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Anti-Epidermal Growth Factor Receptor Monoclonal Antibodies in Metastatic Colorectal Cancer Biotherapy: A Systematic Review

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Abstract: The standard treatment of metastatic colorectal cancer (CRC) is combination of 5-fluorouracil/folinic acid (5-FU/FA) with irinotecan or oxaliplatin-based chemotherapy. Two anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (cetuximab and panitumumab) have been developed recently in an effort to provide yet another therapeutic option against mCRC. Cetuximab is a recombinant human/mouse chimeric immunoglobulin (Ig) G1 anti-EGFR monoclonal antibody (moAb) and panitumumab is a recombinant, fully human, IgG2 anti-EGFR monoclonal antibody. This article reviews the results of clinical trials of two anti-EGFR moAbs (cetuximab and panitumumab) in mCRC which target the external part of EGFR. The Medline, PubMed and Google were searched for clinical trials of moAbs in metastatic CRC published since 2001 up to this study time. The search terms used were 'colorectal cancer', 'anti-epidermal growth factor receptor monoclonal antibodies', 'cetuximab' and 'panitumumab', alone or in combination. About 20 articles were found published on the results EGFR-targeted biotherapy of CRC with moAbs and small molecule inhibitors. However, studies conducted with biotherapy approaches of CRC with other types of moAbs such as anti-vascular endothelial growth factor (VEGF) moAbs (e.g. bevacizumab) and small molecule inhibitors were excluded based on the objective of this review. Totally, six articles were included and reviewed based on the eligibility criteria. Results revealed that the literature search identified 3 trials of cetuximab and 3 trials of panitumumab in metastatic CRC. The clinical trials demonstrate a significant benefit with cetuximab or panitumumab as monotherapy or added to chemotherapy. Similar efficacy profiles were demonstrated for advanced CRC patients treated with panitumumab and cetuximab therapy, with some differences in their adverse event profiles. The results of these and other independent articles showed resistance to therapy in KRAS mutations. In conclusions, in the studies reviewed the anti-EGFR antibodies cetuximab and panitumumab were associated with consistent efficacy modality in the treatment of chemotherapy-refractory met6astatic CRC. The efficacy of anti-EGFR moAbs was limited to patients with Kirsten ras (KRAS) wild-type tumors.

Key words: Colorectal Cancer · Epidermal Growth Factor Receptor/EGFR · Monoclonal Antibodies And/Or Cetuximab and Panitumumab

INTRODUCTION

Colorectal cancer (CRC) is one of the commonest cancers worldwide. It ranks third in terms of incidence (about 1 million new cases in 2002) after lung and breast cancer and fourth in terms of mortality (529 000 deaths in 2002) [1]. In Europe, CRC is the second most common cause of cancer-related death (203, 700 deaths in 2004) after lung cancer [2]. With current predictions estimating that, in 2008, 1.2 million new cases of the disease would be diagnosed and 630,000 people would die as a result of the disease worldwide [3,4].

While early-stage CRC is associated with an excellent 5-year survival rate (90% for localized disease), approximately 20% of patients present with metastatic disease and many patients diagnosed with stage II or III cancer will experience a recurrence and develop distant metastases. The 5-year survival rate for patients with metastatic disease is approximately 10% [5].

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Surgery is the only curative treatment for CRC. However, approximately 25-50% of patients may have a recurrent disease at distant sites following radical surgery. During the past four decades, the antimetabolite 5-Fluorouracil (5-FU) has been the cornerstone of chemotherapy for advanced disease. More recently, new chemotherapeutic drugs with different mechanisms of action such as irinotecan (*topoisomerase I* inhibitor) and oxaliplatin (organoplatinum comlex drug, croslinks DNA and then inhubits DNA replication and transcription) have been demonstrated to be active in combination with 5-FU. Therefore, 5FU-irinotecan or 5FU-oxaliplatin combinations have become the standard first-line regimens in metastatic CRC [6]. Although there is clear evidence that chemotherapy in the first-line setting improves time to disease progression (TTP), overall survival (OS) and quality of life, overall treatment results remain unsatisfactory.

A better understanding of cancer cell biology has suggested many new targets for cancer drug discovery and development. These include the products of oncogenes and tumor-suppressor genes, regulators of cell death pathways, mediators of cellular immortality such as *telomerase* and molecules responsible for microenvironmental molding such as *proteases,* angiogenic factors or *EGFR* [7]. Owing to the remarkable advances in our understanding of the molecular mechanisms of carcinogenesis, target-based therapies are now commonly used as in the treatment of many types of cancer, including CRC.

Cetuximab and panitumumab are the two monoclonal antibodies developed against the epidermal growth factor receptor (EGFR) and that has been approved for the treatment of patients with metastatic CRC [8, 9]. Both cetuximab and panitumumab, when given alone, have been shown to benefit a small proportion of previously treated patients and cetuximab appears to have therapeutic synergy with such chemotherapeutic agents as irinotecan, even in patients previously resistant to this drug; this suggests that cetuximab can reverse cellular resistance to cytotoxic chemotherapy [8]. Recent efforts to improve outcomes have focused on the combination of standard chemotherapy with agents targeting EGFR and the subsequent biological pathways central to CRC pathogenesis. The optimal clinical application of anti-EGFR agents in the management of CRC patients and the identification of predictive markers are the main focus of research in recent years.

Therefore, the objective of this review article was thus to provide an overview of the mechanisms and efficacy results of using several of these key mCRC trials with anti-EGFR monoclonal antibodies (cetuximab and panitumumab). In addition, this paper provides an update on the recent retrospective analyses of mCRC clinical studies with anti-EGFR therapy suggesting that *KRAS* mutational status is an important predictor of resistance to EGFR-targeted therapy.

Methods

Literature Search and Eligibility Criteria: A computerized search was made using PubMed, MEDLINE and Google. Key words used to identify articles included 'metastatic CRC', 'EGFR', 'cetuximab, 'panitumumab' and 'monoclonal antibodies' to identify studies reporting on at least any of the following outcomes: overall mortality; recurrence, relapse, or disease progression; and treatment failure and the corresponding time-to-event outcomes (for example, OS or progression-free survival/PFS) for patients with CRC receiving treatment with cetuximab or panitumumab. Geographic restriction was not made and the language used was English. To increase yield, the references of all retrieved manuscripts and relevant review articles were also searched. Potentially eligible studies were retrieved and reviewed in full text. Eligible studies were published studies that reported on at least 10 patients who had received a diagnosis of metastatic colorectal cancer and received treatment with anti-EGFR antibodies alone or in combination with cytotoxic chemotherapy. All study designs (prospective and retrospective), treatment settings (first line and second line or higher) and treatment strategies (monotherapy and combination with cytotoxic chemotherapy) were considered. Studies conducted with combination therapy of CRC with other types of monoclonal antibodies such as anti-VEGF moAbs (e.g. bevacizumab) were excluded based on the objective of this review. Totally, six articles were included based on eligibility criteria for this review study. However other articles were also considered to review the results of anti-EGFR moAb therapy in CRC with KRAS mutations.

Data Extraction: From each eligible study, bibliographic information and information on study design; patient and treatment characteristics; definitions of outcomes; quality-related items; and numerical data for the outcomes of interest (namely OS, PFS and treatment failure) were extracted.

RESULTS

Clinical Activity of Cetuximab: About 3 studies concerning the clinical activity of cetuximab considered in this review have shown that cetuximab is effective in patients with metastatic CRC whose disease has

Table 1: Efficacy of cetuximab after failure of irinotecan-based chemotherapy regimens [8, 10, 11]

Cetuximab alone	No. patients	RR (%)	Disease control Median	TTP Median OS	(%) (months) (months)
Saltz *et al*. [46]	57	9	33	1.4	6.4
Cunningham *et al*. [17]	111	10.8	32.4	1.5	6.9
*Cetuximab+Chemoth*erapy					
Saltz *et al*. [47]	121	17	48	N/A	N/A
Cunningham *et al*. [17]	218	22.9	55.5	4.1	8.6

Abbreviations: N/A, not available; OS, overall survival; RR, response rate; TTP, time to treatment progression.

progressed on irinotecan-based chemotherapy administered as their last regimen before study entry (Table 1).

The first report of activity was derived from a phase II multicentre trial, in which 121 patients refractory to irinotecan-based chemotherapy expressing EGFR, received cetuximab in combination with irinotecan. A 17% major objective response rate (RR) for irinotecan-refractory patients was obtained with a median duration of response of 6 months [10]. In a multicenter phase II study to evaluate the activity of single-agent cetuximab in irinotecan-refractory CRC, the trial five out of 57 patients (9%) obtained partial responses (PR) [11].

The most complete clinical data for the use of cetuximab in this setting have been obtained with a large, multicenter European randomized phase II clinical trial, named the Bowel Oncology Cetuximab Antibody (BOND-1) study, which compared treatment with cetuximab monotherapy (111 patients) or with cetuximab in combination with irinotecan (218 patients) in advanced CRC patients with EGFR-positive cancer who have failed on an irinotecan-containing regimen as last treatment [8]. In this heavily pretreated patient population, 261/329 (79.3%) patients received two or more types of chemotherapy before study entry. Moreover, 206/329 (62.6%) patients were pretreated also with an oxaliplatin-containing regimen. Partial responses were obtained in 22.9% patients treated with irinotecan plus cetuximab as compared to 10.8% patients treated with cetuximab alone (P<0.007). Similarly, a significantly better disease control (partial responses plus disease stabilization) was observed in the combination arm as compared to cetuximab monotherapy (55.5 vs 32.4%, P< 0.001) [8]. The difference in terms of overall survival (OS) was not significant (median OS; 6.9 vs 8.6 months). Furthermore, a significant improvement in time to treatment progression (TTP) was observed in patients treated with cetuximab plus irinotecan (1.5 months vs 4.1 months; P<0.001). Subgroups analyses revealed that response to treatment was independent from the number of previous lines of chemotherapy. Probability of achieving a response was not correlated to the level of EGFR expression in the tumor. However, the presence and the intensity of skin toxicity were associated with clinical efficacy. In patients with 'acne-like' skin reactions after cetuximab treatment, the response rates were higher than those in patients without skin reactions (25.8 vs 6.3% in the cetuximab plus irinotecan combination arm, P< 0.005). Taken together, these data are particularly relevant for the clinical management of advanced CRC.

Cetuximab treatment is well-tolerated, either as monotherapy or in combination with chemotherapy; in particular, it is not associated with typical chemotherapy-induced side effects, such as myelosuppression, mucositis, nausea-vomiting and hair loss. In the combination studies with irinotecan and cetuximab, grade 3/4 toxicities according to WHO criteria were recorded in 72% of patients treated with cetuximab and irinotecan and 53% receiving cetuximab alone. Main grade 3/4 adverse events occurring in patients receiving cetuximab as monotherapy were acne-like rash (10%), asthenia (11%), dyspnea (10%) and abdominal pain (7%). The most common grade 3/4 toxicity reported in patients receiving cetuximab plus irinotecan were diarrhea (22%), leukopenia (17%), asthenia (14%), acne-like rash (12%) and abdominal pain (6%). Overall, 15% of patients receiving cetuximab and irinotecan discontinued therapy due to side effects compared with 12% receiving cetuximab alone. There were no deaths considered to be related to cetuximab treatment [8,11]. Acneiform skin rash is generally the most common adverse effect associated with cetuximab treatment, with a >60% incidence reported in the majority of the clinical trials. Nearly all skin reactions were seen within the first 5 weeks of therapy. The rash was predominantly on the face and upper trunk and was reversible within 30 days of stopping cetuximab treatment. This adverse effect is thought to be due to cetuximab interference with the physiological role of EGF in the epidermis.

As reported above for BOND study, there seems to be a correlation between the severity of cetuximab-induced skin reaction and the response rate and survival time following cetuximab therapy.

Table 2: Efficacy of panitumumab in combination with chemotherapy in patients with advanced colorectal cancer [13, 12]

		Wild-type K-RAS patients	
n Progression-free survival Overall survival		HR (95% CI)	HR (95% CI)
P value *P* value			
Panitumumab + FOLFOX *vs* FOLFOX	656 0.80 (0.66-0.97) 0.83 (0.67-1.02)	*P* = 0.02	*P* = 0.07
Panitumumab + FOLFIRI *vs* FOLFIRI	597 0.73 (0.59-0.90) 0.85 (0.70-1.04)	*P* = 0.004	*P* = 0.12

CI, confidence interval; FOLFIRI, irinotecan, 5-fluorouracil and leucovorin; FOLFOX, oxaliplatin, leucovorin and 5-fluorouracil; HR, hazard ratio.

An analysis of four phase II studies in different tumors showed that patients who developed the acneiform rash survived longer than those who did not develop it, suggesting that skin rash may be a relevant surrogate of cetuximab clinical efficacy [10]. To explore this hypothesis, a randomized phase I/II study of cetuximab plus irinotecan is currently ongoing to investigate the safety and efficacy of a dose escalation of cetuximab compared with the standard cetuximab dose in patients with irinotecan resistant, EGFR-expressing metastatic CRC.

Clinical Activity of Panitumumab: The efficacy of panitumumab as both monotherapy and combination therapy in advanced CRC has been demonstrated in many studies.

In a one phase-III study, while the addition of panitumumab to best supportive care (BSC) did not increase OS, it significantly prolonged PFS (hazard ratio: 0.54; 95% CI: 0.44-0.66). The overall response rate (RR) was higher in the panitumumab arm (RR: 36%) than the control arm (RR: 10%). This result was robust and persisted at 8 months after treatment [12]. Furthermore, all responders treated with panitumumab had wild-type *KRAS* and an overall response rate of 17%, whereas no patients with mutated *KRAS* responded to panitumumab treatment.

In other two recent studies, a combination of panitumumab plus FOLFOX (oxaliplatin, leucovorin and 5-fluorouracil) displayed a significantly-improved PFS and a trend towards improved OS compared with FOLFOX alone [13]. Similarly, panitumumab plus FOLFIRI (irinotecan, 5-fluorouracil and leucovorin) led to improvements in PFS compared with FOLFIRI alone, although OS was not improved [12] (*Table 2*).

Potential Predictors (*Predictive Biomarkers*) of Response to Anti-EGFR Therapy: The early biomarker, developed in mCRC to correlate with the activity of anti-EGFR antibodies, was confined to merely expressing the target EGFR.

It has been demonstrated that colorectal cancer patients with EGFR-negative tumors have the potential to respond to cetuximab-based therapies, registering a 25% objective RR [14]. Consequently, the presence of the target (EGFR) does not ensure the response to anti-EGFR inhibitors. Furthermore, EGFR analysis by current immunohistochemistry techniques does not seem to have predictive value for the selection or the exclusion of patients for cetuximab, therefore EGFR immunohistochemistry is not warranted currently.

Several studies have been carried out to define a subgroup of patients with potentially differential responses to anti-EGFR antibody therapy and these show that benefits are confined to the subgroup with wild type KRAS tumours. The role of a patient's tumor KRAS mutational status in the treatment of metastatic CRC with anti-EGFR agents has recently become an emerging area of research and interest. K-ras is a guanosine triphosphate(GTP)-binding protein with a critical role in cellular growth and survival pathways [15]. It plays a key role in the RAS/MAPK signaling pathway located downstream of many growth factor receptors, including EGFR and involved in carcinogenesis. The KRAS oncogene is a signal transducer modulated by the EGFR pathway and mutations within the KRAS gene resulting in constitutive protein activity are found in approximately 30%-50% of all CRCs [16, 17]. Mutations of the KRAS protein activate signaling to the downstream RAF/MAPK/extracellular signal-related kinase(ERK) kinase/ERK pathway, resulting in increased proliferation, tumor angiogenesis, metastasis and inhibition of apoptosis, which support continued cancer cell survival, even in the presence of EGFR inhibition (Fig. 1). KRAS mutations result in a constitutive activation of the MAPK pathway and in lack of response with EGFR inhibitors [18].

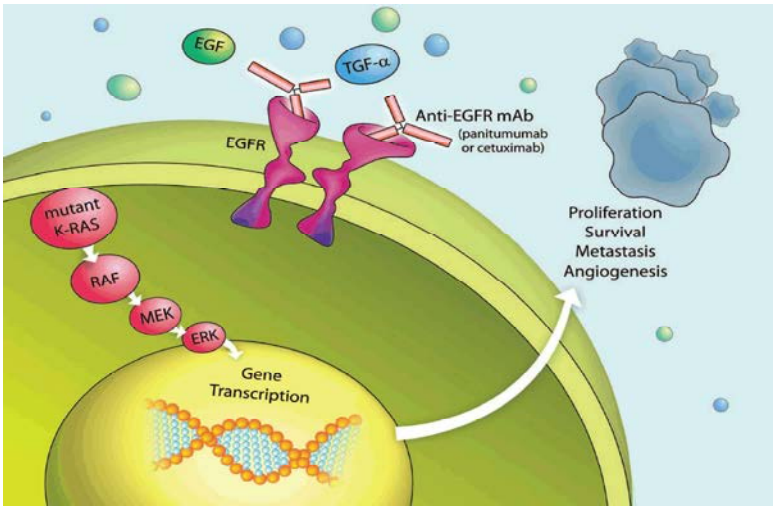

Fig. 1: Mutated K-RAS is active in the presence of EGFR inhibition by anti-EGFR mAbs. In wild-type *KRAS* tumors, anti EGFR mAbs, such as panitumumab or cetuximab, inhibit binding of the ligands EGF and TGF-á to EGFR and inhibit signalin of the RAS pathway. Mutant K-RAS is constitutively active and can promote downstream signaling in the presence of EGFR inhibition, leading to activation of genes that promote cell proliferation, survival, metastasis and angiogenesis. Abbreviations: EGFR, epidermal growth factor receptor; ERK, extracellular signal-related kinase; mAb, monoclonal antibody;MEK, mitogen-activated protein kinase/extracellular signal-related kinase; TGF, transforming growth factor. [19].

DISCUSSION

In this review study it is found that anti-EGFR monoclonal antibodies show promising results in mCRC therapy. The results of many clinical trials with anti-EGFR moAbs in the treatment of advanced mCRC have produced consistent efficacy and safety results after failure of standard chemotherapy combinations. Anti-EGFR monoclonal antibodies have been approved for patients with wild-type KRAS mCRC refractory to 5-FU, irinotecan and oxaliplatin [3].

Most of the positive results in studies of cetuximab in combination with chemotherapy are with irinotecan based regimens. In fact, the most active chemotherapy combinations, including fluoropyrimidine, irinotecan, oxaliplatin and bevacizumab, a humanized monoclonal antibody against human VEGF, obtain median survivals of 18-21 months in patients [8]. However, after failure of these drug combinations, there are no effective treatment options. Therefore, cetuximab as monotherapy or in combination with irinotecan offers a promising new treatment option for this set of patients.In particular, the BOND study indicates that patients with metastatic CRC, which are refractory to irinotecan will respond and have a clinical benefit from the combination of cetuximab plus irinotecan [8].

Other retrospective survival analysis studies [20] show a significant benefit in median overall survival (OS) in patients with wild-type KRAS who received folinic acid, fluorouracil and irinotecan (FOLFIRI) plus cetuximab compared with chemotherapy alone (23•5 vs 20•0 months; p=0•0094). Efficacy findings from trials investigating oxaliplatin-based regimens in patients with mCRC have been modest at best. The phase 2 OPUS study [21] assessed the efficacy of an oxaliplatin-based regimen with or without cetuximab. Patients with wild-type KRAS who received cetuximab had slightly longer progression-free survival (PFS; 7•7 vs 7•2 months; p=0•016), but no overall survival benefit. But patients with mutant KRAS had a decreased PFS and a slight decrease in overall response rate (RR) with addition of cetuximab.

As a result, cetuximab is now indicated for patients expressing *KRAS* wild-type metastatic colorectal cancer. This inclusion of *KRAS* mutation testing as a tool for the selection of appropriate patients for EGFR targeted cancer therapy is regarded as one of the most important advances in personalized cancer therapy [22]. Other potential biomarkers that predict response to cetuximab are under investigation.

This and other data led to the approval of cetuximab for the treatment of patients with EGFR expressing metastatic colorectal cancer, either in combination with

chemotherapy or as a single agent in patients who have failed or are intolerant to oxaliplatin and irinotecan-based therapy. However, resistance to cetuximab was still common, with 50% of cetuximab treated patients exhibiting disease progression.

Similarly the data presented on the panitumumab result section of this paper [13,20,23] and other trials with panitumumab for first-line treatment of advanced colorectal cancer, PFS and RR were improved (in patients with wild type KRAS) in those who received panitumumab compared with in those who did not.

The most promising advance in the management of metastatic colorectal cancer has been in identifying *predictive* and *prognostic molecular biomarkers*. The role of KRAS gene mutation status in the treatment of mCRC with anti-EGFR therapies should be considered for a personalized approach to therapy and incorporated into the final analysis of studies evaluating anti-EGFR moAbs. Published reports so far have investigated the role of K-ras as a selection marker for EGFR inhibitor treatment on tumour samples from uncontrolled studies and include therapy with EGFR inhibitors alone or in combination with chemotherapy. A retrospective analysis reported by Li`ever *et al.* [24] analyzed tumor samples from 30 patients treated with cetuximab. A K-ras mutation was found in 13 tumors (43%) and was significantly associated with absence of response to cetuximab. None of the patients with response to cetuximab harbored a K-ras mutation.

In, the study published by Karapetis *et al*. [22] comparing panitumumab monotherapy with BSC, no clinical benefit to panitumumab at all in patients with the K-ras mutation was evidenced in any clinical end-point, thus confirming the role of the K-ras mutant as a negative predictor of response.

Moreover, in patients with metastatic CRC treated with first-line infused fluorouracil, folinic acid and oxaliplatin with or without cetuximab, the improved RR and PFS associated with cetuximab was confined to those patients having a K-ras wild-type tumour [21,25-27]. It has been hypothesized that irrespective of the level of EGFR expression, the presence of a K-ras mutation is associated with a constitutive activation of the RAS/MAPK pathway, leading to cell proliferation which cannot be significantly inhibited by cetuximab. K-ras mutations have also been implicated in resistance against EGFR TKIs in lung adenocarcinomas [28]. In many trials, beneficial effects of anti-EGFR antibodies were limited to a subgroup of patients with wild-type KRAS tumors. For patients whose tumors harbor KRAS mutations and are resistant to multiple lines of treatment, new therapeutic options must be explored.

This has led to the recommendation that all patients with advanced CRC who are being considered for cetuximab or panitumumab should undergo K-ras testing and if the cancer bears a mutated K-ras gene, they should not receive an antibody that targets EGFR. In addition to KRAS, other molecular markers such as BRAF, PI3K and PTEN, may allow for further personalization of therapy with anti-EGFR monoclonal antibodies [29, 30].

CONCLUSIONS AND FUTURE PERSPECTIVES

Throughout the last decade, significant advancement in our understanding of the molecular mechanisms of metastatic CRC has been made. The treatment of patients with metastatic CRC has improved considerably over the last few years with new combination therapies such as irinotecan and/or oxaliplatin plus 5-FU/FA. However, the majority of patients will experience tumor progression.

Anti-EGFR monoclonal antibodies approved for use in the metastatic setting have broadened the therapeutic armamentarium in the treatment of metastatic CRC. The results of recent clinical trials have demonstrated the effectiveness of anti-EGFR monoclonal antibodies in metastatic CRC, both alone and in combination with other interventions. EGFR monoclonal antibody inhibitors are the only approved therapy to date that has been clearly been shown to reverse chemotherapy resistance clinically.

Cetuximab and panitumumab have become part of standard therapy for patients with metastatic CRC. In this setting, there is now evidence that cetuximab treatment is active in patients with EGFR-expressing tumors after failure of both irinotecan-and oxaliplatin-based regimens. Panitumumab has been shown to be effective as monotherapy in patients with chemotherapy-refractory metastatic colorectal cancer whose tumors have wild-type KRAS: it does not appear to have efficacy in those with mutant KRAS. Currently, panitumumab is only approved for monotherapy; however, combination with chemotherapy is likely to be effective despite insufficient data at this time. Because panitumumab is a fully human monoclonal antibody, it can be administered without hypersensitivity premedication.

The benefits of anti-EGFR antibody therapy are largely limited to KRAS wild-type patients, particularly regarding PFS and RR to treatment. Advances made in the identification of predictive biomarkers such as KRAS mutations allow us to select distinct groups of patients

who are most likely to benefit from anti-EGFR monoclonal antibody therapy.

In line with this the development and application of monoclonal antibodies in targeted therapy of many cancers, including CRC, has such future perspectives:

- With the up-coming of monoclonal antibodies in cancer therapy, progress toward more specific and less toxic therapy for human cancer, including CRC, is in our near future. The developments during the past 25 years in both biologic drugs and targeted small molecules place us on the verge of more cures with less toxicity for cancer patients.
- Given the likely lower toxicity of antibodies vs small molecules, the potential increase in efficacy by conjugation to radioisotopes and other cellular toxins and the ability to characterize the target with clinical diagnostics to improve the drug's clinical performance, it is anticipated that current and future antibody therapeutics will find substantial roles either alone or in combination with other strategies for the treatment of CRC and other cancers.
- To maximize benefits from these new approaches (targeted therapies), it will now be important to identify *predictive factors of response* and to design appropriate *clinical trials* to explore their potential roles in different patient populations.

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