First-line cetuximab improves the efficacy of subsequent bevacizumab for RAS wild-type left-sided metastatic colorectal cancer: an observational retrospective study

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The optimal targeted therapy sequence in patients of RAS wild-type left-sided metastatic colorectal cancer (mCRC) remains controversial, and few studies focus on the impact of first-line targeted agents on second-line ones. We enrolled 101 left-sided mCRC patients with RAS wild-type status, of which 50 cases received bevacizumab plus chemotherapy in both first-line and second-line therapies (Group A) and 51 cases received first-line cetuximab plus chemotherapy followed by second-line bevacizumab-containing regimens (Group B). The progression free survival (PFS) and overall survival (OS) from start of first-line (PFS 1nd and OS 1nd) and second-line (PFS 2nd and OS 2nd) therapy were compared between the two groups. PFS 1nd was comparable (10.0 vs 10.4 months; \( p = 0.402 \)), while PFS 2nd (4.6 vs 7.9 months; \( p = 0.002 \)), OS 1nd (26.8 vs 40.0 months; \( p = 0.011 \)), and OS 2nd (15.2 vs 22.3 months; \( p = 0.006 \)) were all poorer in group A compared with group B. Our study in combination with previous clinical data suggest that first-line application of cetuximab may provide a favorable condition for promoting the effect of subsequent bevacizumab, thus representing the optimal targeted therapy sequence in patients of RAS wild-type left-sided mCRC.

Abbreviations
mCRC Metastatic colorectal cancer
EGFR Epidermal growth factor receptor
VEGF Vascular endothelial growth factor
CR Complete response
PR Partial response
SD Stable disease
PD Progression of disease
ORR Overall response rate
DCR Disease control rate

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In this retrospective study, we focused on RAS wild-type left-sided mCRC patients with different first-line therapies whereas the same second-line biologic agents to investigate the influence of anti-EGFR/VEGF antibodies on anti-VEGF agent, as well as provide some evidence for the appropriate treatment sequence in this particular group of patients.

### Results

#### Patients characteristics.

A total of 101 patients were enrolled in the study, including 50 patients receiving bevacizumab-containing regimens in both first-line and second-line therapies (Group A) and 51 cases receiving first-line cetuximab-containing regimens followed by bevacizumab-containing regimens in second-line therapy (Group B). The clinical baseline features of the 101 patients by treatment groups are shown in Table 1. The cut-off values of age and CEA level were calculated from the medians. Primary tumor resection was conducted in 19 (38.0%) patients from group A and 26 (51.0%) patients from group B, and metastatic lesions resection was conducted in 15 (30.0%) patients from group A and 17 (33.3%) patients from group B at any time during stage IV. Oxaliplatin-based regimens (FOLFOX or XELOX) were implemented in 36 (72.0%) patients from group A and 28 (54.9%) patients from group B, while irinotecan-based regimen (FOLFIRI) was implemented in 12 (24.0%) patients from group A and 20 (39.2%) patients from group B in first-line therapy. The information of third-line therapy can be found as Supplementary information Table S1 online. All factors were balanced between the two groups in statistics (all p > 0.05). The median follow-up time in group A and group B was 50.36 months and 47.31 months respectively.

#### Response rates in group A and group B.

Response parameters are listed in Table 2. During first-line therapy, 22 (44.0%) patients in group A and 33 (64.7%) patients in group B achieved partial response, 26 (52.0%) patients in group A and 13 (25.5%) patients in group B achieved stable disease. Therefore, the first-line ORR in group A was lower than that in group B (44.0% vs 64.7%, p = 0.037), while first-line DCR was comparable between two groups (96.0% vs 90.2%, p = 0.251). During second-line therapy, ORR was 16.0% in group A and 27.5% in group B (p = 0.163), while DCR was 64.0% in group A and 82.4% in group B (p = 0.037), respectively.

#### PFS 1nd and PFS 2nd in group A and group B.

As shown in Fig. 1A, B, patients in group B had a comparable PFS 1nd (hazard ratio [HR] = 1.186; 95% CI, 0.795–1.769; p = 0.402) and better PFS 2nd (HR = 0.513; 95% CI, 0.337–0.783; p = 0.002) compared with patients in group A. Median PFS 1nd was 10.0 months (95% CI, 8.0–11.9 months) in group A and 10.4 months (95% CI, 8.5–12.4 months) in group B. Median PFS 2nd was 4.6 months (95% CI, 2.1–7.0 months) in group A and 7.9 months (95% CI, 5.9–9.8 months) in group B.

Univariate analysis indicated that tumor histological grade, number of metastatic sites and metastases resection were significantly associated with PFS 1nd, while metastases resection, second-line chemotherapy regimens...
and treatment group were significantly associated with PFS 2nd (Tables 2, 3). When it came to the multivariate analysis, none of the above meaningful factors had statistical correlation with PFS 1st and only metastases resection and group B remained independently associated with a better PFS 2nd (Tables 3, 4).

### OS 1st and OS 2nd in group A and group B

As shown in Fig. 1C,D, patients in group B had a better OS 1st (HR = 0.543; 95% CI, 0.338–0.873; \( p = 0.011 \)) and OS 2nd (HR = 0.524; 95% CI, 0.328–0.835; \( p = 0.006 \)) compared with patients in group A. Median OS 1st was 26.8 months (95% CI, 20.0–33.6 months) in group A and 40.0 months (95% CI, 21.6–58.4 months) in group B. Median OS 2nd was 15.2 months (95% CI, 10.8–19.7 months) in group A and 22.3 months (95% CI, 10.0–34.7 months) in group B.

Metastases resection and treatment group were significantly associated with OS 1st as well as OS 2nd in both univariate and multivariate analysis, except that metastases resection failed to show prognostic significance for OS 2nd in multivariate analysis (Tables 5, 6).

### Table 1. Clinicopathological characteristics of mCRC patients based on treatment groups. Treatment group A: bevacizumab-containing regimens in both first-line and second-line therapies. Treatment group B: first-line cetuximab-containing regimens followed by second-line bevacizumab-containing regimens.

| Characteristics                  | Treatment group A | Treatment group B | \( p \) value |
|----------------------------------|-------------------|-------------------|---------------|
| Number of cases (n, %)           |                   |                   |               |
| Age at diagnosis as stage IV (years) |                   |                   |               |
| < 52                             | 27 (54.0)         | 23 (45.1)         | 0.371         |
| ≥ 52                             | 23 (46.0)         | 28 (54.9)         |               |
| Gender                           |                   |                   | 0.891         |
| Male                             | 33 (66.0)         | 33 (64.7)         |               |
| Female                           | 17 (34.0)         | 18 (35.3)         |               |
| WHO PS                           |                   |                   | 0.583         |
| 0–1                              | 39 (78.0)         | 42 (82.4)         |               |
| ≥ 2                              | 11 (22.0)         | 9 (17.6)          |               |
| Tumor histological grade         |                   |                   | 0.109         |
| Well-differentiated              | 3 (6.0)           | 1 (2.0)           |               |
| Moderately differentiated        | 30 (60.0)         | 30 (58.8)         |               |
| Poorly differentiated            | 10 (20.0)         | 18 (35.3)         |               |
| Mucinous                         | 7 (14.0)          | 2 (3.9)           |               |
| Localization of the primary tumor|                   |                   | 0.490         |
| Colon                            | 26 (52.0)         | 30 (58.8)         |               |
| Rectum                           | 24 (48.0)         | 21 (41.2)         |               |
| Number of metastatic sites       |                   |                   | 0.362         |
| 1                                | 20 (40.0)         | 25 (49.0)         |               |
| > 1                              | 30 (60.0)         | 26 (51.0)         |               |
| CEA                              |                   |                   | 0.307         |
| < 19.99                          | 27 (55.1)         | 21 (44.7)         |               |
| ≥ 19.99                          | 22 (44.9)         | 26 (55.3)         |               |
| Primary tumor resection          |                   |                   | 0.189         |
| Yes                              | 19 (38.0)         | 26 (51.0)         |               |
| No                               | 31 (62.0)         | 25 (49.0)         |               |
| Metastases resection             |                   |                   | 0.719         |
| Yes                              | 15 (30.0)         | 17 (33.3)         |               |
| No                               | 35 (70.0)         | 34 (66.7)         |               |
| Chemotherapy used in first-line  |                   |                   | 0.203         |
| Oxaliplatin-based                | 36 (72.0)         | 28 (54.9)         |               |
| Irinotecan-based                 | 12 (24.0)         | 20 (39.2)         |               |
| Others                           | 2 (4.0)           | 3 (5.9)           |               |
| Chemotherapy used in second-line |                   |                   | 0.144         |
| Oxaliplatin-based                | 20 (40.0)         | 25 (49.0)         |               |
| Irinotecan-based                 | 28 (56.0)         | 20 (39.2)         |               |
| Others                           | 2 (4.0)           | 6 (11.8)          |               |
compared with VEGF inhibitors in RAS wild-type left-sided mCRC. In accordance with previous studies, we
retrospective studies have shown that first-line EGFR inhibitors exhibited comparable PFS and superior OS
use of VEGF inhibitors has also been observed in several clinical trials. The possible mechanisms have also
zumab-pretreated cases, and this observation transformed into a prolonged OS. Improved OS by second-line
However, a prolonged OS was observed in cetuximab group in both univariate and multivariate analysis.
also found no statistical difference in PFS between first-line cetuximab- and bevacizumab-containing groups.
show advantage over the second one in prolonging OS, PFS and OS. When comparing the
inhibitor-containing regimens in both first- and second-line treatments. The first strategy has been proved to
plus anti-EGFR agents and second-line chemotherapy plus anti-VEGF agents; first-line chemotherapy combined
anti-EGFR antibodies induced up-regulation of VEGF at least partly contributed to the better PFS and OS for
emerged at least in part by the selection of cancer cell subpopulations with increased angiogenic potential, as
tors induced the emergence of EGFR inhibitor-resistant cells. The acquired resistance to anti-EGFR antibodies
been demonstrated in several experimental researches. Long-term treatment of CRC cells with EGFR inhibi-
tors led to resistance and a 5–10-fold increase in the expression of VEGF was observed. Besides, the EGFR inhibitor-resistant cells were
more sensitive to anti-VEGF agents both in vitro and in vivo. Based on above researches, we may infer that
anti-EGFR antibodies induced up-regulation of VEGF at least partly contributed to the better PFS and OS for
second-line anti-VEGF agents.
Currently, there are three targeted therapeutic strategies in RAS wild-type mCRC: First-line chemotherapy
plus anti-EGFR agents and second-line chemotherapy plus anti-VEGF agents; first-line chemotherapy combined
with anti-VEGF agents followed by second-line chemotherapy combined with anti-EGFR agents; and VEGF
inhibitor-containing regimens in both first- and second-line treatments. The first strategy has been proved to
show advantage over the second one in prolonging OS, PFS and OS. When comparing the latter two strategies, several researches about the second-line choice after progression of first-line treatment
with bevacizumab in mCRC patients has been conducted recently. They found that bevacizumab plus standard
chemotherapy was superior than that of cetuximab combined with chemotherapy in second-line therapy because
the former had longer PFS and OS, although some of the differences were not statistically significant. Based on the above clinical data and the perception that continuation of anti-EGFR antibodies in second-line
is usually not recommended due to low effectiveness, second-line VEGF inhibitor following first-line EGFR
inhibitor when disease progresses might be the most appropriate treatment strategy for RAS wild-type left-sided
mCRC patients.

There were several limitations in our study. First, as a retrospective study, it was less valuable and convincing
due to purely observational nature when compared with prospective studies. Second, only 30 patients in group A and 51 patients in group B were included, and the very finite sample size made the statistical results not accurate
enough to draw an undisputed conclusion. In addition, the targeted therapies were in combination with chemo-
therapy and local treatments (primary tumor or metastases resection) in our study, which might also affect the

### Table 2. Response rate of mCRC patients in two treatment groups. Treatment group A: bevacizumab-
containing regimens in both first-line and second-line therapies. Treatment group B: first-line cetuximab-
containing regimens followed by second-line bevacizumab-containing regimens. Bold values indicate
significant differences between two groups. CR complete response, PR partial response, SD stable disease, PD
progression of disease, ORR overall response rate, DCR disease control rate.

| Parameters | Treatment group A | Treatment group B | p value |
|------------|------------------|------------------|--------|
| Evaluable response to first-line therapy (n, %) | | | |
| CR | 0 (0) | 0 (0) | |
| PR | 22 (44.0) | 33 (64.7) | |
| SD | 26 (52.0) | 13 (25.5) | |
| PD | 2 (4.0) | 5 (9.8) | |
| ORR | 44.0% | 64.7% | 0.037 |
| DCR | 96.0% | 90.2% | 0.251 |
| Evaluable response to second-line therapy (n, %) | | | |
| CR | 0 (0) | 0 (0) | |
| PR | 8 (16.0) | 14 (27.5) | |
| SD | 24 (48.0) | 28 (54.9) | |
| PD | 18 (36.0) | 9 (17.6) | |
| ORR | 16.0% | 27.5% | 0.163 |
| DCR | 64.0% | 82.4% | 0.037 |

### Discussion
To further confirm the optimal sequence of EGFR and VEGF inhibitors in RAS wild-type left-sided mCRC and
explore the influence of first-line biologic agents on second-line ones, we carried out this study and found that
patients treated with first-line cetuximab-containing and second-line bevacizumab-containing regimens had bet-
ter PFS and OS compared to patients with continuation of bevacizumab-containing crossover therapy, and that previous cetuximab use had a promoting effect on the activity of subsequent bevacizumab.

Patients with RAS mutant-type or right-sided mCRC cannot benefit from cetuximab, and only the patients
with both RAS wild-type and left-sided mCRC are candidates for anti-EGFR therapy, while bevacizumab shows
efficacy regardless of the tumor location or RAS mutation status. Several important clinical trials and some
retrospective studies have shown that first-line EGFR inhibitors exhibited comparable PFS and superior OS
compared with VEGF inhibitors in RAS wild-type left-sided mCRC. In accordance with previous studies, we
also found no statistical difference in PFS between first-line cetuximab- and bevacizumab-containing groups.
However, a prolonged OS was observed in cetuximab group in both univariate and multivariate analysis.

In our study, PFS was significantly prolonged in cetuximab-pretreated patients compared with bevaci-
zumab-pretreated cases, and this observation transformed into a prolonged OS. Improved OS by second-line
use of VEGF inhibitors has also been observed in several clinical trials. The possible mechanisms have also
been demonstrated in several experimental researches. Long-term treatment of CRC cells with EGFR inhibi-
tors led to resistance and a 5–10-fold increase in the expression of VEGF was observed. Besides, the EGFR inhibitor-resistant cells were
more sensitive to anti-VEGF agents both in vitro and in vivo. Based on above researches, we may infer that
anti-EGFR antibodies induced up-regulation of VEGF at least partly contributed to the better PFS and OS for
second-line anti-VEGF agents.
outcomes. Nonetheless, we have enrolled patients strictly according to the criteria and tried our effort to balance all the clinicopathological factors between two groups to ensure the accuracy of the results.

Conclusion

Taken together, we further compared the efficacy between first-line cetuximab and bevacizumab in RAS wild-type left-sided mCRC patients with our data, as well as analyzed the influence of first-line anti-EGFR/VEGF agents on second line VEGF inhibitors. Based on our results and the previously reported clinical data, first-line application of anti-EGFR agents provides a favorable condition for promoting the effect of subsequent anti-VEGF agents, and first-line anti-EGFR containing regimens followed by second-line anti-VEGF containing regimens might be the optimal medical strategy for the patients of RAS wild-type left-sided mCRC.

Figure 1. PFS and OS comparison between group A and group B using Kaplan–Meier method. Group A: bevacizumab-containing regimens in both first-line and second-line therapies; Group B: first-line cetuximab-containing regimens followed by second-line bevacizumab-containing regimens. (A) First-line PFS: from the beginning of first-line therapy to first disease progression; (B) Second-line PFS: from the date when second-line therapy started to second progression in disease; (C) First-line OS: from first application of first-line therapy to death resulting from mCRC; (D) Second-line OS: from beginning of second-line therapy to death resulting from mCRC. The difference was significant if \( p < 0.05 \) by log-rank test.
Methods

Patients and study design. In this retrospective study, 101 left-sided mCRC patients with KRAS, NRAS and BRAF wild-type status treated at Sun Yat-Sen University Cancer Center in China from October 2008 to January 2016 were included. Among all these patients, 50 cases received bevacizumab-containing regimens in both first-line and second-line therapies (Group A) and 51 cases received first-line cetuximab plus chemotherapy followed by second-line bevacizumab-containing regimens. Only patients with measurable lesions and underwent tumor assessments during the treatment every 6–8 weeks according to RECIST version 1.1 were eligible. The screening process of enrolled patients is summarized in Fig. 2. Clinicopathological characteristics of the patients are summarized in Table 1.

Definitions. First-line therapy was defined as administration of bevacizumab- or cetuximab-containing regimens for first time after diagnosis of stage IV disease, and second-line therapy was defined as the start of administration of any anti-cancer drugs from disease progression no matter any changes in regimens. Overall response rate (ORR) meant the proportion of patients achieving complete or partial response according to RECIST version 1.1. Disease control rate (DCR) was defined as the proportion of patients who reached stable disease, partial or complete response according to RECIST version 1.1. PFS 1st was measured from the beginning of first-line therapy to first disease progression, and PFS 2nd was calculated from the date when second-line therapy started to second progression in disease. OS 1st referred to the time from first application of first-line therapy to death due to cancer, and OS 2nd was defined as the time from beginning of second-line therapy to death resulting from cancer.

| Variables                              | Univariate analysis | Multivariate analysis |
|----------------------------------------|---------------------|-----------------------|
|                                        | HR 95%CI            | p value               |
|                                        | HR 95%CI            | p value               |
| Age at diagnosis as stage IV (years)   |                     |                       |
| < 52                                   | 1                   |                       |
| ≥ 52                                   | 0.905 (0.608–1.346) | 0.622                 |
| Gender                                 |                     |                       |
| Male                                   | 1                   |                       |
| Female                                 | 0.918 (0.606–1.391) | 0.687                 |
| WHO PS                                 |                     |                       |
| 0–1                                    | 1                   |                       |
| ≥ 2                                    | 1.140 (0.697–1.866) | 0.601                 |
| Tumor histological grade               | 0.030               | 0.389                 |
| Localization of the primary tumor      |                     |                       |
| Colon                                  | 1                   |                       |
| Rectum                                 | 0.757 (0.505–1.134) | 0.176                 |
| Number of metastatic sites             |                     |                       |
| 1                                      | 1                   |                       |
| > 1                                    | 1.768 (1.174–2.662) | 0.006                 |
| CEA                                     |                     |                       |
| < 19.99                                | 1                   |                       |
| ≥ 19.99                                | 0.943 (0.628–1.415) | 0.777                 |
| Primary tumor resection                |                     |                       |
| Yes                                    | 1                   |                       |
| No                                     | 0.835 (0.557–1.249) | 0.380                 |
| Metastases resection                   |                     |                       |
| Yes                                    | 1                   |                       |
| No                                     | 1.627 (1.061–2.494) | 0.026                 |
| Chemotherapy used in first-line        | 0.682               |                       |
| Oxaliplatin-based                      | 1                   |                       |
| Irinotecan-based                       | 0.845 (0.548–1.302) | 0.445                 |
| Others                                 | 1.156 (0.463–2.883) | 0.757                 |
| Treatment group                        |                     |                       |
| Group A                                | 1                   |                       |
| Group B                                | 1.186 (0.795–1.769) | 0.404                 |

Table 3. Univariate and multivariate analysis for factors associated with PFS 1st. Treatment group A: bevacizumab-containing regimens in both first-line and second-line therapies. Treatment group B: first-line cetuximab-containing regimens followed by second-line bevacizumab-containing regimens. Bold values indicate significant differences between two groups.
Statistical analysis. Statistical analyses were performed using SPSS 22.0 software (SPSS Inc, USA). Categorical characteristics, ORR and DCR between two treatment groups were compared using the Pearson Chi square test. Survival probabilities including PFS 1nd, PFS2nd, OS1nd and OS2nd were estimated using the Kaplan–Meier method and survival curves were compared by log-rank test. A multivariate Cox regression model was used to estimate the effects of treatment strategies and other factors on PFS and OS. Only variables with \( p \) value of less than 0.1 in the univariate model were included for further analysis in the multivariate Cox model. A \( p \) value of less than 0.05 was considered statistically significant.

Ethic approval and consent to participate. All methods were carried out in accordance with relevant guidelines and regulations. All experimental protocols were approved by the Research Ethics Committee of Sun Yat-sen University. Informed consent was obtained from all individual participants included in the study.
| Variables | Univariate analysis | Multivariate analysis |
|-----------|---------------------|-----------------------|
|           | HR                  | 95%CI                 | p value | HR                  | 95%CI                 | p value |
| Age at diagnosis as stage IV (years) | | | | | | |
| <52 | 1 | | | | | |
| ≥52 | 0.744 (0.470–1.178) | 0.207 | | | | |
| Gender | | | | | | |
| Male | 1 | | | | | |
| Female | 1.475 (0.912–2.387) | 0.113 | | | | |
| WHO PS | | | | | | |
| 0–1 | 1 | | | | | |
| ≥2 | 1.013 (0.953–1.076) | 0.686 | | | | |
| Tumor histological grade | | | | | | |
| | | | | | | |
| Localization of the primary tumor | | | | | | |
| Colon | 1 | | | | | |
| Rectum | 0.767 (0.479–1.229) | 0.271 | | | | |
| Number of metastatic sites | | | | | | |
| 1 | 1 | | | | | |
| >1 | 1.263 (0.796–2.004) | 0.321 | | | | |
| CEA | | | | | | |
| <19.99 | 1 | | | | | |
| ≥19.99 | 1.088 (0.680–1.740) | 0.724 | | | | |
| Primary tumor resection | | | | | | |
| Yes | 1 | | | | | |
| No | 1.058 (0.662–1.690) | 0.813 | | | | |
| Metastases resection | | | | | | |
| Yes | 1 | | | | | |
| No | 1.932 (1.153–3.239) | **0.012** | 1.732 (1.026–2.924) | **0.040** | | | |
| Chemotherapy used in first-line | | | | | | |
| Oxaliplatin-based | 1 | | | | | |
| Irinotecan-based | 0.727 (0.436–1.210) | 0.219 | | | | |
| Others | 1.092 (0.429–2.780) | 0.853 | | | | |
| Chemotherapy used in second-line | | | | | | |
| Oxaliplatin-based | 1 | | | | | |
| Irinotecan-based | 1.498 (0.934–2.405) | 0.094 | | | | |
| Others | 0.920 (0.321–2.631) | 0.876 | | | | |
| Treatment group | | | | | | |
| Group A | 1 | | | | | |
| Group B | 0.543 (0.338–0.873) | **0.012** | 0.665 (0.373–0.980) | **0.041** | | | |

**Table 5.** Univariate and multivariate analysis for factors associated with OS 1nd. Treatment group A: bevacizumab-containing regimens in both first-line and second-line therapies. Treatment group B: first-line cetuximab-containing regimens followed by second-line bevacizumab-containing regimens. Bold values indicate significant differences between two groups.
Table 6. Univariate and multivariate analysis for factors associated with OS 2nd. Treatment group A: bevacizumab-containing regimens in both first-line and second-line therapies. Treatment group B: first-line cetuximab-containing regimens followed by second-line bevacizumab-containing regimens. Bold values indicate significant differences between two groups.

| Variables                              | Univariate analysis |                  | Multivariate analysis |                  |
|----------------------------------------|---------------------|------------------|-----------------------|------------------|
|                                        | HR                  | 95%CI            | p value               | HR              | 95%CI            | p value               |
| Age at diagnosis as stage IV (years)   |                     |                  |                       |                  |                  |                       |
| < 52                                   | 1                   |                  |                       |                  |                  |                       |
| ≥ 52                                   | 0.755 (0.477–1.197) | 0.232            |                       |                  |                  |                       |
| Gender                                 |                     |                  |                       |                  |                  |                       |
| Male                                   | 1                   |                  |                       |                  |                  |                       |
| Female                                 | 1.503 (0.929–2.432) | 0.097            |                       |                  |                  |                       |
| WHO PS                                 |                     |                  |                       |                  |                  |                       |
| 0–1                                    | 1                   |                  |                       |                  |                  |                       |
| ≥ 2                                    | 1.012 (0.952–1.075) | 0.708            |                       |                  |                  |                       |
| Tumor histological grade               |                     |                  |                       |                  |                  |                       |
| Localization of the primary tumor     |                     |                  |                       |                  |                  |                       |
| Colon                                  | 1                   |                  |                       |                  |                  |                       |
| Rectum                                 | 0.824 (0.519–1.310) | 0.413            |                       |                  |                  |                       |
| Number of metastatic sites             |                     |                  |                       |                  |                  |                       |
| 1                                      | 1                   |                  |                       |                  |                  |                       |
| >1                                     | 1.091 (0.688–1.729) | 0.711            |                       |                  |                  |                       |
| CEA                                     |                     |                  |                       |                  |                  |                       |
| < 19.99                                | 1                   |                  |                       |                  |                  |                       |
| ≥ 19.99                                | 1.124 (0.702–1.798) | 0.627            |                       |                  |                  |                       |
| Primary tumor resection                |                     |                  |                       |                  |                  |                       |
| Yes                                    | 1                   |                  |                       |                  |                  |                       |
| No                                     | 1.066 (0.670–1.697) | 0.788            |                       |                  |                  |                       |
| Metastases resection                   |                     |                  |                       |                  |                  |                       |
| Yes                                    | 1                   |                  |                       |                  |                  |                       |
| No                                     | 1.656 (1.306–2.726) | 0.047            | 1.486 (0.898–2.459)   | 0.124            |                  |                       |
| Chemotherapy used in first-line        |                     |                  |                       |                  |                  |                       |
| Oxaliplatin-based                      | 1                   |                  |                       |                  |                  |                       |
| Irinotecan-based                       | 0.738 (0.445–1.226) | 0.241            |                       |                  |                  |                       |
| Others                                 | 1.085 (0.430–2.738) | 0.863            |                       |                  |                  |                       |
| Chemotherapy used in second-line       |                     |                  |                       |                  |                  |                       |
| Oxaliplatin-based                      | 1                   |                  |                       |                  |                  |                       |
| Irinotecan-based                       | 1.431 (0.892–2.295) | 0.137            |                       |                  |                  |                       |
| Others                                 | 0.827 (0.290–2.354) | 0.722            |                       |                  |                  |                       |
| Treatment group                        |                     |                  |                       |                  |                  |                       |
| Group A                                | 1                   |                  |                       |                  |                  |                       |
| Group B                                | 0.524 (0.328–0.835) | 0.007            | 0.561 (0.350–0.900)   | 0.016            |                  |                       |
Data availability

All authors had access to the primary data.

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References

1. de Gramont, A. et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J. Clin. Oncol.* 18, 2938–2947 (2000).
2. Falcone, A. et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the gruppo oncologico nord ovest. *J. Clin. Oncol.* 25, 1670–1676 (2007).
3. Goldberg, R. M. et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J. Clin. Oncol.* 22, 23–30 (2004).
4. Starling, N., Tilden, D., White, J. & Cunningham, D. Cost-effectiveness analysis of cetuximab/irinotecan vs active/best supportive care for the treatment of metastatic colorectal cancer patients who have failed previous chemotherapy treatment. *Brit. J. Cancer.* 96, 206–212 (2007).
5. Capdevila, J., Javier Ramos, F., Macarulla, T., Elez, E. & Tabernero, J. The role of salvage treatment in advanced colorectal cancer. *Crit. Rev. Oncol. Hemat.* 71, 53–61 (2009).
6. Kelly, H. & Goldberg, R. M. Systemic therapy for metastatic colorectal cancer: current options current evidence. *J. Clin. Oncol.* 23, 4533–4560 (2005).
7. Brule, S. Y. et al. Location of colon cancer (right-sided versus left-sided) as a prognostic factor and a predictor of benefit from cetuximab in NCIC CO17. *Eur. J. Cancer.* 51, 1405–1414 (2015).
8. Moretto, R. et al. Location of primary tumor and benefit from anti-epidermal growth factor receptor monoclonal antibodies in patients with RAS and BRAF wild-type metastatic colorectal cancer. *Oncologist.* 21, 988–994 (2016).
9. Venook, A. P. et al. Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with KRAS wild-type advanced or metastatic colorectal cancer: a randomized clinical trial. *JAMA* 317, 2392–2401 (2017).
10. Heinemann, V. et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 15, 1065–1075 (2014).
11. Schwartzberg, L. S. et al. PEAK: a randomized, multicenter phase ii study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacinumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. *J. Clin. Oncol.* 32, 2240–2247 (2014).
12. Riesco-Martinez, M. C. et al. Cost-effectiveness analysis of different sequences of the use of epidermal growth factor receptor inhibitors for wild-type KRAS unresectable metastatic colorectal cancer. *J Oncol Pract.* 12, e710–e723 (2016).
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