RESEARCH ARTICLE

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Bevacizumab with chemotherapy in patients with *KRAS* wild-type metastatic colorectal cancer: Czech registry data

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ABSTRACT **Aim:** This retrospective analysis investigated the effectiveness of combination therapy with bevacizumab and chemotherapy in the first-line treatment of patients with *KRAS* wild-type metastatic colorectal cancer. **Patients & methods:** Patients with *KRAS* wild-type metastatic colorectal cancer in the CORECT registry who initiated treatment with bevacizumab between 2008 and 2012 were enrolled. Overall survival and progression-free survival were the main effectiveness end points. **Results:** A total of 981 patients were enrolled. Median progression-free survival was 11.3 months (95% CI: 10.7–11.8) and median overall survival was 28.4 months (95% CI: 26.2–30.6). The most common adverse events were thromboembolic disease (4%) and hypertension (3.5%). **Conclusion:** This retrospective analysis shows the effectiveness of bevacizumab with chemotherapy in patients with *KRAS* wild-type metastatic colorectal cancer.

KEYWORDS
• bevacizumab • chemotherapy • colorectal cancer • *KRAS*

Colorectal cancer is among the most common malignant diseases in the Czech Republic, representing the second most prevalent of all malignancies in men and women. More than 50% of patients are diagnosed in the third, or higher, stage of illness [1]. As a result of new treatment strategies, which are based on chemotherapy in combination with targeted therapy medications, patient survival has been extended from 12 months in the era of mere symptomatic care to up to 3 years with combination therapy, while also preserving patient quality of life. Fluorouracil continues to form the basis of chemotherapy, in combination with oxaliplatin or irinotecan and five targeted drugs – the VEGF inhibitors bevacizumab and aflibercept, the anti-EGF receptor (EGFR) monoclonal antibodies, cetuximab and panitumumab and a multikinase inhibitor, regorafenib [2–4]. Currently, mutation analysis of *RAS* is the only predictive factor for colorectal cancer [5]. Patients with wild-type *KRAS* and *NRAS* can be treated with one of the anti-EGFR monoclonal antibodies. A mutated *KRAS* gene is also a negative prognostic marker [6–9]. The aim of our large, retrospective analysis was to ascertain the effectiveness of combination therapy with bevacizumab and chemotherapy in the first-line treatment of metastatic colorectal cancer (mCRC) in the wild-type *KRAS* population.

Patients & methods

Patients with proven wild-type *KRAS* mCRC, who began treatment with bevacizumab between 2008 and 2012, were enrolled from the CORECT registry. The CORECT registry is a noninterventional postregistration database of anonymized data in the Czech Republic, consisting of information from 20 oncologic centers in which targeted therapy is administered to patients with colorectal cancer.

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The evaluation of treatment responses was recommended to be done every 3 months using the RECIST 1.1 criteria by spiral computed tomography (CT) or PET/CT. Adverse events were graded using National Cancer Institute Common Terminology Criteria of Adverse Events (version 3.0). *KRAS* mutational status was determined only in accredited laboratories using different types of comparable assays (Surveyor Scan Kras and NRas Kit, Transgenomic, Inc., CT, USA; or NRAS and KRAS Strip Assays, ViennaLab, Vienna, Austria).

The study was approved by the institutional board of the Czech cancer registry.

• Statistical analysis

Baseline patient characteristics and treatment characteristics were summarized using standard descriptive statistics. Continuous characteristics are presented using median, mean, maximum, 5th and 95th percentile and categorical characteristics are presented using number of occurrence and percentage.

Overall survival (OS) was defined as the time from first-line bevacizumab treatment initiation until death. Progression-free survival (PFS) was defined as the time from first-line bevacizumab treatment initiation until disease progression or death. Patients in whom an event did not occur were censored up to the date of the last visit. The Kaplan–Meier method was used to estimate OS and PFS. All point estimates (median OS and median PFS, among others.) were accompanied by the 95% CI.

Results

Patient and disease characteristics are presented in Table 1. A total of 981 patients (62% males, median age at initiation of first-line treatment, 61 [range: 23–88] years) were included in this analysis. The primary tumor was localized in the colon in 61.7% of patients, and in the rectum in 38.3%. More than half of all patients (58.2%) presented with primarily metastatic disease. Adjuvant chemotherapy was administered in 32.4% of patients, and neoadjuvant or adjuvant radiotherapy of the rectum was performed in 19.4% of patients. The median period from termination of adjuvant therapy to initiation of systemic palliative therapy was 12.9 months.

As shown in Table 2, liver parenchyma was the most common site of metastatic disease (67.2% of patients), followed by infiltration of distant lymph nodes (30%), pulmonary metastases (23.7%) and peritoneal infiltration (17.8%). Two or more sites of metastatic disease were recorded in 44.2% of patients. The most commonly administered chemotherapy regimens were FOLFOX (48.6% of patients), XELOX (28.4%), combinations with irinotecan (13.5%; FOLFIRI 9.3%, XELIRI 4.2%) and

Table 1. Baseline characteristics of patients with metastatic colorectal cancer in the CORECT registry.

Characteristic	Patients (unless stated otherwise), n (%)
Total (n)	981
Males	608 (62.0)
Age at bevacizumab treatment initiation (years), median (minimum–maximum)	61 (23–88)
Localization of primary tumor: – Colon – Rectum	605 (61.7) 376 (38.3)
Primary metastatic: – M0 – M1	 410 (41.8) 571 (58.2)
Histology: – Adenocarcinoma – Other	 976 (99.5) 5 (0.5)
(Neo)adjuvant radiotherapy	190 (19.4)
Adjuvant chemotherapy	318 (32.4)
Time from adjuvant CT termination to first-line initiation†, median (5–95%)	12.9 months (1–67)
Surgery prior first line	870 (88.7)

†Date of adjuvant computed tomography termination is known in 250 patients.

Table 2. Bevacizumab treatment in patients with metastatic colorectal cancer in the CORECT registry.

Characteristic	Patients (unless stated otherwise), n (%)
Total (n)	981
Dose:	
– 5 mg/kg every 2 weeks	598 (61.0)
– 7.5 mg/kg every 3 weeks	382 (39.0)
PS at bevacizumab initiation:	
– Not available	238 (24.3)
– Available	743 (75.7)
– PS 0	377 (50.7)
– PS 1	349 (47.0)
– PS 2 or PS 3	17 (2.3)
Site of metastasis at bevacizumab initiation:	
– Not available	185 (18.9)
– Available	796 (81.1)
– Liver	535 (67.2)
– Lymph nodes	239 (30.0)
– Lung	189 (23.7)
– Peritoneum	142 (17.8)
– Other	129 (16.2)
– Two and more metastatic sites	352 (44.2)
CT regimens:	
– FOLFOX	477 (48.6)
– XELOX	279 (28.4)
– FOLFIRI	91 (9.3)
– XELIRI	41 (4.2)
– Capecitabine	39 (4.0)
– Other	39 (4.0)
– Without CT	15 (1.5)
Bevacizumab treatment terminated	855 (87.2)
Bevacizumab treatment duration, median (5–95%)	7.5 months (1.5–20.3)
Reason for bevacizumab termination:	
– Disease progression	552 (64.6)
– Surgery	50 (5.8)
– Adverse event	50 (5.8)
– CR	31 (3.6)
– Other reason	172 (20.1)
Best response:	
– CR	108 (12.6)
– PR	291 (34.0)
– SD	307 (35.9)
– PD	125 (14.6)
– Not available	24 (2.8)
– CR + PR	399 (46.7)
– CR + PR + SD	706 (82.6)

CR: Complete remission; PD: Progressive disease; PR: Partial response; PS: Performance status; SD: Stable disease.

capecitabine in combination with bevacizumab (4%). Bevacizumab was administered as monotherapy in only 15 (1.5%) patients. Bevacizumab was administered as a 2 weekly regimen at a dose of 5 mg/kg (61% of patients), or as a 3 weekly regimen at a dose of 7.5 mg/kg (39%). The median period of treatment in the first-line setting was 7.5 months.

Complete remission, partial response and stable disease were achieved in 12.6, 34.0 and 35.9% of patients, respectively; the effect of treatment could not be evaluated in 24 patients. Patients terminated treatment due to disease progression (64.6%), adverse events (5.8%) and 3.6% as a result of complete remission. Other nonspecified reasons resulted in treatment termination in

Table 3. Incidence of adverse events.

Adverse events	n (%); n = 981
Patients with adverse events	108 (11.0)
Thromboembolic event	39 (4.0)
Hypertension	34 (3.5)
Proteinuria	12 (1.2)
Bleeding	11 (1.1)
Gastrointestinal perforation	4 (0.4)
Leukopenia	3 (0.3)
Diarrhea	2 (0.2)
Thrombocytopenia	2 (0.2)
(Poly)neuropathy	1 (0.1)
Anemia	1 (0.1)
Nausea	1 (0.1)
Neutropenia	1 (0.1)
Vomiting	1 (0.1)
Other	26 (2.7)

20.1% of patients (Table 2). The two most common adverse events were thromboembolic disease (4%) and hypertension (3.5%) (Table 3). As shown in Table 4, median PFS was 11.3 months (95% CI, 10.7–11.8) and median OS was 28.4 months (95% CI, 26.2–30.6). The percentage of patients surviving and those without progression after 1 year was 86.5 and 44.8%, respectively; after 2 years, the corresponding proportions were 60.4 and 14.7% respectively, and after 3 years, were 38.2 and 7.7%, respectively (Figures 1 & 2).

Discussion

This retrospective analysis of the Czech non-interventional registry of patients with mCRC, who were treated with one of the monoclonal antibodies, evaluated the effectiveness of bevacizumab therapy among patients with *KRAS* wild-type in the first line treatment of colorectal cancer. The registration study for bevacizumab in combination with IFL (irinotecan, fluorouracil, leucovorin) did not analyze the effectiveness of therapy in correlation with the mutational status of *KRAS*, as its importance had not been proven at that time [10]. In this study, OS in the bevacizumab and IFL group reached 20.3 months (HR: 0.66), and time to progression (TTP) was 10.6 months (HR: 0.54). The first randomized study combining bevacizumab with oxaliplatin demonstrated an OS of 21.3 months (p = 0.0769) and a PFS of 9.4 months (p = 0.0023), also without the knowledge of *KRAS* mutational status [11]. The authors of the registration study performed an additional analysis to evaluate treatment effectiveness according to *KRAS* mutational status in the original patient population [4]. However, mutational status was only evaluated in a small sample (28.3% of patients). Median survival of the group treated with IFL + bevacizumab with wild-type *KRAS* was 25.1 months, TTP was 13.5 months; in the group with mutated *KRAS*, OS was 17.5 months and TTP was 7.4 months. In our analysis, we only included patients with wild-type *KRAS* who received first-line treatment for mCRC. In agreement with clinical practice, the majority of our patients received combination treatment with oxaliplatin (77%), and a minority with irinotecan (13.5%). Patients who were not able to receive combination therapy were treated with fluorouracil derivatives only in combination with bevacizumab. This group represented only 8% of all patients included in our analysis. Administration of these regimens is supported by two randomized Phase II studies [12,13] and one randomized Phase III study which compared the effectiveness of capecitabine monotherapy with capecitabine in combination with bevacizumab and with the addition of mitomycin. None of these studies accounted for *KRAS* mutational status. An international multicenter Phase IV study, which evaluated the combination of bevacizumab + FOLFIRI, demonstrated a median OS of 22.2 months and a median TTP of 11.1 months [14]. However, this study and two other studies (BRiTE [15] and BEAT [16]) did not take the mutational status of *KRAS* into consideration. In the literature, data regarding the effectiveness of bevacizumab, based on mutational status in prospective randomized trials, are scarce. A large-pooled analysis of 12 published trials explored the role of *KRAS* as a prognostic biomarker in metastatic colorectal patients treated with bevacizumab [17]. A total of 2266 patients (54% *KRAS* wild-type) were analyzed. The pooled objective response rate was 54.8% for wild-type patients and 48.3% for patients with mutated *KRAS*. The median PFS in patients with wild-type and mutated *KRAS* was 11.8 and

Table 4. Overall survival and progression-free survival from bevacizumab treatment initiation.

Parameter	Overall survival	Progression-free survival
n	981	981
Median (95% CI)	28.4 months (26.2–30.6)	11.3 months (10.7–11.8)
1-year survival (95% CI)	86.5 (84.3–88.8)	44.8 (41.5–48.2)
2-year survival (95% CI)	60.4 (56.9–64.0)	14.7 (12.2–17.3)
3-year survival (95% CI)	38.2 (34.1–42.3)	7.7 (5.5–9.9)

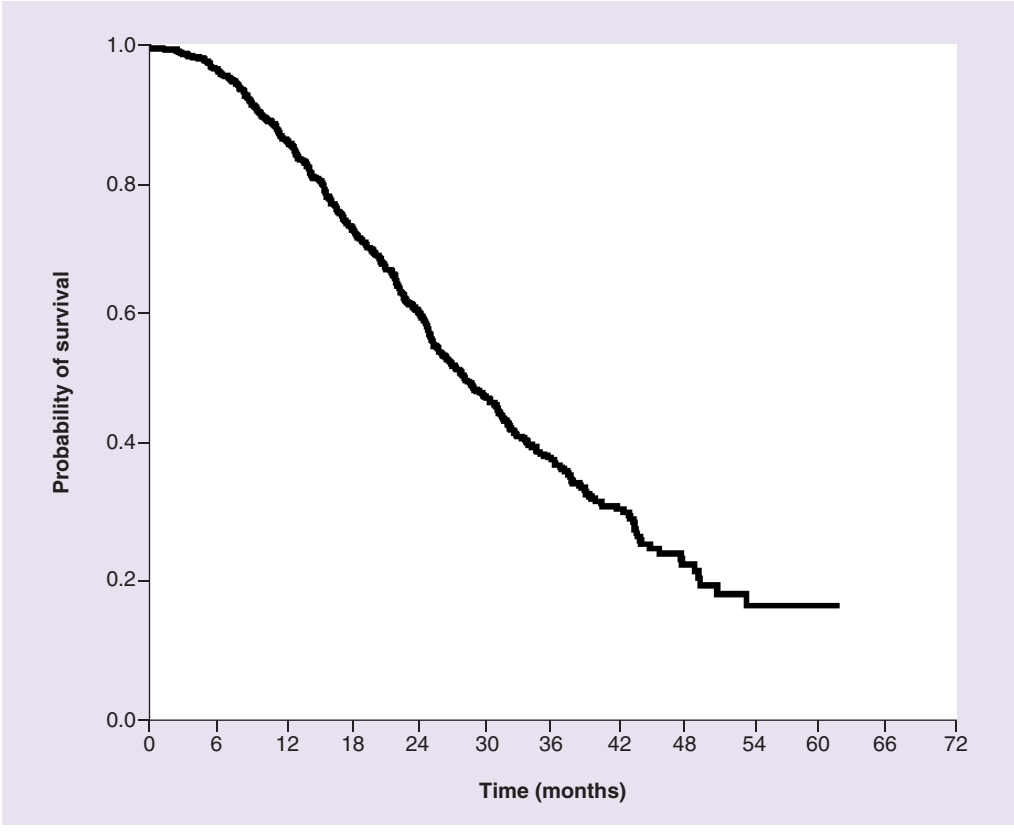

Figure 1. Overall survival (time from first-line bevacizumab treatment initiation until death).

9.42 months, respectively, and *KRAS* wild-type status was associated with a better OS (24.5 and 20.2 months, respectively) [17]. A subgroup analysis from the ML18147 study evaluated outcome according to *KRAS* status in patients treated with bevacizumab plus chemotherapy continued beyond first progression after previous treatment with bevacizumab and chemotherapy [18]. *KRAS* data were available in 616 patients, of which 51% had *KRAS* wild-type. Continuing treatment with bevacizumab was effective independent of *KRAS* status [18]. The results of two other studies are in accordance with these findings [19,20].

KRAS, a transformed oncogene suppressing apoptosis and stimulating proliferation of cells via the *RAS/RAF/MEK/ERK* transduction cascades, was the first biomarker accepted by clinical and regulatory authorities for treatment with anti-EGFR monoclonal antibodies. *KRAS* is mutated in approximately 40% of patients with colorectal cancer [21]. A retrospective analysis of the PRIME study demonstrated within the group of *KRAS* wild-type tumors (no mutations in exon 2) a subgroup of tumors with other mutations in *KRAS* exon 3 and *NRAS* mutations in exon 2 and 3 which do not benefit from panitumumab treatment [22]. These data resulted in an update of the registration label for panitumumab and cetuximab to restrict their use only for patients with non-mutated *KRAS*. Currently, we are lacking any data on the efficacy of bevacizumab treatment in these more well-defined patient populations. A subanalysis of the MAX study [23], determining the influence of *KRAS* and *BRAF* mutational status among patients treated with capecitabine in combination with bevacizumab, found no correlation between *KRAS* mutation and OS or bevacizumab treatment response, among patients with mCRC. On the contrary, mutated *BRAF* was associated with a worse prognosis in OS, but was not predictive of bevacizumab treatment response [24]. The FIRE-3 study compared the effectiveness of FOLFIRI with cetuximab and FOLFIRI with bevacizumab [25]. The primary study end point, treatment response, showed no significant differences between treatment arms in the studied population. With regard to secondary end points, TTP was not significantly different (10.0 and 10.3 months, respectively), whereas median

OS was statistically significant (28.7 months [FOLFIRI + cetuximab] versus 25.0 months [FOLFIRI + bevacizumab]). Importantly, after initiation of this study an amendment to the study protocol, restricting enrolment to only patients with wild-type *KRAS*, was accepted and applied. From a total of 735 enrolled patients, 592 patients were wild-type *KRAS* [25]. The results of our analysis are closer to those obtained in the cetuximab treatment arm. The CALGB/SWOG 80405 trial compared the effectiveness of combination chemotherapy (FOLFIRI or FOLFOX) with bevacizumab or cetuximab in patients with *KRAS* wild-type metastatic colorectal carcinoma [26]. OS for both arms (chemotherapy with cetuximab or chemotherapy with bevacizumab) was similar (29.9 and 29.0 months, respectively), as was the PFS (10.8 and 10.4 months, respectively) [26]. These data clearly demonstrated the effectiveness of bevacizumab in non-mutated *KRAS* tumors. Despite the conflicting results in terms of OS between FIRE and CALGB/SWOG 80405, the latter study established a new benchmark for OS in terms of extending survival beyond 29 months. The results from our analysis are in accordance with those from the CALGB/SWOG trial. These available data demonstrate the effectiveness of bevacizumab treatment in combination with chemotherapy in patients with *KRAS* wild-type tumors, comparable with the efficacy of anti-EGFR antibodies with chemotherapy for the same group of patients. Hence, bevacizumab offers a new treatment alternative to cetuximab or panitumumab in non-mutated *KRAS* patients.

Conclusion & future perspective

This large retrospective analysis evaluated the effectiveness of bevacizumab in combination with chemotherapy in patients with *KRAS* wild-type mCRC. Our results are consistent with other published studies with regard to the effectiveness and safety of combination therapy with bevacizumab, irrespective of *KRAS* mutational status. Data from this analysis confirm the effectiveness of bevacizumab, even in a subgroup of patients with wild-type *KRAS*, which is comparable with the effectiveness of anti-EGFR antibodies [4]. Thus, in *KRAS* wild-type patients,

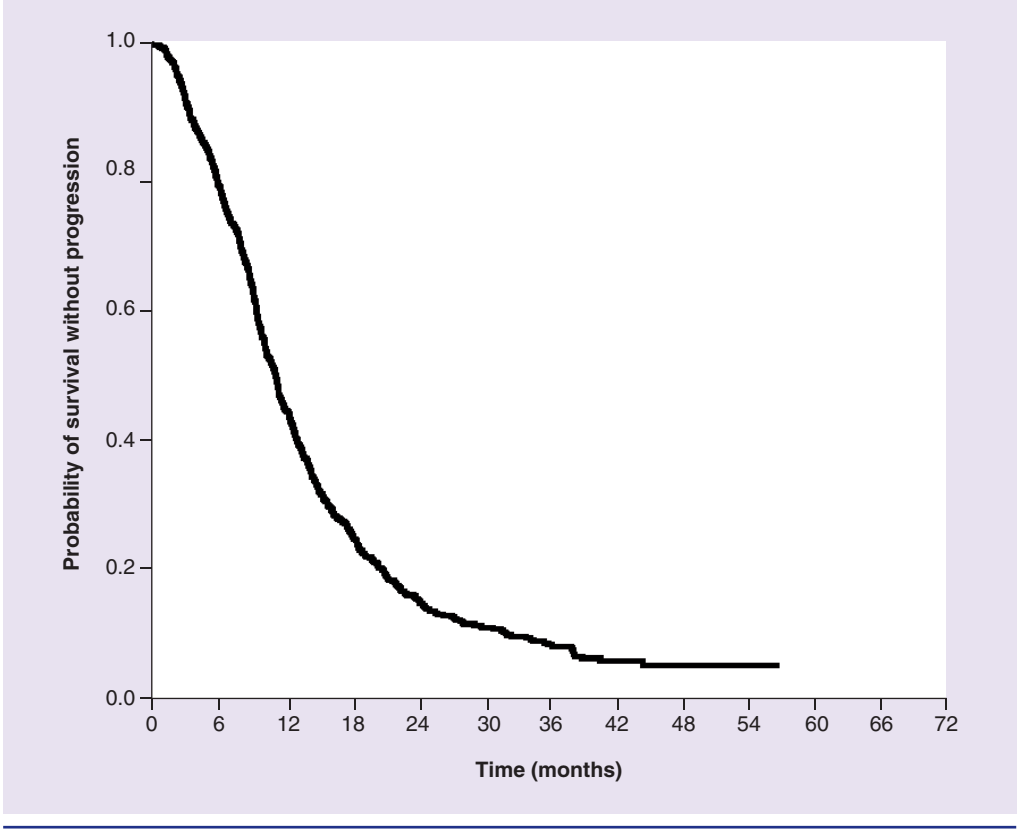

Figure 2. Progression-free survival (time from first-line bevacizumab treatment initiation until disease progression or death).

the decision between which monoclonal antibody to use has reached the level of choosing between chemotherapy regimens based solely on their different toxicological profiles. With regard to future decision-making, ongoing research into expanded *RAS* analysis and the search for predictive biomarkers for bevacizumab, can specify more precisely the subgroups of patients which would benefit mostly from this targeted therapy.

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Ethical conduct

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

EXECUTIVE SUMMARY

Aim of the study

- This retrospective analysis evaluated the effectiveness of combination therapy with bevacizumab and chemotherapy in the first-line treatment of patients with wild-type *KRAS* metastatic colorectal cancer (mCRC) in the Czech Republic.

Patients & methods

- The study included patients from the CORECT registry with wild-type *KRAS* mCRC who initiated bevacizumab treatment between 2008 and 2012.
- RECIST criteria were used to assess treatment response, and the main effectiveness measures were overall survival (OS) and progression-free survival (PFS).

Results

- A total of 981 patients with mCRC received first-line chemotherapy (most commonly FOLFOX, 48.6%), for a median of 7.5 months.
- Complete remission, partial response and stable disease were seen in 12.6, 34.0 and 35.9% of patients, respectively; median PFS was 11.3 months (95% CI: 10.7–11.8) and median OS was 28.4 months (95% CI: 26.2–30.6).
- The most common adverse events were thromboembolic disease (4%) and hypertension (3.5%).

Conclusion

- This large retrospective study demonstrates the effectiveness of bevacizumab in combination with chemotherapy in patients with *KRAS* wild-type mCRC.

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