Exploratory pooled analysis evaluating the effect of sequence of biological therapies on overall survival in patients with RAS wild-type metastatic colorectal carcinoma

Marc Peeters,1 Frédéric Forget,2 Meinolf Karthaus,3 Manuel Valladares-Ayerbes,4 Alberto Zaniboni,5 Gaston Demonty,6 Xuesong Guan,7 Fernando Rivera8

ABSTRACT

Background The aim of this study was to evaluate the optimal sequence of targeted therapies (epidermal growth factor receptor inhibitors (EGFRi) and vascular endothelial growth factor inhibitors (VEGFi)) combined with chemotherapy, in patients with RAS wild-type (WT) metastatic colorectal carcinoma (mCRC). Exploratory analyses of overall survival (OS) for patients treated with either first-line panitumumab (EGFRi) and second-line VEGFi therapy, or first-line bevacizumab (VEGFi) and second-line EGFRi, were conducted.

Methods Patients from PEAK (NCT00819780), PRIME (NCT00364013) and Study 181 (NCT00339183), with RAS WT or RAS WT/BRAF WT tumours, were included in the analyses. OS data were pooled for patients receiving first-line panitumumab (PEAK and PRIME) or first-line bevacizumab (PEAK and 181), followed by second-line VEGFi or EGFRi, respectively.

Results Overall, 104 RAS WT patients were included (n=66 panitumumab→VEGFi, n=38 bevacizumab→EGFRi). At the time of final data analysis, 63.6% versus 92.1% of patients in the panitumumab→VEGFi versus bevacizumab→EGFRi arms had died; median OS was 36.8 versus 27.8 months, respectively (HR 0.65; 95% CI 0.42 to 1.03). The OS HR for patients with RAS WT/BRAF WT mCRC overall was 0.58 (95% CI 0.36 to 0.95) and was 0.56 (95% CI 0.30 to 1.04) in those with left-sided tumours.

Conclusion Although numbers are small, these exploratory analyses suggest a trend towards improved OS for first-line panitumumab plus chemotherapy followed by second-line VEGFi, compared with first-line bevacizumab followed by second-line EGFRi in patients with RAS WT and RAS WT/BRAF WT mCRC. Large prospective randomised trials are needed to further evaluate the optimum sequence of EGFRi/VEGFi in mCRC.

INTRODUCTION

Recent advances in the treatment landscape for metastatic colorectal carcinoma (mCRC) have led to significant improvements in clinical outcomes. In particular, the addition of targeted biological therapies to chemotherapy-based regimens in the first-line setting has increased median overall survival (OS) to 25–30 months for patients with mCRC.1-5 Current first-line treatment options for these patients include 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX) or folinic acid, 5-fluorouracil and irinotecan (FOLFIRI)

Key questions

What is already known about this subject?

► Two classes of targeted therapy are available for upfront treatment of patients with RAS wild-type (WT) metastatic colorectal carcinoma (mCRC): epidermal growth factor receptor inhibitors (EGFRi) and vascular endothelial growth factor inhibitors (VEGFi).

► Results from the available head-to-head studies and meta-analyses generally favour first-line treatment with an EGFRi in patients with RAS WT mCRC, with some authors suggesting that the sequence of biological therapies may be an important factor.

What does this study add?

► Results of the current exploratory pooled analysis suggest a potential survival benefit for patients with RAS WT mCRC who receive first-line EGFRi treatment followed by second-line VEGFi therapy, compared with the reverse sequence.

► The observed benefits appear greatest in patients with RAS WT/BRAF WT mCRC and those with left-sided tumours.

How might this impact on clinical practice?

► These exploratory data provide further evidence supporting upfront EGFRi treatment followed by second-line treatment with a VEGFi in patients with RAS WT mCRC.

► The results of prospective trials evaluating optimal treatment sequencing in patients with RAS WT mCRC are awaited.
chemotherapy schedules combined with either epidermal growth factor receptor inhibitors (EGFRi: panitumumab and cetuximab) or the vascular endothelial growth factor inhibitor (VEGFi) bevacizumab. The cytotoxic triplet FOLFIRI can also be used with VEGFi in selected fit patients. Briefly, PEAK was a phase III PRIME study compared first-line panitumumab (6mg/kg every 2 weeks) plus FOLFIRI arm; 29 (76%) in the VEGFi arm. All patients provided signed informed consent before any study-related procedures were performed. No formal consent was required for these retrospective analyses.

RESULTS
Patients
Overall, 104 patients with RAS WT mCRC from three trials received the specified first-line and second-line treatment sequences of interest and so were included in these exploratory analyses (n=35 from PRIME, n=40 from PEAK, n=29 from 181). Of these patients, 66 were treated with first-line panitumumab followed by second-line VEGFi, 38 received first-line bevacizumab followed by second-line EGFRi (figure 1). A total of 93 patients with RAS WT/BRAF WT disease were included, of whom 58 received first-line panitumumab followed by second-line VEGFi, and 35 received first-line bevacizumab followed by second-line EGFRi. Patients with RAS WT mCRC and all those with RAS WT/BRAF WT tumours who received first-line panitumumab (PEAK and PRIME studies) followed by second-line VEGFi treatment, as well as first-line bevacizumab (PEAK and 181 studies), followed by second-line treatment with an EGFRi. Patients receiving any other sequence of agents, including those who had received both biological agents (ie, a VEGFi and an EGFRi) but not specifically as first-line and second-line therapies, were excluded. OS was also analysed for patients with left-sided RAS WT and RAS WT/BRAF WT tumours receiving first-line panitumumab followed by second-line VEGFi or first-line bevacizumab followed by second-line EGFRi treatment. Primary tumours located in the caecum to transverse colon were coded as right sided. Tumours located from the splenic flexure to rectum were categorised as left sided.

The Kaplan-Meier method was used to analyse OS (from time of treatment with first-line biologic until death) for each treatment sequence. HRs for OS, and associated 95% CIs, were calculated using a Cox proportional hazards model. All analyses are descriptive.

All patients provided signed informed consent before any study-related procedures were performed. No formal consent was required for these retrospective analyses.

METHODS
Data from patients enrolled in the PEAK (NCT00819780), PRIME (Panitumumab Randomized trial In combination with chemotherapy for Metastatic colorectal cancer to determine Efficacy: NCT00364013), and 181 (NCT00339183) studies, whose tumours were RAS WT (for KRAS and NRAS exons 2 (codons 12 and 13), exon 3 (codons 59 and 61) and exon 4 (codons 117 and 146)) or RAS WT/BRAF WT (WT at BRAF exon 15 (codon 600)), were included in these exploratory analyses. The study designs of these trials have been published previously. Briefly, PEAK was a phase II study of first-line panitumumab (6mg/kg every 2 weeks) plus modified FOLFIRI (mFOLFIRI6) versus bevaxacizumab (5mg/kg every 2 weeks) plus mFOLFIRI6 in patients who had not received prior treatment for mCRC. The phase III PRIME study compared first-line panitumumab (6mg/kg every 2 weeks) plus FOLFIRI alone in treatment-naïve patients with mCRC. The phase III 181 study compared second-line panitumumab (6mg/kg every 2 weeks) plus FOLFIRI alone in patients with previously treated mCRC. In all three studies, data for non-study therapies (subsequent/second-line (PRIME and PEAK) or prior/first-line (181)) were not prospectively collected but were extracted from study case report forms, where consent was available.

Patient-level OS data were pooled for all patients with RAS WT mCRC and all those with RAS WT/BRAF WT tumours who received first-line panitumumab (PEAK and PRIME studies) followed by second-line VEGFi treatment, as well as first-line bevacizumab (PEAK and 181 studies), followed by second-line treatment with an EGFRi. Patients receiving any other sequence of agents, including those who had received both biological agents (ie, a VEGFi and an EGFRi) but not specifically as first-line and second-line therapies, were excluded. OS was also analysed for patients with left-sided RAS WT and RAS WT/BRAF WT tumours receiving first-line panitumumab followed by second-line VEGFi or first-line bevacizumab followed by second-line EGFRi treatment. Primary tumours located in the caecum to transverse colon were coded as right sided. Tumours located from the splenic flexure to rectum were categorised as left sided.

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RESULTS
Patients
Overall, 104 patients with RAS WT mCRC from these three trials received the specified first-line and second-line treatment sequences of interest and so were included in these exploratory analyses (n=35 from PRIME, n=40 from PEAK, n=29 from 181). Of these patients, 66 were treated with first-line panitumumab followed by second-line VEGFi, 38 received first-line bevacizumab followed by second-line EGFRi (figure 1). A total of 93 patients with RAS WT/BRAF WT disease were included, of whom 58 received first-line panitumumab followed by second-line VEGFi, and 35 received first-line bevacizumab followed by second-line EGFRi. Patients with RAS WT mCRC and all those with RAS WT/BRAF WT tumours who received first-line panitumumab (PEAK and PRIME studies) followed by second-line VEGFi treatment, as well as first-line bevacizumab (PEAK and 181 studies), followed by second-line treatment with an EGFRi. Patients receiving any other sequence of agents, including those who had received both biological agents (ie, a VEGFi and an EGFRi) but not specifically as first-line and second-line therapies, were excluded. OS was also analysed for patients with left-sided RAS WT and RAS WT/BRAF WT tumours receiving first-line panitumumab followed by second-line VEGFi or first-line bevacizumab followed by second-line EGFRi treatment. Primary tumours located in the caecum to transverse colon were coded as right sided. Tumours located from the splenic flexure to rectum were categorised as left sided.

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the bevacizumab→EGFRi arm). The majority of patients had left-sided tumours (40 patients (61%) receiving panitumumab→VEGFi; 25 patients (66%) receiving bevacizumab→EGFRi). A slight imbalance between treatment arms was observed with respect to the sites of metastatic disease: more patients receiving the panitumumab→VEGFi sequence had colon cancer (53 (80%)) compared with those treated with bevacizumab→EGFRi (22 (58%)) (table 1).

The use of non-study therapies was also generally well balanced between treatment sequences, with most patients receiving EGFRi/VEGFi in combination with chemotherapy (second line for PEAK and PRIME studies, and first line for Study 181) (table 2). Most patients in Study 181 received first-line bevacizumab combined with oxaliplatin-based chemotherapy (22 (76%)), while in PEAK and PRIME, most received second-line EGFRi (PEAK: 8 (89%)) or VEGFi (PEAK: 24 (77%); PRIME: 27 (77%)) with irinotecan-based chemotherapy (table 2). Six patients (9%) from the panitumumab→VEGFi group received the anti-angiogenesis multikinase inhibitor regorafenib in third or later lines of (non-study) treatment, compared with no patients in the bevacizumab→EGFRi arm (data not shown).

### Efficacy

At the time of the data analysis, 63.6% of patients with RAS WT mCRC receiving first-line panitumumab followed by second-line VEGFi, and 92.1% of patients receiving the first-line bevacizumab followed by second-line EGFRi sequence had died (table 3).

Similar results were observed in patients with RAS WT/BRAF WT mCRC: 58.6% and 91.4% of patients had died, respectively (table 3).

In the RAS WT pooled analysis, median OS was 36.8 versus 27.8 months in patients treated with first-line panitumumab followed by second-line VEGFi, compared with first-line bevacizumab followed by second-line EGFRi (HR 0.65; 95% CI 0.42 to 1.03) (figure 2 and table 3). The OS benefit associated with the panitumumab→VEGFi treatment sequence was more pronounced in patients with RAS WT/BRAF WT mCRC (median OS: 41.3 vs 28.9 months in the panitumumab→VEGFi vs bevacizumab→EGFRi groups, respectively; HR 0.58; 95% CI
DISCUSSION AND CONCLUSIONS

We report here the results from exploratory pooled analyses of OS for patients with RAS WT and RAS WT/BRAF WT mCRC, treated with either first-line panitumumab followed by second-line VEGFi, or first-line bevacizumab followed by second-line EGFRi, in three randomised trials: PEAK, PRIME and Study 181. Although the patient numbers were relatively small and the CIs wide, the results suggest a trend towards improved OS for first-line panitumumab plus chemotherapy followed by second-line VEGFi, compared with first-line bevacizumab plus chemotherapy followed by second-line EGFRi. Although an OS benefit was observed in both patient populations, it was most evident in patients with RAS WT/BRAF WT mCRC.

Among patients with RAS WT mCRC, complete resection was performed in six patients from the panitumumab→VEGFi group (9.1%, 95% CI 3.4 to 18.7) and two patients receiving the bevacizumab→EGFRi treatment sequence (5.3%, 95% CI 0.6 to 17.8).

0.36 to 0.95) (figure 2 and table 3). Median OS was most prolonged in patients with left-sided mCRC receiving the panitumumab→VEGFi treatment sequence (43.4 vs 32.4 months in the panitumumab→VEGFi vs bevacizumab→EGFRi groups, respectively; HR 0.61; 95% CI 0.33 to 1.11 and HR 0.56; 95% CI 0.30 to 1.04 in the RAS WT and RAS WT/BRAF WT groups, respectively) (table 3). OS data from the individual studies for patients with RAS WT and RAS WT/BRAF WT mCRC treated with these sequences were consistent with the results from the pooled analysis (online supplementary table 1).

Among patients with RAS WT mCRC, complete resection was performed in six patients from the panitumumab→VEGFi group (9.1%, 95% CI 3.4 to 18.7) and two patients receiving the bevacizumab→EGFRi treatment sequence (5.3%, 95% CI 0.6 to 17.8).
mCRC and in those with left-sided tumours, consistent with previous reports.\(^1\)\(^1\)\(^1\)\(^3\)\(^1\)\(^1\)\(^1\)\(^1\)\(^1\)\(^1\)\(^1\)\(^1\)

Overall, the results from these exploratory analyses are also in line with data from previous reports suggesting a potential clinical benefit for first-line EGFRi treatment compared with first-line VEGFi therapy in RAS WT mCRC.\(^3\)\(^4\)\(^7\)–\(^9\)\(^14\)–\(^17\) These include meta-analyses of head-to-head first-line randomised trials of EGFRis versus bevacizumab (FIRE-3, PEAK and CALGB/SWOG 80405),\(^7\)\(^8\)\(^7\)–\(^9\)\(^14\)–\(^17\) as well as small retrospective analyses suggesting that prior bevacizumab treatment may decrease efficacy of EGFRi therapy.\(^14\)–\(^17\) Similar results were also seen in a retrospective analysis of subsequent therapy use and outcomes in the FIRE-3\(^1\)\(^1\) trial and in analyses from the SPIRITT\(^1\)\(^8\) and Prodigie 18\(^1\)\(^9\) studies. In FIRE-3, an OS benefit was observed for patients receiving first-line EGFRi followed by second-line VEGFi therapy, compared with the reverse sequence.\(^1\)\(^9\) Conversely, after progression on first-line bevacizumab-based therapy in the SPIRITT\(^1\)\(^8\) and Prodigie 18\(^1\)\(^9\) studies, numeric differences in median OS were seen in favour of second-line regimens including bevacizumab rather than panitumumab or cetuximab (although no significant differences were observed between arms).

Table 2 Details of non-study therapy use in PEAK, PRIME and 181 (RAS wild-type population)

|                     | PEAK       | PRIME      | 181        |
|---------------------|------------|------------|------------|
|                     | Panitumab  | Bevacizumab| Panitumab  | VEGFi     |
| Second-line (VEGFi) | →VEGFi (n=31) | →EGFRi (n=9) | →VEGFi (n=35) | →Panitumab (n=29) |
| EGFRi/VEGFi therapy, n (%) | | | | |
| EGFRi/VEGFi monotherapy | 4 (13) | 1 (11) | 2 (6) | 0 (0) |
| EGFRi/VEGFi+oxaliplatin-containing chemotherapy | 2 (6) | 0 (0) | 4 (11) | 22 (76) |
| EGFRi/VEGFi+irinotecan-containing chemotherapy | 24 (77) | 8 (89) | 27 (77) | 0 (0) |
| EGFRi/VEGFi+other chemotherapy* | 1 (3) | 0 (0) | 2 (6) | 7 (24) |

*Other chemotherapy=fluoropyrimidine-based chemotherapy, not known or other chemotherapy.

EGFRi, epidermal growth factor receptor inhibitor; PEAK, Panitumumab Efficacy in combination with mFOLFOX6 Against bevacizumab plus mFOLFOX6 in mCRC subjects with KRAS WT tumours; PRIME, Panitumumab Randomized trial In combination with chemotherapy for Metastatic colorectal cancer to determine Efficacy; VEGFi, vascular endothelial growth factor inhibitor.

Table 3 Pooled analysis of overall survival in patients receiving panitumumab→VEGFi (PEAK and PRIME) versus bevacizumab→EGFRi (PEAK and 181) (RAS wild-type and RAS wild-type/BRAF wild-type populations)

|                     | All RAS WT | Left-sided RAS WT |
|---------------------|------------|-------------------|
|                     | PEAK+PRIME | PEAK+181 | PEAK+PRIME | PEAK+181 |
| Panitumumab→VEGFi   | n=66       | n=38      | n=40       | n=25     |
| OS events, n (%)    | 42 (63.6)  | 35 (92.1) | 21 (52.5)  | 22 (88.0) |
| Median OS, months (95% CI) | 36.8 (30.3 to 43.8) | 27.8 (24.2 to 35.6) | 43.4 (31.6 to 49.4) | 32.4 (23.9 to 41.3) |
| P value*            | 0.10       |         | 0.61       |         |
| HR (95% CI)         | 0.65 (0.42 to 1.03) | 0.61 (0.33 to 1.11) |         |         |

*Log-rank test.

EGFRi, epidermal growth factor receptor inhibitor; OS, overall survival; P E A K, Panitumumab Efficacy in combination with mFOLFOX6 Against bevacizumab plus mFOLFOX6 in mCRC subjects with KRAS WT tumours; PRIME, Panitumumab Randomized trial In combination with chemotherapy for Metastatic colorectal cancer to determine Efficacy; VEGFi, vascular endothelial growth factor inhibitor; WT, wild type.
Figure 2  Kaplan-Meier analysis of overall survival in patients receiving panitumumab → VEGFi (PEAK and PRIME) versus bevacizumab → EGFRi (PEAK and 181) in the (A) RAS wild-type and (B) RAS wild-type/BRAF wild-type populations. Bev, bevacizumab; EGFRi, epidermal growth factor receptor inhibitor; Pmab, Panitumumab Efficacy in combination with mFOLFOX6 Against bevacizumab in mCRC subjects with KRAS WT tumours; PRIME, Panitumumab Randomized trial in combination with chemotherapy for Metastatic colorectal cancer to determine Efficacy; Pmab, panitumumab; VEGFi, vascular endothelial growth factor inhibitor.
Although not directly related to the discussion of optimum sequencing of biologics, our data are also consistent with the results of several other trials. For example, OS benefits have been demonstrated for second-line bevacizumab, \textsuperscript{26} allibeccept\textsuperscript{21} and ramucirumab\textsuperscript{22} versus chemotherapy alone, although after progression on prior bevacizumab (rather than EGFRi) therapy. In contrast, an OS benefit for second-line EGFRi therapy after non-specified first-line mCRC therapy\textsuperscript{25-27} has so far not been observed except in a subgroup of patients from the PICCOLO (Panitumumab, Irinotecan and Cislosporin in COLOrectal cancer) trial whose tumours had high HER3 expression.\textsuperscript{26}

In our analyses, the OS improvement observed in patients with \textit{RAS} WT mCRC receiving first-line panitumumab followed by second-line VEGFi does not seem to be influenced by the type of non-study therapies used, as these were well balanced between treatment sequences. Across all three studies examined, most patients received EGFRi/VEGFi in combination with chemotherapy. The proportions of patients receiving first-line oxaliplatin-based chemotherapy followed by a second-line irinotecan-containing regimen were also comparable between treatment sequences. This is supportive of the view that the different sequence of biologics is the major factor impacting the OS results in our analyses.

Treatment with the anti-angiogenic receptor tyrosine kinase inhibitor regorafenib has been shown to provide survival benefits in patients with mCRC whose disease has progressed after standard therapies.\textsuperscript{27} In our exploratory analyses, a very small imbalance in the use of subsequent regorafenib as third or later line therapy was observed between treatment arms (9\% in the panitumumab→VEGFi arm vs 0\% in the bevacizumab→EGFRi group). However, these results should be interpreted with caution due to the small numbers of patients. Furthermore, data on regorafenib use were not prospectively collected, but were rather extracted from patient case report forms where it was recorded as ‘other’ non-study therapy, and may have therefore been under-reported in the bevacizumab→EGFRi arm.

One of the potential biological mechanisms underlying the OS benefit observed with first-line EGFRi treatment followed by second-line VEGFi therapy is that the emergence of EGFRi resistance does not seem to lead to resistance to VEGFis. Preclinical studies have shown that, at the molecular level, resistance to EGFRis can lead to increased VEGF expression level,\textsuperscript{28-29} and the promotion of angiogenesis, thereby sensitising the tumour to subsequent treatment with a VEGFi.\textsuperscript{214} In contrast, resistance to a VEGFi may result in simultaneous resistance to EGFRis.\textsuperscript{214} This may be due to the hypothesis that VEGFi therapy causes evasion from hypoxia-dependent apoptosis, which normally operates via EGFR/RAS-mediated activation of Akt, and can therefore potentially lead to reduced EGFRi efficacy.\textsuperscript{29} The lower OS benefit observed with the first-line VEGFi→second-line EGFRi treatment sequence may also be due to reduced targeting of EGFRi to the tumour, as a consequence of the VEGFi-mediated decrease in tumour vascularisation.\textsuperscript{30}

Intriguingly, recent studies have indicated that left-sided mCRC tumours are more responsive to EGFRi therapy than right-sided tumours.\textsuperscript{15} Consistent with this, in the present analyses, median OS was most prolonged for patients with left-sided mCRC receiving first-line panitumumab followed by second-line VEGFi treatment, rather than first-line bevacizumab followed by second-line EGFRi treatment. The number of patients with right-sided tumours was too small in the present study to permit analysis of OS by treatment sequence in this population, but as the proportions of patients with right-sided tumours were balanced between sequences, this is unlikely to be a confounding factor.

A key strength of these analyses is that patient-level data were used and the OS data from the PEAK, PRIME and 181 studies are mature. On the other hand, the small sample size, the retrospective nature of the analyses and the use of pooled data from independent trials, which were heterogeneous in their study design, represent limitations of the analyses.

In summary, these exploratory analyses of patient-level OS data from the PEAK, PRIME and 181 studies, suggest that patients with \textit{RAS} WT mCRC derive greater clinical benefit from first-line EGFRi treatment followed by second-line VEGFi therapy than from the reverse sequence. Nonetheless, prospective phase III studies are required to further evaluate the optimal sequence for administering biological therapies in these patients.
employee of Amgen and owns restricted shares in Amgen. FR has acted on advisory boards and/or received research funding from Amgen, Bayer, Celgene, Lilly, Merck Serono, Merck Sharp & Dohme, Roche, Sanofi, and Servier. AZ has no conflicts of interest to declare.

Patient consent Not required.

Ethics approval The original PRIME, PEAK and 181 studies were conducted in accordance with the ethical standards of the relevant institutional and/or national research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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