The Evolving Role of Monoclonal Antibodies in Colorectal Cancer: Early Presumptions and Impact on Clinical Trial Development

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ABSTRACT

Targeted biologic agents have an established role in treating metastatic colorectal cancer (mCRC). Bevacizumab, a recombinant monoclonal antibody against the vascular endothelial growth factor ligand is approved by the U.S. Food and Drug Administration (FDA) for bevacizumab-naïve patients. Cetuximab, a chimeric monoclonal antibody (mAb) against the epidermal growth factor receptor (EGFR) is FDA approved as a single agent, or in combination with irinotecan, in both irinotecan-naïve and refractory patients, and has additional efficacy in combination with oxaliplatin. Panitumumab, a fully human EGFR mAb, is FDA approved as a single agent in refractory patients but has additional efficacy in combination with chemotherapy. After reaching a temporary therapeutic plateau of FDA-approved agents for the treatment of mCRC, pivotal results have developed that critically affect the care for

these patients. Correlative data from randomized trials of EGFR inhibitors across disease settings have demonstrated higher response rates, specifically for patients with wild-type *K-RAS* tumors. The interpretation of the *B-RAF* mutation and other molecular markers may further define the appropriateness of anti-EGFR therapy. Recent literature revealed that the first-line use of combined anti-EGFR therapy plus bevacizumab resulted in inferior outcomes and additional toxicities. Furthermore, the role of biologic agents for locally advanced colon cancer cannot be advocated at this time. With impending changes in the health care system, the economic impact of mAbs will continue to be scrutinized. Hence, as the significance of molecular markers continues to develop, their role as it pertains to the appropriate use of biologic agents in the treatment of mCRC will continue to evolve. *The Oncologist* 2010;15:73–84

INTRODUCTION

Biologic agents have emerged as key components in colorectal cancer (CRC) management. Bevacizumab and cetuximab have been proven to be effective in different combined

chemotherapy treatment settings, whereas panitumumab is approved as monotherapy for heavily pretreated patients with metastatic disease [1–4]. Bevacizumab is a humanized monoclonal antibody that targets the vascular endothelial growth

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Table 1. Properties of biologic agents currently approved for use in CRC

Agent	Recombinant monoclonal antibody	IgG ₁	IgG ₂	Chimeric	Humanized	Human	VEGF	Targets EGFR
Bevacizumab	X	X			X		X	
Cetuximab	X	X		X				X
Panitumumab	X		X			X		X

Abbreviations: CRC, colorectal cancer; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor.

factor (VEGF), particularly VEGF-A, a ligand with a key role in angiogenesis. Cetuximab and panitumumab inhibit the epidermal growth factor receptor (EGFR), which is implicated in several pathways regulating tumor growth and survival (Table 1). Although both cetuximab and panitumumab target EGFR, antibody isotype (IgG₁ versus IgG₂, respectively) and origin may result in different mechanistic properties (antibody-dependent cell mediated cytotoxicity [ADCC]) [5] and safety profiles. Yet a clinical difference is lacking regarding the significance of ADCC. After reaching a therapeutic plateau with the current U.S. Food and Drug Administration (FDA)-approved treatments, recent pivotal data are refining our knowledge base of biologic agents for CRC, providing critical insights for optimal treatment.

METASTATIC CRC

The number of cytotoxic and biologic therapies available to physicians for the treatment of CRC creates a developing therapeutic landscape. Because metastatic disease is usually the setting in which these agents are first developed, most agents have a more mature clinical profile in metastatic CRC (mCRC). This section provides an overview of the currently FDA-approved biologic agents and their evolving role in the treatment of mCRC.

Bevacizumab

Results from the pivotal phase III trial of bevacizumab (5 mg/kg) showed a significantly greater overall survival (OS) time, progression-free survival (PFS), and response rate (RR) when used in combination with irinotecan, bolus 5-fluorouracil (5-FU), and leucovorin (LV), the IFL regimen [1], with a meaningful benefit extending to poor-risk populations [6]. These findings led to the U.S./European Union approval of bevacizumab as a first-line-therapy component for mCRC with any 5-FU–based therapy. Bevacizumab is accompanied by a manageable safety profile. Hypertension is the most commonly reported associated toxicity and may develop in 15%–25% of patients treated with bevacizumab [1, 7]. Thrombosis is a more potentially serious adverse event. A recent pooled analysis of breast

cancer, lung cancer, and CRC patients indicated an overall higher risk for arterial thrombosis (hazard ratio [HR], 2.0; 95% confidence interval [CI], 1.05–3.75; $p = .031$), especially in patients aged ≥ 65 years (4.4% versus 2.6%; $p = .01$), and notably more so in patients aged ≥ 65 years with a prior history of an arterial thrombotic event (17.9% versus 2.2%; $p = .01$) [8]. A recent meta-analysis of multiple malignancies revealed that the incidence of all-grade venous thromboembolism in CRC patients was 19.1% (95% CI, 16.1%–22.6%; relative risk, 1.19; 95% CI, 0.92–1.55) [9]. Other less common but serious reported toxicities may include gastrointestinal perforation (<2%) and wound-healing complications.

Clinical studies have evaluated different chemotherapy regimens in combination with bevacizumab, including: oxaliplatin, 5-FU, and LV (FOLFOX), irinotecan, 5-FU, and LV (FOLFIRI), capecitabine plus irinotecan (CapeIri, XELIRI) and capecitabine plus oxaliplatin (CapeOX, XELOX), producing RRs in the range of 47%–84% [10–12]. The most commonly used bevacizumab-based first-line treatment in the U.S. continues to be FOLFOX plus bevacizumab. Yet irinotecan was the first therapeutic approved after decades of 5-FU as the only available therapy, but was originally commonly provided in the IFL combination. Oxaliplatin was subsequently approved following North Central Cancer Treatment Group (NCCTG) N9741 trial, which found FOLFOX4 to be superior to IFL [13]. Equivalent efficacy with FOLFOX and FOLFIRI was not yet established (without a biologic agent) [14]. Practicing physicians quickly added bevacizumab to their armamentarium in the treatment of mCRC patients and immediately combined oxaliplatin-based therapy with bevacizumab regardless of the absence of a front-line trial to demonstrate the benefits in such a setting. It was presumed that the efficacy of adding bevacizumab to FOLFOX would be similar to that as demonstrated with the IFL regimen.

A direct evaluation of bevacizumab plus oxaliplatin therapy culminated in the international phase III trial N016966, which enrolled 1,401 patients in a 2×2 factorial design [15]. The N016966 trial clarified the nonbiologic-related question of noninferiority between FOLFOX and

CapeOX. The addition of bevacizumab (5 mg/kg every 2 weeks) to the oxaliplatin-based arms was effective, meeting its primary endpoint, with a 1.4-month difference in the median PFS (8.0 months versus 9.4 months; $p = .0023$) [16]. However, secondary endpoint results added a layer of complexity regarding the use of first-line bevacizumab. Unlike prior studies, the addition of bevacizumab did not result in a greater RR (49% versus 47%; $p = .90$) or OS time (21.3 months versus 19.9 months; $p = .0769$). The observed longer PFS, though statistically significant, was less than expected, likely a result of the definition of tumor progression and the high rate of treatment discontinuation without disease progression (62% versus 44%), largely associated with nonbevacizumab-induced toxicity. Expectations of treating U.S. physicians were high because FOLFOX + bevacizumab had been commonly accepted, albeit without a wide base of supportive literature. Evidence-based medicine clearly shows that IFL is inferior to FOLFOX [13], likely making the incremental benefit of bevacizumab to IFL more pronounced. At that time, there were sparse available data regarding the FOLFIRI regimen and bevacizumab.

The phase III Bevacizumab plus Irinotecan in Colorectal Cancer (BICC)-C trial was originally designed to compare three possible irinotecan chemotherapy options—FOLFIRI ($n = 144$) versus modified IFL (mIFL) ($n = 141$) versus CapeIri ($n = 145$)—with a second randomization to celecoxib or placebo (3×2 factorial design); the primary endpoint was PFS [17]. In 2004, following the FDA approval of bevacizumab, the BICC-C trial was subsequently amended to a two-arm trial of FOLFIRI plus bevacizumab (5 mg/kg every 2 weeks) versus mIFL plus bevacizumab (5 mg/kg every 2 weeks). The CapeIri arm was closed to enrollment primarily as a result of a higher rate of grade 3 or 4 diarrhea (47.5%) and was not included in the expanded bevacizumab cohort. Consequently, 117 patients in total were assigned to either FOLFIRI plus bevacizumab ($n = 57$) or mIFL plus bevacizumab ($n = 60$). After a median follow-up duration of 34.4 months, the median OS time with the addition of bevacizumab was longer with FOLFIRI than with mIFL (28.0 months versus 19.2 months; $p = .037$; HR for death, 1.79; 95% CI, 1.12–2.88) [18].

Eastern Cooperative Oncology Group (ECOG) 3200 trial was the first phase III trial to evaluate the combination of oxaliplatin and bevacizumab, comparing FOLFOX4, FOLFOX4 plus bevacizumab (10 mg/kg every 2 weeks), and bevacizumab alone (10 mg/kg every 2 weeks) after progression of disease following irinotecan, 5-FU, and LV [19]. At an interim analysis, the single-agent bevacizumab monotherapy arm was discontinued because of a lack of efficacy. The median OS and PFS rates were higher with

FOLFOX4 plus bevacizumab (12.9 months versus 10.8 months; $p = .0011$) than with FOLFOX4 alone (7.3 months versus 4.7 months; $p < .0001$), respectively. The results of that trial led to the approval of bevacizumab (10 mg/kg) in the second-line setting for bevacizumab-naïve patients. However, the applicability of the trial is limited given that there are few patients naïve to bevacizumab after first-line failure. Of note, the ECOG 3200 study clearly noted no benefit for single-agent bevacizumab.

The use of bevacizumab in previously treated mCRC patients continues to be pursued. Researchers are seeking the potential benefits of continuing bevacizumab therapy following progression. Data from the Bevacizumab Regimens: Investigation of Treatment Effects and Safety (BRiTE) observational registry confirmed that bevacizumab-related toxicity was comparable with that seen in the original FDA registration trial [7]. Furthermore, a notable OS benefit was demonstrated in those patients who continued bevacizumab (5 mg/kg every 2 weeks) therapy in combination with chemotherapy after disease progression on a bevacizumab-based regimen (median OS, 31.8 months). Though these results are intriguing, they should be interpreted carefully given their observational nature. To date, no prospective data support the continuation of bevacizumab as a single agent or in combination after progression of disease. The phase III Southwest Oncology Group (SWOG) S0600 trial was originally a three-arm trial of either FOLFIRI (or irinotecan) plus weekly cetuximab (control arm) versus bevacizumab at two different doses (5 mg/kg versus 10 mg/kg) in patients previously treated with oxaliplatin. The S0600 trial has since been revised to compare FOLFIRI (or irinotecan) plus weekly cetuximab or bevacizumab (5 mg/kg every 2 weeks) in only wild-type *K-RAS* patients. It is the first prospective trial to directly compare the benefit of continuing bevacizumab or initiating cetuximab in previously treated mCRC patients. Primary endpoints include both PFS and OS. The prospective European AIO 0504 trial is evaluating PFS as the primary endpoint when continuing bevacizumab beyond progression and continues to accrue patients [20].

Cetuximab

Cetuximab plus irinotecan is the standard treatment in irinotecan-refractory patients based on pivotal data from the Bowel Oncology with Cetuximab Antibody (BOND) trial, which established this as an effective regimen regardless of prior treatment history [2]. The Monoclonal Antibody Erbitux in a European Pre-License study (MABEL, a large community-based observation registry with >1,100 patients) confirmed that the clinical benefits seen in pivotal trials of cetuximab plus irinotecan following prior

irinotecan-based therapy (weekly, bimonthly, or every 3 weeks) are comparable in the community setting [21].

Subsequent studies support the use of cetuximab in combination for patients with previously treated mCRC without requiring prior irinotecan exposure. The Erbitux® Plus Irinotecan in Colorectal Cancer (EPIC) phase III trial provided the first comparative evidence of greater effectiveness of cetuximab plus irinotecan versus single-agent irinotecan in second-line mCRC patients following oxaliplatin-based therapy; crossover was not allowed [22]. The combination of cetuximab plus irinotecan led to a significantly greater RR (16.4% versus 4.2%; $p < .0001$) and PFS (HR, 0.692; $p < .0001$), and maintained the overall quality of life (QoL), though the primary endpoint (OS) was not met (HR = 0.975; $p = .7115$). Given the frequent use of cetuximab as standard therapy after irinotecan failures in the U.S., the rate of patients receiving cetuximab after progression was high. Indeed, a post hoc analysis revealed that the OS differences may have been undermined by post-trial treatment crossover.

As monotherapy, cetuximab's benefit in terms of OS was confirmed in a large phase III study (the National Cancer Institute of Canada [NCIC] CO.17 trial) in which 572 patients were randomized to cetuximab or best supportive care (BSC) after irinotecan, oxaliplatin, and fluoropyrimidine failures [3]. Crossover was not allowed. The partial RR with single-agent cetuximab was 6.6%, compared with 0% for BSC; 29.6% of patients receiving cetuximab achieved stable disease, versus 10.2% of those with BSC. The median OS time was significantly greater in patients treated with cetuximab (6.1 months versus 4.6 months; $p = .005$) and QoL was better preserved, including less deterioration in physical functioning scores and global health status [23]. Based on these results, the FDA approved an amended indication for cetuximab supported by superior RR, PFS, and OS [24].

In the first-line setting, several phase II studies of cetuximab plus chemotherapy have demonstrated RRs in the range of 41%–68%. Common regimens evaluated include: FOLFOX4 [25], XELOX [26], XELIRI [27], and 5-FU plus folinic acid (the AIO regimen) [28]. This growing body of data makes cetuximab plus chemotherapy an option for those patients ineligible for bevacizumab-based therapy.

The Cetuximab Combined With Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer (CRYSTAL) and Oxaliplatin and Cetuximab in First-Line Treatment of mCRC (OPUS) trials were the first two randomized trials to evaluate cytotoxic chemotherapy with or without cetuximab in the front-line setting [29, 30]. In the CRYSTAL trial ($n = 1,198$), cetuximab plus FOLFIRI resulted in a longer median PFS interval than with FOLFIRI alone (8.9

months versus 8.0 months; $p = .0479$) and a significantly higher RR (46.9% versus 38.7%; $p = .0038$) [29]. Although the CRYSTAL study met its primary endpoint (PFS), the magnitude of the benefit was considered underwhelming. Remarkably, some patients with nonresectable tumors at study entry were converted to surgically resectable. R0 surgical resection rates in the cetuximab arm were threefold higher (4.3% versus 1.5%; $p = .0034$); the PFS benefit associated with cetuximab reached approximately 2 months (11.4 months versus 9.2 months; $p = .0023$). In the randomized phase II OPUS trial, the addition of cetuximab to FOLFOX4 resulted in a greater RR (45.6% versus 35.7%), but no difference in terms of PFS (median, 7.2 months for both groups) was noted [30].

The Continuous Chemotherapy plus Cetuximab or Intermittent Chemotherapy (COIN) study is a randomized three-arm phase III trial including capecitabine. Patients received standard chemotherapy (physician's choice of XELOX or FOLFOX) administered continuously with (arm A) or without (arm B) cetuximab and with a third arm (arm C) of intermittent XELOX or FOLFOX (oxaliplatin for a maximum of 12 weeks and then resumption at progression) [31]. The primary endpoint was OS. Surprisingly, 66% of the patients received XELOX as their baseline regimen. No difference in OS was noted between the continuous and intermittent XELOX or FOLFOX chemotherapy arms (15.8 months versus 14.4 months; HR, 1.084; 80% CI, 1.008–1.165). QoL data were collected and will be presented at a later date. Of note, the results of these above-mentioned studies were initially reported for all accrued patients and were not specific for *K-RAS* status.

EMERGENCE OF BIOMARKERS

Of greater significance to the clinical use of anti-EGFR antibodies has been the identification of reproducible and validated predictive biomarkers. Based on numerous hypothesis-generating small studies [32–37] and retrospective analyses of the CRYSTAL and OPUS trials, the clinical relevance of mutations of the *K-RAS* gene (encoding a small GTPase that functions downstream of the EGFR) has been solidified. *K-RAS* mutations (*K-RAS*^{MT}) are present in 40%–50% of all CRC tumors, commonly in codons 12 or 13 and rarely in codon 61. In the CRYSTAL study, 540 of the 1,198 patients (45%) were evaluable for *K-RAS* status; of these, 64.4% had wild-type *K-RAS* (*K-RAS*^{WT}) tumors [29]. A recently updated stratification analysis of these patients revealed that the therapeutic benefit of cetuximab was greater in patients with *K-RAS*^{WT} tumors [31]. The risk for progression in this cohort was 30% lower than with FOLFIRI alone (9.9 months versus 8.4 months; HR, 0.70; $p = .0012$). Moreover, there was an absolute difference be-

tween treatments in terms of a higher RR in the *K-RAS*^{WT} cohort (57% versus 40%; $p < .0001$). A benefit in terms of the median OS time was seen in the investigational arm in *K-RAS*^{WT} tumors (23.5 months versus 20 months; $p = .0094$). Conversely, for the subset of patients with *K-RAS*^{MT} tumors, the addition of cetuximab to FOLFIRI had little effect, with no significant difference in terms of the PFS time or RR.

Similar results were obtained in the randomized phase II OPUS trial, in which 233 of the 337 patients (69.1%) were evaluable for *K-RAS* mutations analysis (57.5% with *K-RAS*^{WT} tumors) [30]. The updated absolute difference between treatment arms in RR (primary endpoint) was 23%, with a 57% RR in the *K-RAS*^{WT} subset, versus 34% ($p = .0027$) [31]. Adding cetuximab lowered the risk for progression by 43% in the *K-RAS*^{WT} subset relative to FOLFOX4 alone (median PFS time, 8.3 months versus 7.2 months; HR, 0.57; $p = .064$). The OPUS trial confirmed that adding cetuximab to first-line chemotherapy provided no benefit in terms of the RR and PFS and OS times in patients with *K-RAS*^{MT} tumors. In contrast to the earlier smaller retrospective analyses, *K-RAS* was not determined to be prognostic but only predictive for EGFR inhibition in both the CRYSTAL and OPUS trials.

Final results are available from the COIN trial, comparing the continuous XELOX or FOLFOX arm (arm A) with the investigational arm including cetuximab (arm B) [32]. The patient demographics by biomarker analysis were comparable between the two arms. In patients with *K-RAS*^{WT} tumors, the benefit of cetuximab in the investigational arm was surprisingly not appreciated relative to the control arm both in terms of the OS time (17.9 months versus 17 months; $p = .68$) and the PFS interval (8.6 months versus 8.6 months; $p = .60$). The benefit in terms of the RR was marginally significant (57% versus 49%; $p = .049$) when cetuximab was provided. Grade 3 or 4 toxicities of lethargy ($p < .001$) and diarrhea ($p < .001$) were worse in patients who received cetuximab and notably worse in the patients who received XELOX, resulting in a dose reduction for capecitabine from 1,000 mg/m² to 850 mg/m² twice daily (on days 1–14 every 21 days) in 47% of patients. The COIN study is the first trial that has failed to demonstrate any benefit for the use of cetuximab in treatment-naïve patients with *K-RAS*^{WT} tumors in terms of OS, PFS, or RR.

The predictive value of *K-RAS*^{MT} in the refractory treatment setting was also confirmed by the retrospective analysis of the phase III pivotal trial of cetuximab versus BSC (NCIC-CO.17) [38]. The clinical benefit was significant only in patients with *K-RAS*^{WT} tumors. In 394 evaluable patients, 48% had *K-RAS*^{WT} tumors, with a 60% lower risk for progression, translating into an OS benefit and a 45% lower

risk for death. Again, cetuximab was not effective in patients with *K-RAS*^{MT} tumors.

Panitumumab

Results from a phase III trial comparing panitumumab with BSC alone in 463 patients with refractory mCRC found panitumumab (6 mg/kg every 2 weeks) to lead to a significantly longer PFS time than with BSC (HR, 0.054; 95% CI, 0.44–0.66) [4]. Crossover was allowed: 74% crossed over to panitumumab following progression. This design precluded assessment of the OS benefit. Based on the results of this trial, panitumumab was approved by the FDA for EGFR-expressing mCRC patients who had progressed on fluoropyrimidine-, oxaliplatin-, and irinotecan-containing regimens. In contrast to cetuximab, chemotherapy combinations with panitumumab are historically less established.

The benefit of panitumumab is also concentrated in the *K-RAS*^{WT} population. In the pivotal trial described above, *K-RAS*^{WT} patients (57% of the 427 evaluable patients) had a longer PFS interval (HR, 0.45; 95% CI, 0.34–0.59; $p < .0001$), higher RR (17% versus 0%), and better control rate (51% versus 12%). No differences were observed in the *K-RAS*^{MT} group [39]. Two phase III trials have determined the benefit of panitumumab in combination with chemotherapy relative to chemotherapy alone. The role of *K-RAS* was not established at the time of the creation of either study. However, the final reported results were selected for *K-RAS*^{WT} status as a predictive marker for anti-EGFR therapy in both studies. The Panitumumab Randomized Trial in Combination with Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy (PRIME) was a phase III randomized trial of FOLFOX with or without panitumumab in previously untreated patients [40]. Sixty percent of the patients had *K-RAS*^{WT} tumors. The PFS time was longer in the investigational arm (9.6 months versus 8.0 months; $p = .02$; HR, 0.80; 95% CI, 0.66–0.97). The median OS time had not yet been reached in the investigational arm at the interim analysis ($p = .16$). The role of panitumumab was also investigated in combination with FOLFIRI for second-line treatment [41]. The primary endpoint of a PFS difference (5.9 months versus 3.9 months; $p = .004$) was fulfilled with the addition of panitumumab but the OS endpoint was not met ($p = .12$).

The Potential Impact of *B-RAF* and Other Molecular Markers

Interpretation of the presence of the serine-threonine kinase *B-RAF* V600 mutation (present in 5%–10% of all CRC patients) may further impact the benefit of anti-EGFR therapy [42]. Retrospective analyses suggest that the presence of the *B-RAF* mutation may negate any benefit of anti-EGFR

therapy in a *K-RAS*^{WT} tumor. However, the rarity of the *B-RAF* mutation, which in fact may be in fewer patients than originally thought, may limit its validation for further development. Farina et al. [43] recently reported that the presence of the *B-RAF* mutation may be best used as a prognostic marker in stage III colon cancer patients. Of 213 specimens, the *B-RAF* mutation was detected in 19.5% of patients. After a median follow-up of 47 months, the presence of the *B-RAF* mutation was determined to be an independent prognostic indicator for shorter OS (95% CI, 0.21–.078; $p = 0.006$) and shorter disease-free survival (DFS) (95% CI: 0.34–.094; $p = .28$) times [43].

Other downstream signal transduction pathways that may impact the efficacy of anti-EGFR therapy include the phosphatidylinositol 3' kinase (*PI3K*) mutation, phosphatase and tensin homologue deleted on chromosome ten (*PTEN*) mutation, and the AKT, c-met, hepatocyte growth factor, and insulin-like growth factor receptor pathways [44–49]. Multiple phase I–III clinical trials are ongoing evaluating these novel agents, with a strong emphasis on blood and tissue correlatives to validate promising pre-clinical and early clinical molecular markers.

Combined VEGF and EGFR Blockade

Because anti-VEGF and anti-EGFR agents show acceptable individual toxicity profiles and appear to enhance chemotherapy activity by different biological mechanisms, it is logical to investigate their use in combination. Early pre-clinical trials were promising and indicated cytotoxic activity regardless of the addition of standard chemotherapy [50, 51]. The randomized, phase II BOND-2 trial evaluated cetuximab plus bevacizumab with or without irinotecan in 83 bevacizumab- and cetuximab-naïve patients with irinotecan-refractory mCRC [52]. Remarkably, cetuximab plus bevacizumab produced a 20% RR and an impressive median time to progression (TTP) of 4.9 months, whereas cetuximab plus bevacizumab plus irinotecan produced a 37% RR and 7.3-month median TTP. These results are superior to historical data with cetuximab alone (1.5 months; $p < .01$) or cetuximab plus irinotecan (4.1 months; $p < .01$). The BOND-2 trial was the first demonstration of feasibility, safety, and efficacy of noncytotoxic chemotherapy, albeit in multirefractory and bevacizumab-naïve patients, a population increasingly rare given the wide use of front-line bevacizumab.

However, the strategy of combined biologic therapy has not been successful in the first-line setting. The phase III Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) trial investigated panitumumab added to bevacizumab-containing therapy (FOLFOX, 80%; FOLFIRI, 20%; $n = 1,053$) [53]. Earlier phase II studies had indicated

that panitumumab in combination with irinotecan (IFL, $n = 19$; FOLFIRI, $n = 24$) resulted in grade 3 or 4 diarrhea in 58% and 25% of patients, respectively [54]. Yet rather than expanding to larger phase II studies, investigators believed the results of the BOND-2 trial to be so compelling that the PACCE trial was created and quickly accrued. The PACCE trial resulted in unacceptable toxicities in the investigational arm and no difference in efficacy, leading to study discontinuation.

In a similar fashion, the randomized phase III Capecitabine, Irinotecan, and Oxaliplatin in Advanced Colorectal Cancer (CAIRO)-2 trial investigated bevacizumab (7.5 mg/kg every 3 weeks) plus CapeOX (CB arm) with or without cetuximab (CBC arm; $n = 755$) [55]. The CAIRO-2 study provided a maximum of six cycles of oxaliplatin in both arms with continuation of treatment with capecitabine and bevacizumab with or without cetuximab. The primary endpoint was PFS. The investigators noted no statistical difference in the RR or PFS or OS times in the CAIRO-2 trial following the addition of cetuximab. Stratification by *K-RAS* status showed that the benefit with the addition of either cetuximab or panitumumab to the bevacizumab plus chemotherapy regimens was also absent even in *K-RAS*^{WT} patients, and there was a possible detriment in terms of efficacy and toxicity in the *K-RAS*^{MT} population. Of interest is the relatively long PFS time (10.7 months) in the control arm despite the discontinuation of oxaliplatin following six cycles of treatment. Further analysis of CAIRO-2 indicated that the presence of the *B-RAF* mutation is a prognostic marker [56, 57]. The presence of a *B-RAF*^{MT} versus *B-RAF*^{WT} tumor was an independent indicator of a shorter PFS duration regardless of treatment arm—5.9 months versus 12.2 months ($p = .003$) in the CB arm and 6.6 months versus 10.4 months ($p = .010$) in the CBC arm. *B-RAF* was also an independent prognostic marker for OS irrespective of treatment arm—15.0 months versus 24.6 months in the CB arm ($p = .002$) and 15.2 months versus 21.5 months in the CBC arm ($p = .001$) [57].

In a combined cooperative group trial led by the Cancer and Leukemia Group B (CALGB) and SWOG (the CALGB 80405 trial) physicians were given the choice of using FOLFOX or FOLFIRI before patients were randomized to cetuximab, bevacizumab, or combined biologic therapy [58]. The primary endpoint is OS. A recent amendment required *K-RAS*^{WT} status for eligibility, resulting in the suspension of patient accrual for 6 months. Thus far, no additional toxicities have been noted in the combined biologic arm. However, after reopening the trial to patient accrual, and taking into consideration the results of the PACCE and CAIRO-2 trials, cooperative group members opted to suspend enrollment to the combined biologic arm.

Table 2. Key ongoing phase III studies of cetuximab and bevacizumab in the adjuvant treatment of CRC

Protocol	Disease	Regimen	Status	Target accrual	Primary endpoint
NCCTG-0147	Stage III colon	mFOLFOX6 with or without cetuximab	Closed	2,300	DFS
PETACC-8	Stage III colon	FOLFOX4 with or without cetuximab	Active	2,000	DFS
NSABP C-08	Stage II–III colon	mFOLFOX6 with or without bevacizumab ^a	Completed	2,632	DFS
AVANT (Europe)	Stage II–III colon	FOLFOX4 with or without bevacizumab	Active	3,450 (completed)	DFS
ECOG 5202	Stage II high-risk colon ^b	mFOLFOX6 with or without bevacizumab	Active	3,610	DFS
ECOG 5204	Stage II–III rectal	mFOLFOX6 with or without bevacizumab	Closed	2,100	OS

^aPatients assigned to adjuvant chemotherapy plus bevacizumab received an additional 6 months of single-agent bevacizumab.

^bPatients with low-risk disease recurrence based on microsatellite instability high and retention of chromosome 18q were randomized to a third arm of observation only.

Abbreviations: AVANT, (acronym unavailable); CRC, colorectal cancer; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; FOLFOX, oxaliplatin, 5-fluorouracil, and leucovorin; m, modified; NCCTG, North Central Cancer Treatment Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; OS, overall survival; PETACC, Pan-European Trials in Adjuvant Colon Cancer.

This has since been amended to include only the bevacizumab versus cetuximab-based arms. If completed, the CALGB 80405 trial will provide direct evidence of front-line efficacy of bevacizumab versus cetuximab. However, complexity will arise when the final outcome of this trial is available as a result of the “dealer’s choice” option, the amendment inclusive of only *K-RAS*^{WT} patients, and the closed combined biologic arm, requiring larger patient numbers to establish statistical significance.

EARLY-STAGE DISEASE

Understandably, there is considerable interest in evaluating targeted biologic agents as part of postoperative adjuvant therapy for patients with stage II and stage III disease. To this end, several large, phase III trials have been completed or are ongoing (Table 2). Other than oxaliplatin and 5-FU–based treatment, therapeutic development in the adjuvant setting has been limited.

Bevacizumab

Several major phase III trials have evaluated or are currently evaluating the addition of bevacizumab to adjuvant chemotherapy in patients with stage II and/or stage III colon cancer. The recently completed National Surgical Adjuvant Breast and Bowel Project (NSABP) C-08 trial randomized American Joint Committee on Cancer stage II and stage III patients to modified FOLFOX6 (mFOLFOX6) with or without bevacizumab and included a 6-month continuation period of bevacizumab (5 mg/kg every 2 weeks) therapy

following chemotherapy. This maintenance period was a controversial design aspect, because an advantage for single-agent anti-VEGF maintenance was unproven in CRC patients [59]. Toxicities in that trial were noted to be tolerable. After a median follow-up of 3 years, an overall improvement in DFS could not be established with the addition of bevacizumab for 12 months (HR, 0.89; $p = .15$), regardless of stage [60]. When dissected by year, the investigators suggested that the benefit of bevacizumab was significant in the first year, while bevacizumab was administered (HR, 0.6; $p = .0004$), triggering the hypothesis that bevacizumab should be continued for a greater duration to maintain benefit. Yet the investigators failed to fulfill their primary endpoint. Furthermore, the consideration of continuing single-agent bevacizumab was not clearly defined; the duration of therapy that would be considered appropriate for a small efficacy benefit is unknown. The disappointing results of the NSABP C-08 study require an astute assessment of existing and ongoing trials. The randomized, phase III trial of bevacizumab in stage II and stage III rectal cancer patients (ECOG 5204) closed because of poor patient accrual [61].

The AVANT trial is an international adjuvant trial of stage II and III patients. Patients are randomized to FOLFOX4 with or without bevacizumab or to XELOX plus bevacizumab. Bevacizumab was continued for an additional 6 months in both arms. Accrual to that trial was suspended temporarily in 2006 because of a possibly higher rate of treatment-related morbidity in the XELOX plus be-

vacizumab arm; these concerns were unfounded. Preliminary toxicity results revealed a higher incidence of venous thrombosis events (8.3% versus 5.5%) and a higher incidence of hypertension (10.4% versus 1.1%) [62]. Final efficacy results are pending.

The phase III ECOG E5202 study compared mFOLFOX6 with or without bevacizumab with surveillance in stage II colon cancer patients [63]. Notably, this unique trial is the first created specifically for the controversial stage II patient population for whom adjuvant chemotherapy is considered but not mandated. The ECOG 5202 study is prospectively evaluating the use of molecular markers in planning treatment based on the observation that retention of 18q alleles and microsatellite-high (MSI-H) cancers are associated with a favorable outcome. Thus, patients at high risk (MSI stable and/or with loss of 18q heterozygosity) are randomized into one of two active treatment arms—FOLFOX (6 months) with or without bevacizumab (5 mg/kg every 2 weeks for 12 months)—whereas those with low-risk disease (MSI-H and/or retention of 18q) are assigned to an observation-only third arm. The investigational arm was criticized for not including an observation-only arm, given that the role for adjuvant therapy in a stage II patient is not defined and the significance of the molecular markers MSI-H and 18q were previously evaluated in both stage II and stage III patients. The findings of the NSABP C-08 trial resulted in an immediate amendment to the consent form of the ECOG 5202 trial, requiring investigators to consider whether this trial should be pursued further. Although duplicate trials are not encouraged, the accrual completion of the AVANT study provided impetus for continuing the ECOG 5202 trial. Furthermore, the novel approach in subjecting stage II patients to treatment based on their molecular profile may provide better insight into which patients should be provided adjuvant chemotherapy.

Cetuximab

Two large phase III trials are evaluating the role of cetuximab in the adjuvant setting. The Pan-European Trials in Adjuvant Colon Cancer (PETACC)-8 study is a phase III trial of 12 cycles of FOLFOX4 with or without weekly cetuximab in surgically resected stage III colon cancer patients. The primary endpoint is the 3-year DFS rate, with an accrual goal of 2,000 patients. Patients are to be stratified by tumor (T) stage, T₁₋₃ versus T₄, and node (N) stage, N₁ versus N₂. A 23% lower risk for disease recurrence or death (HR, 0.771) is expected between the two treatment arms of the trial, resulting in an absolute gain of 5.6% in the DFS rate—72.2% for the control arm and 77.8% for the treatment arm [64]. The N0147 study is a phase III U.S. trial

that was originally a six-arm trial including adjuvant irinotecan in four arms and was subsequently revised to a two-arm trial of mFOLFOX6 with or without weekly cetuximab. The primary endpoint was the 3-year DFS rate, with an expected accrual of 3,768 patients. Patients were to be substratified by T stage, node stage (N₁ versus N₂), and high versus low histology. Following the impact of *K-RAS* status and the efficacy of anti-EGFR therapy, the PETACC-8 and N0147 trials were temporarily amended to include only patients with *K-RAS*^{WT} tumors. Both trials have resumed patient enrollment. However, a recent notification from the NCCTG following a preplanned interim analysis noted that the trial failed to meet the primary goal of a higher 3-year DFS rate with the addition of cetuximab. That trial is now closed to accrual (Cancer Trials Support Unit, CTSU, monthly update, November 25, 2009). Additionally, there were some initial concerns that the addition of cetuximab to FOLFOX may have been harmful, particularly in elderly patients (aged ≥70 years). It is presumed that the PETACC-8 trial will follow suit. At this time, there is no established role for biologic agents in the adjuvant treatment of colon cancer patients outside a clinical trial.

PHARMACOECONOMIC CONSIDERATIONS

Biologic therapy is an essential component in the treatment landscape of CRC; however, there is a legitimate concern that the financial burden may be disproportionate to the benefit gained, warranting rigorous cost–benefit studies. Pharmacoeconomic studies looking at health care systems in Europe and Japan have demonstrated that the cost per life-year gained with biologics is relatively high, compared with other interventions [65–70]. But their findings have led to conflicting recommendations for biologics. Adding to the complexity is the fact that these studies were conducted prior to the incorporation of predictive biomarkers into clinical practice. Given the concerns about impending U.S. health care reform, cost–benefit studies that include biologic therapies are expected to be an integral component of clinical trials. A companion study to the CALGB 80405 trial surveyed participants about insurance status, cost concerns, and strategies they used to cope with expenses [71]. Patients (*n* = 409) were interviewed at baseline and at 3 months. Fifteen percent of the patients did not have insurance coverage, only 12% discussed cost with their treating physician, 3% purposefully took less drug than prescribed, and 1% sought patient assistance programs. One recent analysis created a hypothetical Markov model for an average male (age, 70 years; body surface area, 1.9 m²) taking into account nine possible treatment regimens [72]. The incremental cost-effectiveness ratio (ICER) with the addition

of biologic therapy was \$170,000 per discounted life-year. The ICER was dependent on sequential lines of therapy rather than any one therapy, with the length of the first-line therapy having the greatest impact for any patient. This amount does not take into account direct drug cost, but is based on the averages sales price provided by the Centers for Medicare and Medicaid Services. With the observational BRiTE trial reporting one of the longest median OS times to date, consideration of cost-effectiveness and benefit must be considered.

Taking into account the field of “personalized medicine” with a focus on molecular markers and underlying tumor biology, a hypothetical economic analysis evaluated *K-RAS* testing and the use of cetuximab. It postulated that, for all patients diagnosed with metastatic disease, *K-RAS* testing would cost \$13 million (\$452/patient) [73]. Taking into account the price of cetuximab and the presumed average duration of therapy in a treatment-naïve patient, the savings with *K-RAS* testing may be as high as \$753 million, resulting in a net \$740 million saving. Although these financial benefits to *K-RAS* testing are impressive, it is important to keep in mind that this analysis is hypothetical, not a prospective pharmacoeconomic model.

The American Society of Clinical Oncology recently created the Cost of Care Task Force to help address these issues. The primary objectives of this committee are to improve prevention, diagnosis, and treatment, eliminate health disparities in cancer care by reinforcing evidence-based medicine, and improve cost-effectiveness for patients and their practitioners. The Cost of Care Task Force recently released a guidance statement emphasizing the intent of this initiative: the importance of physician–patient discussion regarding the cost of care, the creation of educational and supportive tools for providers to enhance effective communication about the cost of care, and in turn, the creation of decision-making tools to allow patients to make informed educated decisions about their treatment [74].

CONCLUSIONS

Earlier this decade, significant modifications developed in the treatment of mCRC. Given the low threshold of efficacy held by 5-FU for several decades, any promising phase II data culminated in early presumptions of efficacy as noted by the global acceptance of FOLFOX plus bevacizumab in treatment-naïve patients and the creation of the phase III PACCE trial.

Although some would state that the therapeutic landscape in the treatment of CRC may appear stagnant, in fact, our current knowledge base of FDA-approved agents is advancing. Biologics are beneficial but may be best suited to a select patient population. In the absence of predictive markers, bevacizumab will continue to be widely used but cannot be advocated in the adjuvant setting. Following one failed adjuvant trial, pending results from a second, and continued accrual in a third, exploration of predictive biomarkers for bevacizumab are sorely needed.

When considering anti-EGFR therapy, *K-RAS* status has a predictive impact on efficacy and toxicity, which in turn may be further compromised by the presence of the *B-RAF* mutation. The *B-RAF* mutation appears to be prognostic in both the early- and late-stating setting. Disappointingly, the role of cetuximab in the adjuvant setting cannot currently be justified. The combination of anti-VEGF and anti-EGFR agents is not beneficial in the front-line setting, even in the presence of *K-RAS*^{WT} tumors. It is unlikely that the combined biologic therapy of anti-VEGF and anti-EGFR therapy will continue to be investigated following the negative results of the PACCE and CAIRO-2 trials and the recent amendment the CALGB 80405 trial.

The standards for treating CRC patients will continue to evolve in the coming years as new data on biologic agents emerge. Research efforts focusing on additional biomarkers will refine our ability to use these agents specifically in patient populations that derive a meaningful benefit. With looming concerns about health care costs, it is also critical to create a pharmacoeconomic framework guiding the clinical use of these agents.

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