

Cetuximab in the Treatment of Colorectal Cancer

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Abstract

Currently there are a number of approved treatments for metastatic colorectal cancer in both the first-line and second-line setting. Although single agents such as 5-fluorouracil, capecitabine, oxaliplatin, and irinotecan show some efficacy in advanced disease, the most recent data indicate that 2- and 3-drug combinations result in better response rates and longer overall survival. In addition to the approved chemotherapeutics, there are a number of biologic-based treatments approved and in development for the treatment of colorectal cancer, including monoclonal antibodies and small molecule inhibitors. Monoclonal antibodies directed against the epidermal growth factor receptor or vascular endothelial growth factor have proven to be safe and effective in the treatment of colorectal cancer. Clinical trials evaluating these agents in the first-line and second-line setting have provided compelling data on which to base treatment decisions. Clinicians now have a wide array of approved treatments from which to choose, a decision often complicated by the relative lack of data combining the chemotherapeutic and biologic agents in specific disease settings. A number of ongoing prospective studies will address remaining issues in the next few years. Until then, clinicians must use the available study data on efficacy and toxicity to guide individualized choices for patients with advanced-stage colorectal cancer.

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Statement of Need

Colorectal cancer is the third most common cancer worldwide, and is associated with a survival rate of 50% worldwide and 66% in the United States. Several chemotherapeutic regimens have been evaluated over the past several decades and overall survival rates for patients with advanced disease may now reach approximately 21 months. Studies are ongoing to identify more effective regimens using combinations of 2 and 3 drugs. Combining novel agents with chemotherapeutic regimens is proving to be an effective advance in the treatment of this disease in both the first- and second-line settings. With several recently completed clinical trials and several ongoing and planned studies, it is essential that physicians treating colorectal cancer patients continue to update their practices according to the most recent findings. Two monoclonal antibodies—one targeting the epidermal growth factor receptor and another targeting vascular epidermal growth factor—have been approved for the treatment of colorectal cancer. The optimal setting and combination for these agents continues to be elucidated. This monograph presents the most current data on chemotherapeutic regimens, monoclonal antibodies, and the combination of both in the treatment of colorectal cancer.

Target Audience

This publication is specifically designed for practicing clinicians, medical oncologists, and radiation oncologists who wish to review and update their knowledge of treating colorectal cancer.

Educational Objectives

Upon completion of this activity, participants should be able to:

1. Discuss the options for the first-line treatment of advanced colorectal cancer.
2. Discuss the options for the second-line and adjuvant treatment of advanced colorectal cancer.
3. Discuss the safety and efficacy of monoclonal antibodies alone and in combination with chemotherapy in the treatment of colorectal cancer.

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Keywords

Colorectal cancer, monoclonal antibodies, chemotherapy

Pre-Test

1. What are the currently approved regimens for the first-line treatment of advanced colorectal cancer?
2. What are the currently approved regimens for the second-line and adjuvant treatment of advanced colorectal cancer?
3. What have clinical trials shown about the safety and efficacy of monoclonal antibodies, either alone or in combination with chemotherapy, for the treatment of advanced colorectal cancer?

Historical Perspective on the Treatment of Colorectal Cancer and EGFR as a Therapeutic Target



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Demographics

Colorectal cancer (CRC) is the third most common cancer worldwide. In 2004, 150,000 new cases are anticipated in the United States, and 800,000 are anticipated throughout the world. Currently, there are approximately 1.2 million Americans who are living with CRC. CRC is also the second deadliest cancer. The survival rate worldwide is about 50%, with an estimated 400,000 deaths expected in 2004; however, the US survival rate is 66%, for an estimated 57,000 deaths in 2004.^{1,2} The incidence of this disease increases with age. The highest incidence is in the 70- to 80-year age group, in which complicating comorbid diseases are common. Therefore, one of most important issues in the management of CRC is how to best care for this age group.

Approved Therapeutic Agents and Combinations

The American Society of Clinical Oncology (ASCO) has released new guidelines for the use of adjuvant therapy in stage II colon cancer.³ The guidelines note that routine adjuvant therapy for stage II patients does not confer a statistically significant survival benefit, and therefore decisions about adjuvant therapy use should be made on a case-by-case basis.

For stage III disease, there is clear evidence that the cure rate increases by approximately 35% with adjuvant therapy. Until recently, the standard treatment was 5-fluorouracil (5-FU) and leucovorin (LV). However, data from the Multicenter International Study of Oxaliplatin/5-FU/LV in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial,⁴ which compared infusional 5-FU/LV with oxaliplatin plus infusional 5-FU/LV (FOLFOX) for adjuvant therapy, indicate that 3-year disease-free survival is increased from 73% to 78% with the addition of oxaliplatin to 5-FU/LV. Patients undergoing treatment with FOLFOX had an increased incidence of grade 3 sensory neuropathy (12.4% during treatment, decreasing to 1.1% at 1-year follow-up). The death rate was 0.5% for both treatment arms.

With respect to advanced disease, clinical trials of various agents as monotherapy have shown response rates of 10–25% and a median overall survival (OS) of 12–14 months. However, an increase in OS to approximately 21 months can be achieved by combining 2 drugs.

In January 2004, data from the North Central Cancer Treatment Group clinical trial N9741 were published.⁵ This study compared irinotecan plus bolus 5-FU/LV (IFL), FOLFOX4 (oxaliplatin 85 mg/m² day 1, LV 200 mg/m² days 1 and 2, 5-FU 400 mg/m² bolus plus 600 mg/m² infusion over 22 hours, days 1 and 2, repeated every 2 weeks), and irinotecan/oxaliplatin (IROX). The median time to progression (TTP) was significantly longer for FOLFOX4

(8.7 months) than it was for IFL (6.9 months) or IROX (6.5 months; $P=.0014$ and $.001$, respectively). The median OS for FOLFOX4 (19.5 months) was significantly longer than for IFL (15.0 months; $P=.0001$) and IROX (17.4 months; $P=.04$). FOLFOX4 also conferred an improved response rate (RR) of 45%, versus 31% for IFL ($P=.002$) or 35% for IROX ($P=.03$). FOLFOX4 was the most favorable regimen in regard to grade 3/4 toxicity. The most common adverse events (AEs) in the IFL, FOLFOX4, and IROX arms, respectively, were nausea (16%, 6%, 19%), vomiting (14%, 3%, 22%), diarrhea (28%, 12%, 24%), neutropenia (40%, 50%, 36%), febrile neutropenia (15%, 4%, 11%), paresthesias (3%, 18%, 7%), and dehydration (9%, 4%, 6%). This study led to the approval of FOLFOX4 as a first-line therapy for CRC.

However, infusion-based 5-FU/LV plus irinotecan (FOLFIRI) treatment does seem to compare favorably with FOLFOX. A study conducted by Tournigand et al⁶ comparing FOLFIRI followed by FOLFOX after progression and vice versa found no significant difference in RR (56% vs 54%), median second progression-free survival (14.2 months vs 10.9 months) or OS (21.5 months vs 20.6 months) between the 2 treatment arms. The toxicity profiles differed, with grade 3/4 mucositis, nausea/vomiting, and grade 2 alopecia the most common AE in the first-line FOLFIRI group, and grade 3/4 neutropenia and neurosensory toxicity most common in the first-line FOLFOX group.

Monoclonal Antibodies in the Treatment of Colorectal Cancer

One interesting new area of research is the use of monoclonal antibodies either to the vascular endothelial growth factor (VEGF) or to the epidermal growth factor receptor (EGFR). A member of the ErbB family of receptors, EGFR regulates intracellular tyrosine kinase activity. Interruption of this signaling pathway can help to regulate the abnormal cell differentiation, proliferation, migration, angiogenesis, and apoptotic factors that are conferred by its upregulation in metastatic cancer cells. Clinically, upregulation is determined by immunohistochemistry to assess EGFR positivity. There is evidence that upregulation of EGFR is present in 60–80% of CRC cases.⁷

On the basis of 2 phase II clinical trials, cetuximab, an anti-EGFR monoclonal antibody, was recently approved as a second-line therapy for CRC patients refractory to irinotecan. The first study, conducted by Cunningham et al,⁸ found that adding cetuximab to irinotecan for patients with metastatic, irinotecan-refractory CRC resulted in a longer TTP, a higher RR, and better OS than was seen with cetuximab alone. The second study, conducted by Saltz et al,⁹

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Phase II Trials of Cetuximab as a Single Agent and in Combination With Chemotherapy



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Cetuximab Plus Irinotecan

Two phase II studies have examined the efficacy of cetuximab in combination with chemotherapeutics. The first study, presented by Saltz et al¹ at the 2001 ASCO meeting, included 121 patients with irinotecan-refractory metastatic CRC whose tumors were EGFR positive as assessed by immunohistochemistry. Patients received a 400 mg/m² cetuximab loading dose followed by 250 mg/m² weekly, while continuing irinotecan at the same dose and schedule on which they had previously progressed. Seventeen percent of patients achieved a partial response (PR), and an additional 31% had stable disease (SD) or a minor response (MR). The most common AEs attributable to cetuximab were allergic reactions (2% grade 3; 1% grade 4), all of which could be managed, and an acne-like skin rash (53% grades 1/2; 8% grade 3). This study presented the first large data set on the use of cetuximab in combination with irinotecan chemotherapy. While therapy was effective and reasonably well tolerated, it must also be noted that these patients had already proven their ability to tolerate irinotecan.

In a second study by Cunningham and colleagues,² 329 EGFR-positive patients whose disease had progressed during treatment or within 3 months after treatment with an irinotecan-based regimen were randomized to receive either cetuximab and irinotecan (at the prestudy dose and schedule) or cetuximab monotherapy. The cetuximab/irinotecan combination group had a significantly higher RR (22.9% vs 10.8%; $P=.007$) and longer TTP (4.1 months vs 1.5 months; $P<.001$) than did the cetuximab-only group. There was no significant difference in median survival between the 2 groups (8.6 months vs 6.9 months; $P=.48$); however, this study was not well powered to detect such a difference, due to the advanced nature of the disease and the heavy pretreatment of many patients, some of whom had already failed both irinotecan as well as oxaliplatin combinations. Toxic effects were more frequent in the combination-therapy group, but their severity and incidence were similar to those that would be expected with irinotecan alone. The most common grade 3/4 AEs for the combination group and the cetuximab-only group, respectively, were diarrhea (21.2% vs 1.7%), asthenia (13.7% vs 10.4%), acne-like rash (9.4% vs 5.2%), neutropenia (9.5% vs 0%), and nausea/vomiting (7.1% vs 4.3%).

Both studies demonstrated a response rate of approximately 20% with cetuximab/irinotecan therapy. These findings led to the approval of cetuximab as a second-line therapy in combination with irinotecan in patients with irinotecan-refractory metastatic CRC.

Cetuximab as a Monotherapeutic Agent

Cetuximab has recently been investigated by Saltz and colleagues³ as a monotherapeutic agent in EGFR-positive patients with

irinotecan-refractory metastatic CRC. For this phase II study, patients were required to have failed an irinotecan-based regimen. Fifty-seven patients received a loading dose of 400 mg/m² intravenous cetuximab over 2 hours. Subsequent weekly treatments were given at a dose of 250 mg/m² over 1 hour. Nine percent of patients achieved a PR, and an additional 36.8% had SD or MR on this regimen. The median OS for the study was 6.4 months. Cetuximab was well tolerated as a single agent. Common AEs included an acne-like skin rash (86% with any grade; 18% with grade 3), and a composite of asthenia, fatigue, malaise, or lethargy (56% any grade; 9% grade 3). A grade 3 allergic reaction requiring discontinuation of study treatment occurred rarely (3.5%). One additional patient experienced a grade 3 allergic reaction that resolved. These data indicate that cetuximab is safe and efficacious as a second-line single agent in advanced CRC. Single-agent cetuximab has been approved for CRC patients who can no longer tolerate irinotecan.

Cetuximab Plus FOLFIRI

Preliminary phase II data for the safety and efficacy of cetuximab plus FOLFIRI as first-line treatment for metastatic CRC were presented at the 2004 ASCO annual meeting.⁴ Twenty-three patients with EGFR-positive CRC received cetuximab at an initial dose of 400 mg/m², followed by 250 mg/m² weekly. Patients also received FOLFIRI every 2 weeks in either a low dose (10 patients) or a high dose (13 patients). Of the 22 patients that were evaluable for efficacy, 46% exhibited a PR, another 41% had SD, and the median TTP was 10.9 months. Three cases of dose-limiting toxicity occurred in the high-dose group (grade 3 diarrhea; grade 3 allergy; grade 4 neutropenia). An additional 29 patients were later enrolled in the high-dose group. Among the 42 patients in the high-dose group, the most common grade 3/4 AEs were diarrhea (14.3%), neutropenia (11.9%), rash (11.9%), and nausea/vomiting (9.5%). An acne-like rash was seen in 59.6% of patients (4.8% grade 3; 0% grade 4).

Cetuximab Plus FOLFOX

As with cetuximab and FOLFIRI, the available data for cetuximab in combination with FOLFOX is preliminary. Tabernero et al⁵ reported phase II data for the use of cetuximab/FOLFOX in the first-line treatment of EGFR-positive metastatic CRC at the 2004 ASCO annual meeting. In this study, 43 patients received a loading dose of cetuximab (400 mg/m²) followed by 250 mg/m² weekly thereafter, plus FOLFOX4. This regimen was continued until disease progression or unacceptable toxicity was seen. None of the patients had received previous chemotherapy for metastatic CRC. Of the

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Phase III Trials of Cetuximab and Future Research Directions



Richard L. Schilsky, MD

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Cetuximab as a Second-Line Therapy

Although cetuximab is approved for use alone or in combination with irinotecan for patients with irinotecan-refractory advanced CRC, it has not been tested for patients who have previously failed oxaliplatin-based regimens, nor has it been tested in combination with FOLFOX. Currently there are 2 phase III trials in progress that will address these issues. The first is enrolling patients who have EGFR-positive metastatic CRC, have failed a 5-FU/oxaliplatin regimen, and have been exposed to irinotecan (personal communication, September 2004). Patients are being randomized to receive either 350 mg/m² irinotecan every 3 weeks or a combination of 350 mg/m² irinotecan every 3 weeks plus cetuximab (400 mg/m² loading dose followed by 250 mg/m² weekly). Therapy is to be continued until disease progression or unacceptable toxicity.

The second trial requires patients to have EGFR-positive metastatic CRC, to have failed an irinotecan regimen, and not to have undergone prior oxaliplatin therapy (personal communication, September 2004). These patients are being randomized to receive either FOLFOX4 or FOLFOX4 plus cetuximab (400 mg/m² loading dose followed by 250 mg/m² weekly). Treatment will continue until disease progression or unacceptable toxicity. Badarinarath and colleagues¹ presented pooled safety data at the 2004 ASCO annual meeting for 38 of the first 40 patients accrued in this trial. The median number of treatment cycles was 3. The most common AEs were asthenia (66%; 8% grade 3/4), neuropathy (66%; 0% grade 3/4), diarrhea (55%; 5% grade 3/4), nausea (71%; 3% grade 3/4), vomiting (42%; 5% grade 3/4), and skin toxicity (55%; 3% grade 3/4). There was 1 severe nonfatal hypersensitivity reaction. These preliminary data indicate toxicity rates in line with expectations for either cetuximab alone or FOLFOX alone. This trial continues to accrue to its target of 1,100 patients.

Cetuximab as a First-Line Therapy

The ongoing Cancer and Leukemia Group B (CALGB) clinical trial 80203 is evaluating cetuximab in a first-line setting.² This trial was designed with a 2-by-2 factorial design in order to evaluate whether or not FOLFIRI and FOLFOX are equivalent in their efficacy as chemotherapy regimens, as well as to ask if the addition of cetuximab to either chemotherapy results in an improvement in OS. The initial goal was to randomize 2,200 patients with metastatic CRC to receive FOLFIRI, FOLFIRI/cetuximab, FOLFOX, or FOLFOX/cetuximab; however, this trial is undergoing design revisions, due to the recent availability of bevacizumab and its indication as a first-line agent. It seems likely that the final trial will compare chemotherapy plus cetuximab with chemotherapy plus bevacizumab or chemotherapy with both antibodies.

Cetuximab as an Adjuvant Therapy

The GI Intergroup is conducting a randomized phase III clinical trial to examine the efficacy of various chemotherapeutics with and without cetuximab in the adjuvant setting for colon cancer.³ Patients in this study must have undergone a curative resection of stage III colon cancer, must not have metastases, and must not have been exposed previously to chemotherapy or biologics. Eligible patients will be randomized into 1 of 6 arms: 12 cycles of FOLFOX with or without cetuximab, 12 cycles of FOLFIRI with or without cetuximab, or 6 cycles of FOLFOX followed by 6 cycles of FOLFIRI, with or without cetuximab. This study is continuing to enroll patients, with a targeted accrual of 4,800 patients.

Alternative Administration Strategies

There has been an interest in exploring ways to reduce the toxicity of chemotherapeutic regimens, especially those containing oxaliplatin, while still maintaining a response. Biologic therapy could play an important role in this process. De Gramont et al⁴ presented data at the 2004 ASCO annual meeting from a phase III trial in metastatic CRC that successfully used an interruption strategy to maintain a response on oxaliplatin-based therapy while reducing toxicity. The next trial in this series will examine the usefulness of a biologic agent in maintaining a longer response in the absence of oxaliplatin.

Future Research Directions

Improved understanding of the mechanisms by which biologic agents interact with chemotherapy at the cellular level is needed in order to determine the optimal combination and schedule for their use. These questions might best be approached first in the laboratory. Such studies would guide future clinical trial design, so that the preferred standard of care for each stage of the disease can be identified.

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evaluated the effect of cetuximab monotherapy in patients with irinotecan-refractory CRC whose tumors overexpressed the EGFR. They found that 9% of these patients achieved a partial response. In both studies, the cetuximab regimen was reasonably well tolerated. Dr. Alan Venook shall explore these studies in more detail later in this monograph.

Bevacizumab, a monoclonal antibody against VEGF, has also shown efficacy in the treatment of metastatic CRC. Hurwitz et al¹⁰ found that the addition of 5 mg/kg bevacizumab to IFL every 2 weeks resulted in a significantly higher RR (44.8% vs 34.8%), longer TTP (10.6 months vs 6.2 months), and longer OS (20.3 months vs 15.6 months) than was seen with IFL plus placebo. Grade 3 hypertension was more common with IFL plus bevacizumab but was easily managed. It is important to note that, based on clinical trials comparing various chemotherapeutic regimens, IFL is no longer considered an option for the first-line treatment of CRC. However, bevacizumab has been approved for use in combination with intravenous 5-FU-based chemotherapy for first-line treatment of metastatic CRC. Other anti-EGFR targeted approaches currently being evaluated for the treatment of advanced CRC include several tyrosine kinase inhibitors, such as erlotinib and gefitinib. Clinical trials of these agents in this disease setting are ongoing.

In summary, 5 different drugs are now approved for the treatment of advanced CRC, and the clinical evidence suggests that giving the drugs in doublets is the best strategy. However, the best reported median survival for any treatment is just over 20 months, and it is unclear if any patients are cured by virtue of treatment for advanced disease. Long-term follow-up on the current studies will be necessary to address that question. There is limited data on the use of 3 drugs together; therefore, additional studies evaluating the combination of anti-VEGF and anti-EGFR novel agents with chemotherapeutic regimens are needed.

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20 patients who could be evaluated, 70% achieved a PR, and 25% had SD. Two patients underwent curative resection of their hepatic metastasis after a confirmed response. Eight serious AEs were observed (4 5-FU-related diarrhea, 1 pulmonary embolism, 1 pneumonia, 1 progressive disease with obstructive jaundice, 1 gout), but none of them were attributable to cetuximab.

Evaluation of Adverse Events

Cetuximab is reasonably well tolerated and has a low toxicity profile. The most common AE seen in the above trials was an acne-like rash. As many as 70–80% of patients who are treated with cetuximab will develop a skin rash that resembles acne, mostly on the face and the upper chest. One of the most provocative observations is the possibility that patients who develop the worst rash are the likeliest to benefit from cetuximab. This interesting correlate has been noted in all of the studies, but prospective studies will be needed to confirm this observation. One very rare AE associated with cetuximab is anaphylaxis. As with any monoclonal antibody therapy, the possibility always exists for a small number of patients to experience respiratory arrest. Therefore, it is a matter of prudence for practicing physicians to be prepared for this when a patient is receiving cetuximab therapy.

In summary, the available phase II trial data indicate that cetuximab has activity in EGFR-expressing metastatic CRC, both alone and in combination with chemotherapeutic regimens. Currently, cetuximab is approved for use as a second-line treatment in combination with irinotecan in patients with advanced irinotecan-refractory cancer or as monotherapy in patients intolerant of irinotecan. Preliminary data suggest that cetuximab is safe and effective as first-line therapy in combination with FOLFIRI or FOLFOX. Further studies will be needed to verify these results.

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QUESTION & ANSWER FORUM

Based on recent trials, what might be the appropriate first-line therapy for metastatic CRC patients?

Dr. Richard Goldberg: The available data indicate that single-agent therapy should not be used in most patients with advanced disease. Both FOLFOX and FOLFIRI are good choices for combination therapy. The place of the biologics, either cetuximab or bevacizumab, in first-line therapy is still a matter of some debate. While clearly the study reported by Hurwitz et al¹ showed striking activity for bevacizumab, this agent was evaluated in combination with IFL, which is no longer considered the standard first-line treatment. Currently there are no phase III data on the combination of bevacizumab or cetuximab with oxaliplatin, although such studies are ongoing. Based on laboratory experiments and preliminary phase II data, I believe that we will find both cetuximab and bevacizumab as active or nearly as active with oxaliplatin-based regimens as they are with irinotecan-based regimens. However, at this point the options have outpaced our evidence, and physicians may have to make a clinical judgment as to what is the best initial therapy.

Dr. Richard Schilsky: This is a complex issue because there are still major gaps in our knowledge. Data reported by Tournigand et al² indicated that FOLFIRI and FOLFOX are equally effective, regardless of which is given first. The efficacy of bevacizumab has been demonstrated in the first-line setting with an irinotecan-based regimen. Taking these 2 findings into consideration, FOLFIRI plus bevacizumab may be a reasonable choice in the first-line. This treatment could be followed by FOLFOX, which is known to be effective in the second-line setting, or irinotecan plus cetuximab, which has also been shown to be an effective second-line treatment in irinotecan-refractory patients.

What is the utility of testing patients for EGFR over-expression before treating with cetuximab?

Dr. Alan Venook: A confounding finding has been the apparent absence of correlation between EGFR staining intensity and response to cetuximab therapy. All of the phase II studies have mandated that patients' tumors be EGFR positive by immunohistochemistry, yet all of these studies found no correlation between the degree of positivity and patients' response. Anecdotally, many people have observed classic responses to cetuximab in patients whose tumors appear to be EGFR negative. The question of whether we should be doing EGFR staining remains. Does EGFR staining enable identification of a group of patients who are more likely to benefit from cetuximab, or does it lead to the potential exclusion of patients who might benefit? Immunohistochemistry is probably not a good predictor for who will or will not respond to cetuximab, but prospective studies are needed to answer these questions.

RS: The FDA-approved immunohistochemistry kit for EGFR testing determines positivity on a 1+ to 3+ scale. However, there are various commercial pathology laboratories that consider specimens with 1+ staining to be negative for overexpression. In the package insert for cetuximab, a 1+ staining would be considered to be suf-

ficient to justify treating the patient. The lesson to be learned here is that different laboratories interpret tests in different ways, and it is important to read laboratory results carefully.

RG: Atkins and colleagues³ found that the tissue fixative used on a sample can influence the results of EGFR immunohistochemistry. Some patients who had their studies done on tissue that was fixed 2 or more years ago may have had false-negative results. The authors recommended retesting if the initial result is negative.

Are physicians considering alternative trial designs to obtain data in a shorter time span?

AV: The gold standard for determining the efficacy of a treatment regimen has been OS. As patients live longer and as we have more effective therapies for second- or even third-line treatments, it may become difficult and time-consuming to demonstrate such a survival advantage with a certain treatment. Physicians are beginning to consider alternative endpoints. Progression-free survival may serve as an endpoint that yields enough information to have a drug approved, to move it into evaluation as a first-line therapy, or to use it in another setting. Adjuvant studies have provided convincing evidence that 3-year disease-free survival is sufficient to determine the efficacy of a regimen in CRC, rather than waiting for OS at 5 years. Another alternative is to select subsets of patients, such as high-risk stage III patients, who will do much more poorly than the average-risk stage III patient. In this case, it may take fewer patients to see the benefit or lack of benefit of a therapy.

RG: Currently we are looking for small incremental advances, which require very large and time-consuming randomized clinical trials to allow detection of small improvements with a high degree of statistical confidence. It will not be possible to rapidly race through a series of phase III trials to test all combinations and permutations of possible therapies and come up with standards of care in the near future. It may be that some uncertainties will persist for decades to come. However, such uncertainty is both a blessing and a curse. It is a blessing because the physician can exploit clinical hunches and design interesting trials to confirm those hunches. It also means that physicians have several choices to offer patients. However, it is not as easy to be assured that one treatment algorithm is the right answer for every patient. In the foreseeable future, physicians will be faced with making individualized therapy plans on a patient-by-patient basis in a manner that we did not have to confront when treatment choices were limited, but I would say that is a sign of success.

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FOLFOX4 + Cetuximab

- FOLFOX4 + cetuximab 400 mg/m² loading then 250 mg/m² per week
- 70% partial response in 25 evaluable patients
- 2 curative resections
- Most common adverse events: diarrhea, neutropenia

FOLFOX4: Irinotecan 85 mg/m² d 1, leucovorin 200 mg/m² d 1 and 2, 5-Fluorouracil 400 mg/m² bolus plus 600 mg/m² 22-hr continuous infusion, d 1 and 2, q2w.

Tabernero et al. / J Clin Oncol 2004.

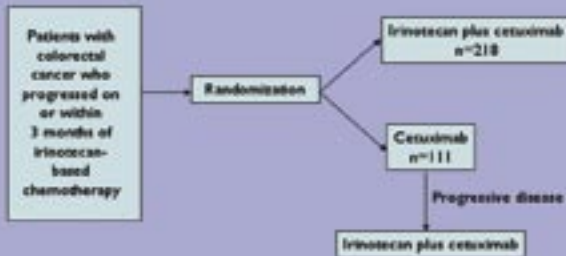
Cetuximab + Irinotecan in Irinotecan-Refractory Advanced Colorectal Cancer (N=120)

Response Data

- Partial response: 27 (22.5%; 95% confidence interval: 15–31%)
- Stable disease: 9 (7.5%; minimum 12 weeks)
- Median duration of response (n=27): 186 days

Sato et al. Proc Am Soc Clin Oncol 2001; Abstract 7.

Randomized Phase III Trial of Cetuximab vs Cetuximab Plus Irinotecan for Advanced Colorectal Cancer: Study Design



Cunningham et al. N Engl J Med 2004.

Randomized Phase III Trial of Cetuximab vs Cetuximab Plus Irinotecan for Advanced Colorectal Cancer

Response Data

	Cetuximab (n=111)	Cetuximab + Irinotecan (n=218)	P value
Partial response	10.8%	22.9%	.0074
Time to progression	1.5 mo	4.1 mo	<.0001
Overall survival	6.9 mo	8.6 mo	Not significant

Cunningham et al. N Engl J Med 2004.

GI Intergroup Phase III Randomized Clinical Trial: Adjuvant Chemotherapy With or Without Cetuximab for Stage III Colon Cancer

Study Arms

1. FOLFOX with cetuximab (12 cycles)
2. FOLFOX without cetuximab (12 cycles)
3. FOLRR1 with cetuximab (12 cycles)
4. FOLRR1 without cetuximab (12 cycles)
5. FOLFOX (6 cycles) followed by FOLRR1 (6 cycles) with cetuximab
6. FOLFOX (6 cycles) followed by FOLRR1 (6 cycles) without cetuximab

Targeted accrual: 4,800 patients

FOLFOX: Irinotecan 5-Fluorouracil/Leucovorin plus oxaliplatin. FOLRR1: Irinotecan 5-Fluorouracil/Leucovorin plus irinotecan.

First-Line Therapy for Metastatic Colorectal Cancer

Treatment Considerations

- Single-agent therapy with most agents should not be used for the treatment of advanced disease
- FOLRR1 and FOLFOX are good choices for combination therapy
- Bevacizumab plus IFL is active, but IFL is no longer the standard of care for first-line therapy
- No data yet on cetuximab or bevacizumab with oxaliplatin; studies are ongoing
- Cetuximab and bevacizumab are likely to be as active with oxaliplatin as they are with irinotecan
- Best choice may depend on clinical judgment until more evidence is available

FOLRR1: Irinotecan 5-Fluorouracil/Leucovorin plus irinotecan. FOLFOX: Irinotecan 5-Fluorouracil/Leucovorin plus oxaliplatin. IFL: Irinotecan plus 5-Fluorouracil/Leucovorin.

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Cetuximab in the Treatment of Colorectal Cancer

CME Post-Test *Circle the correct answer for each question below:*

- In advanced CRC, FOLFOX:
 - Is more effective than IFL in the first-line setting
 - Is more effective than FOLFIRI in the first-line setting
 - Has grade 3/4 mucositis and nausea/vomiting as common AEs
 - Is associated with an OS of 10–14 months
- EGFR:
 - Is downregulated in 60–80% of CRC cases
 - Is the target of bevacizumab
 - Regulates intracellular tyrosine kinase activity
 - Does not play a role in the migration and proliferation of metastatic colorectal cancer cells
- Bevacizumab:
 - Has not been approved for first-line treatment of advanced colorectal cancer
 - Has been shown to be more active with FOLFOX than with FOLFIRI
 - Is an EGFR inhibitor
 - Confers a higher response rate and OS when added to IFL
- Cetuximab has been tested in which of the following phase II trials for CRC:
 - In combination with irinotecan in patients with irinotecan-refractory disease
 - As a monotherapy in patients with irinotecan-refractory disease
 - In combination with FOLFIRI as a first-line treatment for advanced disease
 - All of the above
- In preliminary data from phase III trials of cetuximab presented by Badarinath et al at the 2004 ASCO meeting, the most common AE was:
 - Nausea
 - Diarrhea
 - Neutropenia
 - Fatigue
- Which of the following trials is continuing to accrue patients?
 - CALGB 80203
 - MOSAIC
 - N9741
 - None of the above
- The bevacizumab clinical trial reported by Hurwitz et al:
 - Tested bevacizumab in combination with FOLFIRI
 - Led to the approval of bevacizumab in the second-line setting
 - Found that bevacizumab plus IFL was more effective than IFL in the first-line setting
 - Found that bevacizumab causes grade 3 nausea at a higher rate than placebo
- Cetuximab:
 - Is approved for use as a second-line monotherapy in certain cases
 - Can often cause grade 3/4 diarrhea
 - Targets VEGF
 - Should be used as adjuvant therapy
- EGFR immunohistochemistry testing:
 - Is the best way to predict response to cetuximab
 - Should be repeated if the test sample is older than 2 years
 - Is not affected by the choice of tissue fixative
 - Is the best way to predict a response to FOLFIRI
- In a study comparing FOLFOX with FOLFIRI for CRC, Tournigand et al found FOLFOX to be associated with:
 - Comparably more neutropenia
 - Comparably more diarrhea
 - Comparably more alopecia
 - Comparably more nausea and vomiting

CME Request Form

First name	MI	Last name
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I am a MD or DO licensed to practice in the state(s) of _____ and I have read this CME activity. I hereby request _____ (maximum 1 hour) credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association.

Signature	Date
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Cetuximab in the Treatment of Colorectal Cancer

Evaluation Form

Please take the time to evaluate this material, your answers and suggestions are confidential. Please mail or fax the completed evaluation form to the address or fax number indicated below.

PART 1

Tell us about you

1. What is your primary specialty or occupation? (Check one)

Medical Oncology Pathology Surgery

Radiation Oncology Pharmacology

Other _____

2. What is your main activity? (Check one)

Patient care Clinical research

Administration Teaching/Training

Other _____

3. For how many years have you been active in this area? (Check one)

<5 years 5–10 years 11–19 years

≥20 years

PART 2

Tell us about how you experienced this educational program

4. This program had a number of education objectives; to what extent were these objectives met?

(Please circle the number that best reflects your view: -2 = poor, +2 = outstanding)

Discuss the options for the first-line treatment of advanced colorectal cancer. -2 -1 0 +1 +2

Discuss the options for the second-line and adjuvant treatment of advanced colorectal cancer. -2 -1 0 +1 +2

Discuss the safety and efficacy of monoclonal antibodies alone and in combination with chemotherapy in the treatment of colorectal cancer. -2 -1 0 +1 +2

5. As a result of this program, do you feel that you:

• Have increased your professional knowledge? Yes No

• Will change your disease management approach? Yes No

Please provide your e-mail address, so that Imedex may stay in touch with you for future programs.

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6. Please provide general comments about this educational program or suggestions for future materials.

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