Effect of RAS status on anti-EGFR monoclonal antibodies + 5-FU infusion-based chemotherapy in first-line treatment of metastatic colorectal cancer: A meta-analysis

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A B S T R A C T

Purpose: To investigate the effect of RAS on anti-EGFR moAb + 5-FU infusion based chemotherapy in first-line treatment of mCRC.

Methods: The MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane databases and ClinicalTrials.gov databases were independently reviewed. Primary end points included overall response rate (ORR), progression-free survival (PFS), overall survival (OS) and toxicities. Correlation between RAS status and PFS, OS, ORR or toxicities was expressed as a hazard ratio (HR) or relative risk (RR).

Results: KRAS exon 2 wild-type (-wt) mCRC benefited from adding anti-EGFR moAb (compared with chemotherapy alone: OS: HR 0.88, P = 0.008; PFS: HR 0.74, P < 0.001; ORR: RR 1.34, P = 0.003. Compared with Bevacizumab: OS: HR 0.83, P = 0.003). KRAS exon 2-wt but other RAS mutations mCRC did not benefit from adding anti-EGFR moAb. RAS-wt mCRC benefited from adding anti-EGFR moAb (compared with chemotherapy alone: OS: HR 0.75, P < 0.001; PFS: HR 0.65, P < 0.001; ORR: RR 1.51, P = 0.020. Compared with Bevacizumab: OS: HR 0.79, P = 0.002). KRAS exon 2-wt but BRAF mutation mCRC did not benefit from adding anti-EGFR moAb. Subgroup analysis suggested that anti-EGFR moAb prolonged PFS for male, liver metastasis-only, ECOG 0–1, and colon primary site groups. Anti-EGFR moAb increased controllable grade 3–4 toxicities including rash, diarrhea, and anemia.

Conclusions: Adding anti-EGFR moAb as first-line treatment in RAS-wt mCRC prolonged OS. Whether BRAF mutation is a predictive marker to anti-EGFR moAb is not clear.

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1. Introduction

The 5-year survival rate for metastatic colorectal cancer (mCRC) remains below 10% (Siegel et al., 2012). A first-line regimen of anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (moAb; cetuximab or panitumumab) with 5-FU infusion based chemotherapy by KRAS exon 2 wild-type (-wt) status in mCRC, has increased median progression-free survival (PFS) to 8.3–10.9 months, and overall survival (OS) to 17.0–34.2 months. However, not all reported PFS or OS improvements were significant (Maughan et al., 2011; Bokemeyer et al., 2009; Bokemeyer et al., 2015; Van Cutsem et al., 2011; Van Cutsem et al., 2015; Douillard et al., 2013; Schwartzberg et al., n.d.; Stintzing et al., 2012; Heinemann et al., 2014; Venook et al., 2014).

KRAS and NRAS are closely related RAS oncogene family members (Karnoub and Weinberg, 2008; Fernandez-Medarde and Santos, 2011). Mutations in KRAS and NRAS codons increase guanosine triphosphate-bound RAS proteins, which promote tumor proliferation, invasion, metastasis and drug resistance (Haigis et al., 2008; Diaz et al., 2012; Misale et al., 2012). Besides KRAS exon 2 (codons 12 and 13), oncogenic mutations in the RAS family have been found in KRAS exon 3 (59 and 61), exon 4 (117 and 146); and NRAS exon 2 (12 and 13), exon 3 (59 and 61), and exon 4 (117 and 146) (De Roock et al., n.d.). Clinical trials have shown some patients with KRAS exon 2-wt mCRC to have no response to anti-EGFR moAb, which suggests that KRAS exon 1 mutations are not the only negative predictive markers for anti-EGFR moAb treatment (Allegra et al., 2009).
Seven randomized controlled trials (RCTs) evaluated the efficacy of anti-EGFR moAb + 5-FU infusion based chemotherapy in first-line treatment of mCRC by RAS status, but their results were inconsistent (Maughan et al., 2011; Bokemeyer et al., 2009; Bokemeyer et al., 2015; Van Cutsem et al., 2011; Van Cutsem et al., 2015; Douillard et al., 2013; Schwartzberg et al., n.d.; Stintzing et al., 2012; Heinemann et al., 2014; Venook et al., 2014). Did mCRC patients with RAS-wt benefit from adding anti-EGFR moAb? And how did patients with RAS mutations other than KRAS exon 2 respond to anti-EGFR moAb? Which is better for first-line treatment of mCRC with chemotherapy, anti-EGFR moAb or Bev? Our meta-analysis aimed to evaluate the efficacy and safety of anti-EGFR moAb + 5-FU infusion based chemotherapy in first-line treatment of mCRC according to RAS status.

2. Materials and methods

2.1. Literature search

The MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane databases and ClinicalTrials.gov databases were independently reviewed from their dates of inception to July 2015. The following search terms were used: “colorectal neoplasms” and “mutation” and “antibodies, monoclonal” and “ras Proteins”. Only human studies and RCTs published in English were eligible. Abstracts and information from conferences were also collected independently. Fig. 1 shows a flow chart of the literature search and study selection and results in each step.

2.2. Inclusion criteria

Studies that met the following criteria were included: (1) randomized trials of patients with no prior chemotherapy for mCRC and available RAS status; (2) treatment with 5-FU infusion based chemotherapy, with or without anti-EGFR moAb (cetuximab or panitumumab); (3) use of overall response rate (ORR), PFS, OS and/or toxicities as outcomes to assess tumor response and prognosis. Quality assessment of papers was independently performed using the seven-point Jadad ranking system (Jadad et al., 1996).

2.3. Data collection

Data collection was carried out independently by two reviewers. Disagreements were resolved by discussion between the two or by consulting a third reviewer. The following data was collected from each study: name of study, year of publication, total number of patients included in the study, trial phase, intervention, response criteria, ORR,
PFS, and OS. To assess responses, studies of patients with measurable diseases were evaluated by central radiology review. Toxicities were graded according to the Common Terminology Criteria for Adverse Events (version 2.0 or 3.0).

### 2.4. Statistical analysis

Primary end points included ORR, PFS, OS and toxicities. Association between RAS status and ORR or toxicities was expressed as

#### Table 1

| Study         | Study design (number of patients) | Treatment schedule | KRAS test | NRAS test | BRAF test |
|---------------|----------------------------------|--------------------|-----------|-----------|-----------|
| COIN 2011     | FOLFOX + Cetux. (KRAS exon 2-wt: 117; exons 3, 4-wt: 245) | Cetux.: initial dose 400 mg/m² and 250 mg/m²/week thereafter, Q2W; FOLFOX: oxaliplatin 85 mg/m² over 2 h; fluorouracil 400 mg/m² IV bolus and 2400 mg/m² infuion over 46 h; l-folic acid 175 mg or l-folic acid 350 mg over 2 h, Q2W; | Codons 12, 13, 61 | Codons 12, 61 | Codons 594, 600 |
|               | FOLFOX (KRAS exon 2-wt: 127; exons 3, 4-wt: 240) | FOLFOX: oxaliplatin 85 mg/m² over 2 h; fluorouracil 400 mg/m² IV bolus and 2400 mg/m² infuion over 46 h; l-folic acid 175 mg or l-folic acid 350 mg over 2 h, Q2W. | Codons 12, 13, 61 | Codons 12, 61 | Codons 594, 600 |
| OPLS 2011     | FOLFOX4 + Cetux. (KRAS exon 2-wt: 82; RAS-wt: 38; KRAS exon 2-wt but other RAS-mt: 15) | Cetux.: initial dose 400 mg/m² and 250 mg/m²/week thereafter, Q2W; FOLFOX4: oxaliplatin 85 mg/m²; l-folic acid 200 mg/m²; 5-FU 400 mg/m²/IV bolus and 600 mg/m² 22-hour continuous infusion on days 1 and 2, Q2W. | Codons 12, 13, 59, 61, 117, 146 | – | – |
|               | FOLFOX4 (KRAS exon 2-wt: 97; RAS-wt: 49; KRAS exon 2-wt but other RAS-mt: 16) | FOLFOX4: oxaliplatin 85 mg/m²; l-folic acid 200 mg/m²; 5-FU 400 mg/m²/IV bolus and 600 mg/m² 22-hour continuous infusion on days 1 and 2, Q2W. | Codons 12, 13, 59, 61, 117, 146 | – | – |
| CRYSTAL 2011   | FOLFIRI + Cetux. (KRAS exon 2-wt but other RAS-mt: 32) | Cetux.: initial dose 400 mg/m² and 250 mg/m²/week thereafter, followed after 1 h by FOLFIRI, Q2W. | Codons 12, 13, 59, 61, 117, 146 | – | – |
|               | FOLFIRI (KRAS exon 2-wt: 350; RAS-wt: 189; KRAS exon 2-wt but other RAS-mt: 31) | FOLFIRI: irinotecan 180 mg/m², day 1, infused over 30 to 90 min; leucovorin 200 mg/m² l-form, or 400 mg/m² racemic, infused over 2 h; fluorouracil 400 mg/m² IV bolus and 2400 mg/m² 46-hour continuous infusion, Q2W. | Codons 12, 13, 59, 61, 117, 146 | – | – |
| PRIME 2013     | FOLFOX4 + Panit. (KRAS exon 2-wt: 325; RAS-wt: 259; KRAS exon 2-wt but other RAS-mt: 51) | Panit.: IV over 1 h, 6 mg/kg on day 1 before FOLFOX4, Q2W | Codons 12, 13, 59, 61, 117, 146 | Codons 12, 13, 59, 61, 117, 146 | Codons 600 |
|               | FOLFOX4 (KRAS exon 2-wt: 331; RAS-wt: 253; KRAS exon 2-wt but other RAS-mt: 57) | FOLFOX4: oxaliplatin 85 mg/m² IV infusion on day 1; leucovorin 200 mg/m² IV infusion; fluorouracil 400 mg/m² IV bolus and 600 mg/m² 22-hour continuous infusion on days 1 and 2, Q2W. | Codons 12, 13, 59, 61, 117, 146 | Codons 12, 13, 59, 61, 117, 146 | Codons 600 |
| PEAK 2014      | FOLFIRI + Cetux. (KRAS exon 2-wt: 142; RAS-wt: 88; KRAS exon 2-wt but other RAS-mt: 24) | FOLFIRI: irinotecan 180 mg/m², day 1, infused over 30 to 90 min; leucovorin 200 mg/m² l-form, or 400 mg/m² racemic, infused over 2 h; fluorouracil 400 mg/m² IV bolus and 2400 mg/m² 46-hour continuous infusion, Q2W. | Codons 12, 13, 59, 61, 117, 146 | Codons 12, 13, 59, 61, 117, 146 | Codons 600 |
|               | FOLFIRI (KRAS exon 2-wt: 351; RAS-wt: 189; RAS exon 2-wt but other RAS-mt: 31) | FOLFIRI: irinotecan 180 mg/m², day 1, infused over 30 to 90 min; leucovorin 200 mg/m² l-form, or 400 mg/m² racemic, infused over 2 h; fluorouracil 400 mg/m² IV bolus and 2400 mg/m² 46-hour continuous infusion, Q2W. | Codons 12, 13, 59, 61, 117, 146 | Codons 12, 13, 59, 61, 117, 146 | Codons 600 |
| FIRE3 2013     | FOLFIRI + Bev. (KRAS exon 2-wt: 143; RAS-wt: 82; KRAS exon 2-wt but other RAS-mt: 27) | FOLFIRI: irinotecan 180 mg/m² IV infusion on day 1; leucovorin 200 mg/m² IV infusion; fluorouracil 400 mg/m² IV bolus and 600 mg/m² 22-hour continuous infusion on days 1 and 2, Q2W. | Codons 12, 13, 59, 61, 117, 146 | Codons 12, 13, 59, 61, 117, 146 | Codons 600 |
|               | FOLFIRI (KRAS exon 2-wt: 351; RAS-wt: 189; RAS exon 2-wt but other RAS-mt: 31) | FOLFIRI: irinotecan 180 mg/m², day 1, infused over 30 to 90 min; leucovorin 200 mg/m² l-form, or 400 mg/m² racemic, infused over 2 h; fluorouracil 400 mg/m² IV bolus and 2400 mg/m² 46-hour continuous infusion, Q2W. | Codons 12, 13, 59, 61, 117, 146 | Codons 12, 13, 59, 61, 117, 146 | Codons 600 |
|               | FOLFIRI (KRAS exon 2-wt: 351; RAS-wt: 189; KRAS exon 2-wt but other RAS-mt: 31) | Bev.: 5 mg/kg, Q2W. | Codons 12, 13, 61, 146 | Codons 12, 13, 61, 146 | Codons 600 |
|               | mFOLFOX6/FOLFIRI + Cetux. (KRAS exon 2-wt: 578; RAS-wt: 270) | mFOLFOX6: oxaliplatin 85 mg/m² IV infused over 4 h followed by leucovorin 400 mg/m² IV over 2 h followed by 5-FU 400 mg/m² IV bolus, then 2400 mg/m² continuous IV infusion over 46–48 h. | – | – | – |
|               | mFOLFOX6/FOLFIRI + Bev. (KRAS exon 2-wt: 559; RAS-wt: 256) | FOLFIRI: irinotecan 180 mg/m² IV infused over 90 min followed by leucovorin 400 mg/m² IV over 2 h followed by 5-FU 400 mg/m² IV bolus following leucovorin then 2400 mg/m² continuous IV infusion over 46–48 h. | – | – | – |

Abbreviations: -wt = wild-type; -mt = mutations; Bev. = Bevacizumab; Panit. = panitumumab; Cetux. = cetuximab; IV = intravenous.
relative risk (RR). Association between RAS status and PFS or OS was expressed as a hazard ratio (HR). We also investigated whether efficacy of anti-EGFR mAb + 5-FU infusion based chemotherapy in patients with KRAS exon 2-wt was affected by different prognostic factors, such as sex, age, liver metastasis only, ECOG score, primary lesion and WBC count. Regrettably, only stratified PFS were performed by KRAS exon 2-wt, as stratified HRs of OS were not published until now. Heterogeneity among trials was assessed with Cochrane’s Q statistic. Inconsistency was quantified with the $I^2$ statistic \([100 \% \times (Q - df) / Q]\).
Pennesi et al. (1980) and Begg's funnel plots and Egger's linear regression test were used to assess publication bias (Sterne et al., 2001). All the statistical analyses were performed with STATA 11.0 software.

3. Results

3.1. Study characteristics

Fig. 1 showed the process of literature search and selection. First, 290 papers were found in the databases. Second, 39 RCTs about the efficacy of anti-EGFR moAb in mCRC were screened. Third, 6 RCTs that fit our criteria were included. Fourth, one abstract published in the 2014 ASCO GI annual meetings were included. Because the included RCTs had updated papers, finally, 10 papers that described 7 RCTs of the efficacy and safety of anti-EGFR moAb + 5-FU infusion based chemotherapy by RAS status in first-line treatment of mCRC were included.

The 7 RCTs included 10 papers are randomized, multicenter, controlled trials (Maughan et al., 2011; Bokemeyer et al., 2009; Bokemeyer et al., 2015; Van Cutsem et al., 2011; Van Cutsem et al., 2015; Douillard et al., 2013; Schwartzberg et al., n.d.; Stintzing et al., 2012; Heinemann et al., 2014; Venook et al., 2014). The OPUS (Bokemeyer et al., 2009; Bokemeyer et al., 2015), CRYSTAL (Van Cutsem et al., 2011; Van Cutsem et al., 2015), PRIME (Douillard et al., 2013), PEAK (Schwartzberg et al., n.d.) and FIRE3 (Stintzing et al., 2012; Heinemann et al., 2014), studies provided data of patients with RAS-wt mCRC, whereas the COIN (Maughan et al., 2011) and CALGB/SWOG 80405 (Venook et al., 2014) studies provided data of patients with KRAS exon 2-wt mCRC. In the COIN (Maughan et al., 2011) study, for the OS HR of patients with KRAS exon 2-wt, only data calculated after pooling both the OxCap and OxFU arms together were available (Table 1). A total of 4166 patients with KRAS exon 2-wt mCRC were considered in the meta-analysis, of whom 2102 were in anti-EGFR moAb + 5-FU infusion based chemotherapy groups, and 2064 were in control groups. Of 2004 patients with RAS-wt mCRC, 1004 were in anti-EGFR moAb + 5-FU infusion based chemotherapy groups, and 1000 in control groups. Of 318 patients with KRAS exon 2-wt but other RAS mutations, 156 were in anti-EGFR moAb + 5-FU infusion based chemotherapy groups, and 162 were in control groups. Jadad scores of the 10 papers were 6–7, which meant they were papers with high quality. Details are shown in Table 1.

3.2. Efficacy according to tumor RAS status

3.2.1. KRAS exon 2-wt and PFS, OS and ORR

Patients with KRAS exon 2-wt mCRC benefited from anti-EGFR moAb + 5-FU infusion based chemotherapy. Compared with
Fig. 4. PFS by baseline risk factor.
chemotherapy alone, adding anti-EGFR moAb significantly improved PFS (HR: 0.74; CI: 0.65–0.83; P < 0.001, fixed-effect model; 4 studies, 1745 patients; I² = 0.0%, P = 0.456; Fig. 2a), OS (HR: 0.88; CI: 0.80–0.97; P = 0.008, fixed-effect model; 4 studies, 2230 patients; I² = 44.1%, P = 0.147; Fig. 2b) and ORR (RR: 1.34; CI: 1.10–1.62, P = 0.003; 4 studies, 2230 patients; I² = 81.5%, P = 0.001; Fig. 2c). Compared with Bevacizumab (Bev) + 5-FU infusion based chemotherapy, adding anti-EGFR moAb did not prolong PFS (HR: 1.02; CI: 0.93–1.12, P = 0.706, fixed-effect model; 3 studies, 2014 patients; I² = 8.2%, P = 0.337; Fig. 2a). But adding anti-EGFR moAb significantly prolonged OS (HR: 0.83; CI: 0.73–0.94; P = 0.003, fixed-effect model; 3 studies, 2014 patients; I² = 55.9%, P = 0.103; Fig. 2b), and adding anti-EGFR moAb did not improve ORR (RR: 1.07; CI: 0.96–1.20, P = 0.21; 2 studies, 2014 patients; I² = 0.0%, P = 0.896; Fig. 2c).

3.2.2. KRAS exon 2-wt with other RAS mutations; PFS and OS

PFS was shorter in anti-EGFR moAb + 5-FU infusion based chemotherapy arms compared with Bev + 5-FU infusion based chemotherapy arms (HR: 1.62, CI: 1.08–2.42, P = 0.019, fixed-effect model; 2 studies, 116 patients; I² = 62.7%, P = 0.101; Fig. 3a). No difference of OS was observed between adding anti-EGFR moAb and Bev (HR: 0.72, CI: 0.25–2.05, P = 0.534, random-effect model; 2 studies, 116 patients; I² = 77.8%, P = 0.034; Fig. 3b). No difference of PFS and OS was observed between adding anti-EGFR moAb and chemotherapy alone (PFS; HR: 1.06, CI: 0.73–1.54, P = 0.767, fixed-effect model; 3 studies, 202 patients; I² = 0.0%, P = 0.471; Fig. 3a; OS: HR: 1.29, CI: 0.94–1.78, P = 0.113; 3 studies, 202 patients; I² = 0.0%, P = 0.866; Fig. 3b). The effect of anti-EGFR moAb on KRAS exon 2-wt but other RAS mutations mCRC patients was consistent with KRAS exon 2 mutations (Douillard et al., 2013).

3.2.3. RAS-wt but BRAF mutation and PFS and OS

Further retrospective analysis of CRYSTAL and OPUS enlarged the sample and provided more evidence about the relationship between efficacy of anti-EGFR moAb + 5-FU infusion based chemotherapy and BRAF status (Bokemeyer et al., 2012). Totally, three papers included four RCTs performed BRAF testing (n = 182) (Schwartzberg et al., n.d.; Heinemann et al., 2014; Bokemeyer et al., 2012). Because NRAS and BRAF were mutually exclusive (De Roock et al., n.d.), we pooled the HRs of four studies. Conclusively, RAS-wt but BRAF mutation mCRC patients did not benefit from adding anti-EGFR moAb (PFS, HR 0.84, CI 0.57–1.28, P = 0.403, fixed-effect model; 4 studies, 182 patients; I² = 58.5%, P = 0.088, Fig. 3c; OS: HR 0.78, CI 0.54–1.14, P = 0.159, fixed-effect model; 4 studies, 182 patients; I² = 0.0%, P = 0.475; Fig. 3d).

3.3. Subgroup analysis

Estimation of the effect of anti-EGFR moAb (vs. chemotherapy alone) on PFS was stratified by various prognostic factors (Fig. 4). Only HRs of PFS in patients with KRAS exon 2-wt mCRC were available in 3 RCTs (Maughan et al., 2011; Bokemeyer et al., 2009; Bokemeyer et al., 2015; Douillard et al., 2013). A random-effect model was used to perform the meta-analysis due to the heterogeneity in some subgroups.

3.3.1. Sex

PFS was improved by anti-EGFR moAb + 5-FU infusion based chemotherapy, significantly for male mCRC patients (HR: 0.79, CI: 0.68–0.92, P = 0.003, 926 patients), but not significantly for female patients (HR: 0.83, CI: 0.56–1.24; P = 0.373, 490 patients).

3.3.2. Age

Anti-EGFR moAb + 5-FU infusion based chemotherapy improved PFS for mCRC patients both younger and older than 65 years; differences were not significant (<65 years: HR: 0.76, CI: 0.54–1.06, P = 0.105, 842 patients; ≥65 years: HR: 0.88; CI: 0.72–1.06, P = 0.179, 574 patients).

3.3.3. Liver metastasis only

Anti-EGFR moAb + 5-FU infusion based chemotherapy improved PFS significantly for patients with liver metastasis alone (HR: 0.72; CI: 0.54–0.95, P = 0.018, 317 patients), but not significantly for patients with other metastasis (HR: 0.84, CI: 0.65–1.08; P = 0.171, 1099 patients).

3.3.4. ECOG

Anti-EGFR moAb + 5-FU infusion based chemotherapy improved PFS for patients with ECOG 0–1 (HR: 0.72, CI: 0.55–0.95, P = 0.019, 779 patients). However, improvement was not significant for patients with ECOG 2 (HR: 1.36, CI: 0.52–3.53; P = 0.528, 55 patients).

3.3.5. Primary site

Anti-EGFR moAb + 5-FU infusion based chemotherapy improved PFS for patients with colon primary sites (HR: 0.81, CI: 0.69–0.97, P = 0.018, 731 patients). However, improvement was not significant for patients with rectal primary sites (HR: 0.90, CI: 0.72–1.13; P = 0.360, 422 patients).

3.3.6. WBC count

Anti-EGFR moAb + 5-FU infusion based chemotherapy improved PFS in patients with WBC count both below and above or equal to 10,000, but not significantly (<10,000: HR: 0.65, CI: 0.34–1.25, P =
0.201, 568 patients; ≥10,000: HR: 1.03; CI: 0.75–1.41, P = 0.867, 187 patients).

3.4. Toxicities

Grade 3–4 toxicities from the 4 RCTs (Maughan et al., 2011; Bokemeyer et al., 2009; Bokemeyer et al., 2015; Van Cutsem et al., 2011; Van Cutsem et al., 2015; Douillard et al., 2013) are detailed in Table 2. A random-effect model was used for the meta-analysis due to heterogeneity of some subgroups. Our meta-analysis found adding anti-EGFR moAb increased risk of grade 3–4 toxicities, including rash (RR, 20.71; CI: 10.51–40.80; P < 0.001), diarrhea (RR, 1.80; CI: 1.42–2.20; P < 0.001), and anemia (RR, 3.03; CI: 1.37–6.72; P = 0.006). The two arms showed no significant differences in rates of other toxicities, including neutropenia, neurologic toxicities, infusion-related reaction, and leukopenia (Fig. 5).

3.5. Publication bias

No evidence for publication bias was shown in PFS (Begg’s test: z = 0.75, P = 0.452; Egger’s test: τ = −1.31, P = 0.261, Fig. 6) and OS.

![Table 2: Toxicities](image)
FIRE3 studies). Whether BRAF mutation is a predictive marker to anti-EGFR moAb needs more data to answer.

For KRAS exon 2-wt mCRC patients, adding anti-EGFR moAb significantly improved PFS, OS and ORR compared with chemotherapy alone (COIN, OPUS, CRYSTAL and PRIME studies). Compared with adding Bev to 5-FU infusion based chemotherapy, adding anti-EGFR moAb significantly prolonged OS, but did not improve PFS and ORR (PEAK and FIRE3 studies). KRAS exon 2-wt but other RAS mutations mCRC patients did not benefit from adding anti-EGFR moAb. Patients with KRAS exon 2-wt but with BRAF mutation did not benefit from adding anti-EGFR moAb. Whether BRAF mutation is a predictive marker to anti-EGFR moAb needs more data to answer.

In conclusion, our meta-analysis suggests that patients with KRAS exon 2-wt mCRC benefit more from anti-EGFR moAb + 5-FU infusion based chemotherapy than do those with KRAS exon 2-wt mCRC; and patients with KRAS exon 2-wt but other RAS mutations did not benefit from adding anti-EGFR moAb—similar to patients with KRAS exon 2 mutated tumors. BRAF mutation is still not the predictive marker to anti-EGFR moAb. Whether BRAF mutation is a predictive marker to anti-EGFR moAb needs more data to answer. Which is the better choice for backbone chemotherapy in first-line treatment and which is the optimal sequence for addition of target drugs will become clearer. With development of molecular studies, more really beneficial patients to anti-EGFR moAb will be enriched.

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![Publication bias](image)
