0)</td>
<td>7 (15.2)</td>
<td>0.194</td>
</tr>
<tr>
<td>No</td>
<td>69 (80.0)</td>
<td>30 (75.0)</td>
<td>39 (84.7)</td>
<td></td>
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<tr>
<td>Serum levels, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEA (high)</td>
<td>62 (66.7)</td>
<td>30 (75.0)</td>
<td>32 (76.1)</td>
<td>0.552</td>
</tr>
<tr>
<td>LDH (high)</td>
<td>32 (52.5)</td>
<td>15 (53.5)</td>
<td>17 (51.5)</td>
<td>0.539</td>
</tr>
<tr>
<td>Haemoglobin (low)</td>
<td>22 (28.6)</td>
<td>10 (27.7)</td>
<td>12 (29.2)</td>
<td>0.544</td>
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<tr>
<td>Grade of differentiation, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>12 (12.9)</td>
<td>5 (15.6)</td>
<td>7 (21.2)</td>
<td>0.693</td>
</tr>
<tr>
<td>2</td>
<td>43 (46.2)</td>
<td>22 (68.7)</td>
<td>21 (63.6)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>9 (9.7)</td>
<td>5 (15.6)</td>
<td>4 (12.1)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy scheme, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>FOLFOX/XELOX</td>
<td>58 (62.4)</td>
<td>13 (29.5)</td>
<td>22 (44.8)</td>
<td>0.095</td>
</tr>
<tr>
<td>FOLFOX/XELOX-B</td>
<td>35 (37.6)</td>
<td>31 (70.5)</td>
<td>27 (55.1)</td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant differences. CEA, carcinoembryonic antigen; LDH, lactate dehydrogenase.

a shorter PFS (10.1 vs. 7.9 months, respectively; HR=0.72; 95% CI: 0.58-0.90; P=0.004) and OS (26.0 vs. 20.2 months, respectively; HR=0.78; 95% CI: 0.62-0.99; P=0.04). Thus, the presence of RAS mutations is considered to be a negative predictive factor of response to anti-EGFR therapies. However, its role as a prognostic factor for OS in patients treated with chemotherapy alone, or in combination with bevacizumab, remains unclear.
outcome (23-25). Kim et al analyzed 103 patients evaluable for KRAS mutation status treated with chemotherapy without anti-EGFR therapy, and they did not observe differences in response rate, PFS or OS according to RAS status (25). Two large collaborative studies of the KRAS by the Colorectal Cancer Collaborative Group (RASCAL) reported conflicting results (26,27). While the first RASCAL study reported an increased risk of recurrence and mortality associated with KRAS mutations, the second study refined this observation to report a significant prognostic value in failure-free survival only with the G12V mutation in Dukes’ C patients. It is difficult to compare the results of all these retrospective studies, since there are several confounding factors that may affect the findings. The majority of these series are based on small patient samples, and none of the previously published studies incorporated in their analysis the presence of NRAS mutation; however, it is remarkable that most conclude that there is no association between RAS mutation status and patient outcome.

Regarding our second objective, we observed no association between RAS mutation status and the efficacy of bevacizumab. We observed that patients with RAS mutation presented with a longer median PFS and OS when treated with bevacizumab; however, the difference was not statistically significant. Furthermore, we observed no difference in PFS or OS in patients treated with bevacizumab according to the RAS status. Our findings suggest that RAS mutational status has no predictive value for bevacizumab outcome in patients with advanced CRC. Our findings are consistent with previous retrospective studies. Hurwitz et al observed no apparent association between the improved PFS and KRAS status for patients treated with bevacizumab and irinotecan and fluoropyrimidine chemotherapy (28). More recently, the MAX study confirmed that KRAS mutation status was neither prognostic for OS nor predictive for bevacizumab outcome in patients with advanced CRC (29). These two studies analyzed the role of KRAS mutations in patients treated with irinotecan-or mytomycin-based chemotherapy plus bevacizumab, which are not the most commonly used chemotherapeutic regimens worldwide in the first-line setting. Kim et al (30) published a

Table II. Response to treatment, n (%).

<table>
<thead>
<tr>
<th>Response</th>
<th>RAS mutation</th>
<th>RAS wild-type</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0 (0.0)</td>
<td>2 (4.5)</td>
<td>0.129</td>
</tr>
<tr>
<td>Partial response</td>
<td>24 (48.9)</td>
<td>24 (54.4)</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>12 (24.4)</td>
<td>7 (15.9)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>10 (20.4)</td>
<td>6 (13.6)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. (A) Progression-free survival (PFS) and (B) overall survival (OS) by RAS status. WT, wild-type; mut, mutation.

Figure 2. (A) Progression-free survival (PFS) and (B) overall survival (OS) of patients with tumours harbouring RAS mutations according to treatment with bevacizumab.

References