A randomized Phase II clinical study of combining panitumumab and bevacizumab, plus irinotecan, 5-fluorouracil, and leucovorin (FOLFIRI) compared with FOLFIRI alone as second-line treatment for patients with metastatic colorectal cancer and KRAS mutation

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Background: This study investigated the efficacy and safety of a new treatment strategy of combining panitumumab and bevacizumab, plus irinotecan, 5-fluorouracil, and leucovorin (FOLFIRI) versus FOLFIRI alone as second-line chemotherapy for metastatic colorectal cancer (mCRC) patients with known V-Ki-ras2 Kirsten rat sarcoma viral oncogene (KRAS) mutation status.

Methods: Patients with mCRC who had known KRAS tumor status and unsuccessful previous oxaliplatin-based chemotherapy were included in the study. They were randomly assigned to two groups to receive panitumumab and bevacizumab plus FOLFIRI, or FOLFIRI alone. In panitumumab and bevacizumab plus FOLFIRI group, patients were given 4 mg/kg panitumumab and bevacizumab plus FOLFIRI every 2 weeks.

Results: In all, 65 patients were assigned to panitumumab and bevacizumab plus FOLFIRI group, and 77 to FOLFIRI alone group. For WT KRAS patients, the median progression-free survival (PFS) was 5.7 months (95% confidence interval [CI], 2.4–7.5 months) for panitumumab and bevacizumab plus FOLFIRI and 3.8 months (95% CI, 3.0–6.7 months) for FOLFIRI alone; median overall survival (OS) was 15.2 months (95% CI, 8.9–19.7 months) for panitumumab and bevacizumab plus FOLFIRI and 11.0 months (95% CI, 8.2–15.4 months) for FOLFIRI alone. For MU KRAS patients, median PFS was 5.1 months (95% CI, 2.7–10.2 months) for panitumumab and bevacizumab plus FOLFIRI and 4.1 months (95% CI, 2.5–8.4 months) for FOLFIRI alone. For MU KRAS patients, median OS was 12.8 months (95% CI, 7.8–15.8 months) for panitumumab and bevacizumab plus FOLFIRI and 10.5 months (95% CI, 6.1–15.3 months) for FOLFIRI alone. Grade 3 and 4 adverse events were associated with panitumumab and bevacizumab plus FOLFIRI but tolerable among patients.

Conclusion: Patients with mCRC can be safely and efficiently treated with second-line chemotherapy of combining panitumumab and bevacizumab plus FOLFIRI, despite their KRAS mutation status.

Keywords: metastatic colorectal cancer, panitumumab, bevacizumab, FOLFIRI, second-line chemotherapy

Introduction

Colorectal cancer (CRC) is one of the three most common cancers in men, and one of the two most common cancers in women worldwide.1 Every year, more than 1 million
patients are diagnosed with CRC and most of them develop into metastatic colorectal cancer (mCRC). The standard single-agent chemotherapy for patients with mCRC typically uses regimen of 5-fluorouracil (5-FU) or leucovorin, oxaliplatin and folinic acid, 5-FU and irinotecan (FOLFIRI). Recently, as we gained advanced knowledge on the underlying mechanisms of mCRC, the combination chemotherapy including targeted regimens, such as aflibercept, regorafenib, cetuximab, panitumumab, and bevacizumab, into traditional chemo-reagents for mCRC had shown a significant impact on extending patients’ long-term survival.

The human homolog of V-Ki-ras2 Kirsten rat sarcoma viral oncogene (KRAS) is a GTPase protein that also acts as an oncogenic regulator. The mutation of KRAS is commonly found in various types of cancers, including mCRC. Studies demonstrated that KRAS mutation is highly associated with poor prognosis in patients with CRC. Panitumumab is an anti-epidermal growth factor receptor (EGFR) human monoclonal antibody, and has been applied in both first- and second-chemotherapy settings for patients with mCRC. However, clinical evidence showed mCRC patients with KRAS mutation, approximately 30%–50% of total patients with mCRC, responded poorly to panitumumab chemotherapy.

Bevacizumab is another human monoclonal antibody, thus has been utilized in target-specific chemotherapy for patients with mCRC. Unlike panitumumab, the target of bevacizumab is vascular endothelial growth factor (VEGF). It was suggested that KRAS protein might regulate the VEGF pathway to exert an angiogenic effect, and bevacizumab was shown to improve patients’ OS and response rates (RRs) in irinotecan-based chemotherapy of mCRC. However, it is not clear whether mCRC patients with mutated KRAS would directly benefit from bevacizumab chemotherapy.

Recently, two clinical studies demonstrated that combining panitumumab and bevacizumab plus FOLFIRI improved prognosis in patients with mCRC in second-line chemotherapy settings. However, these studies did not specify the relevance of KRAS mutation in combination chemotherapy. In the present study, we used a similar strategy of combining panitumumab and bevacizumab plus FOLFIRI as a second-line treatment option for patients with mCRC, and examined the patients’ response to treatment based on their KRAS mutation status.

Patients and methods

Patients

Eligible patients were between ≥18 and ≤85 years of age, having Eastern Cooperative Oncology Group (ECOG) performance status ≤2, diagnosed with metastatic adenocarcinoma of colon or rectum with at least one unidimensionally measurable lesion ≥20 mm based on magnetic resonance imaging (MRI) or computerized tomography (CT) imaging. Patients had to have only one prior oxaliplatin- or 5-FU-based chemotherapy but still diagnosed with disease progression within 6 months of first-line treatment. Patients had to have adequate hematologic, renal, and hepatic functions, and without any prior anti-VEGF or anti-EGFR treatment for mCRC.

Patients were excluded if they had received prior anti-EGFR or anti-VEGF therapy, had major surgery, hormonal therapy, immunotherapy within 4 weeks, or radiotherapy within 2 weeks of our study.

The protocol and treatment plan was approved by the Ethics Committee and Clinical Study Review Committee at Shandong Tumor Hospital. All patients provided signed consent forms before any procedures were conducted.

Study design and treatment schedule

This was an open-label, randomized, Phase II clinic study comparing the efficacy and safety of combining panitumumab and bevacizumab plus FOLFIRI. Patients were randomly stratified into two groups. In panitumumab and bevacizumab plus FOLFIRI group, patients were given 4 mg/kg panitumumab and 4 mg/kg bevacizumab plus FOLFIRI, every 2 weeks. Panitumumab and bevacizumab were administrated during a 90-minute infusion period before chemotherapy. In FOLFIRI alone group, patients were given FOLFIRI only (180 mg/m² irinotecan, 400 mg/m² racemic leucovorin by intravenous [IV] infusion on day 1 and FU 400 mg/m² intravenous bolus on day 1, followed by 2,400 mg/m² continuous infusion over days 1 and 2), every 2 weeks.

Responses were initially assessed by investigators, then confirmed by an independent radiologist blinded to the study, based on Response Evaluation Criteria in Solid Tumors (RECIST) every 8 weeks until disease progression. All patients were followed up on safety at least 45 days after the last study, and on survival every 90 days. During and after treatments, toxicity profiles were assessed for each patient. The adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.
Panitumumab plus bevacizumab for KRAS mCRC

Patients screened for eligibility (n=174)

Ineligible patients (n=32)

Eligible patients (n=142)

Panitumumab and bevacizumab plus FOLFIRI (n=65)

FOLFIRI alone (n=77)

Tumor sample available and KRAS tested (n=57)

Tumor sample available and KRAS tested (n=69)

WT KRAS panitumumab and bevacizumab plus FOLFIRI (n=30)

MU KRAS panitumumab and bevacizumab plus FOLFIRI (n=27)

WT KRAS FOLFIRI alone (n=35)

MU KRAS FOLFIRI alone (n=34)

Figure 1 CONSORT diagram for flow of patients through the study.

Abbreviations: FOLFIRI, fluorouracil, leucovorin, and irinotecan; KRAS, V-Ki-ras2 Kirsten rat sarcoma viral oncogene; WT, wild-type; MU, mutant.

KRAS determination
KRAS mutation was determined by an allele-specific PCR method according to the previous study. Briefly, paraffin-embedded tumor tissues were deparaffinized, and DNA was extracted. A KRAS mutation kit (DXS, Farnham, UK) was used to detect seven mutated sites on codons 12 and 13, Gly12Asp, Gly12Ala, Gly12Val, Gly12Ser, Gly12Arg, Gly12Cys, and Gly13Asp. An experienced statistician at Core Clinical Laboratory then performed blinded KRAS analysis to validate the PCR results.

Statistical analysis
The primary endpoints were RR, OS, and PFS. Secondary endpoints were AEs. Statistical analysis was performed with a windows-based SPSS software (version 11.0). Sample size calculations were conducted with the assumption of one-sided 10% α, 80% power, and a 1:1 randomization. OS and PFS were estimated using the Kaplan–Meier model with a confidence interval (CI) of 95% for event-free probabilities and differences in probabilities, calculated by the Brookmeyer and Crowley method. Hazard ratios (HRs) were estimated by the Cox proportional hazards regression model.

Results
Patients
Between June 2010 and May 2014, there were a total of 142 patients who were eligible for the study. The CONSORT diagram is shown in Figure 1. Among all eligible patients, 65 (46%) were assigned to panitumumab and bevacizumab plus FOLFIRI and 77 (54%) to FOLFIRI alone. Of those patients, 126 (89%) had test results of KRAS screening: 65 patients (52%) having wild-type (WT) KRAS
tumors and 61 patients (48%) having mutant (MU) KRAS tumors.

Baseline demographics and disease characteristics of the patients were stratified between those with WT and MU KRAS tumors, and balanced between two groups (panitumumab and bevacizumab plus FOLFIRI versus FOLFIRI alone), and balanced among (Table 1). For patients with WT KRAS tumors, the median ages were 59 years (21–82 years) in panitumumab and bevacizumab plus FOLFIRI group, and 62 years (25–80 years) in FOLFIRI alone group. For patients with MU KRAS tumors, the median ages were 61 years (22–79 years) in panitumumab and bevacizumab plus FOLFIRI group, and 60 years (29–85 years) in FOLFIRI alone group. For Eastern Cooperative Oncology Group performance status (ECOG PS), the majority of the patients had ECOG PS ≤2. For patients with WT KRAS tumors, 93% of those in panitumumab and bevacizumab plus FOLFIRI group, and 91% of those in FOLFIRI alone group, had ECOG PS of 0 and 1, respectively. For patients with MU KRAS tumors, 93% of those in panitumumab and bevacizumab plus FOLFIRI group, and 94% of those in FOLFIRI alone group, had ECOG PS of 0 and 1, respectively. In each group, for patients with either WT or MU KRAS tumors, about 60% of them had a primary tumor site in colon, and about 60% of them received first-line chemotherapy of FOLFOX.

**Efficacy**

PFSSs and OSs were examined for patients with WT KRAS and MU KRAS tumors (Figure 2).

For patients with WT KRAS tumors, the median PFS was 5.7 months (95% CI, 2.4–7.5 months) for panitumumab and bevacizumab plus FOLFIRI and 3.8 months (95% CI, 3.0–6.7 months) for FOLFIRI alone. There was a significant improvement in PFS with panitumumab and bevacizumab plus FOLFIRI versus FOLFIRI alone (HR =0.45; 95% CI, 0.22–0.64; P<0.01, Figure 2A). Median OS was 15.2 months (95% CI, 8.9–19.7 months) for panitumumab and bevacizumab plus FOLFIRI and 11.0 months (95% CI, 8.2–15.4 months) for FOLFIRI alone. There was also a significant improvement in OS with panitumumab and bevacizumab plus FOLFIRI versus FOLFIRI alone (HR =0.79; 95% CI, 0.47–0.89; P<0.01, Figure 2B).

For patients with MU KRAS tumors, the median PFS was 5.1 months (95% CI, 2.7–10.2 months) for panitumumab and bevacizumab plus FOLFIRI and 4.1 months (95% CI, 2.5–8.4 months) for FOLFIRI alone. There was a significant improvement in PFS with panitumumab and bevacizumab plus FOLFIRI versus FOLFIRI alone (HR =0.45; 95% CI, 0.22–0.64; P<0.01, Figure 2A). Median OS was 15.2 months (95% CI, 8.9–19.7 months) for panitumumab and bevacizumab plus FOLFIRI and 11.0 months (95% CI, 8.2–15.4 months) for FOLFIRI alone. There was also a significant improvement in OS with panitumumab and bevacizumab plus FOLFIRI versus FOLFIRI alone (HR =0.79; 95% CI, 0.47–0.89; P<0.01, Figure 2B).

For patients with MU KRAS tumors, the median PFS was 5.1 months (95% CI, 2.7–10.2 months) for panitumumab and bevacizumab plus FOLFIRI and 4.1 months (95% CI, 2.5–8.4 months) for FOLFIRI alone. There was a significant improvement in PFS with panitumumab and bevacizumab plus FOLFIRI versus FOLFIRI alone (HR =0.45; 95% CI, 0.22–0.64; P<0.01, Figure 2A). Median OS was 15.2 months (95% CI, 8.9–19.7 months) for panitumumab and bevacizumab plus FOLFIRI and 11.0 months (95% CI, 8.2–15.4 months) for FOLFIRI alone. There was also a significant improvement in OS with panitumumab and bevacizumab plus FOLFIRI versus FOLFIRI alone (HR =0.79; 95% CI, 0.47–0.89; P<0.01, Figure 2B).

**Table 1 The demographics and disease characteristics of patients**

<table>
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<tr>
<th>Characteristics</th>
<th>WT KRAS</th>
<th>MU KRAS</th>
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<tr>
<td></td>
<td>Panitumumab and bevacizumab plus FOLFIRI (n=30)</td>
<td>Panitumumab and bevacizumab plus FOLFIRI (n=27)</td>
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<tr>
<td></td>
<td>FOLFIRI alone (n=35)</td>
<td>FOLFIRI alone (n=34)</td>
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<tr>
<td></td>
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<td>60</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Median</td>
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<td>7</td>
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<td>Primary tumor</td>
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<td>Colon</td>
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<td>Rectum</td>
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<td>Liver only</td>
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<td>First-line chemotherapy</td>
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<td>FOLFOX</td>
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<td>63</td>
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<tr>
<td>XELOX</td>
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</table>

**Abbreviations:** WT, wild-type; KRAS, V-Ki-ras2 Kirsten rat sarcoma viral oncogene; FOLFIRI, fluorouracil, leucovorin, and irinotecan; MU, mutant; No, number; ECOG PS, Eastern Cooperative Oncology Group Performance Status.
Panitumumab and bevacizumab for KRAS mCRC

Figure 2 Progression-free survival (A) or overall survival (B) for wild-type (WT) KRAS, and progression-free survival (C) or overall survival (D) for mutant (MU) KRAS were examined.

Abbreviations: KRAS, V-Ki-ras2 Kirsten rat sarcoma viral oncogene; FOLFIRI, fluorouracil, leucovorin, and irinotecan.

Panitumumab and bevacizumab plus FOLFIRI versus FOLFIRI alone (HR = 0.65; 95% CI, 0.37–0.88; P < 0.05, Figure 2C). Median OS was 12.8 months (95% CI, 7.8–15.8 months) for panitumumab and bevacizumab plus FOLFIRI and 10.5 months (95% CI, 6.1–15.3 months) for FOLFIRI alone. There was also a significant improvement in OS with panitumumab and bevacizumab plus FOLFIRI versus FOLFIRI alone (HR = 0.44; 95% CI, 0.19–0.61; P < 0.05, Figure 2D).

The RRs are shown in Table 2. For patients who had WT KRAS tumors, the objective response rate (OR) was 47%
Table 2 Response rates of the patients

<table>
<thead>
<tr>
<th>Assessment</th>
<th>WT KRAS</th>
<th>FOLFIRI alone (n=35)</th>
<th>MU KRAS</th>
<th>FOLFIRI alone (n=34)</th>
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</thead>
<tbody>
<tr>
<td>Objective response</td>
<td>14 47</td>
<td>12 44</td>
<td>10 29</td>
<td>10 29</td>
</tr>
<tr>
<td>Complete response</td>
<td>1 3</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Partial response</td>
<td>13 44</td>
<td>12 44</td>
<td>10 29</td>
<td>10 29</td>
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<tr>
<td>Stable disease</td>
<td>5 17</td>
<td>8 30</td>
<td>8 24</td>
<td>8 24</td>
</tr>
</tbody>
</table>

Abbreviations: WT, wild-type; KRAS, V-Ki-ras2 Kirsten rat sarcoma viral oncogene; FOLFIRI, fluorouracil, leucovorin, and irinotecan; MU, mutant; No, number.

Table 3 Grade 3 and 4 adverse events (AEs) of the patients

<table>
<thead>
<tr>
<th>AEs</th>
<th>WT KRAS</th>
<th>FOLFIRI alone (n=35)</th>
<th>MU KRAS</th>
<th>FOLFIRI alone (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with AEs</td>
<td>28 93</td>
<td>21 60</td>
<td>25 93</td>
<td>19 56</td>
</tr>
<tr>
<td>Skin toxicity</td>
<td>12 40</td>
<td>5 18</td>
<td>20 74</td>
<td>5 15</td>
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<tr>
<td>Neutropenia</td>
<td>7 23</td>
<td>3 9</td>
<td>8 30</td>
<td>2 6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 17</td>
<td>2 6</td>
<td>5 19</td>
<td>1 3</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>4 13</td>
<td>1 3</td>
<td>5 19</td>
<td>0 0</td>
</tr>
<tr>
<td>Mucositis</td>
<td>5 17</td>
<td>1 3</td>
<td>4 15</td>
<td>2 6</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>4 13</td>
<td>1 3</td>
<td>4 15</td>
<td>0 0</td>
</tr>
<tr>
<td>Dehydration</td>
<td>2 7</td>
<td>0 0</td>
<td>2 7</td>
<td>0 0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 17</td>
<td>2 6</td>
<td>4 15</td>
<td>1 3</td>
</tr>
<tr>
<td>Bleeding</td>
<td>7 23</td>
<td>1 3</td>
<td>6 22</td>
<td>2 6</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>4 13</td>
<td>0 0</td>
<td>5 19</td>
<td>1 3</td>
</tr>
</tbody>
</table>

Abbreviations: WT, wild-type; KRAS, V-Ki-ras2 Kirsten rat sarcoma viral oncogene; FOLFIRI, fluorouracil, leucovorin, and irinotecan; MU, mutant; No, number.

Grade 3 and 4 AEs for the patients with both WT and MU KRAS tumors are listed in Table 3. The incidence rates of grade 3 and 4 AEs in the WT KRAS patients in the panitumumab and bevacizumab plus FOLFIRI group and FOLFIRI alone group were 93% and 60%, respectively. The incidence rates of grade 3 and 4 AEs in the MU KRAS patients in the panitumumab and bevacizumab plus FOLFIRI group and FOLFIRI alone group were 93% and 56%, respectively.

Moreover, despite KRAS tumor status, more patients experienced antibody-associated grade 3 and 4 AEs, including hypertension, bleeding, and proteinuria. For patients with WT KRAS tumors, the incidence rates of severe hypertension, bleeding, and proteinuria were 17%, 23%, and 13%, respectively, in panitumumab and bevacizumab plus FOLFIRI group. Those were higher than the rates of 6%, 3%, and 0%, in FOLFIRI alone group (P<0.01). For patients with MU KRAS tumors, the incidence rates of severe hypertension, bleeding, and proteinuria were 15%, 22%, and 19%, respectively, in panitumumab and bevacizumab plus FOLFIRI group, also significantly higher than the rates of 3%, 6%, and 3%, in FOLFIRI alone group (P<0.01).

Discussion

There have been two recent clinical studies, both in China, analyzing the treatment effects of combining anti-EGFR mAb and anti-VEGF mAb for patients with previously treated mCRC. However, neither of them correlated their results with KTAS mutation. Our study is the first to prospectively examine the efficacy and safety of combining panitumumab and bevacizumab according to the KRAS tumor status in patients with prior but failed first-line chemotherapy. And we

(95% CI, 32%–59%) in panitumumab and bevacizumab plus FOLFIRI group, significantly better than 26% (95% CI, 13%–41%) in FOLFIRI alone group (P<0.001). For patients who had MU KRAS, the OR was 44% (95% CI, 22%–53%) in panitumumab and bevacizumab plus FOLFIRI group, also significantly better than 29% (95% CI, 19%–55%) in the FOLFIRI alone group (P<0.05).
demonstrated that, despite tumor status, panitumumab and bevacizumab plus FOLFIRI was effective in improving PFS and OS in patients with both WT and MU KRAS tumors.

In our study, for FOLFIRI alone treatment, the median PFSs were 3.8 months for patients with WT KRAS tumors and 4.1 months for patients with MU KRAS tumors; the median OSs were 11.0 months for patients with WT KRAS tumors and 10.5 months for patients with MU KRAS tumors; and ORs were 26% for patients with WT KRAS tumors and 29% for patients with MU KRAS tumors. These data were consistent with previous studies while using a similar second-line chemotherapy setting of biweekly treatment of FOLFIRI, reporting PFS ranging from 2 to 7 months, OS ranging from 8 to 15 months and disease-control rates ranging from 20% to 50%.

Thus, it suggests that, even the sample size of our study was smaller than previous ones, it was unlikely to confound the results of our study due to sampling errors.

Most importantly, we demonstrated that, despite the KRAS status, both WT and MU patients may benefit from the second-line chemotherapy combining panitumumab and bevacizumab. For patients with WT KRAS tumors, absolute improvements were observed in both PFS (5.7 months for panitumumab and bevacizumab plus FOLFIRI versus 3.8 months for FOLFIRI alone) and OS (15.2 months for panitumumab and bevacizumab plus FOLFIRI versus 11.0 months for FOLFIRI alone). Similar results were observed in MU KRAS patients, with absolute improvements in PFS (5.1 months versus 4.1 months) and OS (12.8 months versus 10.5 months), comparing panitumumab and bevacizumab plus FOLFIRI group and FOLFIRI alone group. This result is very encouraging as previous clinic trials showed that only those patients with WT KRAS tumors responded positively to panitumumab chemotherapy. However, it was not clear, at least from current study, whether the combined regimen of bevacizumab was solely responsible for the survival improvements in patients with MU KRAS tumors, or adding bevacizumab into panitumumab resulted in synergic effects on patients with MU KRAS tumors. Thus, future clinical studies comparing treatment effects between combination chemotherapy (panitumumab and bevacizumab) and mono-agent chemotherapy (panitumumab or bevacizumab) would help to optimize the treatment strategy of second-line chemotherapy for patients with mCRC.

Overall, our study clearly demonstrated that combination chemotherapy of panitumumab and bevacizumab plus FOLFIRI was effective in treating patients with mCRC in second-line setting with tolerable toxicity profiles. Patients with both WT and MU KRAS tumors can benefit from this combination chemotherapy.

Disclosure
The authors report no conflicts of interest in this work.

References


