ABSTRACT • Colorectal cancer represents 8% of metastatic cancers. For decades, the gold standard therapy has been infusional chemotherapy with 5-Fluorouracil (5-FU) associated to folinic acid. The discovery of irinotecan, oxaliplatin and oral forms of 5-FU in the nineties is considered a milestone in the treatment of this disease. Since 2004, targeted therapy with monoclonal antibodies including anti-EGFR and angiogenesis inhibitors showed superiority in terms of mortality compared to conventional therapy. Metastatic colorectal cancer, however, remains an incurable disease. We present the current treatments of metastatic colorectal cancer, the clinical development of these emerging treatments, and their position in the Lebanese health care system.

Keywords: metastatic colorectal cancer, chemotherapy, monoclonal antibodies

LIST OF ABBREVIATIONS

5-FU : 5-Fluorouracil
5-FULV : 5-Fluorouracil/Leucovorin
APC : Protein coding
ASPECT : A Study of Panitumumab Efficacy and safety Compared to Cetuximab Trial
BRAF : V-Raf murine sarcoma viral oncogene homolog B1
CORRECT : Regorafenib monotherapy for previously treated metastatic colorectal cancer
CRC : Colorectal Cancer
CRYSTAL : Cetuximab Combined With Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer
CYP3A4 : Cytochrome P
DNA : DeoxyriboNucleic acid
EGF : Epidermal Growth Factor
EGFR : Epidermal Growth Factor Receptor
FGFR : Fibroblast Growth Factor Receptor
FIRE : Trial comparing Cetuximab and bevacizumab
FOLFIRI : 5-FULV + Irinotecan
FOLFOX : 5-FULV + Oxaliplatin
FOLFOXIRI : 5-FULV + Oxaliplatin + Irinotecan
GSK3B : Glycogen Synthase Kinase 3B
HER : Human Epithelial Growth Factor Receptor
Ig : Immunoglobulin
KRAS : Kirsten RAt Sarcoma 2 viral oncogene homolog
MAPK : Mitogen Activated Protein Kinase
mCRC : metastatic colorectal cancer
mFOLFOX6 : Fluorouracil, Leucovorin, and Oxaliplatin (mFOLFOX6) or Bevacizumab + mFOLFOX6 in Patients With Previously Untreated, Unresectable, Wild-Type KRAS Exon 2 Metastatic Colorectal Cancer
mFOLFOXIRI : A Randomized, Multicenter Phase II Study of Panitumumab + Modified Fluorouracil, Leucovorin, and Oxaliplatin (mFOLFOXIRI) or Bevacizumab + mFOLFOX6 in Patients With Previously Untreated, Unresectable, Wild-Type KRAS Exon 2 Metastatic Colorectal Cancer
mFOLFOX + Bevacizumab : Modified Fluorouracil, Leucovorin, and Oxaliplatin + Bevacizumab
mFOLFOXIRI + Bevacizumab : Modified Fluorouracil, Leucovorin, and Oxaliplatin + Bevacizumab
mFOLFOX6 : Modified Fluorouracil, Leucovorin, and Oxaliplatin
OR : Overall response
ORR : Overall response rate
OS : Overall survival
PDGFR : Platelet Derived Growth Factor
PEAK : A Randomized, Multicenter Phase II Study of Panitumumab + Modified Fluorouracil, Leucovorin, and Oxaliplatin (mFOLFOXIRI) or Bevacizumab + mFOLFOX6 in Patients With Previously Untreated, Unresectable, Wild-Type KRAS Exon 2 Metastatic Colorectal Cancer
PFS : Progression free survival
PFSF : Progression free survival
PI3K/AKT : Phosphoinositide 3-kinase
PIGF : Placental growth factor
PIGF : Placental growth factor
PIGF : Phosphoinositide 3-kinase
PR : Progression free disease
PRIME : Panitumumab Randomized trial in combination with chemotherapy for Metastatic colorectal cancer to determine Efficacy
PR : Progression rate
RR : Response rate
UGT1A : UDP-glucuronosyltransferase 1A
VEGF : Vascular Endothelial Growth Factor
VEGF : Vascular Endothelial Growth Factor Receptor
VELOUR : Phase III study of afiblercept and FOLFIRI in patients with metastatic colorectal cancer after failure of an oxaliplatin regimen.
WT : Wild

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BACKGROUND

Metastatic colorectal cancer (mCRC) is a major cause of morbidity and mortality throughout the world. It is the fourth most common cancer diagnosed in the U.S. and the second leading cause of cancer death in 2014. In Lebanon, colorectal cancer is the third leading cause of death from cancer and the most common cancer both sex combined [1-2]. In 2012, according to national cancer statistics, the number of eligible new cases diagnosed in the hospital system was 2035, 979 men and 1056 women [3].

About 75% of patients with CRC have sporadic disease with no apparent evidence of having inherited the disorder. The remaining 25% of patients have a family history of CRC suggesting a hereditary contribution, common exposures among family members, or a combination of both.

Numerous factors are found important in the development of CRC including high risk luminal environment, inflammation, as well as lifestyle factors such as diet, tobacco and alcohol consumption. In recent years, focus has turned towards the genetics and molecular biology of CRC and several interesting and promising correlations and pathways have been discovered. The major genetic pathways of CRC are the chromosome instability pathway representing the pathway of sporadic CRC through the KRAS, APC and p53 mutations, and the microsatellite instability pathway of hereditary non-polyposis through mutations in mismatch repair genes [4].

Metastases are observed in 40-60% of cases of CRC of which 25% are synchronous. Among patients without metastases at diagnosis, the risk of metachronous is 30-40% [5]. Without any treatment, patients with mCRC have a median survival of seven months.

In some cases, the metastases reveal the cancer (precesive metastases) whose primary site is not known and should be identified. Approximately 30-50% of CRC patients develop liver metastases, responsible alone for two thirds of the deaths. Being able to consider their resection is a major challenge since the resection significantly improves the survival of patients. The extra-hepatic locations are rare and of poor prognosis.

Currently, a multitude of clinical evidences have shed a new light on the issues such as the selection and duration of therapy, the associations with targeted agents and treatments tailored towards the clinic and molecular factors. Moreover, knowledge of prognostic and predictive biomarkers such as mutation in KRAS, NRAS, and BRAF, is of growing interest to allow a better selection of drugs and treatment strategies.

The aim of this paper is to review the updates to the management of mCRC.

THERAPEUTIC STRATEGIES in the TREATMENT of mCRC

The objectives of the management of patients with mCRC are generally palliative rather than curative, with the exception of a small proportion of patients with resectable liver metastases and controllable by radiofre-

quency (or cryotherapy) or locoregional treatment by direct injection of radioactive spheres [6].

Recent advances in chemotherapy regimens have increased the median overall survival (OS) from 6 months to over 30 months through the targeted therapy and double or triple combination protocols [7].

The three active agents for mCRC, known as conventional chemotherapy, are fluoropyrimidines (5-FU or its oral prodrug), irinotecan and oxaliplatin. The associations FOLFOX/XELOX and FOLFIRI are commonly used in the Lebanese hospitals [8] with no evidence from literature of differences between both regimens in terms of OS [9]. Triple associations such as FOLFOXIRI induce a median OS without disease progression with greater response rate than FOLFIRI regimen, but are associated with a poor safety profile [10]. In fact, the FOLFOXIRI has been compared to FOLFIRI in two randomized clinical trials in unresectable patients: in both studies, FOLFOXIRI led to an increased in R0 secondary resection rates: 6% vs 15% (p = 0.033) in the Gruppo Oncologico Nord Ostvest (GONO) trial and 4% vs 10% (p = 0.08) in the Gastrointestinal Committee of the Hellenic Oncology Research Group (HORG) trial. In a follow-up study of the GONO trial, the 5-year survival rate was higher in the group receiving FOLFOXIRI (15% vs 8%) with a median OS of 23.4% vs 16.7% month (p = 0.026) [11-13].

The addition of targeted therapies to these four cytotoxic regimens has shown better outcomes in the majority of cases. However, the best strategy sequence and the respective roles of each combination are still debated.

PRINCIPAL AGENTS USED in the TREATMENT of mCRC

Table I summarizes the principal drugs used to treat mCRC.

Cytotoxic chemotherapy drugs

Cytotoxic drugs induce acute cell death (necrosis), programmed cell death (apoptosis), growth arrest or differentiation. Many antineoplastic drugs have multiple actions on the cell:

5-FU is activated to 5-fluorodeoxyuridylate, which, in the presence of a reduced folate co-factor, inhibits the enzyme thymidylate synthase. This blocks the production of thymidine phosphate which is required for DNA synthesis. The 5-fluorodeoxyuridylate may also be fraudulently incorporated into DNA causing a form of DNA damage [14].

Capecitabine is an orally bioavailable 5-FU prodrug that undergoes sequential hydrolysis and deamination reactions in the liver to produce 5’-deoxy-5-fluorouridine. It is converted to 5-FU by thymidine phosphorylase (also known as platelet-derived growth factor). As this enzyme is abundant in tumor tissue there is some tumor specificity in the patient’s exposure to 5-FU.

The adverse effects, such as hand and foot syndrome, of capecitabine resemble those of 5-FU when given by protracted infusion.
Other oral 5-FU prodrugs (e.g., S-1, UFT) have been the subject of extensive clinical trials [15]. These are mostly combinations of 5-FU prodrugs with uracil, which is an inhibitor of dihydropyrimidine dehydrogenase, a ubiquitous enzyme that rapidly degrades 5-FU.

**Oxaliplatin** is a diaminocyclohexane platinum derivative and a bifunctional alkylator capable of reacting with adjacent guanine residues in DNA. It provides either intra- or inter-strand DNA cross-links, which interfere with DNA processing.

Oxaliplatin was evaluated as the first-line metastatic combination with 5-FULV (FOLFOX4). Three trials showed a significant improvement in the objective response and a progression-free survival, but no significant difference in term of OS [16]. The two limiting toxicities of FOLFOX4 were neutropenia and the specific reversible sensory neuropathy of oxaliplatin. The results of the OPTIMOX 1 study [17] showed that a “stop and go” approach using oxaliplatin-free interval resulted in a decrease in neurotoxicity without affecting the OS. Therefore, the panel recommends adjusting the schedule/timing of the administration of this drug as a means of limiting this adverse effect. The current clinical data are insufficient to support the routine use of calcium/magnesium infusions to prevent the oxaliplatin-related neurotoxicity.

**Irinotecan** is a topoisomerase I inhibitor used to treat several solid tumor types, especially in combination with other chemotherapeutic agents in the treatment of mCRC. Inhibition of topoisomerase I by irinotecan and its active metabolite, SN-38, prevents re-ligation of single-stranded DNA breaks induced during DNA synthesis phase of cellular replication. Cell death ultimately occurs. Adverse effects include severe diarrhea, myelosuppression and neutropenia, likely induced by inefficient metabolism and excretion of SN-38, which undergoes glucuronidation primarily in the liver by UGT1A prior to excretion through the kidneys. UGT1A locus is alternatively spliced to produce nine isoenzymes and the UGT1A1 isoform is solely responsible for the phase II metabolism of bilirubin, numerous endogenous hormones and pharmacologic compounds, including irinotecan. Thus, genetic variation in UGT1A correlates with adverse events caused by irinotecan toxicity [18].

Evidence indicates that, at relatively high irinotecan level (> 250 mg/m²), patients who are homozygous for the UGT1A1*28 variant experience a greater risk of clinically important neutropenia, especially with particular chemotherapy agents/oxaliplatin [19]. That’s why it is reasonable to determine the UGT1A genetic background to assist in toxicity management. Unfortunately, this molecular testing is not present in our Lebanese hospitals to date.

Irinotecan is also an inhibitor of acetyl cholinesterase and patients may experience an acute onset of cholinergic-like symptoms including lacrimation, sweating, abdominal cramping and diarrhea.

Irinotecan, in combination with fluorouracil (FOLFIRI), in the second-line, is considered a good standard in the palliative treatment of mCRC. Several studies [20-21] have shown a significant increase in the response rate, PFS and OS with FOLFIRI compared to 5-FULV alone.

**MODULATORS of the TARGETED BIOLOGICAL RESPONSE**

As observed in a retrospective cohort study conducted in Lebanese hospitals [8], approximately 75% of patients with mCRC receive a biological agent during their treatment course targeting one of two main pathways: the EGFR cascade and the VEGF signaling.
TABLE II
SUMMARY of the ANTIANGIOGENIC DRUGS CURRENTLY APPROVED for mCRC TREATMENT: BEVACIZUMAB, AFLIBERCEPT & REGORAFENIB

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approval date</th>
<th>Mechanism of action</th>
<th>Indication</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>2004</td>
<td>Extracellular</td>
<td>1st/2nd line mCRC + combination chemotherapy</td>
<td>5-10 mg/kg IV every 2 weeks in combination with FOLFOX or FOLFIRI</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>2012</td>
<td>Extracellular</td>
<td>2nd line in mCRC + FOLFOX/FOLFIRI</td>
<td>4 mg/kg IV every 2 weeks in combination with FOLFIRI</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>2006</td>
<td>Extracellular</td>
<td>1st line mCRC, in refractory/progressive disease</td>
<td>160 mg daily for 21 days of an every 28 d cycle</td>
</tr>
</tbody>
</table>

**Monoclonal Antibodies**, such as Bevacizumab, are recombinant humanized IgG1 monoclonal antibodies directed against VEGF-A. Bevacizumab is the first antiangiogenic agent to be approved in mCRC treatment, because of response rate and survival benefit [25-26].

Inhibitors of angiogenesis

Angiogenesis is a central mechanism in human CRC development and growth [24]. In particular, VEGF is closely associated with the induction of neoangiogenesis in human colon cancer and is one of the most important endogenous ligands of receptors present on the endothelial cell plasma membrane; it’s binding leads to intracellular signaling and, ultimately, gene transcription that promotes endothelial proliferation, migration, and tube formation of endothelial cells resulting in tumor growth and metastasis.

Given the crucial importance of neoangiogenesis in mCRC, anti-VEGF pathway therapies have been intensively investigated. The monoclonal antibody bevacizumab is the first antiangiogenic agent to be approved in mCRC treatment, because of response rate and survival benefit [25-26].

The three antiangiogenic agents available within Lebanese hospitals are presented in Table II. Bevacizumab is a recombinant humanized IgG1 monoclonal antibody (7% murine) directed against VEGF-A.

After showing its efficacy in several murine xenograft models of human tumors, bevacizumab alone or in combination with other cytotoxic agents, was shown to be well tolerated in phase I trials apart from some side effects such as thromboembolic events, bleeding, hypertension and proteinuria.

The association of bevacizumab with 5-FU increased the OS (12.9 months for FOLFOX4/bevacizumab vs 10.8 months for FOLFOX4 alone) and the disease free progression (DFP) significantly (7.3 months vs 4.7 months respectively). In November 2012, bevacizumab was approved in combination with chemotherapy based on fluoropyrimidine, irinotecan or oxaliplatin for the treatment of mCRC disease. This approval allows the patients, who received first-line treatment with bevacizumab plus irinotecan-based chemotherapy or with oxaliplatin, to continue receiving bevacizumab plus other chemotherapy based on oxaliplatin or irinotecan as second-line treatment after progression of the disease. In the Lebanese hospitals, the practice is to preferably use the protocol FOLFOX-Bevacizumab as first-line [8].

Aflibercept also known as VEGF Trap, is a fully human soluble recombinant protein composed of extracellular domains from both VEGFR-1 and VEGFR-2 fused to the Fc (a) region of human IgG1 [27]. It was designed to act as a decoy VEGF receptor, binding VEGF-A, VEGF-B, and PIGF, subsequently preventing their interactions with VEGFR-1 and VEGFR-2 [28-29].
Afblibercept was studied in combination with FOLFIRI in a prospective, randomized, double-blind, multicenter, study on patients with mCRC previously treated with an oxaliplatin-based chemotherapy regimen. Patients were randomized either to FOLFIRI plus afblibercept (4 mg/kg intravenously every 2 weeks) or FOLFIRI plus placebo. The afblibercept arm showed significant improvement in the primary endpoint of OS (13.50 months vs 12.06 months). PFS and ORR were also increased (6.90 months vs 4.67 months and 19.8% vs 11.1% respectively). In subgroup analyses of patients with or without prior-bevacizumab regimen, PFS was significantly improved in both. OS was significantly improved in the bevaci-zumab-naïve subset, but did not achieve significance in the prior-bevacizumab subset.

Based on these results, the FDA approved, on August 2012, the use of afblibercept in combination with FOLFIRI for the treatment of patients with mCRC that is resistant to or that has progressed after an oxaliplatin-containing regimen. Both antiangiogenic-associated and chemotherapy-related adverse effects were seen with greater incidence in the afblibercept arm (83.5% of grade 3 or 4 adverse events). The antiangiogenic toxicities described were hypertension, hemorrhage, and arterial and venous thromboembolism, diarrhea, and asthenia.

**Regorafenib** is an oral small-molecule multikinase inhibitor, inhibiting multiple oncogenic kinases, PDGF, FGFR and VEGFR-1. Its mechanism is not clearly understood, but studies have shown that it induces expression of PUMA, p53 target and critical mediator of apoptosis in colorectal cells after inhibition of ERK and activation of GSK3β through the cascade of NF-kB [30-31].

Regorafenib was approved for the treatment of mCRC patients previously treated with fluoropyrimidine, oxaliplatin, or irinotecan-based chemotherapy regimens, with prior anti-VEGF and/or anti-EGFR (KRAS wild) therapies. Regorafenib was evaluated in the Phase III CORRECT trial [32] on patients with mCRC who had progressed during or within three months after the above therapies. Patients on the study were randomized to receive either regorafenib (160 mg/day/21 days) or placebo. Treatment with regorafenib was associated with a modest but significant increase in survival (6.4 months vs 5.0 months). The CORRECT trial showed a survival benefit with regorafenib in an extensively treated patient population, also about 40% of patients achieved disease stabilization. Adverse events associated with regorafenib are hand-foot skin reaction, fatigue, diarrhea, mucositis, dysphonia, weight loss, infection, hypertension (impaired angiogenesis). Hepatotoxicity (sometimes fatal), increased incidence of hemorrhage, myocardial ischemia, infarction, reversible post leukoencephalopathy syndrome, gastrointestinal perforation and fistula are rare and should be closely monitored.

The bioavailability of regorafenib is 69% after oral administration in tablet form. Absorption is dependent on the fat content of a meal (better with low-fat diet). It is metabolized by CYP3A4 and UGT1A9 to two active metabolites (M-2 & M-5) and is excreted primarily by the feces [33].

Regorafenib may interact strongly with CYP3A4 inducers (rifampin, phenytoin, and carbamazepine), CYP3A4 inhibitors (ketoconazole, voriconazole, grapefruit juice, clarithromycin, itraconazole) and substrates of UGT1A1 (irinotecan) [34].

**EGFR (epidermal growth factor receptor) inhibitors**

EGFR is a transmembrane cell surface glycoprotein and a member of the human epithelial growth factor receptor (HER) family of tyrosine kinases. Binding of ligands to the EGFR leads to homodimerization or heterodimerization of HER family members and results in autophosphorylation of intracellular tyrosine residues, initiating several key cell-signaling pathways including RAS/RAF/MAPK axis, involved in cell proliferation and PI3K/PIK pathway, involved in cell survival and motility. Binding to EGFR enhances processes critical to tumor growth and progression such as angiogenesis, apoptosis inhibition, tumor invasiveness and metastatic spread [35]. RAS is one of the most important molecules in the signaling pathway downstream of the EGFR. Three human RAS genes have been identified: HRAS, KRAS and NRAS. Since the activation of the EGFR leads to activation of KRAS, it was hypothesized that mutations in signaling pathway downstream of the EGFR may result in receptor independent pathway activation that renders the tumors unresponsive to EGFR blockade at the cell surface. Mutations in KRAS codons 12 and 13 (exon 2) are present in 35-45% of CRC with high concordance between primary and metastatic lesions and have been established as predictors of lack of response to anti-EGFR treatment. Consequently, KRAS exon 2 mutation testing is widely implemented for selection of patients with wild-type mCRC for anti-EGFR treatment. A moderate response rate of 40-60%, also in KRAS exon wild-type tumors, has motivated assessment of the predictive role of additional alterations, primarily within the RAS-RAF-MAPK and PI3K-AKT-mTOR pathways. Additional mutations in KRAS as well as NRAS (effector binding domains identical to KRAS and present in 10% of mutations) have been suggested to infer resistance to anti-EGFR therapies and the European label for panitumumab treatment was recently modified to require testing also for KRAS mutations outside of exon 2 and for NRAS mutations. The added treatment predictive value of mutation in BRAF (principal effector of KRAS and present in 8% of mutations), PIK3Ca and PTEN is more uncertain [36]. According to the most current data, the BRAF biomarker is deemed to be a negative predictive biomarker as well as a prognostic biomarker.

The BRAF and KRAS status must be determined to be wild-type to produce a positive response to anti-EGFR therapies.
Figure 1 shows the important role of the BRAF & KRAS status in the response of anti-EGFR drugs.

Testing is based on lesions with greater than 50% tumor. This is a tumor percentage that can be easily obtained from an untreated primary lesion or a well-defined metastasis without treatment or extensive inflammatory infiltrate. It is estimated that 20% of patients present with metastatic disease, so mutation testing based on a primary lesion is not always feasible. Although most studies have found that metastases maintain the mutation profile of the primary lesion in more than 90% of cases, 54-60% discordance may arise for technical reasons or, rarely, because of metastases from separate primaries. For this reason, it is preferable to test the metastases rather than the primary tumor, if possible, because it’s the former that is being treated by the EGFR targeted therapy.

Two monoclonal antibodies that block EGFR signaling and prevent endogenous receptor activating ligands are currently approved for the treatment of mCRC: cetuximab and panitumumab. The efficacy of these drugs is limited to patients with wild-type (non-mutated) KRAS (KRAS WT) (cetuximab) and non-mutated RAS (panitumumab) tumors.

A multitude of recent clinical trials have indicated that expanded RAS testing is more effective than traditional KRAS testing for patients with CRC. As a result of these findings, the number of patients with CRC who are eligible for EGFR inhibitors has been reduced to approximately 40% [37].

Cetuximab is a recombinant human/mouse chimeric IgG1 monoclonal antibody that binds specifically to the extracellular domain of the EGFR on both normal and tumor cells, and competitively inhibits the binding of EGF and other ligands, such as transforming growth factor-α. The recommended dose of cetuximab, in combination with irinotecan or as monotherapy, is 400 mg/m² as an initial loading dose administered as a 120-minute IV infusion. The recommended weekly maintenance dose is 250 mg/m² infused over 60 minutes. WT KRAS status is required for initiation of treatment with cetuximab but further studies also show that WT RAS status (mutations at exons 2, 3 and 4 of KRAS, NRAS and BRAF) is mandatory prior to initiation of treatment with cetuximab using a validated method of analysis, newly applied in Lebanon.

The addition of cetuximab improved the resection rate of initially unresectable, liver-limited, KRAS WT mCRC...
when compared with the corresponding chemotherapy regimen alone. The efficacy of cetuximab was derived from two randomized controlled trials. The CRISTAL study is a phase III, multicenter, open-label randomized controlled trial, which compared cetuximab in combination with FOLFIRI with FOLFIRI alone. The OPUS study trial is a phase II, multicenter, open-label randomized controlled trial, which compared cetuximab in combination with FOLFROX4 with FOLFROX4 alone [38-39]. The results of the CRISTAL trial for the KRAS WT subgroup showed a statistically significant increase in PFS with cetuximab in combination with FOLFIRI (9.9 months vs 8.7 months). The OPUS trial also showed a statistically significant increase in PFS with a median PFS of 7.7 months for cetuximab in combination with FOLFOX compared with 7.2 months for FOLFOX alone. The RR was also improved: 60.7% in the cetuximab + FOLFOX vs 37.0% FOLFOX alone. The OPUS trial included 30.5% patients with additional RAS mutations; those in the cetuximab + FOLFOX arm had inferior survival, PFS and objective RR than those assigned to receive FOLFOX alone. Safety evaluations showed no new findings attributable to cetuximab when comparing WT and mutated RAS populations: the inferior outcome was due to lack of efficacy in combination with the known toxicity profile. As a result, some evidence of WT RAS status and of KRAS (and NRAS) is required before initiating treatment with cetuximab and that this drug is contraindicated in patients whose tumors are KRAS-mutated should not be treated with panitumumab. The recently completed PEAK PRIME trial randomized untreated patients with mCRC from two randomized controlled trials. The CRYSTAL study is a phase III, multicenter, open-label randomized controlled trial, which compared cetuximab in combination with chemotherapy in earlier lines of treatment is a less common and more complex issue. For RAS WT patients the optimal targeted agent in first-line therapy remains undefined with the addition of either bevacizumab or an anti-EGFR antibody supported by multiple phase III trials randomized untreated patients with mCRC to FOLFOX chemotherapy and panitumumab versus FOLFOX chemotherapy. The results of the study are shown in Table III. Patients with WT KRAS mCRC who reported grades 2 to 4 skin toxicities (rash, acneform dermatitis, pruritus, dry skin, skin fissures or erythema), diarrhea and electrolytes deficiencies (hypokalemia) had longer PFS and OS as well as ORR. The development of skin toxicity is an early clinical indicator of the panitumumab regimen’s efficacy. This updated analysis confirms the value of adding panitumumab to FOLFOX in the first-line treatment of patients whose tumors are determined to be WT KRAS. Because crossover to an EGFR-targeted monoclonal antibody after progression on FOLFOX was permitted, potential survival differences may be attenuated related to panitumumab. PRIME also confirms that patients whose tumors are KRAS-mutated should not be treated with panitumumab. The recently completed PEAK study (also panitumumab in first-line treatment but phase II trial) is the first head-to-head analysis of FOLFOX combined with either panitumumab or bevacizumab in KRAS WT mCRC (Table III). The use of panitumumab in second-line treatment of KRAS WT mCRC comes from two large phase III randomized trials, and two single-arm phase II trials (Table III). To summarize, the addition of a biological agent to a chemotherapy backbone containing oxaliplatin or irinotecan may increase the number of patients potentially eligible for resection and improve outcomes.

COMPARATIVE DATA BETWEEN mCRC TARGETED THERAPIES

The ASPECT trial is an open-labeled, randomized, phase III trial designed to compare the effects of panitumumab and cetuximab for monotherapy of chemorefractory patients with KRAS WT tumors. The ORR was 22% for the panitumumab arm compared to 19.8% for the cetuximab arm. The PFS was 4.1 months in patients treated with panitumumab versus 4.4 months in patients treated with cetuximab. The study met its primary endpoint, demonstrating that panitumumab was non-inferior to cetuximab for OS (10.4 months vs 10 months). Therefore, based on these results and those from other previous trials, there is no therapeutic preference in clinical practice for using cetuximab versus panitumumab either as monotherapy or in combination with chemotherapy in naïve or chemorefractory mCRC.

Treatment selection is an art more than an algorithm. The first step is to take into account the goal of therapy and the toxicity profile that the patient is willing to live with. The use of anti-EGFR antibody treatment in combination with chemotherapy in earlier lines of treatment is a less common and more complex issue. For RAS WT patients the optimal targeted agent in first-line therapy remains undefined with the addition of either bevacizumab or an anti-EGFR antibody supported by multiple phase III trials.
trials. Several factors may lead the clinician to prefer an anti-EGFR antibody to bevacizumab. In patients with a contraindication to bevacizumab, the addition of anti-EGFR antibody to chemotherapy improves PFS and ORR compared with chemotherapy alone.

The consistent effects on response and survival from RAS mutations outside of KRAS exon 2 clearly suggests that mutation testing for ant-EGFR prediction should move from selective KRAS testing to broader RAS testing. Recently, data from the FIRE-3 study [45-46], which is the first head-to-head comparison between two biological agents for the treatment of mCRC, have been designed to compare FOLFIRI + cetuximab with FOLFIRI + bevacizumab in the first-line setting for patients with KRAS exon 2 WT mCRC. The primary endpoint of this study, the ORR, was not met (62% for FOLFIRI-cetuximab vs 58% for FOLFIRI-bevacizumab). No difference in PFS was observed (10.0 months vs 10.3 respectively), however, a significant difference in OS was observed in favor of FOLFIRI-cetuximab (28.7 months vs 25.0 respectively). In a preliminary analysis, the effects of mutations in KRAS and BRAF on ORR, PFS, and OS were evaluated. Patients with WT RAS had a median OS of 33.1 months in the FOLFIRI-cetuximab group vs 25.6 months with FOLFIRI-bevacizumab. However, in patients with mutant RAS, there was no difference between the two regimens. Therefore, a complete determination of RAS status may be necessary before prescribing EGFR inhibitors in first-line treatment of mCRC, and the prescription of cetuximab should be restricted to patients with WT RAS (and WT KRAS). Thus far, the factors that contribute to the difference in OS are unclear.

Figure 2 summarizes the therapeutic strategies in the treatment of metastatic colorectal cancer.

**CONCLUSION and PERSPECTIVES**

The outlook for the adjuvant treatment of CRC results out of the progress in the treatment of mCRC for the last five years. Such progress has been marked by the advent of combination therapies and the very recent emergence of biotherapy improving the effectiveness of chemotherapy. With the discovery of selective targeted drugs, a new era for the treatment of mCRC has been opened. Adding these drugs, such as bevacizumab and/or cetuximab, to standard chemotherapy resulted in improved PFS and OS in patients with mCRC, either as first or second-line of therapy.

Considering the substantial cost of targeted therapies for mCRC, their cost-effectiveness has also to be measured within the Lebanese society’s perspective. This type of evaluation is currently ongoing based on data from two Lebanese university hospitals [8].

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**TABLE III**

<table>
<thead>
<tr>
<th>TRIALS</th>
<th>KRAS status</th>
<th>Treatment regimen (control)</th>
<th>PFS (months)</th>
<th>Hazard ratio</th>
<th>Median OS (month)</th>
<th>Hazard ratio</th>
<th>ORR</th>
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</thead>
<tbody>
<tr>
<td><strong>First line</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PRIME (N = 1183)</td>
<td>KRAS WT</td>
<td>FOLFOX4 + P</td>
<td>9.6</td>
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<td>23.9</td>
<td>0.83</td>
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<tr>
<td></td>
<td>(FOLFOX4)</td>
<td>8.0</td>
<td>19.7</td>
<td>48%</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>KRAS MT</td>
<td>FOLFOX4 + P</td>
<td>7.3</td>
<td>1.29*</td>
<td>15.5</td>
<td>1.24</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>(FOLFOX4)</td>
<td>8.8</td>
<td>19.3</td>
<td>40%</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>PEAK (N = 285)</td>
<td>KRAS WT</td>
<td>FOLFOX + P</td>
<td>10.9</td>
<td>0.87</td>
<td>Not reached</td>
<td>0.72</td>
<td>58%</td>
</tr>
<tr>
<td></td>
<td>FOLFOX + Bev</td>
<td>10.1</td>
<td>25.4</td>
<td>54%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Second line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N = 1186)</td>
<td>KRAS WT</td>
<td>FOLFIRI + P</td>
<td>5.9</td>
<td>0.73*</td>
<td>14.0</td>
<td>0.85</td>
<td>35%</td>
</tr>
<tr>
<td>Peeters et al.</td>
<td>FOLFIRI</td>
<td>3.9</td>
<td>12.5</td>
<td>10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>KRAS MT</td>
<td>FOLFIRI + P</td>
<td>5.0</td>
<td>0.85</td>
<td>11.8</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FOLFIRI</td>
<td>4.9</td>
<td>11.1</td>
<td>14%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PICCOLO (N = 460)</td>
<td>KRAS WT</td>
<td>IrPan NR</td>
<td>0.78*</td>
<td>10.4</td>
<td>1.01</td>
<td>34%*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Irinotecan</td>
<td>NR</td>
<td>10.9</td>
<td>12%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPIRITT (N = 182)</td>
<td>KRAS WT</td>
<td>FOLFIRI + P</td>
<td>7.7</td>
<td>1.01</td>
<td>18.0</td>
<td>1.06</td>
<td>32%</td>
</tr>
<tr>
<td></td>
<td>FOLFIRI + Bev</td>
<td>9.2</td>
<td>21.4</td>
<td>19%</td>
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<td></td>
</tr>
</tbody>
</table>

Ct: 95% confidence interval  
PFS: progression-free survival  
OS: overall survival  
ORR: objective response rate  
N: number of patients  
KRAS: Kirsten rat sarcoma gene  
FOLFOX: infusional 5-Fluorouracil/folinic acid/oxaliplatin  
P: panitumumab  
MT: mutated  
WT: wild-type (nonmutated)  
Bev: bevacizumab  
FOLFIRI: infusional 5-Fluorouracil/folinic acid/irinotecan  
IrPan: irinotecan/panitumumab  
NR: not reported  
*p < 0.05
Chemotherapy for metastatic colorectal cancer in a patient appropriate for intensive therapy

**Initial therapy**
- FOLFOX or XELOX or
- FOLFOX + Bevacizumab or
- XELOX + Bevacizumab

**OR**
- FOLFOX + Cetuximab or Panitumumab (KRAS/NRAS WT gene only)

**Therapy after 1st progression**
- FOLFIRI or FOLFIRI + Bevacizumab or
- FOLFIRI + ziv-Aflibercept or Irinotecan or
- Irinotecan + Bevacizumab or
- FOLFIRI + Cetuximab or Panitumumab (KRAS/NRAS WT gene only) or
- Irinotecan +
- Cetuximab or Panitumumab (KRAS/NRAS WT gene only)

**Therapy after 2nd progression**
- Cetuximab or Panitumumab (KRAS/NRAS WT gene only) + Irinotecan or
- Regorafenib

**Therapy after 3rd progression**
- Regorafenib (if not given previously) or clinical trial or best supportive care

- FOLFOX or XELOX or
- FOLFOX + Bevacizumab or
- XELOX + Bevacizumab

**REFERENCES**


25. Bendell JC, Bekaii-Saab TS, Cohn AL et al. Treatment patterns and clinical outcomes in patients with metastatic colorectal cancer initially treated with FOLFIRI-Bevacizumab or FOFLIRI–Beveravizumab: Results from ARIE5, a bevacizumab observational cohort study. The Oncologist 2012; 17: 1486-95.


