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 anti-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.

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. Consequently, the overall five-year survival remains very poor about 10% for patients at metastatic stage of this disease (mCRC). 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. 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. 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

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**Box 1. Drug summary**

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Cetuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>Launched</td>
</tr>
<tr>
<td>Indication</td>
<td>For treatment of EGFR-expressing metastatic colorectal cancer</td>
</tr>
<tr>
<td>Pharmacology description</td>
<td>Epidermal growth factor receptor binding FAB</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Protein structure</td>
<td>Protein chemical formula: C(<em>{6484})H(</em>{10042})N(<em>{1732})O(</em>{2023})S(_{36})</td>
</tr>
<tr>
<td>Pivotal trial(s)</td>
<td>[11, 12, 15]</td>
</tr>
</tbody>
</table>

The protein structure and the chemical formula are adapted from http://www.drugbank.ca/drugs/DB00002

**Box 2. Drug summary**

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Panitumumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>III</td>
</tr>
<tr>
<td>Indication</td>
<td>For treatment of EGFR-expressing metastatic colorectal cancer</td>
</tr>
<tr>
<td>Pharmacology description</td>
<td>Panitumumab (ABX-EGF) is a recombinant human IgG2 monoclonal antibody that binds specifically to the human epidermal growth factor receptor (EGFR)</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Protein structure</td>
<td>Not available</td>
</tr>
<tr>
<td>Protein chemical formula</td>
<td>C(<em>{6398})H(</em>{9878})N(<em>{1694})O(</em>{2016})S(_{48})</td>
</tr>
<tr>
<td>Pivotal trial(s)</td>
<td>PRIME trial [18]</td>
</tr>
</tbody>
</table>

The protein chemical formula and description are adapted from http://www.drugbank.ca/drugs/DB01269
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demonstrated the same results. 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 chemotherapyy, significantly lead to an improvement in Overall Survival (OS) compared with chemotherapy alone. Also in another study, higher Progression Free Survival (PFS) was observed in WT KRAS patients treated with cetuximab in the first line chemotherapy. 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 resectable. 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 oxaliplatin) 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. 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]. 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.

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). Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFOX 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-FOLFOXIRI 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). The combination of panitumumab with decitabine (a hypomethylating agent) was also well tolerated and showed activity in previously cetuximab treated mCRC patients. Some studies also compared the application of panitumumab with bevacicizumab (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.

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). In ASPECT 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: cetuximab10.0 and panitumumab 10.4...
months. HR:0.97, 95% CI:0.84-1.11, p=0.0007). Considering achieved results, non-inferiority endpoint was met in ASPECT 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 1. The clinical outcome of cetuximab and panitumumab administration as monotherapy and in combination with chemotherapy in mCRC patients

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Treatment option</th>
<th>Patients</th>
<th>Endpoint</th>
<th>p-value</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kennecke H et al 2013</td>
<td>Mono PMab</td>
<td>178 (141 PMab, 37 CMab Combo)</td>
<td>OS: 7.7 vs. 8.3 Months</td>
<td>0.03</td>
<td>10</td>
</tr>
<tr>
<td>Price et al 2014</td>
<td>Mono CMab vs Mono PMab in refractory mCRC</td>
<td>999 (499 PMab and 500 CMab)</td>
<td>OS: 10.0 vs. 10.4 Months, PFS: 4.4 vs. 4.1 Months, ORR: 19.8% vs. 22%</td>
<td>0.0007</td>
<td>12</td>
</tr>
<tr>
<td>Bokemeyer C et al 2012</td>
<td>CMab Combo</td>
<td>845 KRAS wild-type tumors</td>
<td>OS: Improved, PFS: Improved, ORR: Improved</td>
<td>0.0062</td>
<td>13</td>
</tr>
<tr>
<td>Pietrantonio F et al 2013</td>
<td>Mono PMab</td>
<td>30 CMab pretreated KRAS WT mCRC</td>
<td>DCR: 67%, ORR: 30%, PFS: 4.2 Months, OS: 9.6 Months</td>
<td>0.12</td>
<td>19</td>
</tr>
<tr>
<td>NCT00115765 2013</td>
<td>BMab Combo</td>
<td>BMab+Oxaliplatin 410</td>
<td>OS: BMab Combo=24.5 Months and PFS: BMab Combo=19.4 Months, ORR: BMab Combo=24.3 Months</td>
<td>0.005</td>
<td>34</td>
</tr>
<tr>
<td>PEAK trial 2014</td>
<td>Pmab Combo</td>
<td>278</td>
<td>OS: Pmab Combo=34.2 Months, BMab Combo=24.3 Months</td>
<td>0.009</td>
<td>47</td>
</tr>
<tr>
<td>Santos-Ramos B et al 2013</td>
<td>Cmab Combo</td>
<td>227</td>
<td>PFS: Cmab Combo=11.7 Months, BMab Combo=9.6 Months</td>
<td>-</td>
<td>48</td>
</tr>
<tr>
<td>Pietrantonio F et al 2012</td>
<td>BMab Combo</td>
<td>96</td>
<td>OS: BMab Combo=22.7 Months, BMab Combo=18.7 Months</td>
<td>0.55</td>
<td>50</td>
</tr>
<tr>
<td>Modest DP et al 2012</td>
<td>CMab Combo</td>
<td>54 KRAS p.G13D mutated patients</td>
<td>ORR: CMab=58%, BMab=57%, PFS: CMab=8.0 Months, BMab=8.7 Months, OS: CMab=9.7 Months, BMab=14.9 Months</td>
<td>0.9</td>
<td>51</td>
</tr>
<tr>
<td>Dotan E et al 2012</td>
<td>CMab+BMab Combo, CMab Combo</td>
<td>23: 12 CMab+BMab Combo, And 11 Cmab Combo</td>
<td>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</td>
<td>0.72</td>
<td>52</td>
</tr>
<tr>
<td>EPOC trial 2014</td>
<td>Chemotherapy</td>
<td>257 patient with resectable colorectal liver metastases</td>
<td>PFS: Chemotherapy=14.1 Months, CMab Combo=20.5 Months</td>
<td>0.003</td>
<td>58</td>
</tr>
</tbody>
</table>

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.
pulmonary embolism and fatalities. 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.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Patients</th>
<th>Most common side effect</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cao Y et al 2010</td>
<td>Mono Cmab</td>
<td>3081</td>
<td>Grade 3 and 4 Hypomagnesemia (5.6%; 95% CI=3.0-10.2). All grade Hypomagnesemia (36.7%; 95% CI=22-54.4).</td>
<td>24</td>
</tr>
<tr>
<td>Cao Y et al 2010</td>
<td>Mono Cmab</td>
<td>1324</td>
<td>Grade 3 and 4 Hypokalemia [6.2% (95% CI 4.9-7.7)]. All-grade Hypokalemia [8.0% (95% CI 4.5-13.9)]</td>
<td>25</td>
</tr>
<tr>
<td>Amgen trial 2013 NCT00889635</td>
<td>Mono Pmab</td>
<td>203</td>
<td>Abdominal pain, Dehydration and Dyspnea 6/203 (2.96%)</td>
<td>29</td>
</tr>
<tr>
<td>Merck KGaA CRYSTAL trial 2014</td>
<td>Cmab Combo</td>
<td>600</td>
<td>Diarrhea 36/600 (6.00%) Catheter related infection 8/600 (1.33%) Central line infection 10/600 (1.67%) Hypomagnesaeemia 13/600 (2.17%)</td>
<td>36</td>
</tr>
<tr>
<td>NCT00083720 2011</td>
<td>Mono Cmab</td>
<td>85</td>
<td>Death 1/85 (1.18%) Dyspnea 3/85 (3.53%)</td>
<td>37</td>
</tr>
<tr>
<td>Herbert Hurwitz clinical trial 2013 NCT00290615</td>
<td>CMab+Bmab Combo</td>
<td>30</td>
<td>Diarrhea 6/203 (30.00%)</td>
<td>38</td>
</tr>
<tr>
<td>NCT00252564 2011</td>
<td>CMab+BMab Combo</td>
<td>123</td>
<td>Anemia in CMab 28/121 (23.14%) and in BMab 45/118 (38.14%) Leukopenia 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%) Thrombocytocytopenia in CMab 22/121 (18.18%) and in BMab 42/118 (35.59%)</td>
<td>39</td>
</tr>
<tr>
<td>OPUS clinical trial 2011 NCT00125034</td>
<td>CMab Combo</td>
<td>170</td>
<td>Pulmonary embolism 5/170 (2.94%)</td>
<td>40</td>
</tr>
<tr>
<td>NCT00193219 2013</td>
<td>CMab+BMab Combo</td>
<td>31</td>
<td>Thrombosis/Thrombus/Embolism 4/31 (12.90%)</td>
<td>41</td>
</tr>
<tr>
<td>Amgen Trial 2013 NCT00115765</td>
<td>PMab+BMab Combo</td>
<td>518</td>
<td>Diarrhea 63/518 (12.16%) Fibril neutropenia 20/518 (3.86%)</td>
<td>34</td>
</tr>
<tr>
<td>M.D. Anderson Cancer Center NCT00354978 2011</td>
<td>BMab Combo</td>
<td>43</td>
<td>Nausea 24/518 (4.63%) Vomiting 27/518 (5.21%)</td>
<td>44</td>
</tr>
<tr>
<td>Yamaguchi K et al 2014</td>
<td>Mono Cmab</td>
<td>2126</td>
<td>Infusion reactions in114 patients (5.7%). Grade 3-4 Infusion reactions in 22 patients (1.1%).</td>
<td>56</td>
</tr>
<tr>
<td>PETACC-8 2014</td>
<td>Mono Cmab</td>
<td>791 Cmab Combo</td>
<td>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%</td>
<td>57</td>
</tr>
<tr>
<td>EPOC trial 2014</td>
<td>Chemotherapy CMab Combo</td>
<td>257 Patient with resectable Colorectal liver metastases Pulmonary embolism and Death: Chemotherapy =1 case, CMab Combo=3 cases Skina rash: Chemotherapy=1% , CMab Combo=15%</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>COIN-B trial 2014</td>
<td>Intermittent Mono CMab Continuous Mono CMab</td>
<td>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%, Continuous Mono CMab=25% Lethargy: Intermittent Mono CMab=26%, Continuous Mono CMab=21%</td>
<td>59</td>
<td></td>
</tr>
</tbody>
</table>
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 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 about 0.2% 30. A noticeable fact which was observed was that patients with grade 2 or 3 skin-related adverse 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.

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\textsuperscript{44}. 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=0.111) (OS for Bmab+Oxaliplatin 24.5 months vs. Bmab+Oxaliplatin+ Pmab 19.4 months, HR=1.43, CI; 95%, p=0.055)\textsuperscript{44}. 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\textsuperscript{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\textsuperscript{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\textsuperscript{34,35}, but in comparison to bevacizumab, OS was significantly improved when panitumumab was combined with mFOLFOX6 in mCRC patients\textsuperscript{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\textsuperscript{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)\textsuperscript{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)\textsuperscript{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\textsuperscript{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)\textsuperscript{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 VEGF's 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\textsuperscript{54}, 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 response\textsuperscript{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 mFOLF- 
OX6 and FOLFIRI with cetuximab resulted in a better 
objective response rate and overall survival in com-
parison 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-
manded 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 
both to patients and clinics. Maximum effectiveness 
and minimum adverse effects are among these factors. 
Comparing cetuximab and panitumumab in many clin-
ic 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, applica-
tion 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 
confered 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 appropi-
ate method for selection of patients through the use of 
ovel 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-
gful difference based on treatment related side ef-
ects. 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-
lishment 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 pani-
tumumab, 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-
mbased 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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