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REVIEW

Role of targeted therapy in metastatic colorectal cancer

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Abstract

Colorectal cancer (CRC) is a significant cause of cancer-related morbidity and mortality all over the world. Improvements of cytotoxic and biologic agents have prolonged the survival in metastatic CRC (mCRC), with a median overall survival of approximately 2 years and more in the past two decades. The biologic agents that have proven clinical benefits in mCRC mainly target vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR). In particular, bevacizumab targeting VEGF and cetuximab and panitumumab targeting EGFR have demonstrated significant survival benefits in combination with cytotoxic chemotherapy in the first-line, second-line, or salvage setting. Aflibercept, ramucirumab, and regorafenib are also used in second-line or salvage therapy. Recent retrospective analyses have shown that *KRAS* or *NRAS* mutations were negative predictive markers for anti-EGFR therapy. Based on the evidence from large randomized clinical trials, personalized therapy is necessary for patients with mCRC according to their tumor biology and characteristics. The aim of this paper was to summarize the results of the major randomized clinical trials and highlight the benefits of the molecular targeted agents in patients with mCRC.

Key words: Metastatic colorectal cancer; Aflibercept; Ramucirumab; Regorafenib; Cetuximab; Panitumumab; Targeted therapy; Bevacizumab

Core tip: The development of molecular targeted agents contributes to prolonging survival of patients with metastatic colorectal cancer (mCRC). One anti-vascular endothelial growth factor agent, bevacizumab, and two anti-epidermal growth factor receptor (EGFR) agents, cetuximab and panitumumab, have demonstrated clinical benefits in first-line, second-line, or salvage therapy in combination with cytotoxic chemotherapy. Moreover, *RAS* mutation has been proven to be a negative biomarker for anti-EGFR therapy in recent retrospective analyses. This article summarizes the evidence from large clinical trials and highlights the benefit of the molecular targeted agents in patients with mCRC.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common causes of cancer-related mortality[1]. Earlier diagnosis through screening colonoscopy and improvements of treatment techniques have contributed to prolonged survival in the curable stage of CRC[2]. Nevertheless, metastases are present in about 25% of patients with CRC at the time of diagnosis, and almost 50% of patients with CRC in total will develop metastases. Unfortunately, although the prognosis is usually limited in metastatic CRC (mCRC), systemic chemotherapy can control the disease, alleviate the symptoms related to cancer, and prolong survival[3]. Systemic chemotherapy for mCRC consists mainly of fluoropyrimidines [intravenous 5-fluorouracil (5-FU) and oral capecitabine], irinotecan, and oxaliplatin. The most common treatment regimens for mCRC are FOLFIRI [bolus and infusional 5-FU/leucovorin (LV) plus irinotecan], FOLFOX (bolus and infusional 5-FU/LV plus oxaliplatin), and CapeOX (oral capecitabine plus oxaliplatin). These combination therapies have contributed to improving the response rate (RR) and prolonging survival in patients with mCRC[4-6].

Since the Mid 2000s, biologic agents have been developed and demonstrated further clinical benefit in combination with cytotoxic chemotherapy. The biologic agents used for mCRC target angiogenesis (bevacizumab, aflibercept, ramucirumab, and regorafenib) and the epidermal growth factor receptor (EGFR) (cetuximab and panitumumab)[7]. Bevacizumab has shown clinical benefit with both irinotecan-based and oxaliplatin-based regimens[8-11]. Moreover, the continuation of bevacizumab after failure of first-line bevacizumab-containing chemotherapy was found to contribute to prolonging the survival of patients with mCRC[12]. Anti-EGFR antibody agents, cetuximab and panitumumab, demonstrated a survival benefit in mCRC patients[13,14]. At first, these agents were used in all mCRC patients, and then, no benefit of anti-EGFR agents was observed in mCRC tumors with activating mutation of *KRAS* exon 2[15-17]. In addition, several recent studies have shown that all-*RAS* mutations in exon 2, 3, or 4 of *KRAS* or *NRAS* were negative predictive factors for anti-EGFR treatment[18-20]. From these results, cetuximab and panitumumab have been used only in mCRC patients with *RAS* wild type.

The results of the major randomized clinical trials are summarized, and the benefits of the molecular targeted agents in patients with mCRC are highlighted.

ANTI-ANGIOGENIC AGENTS

Angiogenesis is a constitutional process to form a new vascular network, through budding from host vascular endothelial cells and inserting into the pre-existing blood vessels. Especially in malignant tumors, angiogenesis plays important roles in tumor progression, invasion, and metastasis to distant organs[21]. Vascular endothelial growth factor (VEGF) is one of the important factors that regulate tumor angiogenesis. VEGF is a family of secreted polypeptides that consists of five members [VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PIGF)][22,23]. The members of the VEGF family bind to three variants of receptors, VEGFR-1 (FLT-1), VEGFR-2 (FLK-1/KDR), and VEGFR-3 (FLT-4)[24,25]. VEGFR-2 is mainly responsible for the angiogenic pathway, whereas VEGFR-1 can act as a soluble circulating form that regulates VEGF binding to cell surface receptor[26].

Anti-angiogenic agents exert their anti-neoplastic activities not only by inhibiting tumor angiogenesis but also by normalizing the tumor blood vessels. Vessel normalization ensures drug delivery to the tumor, which can increase the efficacy of cytotoxic agents[27]. Thus, inhibition of angiogenesis has become a key strategy in cancer treatment[28,29].

Bevacizumab

Bevacizumab is a recombinant humanized monoclonal IgG antibody that selectively binds to VEGF-A, and it demonstrates anti-tumor activity by blocking VEGFR2[30,31]. It was first approved in 2004 by the United States Food and Drug Administration (FDA) for CRC in combination with other cytotoxic agents. Because of its functional activity, adverse events are mainly related to blood vessels. In several large trials, vascular-related adverse events such as hypertension, arterial/venous thromboembolic events, bleeding, gastrointestinal perforation, wound healing complications, fistula/intra-abdominal abscess, and proteinuria were reported[32,33]. Rarely, reversible posterior leukoencephalopathy, which can cause various neurological symptoms, has been reported[34]. Most of these adverse events are manageable by appropriate medication and withdrawal of bevacizumab.

First-line treatment: The benefit of bevacizumab added to chemotherapy was first reported in the AVF2107g trial[8], in which 813 previously untreated mCRC patients were randomly assigned to either IFL (irinotecan, fluorouracil, and leucovorin) plus bevacizumab or IFL plus placebo. The addition of bevacizumab showed significant improvements in overall survival [OS, 20.3 mo *vs* 15.6 mo, hazard ratio (HR) = 0.66, $P < 0.001$], progression-free survival (PFS, 10.6 mo *vs* 6.2 mo, HR = 0.54, $P < 0.001$), and RR (44.8% *vs* 34.8%, $P = 0.004$). From this result, the FDA first approved bevacizumab in combination with 5-FU-based first-line chemotherapy in mCRC. Later, FOLFIRI plus bevacizumab showed a further survival benefit compared with modified IFL (mIFL) plus bevacizumab in the phase Ⅲ BICC-C trial[35]. The FOLFIRI arm had

a trend to longer PFS (11.2 mo *vs* 8.3 mo, *P* = 0.037) and OS (28.0 mo *vs* 19.2 mo, *P* = 0.28) compared with the mIFL arm. The RR was not significantly different between the two arms (57.9% *vs* 53.3%). Based on these results, FOLFIRI plus bevacizumab also became one of the standard regimens in the first-line treatment of mCRC.

Oxaliplatin-based chemotherapy combined with bevacizumab was evaluated in the NO16966 trial[9,36]. In this pivotal 2x2 factorial randomized phase Ⅲ trial, 1400 mCRC patients were assigned to oxaliplatin-based first-line chemotherapy (FOLFOX4/CapeOX) with or without bevacizumab. Although the median OS (21.3 mo *vs* 19.9 mo, HR = 0.89, *P* = 0.0769) and RR [38% *vs* 38%, odds ratio (OR) = 1.00, *P* = 0.99] were not significantly different between the two arms, the median PFS was significantly improved in the bevacizumab-containing arm compared with the placebo arm (9.4 mo *vs* 8.0 mo, HR = 0.83, *P* = 0.0023). Similar results were shown in the randomized phase Ⅱ TREE-1/2 trial, which evaluated the safety and efficacy of bevacizumab added to chemotherapy (mFOLFOX6/bFOL/CapeOX)[37]. Moreover, the benefit of cetuximab added to chemotherapy plus bevacizumab was evaluated in the CAIRO2 trial[38]. However, in this phase Ⅲ trial, the combination of CapeOX plus cetuximab and bevacizumab resulted in a significant decrease in PFS and no difference in OS and RR compared to CapeOX plus bevacizumab alone. In the *KRAS* wild type population, there were no significant differences in PFS (10.5 mo *vs* 10.4 mo, *P* = 0.30) and OS (21.8 mo *vs* 22.4 mo, *P* = 0.64), while RR was higher in chemotherapy with cetuximab than in chemotherapy without cetuximab. In the CAIRO2 trial, although patients with *KRAS* mutant type might have had a worse outcome for PFS and OS, no survival benefit of adding cetuximab onto bevacizumab plus chemotherapy was observed even in the *KRAS* wild population. Moreover, a meta-analysis also showed the poor prognosis of the combination of anti-EGFR agents and bevacizumab[39].

Tegafur/gimeracil/oteracil (S-1) plus oxaliplatin (SOX regimen) for mCRC patients showed efficacy and safety in several trials from Asia[40]. The phase Ⅲ SOFT trial investigated the non-inferiority of SOX plus bevacizumab in comparison with mFOLFOX6 plus bevacizumab[41]. The median PFS was 11.7 mo in the SOX plus bevacizumab arm compared with 11.5 mo in the mFOLFOX6 plus bevacizumab arm [HR = 1.04, *P* = 0.015 (non-inferiority)], and OS was 29.6 mo *vs* 29.7 mo [HR = 1.018, *P* = 0.0133 (non-inferiority)].

Recently, a combination of all cytotoxic agents (5-FU, oxaliplatin, and irinotecan) was developed to maximize tumor response as the FOLFOXIRI regimen in the treatment of mCRC[42]. Based on this strategy, the efficacy and safety of FOLFOXIRI plus bevacizumab were evaluated in the TRIBE trial[43]. In this trial, 508 mCRC patients were randomly assigned to receive FOLFOXIRI plus bevacizumab or FOLFIRI plus bevacizumab. Although FOLFOXIRI plus bevacizumab did not improve OS (31.0 mo *vs* 25.8 mo, HR = 0.83, *P* = 0.125), a prolonged PFS (12.1 mo *vs* 9.7 mo, HR = 0.77, *P* = 0.006) and a higher RR (65% *vs* 53%, OR = 1.64, *P* = 0.006) were observed in the FOLFOXIRI plus bevacizumab arm compared with the FOLFIRI plus bevacizumab arm. The incidence of grade 3/4 adverse events, especially neutropenia, diarrhea, and stomatitis, was significantly higher in the FOLFOXIRI plus bevacizumab arm than in the FOLFIRI plus bevacizumab arm.

In elderly patients, there is no clear evidence of safety with the combination of bevacizumab with oxaliplatin or irinotecan-based chemotherapy. The AVEX trial was designed to evaluate the efficacy and safety of bevacizumab plus capecitabine in mCRC patients aged 70 years and older[44]. In this trial, 280 elderly patients with a median age of 76 years (range 70-87 years) were randomized to bevacizumab plus capecitabine or capecitabine alone. PFS was improved with the addition of bevacizumab compared to capecitabine alone (9.1 mo *vs* 5.1 mo, HR = 0.53, *P* < 0.0001). Improved RR was also observed with bevacizumab plus capecitabine (19.3% *vs* 10.0%, *P* = 0.042), though OS was not significantly different (20.7 mo *vs* 16.8 mo, HR = 0.79, *P* = 0.182). Although the incidence of grade 3 or worse adverse events related to chemotherapy was slightly higher in the combination group (40% *vs* 22%), the combination of bevacizumab and capecitabine was a well-tolerated regimen (Table 1).

Second-line and salvage treatment or beyond progression: In the E3200 trial, FOLFOX plus bevacizumab as second-line therapy in patients with mCRC after first-line irinotecan-based therapy without bevacizumab demonstrated significantly longer PFS and OS compared with the control arm of FOLFOX alone (PFS 7.3 mo *vs* 4.7 mo, HR = 0.61, *P* < 0.0001; OS 12.9 mo *vs* 10.8 mo, HR = 0.75, *P* = 0.0011)[45]. It should be noted that bevacizumab was not administered in first-line therapy, and the dose of bevacizumab was higher (10 mg/kg) in this trial.

Furthermore, continuation of bevacizumab after disease progression in patients previously treated with bevacizumab seemed to have benefit in the large observational BRiTE study[46]. Based on this result, an open-label, phase Ⅲ, ML18147 trial was conducted to evaluate the survival benefit of continuing bevacizumab as second-line chemotherapy[12]. The use of bevacizumab beyond progression showed better OS (11.2 mo *vs* 9.8 mo, HR = 0.81, *P* = 0.0062) and PFS (5.7 mo *vs* 4.1 mo, HR = 0.68, *P* < 0.0001) compared with chemotherapy alone.

TAS-102 is a novel oral cytotoxic agent that contains the thymidine-based nucleic acid analogue, trifluridine, and a thymidine phosphorylase inhibitor, tipiracil hydrochloride. In salvage line treatment of mCRC, it was reported that TAS-102 could significantly improve OS compared with placebo in the RECOURSE trial[47]. Recently, the phase Ⅰ/Ⅱ C-TASK FORCE trial was conducted to investigate the efficacy and safety of

Table 1 Clinical trials of anti-angiogenic therapies in metastatic colorectal cancer

Trial name	Regimens	*n*	ORR	PFS (mo)	OS (mo)
First-line chemotherapy					
AVF2017g	IFL + Bevacizumab	402	44.8%	10.6	20.3
BICC-C	FOLFIRI + Bevacizumab	57	57.9%	11.2	28.0
NO16966	FOLFOX/CapeOX + Bevacizumab	699	38%	9.4	21.3
TREE-1/2	FOLFOX + Bevacizumab	71	52%	9.9	26.1
CAIRO2	CapeOX + Bevacizumab	378	50%	10.7	20.3
SOFT	SOX + Bevacizumab	256	61.5%	11.7	29.6
TRIBE	FOLFOXIRI + Bevacizumab	252	65.1%	12.1	31.0
AVEX[1]	Capecitabine + Bevacizumab	140	19.3%	9.1	20.7
Second-line, salvage-line chemotherapy, or beyond progression					
E3200	FOLFOX + Bevacizumab	286	22.7%	7.3	12.9
ML18147	Chemotherapy + Bevacizumab	410	5.4%	5.7	11.2
C-TASK FORCE	TAS-102 + Bevacizumab	25	4.0%	5.6	11.2
VELOUR	FOLFIRI + Aflibercept	612	19.8%	6.9	13.5
RAISE	FOLFIRI + Ramucirumab	536	13.4%	5.7	13.3
CORRECT	Regorafenib	505	1.0%	1.9	6.4

[1]AVEX trial enrolled mCRC patients aged 70 years and older. ORR: Objective response rate; PFS: Progression-free survival; IFL: Bolus 5-fluorouracil/leucovorin/irinotecan; FOLFIRI: Bolus and infusional 5-fluorouracil/leucovorin/irinotecan; FOLFOX: Bolus and infusional 5-fluorouracil/leucovorin/oxaliplatin; CapeOX: Capecitabine/oxaliplatin; SOX: S-1 (tegafur/gimeracil/oteracil)/oxaliplatin; FOLFOXIRI: Infusional 5-fluorouracil/leucovorin/irinotecan/oxaliplatin; OS: Overall survival; mCRC: Metastatic colorectal cancer.

TAS-102 plus bevacizumab in the salvage line setting. Median OS was 11.2 mo and PFS was 5.6 mo. In addition, although the RR was only 4.0%, the disease control rate was 72% with tolerable toxicity. However, the sample size was quite small (n = 25)[48] (Table 1).

Aflibercept

Aflibercept is a recombinant fusion protein that can bind to VEGF-A, VEGF-B, and PIGF. It can act as a soluble decoy receptor, preventing these ligands from binding to their receptors and inhibiting the VEGF pathway. In the VELOUR study, aflibercept plus FOLFIRI demonstrated significant improvements in OS (13.5 mo *vs* 12.1 mo, HR = 0.82, P = 0.032) and PFS (6.9 mo *vs* 4.7 mo, HR = 0.76, P < 0.0001) compared with placebo plus FOLFIRI in previously treated mCRC patients[49]. The RR was 19.8% in the aflibercept plus FOLFIRI arm and 11.1% in the FOLFIRI alone arm (P = 0.0001). The profile of adverse events was similar to that previously reported with bevacizumab, but some adverse events associated with cytotoxic agents were reported at a higher incidence in the aflibercept arm (Table 1).

Ramucirumab

Ramucirumab is a human IgG-1 monoclonal antibody targeting the extracellular domain of VEGFR-2, which is the primary mediator of the VEGF pathway. By binding to VEGFR-2, ramucirumab prevents all VEGF ligands from binding to VEGFR-2 and inhibits the VEGF pathway. In the phase Ⅲ RAISE study, 1072 patients with disease progression on bevacizumab, oxaliplatin, and fluoropyrimidine were randomized to ramucirumab plus FOLFIRI or FOLFIRI alone as second-line treatment[50]. Ramucirumab plus FOLFIRI demonstrated better OS (13.3 mo *vs* 11.7 mo, HR = 0.84, P = 0.0219) and PFS (5.7 mo *vs* 4.5 mo, HR = 0.79, P < 0.0005) than FOLFIRI alone. The RR was similar in the two arms (13.4% in ramucirumab plus FOLFIRI *vs* 12.5% in FOLFIRI alone), as was the frequency of serious adverse events (36% in ramucirumab plus FOLFIRI *vs* 31% in FOLFIRI alone). From this result of RAISE, ramucirumab was approved in 2015 by FDA for mCRC in combination with FOLFIRI (Table 1).

Regorafenib

Regorafenib is an oral multi-kinase blocker that inhibits the activity of several protein kinases related to the angiogenic pathway (VEGFR-1, VEGFR-2, VEGFR-3, TIE-2), the oncogenic pathway (KIT, RET, RAF1, BRAF), and the tumor microenvironment (PDGFR and FGFR)[51]. The CORRECT trial was conducted to evaluate the efficacy and safety of regorafenib in patients with mCRC who had progressed after all approved standard therapies[52]. Patients treated with regorafenib had slightly prolonged OS (6.4 mo *vs* 5.0 mo, HR = 0.77, P = 0.0052) and PFS (1.9 mo *vs* 1.7 mo, HR = 0.49, P < 0.0001) compared with placebo. The most frequent adverse events of grade 3 or higher were hand-foot skin reaction, fatigue, diarrhea, hypertension, and rash or desquamation. Of note, fatal drug-induced liver injury was observed (Table 1).

ANTI-EGFR AGENTS

EGFR is a transmembrane glycoprotein that belongs to the human epidermal growth factor receptor (HER)-erbB family of tyrosine kinase receptors[53]. Ligand binding to EGFR leads to the autophosphorylation of the intracellular domain and activates the downstream signaling pathway, including RAS/RAF/MAPK, STAT, and PI3K/AKT. The activation of the signaling pathway modulates cell proliferation, adhesion, angiogenesis,

migration, and metastasis[54,55].

Cetuximab and panitumumab are anti-EGFR monoclonal antibodies used for mCRC in daily practice. The mechanisms of cetuximab and panitumumab are described below. At present, the use of cetuximab or panitumumab is restricted only to mCRC patients with *KRAS* and *NRAS* wild type because it was found that cetuximab or panitumumab had no effect in mCRC patients with the activating mutation of *KRAS* and *NRAS* oncogene[20,56].

Cetuximab

Cetuximab is a chimeric, anti-EGFR monoclonal antibody of the IgG1 class targeted against the extracellular domain of the EGFR. By binding to the EGFR, cetuximab blocks intracellular EGFR signaling and modulates tumor cell growth by inhibiting proliferation, angiogenesis, and differentiation, stimulating apoptosis, and preventing metastasis[57,58]. Cetuximab was first approved in 2004 in combination with irinotecan for mCRC patients with irinotecan-refractory disease. After that, several experimental analyses showed that the activating mutation of *KRAS* exon 2 was associated with intrinsic resistance to cetuximab. Given these findings, cetuximab was used only in mCRC patients with *KRAS* wild type[15,56]. Moreover, recently, some reports revealed that use of anti-EGFR drugs for mCRC contributed to acquisition of a *KRAS* mutation[59,60]. Misale *et al*[59] offered two possible explanations for the discordant results of *KRAS*: Heterogeneity of *KRAS* status within the primary tumor; and clonal selection during the process of metastasis. In this report, among 10 patients with *KRAS* wild type who acquired resistance to anti-EGFR therapy, 6 patients had the *KRAS* mutation after progression on anti-EGFR therapy. In the six patients for whom sufficient pre-treatment tumor samples were available for *KRAS* testing, *KRAS* mutations were found to be absent at pre-treatment. Similarly, Diaz *et al*[60] showed that emergence of mutant *KRAS* from wild type *KRAS* was a mediator of acquired resistance to anti-EGFR antibodies. These results indicate that treatment with anti-EGFR antibodies is associated with the acquisition of secondary *KRAS* mutations.

The most common toxicities are skin rash and hypomagnesemia[61,62]. To prevent severe skin toxicity, preventive skin treatments are often performed for patients treated with cetuximab.

First-line treatment in KRAS-WT mCRC: The efficacy of cetuximab combined with chemotherapy in the first-line setting for mCRC was evaluated in two pivotal clinical trials: The phase Ⅲ CRYSTAL study and the phase Ⅱ OPUS study[63-66].

In the CRYSTAL study, 1198 mCRC patients were randomly assigned to two treatment groups: FOLFIRI plus cetuximab or FOLFIRI alone. Tumor samples from 1063 patients were used for *KRAS* mutation analysis, and 397 patients (37%) had *KRAS* codon 12 and 13 mutations. Of 666 patients (63%) with *KRAS* wild type, the benefit of addition of cetuximab to FOLFIRI was demonstrated as significantly improved RR (57.3% *vs* 39.7%, OR = 2.07, $P < 0.001$), PFS (9.9 mo *vs* 8.4 mo; HR = 0.70, $P = 0.0012$), and OS (23.5 mo *vs* 20.0 mo; HR = 0.80, $P = 0.0093$) compared with FOLFIRI alone. In the OPUS study, 337 mCRC patients received either FOLFOX-4 alone or FOLFOX-4 plus cetuximab. *KRAS* analysis was performed in 315 of the 337 cases. Among these patients, 179 (57%) were *KRAS* wild type. In the *KRAS* wild type population, patients treated with cetuximab in combination with FOLFOX-4 demonstrated a higher RR (57% *vs* 34%; OR = 2.551, $P = 0.0027$) and a better PFS (8.3 mo *vs* 7.2 mo; HR = 0.567, $P = 0.0064$) compared with those treated with FOLFOX-4 alone. No benefit in terms of OS was observed (22.8 mo *vs* 18.5 mo; HR = 0.855, $P = 0.39$).

In contrast, the phase Ⅲ COIN trial including 1630 patients with mCRC who were randomized to an oxaliplatin-based regimen (FOLFOX or CapeOX) with or without cetuximab did not show any benefit with the addition of cetuximab to chemotherapy in terms of PFS (8.6 mo *vs* 8.6 mo; HR = 0.96, $P = 0.60$) and OS (17.0 mo *vs* 17.9 mon; HR = 1.04, $P = 0.67$) compared with chemotherapy alone, even in the *KRAS* wild type population[67,68]. However, exploratory subgroup analyses demonstrated that the cohort of patients treated with FOLFOX plus cetuximab showed improved PFS (HR = 0.72, $P = 0.037$), while the cohort of CapeOX plus cetuximab had no significant difference in PFS compared with chemotherapy alone (HR = 1.02, $P = 0.88$). The RR improved from 57% to 64% with the addition of cetuximab to the oxaliplatin-based regimen. In the COIN trial, exploratory analyses were conducted in order to identify somatic molecular profile of the EGFR pathway, and its relationship to the site of the primary and metastases[69]. *KRAS* mutations were more common in the right colon as compared to those from the left colon, and *BRAF* mutations were more common from the transverse and right colon as compared to those from the left colon. *KRAS* mutations were associated with lung-only metastases, *BRAF* mutations with peritoneal and nodal-only metastases, and microsatellite instability was associated with nodal-only metastases. At the point of differences between primary cites, other study reported that hepatic and pulmonary metastases were more frequently found in left-sided carcinomas, and peritoneal metastasis in right-sided carcinomas in the analyses based on 17641 patients with mCRC[70]. Moreover, NORDIC Ⅶ was conducted to investigate the efficacy of cetuximab combined with the FLOX regimen[71]. Patients were randomized to the following three arms: FLOX alone, cetuximab and FLOX, or cetuximab combined with intermittent FLOX. Even in patients with *KRAS* wild type, there was no evidence that cetuximab adds a significant benefit to NORDIC FLOX in first-line treatment of mCRC. From these negative results of the COIN and NORDIC Ⅶ studies, it seems that neither CapeOX nor FLOX is suitable for combination therapy with cetuximab.

Table 2 Clinical trials of anti-epidermal growth factor receptor therapies in metastatic colorectal cancer with *KRAS* wild type

Trial name	Regimens	*n*	ORR	PFS (mo)	OS (mo)
First-line chemotherapy					
CRYSTAL	FOLFIRI + Cetuximab	316	57.3%	9.9	23.5
OPUS	FOLFOX + Cetuximab	159	57%	8.3	22.8
COIN	FOLFOX/CapeOX + Cetuximab	362	64%	8.6	17.0
NORDIC-Ⅶ	FLOX + Cetuximab	97	46%	7.9	20.1
PRIME	FOLFOX + Panitumumab	325	55%	9.6	23.9
Second-line, salvage-line chemotherapy, or beyond progression					
20050181 trial	FOLFIRI + Panitumumab	303	36%	6.7	14.5
PICCOLO	Irinotecan + Panitumumab	230	34%	5.5	10.4
CO.17	Cetuximab	117	13%	3.7	9.5
20020408 trial	Panitumumab	124	17%	12.3 wk	8.1

ORR: Objective response rate; PFS: Progression-free survival; OS: Overall survival; FOLFIRI: Bolus and infusional 5-fluorouracil/leucovorin/irinotecan; FOLFOX: Bolus and infusional 5-fluorouracil/leucovorin/oxaliplatin; CapeOX: Capecitabine/oxaliplatin; FLOX: Bolus 5-fluorouracil/leucovorin/oxaliplatin.

In adding cetuximab to cytotoxic chemotherapy, the FOLFOX or FOLFIRI regimen is considered the best partner in mCRC patients with *KRAS* wild type. Thus, based on the positive results of the CRYSTAL and OPUS studies, the addition of cetuximab to FOLFOX or FOLFIRI was established as a gold standard in mCRC patients with *KRAS* wild type (Table 2).

Second-line and salvage treatment in KRAS-WT mCRC: Cetuximab monotherapy was compared with best supportive care (BSC) in heavily pretreated patients with mCRC after failure of fluoropyrimidines, irinotecan, and oxaliplatin (NCIC CO.17 trial)[72]. A total of 572 mCRC patients were randomized to cetuximab plus BSC or BSC alone. Cetuximab improved OS and PFS and preserved quality of life measures. After the CO.17 trial, a retrospective analysis was performed to determine whether *KRAS* mutation status was associated with survival in the cetuximab and BSC groups[16]. A total of 69% (394/572) of the cases were examined for *KRAS* mutation status. A *KRAS* mutation was detected in 40.9% of the cetuximab group and in 42.3% of the BSC group. For patients with *KRAS* wild tumors, treatment with cetuximab compared with supportive care alone significantly improved OS (9.5 mo *vs* 4.8 mo; HR = 0.55; $P < 0.001$) and PFS (3.7 mo *vs* 1.9 mo; HR = 0.40; $P < 0.001$).

The efficacy of cetuximab in combination with chemotherapy in the salvage setting was evaluated in two randomized clinical trials: The BOND-1 trial and the EPIC trial[13,14]. The BOND-1 trial was a randomized phase Ⅲ study that enrolled 329 patients with irinotecan-resistant mCRC. The superiority of cetuximab plus irinotecan in terms of RR and PFS was demonstrated compared with cetuximab alone. In the phase Ⅲ EPIC trial, 1298 mCRC patients who experienced first-line fluoropyrimidine and oxaliplatin treatment failure were randomly assigned to either irinotecan plus cetuximab or irinotecan alone. The addition of cetuximab to irinotecan improved RR and PFS compared with irinotecan alone. However, both trials did not show the benefit of cetuximab in combination with chemotherapy with respect to OS compared with monotherapy. So far, the detailed results of *KRAS* status in the BOND and EPIC trials have not been published (Table 2).

Panitumumab

Panitumumab is a fully human, monoclonal antibody targeting the EGFR with high affinity. The mechanism of inhibiting EGFR signaling pathway is similar to that of cetuximab, as described above[73]. Panitumumab was first approved in 2006 by the United States FDA for the treatment of EGFR-expressing mCRC with disease progression despite prior treatment. The most common toxicities are skin rash and hypomagnesemia, like cetuximab. The utility of preventive skin treatment in panitumumab therapy has been reported in prospective studies[74,75].

First-line treatment in KRAS-WT mCRC: The phase Ⅲ PRIME study was conducted in chemo-naive mCRC patients to evaluate the efficacy of panitumumab in combination with the FOLFOX-4 regimen in the first-line setting[76]. In the PRIME study, 1183 mCRC patients were randomly assigned to receive FOLFOX-4 with or without panitumumab. The *KRAS* status of the tumors was available in 1096 of these patients (93%), and 440 patients (40%) had a mutation of *KRAS* status. In the *KRAS* wild type population, the FOLFOX-4 plus panitumumab arm had significantly improved PFS compared with the FOLFOX-4 arm (9.6 mo *vs* 8.0 mo; HR = 0.80, $P = 0.002$). There was no significant difference between FOLFOX-4 plus panitumumab and FOLFOX-4 alone in terms of OS and RR (OS 23.9 mo *vs* 19.7 mo, HR = 0.83, $P = 0.072$; RR 55% *vs* 48%, OR = 1.35, $P = 0.068$). This result of the PRIME study was similar to that of the OPUS trial. From the results of these two studies (phase Ⅱ OPUS and phase Ⅲ PRIME), the efficacy of the addition of anti-EGFR agents to oxaliplatin-based chemotherapy was demonstrated (Table 2).

Second-line and salvage treatment in KRAS-WT mCRC: The role of panitumumab in combination with chemotherapy in the second-line or salvage setting for mCRC was evaluated in the following two trials. First, in the phase Ⅲ 20050181 trial, 1186 patients were enrolled and randomized to two treatment arms: FOLFIRI plus panitumumab and FOLFIRI alone[77,78]. The *KRAS* status of the tumors was investigated in 1083 cases (91%), and *KRAS* mutation was found in 45% (486/1083). In the wild type *KRAS* population, addition of panitumumab to the FOLFIRI regimen led to a significant improvement in PFS compared with FOLFIRI alone (6.7 mo *vs* 4.9 mo; HR = 0.82, *P* = 0.023). However, addition of panitumumab to chemotherapy did not show a significant difference in OS; and the FOLFIRI plus panitumumab arm had a trend to better OS than the FOLFIRI arm (14.5 mo *vs* 12.5 mo; HR = 0.92, *P* = 0.37). The RR was significantly higher in the panitumumab-containing regimen (36% *vs* 10%; OR = 5.50, *P* < 0.0001). Second, in the PICCOLO trial, irinotecan plus panitumumab was compared with irinotecan alone as a salvage treatment in patients with fluorouracil-resistant mCRC[79]. Whereas no significant difference was observed in OS between the groups (10.4 mo *vs* 10.9 mo; HR = 1.01, *P* = 0.91), the irinotecan plus panitumumab group had a longer PFS (5.5 mo *vs* 4.7 mo; HR = 0.78, *P* = 0.015) and a higher RR (34% *vs* 12%; OR = 4.12, *P* < 0.0001) than the irinotecan monotherapy group.

The efficacy of panitumumab monotherapy for *KRAS* wild type mCRC was evaluated in the phase Ⅲ 20020408 study[17,80]. Patients with mCRC were randomly assigned to either panitumumab monotherapy or BSC alone. Patients treated with panitumumab had better RR and PFS compared with those with BSC (RR 17% *vs* 0%; PFS 12.3 wk *vs* 7.3 wk, HR = 0.45, *P* < 0.0001). Although no significant difference in OS was observed between the panitumumab arm and the BSC arm (8.1 mo *vs* 7.6 mo; HR = 0.99), this was because 76% (90/119) of patients with BSC received panitumumab treatment after progression under the cross-over protocol (Table 2).

The benefit of panitumumab treatment for mCRC patients with cetuximab-refractory disease was evaluated in several clinical trials. In the PANERB trial, 106 mCRC patients with *KRAS* wild type who experienced progression on cetuximab-based chemotherapy were enrolled[81]. Of the 106 patients, 48 (45%) had an objective response with the cetuximab-containing treatment. Among these 48 patients, 15 (31%) had an objective response, and 23 (47%) in total had a clinical benefit with panitumumab therapy. On the other hand, 28 of 106 patients had disease progression on cetuximab-based treatment. Of these 28 patients, only 4 patients (14%) had clinical benefit with panitumumab therapy. Moreover, some clinical trials showed that panitumumab was not active (RR, 0%) as a salvage therapy in patients with cetuximab-resistant *KRAS* wild type mCRC[82,83].

TREATMENT STRATEGY ACCORDING TO KRAS OR ALL RAS WILD TYPE mCRC

Anti-VEGFR and anti-EGFR treatments for patients with KRAS wild type mCRC

Recently, three large randomized clinical trials (PEAK, FIRE-3, and CALGB/SWOG 80405) were conducted to compare anti-EGFR agent-containing chemotherapy with bevacizumab-containing chemotherapy in *KRAS* wild type mCRC patients in the first-line setting (Table 3).

First, the phase Ⅱ PEAK study was conducted in 285 mCRC patients with wild-type *KRAS* to compare FOLFOX plus panitumumab with FOLFOX plus bevacizumab as first-line treatment[18]. Although median PFS was similar between the panitumumab arm and the bevacizumab arm (10.9 mo *vs* 10.1 mo; HR = 0.87, *P* = 0.353), median OS was significantly prolonged in the panitumumab arm compared with the bevacizumab arm (34.2 mo *vs* 24.3 mo; HR = 0.62, *P* = 0.009). The RR was 57.8% in the panitumumab arm and 53.5% in the bevacizumab arm. Second, the phase Ⅲ FIRE-3 study was conducted to evaluate the superiority of FOLFIRI plus cetuximab to FOLFIRI plus bevacizumab in mCRC patients with *KRAS* wild type as first-line treatment[19]. A total of 592 patients with *KRAS* wild type tumors were randomly assigned and received treatment, with 297 in the FOLFIRI plus cetuximab group and 295 in the FOLFIRI plus bevacizumab group. The FIRE-3 study did not show differences in terms of RR (62% in the cetuximab group *vs* 58% in the bevacizumab group; OR = 1.18, *P* = 0.18) and PFS (10.0 mo in the cetuximab group *vs* 10.3 mo in the bevacizumab group; HR = 1.06, *P* = 0.55), while OS was prolonged in the cetuximab-containing regimen (28.7 mo in the cetuximab group *vs* 25.0 mo in the bevacizumab group; HR = 0.77, *P* = 0.017). Finally, in the CALGB/SWOG 80405 study, 1137 patients with *KRAS* wild type were randomized to two arms: Cytotoxic chemotherapy (FOLFOX or FOLFIRI) plus cetuximab or bevacizumab[84]. No benefit of the cetuximab-containing regimen was observed for PFS (10.4 mo *vs* 10.8 mo; HR = 1.04, *P* = 0.55) or OS (29.9 mo *vs* 29.0 mo; HR = 0.925, *P* = 0.34) compared with the bevacizumab-containing regimen. The RR was significantly higher in the cetuximab arm than in the bevacizumab arm (65.6% *vs* 57.2%, *P* = 0.02).

The efficacy of panitumumab combined with FOLFIRI in the second-line setting was evaluated in the phase Ⅱ SPIRITT study[85]. The SPIRITT study compared FOLFIRI in combination with panitumumab or bevacizumab for *KRAS* wild type mCRC patients with progression on a bevacizumab-containing oxaliplatin-based regimen. A total of 182 patients were randomly assigned to FOLFIRI combined with panitumumab or bevacizumab. Median PFS and OS were similar between the FOLFIRI with panitumumab arm and the FOLFIRI with bevacizumab arm (PFS 7.7 mo *vs* 9.4 mo, HR = 1.01, *P* = 0.97; OS 18.0 mo *vs* 21.4 mo; HR = 1.06, *P* = 0.75). The RR

Table 3 Clinical trials comparing anti-epidermal growth factor receptor therapy *vs* anti-vascular endothelial growth factor therapy in metastatic colorectal cancer with *KRAS* wild type

Trial name	Regimens	*n*	ORR	PFS (mo)	OS (mo)
First-line chemotherapy					
PEAK	FOLFOX + Panitumumab	142	57.8%	10.9	34.2
	FOLFOX + Bevacizumab	143	53.5%	10.1	24.3
	(HR, *P*-value)		-	HR = 0.87	HR = 0.62
				P = 0.353	*P* = 0.009
FIRE-3	FOLFIRI + Cetuximab	297	62%	10.0	28.7
	FOLFIRI + Bevacizumab	295	58%	10.3	25.0
	(HR, *P*-value)		OR = 1.18	HR = 1.06	HR = 0.77
			P = 0.18	*P* = 0.55	*P* = 0.017
CALGB/SWOG 80405	Chemotherapy[1] + Cetuximab	578	65.6%	10.4	29.9
	Chemotherapy[1] + Bevacizumab	559	57.2%	10.8	29.0
	(HR, *P*-value)		*P* = 0.02	HR = 1.04	HR = 0.925
				P = 0.55	*P* = 0.34
Second-line chemotherapy					
SPIRITT	FOLFIRI + Panitumumab	91	32%	7.7	18.0
	FOLFIRI + Bevacizumab	91	19%	9.2	21.4
	(HR, *P*-value)		-	HR = 1.01	HR = 1.06
				P = 0.97	*P* = 0.75

[1]Chemotherapy regimens were FOLFOX or FOLFIRI. ORR: Objective response rate; PFS: Progression-free survival; OS: Overall survival; HR: Hazard ratio; OR: Odds ratio; FOLFIRI: Bolus and infusional 5-fluorouracil/leucovorin/irinotecan; FOLFOX: Bolus and infusional 5-fluorouracil/leucovorin/oxaliplatin.

was 32% in the panitumumab arm and 19% in the bevacizumab arm.

Treatment outcome of anti-EGFR therapy for patients with RAS wild type mCRC

An activating mutation of *KRAS* exon 2 has been found to be a negative predictive marker in mCRC, as described above. *KRAS* status was used for patient selection for anti-EGFR treatment. *NRAS* is one of the *RAS* oncogene family members, and somatic mutations like *KRAS* gene have been detected within the *NRAS* gene. A retrospective analysis of the PRIME study showed that 17% of patients with *KRAS* exon 2 wild type had mutations in *RAS* exons (*KRAS* exon 3, 4 and *NRAS* exon 2, 3). An activating mutation of *NRAS* exon 4 was not detected in this analysis[19]. Patients with all-*RAS* wild type who received panitumumab plus FOLFOX had a prolonged OS compared with those with *KRAS* exon 2 wild type (25.8 moin *RAS* wild type and 23.9 mo in *KRAS* wild type). A similar outcome was demonstrated in the CRYSTAL study[86]. From these results, the negative predictive factors were any mutations in either *KRAS* or *NRAS* codons 12, 13, 59, 61, 117, and 146 hotspots. Now, all-*RAS* wild type patients can be defined as those without the above mutations.

All-*RAS* subset analyses were performed in three randomized clinical trials that compared anti-EGFR agent-containing chemotherapy with bevacizumab-containing chemotherapy: PEAK, FIRE-3, and CALGB/SWOG 80405. In PEAK and FIRE-3, a further survival benefit was observed in the anti-EGFR arm compared with the bevacizumab arm in mCRC patients with *RAS* wild type (OS in PEAK, 41.3 mo *vs* 28.9 mo, HR = 0.63, *P* = 0.058; OS in FIRE-3, 33.1 mo *vs* 25.6 mo, HR = 0.70, *P* = 0.011)[18,19]. In contrast, CALGB/SWOG 80405 demonstrated no significant difference in OS between cetuximab plus chemotherapy and bevacizumab plus chemotherapy even in the *RAS* wild type population (32.0 mo *vs* 31.2 mo, HR = 0.90, *P* = 0.40)[84]. The outcomes of these trials were discussed in several groups[87-90]. Meta-analyses of the three studies were performed for the *RAS* wild type subset in order to compare anti-EGFR therapy with anti-VEGF therapy[87]. Although no significant difference in PFS was observed between anti-EGFR and anti-VEGF agents combined with chemotherapy (HR = 0.92, 95%CI: 0.71-1.18, *P* = 0.50), the anti-EGFR arm had better OS (HR = 0.77, 95%CI: 0.63-0.95, *P* = 0.016) and RR (OR = 1.46, 95%CI: 1.13-1.90, *P* = 0.004) compared with the anti-VEGF arm. On the other hand, these three clinical trials aimed to reveal the superiority of anti-EGFR therapy compared with anti-VEGF therapy in *KRAS* wild type mCRC, but they did not meet the primary endpoints of their studies; the primary endpoint was PFS in PEAK, RR in FIRE-3, and OS in CALGB/SWOG 80405. Although anti-EGFR therapy in the first-line setting has a favorable trend compared with anti-VEGF therapy, the treatment strategy in *RAS* wild type mCRC has been controversial. In the future, one ongoing clinical trial may resolve this problem. The phase Ⅲ STRATEGIC-1 by GERCORE is now ongoing to investigate the appropriate sequential strategy for *RAS* wild type mCRC[91]. In the STRATEGIC-1 trial, patients are randomized to receive either FOLFIRI plus cetuximab as first-line followed by oxaliplatin-based regimen combined with bevacizumab as second-line, or an oxaliplatin-based regimen by OPTIMOX plus bevacizumab as first-line followed by an irinotecan-based regimen combined with bevacizumab as second-line and by anti-EGFR therapy with or without irinotecan as third-line. We eagerly await the results of this trial (Table 4).

Table 4 Treatment outcome by anti-epidermal growth factor receptor therapy as first-line treatment in metastatic colorectal cancer with *RAS* wild type

Trial name	Regimens	*n*	ORR	PFS (mo)	OS (mo)
CRYSTAL	FOLFIRI + Cetuximab	178	66.3%	11.4	28.4
	FOLFIRI	189	38.6%	8.4	20.2
	(HR, *P*-value)		OR = 3.31	HR = 0.56	HR = 0.69
			P < 0.001	*P* = 0.0002	*P* = 0.0024
PRIME	FOLFOX + Panitumumab	259	-	10.1	25.8
	FOLFOX	253	-	7.9	20.2
	(HR, *P*-value)		-	HR = 0.72	HR = 0.77
				P = 0.004	*P* = 0.009
PEAK	FOLFOX + Panitumumab	88	63.6%	13.0	41.3
	FOLFOX + Bevacizumab	82	60.5%	9.5	28.9
	(HR, *P*-value)		-	HR = 0.65	HR = 0.63
				P = 0.029	*P* = 0.058
FIRE-3	FOLFIRI + Cetuximab	171	65%	10.4	33.1
	FOLFIRI + Bevacizumab	171	60%	10.2	25.6
	(HR, *P*-value)		OR = 1.28	HR = 0.93	HR = 0.70
			P = 0.32	*P* = 0.54	*P* = 0.011
CALGB/SWOG 80405	Chemotherapy[1] + Cetuximab	270	68.6%	11.4	32.0
	Chemotherapy[1] + Bevacizumab	256	53.8%	11.3	31.2
	(HR, *P*-value)		*P* < 0.01	HR = 1.1	HR = 0.9
				P = 0.31	*P* = 0.4

[1]Chemotherapy regimens were FOLFOX or FOLFIRI. ORR: Objective response rate; PFS: Progression-free survival; OS: Overall survival; HR: Hazard ratio; OR: Odds ratio; FOLFIRI: Bolus and infusional 5-fluorouracil/leucovorin/irinotecan; FOLFOX: Bolus and infusional 5-fluorouracil/leucovorin/oxaliplatin.

OTHER TARGETED AGENTS

The efficacy of chemotherapy combined with tyrosine kinase inhibitor of the EGFR (gefitinib or erlotinib) was evaluated in several phase Ⅱ studies. First, a total of 27 patients with pretreated mCRC received FOLFOX plus gefitinib in the single-arm phase Ⅱ study[92]. The RR was 33% and median PFS was 5.4 mo. Most common grade 3/4 toxicities were neutropenia (48%) and diarrhea (48%). Second, the phase Ⅱ study was conducted in 100 mCRC patients to compare FOLFIRI plus gefitinib with FOLFIRI alone as first-line setting[93]. The adding gefitinib to FOLFIRI demonstrate no improvement of RR (47.9% *vs* 45.1%) or PFS (8.3 mo *vs* 8.3 mo) compared with FOLFIRI alone, but had more toxicities with grade 3/4 (67.3% *vs* 52.1%). Finally, the efficacy of capecitabine plus erlotinib in chemo-naïve mCRC patiens was evaluated in a small sample size phase Ⅱ study[94]. A total of thirteen patients with mCRC were enrolled in this phase Ⅱ study. The RR was 20% (2/10), but 4 of 13 patients discontinued therapy because of adverse events. From these results, the adding the EGFR tyrosine kinase inhibitor with chemotherapy showed high toxicities and no improvement of ORR.

Two targeted agents, ganitumab and conatumumab, were evaluated in the randomized phase Ⅱ study in mCRC patients with mutant *KRAS* as second-line setting[95]. Ganitumab is a human IgG monoclonal antibody targeting the type Ⅰ insulin-like growth factor receptor and conatumumab is a fully human monoclonal IgG1 antibody targeting the proapoptoic death receptors 5. A total of 155 patients were randomized 1:1:1 to receive FOLFIRI plus conatumumab, ganitumab, or placebo. The median PFS was 6.5 mo (HR = 0.69; *P* = 0.147), 4.5 mo (HR = 1.01; *P* = 0.998), and 4.6 mo. The median OS was similar between three arms (12.3 mo *vs* 12.4 mo *vs* 12.0 mo).

Recently, the clinical benefit of dual-targeted therapy with trastuzumab and lapatinib in patients with KRAS wild type, HER2-positive mCRC in the phase Ⅱ HERACLES study[96]. In the HERACLES study, 914 patients with *KRAS* exon 2 wild type were screened, and 48 (5%) patients were identified as HER2-positive status. A total of 27 patients with HER2-positive received trastuzumab plus lapatinib treatment as salvage setting. The ORR was 30% and the toxicity was tolerable. The combination of trastuzumab plus lapatinib might be a novel therapeutic option for patients with HER2-positive mCRC.

CONCLUSION

The development of biological and cytotoxic agents has contributed to prolonged survival in mCRC patients, with a median OS of approximately two years and more. In the past two decades, many beneficial therapeutic options and regimens have appeared in daily practice for mCRC, based on the results from randomized clinical trials. Personalized therapy should be performed for mCRC patients according to their clinical and biological factors, such as performance status, organ function, metastasis sites, and tumor biology including *RAS* status. Especially in *RAS* wild type mCRC, anti-EGFR agents, such as cetuximab and panitumumab, have been shown to improve objective response and survival in several clinical trials. Anti-EGFR agents are absolutely key drugs for the *RAS* wild type population. Based on the evidence for anti-EGFR therapy as first-line, second-

line, and salvage therapy, we should plan personalized treatment strategies for patients with *RAS* wild type mCRC. On the other hand, bevacizumab in combination with chemotherapy has demonstrated clinical benefits in any treatment line. Bevacizumab has been shown to fit any cytotoxic regimens, such as FOLFOX, CapeOX, FOLFIRI, FOLFOXIRI, SOX, or TAS-102. Moreover, continuing bevacizumab beyond progression prolonged survival in mCRC patients who experienced clinical benefit in prior bevacizumab-containing chemotherapy. In addition, we have many biological agents for the second-line or salvage therapy, such as aflibercept, ramucirumab, and regorafenib. Based on the evidence and patients' characteristics, it will be necessary to construct personalized therapy for mCRC patients.

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