Cetuximab-based or bevacizumab-based first-line treatment in patients with *KRAS* p.G13D-mutated metastatic colorectal cancer: a pooled analysis

Dominik Paul Modest[a], Anke Reinacher-Schick[c,d], Sebastian Stintzing[a], Clemens Giessen[a], Andrea Tannapfel[e], Ruediger Paul Laubender[b], Thomas Brodowicz[g,h], Regina Knittelfelder[g], Damir Vrbanec[i], Wolff Schmiegel[c,d,f], Volker Heinemann[a] and Christoph C. Zielinski[g,h]

***KRAS* p.G13D mutant metastatic colorectal cancer (mCRC) has been identified as representing a cetuximab-sensitive subtype of *KRAS* mutant mCRC. This analysis aims to answer the question of whether first-line treatment of p.G13D mCRCs should include cetuximab or bevacizumab. Fifty-four patients with p.G13D mutant mCRC were pooled in this analysis. All patients underwent systemic first-line treatment with a fluoropyrimidine and oxaliplatin/irinotecan that was combined with either cetuximab or bevacizumab. The analysis of cetuximab-based and bevacizumab-based regimens in mCRC patients with p.G13D-mutated tumours indicated comparable data for the overall response rate (58 vs. 57%) and progression-free survival (8.0 vs. 8.7 months; hazard ratio: 0.96, *P*=0.9). Overall survival (OS) was 20.1 months in patients treated with cetuximab-based first-line therapy compared with 14.9 months in patients receiving bevacizumab-containing regimens (hazard ratio: 0.70, *P*=0.29). Logistic regressions modelling OS revealed oxaliplatin-based first-line treatment to correlate with a poor outcome (*P*=0.03). Moreover, a strong trend in favour of capecitabine compared with infusional 5-FU (*P*=0.06) was observed. Response to treatment correlated with OS in patients receiving cetuximab-based, but not bevacizumab-based regimens. This retrospective pooled analysis suggests comparable efficacy of cetuximab-based and bevacizumab-based first-line therapy in patients with p.G13D mutant mCRC. The combination with capecitabine and irinotecan was associated with a more favourable outcome compared with infusional 5-FU and oxaliplatin. *Anti-Cancer Drugs* 23:666–673 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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[a]Department of Medicine III, Klinikum Grosshadern, [b]Institute of Medical Informatics, Biometry, and Epidemiology, University of Munich, Munich, Germany, [c]Department of Internal Medicine, Knappschaftskrankenhaus, [d]Center for Clinical Studies in Oncology, [e]Institute of Pathology, Ruhr-University, [f]Department of Gastroenterology and Hepatology, Berufsgenossenschaftliche Kliniken Bergmannsheil Bochum, Germany, [g]CECOG, Central European Cooperative Oncology Group, [h]Department of Medicine I, Clinical Division of Oncology, Medical University of Vienna, Vienna, Austria and [i]KBC Rebro, Oncology Department, Zagreb, Croatia

Correspondence to Dr Dominik Paul Modest, MD, Department of Medicine III, Klinikum Grosshadern, Marchioninistrasse 15, University of Munich, Munich, Germany
Tel: +49 897 0950; fax: +49 897 095 5256;
e-mail: dominik.modest@med.uni-muenchen.de

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Introduction

Mutations of the Kirsten-RAS (*KRAS*) protein are reported to occur in ~40% of metastatic colorectal cancers (mCRC). These mutations of *KRAS* are detected in codons 12 (~80%) and 13 (~20%) and far less frequently in codons 61 and 146 [1–4]. *KRAS* mutations of codon 13 (p.G13D) have been shown to be associated with a more aggressive biology in mCRC compared with other *KRAS* mutations [5–8].

Mutations in the *KRAS* proto-oncogene have been identified as determinants of a poor response to anti-epidermal growth factor receptor (EGFR) antibodies such as cetuximab and panitumumab, leading to an exclusion of affected mCRC patients from anti-EGFR therapy [9–18]. Several other studies did not identify the *KRAS* wild type to be a powerful predictor of response to anti-EGFR antibodies [19–21]. However, *KRAS* mutant mCRCs are generally treated with bevacizumab-based regimens as the activity of bevacizumab is considered to be independent of *KRAS* mutation [22].

A new aspect in terms of treatment of *KRAS*-mutated mCRC emerged when *KRAS* codon 13 (p.G13D)-mutated mCRC was reported to represent a cetuximab-sensitive subspecies. Data indicating a benefit of cetuximab-based regimens in p.G13D-mutated tumours were shown in first-line treatments as well as in chemorefractory cases [8,23]. These findings were complemented by an analysis of *KRAS* subgroups in three randomized phase III trials with panitumumab. In contrast to data from the OPUS trial [23], Peeters and colleagues reported a significant disadvantage in terms of overall survival (OS) in patients with *KRAS* p.G13D mutant mCRC when FOLFOX was combined with panitumumab as first-line therapy in comparison with FOLFOX alone. However,

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the same population showed a very strong trend toward longer OS in patients treated with FOLFIRI plus panitumumab as a second-line therapy compared with patients who received FOLFIRI alone. No trend for panitumumab in patients with *KRAS* p.G13D mutant mCRC was observed in a trial that compared panitumumab versus placebo as monotherapy [24].

As p.G13D-mutated mCRC represents an aggressive type of tumour correlating with a short survival [8,23], the choice of first-line treatment may play a crucial role in the outcome of affected patients.

In the present analysis, we investigate patients with mCRC characterized by a *KRAS* p.G13D mutation. The study aims to analyse the question of whether mCRCs with the *KRAS* p.G13D mutation should be treated with cetuximab-based or bevacizumab-based first-line treatment. As conflicting data concerning the application of oxaliplatin or irinotecan in combination with EGFR-antibodies in patients with *KRAS* p.G13D mutant mCRC have been reported, we investigated the role of chemotherapeutic agents to identify favourable options of first-line treatment. Furthermore, we evaluated the prognostic value of the radiologic response to first-line treatment for progression-free survival (PFS) and OS in cetuximab-based versus bevacizumab-based regimens.

Methods

Patients

The present analysis investigated 54 mCRC patients with a confirmed *KRAS* mutation of codon 13 (p.G13D) who received first-line therapy for mCRC. Patients were treated within the AIO KRK-0104-NCT00254137 (nine patients) [19], AIO KRK-0306-NCT00433927 (19 patients), AIO KRK-0604 (four patients) [24]. The CECOG trial-NCT00286130 [25] (14 patients) or outside a study within an observational cohort at the medical department III, University of Munich (eight patients). A total of 33 patients received cetuximab-based first-line therapy, whereas 21 patients were treated with bevacizumab-containing regimens. The protocols of the clinical trials were approved by an independent ethics committee and governmental authorities. The trials were conducted in accordance with the Declaration of Helsinki (1996). All patients treated within a clinical trial provided written and oral informed consent to be treated within the respective study.

KRAS mutation detection

KRAS tests were performed as described in previous papers [1,18,26].

Treatment schedules

The AIO KRK-0104 study was designed as an open-label, randomized phase II study as reported previously by Moosmann *et al.* [19]. It was conducted at 35 centres in Germany. In both study arms, cetuximab was given at an initial dose of 400 mg/m^2 as a 120-min infusion, followed by weekly infusions of 250 mg/m^2 over 60 min. Patients in arm A received chemotherapy with CAPIRI (i.e. oral capecitabine 800 mg/m^2 twice daily on days 1 through 14, followed by a 1-week rest period plus irinotecan 200 mg/m^2 as a 30-min intravenous infusion on day 1). In patients older than 65 years, doses were further reduced by 20%. Patients in arm B received chemotherapy with CAPOX (i.e. capecitabine 1.000 mg/m^2 twice daily on days 1 through 14, followed by a 1-week rest period plus oxaliplatin 130 mg/m^2 as a 120-min intravenous infusion on day 1). Treatment cycles were repeated every 3 weeks until disease progression or unacceptable toxicity occurred [19].

The AIO KRK-0604 study was designed as an open-label, randomized phase II study as reported previously by Reinacher-Schick *et al.* [25]. Patients were randomized to one of the following regimens: bevacizumab 7.5 mg/kg bodyweight plus CAPOX (oxaliplatin 130 mg/m^2 on day 1 + capecitabine 1000 mg/m^2 on days 1–14) every 3 weeks or bevacizumab 7.5 mg/kg bodyweight plus CAPIRI (irinotecan 200 mg/m^2 on day 1 + capecitabine 800 mg/m^2 on days 1–14) every 3 weeks. Treatment was provided until progression of the tumour was evident or unacceptable toxicity occurred [25].

The ongoing AIO KRK-0306 study was designed as a randomized study and is presently being conducted at 177 centres in Germany and Austria. This trial compares FOLFIRI plus cetuximab with FOLFIRI plus bevacizumab. The study was closed for patients with *KRAS* mutant mCRC in 2009. Therefore, only those patients with *KRAS*-mutated mCRC could be analysed in the present analysis. FOLFIRI was applied as reported previously by Tournigand *et al.* [27]. The regimen was repeated every 2 weeks. Cetuximab was given at an initial dose of 400 mg/m^2 as a 120-min infusion, followed by weekly infusions of 250 mg/m^2 over 60 min. Bevacizumab was given at 5 mg/kg bodyweight on day 1 of each treatment cycle. Treatment was performed until disease progression or unacceptable toxicity occurred.

The CECOG study was a two-arm randomized multicentre, open-label, parallel-group phase II study involving 28 participating centres across 13 countries (CECOG/CORE1.2.001). Eligible patients were centrally randomized 1 : 1, using a minimization technique, stratifying patients according to study site, the number of organs involved and prior neoadjuvant/adjuvant therapy. Patients received cetuximab (400 mg/m^2 initial infusion day 1, then 250 mg/m^2 weekly), and then either in arm A: oxaliplatin (day 1 100 mg/m^2) with FA [400 mg/m^2 (racemic) or 200 mg/m^2 (L-form)] plus 5-FU (400 mg/m^2 bolus plus 2400 mg/m^2 as a 46-h continuous infusion) every 2 weeks (FOLFOX6), or in arm B: irinotecan (180 mg/m^2) with the 5-FU/FA regimen described (FOLFIRI) [25].

Eight patients of an observational cohort of the University of Munich were included in this analysis. These patients received FOLFIRI plus bevacizumab (four cases) according to the FIRE 3 protocol or FOLFOX6 as described above plus bevacizumab (four cases). Bevacizumab was given at 5 mg/kg bodyweight on day 1 of each treatment cycle.

End Points

The present investigation was performed as an exploratory retrospective pooled analysis. Radiological tumour response (CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease) was assessed according to the RECIST 1.0 criteria. Response evaluation was performed at 6–12-week intervals. PFS was defined as the interval between randomization and first documentation of progression or death; OS was calculated as the time between randomization and death due to any reason. Patients alive were censored at the last time point of patient contact.

Statistical analysis

Data were summarized by properly chosen measures of location and spread for continuous variables and by proportions for discrete variables. Fisher's exact test was applied to estimate differences in response or baseline characteristics. Differences in OS and PFS were estimated using the Kaplan–Meier method and were compared between the groups using log-rank tests. For modelling OS, we used the Cox proportional hazards regression model, where covariates were selected from a set of candidate variables [study, 5-FU vs. capecitabine, irinotecan vs. oxaliplatin, cetuximab vs. bevacizumab, sex, Eastern Cooperative Oncology Group (ECOG)-status 0 + 1 vs. 2, primary tumour site, liver metastasis, lung metastasis, peritoneal metastasis, other metastasis] by relying on the backward elimination algorithm using likelihood ratio tests. We used complete cases and the variable selection level for all variables was set to 0.05. For the final model the hazard ratios, the 95% confidence interval and the *P*-value resulting from Wald tests of the selected covariates were estimated. All statistical analyses were performed using R (version 2.13.0; The R Foundation for Statistical Computing/R Development Core Team, GNU General Public License) and PASW (version 18; IBM, New York, New York, USA). All statistical tests were performed two sided and a *P*-value of less than 0.05 was considered as statistically significant.

Results

Study population

This exploratory analysis included 54 patients who received first-line treatment for mCRC. The characteristics of the patients analysed in this study were not significantly different in terms of age, sex, ECOG status or primary disease sites when compared between the different subgroups (cetuximab-based or bevacizumab-based first-line therapy) (Table 1).

Table 1 Patient characteristics

	n (%)		
	Cetuximab-based first-line treatment	Bevacizumab-based first-line treatment	*P*-value
Number of patients	33	21	
Age years (range)			
Median	64	65	0.78
Range	35–76	40–75	
Sex			
Female	11 (33)	9 (43)	0.57
Male	22 (67)	12 (57)	
ECOG			
0–1	31 (94)	20 (95)	0.50
2	2 (6)	1 (5)	
Primary tumour site			
Colon	23 (70)	12 (71)	1.00
Rectum	10 (30)	5 (29)	
Not assessed		4	
Disease site			
Liver	28 (85)	19 (90)	0.69
Lung	16 (48)	8 (47)	1.00
Peritoneum	3 (9)	2 (12)	1.00
Other	13 (39)	4 (24)	0.35
First-line chemotherapy			
Capecitabine	9 (27)	4 (19)	0.54
5-FU	24 (73)	17 (81)	
First-line chemotherapy			
Irinotecan	21 (64)	15 (71)	0.77
Oxaliplatin	12 (36)	6 (29)	

Characteristics of patients. Percentages are on the basis of nonmissing data, *P*-values given for age: independent-samples median test, other parameters: Fisher's exact test.
EGOC, Eastern Cooperative Performance Score.

Impact of targeted agents on efficacy of first-line treatment in *KRAS* P.G13D-mutated mCRCs

Thirty-three patients in our analysis received cetuximab-based first-line treatment, whereas 21 patients were treated with bevacizumab-based regimens. The overall response was similar for both strategies, reaching 58% in cetuximab-based and 57% in bevacizumab-based therapies ($P = 1.00$).

Progression-free survival reached 8 months in patients treated with the cetuximab-based regimens compared with 8.7 months in the bevacizumab-based regimens ($P = 0.9$) (Table 2, Fig. 1).

Impact of targeted agents on overall survival

OS in our *KRAS* p.G13D cohort was 20.1 months in patients receiving cetuximab-based therapies and 14.9 months in patients receiving bevacizumab-based therapies ($P = 0.29$) (Table 2, Fig. 2).

Impact of response on PFS and OS in *KRAS* P.G13D-mutated mCRC

Responders to first-line therapy showed a longer PFS (8.4 months responders vs. 5.8 months nonresponders, $P = 0.19$) and OS (21.1 months responders vs. 11.0 months nonresponders, $P = 0.47$) in cetuximab-based therapies. No impact of response on PFS (8.3 months responders vs. 9.4 months nonresponders, $P = 0.81$) and OS (13.6 months responders vs. 16.3 months nonresponders, $P = 0.44$) was observed in the bevacizumab-based regimen (Table 3).

Study treatment versus nonstudy treatment influencing PFS and OS of patients with *KRAS* P.G13D mutant mCRC receiving the bevacizumab-based regimen

Patients treated in accordance with ongoing study protocols at the Medical Department III at the hospital of the University of Munich with bevacizumab-based regimens showed a slightly superior outcome compared with patients treated with bevacizumab-containing protocols within the AIO KRK 0306 trial or AIO KRK-0604 trial. PFS reached 9.4 months for patients treated off-study, compared with 8.3 months for patients treated within a study. OS was 16.0 months for nonstudy participants and 13.6 months in patients treated within a clinical trial (data not shown in a table).

Logistic regressions modelling overall survival in patients with P.G13D mutant mCRC

Logistic regressions modelling OS showed that liver and peritoneal metastasis as well as ECOG 2 status correlated significantly with poor survival in our study cohort. In terms of treatment parameters, a significant risk of death was observed in patients treated with the oxaliplatin-containing first-line regimen ($P = 0.03$). Moreover, a strong trend ($P = 0.06$) of a reduction in the risk of death was found in favour of capecitabine when compared with infusional 5-FU. The targeted agent (cetuximab vs. bevacizumab) did not show a trend in this analysis (Table 4).

Discussion

When the *KRAS* mutation became the biomarker for directing anti-EGFR agents in mCRC, all patients bearing *KRAS*-mutated tumours were excluded from therapies containing cetuximab or panitumumab [9–18]. Interestingly, patients with *KRAS* mutant mCRC treated within the AIO KRK 0306 trial showed a favourable OS when treated within the cetuximab arm compared with the bevacizumab arm (22.7 vs. 18.7 months, $P = 0.55$). Therefore, a certain activity of anti-EGFR agents in patients with *KRAS* mutant mCRC might be suspected [28]. These findings are complemented by reports suggesting the *KRAS* p.G13D mutation to be associated with cetuximab sensitivity [8,23]. In terms of these reports and the poor prognosis of p.G13D-mutated mCRC [5–8,23], all treatment options should be taken into account for these patients. Whereas anti-EGFR agents are used according to the *KRAS* mutation status, bevacizumab is given independently of the *KRAS* mutation, as it is assumed to be active in all subtypes of mCRC [22]. Unfortunately, to our knowledge, no data on the subtypes of *KRAS* mutation correlated with the outcome of patients receiving bevacizumab-based first-line treatment are available yet.

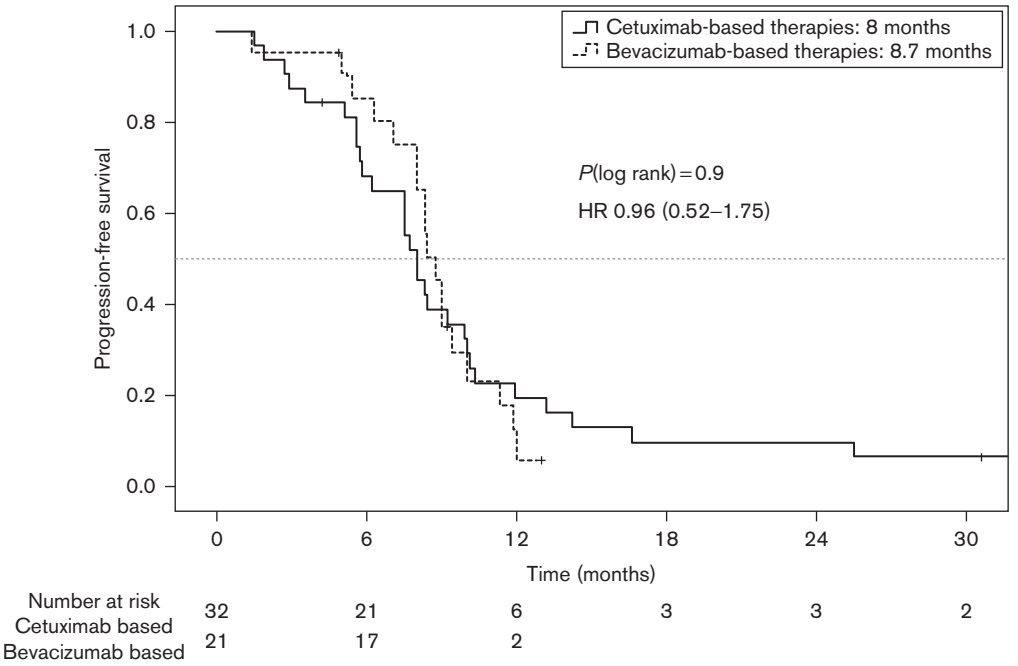
Within our study population, the overall response rate (ORR) in patients with p.G13D-mutated mCRC reached 58% in the cetuximab-based therapies compared with 57% in bevacizumab-based first-line therapies. Response in the cetuximab-based group compares with 40.5% ORR reported from a pooled analysis of the OPUS trial and the CRYSTAL trial [23]. Patients with *KRAS* mutant mCRC showed an ORR of 43% in a translational study

Table 2 Treatment efficacy of first-line regimens in p.G13D-mutated metastatic colorectal cancer

	Cetuximab-based first-line treatment ($n = 33$)	Bevacizumab-based first-line treatment ($n = 21$)	*P*-value	Hazard ratio (95% CI)
ORR (CR + PR)	58%	57%	1.00	
DCR (CR + PR + SD)	91%	95%	1.00	
PFS (months) 95% CI	8.0 (6.9–9.1)	8.7 (7.9–9.5)	0.9	0.96 (0.52–1.75)
OS (months) 95% CI	20.1 (14.4–25.8)	14.9 (10.3–19.5)	0.29	0.70 (0.36–1.35)

Percentages are on the basis of nonmissing data. *P*-values ORR and DCR: Fisher's exact test. *P*-values PFS and OS: log rank. Hazard ratio: Cox regression.
CI, confidence interval; CR, complete remission; DCR, disease control rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial remission; SD, stable disease.

Fig. 1



Progression-free survival of patients with p.G13D mutant mCRC receiving either cetuximab-based or bevacizumab-based first-line treatment. HR, hazard ratio; mCRC, metastatic colorectal cancer.

of bevacizumab-based first-line treatment, giving no differentiation between *KRAS* p.G13D and other *KRAS* mutations [22].

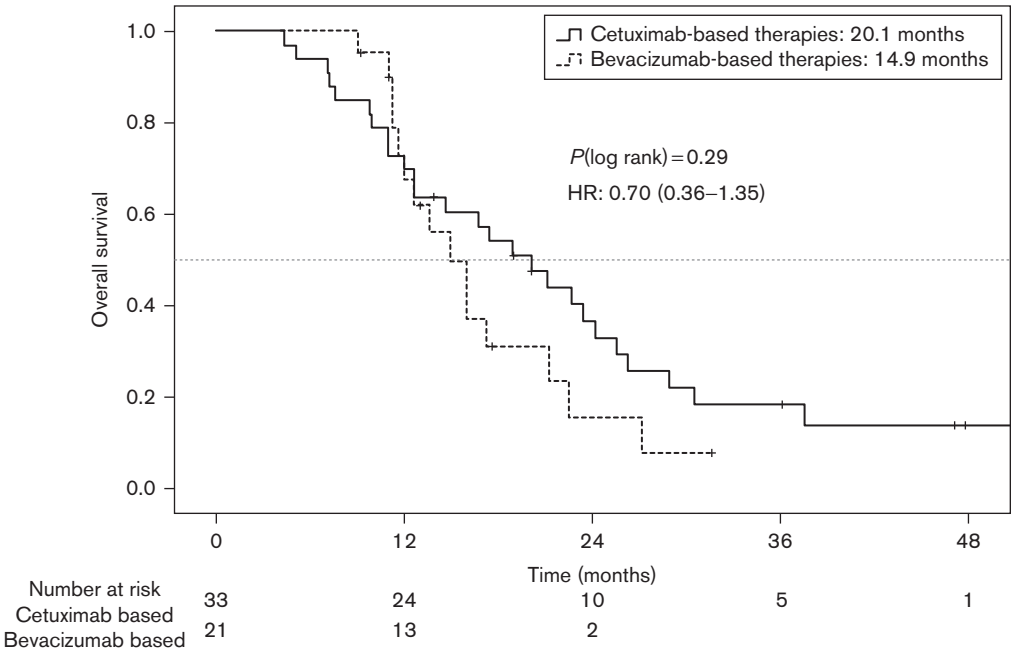
PFS reached comparable durations in cetuximab-based and bevacizumab-based regimens within this analysis (8.0 vs. 8.7 months). These findings compare favourably to the pooled analysis of p.G13D mutant mCRC in the OPUS trial and the CRYSTAL trial (7.4 months) [23] as well as to the PFS reported for patients with the *KRAS* mutant tumours undergoing bevacizumab-based treatments (9.3 months) [22].

Whereas patients undergoing cetuximab-containing regimens showed an OS of 20.1 months, patients receiving bevacizumab-containing treatments showed an OS of 14.9 months. This outcome in cetuximab first-line-treated patients appears to be slightly superior compared with those reported from CRYTSAL and OPUS (15.4 months) [23]. OS in patients with p.G13D-mutated mCRC undergoing bevacizumab-based first-line treatment was 14.9 months in our pooled analysis and compares to 19.9 months reported for *KRAS* mutant mCRC without differentiation of the *KRAS* subtype treated with IFL plus bevacizumab [22].

The absence of any prognostic effect of initial response to first-line treatments containing bevacizumab as seen in this pooled analysis has not been described before. It is known that the p.G13D mutation in mCRC correlates with high S-phase fractions [5]. Therefore, an aggressive biology might be suspected and may possibly explain the minor role of response in this special subtype of mCRC. Moreover, a response-independent benefit of bevacizumab has been reported [29]. Nevertheless, response was linked to a more favourable outcome in the cetuximab-based regimens in our cohort, although no significance was reached. As cetuximab targets the tumour cells themselves, the initial reduction in tumour size could be associated with a clinical benefit in this cohort, showing a high rate of multiorgan involvement [5–7].

Modelling OS by a backward elimination algorithm revealed oxaliplatin instead of irinotecan (0.03) as a treatment option to correlate with poor survival in our cohort. This finding is in agreement with previous reports on oxaliplatin-based treatment of *KRAS* mutant mCRC [26,30,31] and specifically an analysis of panitumumab-based trials. Peeters *et al.* [24] described a significant disadvantage in OS in patients with *KRAS* p.G13D mutant mCRC who received FOLFOX plus panitumumab instead of FOLFOX alone. In contrast, patients with *KRAS* p.G13D mutant mCRC treated within the 20050181 trial seemed to benefit when panitumumab was added to FOLFIRI as second-line therapy [24]. However, Tejpar *et al.* [23] reported a benefit from cetuximab in patients with p.G13D mutant mCRC in both an oxaliplatin-based and an irinotecan-based

Fig. 2



Overall survival of patients with p.G13D mutant mCRC receiving either cetuximab-based or bevacizumab-based first-line treatment. HR, hazard ratio; mCRC, metastatic colorectal cancer.

Table 3 Progression-free and overall survival depending on the overall response rate in patients with *KRAS* p.G13D mutant mCRC

Therapy	Response (ORR)	*N*	PFS (months) (95% CI)	OS (months) (95% CI)
Cetuximab-based first-line treatment	Responder	19	8.4 (6.5–10.3)	21.1 (15.7–26.5)
	Nonresponder	14	5.8 (2.3–9.3)	11.0 (0–24.9)
	Response not assessable	3		
	P-value		0.19	0.47
	HR (95% CI)		0.61 (0.29–1.29)	0.74 (0.32–1.69)
Bevacizumab-based first-line treatment	Responder	12	8.3 (7.8–8.8)	13.6 (8.8–18.4)
	Nonresponder	9	9.4 (7.5–11.6)	16.0 (12.8–19.2)
	P-value		0.81	0.44
	HR (95% CI)		1.12 (0.43–2.90)	1.50 (0.54–4.18)

CI, confidence interval; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Table 4 Multivariate analysis modelling overall survival in patients with *KRAS* p.G13D mutant mCRC

Variables	*N*	Hazard ratio (95% CI)	*P*-value (Wald-test)
ECOG 2 vs. ECOG 0/1	50	6.95 (1.68–28.90)	0.008
Liver metastasis present/not	50	6.29 (1.67–23.68)	0.007
Peritoneal metastasis present/not	50	8.76 (2.70–28.43)	0.0003
Bevacizumab vs. cetuximab	50	0.78 (0.37–1.67)	0.52
Capecitabine vs. 5-FU	50	0.40 (0.15–1.06)	0.06
Oxaliplatin vs. irinotecan	50	2.38 (1.09–5.21)	0.03

Logistic regressions, only complete cases were included; hazard ratio>1 means that the first parameter is more likely to be coexisting.
CI, confidence interval; ECOG, Eastern Cooperative Performance Score.

regimen. It is important to note that their analysis was limited by the small number of patients receiving oxaliplatin-based chemotherapy. Although no significance was reached in logistic regressions modelling OS on capecitabine versus 5-FU treatment, a strong trend favouring capecitabine was observed ($P = 0.06$). No comparable data on oral versus infusional 5-FU are available yet. Explanations for this finding are therefore speculative in nature. Nevertheless, the high rate of mitotic cells observed in earlier studies [5] may be an interesting characteristic of p.G13D mutant tumours in terms of these data. Continuous chemotherapy possibly

represents an option to inhibit growth more effectively in this highly aggressive subtype of mCRC.

Our findings might be biased by the heterogenous chemotherapies applied, together with the targeted agents, and by heterogenous applications of second-line treatments, which are not reported for a substantial number of patients analysed in this paper. Potentially, the number of patients who received all available drugs suitable for p.G13D-mutated mCRC (fluoropyrimidine, irinotecan, oxaliplatin, bevacizumab and cetuximab) might be higher within the group of first-line cetuximab-treated patients. This analysis is limited by its retrospective nature and the number of patients included. Prospectively planned translational trials in patients with p.G13D mutant mCRC are needed.

To our knowledge, this is the first analysis of mCRC focussing on p.G13D mutant tumours comparing different strategies of first-line treatment including bevacizumab-treated patients. This retrospective pooled analysis suggests that cetuximab-based first-line therapy in p.G13D mutant mCRC might represent an active treatment. Regarding chemotherapy, irinotecan and capecitabine appear as favourable partners.

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Conflicts of interest

C.C.Z., Advisory boards: Merck-Serono, Roche, Pfizer; V.H., Advisory boards, Honoraria, lectures, travel support: Merck-Serono, Roche; T.B., Lectures: Merck-Serono, Roche; W.S., Honoraria: Merck, Roche, Abbot, Pfizer, Astra-Zeneca, Amgen, Falk, Advisory boards: Amgen, Roche, Astra-Zeneca, Research funding: Roche, Sanofi-Aventis, Pfizer, Travel support: Roche, Merck; A.R.S., Honoraria: Amgen, Pfizer, Roche, Sanofi-Aventis, Travel support: Amgen, Sanofi-Aventis, Roche, Advisory boards: Roche, Amgen, Pfizer; A.T., Honoraria: Amgen, Pfizer, Roche, Merck, Sanofi-Aventis, Research support: Roche, Sanofi-Aventis; C.G., Travel support: Roche; S.S., Travel support: Merck-Serono; D.P.M., Travel support: Merck-Serono, Honoraria: Amgen; R.P.L., Travel support: Merck-Serono; D.V., no conflicts of interest; R.K., no conflicts of interest.

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