Review Article

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

Mohammad Hossein Yazdi [1], Mohammad Ali Faramarzi [2], Shekoufeh Nikfar [3], and Mohammad Abdollahi [4*]

1. Department of Research and Development, Pasteur Institute of Iran, Karaj, Iran
2. Department of Pharmaceutical Biotechnology, Faculty of Pharmacy and Biotechnology Research Center, Tehran University of Medical Sciences, Tehran, Iran
3. Department of Pharmacoeconomics and Pharmaceutical Administration, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
4. Department of Toxicology and Pharmacology, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, and Endocrinology & Metabolism Research Center, Institute of Clinical Endocrine Sciences, Tehran University of Medical Sciences, Tehran, Iran

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.

*** Corresponding author:**
Mohammad Abdollahi , Ph.D., Department of Toxicology and Pharmacology, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, and Endocrinology & Metabolism Research Center, Institute of Clinical Endocrine Sciences, Tehran University of Medical Sciences, Tehran, Iran
E-mail:
Mohammad.Abdollahi@UToronto.Ca;
Mohammad@tums.ac.ir
Received: 12 Mar 2015
Accepted: 20 Jun 2015

Avicenna J Med Biotech 2015; 7(4): 134-144

Keywords: Anti-EGFR drugs, Cetuximab, Metastatic colorectal cancer, Panitumumab

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 cancer [1]. 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

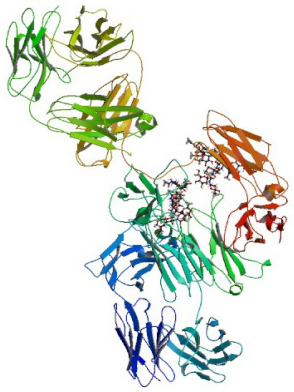
cell proliferation, invasion, metastasis, and neovascularization (Box 1) [7]. Panitumumab is a fully human Mab with the same properties as cetuximab (Box 2). Clinical use of anti-EGFR Mabs has shown variable data in different line settings of mCRC therapy. For instance, some studies have demonstrated 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	$C_{6484}H_{10042}N_{1732}O_{2023}S_{36}$
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 results [12]. 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 alone [13]. Also in another study, higher Progression Free Survival (PFS) was observed in WT KRAS patients treated with cetuximab in the first line chemotherapy [14]. 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 stasus of metastases from unresectable to resectable [15]. 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 surgery [16]. 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 months [8].

Application of panitumumab in the first line treatment of mCRC in combination with chemotherapy also created thehope 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 patients [20]. 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 arms [21].

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 cetiximab 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: cetuximab10.0 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 *et al* 2013	Mono PMab CMab Combo	178 (141 PMab, 37 CMab Combo)	OS:7.7 *vs.* 8.3 Months	0.03	10
Price *et al* 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 *et al* 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 *et al* 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 PFS: BMab Combo=11.4 Months and PMab with BMab Combo=10 Months	0.005 0.0011	34
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 *et al* 2013	Cmab Combo Bmab Combo	227	PFS: CMab Combo=11.7 Months BMab Combo=9.6 Months	-	48
Pietrantonio F *et al* 2012	CMab Combo BMab Combo	96	OS: CMab Combo=22.7 Months BMab Combo=18.7 Months	0.55	50
Modest DP *et al* 2012	CMab Combo Bmab Combo	54 KRAS p.G13D mutated pateints	ORR: CMab=58% BMab=57% PFS: CMab=8.0 Months BMab=8.7 Months OS: CMab=20. Months BMab=14.9 Months	- 0.9 0.2	51
Dotan E *et al* 2012	CMab+BMab Combo, CMab Combo	23: 12 CMab+BMab Combo, And 11 Cmab Combo	ORR: CMab+BMab Combo,= 36% CMab Combo,=72% PFS: CMab+BMab Combo,=8.7 Months CMab Combo,=14.4 Months OS: CMab+BMab Combo,=18 Months CMab Combo,=42.5 Months	0.72 0.52	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: Overal 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 trial [22].

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 rash [23], hypomagnesemia [24], hypokalemia [25] and infusion reaction [26]. 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 *et al* 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 *et al* 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 Camb 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 *et al* 2014	Mono Cmab	2126	Infusion reactions in114 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/m^2; 250 mg/m^2 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 observed [12]. 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 antibodies [31-33]. 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+FOLOFX arm was 49/118 (41.53%) [39]. In fact, addition of cetuximab to bevacizumab+FOLOFX 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 study [39], 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 cetuximab [12].

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 observed [42]. 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 rate [44]. The combination of bevacizumab with oxaliplatin in another clinical trial resulted in better OS and PFS rate compared to the stuation when panitumumab was added to bevacizumab and oxaliplatin (PFS for Bmab+Oxaliplatin 11.4 months *vs*. Bmab+Oxalipaltin+ Pmab 10 months, HR=1.27 CI; 95%, p=0.011) (OS for Bmab+Oxaliplatin 24.5 months *vs*. Bmab+Oxalipaltin+ 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 patients [45]. 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 significant [46]. 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 pervious 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 patients [47].

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 B [52]. 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 oxaliplatin [54], albeitthe 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 response [55]. 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 mFOLFOX6 and FOLFIRI with cetuximab resulted in a better objective response rate and overall survival in comparison 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 selection of reliable patients before starting the interventional 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 chemotherapeutic agents in comparison to anti-EGFR inhibitors 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 showed maximum effectiveness when combined to routine chemotherapy. Although some clinical trials compared the effects of bevacizumab and cetuximab and/or panitumumab, 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 ability to be replaced by chemotherapy.

The recommended dose and schedule for cetuximab is 400 mg/m^2 administered intravenously as a 120 *min* infusion as an initial dose, followed by 250 mg/m^2 infused over 30 *min* weekly. For panitumumab, recommended 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, application of cetuximab is not always associated with good results. In EPOC trial, cetuximab when combined with fluoropyrimidine and oxaliplatin showed the controversial results and even worsened the PFS [17]. Panitumumab also helped chemotherapy to be more efficient [18]. In many randomized clinical trials, significant improvements in tumor response rates and progression free survival were observed when panitumumab was combined with chemotherapy or used as monotherapy in chemorefractory mCRC individuals. But in contrast to cetuximab, panitumumab mostly confered PFS benefit. The positive fact about panitumumab is its ability to improve treatment outcome among previously cetuximab treated mCRC patients [19,20]. Meanwhile, regarding the key role of KRAS status, it is fundamentally important to have an appropriate 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. Between cetuximab and panitumumab, there is no meaningful difference based on treatment related side effects. As mentioned before, most common adverse effects of anti-EGFR therapy are skin rash, electrolyte abnormality and infusion reaction. But some detrimental side effects such as lung infection and embolism 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 observed that in combination therapy of bevacizumab based chemotherapy with cetuximab and/or panitumumab, 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 bevacizumab based chemotherapy [34,35,39]. Nevertheless, to establish 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.

Acknowledgement

This invited paper is the outcome of a financially non-supported study. The authors declare no conflict of interest.

References

1. Frestad D, Perner A, Pedersen UG. Acute onset and rapid progression of multiple organ failure in a young adult with undiagnosed disseminated colonic adenocarcinoma. BMJ Case Rep 2014;2014.
2. Sanoff HK, Sargent DJ, Campbell ME, Morton RF, Fuchs CS, Ramanathan RK, et al. Five-year data and prognostic factor analysis of oxaliplatin and irinotecan combinations for advanced colorectal cancer: N9741. J Clin Oncol 2008;26:5721-5727.

3. Gullick WJ. Prevalence of aberrant expression of the epidermal growth factor receptor in human cancers. Br Med Bull 1991;47:87-98.
4. Herbst RS, Shin DM. Monoclonal antibodies to target epidermal growth factor receptor-positive tumors: a new paradigm for cancer therapy. Cancer 2002;94:1593-1611.
5. US Food and Drug Administration. FDA approves Erbitux for colorectal cancer. Available at: www.Fda.Gov [Last accessed 2004].
6. US Food and Drug Administration. FDA approves Vectibix (panitumumab) to treat metastatic colorectal carcinoma. Available at: www.Fda.Gov [Last accessed 2007].
7. Cheng L, Ren W, Xie L, Li M, Liu J, Hu J, et al. Anti-EGFR MoAb treatment in colorectal cancer: limitations, controversies, and contradictories. Cancer Chemother Pharmacol 2014;74(1):1-13.
8. Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 2008;359(17):1757-1765.
9. Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008;26(10):1626-1634.
10. Kennecke H, Chen L, Blanke CD, Cheung WY, Schaff K, Speers C. Panitumumab monotherapy compared with cetuximab and irinotecan combination therapy in patients with previously treated KRAS wild-type metastatic colorectal cancer. Curr Oncol 2013;20(6):326-332.
11. Soeda H, Shimodaira H, Gamoh M, Ando H, Isobe H, Suto T, et al. Phase II trial of cetuximab plus irinotecan for oxaliplatin- and irinotecan-based chemotherapy-refractory patients with advanced and/or metastatic colorectal cancer: evaluation of efficacy and safety based on KRAS mutation status (T-CORE0801). Oncology 2014; 87(1):7-20.
12. Price TJ, Peeters M, Kim TW, Li J, Cascinu S, Ruff P, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. Lancet Oncol 2014;15(6):569-579.
13. Bokemeyer C, Van Cutsem E, Rougier P, Ciardiello F, Heeger S, Schlichting M, et al. Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: pooled analysis of the CRYSTAL and OPUS randomised clinical trials. Eur J Cancer 2012;48(10):1466-1475.
14. Piessevaux H, Buyse M, Schlichting M, Van Cutsem E, Bokemeyer C, Heeger S, et al. Use of early tumor shrinkage to predict long-term outcome in metastatic colorectal cancer treated with cetuximab. J Clin Oncol 2013;31(30): 3764-3775.
15. Raoul JL, Van Laethem JL, Peeters M, Brezault C, Husseini F, Cals L, et al. Cetuximab in combination with irinotecan/5-fluorouracil/folinic acid (FOLFIRI) in the initial treatment of metastatic colorectal cancer: a multicentre two-part phase I/II study. BMC cancer 2009;9: 112.
16. Ye LC, Liu TS, Ren L, Wei Y, Zhu DX, Zai SY, et al. Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. J Clin Oncol 2013;31 (16):1931-1938.
17. Primrose J, Falk S, Finch-Jones M, Valle J, Sherlock D, Hornbuckle J, et al. A randomized clinical trial of chemotherapy compared to chemotherapy in combination with cetuximab in k-RAS wild-type patients with operable metastases from colorectal cancer: The new EPOC study. J Clin Oncol 2013;31(15):3504.
18. Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol 2010;28(31):4697-4705.
19. Pietrantonio F, Perrone F, Biondani P, Maggi C, Lampis A, Bertan C, et al. Single agent panitumumab in KRAS wild-type metastatic colorectal cancer patients following cetuximab-based regimens: Clinical outcome and biomarkers of efficacy. Cancer Biol Ther 2013;14(12):1098-1103.
20. Garrido-Laguna I, McGregor KA, Wade M, Weis J, Gilcrease W, Burr L, et al. A phase I/II study of decitabine in combination with panitumumab in patients with wild-type (wt) KRAS metastatic colorectal cancer. Invest New Drugs 2013;31(5):1257-1264.
21. Schwartzberg L, Rivera-Herreros F, M. Karthaus. A randomized phase 2 study of mFOLFOX6 with either panitumumab or bevacizumab as 1st-line treatment in patients with unresectable wild-type KRAS metastatic colorectal cancer (mCRC). J Clin Oncol 2013;30:446.
22. Price TJ, Peeters M, Kim TW, Li J, Cascinu S, Ruff P, et al. ASPECCT: a randomized, multicenter, open-label, phase 3 study of panitumumab (pmab) vs cetuximab (cmab) for previously treated wild-type (WT) KRAS metastatic colorectal cancer (mCRC). Eur J Cancer 2013; 49:18.
23. Su X, Lacouture ME, Jia Y, Wu S. Risk of high-grade skin rash in cancer patients treated with cetuximab--an antibody against epidermal growth factor receptor: systemic review and meta-analysis. Oncology 2009;77(2): 124-133.
24. Cao Y, Liao C, Tan A, Liu L, Gao F. Meta-analysis of incidence and risk of hypomagnesemia with cetuximab for advanced cancer. Chemotherapy 2010;56(6):459-465.
25. Cao Y, Liu L, Liao C, Tan A, Gao F. Meta-analysis of incidence and risk of hypokalemia with cetuximab-based therapy for advanced cancer. Cancer Chemother Pharmacol 2010;66:37-42.
26. Chen P, Wang L, Li H, Liu B, Zou Z. Incidence and risk of hypomagnesemia in advanced cancer patients treated with cetuximab: A meta-analysis. Oncol Lett 2013;5(6): 1915-1920.
27. Seymour MT, Brown SR, Middleton G, Maughan T, Richman S, Gwyther S, et al. Panitumumab and irinotecan versus irinotecan alone for patients with KRAS wild-type, fluorouracil-resistant advanced colorectal can-

cer (PICCOLO): a prospectively stratified randomised trial. Lancet Oncol 2013;14(8):749-759.

28. Alberts SR, Sargent DJ, Nair S, Mahoney MR, Mooney M, Thibodeau SN, et al. Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer: a randomized trial. JAMA 2012;307(13):1383-1393.
29. ClinicalTrials.gov [Internet]. USA: National Institutes of Health; 2004-2013. ABX-EGF (Panitumumab) Monotherapy in Subjects With Metastatic Colorectal Cancer. 2007 August 9 [2014 Dec 20]; [about 5 screens]. Available from: https://clinicaltrials.gov/ct2/show/record/NCT00089635?term=Panitumumab+and+colorectal+cancer&recr=Completed&rslt=With&rank=3&sect=X430156
30. Boku N, Sugihara K, Kitagawa Y, Hatake K, Gemma A, Yamazaki N, et al. Panitumumab in Japanese patients with unresectable colorectal cancer: a post-marketing surveillance study of 3085 patients. Jpn J Clin Oncol 2014;44(3):214-223.
31. Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 2007; 25(13):1658-1664.
32. Saltz LB, Meropol NJ, Loehrer PJ Sr, Needle MN, Kopit J, Mayer RJ. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. J Clin Oncol 2004;22(7):1201-1208.
33. Lenz HJ, Van Cutsem E, Khambata-Ford S, Mayer RJ, Gold P, Stella P, et al. Multicenter phase II and translational study of cetuximab in metastatic colorectal carcinoma refractory to irinotecan, oxaliplatin, and fluoropyrimidines. J Clin Oncol 2006;24(30):4914-4921.
34. ClinicalTrials.gov [Internet]. USA: National Institutes of Health; 2005-2013. PACCE: Panitumumab Advanced Colorectal Cancer Evaluation Study. June 26, 2005 [cited 20014 Dec 20]; Available from: https://clinicaltrials.gov/ct2/show/results/NCT00115765?term=Panitumumab+and+colorectal+cancer&rank=9&sect=X30156#evnt
35. Giusti RM, Cohen MH, Keegan P, Pazdur R. FDA review of a panitumumab (Vectibix) clinical trial for first-line treatment of metastatic colorectal cancer. Oncologist 2009;14(3):284-290.
36. ClinicalTrials.gov [Internet]. USA: National Institutes of Health; 2005-2014. Cetuximab Combined With Irinotecan in First-line Therapy for Metastatic Colorectal Cancer (CRYSTAL). September 8, 2005 [cited 20014 Dec 20]; Available from: https://clinicaltrials.gov/ct2/show/results/NCT00154102?term=cetuximab+and+metastatic+colorectal+cancer&rank=1&sect=X30156#evnt.
37. ClinicalTrials.gov [Internet]. USA: National Institutes of Health; 2004-2011. Erbitux (Cetuximab) Given Alone to Patients With EGFR-Negative Metastatic Colon or Rectal Cancer That is Refractory to Chemotherapy. May 28, 2004 [cited 20014 Dec 20]; Available from: https://clinicaltrials.gov/ct2/show/results/NCT00083720?term=Cetuximab+and+colorectal+cancer&recr=Completed&rslt=With&type=Intr&rank=3&sect=X30156#evnt.
38. ClinicalTrials.gov [Internet]. USA: National Institutes of Health; 2006-2013. Capecitabine, Cetuximab, Oxaliplatin, and Bevacizumab in Treating Patients With Metastatic or Recurrent Colorectal Cancer That Cannot Be Removed By Surgery. February 9, 2006 [cited 20014 Dec 20]; Available from: Available at: https://clinicaltrials.gov/ct2/show/results/NCT00290615?term=Cetuximab+and+colorectal+cancer&recr=Completed&rslt=With&type=Intr&rank=4&sect=X30156#evnt.
39. ClinicalTrials.gov [Internet]. USA: National Institutes of Health; 2006-2013. Cetuximab, Bevacizumab & 5FU/Leucovorin vs. Oxaliplatin, Bevacizumab & 5FU/Leucovorin in Metastatic Colorectal Cancer. November 9, 2005 [cited 20014 Dec 20]; Available from: https://clinicaltrials.gov/ct2/show/results/NCT00252564?term=cetuximab+and+metastatic+colorectal+cancer&rank=33&sect=X430156#othr.
40. ClinicalTrials.gov [Internet]. USA: National Institutes of Health; 2005-2014. Oxaliplatin and Cetuximab in First-line Treatment of Metastatic Colorectal Cancer (mCRC) (OPUS). July 28, 2005 [cited 20014 Dec 20]; Available from: https://clinicaltrials.gov/ct2/show/results/NCT00125034?term=Cetuximab+and+colorectal+cancer&recr=Completed&rslt=With&type=Intr&rank=6&sect=X30156#evnt.
41. ClinicalTrials.gov [Internet]. USA: National Institutes of Health; 2005-2013. Bevacizumab and Cetuximab in Combination With FOLFOX6 in Patients With Metastatic Colorectal Cancer. September 12 [cited 20014 Dec 20]; Available from: https://clinicaltrials.gov/ct2/show/NCT00193219?term=NCT00193219&rank=1.
42. ClinicalTrials.gov [Internet]. USA: National Institutes of Health; 2010-2014. A Study of BIBW 2992 (Afatinib) in Patients With Metastatic Colorectal Cancer. June 28, 2010 [cited 20014 Dec 20]; Available from: https://clinicaltrials.gov/ct2/show/results/NCT01152437?term=cetuximab+AND+afatinib&rank=3&sect=X30156#evnt.
43. McCormack PL, Keam SJ. Bevacizumab: a review of its use in metastatic colorectal cancer. Drugs 2008;68(4): 487-506.
44. ClinicalTrials.gov [Internet]. USA: National Institutes of Health; 2006-2011. Study of FOLFIRI Plus Bevacizumab in Colorectal Cancer Patients. July 18, 2006 [cited 20014 Dec 20]; Available from: https://clinicaltrials.gov/ct2/show/results/NCT00354978?term=bevacizumab+and+colorectal+cancer&recr=Completed&rslt=With&type=Intr&sect=X430156#othr.
45. Grothey A, Sugrue MM, Purdie DM, Dong W, Sargent D, Hedrick E, et al. Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: results from a large observational cohort study (BRiTE). J Clin Oncol 2008;26(33): 5326-5334.
46. Loupakis F, Cremolini C, Masi G, Lonardi S, Zagonel V, Salvatore L, et al. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. N Engl J Med 2014;371(17):1609-1618.
47. Schwartzberg LS, Rivera F, Karthaus M, Mazola G, Canon JL, Hecht JR, et al. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6)

or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J Clin Oncol 2014;32(21): 2240-2247.

48. Santos-Ramos B, Fernández-Fernández R, Marín-Gil R, Espinosa-Bosch M, Peiró-Moreno S, Pérez-Guerrero C, et al. Use of monoclonal antibodies for metastatic colorectal cancer in the Andalusian public health system. Int J Clin Pharm 2013;35(4):550-553.
49. Hashemi S, Faramarzi MA, Ghasemi Falavarjani K, Abdollahi M. Bevacizumab for choroidal neovascularization secondary to age-related macular degeneration and pathological myopia. Expert Opin Biol Ther 2014;14(12): 1837-1848.
50. Pietrantonio F, Garassino MC, Torri V, de Braud F. Reply to FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer-subgroup analysis of patients with KRAS-mutated tumours in the randomised German AIO study KRK-0306. Ann Oncol 2012;23(10):2771-2772.
51. Modest DP, Reinacher-Schick A, Stintzing S, Giessen C, Tannapfel A, Laubender RP, et al. Cetuximab-based or bevacizumab-based first-line treatment in patients with KRAS p.G13D-mutated metastatic colorectal cancer: a pooled analysis. Anticancer Drugs 2012;23(6):666-673.
52. Dotan E, Meropol NJ, Burtness B, Denlinger CS, Lee J, Mintzer D, et al. A phase II study of capecitabine, oxaliplatin, and cetuximab with or without bevacizumab as frontline therapy for metastatic colorectal cancer. A Fox Chase extramural research study. J Gastrointest Cancer 2012;43(4):562-569.
53. Saltz L, Badarinath S, Dakhil S, Bienvenu B, Harker WG, Birchfield G, et al. Phase III trial of cetuximab, bevacizumab, and 5-fluorouracil/leucovorin vs. FOL FOX-bevacizumab in colorectal cancer. Clin Colorectal Cancer 2012;11(2):101-111.
54. Joulain F, Proskorovsky I, Allegra C, Tabernero J, Hoyle M, Iqbal SU, et al. Mean overall survival gain with aflibercept plus FOLFIRI vs placebo plus FOLFIRI in patients with previously treated metastatic colorectal cancer. Br J Cancer 2013;109(7):1735-1743.
55. Tabernero J, Van Cutsem E, Lakomý R, Prausová J, Ruff P, van Hazel GA, et al. Aflibercept versus placebo in combination with fluorouracil, leucovorin and irinotecan in the treatment of previously treated metastatic colorectal cancer: prespecified subgroup analyses from the VELOUR trial. Eur J Cancer 2014;50(2):320-331.
56. Yamaguchi K, Watanabe T, Satoh T, Ishiguro M, Izawa M, Inoshiri S, et al. Severe infusion reactions to cetuximab occur within 1 h in patients with metastatic colorectal cancer: results of a nationwide, multicenter, prospective registry study of 2126 patients in Japan. Jpn J Clin Oncol 2014;44(6):541-546.
57. Taieb J, Tabernero J, Mini E, Subtil F, Folprecht G, Van Laethem JL, et al. Oxaliplatin, fluorouracil, and leucovorin with or without cetuximab in patients with resected stage III colon cancer (PETACC-8): an open-label, randomised phase 3 trial. Lancet Oncol 2014;15(8):862-873.
58. Primrose J, Falk S, Finch-Jones M, Valle J, O'Reilly D, Siriwardena A, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. Lancet Oncol 2014;15(6):601-611.
59. Wasan H, Meade AM, Adams R, Wilson R, Pugh C, Fisher D, et al. Intermittent chemotherapy plus either intermittent or continuous cetuximab for first-line treatment of patients with KRAS wild-type advanced colorectal cancer (COIN-B): a randomised phase 2 trial. Lancet Oncol 2014;15(6):631-639.