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REVIEW ARTICLE

Efficacy of Biological Therapies for the Treatment of Metastatic Colorectal Carcinoma

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ABSTRACT

Colorectal cancer is one of the most frequently diagnosed malignancies in the world. In Hong Kong, colorectal cancer is the second most common cancer and accounted for 16% of all new cancer cases in 2008. Despite recent advances in therapy, the prognosis of such patients remains poor. The introduction of novel targeted therapies that inhibit vascular endothelial growth factor (e.g. bevacizumab) and epidermal growth factor receptor (e.g. cetuximab and panitumumab) have revolutionised the management of metastatic colorectal cancer. The identification of biomarkers associated with disease management, including KRAS *and* BRAF *mutations, is changing the colorectal cancer treatment paradigm. Clinical and molecular predictors of response can help identify patients who could benefit from targeted therapies. This article reviews the evidence for the use of these novel biological agents in metastatic colorectal cancer, as well as the role of biological markers in the selection of appropriate therapies for the treatment for metastatic colorectal cancer.*

Key Words: *Colorectal neoplasms; DNA mutational analysis; Genes, ras; Proto-oncogene proteins; ras Proteins*

中文摘要

生物療法對於治療轉移性大腸直腸癌的效用

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大腸直腸癌是現今全世界最常見的惡性腫瘤之一。在香港，大腸直腸癌亦是第二種最常見的惡性腫瘤，2008年新診斷的癌症個案中便有16.4%屬大腸直腸癌。可惜，儘管治療方法有進步，但轉移性大腸直腸癌患者的預後仍然很差。最新的標靶療法抑制血管內皮生長因子（如bevacizumab）和表皮生長因子受體（如cetuximab及panitumumab），對醫治轉移性大腸直腸癌來說是一項革命性的發展。與病情處理有關的生物標記，包括*KRAS*及*BRAF*基因突變，正改變大腸直腸癌的治療模式。臨床及分子預測指標有助確定哪些病人可以受惠於標靶療法。本文回顧使用生物制劑在轉移性大腸直腸癌的實證，以及生物標記在轉移性大腸直腸癌患者中選擇適合療法的角色。

INTRODUCTION

The American Cancer Society estimated that in the United States alone, 141,210 people would be diagnosed with colorectal cancer (CRC) and that 49,380 would die of the disease in 2011.[1] In Hong Kong, CRC is the second most common cancer and accounted for 16% of all new cancers in 2008. In 2008 alone, 4301 new patients were diagnosed with CRC. Locally, it is

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the third leading cause of cancer deaths in men and second leading cause in women. In 2009, there were 1752 deaths caused by CRC, accounting for 14% of all cancer deaths.[2]

As recently as 15 years ago, median overall survival (OS) following the diagnosis of stage IV CRC was 12 months. Since that time, OS has now increased to 25 months.[3,4] These increases in survival have been associated with improvements in best supportive care as well as the introduction of new agents.

Until 15 years ago, the only chemotherapeutic agent available for metastatic colorectal carcinoma (mCRC) was 5-fluorouracil (5FU). The mid-to-late 1990's saw the introduction of three new chemotherapeutic agents: irinotecan (a topoisomerase I inhibitor), capecitabine (a 5FU pro-drug), and oxaliplatin (an organoplatinum complex). Since 2000, three biologics have been licensed for use in mCRC: bevacizumab (a vascular endothelial growth factor [VEGF] inhibitor), cetuximab and panitumumab (both epidermal growth factor receptor [EGFR] inhibitors). There are, however, relatively few new drugs under development, although two new biological agents, aflibercept (VEGF trap) and regorafenib have recently demonstrated survival benefits in phase III studies. All available agents are associated with some toxicities as well as expense. It is therefore important to increase our understanding of how best to use them for the patient management.

The treatment paradigm for mCRC has evolved. For a selected group of patients (e.g. those with oligometastatic liver disease or limited lung metastases), treatment is now potentially curative. Unfortunately, for the majority of mCRC patients, the aim of treatment is to palliate (i.e. maximise survival, maintain quality of life as well as minimise adverse effects [AEs] and symptom control).

This paper presents evidence relating to the use of novel biological agents in the treatment of mCRC.

BIOLOGICAL AGENTS FOR THE TREATMENT OF METASTATIC COLORECTAL CARCINOMA

Vascular Endothelial Growth Factor Inhibitor: Bevacizumab

Angiogenesis is the formation of new blood vessels. Tumours cannot grow beyond 2 mm in diameter without an independent blood supply, while larger tumours are dependent on their blood supply for survival and further growth.[5,6] This makes angiogenesis a useful target for preventing tumour progression, especially as the process of angiogenesis is not generally required in adults except during pregnancy and wound healing.

VEGF is a family of ligands that stimulate angiogenesis. It is normally secreted in response to hypoxia, but many tumours produce high levels of VEGF even at normal oxygen tensions.[7,8] High VEGF expression has been associated with reduced OS,[9-13] disease progression,[9] risk of relapse, lymph node involvement,[14-16] and malignant pleural effusion.[17] The genetic stability of VEGF makes continued targeting of VEGF a viable and important antitumour strategy.[8] The most important member of this family is VEGF-A (previously referred to simply as VEGF), which is highly expressed in CRC tissue.[18]

Bevacizumab is the first humanised monoclonal antibody directed against VEGF and was approved by the United States Food and Drug Administration in 2004 for the treatment of mCRC.[19] Bevacizumab binds to extracellular VEGF, in turn preventing it from binding to VEGF receptors, thereby inhibiting its biological activity.[20]

Bevacizumab as First-line Therapy

The Hurwitz et al's study[21] recruited 813 patients with mCRC who had not previously been treated for CRC. All the patients received bolus IFL (irinotecan, 5FU, and leucovorin) and study subjects were randomised to receive either bevacizumab (n = 402) or placebo (n = 411). This study demonstrated longer median progression-free survival (PFS) in the bevacizumab group (10.6 months) than the placebo group (6.2 months; $p<0.001$). This difference in PFS translated to a difference in median OS of 20.3 months in bevacizumab group (Table) versus 15.6 months in the placebo group ($p<0.001$). However, the Hurwitz et al's study used bolus IFL (an uncommon regimen in modern times) as the chemotherapeutic backbone.

BICC-C, a two-phase study compared three chemotherapeutic backbones in mCRC: FOLFIRI (leucovorin, 5FU, irinotecan), IFL, and CapeIRI (capecitabine and irinotecan).[22,23] The CapeIRI arm was associated with a high level of toxicity and was discontinued in the second phase. All patients in the second phase were prescribed bevacizumab. The main conclusion of BICC-C was that patients on FOLFIRI had longer PFS compared to either IFL or CapeIRI.

It was not possible to make direct comparisons of bevacizumab therapy in this study as bevacizumab was not randomised in phase 2. However, indirect comparisons seem to indicate that patients in the second phase (with bevacizumab therapy) survived longer than those in the first phase (without bevacizumab therapy).

The Saltz study had a two-by-two factorial design: patients were randomised first to XELOX (capecitabine and oxaliplatin) or FOLFOX-4 (leucovorin, 5FU and oxaliplatin).[24] Therefore all patients received an oxaliplatin-containing regimen. The second randomisation was to either bevacizumab or placebo.[25] In this study, median PFS was longer in the bevacizumab than the placebo group (Table), but there were no significant differences in response rates or OS.

The discrepancy between the results of the Hurwitz and Saltz studies may have arisen because many patients on bevacizumab in the latter study stopped treatment early (most commonly due to neurotoxicity). For patients who continued on bevacizumab, PFS was longer (10.4 months compared to 7.9 months on placebo [p<0.0001], in the pre-specified analysis).[21]

Anecdotally, clinicians have tended to treat older patients less aggressively in the belief that they are less fit. In these patients, fluoropyrimidine monotherapy is frequently used. The MAX study was designed to evaluate an effective but low-toxicity regimen suitable for older patients that was commonly used in routine clinical practice.[26] Patients recruited to the MAX study were older than those usually seen in clinical studies (median age 69[26] vs late 50's in many clinical trials[21,24]).

In the MAX study, patients were randomised to receive capecitabine (C); capecitabine plus bevacizumab (CB); or capecitabine, bevacizumab and mitomycin C (CBM). The aim was to avoid using oxaliplatin or irinotecan doublets in the initial chemotherapeutic backbone. The primary outcome was PFS.

The MAX study demonstrated that older patients with mCRC also benefited from bevacizumab treatment (Table).[26] In both bevacizumab arms, PFS was longer than in patients only on capecitabine (CB vs C, p<0.001; CBM vs C, p<0.001). In a subgroup analysis, patients with liver-only disease treated with bevacizumab also had longer PFS, though there was no impact on OS.

The main AE in MAX was hand-foot syndrome (26% and 28% in the CB and CBM groups respectively, compared to 16% in the C group). This phenomenon is typical of capecitabine and may in part represent cumulative toxicity, due to the more prolonged treatment of patients on bevacizumab. There was also a small increase in the rate of arterial thromboembolic events in bevacizumab patients (2.5% and 3.8% in CB and CBM groups respectively, but none in non-bevacizumab treated patients). This modest risk increase was not related to age, a history of arterial thromboembolic events, or vascular risk factors.[27]

Bevacizumab as Second-line Therapy

The Giantonio study recruited 829 mCRC patients previously treated with 5FU and irinotecan and randomised them to one of three study groups: FOLFOX-4 (n = 291), bevacizumab alone (n = 243), or bevacizumab and FOLFOX-4 (n = 286).[28] Patients in the group randomised to receive bevacizumab and FOLFOX-4 had longer PFS (p=0.0001) and OS (p=0.0011) compared to those randomised to receive FOLFOX-4 alone. Another important conclusion of their study was that bevacizumab should not be used as monotherapy.

The BRiTE study was a non-randomised, observational

Table. Summary of clinical trials: bevacizumab for first-line treatment of metastatic colorectal cancer.*

Regimen	ΔRR	PFS	ΔPFS	HR	OS	ΔOS	Reference
IFL + bev	10%†	10.6	4.4	0.54†	20.3	4.7†	Hurwitz et al,[21] 2004
XELOX/FOLFOX-4 + bev	-2%	9.4	1.4	0.83†	21.3	1.4	Saltz et al,[24] 2008
Capecitabine + bev (MAX study)	7.8%	8.5	2.8	0.63†	18.9	-2.5	Tebbutt et al,[26] 2010

Abbreviations: IFL=irinotecan, 5-fluorouracil and leucovorin; bev = bevacizumab; XELOX = capecitabine and oxaliplatin; FOLFOX-4 = leucovorin, 5-fluorouracil and oxaliplatin; ΔRR = increase in response rate in bevacizumab-treated patients compared to non–bevacizumab-treated patients; PFS = progression-free survival; ΔPFS = increase in progression-free survival in bevacizumab-treated patients compared to non–bevacizumab-treated patients; HR = hazard ratio; OS = overall survival.

* Median survival is reported here in months. The hazard ratio reported is for PFS.

† p<0.05.

cohort of 1953 patients who received first-line therapy with bevacizumab.[29] Of these, 1445 were recruited following first-progression and classified into three groups. The first group (n = 253) received no further treatment (median OS, 12.6 months), the second (n = 531) received therapy that did not include bevacizumab (median OS, 19.9 months), and the third (n = 642) received therapy that included bevacizumab (median OS, 31.8 months; p<0.001). Patients on bevacizumab were more likely to develop hypertension deemed to require treatment than those not treated with bevacizumab (24.6% vs 19.2%).

ML18147 is a prospective, open-label, randomised, phase III study that has recruited 822 patients to date; bevacizumab is part of their first-line therapy for mCRC (ClinicalTrials.gov: NCT00700102). Patients are recruited following first progression and randomised to standard second-line chemotherapy with or without bevacizumab. The primary endpoint of the study is OS. Secondary endpoints are OS from start of first-line therapy, PFS, overall RR, and safety. Accrual for ML18147 was completed in May 2010 and the final report is expected in 2012.

SUMMARY

Available data support the use of bevacizumab for first-line therapy of mCRC, which has been shown to be effective in combination with all chemotherapy regimens. While the evidence strongly supports its use in combination with irinotecan, mCRC patients taking 5FU and capecitabine may also benefit from combination therapy involving bevacizumab with oxaliplatin. The evidence does not support the use of bevacizumab as monotherapy.

The evidence shows benefit in second-line treatment of mCRC if patients are bevacizumab naïve. Following first progression, there may be benefit in maintaining bevacizumab while switching the chemotherapeutic backbone. Further evidence from randomised trials is pending. To date, there is no evidence to support the use of bevacizumab as third-line therapy for mCRC.

Epidermal Growth Factor Receptor Inhibitors: Cetuximab and Panitumumab

EGFR is a member of the EGFR family of receptor tyrosine kinases. The binding of epidermal growth factor (EGF)[30] or transforming growth factor alpha (TGFα)[31] to EGFR leads to activation of a number of signalling cascades that ultimately result in cellular proliferation. EGFR is overexpressed in a wide variety of tumours,[32-35] including CRC, where it is associated with aggressive clinical progression.[36]

Currently, there are two EGFR inhibitors of benefit in CRC on the market, cetuximab and panitumumab. Cetuximab is a chimeric monoclonal antibody, while panitumumab is a fully human monoclonal antibody. Both cetuximab and panitumumab bind competitively to EGFR without activating it, and prevent the natural EGFR ligands, EGF and TGFα, from binding.[37] Cetuximab and panitumumab down-regulate EGFR on the cell membrane,[37] inhibit cell division and tumour growth,[38,39] and induce apoptosis in tumour cells.[40] Consequently, they decrease the production of matrix metalloproteinases[41] (thus reducing metastatic potential) as well as the production of VEGF (thus inhibiting angiogenesis).[42-45]

Epidermal Growth Factor Receptor Inhibitors as First-line Therapy

Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer (CRYSTAL) was a trial of cetuximab as first-line therapy. In this trial, 1198 patients with previously untreated mCRC were randomised to receive either FOLFIRI (n = 599) or FOLFIRI plus cetuximab (n = 599).[46] The study demonstrated only a small difference in PFS (p = 0.046), but no difference in OS.

Epidermal Growth Factor Receptor Inhibitors as Second- and Third-line Therapy

The ERBITUX Plus Irinotecan for Metastatic Colorectal Cancer (EPIC) was a randomised, open-label trial of cetuximab as second-line therapy, which randomised 1298 patients to receive either cetuximab and irinotecan or irinotecan alone.[47] With cetuximab therapy, improvements in PFS (p≤0.0001) and response rate (16.4% vs 4.2%, p<0.0001) were evident, but there was no improvement in OS.

The CO17 study entailed third-line cetuximab therapy. The study involved 572 patients with mCRC who had previously been treated with fluoropyrimidine, irinotecan, and oxaliplatin or had contraindications to treatment with these therapies.[48] All patients had EGFR-positive tumours on immunohistochemistry and had never received EGFR inhibitor therapy before. Patients were randomised to receive either cetuximab plus best supportive care (n=287) or best supportive care

alone (n=285). In this study, cetuximab therapy was associated with improvements in OS (p=0.005) and PFS (p<0.001).

Skin toxicity is a major AE of EGFR inhibitors. This AE is linked to treatment efficacy.[48,49] In patients not developing a significant rash, there are some data suggesting possible benefit with a dose-escalation strategy. It appears that patients must tolerate this AE in order to gain the associated survival benefit.

SUMMARY RECOMMENDATIONS FOR EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITOR THERAPY

The EGFR inhibitors can be used as monotherapy or in combination with chemotherapy, for the treatment of mCRC; no loss of activity was observed when used as second- or third-line therapy. Conversely, unlike chemotherapy, EGFR inhibitors may be more active in refractory disease.

Influence of Biomarkers on Choice of Biologics Therapy

Efficacy of Epidermal Growth Factor Receptor Inhibitors in Patients with KRAS *Mutations*

KRAS encodes a small GTP-binding protein that acts as a self-inactivating signal transducer by cycling from GDP- to GTP-bound states in response to stimulation of a cell surface receptor (including EGFR).[50] *KRAS* may harbour activating mutations in codons 12 and 13 that render it constitutively active in CRC and are associated with a poor prognosis.[51,52] In 2008, Karapetis et al[53] published a subgroup analysis of the CO17 study[48] looking at the predictive and prognostic effects of *KRAS* mutation status. Of the 394 patients in whom cell samples were obtained, 42.3% had *KRAS* mutations. Karapetis et al[53] found that the patient subset who benefited from cetuximab was confined to the 225 patients with wild-type *KRAS* (PFS, p<0.001; OS, p<0.001). No benefit was noted in patients with *KRAS* mutations.

For first-line therapy, the CRYSTAL study also found that the subgroup with wild-type *KRAS* derived the PFS benefit with cetuximab and irinotecan-based chemotherapy and that this also translated into an OS benefit.

The COntinuous chemotherapy plus cetuximab, or INtermittent chemotherapy (COIN) study was a randomised, open-label, phase III trial of first-line cetuximab with oxaliplatin-based chemotherapy.[54] It recruited 1630 patients (1316 of these had *KRAS* mutations) with previously untreated mCRC. All patients were treated with oxaliplatin and fluoropyrimidine (either capecitabine or 5FU / leucovorin), and then randomised to receive cetuximab (n=815) or no treatment (n=815). Cetuximab did not confer any PFS or OS benefit. However, patients on cetuximab did have a better overall response rate (ORR) than those not receiving cetuximab (ORR=64% vs 57%, p=0.049).

Evidence for the importance of *KRAS* mutations in first-line panitumumab therapy comes from the PRIME study, which was a phase III randomised trial of panitumumab in which all patients received FOLFOX-4.[55] In the wild-type *KRAS* group, a benefit was seen in PFS (p=0.02), but did not translate into longer OS. In the mutant *KRAS* group, patients receiving panitumumab plus chemotherapy had shorter PFS (p=0.02) than those receiving chemotherapy alone. There was also a trend towards worse OS in the mutant *KRAS* group, although this did not attain statistical significance (p=0.068).

For second-line therapy, a re-analysis of the EPIC study by *KRAS* status found that patients with wild-type *KRAS* had improvements in both PFS (p=0.0012) and OS (p=0.0093).[3] For panitumumab, the Peeters study found that for patients with wild-type *KRAS*, the addition of panitumumab was associated with longer PFS (p=0.004), but OS was no different.[56] Panitumumab was not efficacious in the mutant *KRAS* group, although there was no evidence of any detrimental impact of panitumumab with an irinotecan-based chemotherapy backbone.

The NORDIC VII study[57] involved 566 patients with previously untreated mCRC randomised to receive continuous 5FU, folinic acid and oxaliplatin (FLOX); continuous FLOX plus cetuximab; or intermittent FLOX plus continuous cetuximab. In the subgroup analysis, only patients with *KRAS* mutations had a trend towards benefit (PFS, p=0.07, but for OS there was no benefit), while no differences were noted in patients with wild-type *KRAS*.

The discrepancy between NORDIC VII and the other studies are difficult to explain, but FLOX was associated with high rates of diarrhoea and some of the difference may be due to investigators tapering doses of

chemotherapy or even withdrawing it due to mucosal toxicity.

In summary, patients with activating mutations in *KRAS* do not derive benefit from EGFR inhibitor therapy. Hence, EGFR inhibitors should be restricted to patients with *KRAS* wild-type advanced CRC. Moreover, a negative interaction between oxaliplatin and EGFR inhibitors in *KRAS* mutant tumours is apparent, reinforcing the requirement to restrict the use of these agents to *KRAS* wild-type tumours.

Efficacy of Epidermal Growth Factor Receptor Inhibitors in Patients with BRAF *Mutations*

The main conclusion of the Karapetis and related studies was that *KRAS* mutations (with the possible exception of the G13D mutation[58]) reliably predicted resistance to treatment with EGFR inhibitors.[53,59] Nevertheless, wild-type *KRAS* does not guarantee a response to EGFR inhibitors. Other possible mediators of resistance include *BRAF* (serine/threonine-protein kinase B-raf).

Like *KRAS, BRAF* is also involved in the transduction of mitogenic signals from the cell membrane to the nucleus. Mutations in *BRAF* are also prognostic and patients with *BRAF* mutations have lower survival rates than those with wild-type *BRAF*.[60-62]

Di Nicolantonio et al[63] reported retrospective outcomes from 113 mCRC patients. Of the 79 patients with wild-type *KRAS*, 11 had a V600E mutation in *BRAF*, none of whom responded to cetuximab or panitumumab therapy. These findings suggest that *BRAF* may be an additional marker of resistance to this class of drugs. However, an analysis of the CRYSTAL study did not support *BRAF* as a predictive biomarker, and further data are required to evaluate this issue definitively.

Efficacy of Bevacizumab in Patients with KRAS *and* BRAF *Mutations*

The Hurwitz study reported *KRAS* status retrospectively on around 20% of the patients.[64] Tumours were scored retrospectively for mutations in *KRAS, BRAF* and p53, but no relationship was found with outcomes after bevacizumab therapy.[64] Tumours were also scored for VEGF expression, thrombospondin-2 and microvessel density. Again, these did not affect responses to bevacizumab.[65]

The MAX study managed to obtain tissue samples from 66.9% of patients retrospectively.[66] *KRAS* and *BRAF* mutation status did not influence outcomes from bevacizumab therapy.

Other Biomarkers That May Predict Bevacizumab Efficacy

There are a range of potential biomarkers for bevacizumab efficacy that are yet to be examined. These include imaging, hypertension, circulating biomarkers (e.g. VEGF), circulating endothelial cells, *in situ* biomarkers and single nucleotide polymorphisms (SNPs).[67] VEGF D expression and VEGF A SNPs are mentioned here. Bevacizumab only targets VEGF A, but there are other members of the same VEGF family, including VEGF B, C, and D. There is a high degree of redundancy in most biological signalling and it is plausible that signalling via one of these alternative molecules may be responsible for bevacizumab resistance.

Tissue samples from the MAX study were studied retrospectively and scored for expression of other VEGF family members. Low VEGF-D expression was associated with increased bevacizumab efficacy, while high VEGF-D expression was associated and vice versa.[68] VEGF-D expression is therefore a potential biomarker for predicting bevacizumab efficacy. Such data are biologically plausible and are potentially practice changing. However, as they have only been observed in a single study, the results are considered preliminary and require validation using the CAIRO2 dataset, as an independent study. A second candidate biomarker is VEGF A SNPs. In humans, VEGF A is highly polymorphic, with multiple SNPs present in the regulatory part of the gene. These SNPs may change VEGF A production or expression. DNA extracted from patients participating in the MAX study is currently being evaluated to examine the predictive and prognostic effect of different VEGF A SNPs on bevacizumab efficacy.

CONCLUSIONS

Bevacizumab and the EGFR inhibitors (cetuximab and panitumumab) play important roles in the treatment of mCRC.

Bevacizumab improves PFS (and sometimes OS) when used first-line. It is effective with all standard chemotherapy agents and has an easily manageable safety profile that does not significantly impact quality of life.

EGFR inhibitors also extend PFS (and sometimes OS) in (wild-type *KRAS*) patients when used first-line. Survival benefits were also observed when used as third-line therapy. Skin toxicity is a common AE, which has the potential to impact quality of life.

Bevacizumab therapy (with either FOLFIRI or capecitabine as the chemotherapeutic backbone) is better tolerated than EGFR inhibitor therapy and may therefore be preferred first-line, with an option to sequence onto an oxaliplatin-based regimen later. EGFR inhibitors (usually used in combination with irinotecan) may then be reserved for later use. In older patients who are unable to tolerate irinotecan, EGFR inhibitor monotherapy may be a viable option.

The results of CALGB/SWOG 80405, a randomised phase III trial comparing bevacizumab and cetuximab head-to-head as first-line therapy, should be available in 2012 (ClinicalTrials.gov: NCT00265850). This study will further inform clinical decisions regarding the first-line treatment of mCRC.

The identification of biomarkers associated with resistance (specifically, *KRAS* and *BRAF* mutations) is changing the CRC treatment paradigm, with clinical and molecular predictive markers of response increasingly used to identify patients who could benefit from targeted therapies. Based on the evidence, bevacizumab may clearly be recommended for use in patients with mutant *KRAS* (and probably mutant *BRAF*), because EGFR inhibitors are not indicated in this patient group. However, for the treatment of wild-type *KRAS*/*BRAF* tumours, the situation is less clear as bevacizumab and EGFR inhibitors may both be viable options. However, around 50% of CRC tumours may harbour activating mutations of *KRAS* or *BRAF*,[66] thus excluding EGFR inhibitor therapy, and leaving bevacizumab as the first-line biologic for these patients.

There are potential biomarkers in development that may allow clinicians to target VEGF inhibitor therapy in the future. Advances in knowledge regarding resistance mechanisms may lead to strategies for overcoming resistance and thus provide continued improvements in survival for patients with mCRC.

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