

A Comprehensive Review of Clinical Trials on EGFR Inhibitors Such as Cetuximab and Panitumumab as Monotherapy and in Combination for Treatment of Metastatic Colorectal Cancer

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Abstract

Metastatic colorectal cancer is the fourth most common cause of death due to cancer after those of lung, stomach, and liver. Anti epidermal growth factor receptor drugs as a targeting therapy seem to be good candidates for curing metastatic colorectal cancer. Two available anti epidermal growth factor receptor monoclonal antibodies are cetuximab and panitumumab which have been approved for metastatic colorectal cancer treatment. Through the available literature on NCBI and clinical trials, 31 clinical trials in which cetuximab or panitumumab as monotherapy or in combination with chemotherapy were used for the treatment of metastatic colorectal cancer patients in different line settings and 12 clinical trials in which bevacizumab was used for being compared with anti epidermal growth factor receptor monoclonal antibodies or chemotherapy were chosen for reviewing and comparing the results of overall survival, progression free survival and adverse effects. Cetuximab and panitumumab are well accepted for the treatment of mCRC patients at all stages in different line settings. Although cetuximab administration in metastatic colorectal cancer patients is mostly associated with better overall survival and panitumumab results in better progression free survival, to confirm the superiority of each of them in the treatment protocol of epidermal growth factor receptor monoclonal antibodies, more clinical trials with larger sample size are needed. Through current available data from clinical studies, it can be concluded that the best treatment outcome is achieved by a combination of anti epidermal growth factor receptor monoclonal antibodies with conventional chemotherapy.

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Introduction

Despite all advances in the therapeutic modalities for Colorectal Cancer (CRC), this malignancy continues to be the fourth most common cause of cancer death after lung, stomach, and liver cancer¹. Consequently, the overall five-year survival remains very poor about 10% for patients at metastatic stage of this disease (mCRC)². However, with the introduction of several chemotherapeutic agents such as irinotecan and oxaliplatin in combination with fluorouracil or leucovorin, the hope for survival of mCRC patients has been created and development of drug resistance results in investigating other therapeutic options. The abnormal

extra expression of the Epidermal Growth Factor Receptor (EGFR) is frequently associated with many human malignancies including mCRC^{3,4}. Therefore, anti-EGFR drugs seem proper candidates for the treatment of mCRC using targeted therapy. Currently, two clinically available anti-EGFR Monoclonal antibodies (Mabs) are cetuximab and panitumumab, which reached FDA approval in 2004 and 2007 respectively, for the treatment of mCRC^{5,6}. Cetuximab is a chimeric (mouse/human) Mab given by intravenous infusion, binds to the EGFR, stops the binding and activation of the downstream signaling pathways and prevents the

cell proliferation, invasion, metastasis, and neovascularization (Box 1) ⁷. Panitumumab is a fully human Mab with the same properties as cetuximab (Box 2). Clinical use of anti-EGFR Mabs has shown variable data in different line settings of mCRC therapy. For instance, some studies have demonstrated a survival benefit of single-agent therapy of cetuximab or panitumumab in the third line setting ^{8,9} while another study showed the superiority and better overall survival of cetuximab-irinotecan combination in comparison to panitumumab monotherapy in previously treated mCRC patients ¹⁰. However, the heterogeneity of study population and many other factors may justify these various results.

In the present review, in order to better understand the advantage and/or disadvantage of application of anti-EGFR therapy in different line settings of mCRC treatment, both as monotherapy and in combination with chemotherapy, and corresponding adverse effects, recent clinical trials were compared with each other.

Comparison of cetuximab and panitumumab in combination or monotherapy of mCRC

Most of clinical trials include the anti-EGFR therapy in the treatment protocol of mCRC in conventional chemotherapy refractory patients. In this regard, anti-EGFR Mabs are usually used in combination with some chemotherapeutic agents in second or third line setting for treatment. However, in some clinical trials after chemotherapy failure, anti-EGFR Mabs have been used in monotherapy. An important factor to select the cetuximab or panitumumab for the treatment of mCRC patients is the Kirsten Rat Sarcoma viral oncogene (KRAS) mutation status. In fact, mutation in the KRAS gene is considered as a negative predictor of response to cetuximab and/or panitumumab. In a study conducted on Japanese patients with mCRC, the response rate (RR) to cetuximab plus irinotecan therapy was around 17.9 and 0% in the KRAS wild-type (WT KRAS) and mutant subgroups, respectively ¹¹. Studies about the application of panitumumab in mCRC patients also

Box 1. Drug summary

Drug name	Cetuximab
Phase	Launched
Indication	For treatment of EGFR-expressing metastatic colorectal cancer
Pharmacology description	Epidermal growth factor receptor binding FAB
Route of administration	Intravenous
Protein structure	



Protein chemical formula	C ₆₄₈₄ H ₁₀₀₄₂ N ₁₇₃₂ O ₂₀₂₃ S ₅₆
Pivotal trial(s)	[11, 12, 15]
The protein structure and the chemical formula are adapted from http://www.drugbank.ca/drugs/DB00002	

Box 2. Drug summary

Drug name	Panitumumab
Phase	III
Indication	For treatment of EGFR-expressing metastatic colorectal cancer
Pharmacology description	Panitumumab (ABX-EGF) is a recombinant human IgG2 monoclonal antibody that binds specifically to the human epidermal growth factor receptor (EGFR)
Route of administration	Intravenous
Protein structure	Not available
Protein chemical formula	C ₆₃₉₈ H ₉₈₇₈ N ₁₆₉₄ O ₂₀₁₆ S ₄₈
Pivotal trial(s)	PRIME trial [18]
The protein chemical formula and description are adapted from http://www.drugbank.ca/drugs/DB01269	

demonstrated the same results¹². The first line treatment options for patients with mCRC are varied and range from single drug to highly effective four-drug combination, but the best option is designated based on tumor and patient related factors and differs case by case. Cetuximab can be involved in the first line treatment of mCRC patient.

In one study of 845 patients with KRAS wild-type tumors, adding cetuximab to the first line chemotherapy, significantly led to an improvement in Overall Survival (OS) compared with chemotherapy alone¹³. Also in another study, higher Progression Free Survival (PFS) was observed in WT KRAS patients treated with cetuximab in the first line chemotherapy¹⁴. In addition, the combination of cetuximab with irinotecan/5-fluorouracil/folinic acid (FOLFIRI) in the initial treatment of mCRC in another clinical trial was not only well tolerated, but also in one-quarter of patients changed the status of metastases from unresectable to resectable¹⁵. Although it should be noticed that the combination of anti-EGFR with chemotherapeutic agents is not always allowed to be prescribed and some combinations should be avoided (e.g., oral or bolus fluoropyrimidines, oxaliplatin and cetuximab or panitumumab), but many studies indicate the benefits of combination therapy in the treatment of mCRC in different line settings.

In a randomized controlled trial of cetuximab plus chemotherapy for patients with WT KRAS unresectable colorectal liver-limited metastases, the combination of cetuximab with FOLFIRI (fluorouracil, leucovorin, and irinotecan) or mFOLFOX6 (modified fluorouracil, leucovorin, and oxaliplatin) in one arm and chemotherapy alone in another arm were compared and results showed that patients in the combination arm had improved objective response rates (57.1 vs. 29.4%; $p < 0.01$), increased 3-year OS rate (41 vs. 18%; $p = 0.013$) and prolonged median survival time MST (30.9 vs. 21.0 months; $p = 0.013$). In this study, patients who had resection of liver metastases had a significantly improved MST (46.4 vs. 25.7 months; $p < 0.01$) compared with those who did not undergo surgery¹⁶. However, the combination of cetuximab with chemotherapy is not always associated with positive response; in contrast to above studies, the results of EPOC trial raised strong doubt about this strategy as in this experiment, patients with operable metastases from colorectal cancer were randomized to receive fluoropyrimidine and oxaliplatin with or without cetuximab for 12 weeks before and then 12 weeks following surgery. In patients with resectable liver metastases, progression free survival was significantly worse in the cetuximab plus arm [14.8 vs. 24.2 months, Hazard Ratio (HR) (95% Confidence Interval (CI)) 1.50037 (1.000707 to 2.249517) $p < 0.048$]¹⁷. Whereas most of the clinical trials used cetuximab in the first line setting of their treatment protocol, cetuximab in the randomized clinical trial also resulted in a significant improvement in overall survival from 4.8 months to 9.5 months⁸.

Application of panitumumab in the first line treatment of mCRC in combination with chemotherapy also created the hope for a better treatment outcome. In a PRIME phase III trial, to compare the combination of panitumumab with folinic acid, 5 fluorouracil and oxaliplatin (FOLFOX4) and FOLFOX4 alone in mCRC patients, in the first line setting, panitumumab has demonstrated significant improvement in progression free survival (median PFS, 9.6 vs. 8.0 months, respectively; HR, 0.80; 95% CI, 0.66 to 0.97; $p = 0.02$), though the overall survival has not increased significantly in panitumumab-FOLFOX4 versus FOLFOX4 (median OS, 23.9 vs. 19.7 months, respectively; HR, 0.83; 95% CI, 0.67 to 1.02; $p = 0.072$)¹⁸. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second line treatment in patients with metastatic colorectal cancer also showed only improvement in PFS of patients with combination therapy (HR=0.73; 95% CI, 0.59 to 0.90; $p = 0.004$); median PFS was 5.9 months for panitumumab-FOLFIRI versus 3.9 months for FOLFIRI, overall survival has not been changed significantly and median OS was 14.5 months versus 12.5 months, respectively (HR=0.85, 95% CI, 0.70 to 1.04; $p = 0.12$). Administration of panitumumab in monotherapy regimen for WT KRAS mCRC patients following cetuximab-based regimens resulted in 67% disease control rate and 30% objective response rate, with meaningful change in PFS (4.2 months) and OS (9.6 months)¹⁹. The combination of panitumumab with decitabine (a hypomethylating agent) was also well tolerated and showed activity in previously cetuximab treated mCRC patients²⁰. Some studies also compared the application of panitumumab with bevacizumab (anti VEGF monoclonal antibody) for the treatment of mCRC. In a phase II PEAK study, to compare the FOLFOX regime in combination with either panitumumab or bevacizumab in 285 previously untreated mCRC patients (first line treatment), results indicated the similar Overall Response Rate (ORR). The PFS was also similar between arms²¹.

In a study to compare the panitumumab monotherapy with cetuximab and irinotecan combination therapy as third line treatment setting in patients with KRAS wild-type mCRC, median overall survival was 7.7 months for the panitumumab group and 8.3 months in the cetuximab-irinotecan group and the survival outcomes were similar regardless of the therapy selected (HR:1.28; $p = 0.34$)¹⁰. In ASPECCT trial, to compare cetuximab and panitumumab in mCRC chemorefractory patients (as monotherapy in third line setting), the application of cetuximab resulted in a bit lower overall response rate than panitumumab (ORR: cetuximab 19.8% and panitumumab 22%), while, the Progression Free Survival (PFS) of cetuximab was around 3 months longer (PFS: 4.4 vs. 4.1 months. HR: 1.00, 95% CI: 0.88-1.14). The overall survival of both drugs was equal (OS: cetuximab 10.0 and panitumumab 10.4

Table 1. The clinical outcome of cetuximab and panitumumab administration as monotherapy and in combination with chemotherapy in mCRC patients

Clinical Trial	Treatment option	Patients	Endpoint	p-value	Ref
Kennecke H <i>et al</i> 2013	Mono PMab CMab Combo	178 (141 PMab, 37 CMab Combo)	OS: 7.7 vs. 8.3 Months	0.03	10
Price <i>et al</i> 2014 ASPECCT	Mono CMab vs. Mono PMab in refractory mCRC	999 (499 PMab and 500 CMab)	OS: 10.0 vs. 10.4 Months PFS: 4.4 vs. 4.1 Months ORR: 19.8% vs. 22%	0.0007	12
Bokemeyer C <i>et al</i> 2012 CRYSTAL and OPUS	CMab Combo	845 KRAS wild-type tumors	OS: Improved PFS: Improved ORR: Improved	0.0062 ≤0.0001 ≤0.0001	13
Pietrantonio F <i>et al</i> 2013	Mono PMab	30 CMab pretreated KRAS WT mCRC	DCR: 67% OBR: 30% PFS: 4.2 Months OS: 9.6 Months	0.12	19
NCT00115765 2013	BMab Combo PMab with BMab Combo	BMab+Oxaliplatin 410 PMab with BMab+Oxaliplatin 413	OS: BMab Combo=24.5 Months and PMab with BMab Combo=19.4	0.005	34
			PFS: BMab Combo=11.4 Months and PMab with BMab Combo=10 Months	0.0011	
PEAK trial 2014	PMab Combo BMab Combo	278	OS: PMab Combo=34.2 Months BMab Combo=24.3 Months PFS: Similar between two arms	0.009	47
Santos-Ramos B <i>et al</i> 2013	CMab Combo BMab Combo	227	PFS: CMab Combo=11.7 Months BMab Combo=9.6 Months	-	48
Pietrantonio F <i>et al</i> 2012	CMab Combo BMab Combo	96	OS: CMab Combo=22.7 Months BMab Combo=18.7 Months	0.55	50
Modest DP <i>et al</i> 2012	CMab Combo BMab Combo	54 KRAS p.G13D mutated patients	ORR: CMab=58% BMab=57%	-	51
			PFS: CMab=8.0 Months BMab=8.7 Months	0.9	
			OS: CMab=20. Months BMab=14.9 Months	0.2	
Dotan E <i>et al</i> 2012	CMab+BMab Combo, CMab Combo	23: 12 CMab+BMab Combo, And 11 CMab Combo	ORR: CMab+BMab Combo,= 36% CMab Combo,=72%	0.72	52
			PFS: CMab+BMab Combo,=8.7 Months CMab Combo,=14.4 Months		
			OS: CMab+BMab Combo,=18 Months CMab Combo,=42.5 Months	0.52	
EPOC trial 2014	Chemotherapy CMab Combo	257 patient with resectable colorectal liver metastases	PFS: Chemotherapy=14.1 Months CMab Combo=20.5 Months	0.003	58

Endpoints resulting from recent clinical trials of administering cetuximab and panitumumab as monotherapy or in combination with conventional chemotherapy in mCRC patients. OS: Overall Survival, PFS: Progression Free Survival, ORR: Overall Response Rate, DCR: Disease Control Rate, OBR: Objective Response Rate, PMab: Panitumumab, CMab: Cetuximab, BMab: Bevacizumab, Combo: Combination with chemotherapy. Mono: Monotherapy of Mab.

months. HR:0.97, 95% CI:0.84-1.11, p=0.0007). Considering achieved results, non-inferiority endpoint was met in ASPECCT trial²².

Although several studies are available to compare the effectiveness of cetuximab and panitumumab in mCRC patients (Table 1), regarding these mentioned trials, it can be concluded that cetuximab in combination with chemotherapy can offer better overall survival when compared to panitumumab plus chemotherapy. On the other side, in many randomized clinical trials, significant improvements in tumor response rates and progression free survival have been observed when panitumumab is combined with chemotherapy or used as monotherapy in chemorefractory mCRC individuals. Therefore, the priority of cetuximab or panitumumab and the decision of treatment option between these two available anti-EGFR Mabs depend mostly on the patient condition and clinical availability which should be

considered by physicians. Regarding the role of KRAS status in the response rate of anti-EGFR therapy, it is fundamentally important to have an improved patient selection through the use of novel predictive biomarkers.

Comparison of the side effects of cetuximab and panitumumab in combination or monotherapy of mCRC

In contrast to traditional chemotherapeutic drugs, anti-EGFR Mabs do not cause systemic toxicities including nausea, vomiting, diarrhea, alopecia, and bone marrow suppression. However, their most common adverse effects are skin rash²³, hypomagnesemia²⁴, hypokalemia²⁵ and infusion reaction²⁶. Different grades of these side effects can be observed among mCRC patients treated with these drugs. Severe infections (≥grade 3) were sometimes reported in cetuximab and/or panitumumab trials as a treatment side effect, which caused the disruption of treatment, and even led to

Table 2. Most common adverse effects of cetuximab and panitumumab administration in mCRC patients

Study	Treatment	Patients	Most common side effect	Ref
Cao Y <i>et al</i> 2010	Mono CmaB	3081	Grade 3 and 4 Hypomagnesemia (5.6%; 95% CI=3.0-10.2). All grade Hypomagnesemia (36.7%; 95% CI=22-54.4).	24
Cao Y <i>et al</i> 2010	Mono CmaB	1324	Grade 3 and 4 Hypokalemia [6.2% (95% CI 4.9-7.7)]. All-grade Hypokalemia [8.0% (95% CI 4.5-13.9)]	25
Amgen trial 2013 NCT00089635	Mono PmaB	203	Abdominal pain, Dehydration and Dyspnoea 6/203 (2.96%)	29
Merck KGaA CRYSTAL trial 2014	CMaB Combo	600	Diarrhea 36/600 (6.00%) Catheter related infection 8/600 (1.33%) Central line infection 10/600 (1.67%) Hypomagnesaemia 13/600 (2.17%)	36
NCT00083720 2011	Mono CmaB	85	Death 1/85 (1.18%) Dyspnea 3/85 (3.53%)	37
Herbert Hurwitz clinical trial 2013 NCT00290615	CMaB+BmaB Combo	30	Diarrhea 6/30 (20.00%)	38
NCT00252564 2011	CMaB+BmaB Combo BmaB Combo	CMaB Combo: 123 BmaB Combo: 124	Anemia in CMaB 28/121 (23.14%) and in BmaB 45/118 (38.14%) Leucopenia in CMaB 26/121 (21.49%) and in BmaB 37/118 (31.36%) Neutropenia in CMaB 19/121 (15.70%) and in BmaB 49/118 (41.53%) Thrombocytopenia in CMaB 22/121 (18.18%) and in BmaB 42/118 (35.59%)	39
OPUS clinical trial 2011 NCT00125034	CMaB Combo	170	Pulmonary embolism 5/170 (2.94%) Anorexia 3/170 (1.76%)	40
NCT00193219 2013	CMaB+BmaB Combo	31	Thrombosis/Thrombus/Embolism 4/31 (12.90%)	41
Amgen Trial 2013 NCT00115765	PMaB+BmaB Combo	518	Diarrhea 63/518 (12.16%) Fibril neutropenia 20/518 (3.86%) Nausea 24/518 (4.63%) Vomiting 27/518 (5.21%) Sepsis 16/518 (3.09%)	34
M.D. Anderson Cancer Center NCT00354978 2011	BmaB Combo	43	Alopecia 22/43 (51.16%) Nausea, Fatigue and Hemorrhage 19/43 (44.19%)	44
Yamaguchi K <i>et al</i> 2014	Mono CmaB	2126	Infusion reactions in 114 patients (5.7%). Grade 3-4 Infusion reactions in 22 patients (1.1%).	56
PETACC-8 2014	Mono CmaB CMaB Combo	Mono CMaB: 791 CMaB Combo: 811	Grade 3 or 4 Acne-like rash: CMaB=27% CMaB Combo=≤1% Diarrhea: 14% vs. 9% Mucositis: 63% vs. 10% Infusion-related reactions: 55% vs. 30%	57
EPOC trial 2014	Chemotherapy CMaB Combo	257 Patient with resectable Colorectal liver metastases	Grade 3, 4 Neutopenia: Chemotherapy=15%, CMaB Combo=4% Pulmonary embolism and Death: Chemotherapy=1 case, CMaB Combo=3 cases Skina rash: Chemotherapy=1% , CMaB Combo=15%	58
COIN-B trial 2014	Intermittent Mono CMaB Continuous Mono CMaB	64 patients Intermittent Mono CMaB 66 patients Continuous Mono CMaB	Grade 3, 4 Skin rash: Intermittent Mono CMaB=27%, Continuous Mono CMaB=22% Neutropenia: Intermittent Mono CMaB=29%, Continuous Mono CMaB=33% Diarrhea: Intermittent Mono CMaB=18%, Continues Mono CMaB=25% Lethargy: Intermittent Mono CMaB=26%, Continues Mono CMaB=21%	59

Most common adverse effects of cetuximab and panitumumab therapy as a sinle agent or in combination with chemotherapy in recent clinical trials. PMaB: Panitumumab, CMaB: Cetuximab, BmaB: Bevacizumab, FOLFOX: Oxaliplatin, 5-fluorouracil and leucovorin, FOLFIRI: Fluorouracil, leucovorin and Irinotecan, Combo: Combination with Chemotherapy. Mono: Monotherapy of Mab

pulmonary embolism and fatalities ^{27,28}. However, many of these side effects also seem to be related to chemotherapeutic part of treatment regimen when combination of anti-EGFR with routine chemotherapy is considered. In this section of study, some reported side effects of cetuximab and panitumumab clinical trials were reviewed and these events between different arms of treatment in these studies were compared (Table 2).

In Amgen trials, to study the panitumumab monotherapy in mCRC patients with a history of treatment

with fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy from the 203 enrolled patients, who received intravenous (IV) infusion of panitumumab at a dose of 6 mg/kg once every 2 weeks, most reported adverse effects were abdominal pain, dehydration and dyspnea 6/203 (2.96%) ²⁹. In a randomized, multicenter, open-label, non-inferiority phase 3 study conducted by Price *et al*, in order to compare the efficacy of cetuximab and panitumumab in chemotherapy refractory mCRC patients when drug schedule was panitumumab for 499 patients (6 mg/kg once every 2 weeks) in

one arm and cetuximab for 500 patients (initial dose 400 mg/m²; 250 mg/m² once a week thereafter) in another arm, the incidence of adverse events of any grade and grade 3-4 was equal between two arms. Grade 3-4 skin toxicity occurred in 62/499 (13%) patients in panitumumab treated group and 48/500 (10%) patients in cetuximab group. The chance of grade 3-4 infusion reactions was lesser in patients treated by panitumumab than cetuximab [(1 (<0.5%) patient vs. 9 (2%) patients)], and the occurrence of grade 3-4 hypomagnesemia was higher in the panitumumab group [(35 (7%) vs. 13 (3%)]. Also one treatment-related fatal adverse event, a lung infection in a patient given cetuximab was observed¹². In a post-marketing surveillance study of panitumumab monotherapy in 3085 Japanese patients with mCRC, the most common adverse drug reaction was skin disorders (78.4%). Also, the chance of all grades of electrolyte abnormalities was 19.3%, interstitial lung disease was 1.3% (mortality rate: 0.6%), infusion reaction was 1.5%, and cardiac disorders was about 0.2%³⁰. A noticeable fact which has been observed in different clinical trials to study the effect of anti-EGFR antibodies in mCRC treatment is that patients with grade 2 or 3 skin-related adverse events had higher response rates and longer PFS than patients with grade 1 events. These findings are consistent with studies associating skin toxicity with response to anti-EGFR antibodies³¹⁻³³. Therefore, the selection of treatment protocol among available options should be done by considering the patient's condition and probable chance of treatment success.

The addition of panitumumab to bevacizumab plus irinotecan or oxaliplatin based chemotherapy for mCRC patients also resulted in an increased risk of febrile neutropenia (Pmab. plus Bmab with chemotherapy as first arm: 20/518 [(3.86%) and Bmab with chemotherapy as second arm: 9/510 (1.76%)], diarrhea [(63/518 (12.16%) vs. 15/510 (2.94%)], nausea [(24/518 (4.63%) vs. 7/510 (1.37%)] and vomiting [(27/518 (5.21%) vs. 10/510 (1.96%)]³⁴. In another experiment, to study the effect of chemotherapy and bevacizumab with or without panitumumab in the first line treatment of mCRC, results showed that those individuals who received panitumumab in combination with bevacizumab and chemotherapy experienced a higher incidence of death (9% vs. 4%)³⁵.

Cetuximab in several clinical trials also showed different adverse effect. In CRYSTAL clinical trial with 600 mCRC patients, to compare the efficacy of cetuximab plus FOLFIRI and FOLFIRI chemotherapy alone, the most common observed side effects were as follows: diarrhea [(36/600 (6.00%) in Cmab vs. 21/602 (3.49%) in FOLFIRI], catheter related infection [(8/600 (1.33%) vs. 1/602 (0.17%)], central line infection [(10/600 (1.67%) vs. 4/602 (0.66%)] and hypomagnesemia [(13/600 (2.17%) vs. 1/602 (0.17%)]³⁶. In another study using cetuximab for the treatment of 85 mCRC patients, one case of treatment related death

was observed and the rate of dyspnea was around 3/85 (3.53%)³⁷. Also, cetuximab in combination with capecitabine, oxaliplatin, and bevacizumab for the treatment of 30 mCRC patients caused the diarrhea as the most common side effect [(6/30 (20.00%)]³⁸. Although panitumumab and its combination with bevacizumab and chemotherapy showed detrimental effects^{34,35}, controversial results were obtained when cetuximab was added to bevacizumab+FLOFOX chemotherapy as the incidence of leukopenia in cetuximab arm was 26/121 (21.49%) while in bevacizumab+FLOFOX was 37/118 (31.36%), or thrombocytopenia was 22/121 (18.18%) vs. 42/118 (35.59%); also, the incidence of neutropenia in cetuximab arm was 19/121 (15.70%) while in bevacizumab+FLOFOX arm was 49/118 (41.53%)³⁹. In fact, addition of cetuximab to bevacizumab+FLOFOX not only didn't increase the incidence of common side effects (as panitumumab did), but also in many cases the rate of side effects considerably dropped. It is noticeable that although cetuximab and panitumumab are both anti-EGFR antibodies, but the combination of these Mabs with an anti VEGF antibody resulted in a different outcome and side effects. It is well accepted that neutropenia can increase the risk of infection due to the central role of neutrophil against infectious diseases and regarding the results of the above study³⁹, decrease in the incidence of neutropenia in cetuximab plus arm can be considered as an advantage of this combination but this is questionable since some studies reported more therapeutic related infections due to administration of cetuximab¹².

In comparison to afatinib as a tyrosine kinase inhibitor for the treatment of mCRC patients, cetuximab also showed lower incidence of adverse effects as the rate of diarrhea and vomiting in cetuximab treated patients was 0/14 (0.00%) and 1/14 (7.14%), respectively, and for afatinib treated patients was 4/36 (11.11%) and 5/36 (13.89%). Meanwhile, the nausea was observed in afatinib group in 4/36 (11.11%) of patients while in the cetuximab group, it has not been observed⁴². Regarding cited studies, it can be concluded that although both cetuximab and panitumumab are associated with some adverse effects, the incidence of these problems, especially when combination of different biological molecules is chosen for mCRC treatment, is depressed by cetuximab than panitumumab. While more studies with larger sample size are needed for better justification, with current available data, selection of best treatment can be done on the basis of lower incidence of side effects.

Comparison of the EGFR Mabs with VEGF Mabs and their combination for mCRC treatment

Bevacizumab acts as anti Vascular Endothelial Growth Factor (VEGF) and is used to inhibit VEGF function in vascular endothelial cells and inhibit tumor angiogenesis. Application of bevacizumab plus chemotherapy in most randomized controlled trials of mCRC patients showed a significant increase in the PFS or

disease free survival rate⁴⁴. The combination of bevacizumab with oxaliplatin in another clinical trial resulted in better OS and PFS rate compared to the situation when panitumumab was added to bevacizumab and oxaliplatin (PFS for Bmab+Oxaliplatin 11.4 months vs. Bmab+Oxaliplatin+ Pmab 10 months, HR=1.27 CI; 95%, p=0.011) (OS for Bmab+Oxaliplatin 24.5 months vs. Bmab+Oxaliplatin+ Pmab 19.4 months, HR=1.43, CI; 95%, p=0.005)³⁴. The results of this study indicate the superiority of bevacizumab plus chemotherapy than both panitumumab and bevacizumab plus chemotherapy. Bevacizumab beyond first progression is also associated with a longer median OS time and has an important role in improving the overall success of therapy for mCRC patients⁴⁵. Application of FOLFOXIRI plus bevacizumab in comparison to FOLFIRI plus bevacizumab resulted in better PFS rate as 12.1 months in the first group and 9.7 months in the second group (HR=0.75; 95% CI=0.62 to 0.90; p=0.003). OS was also longer in the first group, but it was not significant⁴⁶. These results may imply to the benefits of the combination of bevacizumab with oxaliplatin.

In a study to compare the panitumumab plus modified FOLFOX6 and bevacizumab plus modified FOLFOX6 for the treatment of mCRC patients, the obtained results showed similar PFS between the two arms and median OS of 34.2 months and 24.3 months in the panitumumab and bevacizumab arms, respectively (HR, 0.62; 95% CI, 0.44 to 0.89; p=0.009). Regarding the results of previous mentioned studies, although the addition of panitumumab to the bevacizumab and chemotherapy caused the OS to decrease, thereby increasing the incidence of side effects^{34,35}, but in comparison to bevacizumab, OS was significantly improved when panitumumab was combined with mFOLFOX6 in mCRC patients⁴⁷.

Santos *et al* have shown that in mCRC patients treated with cetuximab or bevacizumab, the median PFS was around 11.7 months in the cetuximab arm and 9.6 months for bevacizumab arm^{48,49}. In addition, combination of FOLFIRI and cetuximab resulted in prolonged overall survival in comparison to FOLFIRI plus bevacizumab in first line treatment for mCRC patients (22.7 vs. 18.7 months), although this difference was not statistically significant (HR=0.86, 95% CI, 0.55-1.35; p=0.55)⁵⁰. Cetuximab also showed a superiority in the first line treatment of mCRC patients with KRAS p.G13D-mutation in comparison to bevacizumab as OS was 20.1 months in patients treated with cetuximab and 14.9 months in patients receiving bevacizumab-containing regimens (hazard ratio: 0.70, p=0.29)⁵¹. In a phase II study of capecitabine, oxaliplatin, and cetuximab with (arm A) or without (arm B) bevacizumab, results showed an overall response rate of 54% (36.4% in arm A and 72.7% in arm B). PFS in this study was 8.7 months in arm A and 14.4 months in arm B. Also, the median overall survival was 18.0 months in arm A and 42.5 months in arm B⁵². Also in

Phase III trial, in order to study the effect of cetuximab plus bevacizumab, and 5-fluorouracil/leucovorin in comparison to FOLFOX-bevacizumab in mCRC patients, results showed that cetuximab plus bevacizumab, and 5-fluorouracil/leucovorin was not superior to FOLFOX6-bevacizumab in terms of 12-month PFS (45%/32%, respectively) and overall response rate (52%/41%, respectively)⁵³. Regarding all mentioned trials, cetuximab has more privileges to bevacizumab since it can be combined with chemotherapy for mCRC treatment, but is not an appropriate candidate in combination with bevacizumab and in chemotherapy regimen and this combination is not beneficial for mCRC treatment.

Aflibercept is another anti VEGF inhibitor that binds to circulating VEGFs and acts like a VEGF trap, inhibits the neovascularization in the choriocapillaris or the tumor. Aflibercept in combination with 5-fluorouracil, leucovorin and irinotecan (FOLFIRI) significantly improved survival in a phase III study of patients with mCRC who had a history of treatment with oxaliplatin⁵⁴, albeit the outcome of aflibercept treatment in mCRC patients mainly depended on the history of previous treatment with bevacizumab. Patients who received bevacizumab before aflibercept usually showed a weak response⁵⁵. Due to lack of large clinical trials, it is difficult to compare aflibercept efficacy and safety as monotherapy and in combination with Mabs in this field. But regarding the results of studies on bevacizumab and its combination with cetuximab and panitumumab, it can be concluded that combining VEGF and EGFR inhibitors in metastatic colorectal cancer is not always advantageous. However, any of these agents can lead the treatment to success in combination with chemotherapy.

Conclusion

In many cases, cancer becomes metastatic before correct diagnosis and makes the treatment difficult. Although by introducing different chemotherapeutic agents such as irinotecan and oxaliplatin in combination with fluorouracil or leucovorin, the hope for survival is created in patients with mCRC, most of these patients fail to be cured due to the development of drug resistance. This drug resistance urges researchers to explore an alternative approach for chemo refractory patients and for those who do not respond to conventional chemotherapy.

Anti-EGFR antibodies can be considered as appropriate candidates for mCRC patients who have no response to chemotherapy. Results of many clinical trials showed the effectiveness of these Mabs in the treatment of mCRC patients in different line settings and at any progressive stage. However, it should not be ignored that neither conventional chemotherapy nor anti-EGFR therapy alone will not help mCRC patients, rather the best achievement is only accessible when anti-EGFR Mabs are used in combination with routine

chemotherapy. For example, combination of mFOLF-
OX6 and FOLFIRI with cetuximab resulted in a better
objective response rate and overall survival in compar-
ison to each chemotherapy regimen alone ¹⁶. Or in a
PRIME phase III trial, administration of panitumumab
plus FOLOX4 significantly increased the PFS in
mCRC patients compared to FOLFOX4 alone ¹⁸.

An important factor in deciding to include the
cetuximab or panitumumab in the treatment of mCRC
patients is the KRAS mutation status. In fact, the selec-
tion of reliable patients before starting the interven-
tional treatment provides an opportunity to increase
the response rate and chance of treatment success. This
is a unique trait of anti-EGFR therapy. Also, despite
high drug resistance to conventional chemotherapy
which is considered as a main challenge, resistance to
cetuximab and panitumumab among mCRC patients
seems unlikely. The only superiority of routine chemo-
therapeutic agents in comparison to anti-EGFR inhibi-
tors is their easy access due to their generic availability
and lower price. In addition to anti-EGFR inhibitors,
anti VEGF Mabs such as bevacizumab also showed
effectiveness in the treatment of mCRC. But like
cetuximab and panitumumab, bevacizumab also show-
ed maximum effectiveness when combined to routine
chemotherapy. Although some clinical trials compared
the effects of bevacizumab and cetuximab and/or pani-
tumumab, additional clinical trials are still required to
evaluate the superiority of anti-EGFR or anti VEGF
inhibitors. However, regarding what was reviewed in
this article, anti-EGFR therapy does not have the abil-
ity to be replaced by chemotherapy.

The recommended dose and schedule for cetuximab
is 400 mg/m² administered intravenously as a 120 min
infusion as an initial dose, followed by 250 mg/m² in-
fused over 30 min weekly. For panitumumab, recom-
mended dose is usually 6 mg/kg every 14 days as an
intravenous infusion over 60 min. The best treatment
option is usually selected by considering factors related
to both patients and clinics. Maximum effectiveness
and minimum adverse effects are among these factors.
Comparing cetuximab and panitumumab in many clinical
trials, better overall survival is often achieved by
cetuximab plus chemotherapy and better progression
free survival with panitumumab plus chemotherapy.
Also, cetuximab in comparison to best supportive care
can significantly improve the overall survival in the
first line setting of mCRC treatment. However, appli-
cation of cetuximab is not always associated with good
results. In EPOC trial, cetuximab when combined with
fluoropyrimidine and oxaliplatin showed the contro-
versial results and even worsened the PFS ¹⁷.
Panitumumab also helped chemotherapy to be more
efficient ¹⁸. In many randomized clinical trials, signifi-
cant improvements in tumor response rates and pro-
gression free survival were observed when panitumu-
mab was combined with chemotherapy or used as
monotherapy in chemorefractory mCRC individuals.

But in contrast to cetuximab, panitumumab mostly
conferred PFS benefit. The positive fact about pani-
tumumab is its ability to improve treatment outcome
among previously cetuximab treated mCRC patients
^{19,20}. Meanwhile, regarding the key role of KRAS sta-
tus, it is fundamentally important to have an appropri-
ate method for selection of patients through the use of
novel predictive biomarkers to enhance the chance of
treatment success.

The other important factor in treatment decision
making is minimum adverse effects of therapy. Be-
tween cetuximab and panitumumab, there is no mean-
ingful difference based on treatment related side ef-
fects. As mentioned before, most common adverse
effects of anti-EGFR therapy are skin rash, electrolyte
abnormality and infusion reaction. But some detri-
mental side effects such as lung infection and embo-
lism and treatment related death were observed by the
application of cetuximab. However, these observed
side effects is not a justifiable evidence to consider
cetuximab inferior in comparison to panitumumab. In
contrast to the application of one biological drug from
anti-EGFR and anti VEGF inhibitors, it was also ob-
served that in combination therapy of bevacizumab
based chemotherapy with cetuximab and/or panitumu-
mab, the addition of panitumumab was associated with
detrimental effects and it raised the incidence of side
effects, while the incidence of side effects has been
lowered when cetuximab was combined with bevacizu-
mab based chemotherapy ^{34,35,39}. Nevertheless, to estab-
lish the superiority of cetuximab or panitumumab for
treatment of mCRC, clinical trials with larger sample
size are needed. On the other hand, although fewer side
effects are an advantage of any therapeutic modality, a
noticeable fact about the application of anti-EGFR
therapy is that more effectiveness is reported in those
patients with more side effects. Regarding the results
of mentioned clinical trials, the decision of treatment
option between these two available anti-EGFR Mabs as
stated before depends mostly on the patient condition
and clinical access.

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