Chapter 17

Anti-Epidermal Growth Factor Receptor (EGFR) Treatment in Patients with Metastatic Colorectal Cancer

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Additional information is available at the end of the chapter

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Abstract

Colorectal cancer is one of the most common cancer types and still a major public health problem. Approximately a half of the patients develop metastasis during the course of disease. Prognosis of metastatic colorectal cancer (mCRC) is poor with best supportive care alone (median survival: 6 months). Fortunately, combination chemotherapy has significantly improved survival up to 17–22 months. Cetuximab and panitumumab, the two monoclonal antibodies (mAbs) against epidermal growth factor receptor (EGFR), provide significant clinical benefit in only RAS wild (WT) mCRC. Major side effects are skin toxicity, infusion reactions, fatigue, and electrolyte imbalances. When these mAbs are combined with chemotherapy, overall survival could be as long as 24 months. However, RAS WT status does not ensure response to anti-EGFR mAbs. In addition, RAS WT patients consequently develop resistance to these agents after an initial responsive period. Therefore, understanding the primary and secondary resistance mechanisms apart from RAS status is very important to improve outcomes of mCRC patients. Oncogenic activation of EGFR downstream signaling effectors (KRAS, BRAF, PTEN, and PIK3CA) appears to be the main components of resistance. In future, a comprehensive biomarker analysis will probably help to identify the mCRC patients who will truly benefit from anti-EGFR mAbs.

Keywords: cetuximab, metastatic colorectal cancer, panitumumab, RAS, survival

1. Introduction

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers in both genders (second in females and third in males) [1]; and it is also the third common cause of cancer-related death

in both genders [2, 3]. Although the mortality rate of CRC has been decreasing in Western countries, its incidence has been increasing worldwide [1].

CRC can spread by lymphatic, hematogenous and transperitoneal dissemination. The most common metastatic sites are the regional lymph nodes, liver, lungs, and peritoneum. Approximately 50–60% of patients with CRC develop metastasis, and local recurrence is included in 15% of the patients who have first relapse [4].

Survival of metastatic colorectal cancer (mCRC) is approximately 5–6 months with best supportive care (BSC) alone, and chemotherapeutic agents have been shown to provide significant survival benefit. Fluoropyrimidines have been the mainstay of the systemic treatment of mCRC for several years. Median survival of patients with mCRC increased up to 12–14 months and 17–22 months with fluoropyrimidines alone and its combinations with irinotecan and/or oxaliplatin, respectively [5–7]. Also, addition of target-directed cancer drugs, such as monoclonal antibodies (mAbs) against VEGF (e.g., bevacizumab, aflibercept) and EGFR (e.g., cetuximab and panitumumab), have remarkably improved the outcomes of mCRC [8–13]. Unfortunately, targeted therapies, including anti-EGFR drugs, are active only in a fraction of patients and most of them subsequently become resistant to the treatment. Therefore, identification of the genetic alterations associated with the clinical response and resistance to anti-EGFR mAbs is important to improve outcomes of patients with mCRC.

2. Epidermal growth factor receptor and KRAS mutation

Epidermal growth factor receptor (EGFR) is a transmembrane tyrosine kinase receptor that presents on the surface of normal epithelium. It is over-expressed in up to 80% of colorectal tumors [14, 15] and mediates cell differentiation, proliferation, migration, angiogenesis and apoptosis [16].

The EGFR signaling acts through at least two parallel intracellular pathways: mitogen-activated protein kinases (MAPK) and phosphor-inositol kinases (PI3K). MAPK form the major cell proliferation signaling pathways from the cell surface to the nucleus through a series of genes, including RAS, RAF, and MEK. Various signals, such as EGF, amphiregulin, amphiregulin, and heparin-binding EGF, could stimulate EGFR. After dimerization and phosphorylation of the stimulated EGFR, RAS is activated [17]. RAS activation, which starts the PI3K and RAF cascades, is the central distributor of the signal. Activation of PI3K/AKT pathway inhibits apoptosis, whereas RAF activation stimulates cellular proliferation. Hence, mutations in the KRAS gene may result in an independent activation of the downstream signaling of tumor growth [17]. Prospective randomized trials elucidated that presence of mutation in KRAS gene leads to non-response to anti-EGFR–based treatment in mCRC [8–12, 18–20].

Incidence of KRAS mutations is approximately 28.7% in all human cancers, thus it is considered one of the causal cancer genes [17]. RAS mutations occur in the early phases of cancer development and are preserved during tumor progression. KRAS mutation rate in CRC is 36%

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and most common point mutations are located in codons 12 (80%) and 13 (15%) of exon 2, while codon 61, 117, and 146 mutations are less common [17, 21]. Unusual KRAS mutations affecting more than one codon and insertions are rare. The discordance of KRAS status between primary tumor and synchronous metastasis in the same patient tends to be low (ranging from 0 to 31%) [22]. In addition, KRAS status is not different between CRC biopsies before and after neoadjuvant therapy [23], or the biopsy and resection specimens of CRC [21, 24]. Because the data are limited, routine rebiopsy of metastases for RAS mutation analysis in recurrent disease is not recommended currently. In contrast, RAS mutations vary significantly between synchronous primary CRC lesions, therefore the mutation status of the metastasis is unpredictable [21].

3. Anti-EGFR mAbs in mCRC

Cetuximab (Erbitux) and panitumumab (Vectibix) are the two anti-EGFR mAbs active for the treatment of mCRC. Both are effective only in the wild type (WT) RAS (NRAS and KRAS) tumors (approximately 40% of all mCRCs) [8–12, 18–20]. Therefore, it is well established that KRAS and NRAS mutation status (exons 2, 3, and 4) should be known before initiating anti-EGFR based treatment for mCRC [25].

3.1. Mechanism of action

Cetuximab and panitumumab keep EGFR in an inactive state by binding to the extracellular ligand-binding site of EGFR when the ligand is unbound (acting as competitive antagonists). Consequently, intracellular signaling pathways of EGFR (RAS/RAF/MAPK and PI3K/PTEN/AKT) related to cell proliferation, invasion, and survival are inhibited [26][**Figure 1**]. Both cetuximab, an IgG1 type chimeric monoclonal antibody, and panitumumab, an IgG2 type fully human monoclonal antibody, induce apoptosis by inhibiting EGFR. Also, these molecules, especially cetuximab, activate antibody-dependent cellular cytotoxicity, inhibit metastasis and angiogenesis by blocking ligand-induced phosphorylation of EGFR on endothelial cells [16, 27, 28].

3.2. Predictive markers for response

The identification of patients with mCRC who are most likely to respond to the anti-EGFR mAbs is an important clinical question. Although there are no accepted predictive markers of response to bevacizumab or to chemotherapeutics, there are some analyses to select individuals who might benefit from anti-EGFR mAbs.

3.3. RAS mutations

Activating KRAS mutations cause constitutive activation of the RAS-RAF-ERK pathway, even in the absence of EGFR ligands. Consequently, tumor becomes resistant to anti-EGFR therapy [16, 17, 21, 29]. Prospective randomized studies showed that KRAS mutations are negative predictors of the response to anti-EGFR–based treatment [8–12, 18–20]. Thus, panitumumab and cetuximab are approved only for patients with WT KRAS tumors.

All KRAS mutations may not be similar for prediction of anti-EGFR therapy [30–33]. Although some retrospective studies suggest that patients with KRAS p.G13D mutation benefit more from cetuximab than those with KRAS codon 12 mutations [32], this benefit could not be confirmed in a prospective trial [33]. Therefore, data are not enough to change the clinical practice or to draw any firm conclusions about the effectiveness of anti-EGFR mAbs in mCRC with KRAS p.G13D mutation.

Almost 60% of CRC patients with WT KRAS mutation also have poor response to anti-EGFR–based treatment [34], suggesting the possibility of other molecular determinants of response. Heterogeneity of neoplastic cells that harbor specific RAS mutations within a single tumor may also influence response to EGFR-targeted agents [35]. Lower frequency mutations in KRAS apart from exon 2 or in NRAS may also cause resistance to anti-EGFR therapies [18, 36–41]. NRAS mutations in mCRC are less common than KRAS mutations (approximately 5%) and develop most often in codons 61, 12, and 13 [21]. The PRIME trial, in which patients with mCRC were randomly assigned to first-line FOLFOX with or without panitumumab, revealed that 17% of the patients with KRAS exon 2 WT tumors had other mutations in KRAS exons 3 and 4 and in NRAS exons 2, 3, and 4 [38]. These additional mutations were also associated

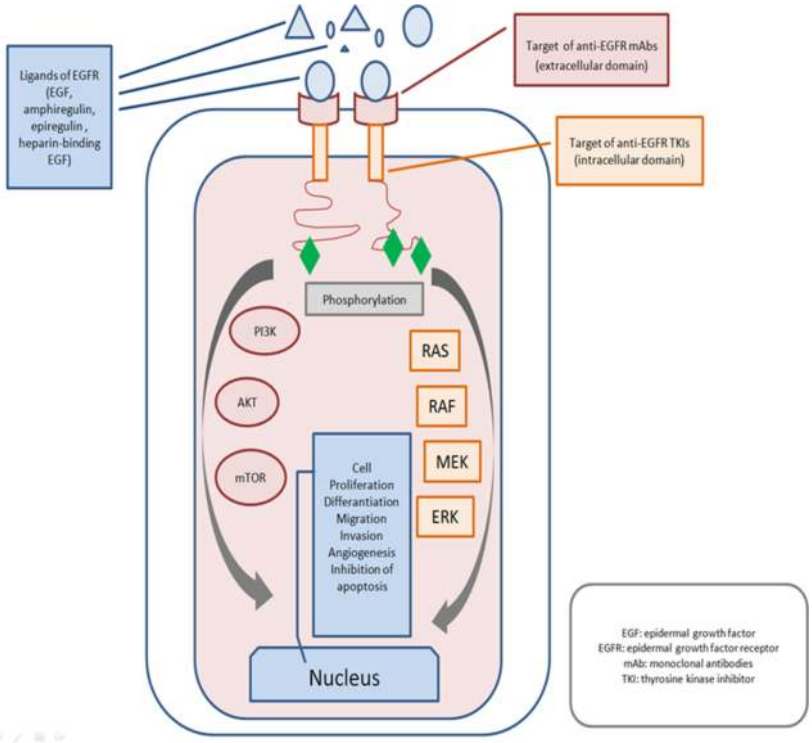

Figure 1. Epidermal growth factor receptor pathway as a therapeutic target for metastatic colorectal cancer.

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with unresponsiveness to panitumumab, and poorer progression-free and overall survival in the panitumumab arm. Currently, testing for all RAS mutations (KRAS and NRAS exons 2, 3, and 4) rather than just those in KRAS exon 2 is the preferred approach to select appropriate patients with mCRC for anti-EGFR mAbs, since anti-EGFR mAbs are neither beneficial nor recommended for mCRC with any KRAS or NRAS mutations [42].

3.4. Other biomarkers

As mentioned before, WT RAS status does not ensure a response to EGFR-targeted therapies. Interestingly, the expression of the EGFR protein has not been strongly associated with clinical response to cetuximab in mCRC [43]. Majority of patients with EGFR-positive mCRC do not respond to anti-EGFR therapies [44, 45], while objective response is possible with EGFR-negative tumors [46–48]. Therefore, selection of patients for anti-EGFR mAbs based upon EGFR expression is not recommended. Likewise, EGFR mutations are rare in mCRC, and somatic mutations in the EGFR tyrosine kinase domain are not associated with cetuximab sensitivity [49]. However, it has been reported that over-expression of genes encoding amphiregulin and epiregulin, the two EGFR ligands, is strongly associated with better response to cetuximab in patients with mCRC [43].

Results of studies about association between EGFR copy number and response to anti-EGFR therapy are conflicting [44, 50–53]. Thus, EGFR amplification test to select patients for therapy is not standard in clinical practice.

BRAF mutations, which are mutually exclusive with KRAS mutations, are found in about 5 to 10% of mCRCs. BRAF mutations are associated with poor prognosis [54] and resistance to anti-EGFR agents in the second-line setting and beyond [50, 55]. Although randomized trials confirm the prognostic value of BRAF mutations, it does not have predictive role for anti-EGFR agents in first-line setting [56, 57]. Currently, BRAF mutation analysis should not be used for the selection of patients with WT RAS mCRC for anti-EGFR therapy.

Mutations of other genes, including phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) [58], p53 [59], PTEN [50] and genes involved in the insulin-like growth factor 1 (IGF1) signaling pathway [60, 61], or polymorphisms in EGF [62] may also have an impact on response to anti-EGFR mAbs. However, these biomarkers are not mature enough to be incorporated into clinical practice.

4. Clinical efficacy of anti-EGFR mAbs in mCRC

4.1. Cetuximab

4.1.1. Cetuximab monotherapy

In a randomized phase III trial, cetuximab monotherapy and BSC were compared in patients with mCRC who had failed or were intolerant of all standard therapies (n = 572) [63]. Partial response rate was 8% with cetuximab and overall survival (OS) was significantly improved

with cetuximab (6.1 vs. 4.6 months). Subgroup analysis revealed that only patients with KRAS WT tumor provided survival benefit from cetuximab [19, 64]. Among patients with mutated KRAS, survival was similar in cetuximab and BSC arms.

4.1.2. Cetuximab combinations

4.1.2.1. Combination with irinotecan

A phase II study compared efficacy of cetuximab plus irinotecan and single agent irinotecan in 138 patients with irinotecan-refractory mCRC [65]. Partial response rate and time to tumor progression (TTP) were 15% and 6.5 months, respectively.

The BOND trial, a larger randomized phase II trial, compared irinotecan plus cetuximab versus cetuximab alone in 329 patients with irinotecan-refractory mCRC [9]. Combination therapy was significantly better than single agent cetuximab in terms of response rate (22.9% vs. 10.8%) and TTP (4.1 vs. 1.5 months); however, median survival was similar (8.6 vs. 6.9 months). In addition, benefit of adding cetuximab to irinotecan in patients with oxaliplatin-refractory mCRC has been reported in the EPIC trial [66]. Both objective response rates (16 vs. 4%) and PFS (4 vs. 2.6 months) were significantly higher with irinotecan plus cetuximab compared with single agent irinotecan. However, OS was similar (10.7 vs. 10 months), probably because of cross-over.

Study	Year	Population	Patient number	Regimen	Median PFS (month)	*p**	Median OS (month)	*p**	Response rate (%)	*p**
CRYSTAL[57]	2009	All	599	FOLFIRI	8	**0.048**	18.6	0.31	38.7	**0.0038**
			599	FOLFIRI + Cetuximab	8.9		19.9		46.9	
		KRAS WT subgroup	350	FOLFIRI	8.4	**0.0012**	20	**0.0093**	39.7	**<0.001**
			316	FOLFIRI + Cetuximab	9.9		23.5		57.3	
		KRAS MT subgroup	183	FOLFIRI	7.7	0.26	16.7	0.75	36.1	0.35
			214	FOLFIRI + Cetuximab	7.4		16.2		31.3	
OPUS[18]	2009	All	168	FOLFOX4	7.2	0.62	18	0.91	36	0.064
			169	FOLFOX4 + Cetuximab	7.2		18.3		46	
		KRAS WT subgroup	97	FOLFOX4	7.2	**0.0064**	18.5	0.39	34	**0.0027**
			82	FOLFOX4 + Cetuximab	8.3		22.8		57	
		KRAS	59	FOLFOX4	8.6	0.0153	17.5	0.2	53	0.029

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Study	Year	Population	Patient number	Regimen	Median PFS (month)	*p**	Median OS (month)	*p**	Response rate (%)	*p**
		MT subgroup	77	FOLFOX4 + Cetuximab	5.5		13.4		34	
COIN[67]	2011	KRAS WT group	367	FOLFOX/ XELOX	8.6	0.60	17.9	0.68	57	0.049
			362	FOLFOX/ XELOX + Cetuximab	8.6		17		64	
		KRAS WT group	127	FOLFOX	9.2	0.056	–	–	–	–
			117	FOLFOX + Cetuximab	9.0		–		–	
		KRAS WT group	240	XELOX	8.0	0.56	–	–	–	–
			245	XELOX + Cetuximab	8.4		–		–	
		KRAS MT group	268	FOLFOX/ XELOX	-	-	14.8	0.80	-	-
			297	FOLFOX/ XELOX + Cetuximab	–		13.6		–	
NORDIC-VII[68]	2012	All	185	Nordic FLOX (control group)	7.9	–	20.4	–	41	–
			194	FLOX + Cetuximab	8.3	0.31	19.7	0.67	49	0.15
			187	intermittent FLOX + Cetuximab	7.3	N/A	20.3	0.79	47	N/A
		KRAS WT subgroup	97	Nordic FLOX (control group)	8.7	–	22	–	47	–
			97	FLOX + Cetuximab	7.9	0.66	20.1	0.48	46	0.89
			109	intermittent FLOX + Cetuximab	7.5	N/A	21.4	0.66	51	N/A
		KRAS MT	58	Nordic FLOX (control	7.8	–	20.4	–	40	–

Study	Year	Population	Patient number	Regimen	Median PFS (month)	*p**	Median OS (month)	*p**	Response rate (%)	*p**
		subgroup		group)						
			72	FLOX + Cetuximab	9.2	**0.07**	21.1	0.89	49	0.31
			65	intermittent FLOX + Cetuximab	7.2	N/A	20.5	0.84	42	N/A
CALGB /SWOG[69] 80405 (study is ongoing)	2014	KRAS WT group	578	FOLFIRI or mFOLFOX6 + Cetuximab	10.45	N/A	29.93	0.34	–	–
			559	FOLFIRI or mFOLFOX6 + Bevacizumab	10.84		29.04		–	

*95% confidence interval.
PFS, progression-free survival; OS, overall survival; All, all patients group; WT, wild type; MT, mutant type; N/A, not available; KRAS, KRAS exon 2, codons 12 and 13; FOLFIRI, irinotecan, fluorouracil, and leucovorin; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; XELOX, capecitabine and oxaliplatin; FLOX, fluorouracil, leucovorin, and oxaliplatin.

Table 1. Clinical trials of cetuximab plus chemotherapy as first-line treatment for metastatic colorectal cancer.

The CRYSTAL trial enrolled 1200 patients with mCRC and investigated the role of adding cetuximab to FOLFIRI as first-line therapy [8]. Response rate (47 vs. 39%) and median PFS (8.9 vs. 8 months), the primary end point of the study, were significantly better with FOLFIRI plus cetuximab compared with FOLFIRI alone, while OS was not significantly different between groups. An updated analysis of the CRYSTAL trial also demonstrated that adding cetuximab to FOLFIRI significantly improves OS (23.5 vs. 20 months), PFS (9.9 vs. 8.4 months), and response rate (57.3% vs. 39.7%) in patients with WT KRAS tumor. Perhaps more importantly, the rate of surgery for metastasis (7.9 vs. 4.6%, $p = 0.06$) and the rate of R0 resection (5.1 vs. 2%, $p = 0.02$) were both higher in patients with KRAS WT tumors who received cetuximab plus FOLFIRI compared with FOLFIRI alone [57]. Adverse effects that were more frequent with cetuximab were grade 3 or 4 diarrhea, skin toxicity, and infusion reactions. Based in large part on these data, cetuximab was approved for use in combination with FOLFIRI for first-line treatment of patients with KRAS WT mCRC [**Table 1**].

4.1.2.2. Combination with oxaliplatin

Randomized trials revealed conflicting results about benefits of adding cetuximab to oxaliplatin-based regimens. Three trials have evaluated the addition of cetuximab to oxaliplatin-

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based chemotherapy (FOLFOX/CAPOX) in first-line treatment of KRAS WT mCRC [18, 67, 68]. In randomized multicenter phase II OPUS study, FOLFOX4 plus cetuximab was compared with FOLFOX4 alone. Cetuximab provided significantly better response rate (61 vs. 37 %) and PFS (7.7 vs. 7.2 months) among patients with KRAS exon 2 WT tumors. However, median OS did not improve with addition of cetuximab (22.8 vs. 18.5) [18].

In randomized phase III MRC COIN study, adding cetuximab to oxaliplatin-based chemotherapy in patients with KRAS exon 2 WT mCRC increased response rate (64 vs. 57%) with no benefit in PFS (8.6 months in both groups) or OS (17.9 vs. 17) [67]. Likewise, another phase III study (NORDIC-VII) showed no survival benefit with the addition of cetuximab to FLOX regimen even in the KRAS WT group [68].

On the other hand, recently published randomized phase III CALGB/SWOG 80405 trial, in which 73% of the enrolled patients received FOLFOX as chemotherapy backbone, demonstrated that FOLFOX plus cetuximab can be effective as first-line treatment of patients with KRAS WT mCRC [69].

Converting initially unresectable isolated liver metastases to resectable status is another important issue for patients with mCRC, as R0 resection of isolated metastasis provide significant survival benefit. In the OPUS trial, addition of cetuximab to FOLFOX4 significantly increased ability for R0 resection of isolated liver metastasis [18]. In addition, the randomized phase II CELIM trial demonstrated that adding cetuximab to either irinotecan or oxaliplatin-based chemotherapy has similar efficacy in patients with initially unresectable liver metastases [70]. However, the efficacy of cetuximab-oxaliplatin combination for downstaging patients with isolated CRC liver metastases is unsettled. Recently, the randomized EPOC trial demonstrated that adding cetuximab to FOLFOX in patients with KRAS WT and potentially resectable isolated liver metastases was associated with worse PFS (14.8 vs. 24.2 months) [71]. Therefore, FOLFOX plus cetuximab should be used with caution in perioperative metastatic setting.

4.2. Panitumumab

4.2.1. Panitumumab monotherapy

In a multicenter trial ($n = 463$) adding panitumumab to BSC provided a 10% objective response rate in patients with mCRC refractory to standard treatment options [12, 72]. However, there was no significant PFS benefit, probably because of cross-over. Re-analysis according to KRAS status demonstrated that benefit of panitumumab monotherapy was restricted to KRAS WT tumors. Partial response rates in patients with KRAS WT and mutant tumors were 17% and 0%, respectively [73]. Although efficacy of panitumumab is similar to cetuximab monotherapy [63, 74], there is no data supporting to switch the anti-EGFR mAbs cetuximab and panitumumab after one of them fails.

4.2.2. Panitumumab combinations

There are increasing data supporting the efficacy of panitumumab in combination with oxaliplatin- or irinotecan-based regimens in patients with WT RAS tumors [10, 75–80].

4.2.2.1. Combination with irinotecan

The efficacy of first-line FOLFIRI-panitumumab combination in mCRC was evaluated in a single-arm phase II study. This regimen was well tolerated and response rates were 48% and 29% in the KRAS WT and mutant subsets, respectively [81]. Except this study, data regarding to FOLFIRI-panitumumab combination at first-line setting is mainly based on extrapolation from data in the second-line treatment. As an example, in a randomized phase III study (Study 181) the combination of panitumumab and FOLFIRI provide significant PFS benefit (5.9 vs. 3.9 months), but there was no difference in OS in patients with WT KRAS mCRC [11].

4.2.2.2. Combination with oxaliplatin

The phase III PRIME study compared panitumumab plus FOLFOX and FOLFOX alone as first-line treatment of patients with pan-RAS WT mCRC. Addition of panitumumab to FOLFOX significantly improved both PFS (10.1 vs. 9.2 months) and OS (23.8 vs. 19.4 months) [38]. Importantly, addition of panitumumab deteriorated PFS (7.3 vs. 8.9 months) in patients with KRAS mutation, consistent with other trials testing the addition of panitumumab or cetuximab to oxaliplatin-based chemotherapy [**Table 2**]. In addition, 17% of those with non-mutated KRAS exon 2 had other RAS mutations. These mutations were associated with worse PFS and OS with adding panitumumab to FOLFOX, similar to KRAS exon 2 mutations [38].

Study	Year	Population	Patient number	Regimen	Median PFS (month)	*p**	Median OS (month)	*p**	Response rate (%)	*p**
PRIME[10]	2010	KRAS WT group	331	FOLFOX4	8.0	**0.02**	19.7	0.072	48	0.068
			325	FOLFOX4 + Panitumumab	9.6		23.9		55	
		KRAS MT group	219	FOLFOX4	8.8	**0.02**	19.3	0.068	40	–
			221	FOLFOX4 + Panitumumab	7.3		15.5		40	

*95% Confidence interval.
PFS, progression-free survival; OS, overall survival; All, all patients group; WT, wild type; MT, mutant type; N/A, not available; KRAS, KRAS exon 2, codons 12 and 13; FOLFOX, fluorouracil, leucovorin, and oxaliplatin.

Table 2. Selected phase III trial of panitumumab plus chemotherapy as first-line treatment for metastatic colorectal cancer.

4.2.3. Cetuximab versus panitumumab

Data are limited about head-to-head comparison of panitumumab and cetuximab in mCRC. The ASPECCT trial, a randomized non-inferiority phase III study, showed that median OS was similar in patients with chemorefractory KRAS exon 2 WT mCRC who were treated with panitumumab (6 mg/kg once every 2 weeks) alone and with cetuximab (initial dose 400

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mg/m^2, 250 mg/m^2 once a week thereafter) alone [82]. In addition, the incidence of any grade and grade 3–4 adverse events was similar in both treatment groups. However, the incidence of grade 3–4 infusion reactions was lower and grade 3–4 hypomagnesemia is higher with panitumumab compared with cetuximab [83]. Currently, there are no data supporting to use panitumumab or cetuximab beyond progression under an anti-EGFR mAb or to switch to cetuximab or panitumumab after one of them fails.

4.2.4. Bevacizumab versus cetuximab or panitumumab in combination with chemotherapy

Three trials have compared the benefits of anti-EGFR mAbs and anti-VEGF bevacizumab in combination with chemotherapy in RAS WT mCRC and the results are mixed.

In the FIRE-3 trial, patients with mCRC were randomly assigned to FOLFIRI with either bevacizumab or cetuximab as first-line treatment [20, 39]. Patients who had pan-RAS WT tumor had significantly better objective response rates (76 vs. 65 %) and OS (33.1 vs. 25.9 months) with cetuximab compared with bevacizumab, while PFS were not different between groups (10.5 vs. 10.4 months). Grade 1–2 emesis, hypertension, abscesses, and bleeding were more frequent with bevacizumab, and grade 1–2 hypocalcemia, and grade 3–4 skin toxicity, infusion reactions, and hypomagnesemia were more common with cetuximab. The reason for longer OS, in the absence of a better PFS, is unclear. Patients were on protocol-specified therapy for 5 months and the survival curves did not diverge until 24 months, suggesting that subsequent therapies beyond first-line treatment, which were not detailed in the report, may be important.

In the phase II PEAK trial, FOLFOX plus panitumumab was compared with FOLFOX plus bevacizumab as first-line treatment of mCRC [84]. For patients with KRAS exon 2 WT tumors, OS was significantly better (34 vs. 24 months) with panitumumab, while PFS was similar. When only pan-RAS WT patients were included, PFS was significantly better with panitumumab (13 vs. 9.5 months) but the statistical significance of the difference in OS disappeared, although potentially clinically meaningful (41 vs. 29 months, $p = 0.06$).

The recently published phase III CALGB/SWOG 80405 trial, in which patients with KRAS exon 2 WT mCRC were randomly assigned to cetuximab or bevacizumab plus chemotherapy (FOLFOX or FOLFIRI) as first-line treatment, demonstrated that both OS (29.9 vs. 29 months) and PFS (10.4 vs. 10.8 months) were similar [69]. FOLFOX was chosen in more than 70% of patients in this study. When only pan-RAS WT patients were analyzed, objective response rates were significantly higher with cetuximab (69 vs. 54 %), while OS (32 vs. 31.2 months) and PFS (11.4 vs. 11.3 months) were similar in both arms [85]. In conclusion, whether it is preferable to add an anti-EGFR mAb rather than bevacizumab to first-line chemotherapy in RAS WT mCRC is unclear [**Table 1**]. Preferring an anti-EGFR mAb rather than bevacizumab appears to be reasonable for patients with symptomatic tumors, in which response rate is a clinically more important purpose or if the use of bevacizumab is contraindicated. In addition, anti-EGFR mAbs appear to be not superior to bevacizumab in second-line therapy and beyond. In a phase II study (SPIRITT trial), patients with KRAS WT mCRC were randomized to FOLFIRI plus bevacizumab or FOLFIRI plus panitumumab as second-line therapy after failure of first-

line bevacizumab plus oxaliplatin-based chemotherapy. PFS was similar in both group (9.2 vs. 7.7 months) [86].

4.2.5. Simultaneous use of cetuximab/panitumumab and bevacizumab

Two trials evaluated the addition of an anti-EGFR mAb to chemotherapy plus bevacizumab as first-line treatment of mCRC. The PACCE trial compared the efficacy of adding panitumumab to first-line oxaliplatin- (n = 823) or irinotecan (n = 230)-based chemotherapy plus bevacizumab [87]. The panitumumab/oxaliplatin group had significantly worse PFS and OS. Similar detrimental effect of dual antibody therapy was also observed in the CAIRO2 trial, which compared first-line XELOX plus bevacizumab with or without cetuximab [88]. PFS was significantly worse with the addition of cetuximab even in patients with KRAS WT tumors. These results suggest that using bevacizumab and panitumumab/cetuximab is not appropriate, at least in the first-line setting.

5. Toxicity profile of the anti-EGFR mAbs

The most common adverse effects associated with cetuximab and panitumumab are fatigue, acneiform rash, nausea, electrolyte imbalances, and infusion reactions [89–91].

5.1. Skin toxicity

Anti-EGFR therapies are associated with a variety of cutaneous side effects. Acneiform rash is the most common skin toxicity and occurs in up to two-thirds of patients. Interestingly, severity of rash correlates with better response rates [89, 92, 93]. Moreover, the EVEREST trial suggests that cetuximab dose escalation gradually, even up to 500 mg/m^2 weekly, could safely increase response rates in patients who have no or a mild skin reaction within the first 3 weeks of therapy [94]. However, cetuximab dose escalation according to grade of early skin reactions is not a standard approach currently, since OS benefit could not be shown. Pruritus, another common cutaneous adverse effect of anti-EGFR mAbs, is more common with panitumumab (55% any grade) compared to cetuximab (18% any grade) [95].

5.2. Electrolyte disorders

Magnesium-wasting syndrome is observed in 22% of patients receiving anti-EGFR mAbs [90, 96] and consequent hypomagnesemia may be more prominent when oxaliplatin is used concomitantly [97]. Hypokalemia is another important electrolyte disorder observed in approximately 8% of patients receiving cetuximab [98]. Hypomagnesemia may lead to secondary hypocalcemia and refractory hypokalemia. Thus, serum levels of magnesium, potassium, and calcium should be monitored periodically during and for at least 8 weeks after anti-EGFR containing therapy.

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5.3. Infusion reactions

Infusion reactions are more common with cetuximab (25%) compared with panitumumab (4%), and more frequently observed in some areas of the middle southeastern United States [91]. Most of the infusion reactions are severe and occur within 3 hours of the first infusion. Cetuximab infusion should not exceed 5 mL/minute and premedication with an H1 receptor antagonist is recommended. For patients who develop a severe reaction to cetuximab despite premedication, desensitization or switching to panitumumab may be considered. Given the lower rates of infusion reactions compared with cetuximab, routine premedication is not recommended prior to panitumumab infusion.

5.4. Venous thromboembolism

Although not common, anti-EGFR mAbs may increase the risk of venous thromboembolism, but not arterial thromboembolism, as shown in a meta-analysis [99].

6. Anti-EGFR mAbs for geriatric population

Approximately 70% of CRC cases develop over the age of 65 [100]. The efficacy and main principles of mCRC treatment in the elderly are similar to younger patients. However, organ function decline and comorbidities are more common in the elderly and make them more vulnerable to side effects of systemic cancer therapies.

Because the number of older patients enrolled in clinical trials is small and these patients usually have good performance status [101, 102], good quality evidence about safety and efficacy of anti-cancer treatments in the elderly is limited. The majority of elderly patients are neither fit nor frail, and there is no evidence to support or refute the benefit and safety of therapy. Individualized treatment decision according to functional status, comorbidities, toxicity profile of the drugs is essential in older patients.

Few data are available about the safety and efficacy of anti-EGFR mAbs in the elderly mCRC patients. However, only older age should not be considered as an absolute contraindication to use anti-EGFR mAbs in mCRC. A retrospective study including heavily pretreated KRAS WT mCRC patients older than 70 years (n = 56) demonstrated that addition of cetuximab to irinotecan was tolerable and beneficial in the elderly similar to younger patients [103]. Another study analyzed 305 elderly and 352 younger (<65 years old) mCRC patients receiving chemotherapy plus cetuximab. Efficacy and the prevalence of side effects was similar in older and younger patients [104]. In contrast, a phase II trial of capecitabine plus cetuximab as first-line treatment of mCRC demonstrated that rate of acneiform rash was higher in the elderly (n = 66) [105].

Panitumumab monotherapy provides similar PFS benefit in the elderly compared with younger patients and may be a well-tolerated first-line option for frail elderly patients with WT RAS mCRC, as shown in a phase II study [12, 106]. A retrospective study demonstrated

that toxicity-related dose reductions for panitumumab were required in about one-fourth of frail elderly patients receiving first-line or second-line therapy for mCRC (n = 40) [107].

6.1. Anti-EGFR mAbs for patients with poor performance status

Regardless of age, individuals with a poor performance status (PS) (e.g., Eastern Cooperative Oncology Group [ECOG] PS ≥2, Karnofsky PS <60) usually cannot tolerate chemotherapy and have a poor prognosis [108]. However, particularly if PS decline is cancer related, patients with mCRC who have a PS of 2 should be considered for chemotherapy. FU or capecitabine alone, or cetuximab/panitumumab monotherapy (if RAS WT) are appropriate options for patients who are not candidates for combination chemotherapy including oxaliplatin or irinotecan because of their poor performance status.

6.2. Mechanisms of resistance to anti-EGFR treatment

Unfortunately, after a variable period of responsive phase, secondary resistance to anti-EGFR mAbs develop. Therefore, it is a clear priority to understand the molecular and cellular basis of primary and acquired resistance to cetuximab and panitumumab. The mutational status of the EGFR signaling effectors (KRAS, BRAF, or PIK3CA) appears to be the main components of resistance.

6.3. KRAS/NRAS/BRAF mutations

Prospective randomized studies showed that KRAS mutations are predictive of non-response to anti-EGFR based treatment [8–12, 18–20]. However, KRAS mutation status is not enough to select appropriate patients for anti-EGFR mAbs, because almost 60% of patients with KRAS WT mCRC also have poor response to anti-EGFR mAbs [34]. Mutations in KRAS outside of exon 2 and mutations in NRAS are also associated with lack of response to anti-EGFR mAbs [38]. Thus, all patients with newly diagnosed mCRC should be tested for RAS mutation status, as RAS mutation is the major cause of primary resistance to anti-EGFR mAbs.

BRAF oncogene encodes BRAF protein that is a member of RAS/RAF/MAPK pathway [109]. BRAF and KRAS mutations are mutually exclusive [110]. BRAF gene mutation (V600E) rate is 5–9% among patients with mCRC [111, 112]. Although BRAF mutation is a poor prognostic factor for mCRC, as shown in the CRYSTAL and PETACC-3 studies [57, 113], the use of BRAF as a predictive marker is unclear. BRAF mutation status does not predict the response to either panitumumab or cetuximab in the first-line treatment of mCRC, as demonstrated in the CRYSTAL and the PRIME studies [10, 57]. In contrast to the results in the first-line treatment, BRAF mutation is a predictor of resistance to anti-EGFR treatment in the second-line therapy or beyond [36, 50, 55].

Interestingly, vemurafenib, an orally administered BRAF V600 kinase inhibitor, has insufficient activity when used alone in BRAF-mutated mCRC patients [114]. Vemurafenib resistance in mCRC may be because of feedback activation of EGFR signaling [115, 116].

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6.4. Hyperactivation of PI3K-PTEN axis

Although 41% of mCRC patients do not have RAS or BRAF mutation, they do not respond to anti-EGFR mAbs [55]. Oncogenic activation of the members of EGFR downstream pathways other than RAS/RAF/MAPK (e.g., PI3K/PTEN pathway) might be responsible for the resistance to anti-EGFR mAbs. It is well established that activating mutation in PI3KCA or inactivation of PTEN phosphates can deregulate PI3K signaling pathway [117].

Mutation in PI3KCA and loss of PTEN are associated with resistance to anti-EGFR mAbs [118–120]. BRAF negative, PTEN expressing, and PI3K non-expressing CRCs have higher response rate and longer PFS and OS than others, suggesting that PI3K expression and PTEN loss might be used as predictors of response to anti-EGFR mAbs in mCRC patients with WT KRAS [121].

The role of PI3K mutation on response to anti-EGFR mAbs in mCRC has been evaluated in a number of studies [40, 58, 118, 122, 123]. Two of these studies demonstrated that PI3KCA mutation and PTEN loss, which cause PI3K pathway activation, are significant predictors of resistance to anti-EGFR mAbs [118, 122]. In contrast, PI3KCA mutation was not associated with response to anti-EGFR mAbs in chemorefractory mCRC patients in another study [123]. PTEN inactivation is another predictor of resistance to anti-EGFR mAbs [118–120]. Moreover, PI3K expression and PTEN loss are also associated with decreased survival in addition to poor response to anti-EGFR mAbs [117].

Study	Year	Population	Patient number	Regimen	Median PFS (month)	*p**	Median OS (month)	*p**	Response rate (%)	*p**
Reidy et al.[128]	2010	All	23	IMC-A12 (anti-IGF-1R antibody)	5.9	–	5.2	–	0	–
			21	IMC-A12 (anti-IGF-1R antibody) + Cetuximab	6.1		4.5		5	
		KRAS WT group	20	IMC-A12 (anti-IGF-1R antibody) + Cetuximab	9.4		10.9		0	

*95% confidence interval.
PFS, progression-free survival; OS, overall survival; All, all patients group; WT, wild type; MT, mutant type; N/A: not available; KRAS, KRAS exon 2, codons 12 and 13; anti-IGF-1R, insulin-like growth factor-1 receptor inhibitor.

Table 3. Selected phase II study of an insulin-like growth factor-1 receptor inhibitor for metastatic colorectal cancer refractory to cetuximab or panitumumab

6.5. Hyperexpression or hyperactivation of type 1 insulin-like growth factor receptor (IGF-1R)

The type 1 insulin-like growth factor receptor (IGF-1R) is a tyrosine kinase receptor that functions by activating downstream signaling pathways, including MAPK and PI3K/AKT. IGF-1R overexpression, which may cause neoplastic transformation of cultured cells, is present

in several types of human tumors [124, 125], and its downregulation can inhibit the growth of tumor cells [126]. These findings make IGF-1R an attractive candidate as an anti-cancer therapeutic target. A previous study showed that combination therapy of mAbs targeting IGF-1R and EGFR results in further inhibition of CRC cell-line growth [127]. A phase II study evaluated the safety and the efficacy of human anti-IGF-1R mAb (either alone or in combination with cetuximab) in mCRC patients, and both treatment modalities were reported as insufficient in chemorefractory mCRC patients [128] [**Table 3**].

6.6. EGFR-tyrosine kinase inhibitors in mCRC

The orally active EGFR-tyrosine kinase inhibitors erlotinib and gefitinib prevent downstream signaling of the receptor and are inactive as monotherapy of mCRC [129, 130]. Promising results have been reported in phase II trials of erlotinib with capecitabine and oxaliplatin [131] and gefitinib plus FOLFOX in mCRC patients [132, 133]. However, randomized trials are required to evaluate the benefits of gefitinib or erlotinib in combination with chemotherapy by comparing chemotherapy alone.

7. Future perspectives

The mAbs targeting EGFR (cetuximab and panitumumab) have shown remarkable efficacy in the treatment of mCRCs. Despite the significance of KRAS mutations, the efficacy of anti-EGFR monoclonal antibodies in the 60–70% of mCRC patients with KRAS WT tumors is still limited, with response rates between 10 and 40% [134]. Similar to other targeted therapies, anti-EGFR drugs are active only in a fraction of patients and most of them subsequently become resistant to the treatment. Accordingly, two major challenges need to be addressed to optimize the efficacy of anti-EGFR therapies. The first is to identify the genetic alterations associated with the clinical response to anti-EGFR mAbs. The second is the elucidation of the molecular basis for primary or acquired resistance to these drugs. It seems likely that a comprehensive biomarker analysis will be required to identify the mCRC patients who will truly benefit from anti-EGFR mAbs.

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