

Expanded treatment options in metastatic disease

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In the past 5 years, the armamentarium of therapeutic agents for metastatic colorectal cancer (mCRC) has expanded substantially to include three cytotoxic agents (irinotecan, oxaliplatin, and capecitabine) and three biologic ones (bevacizumab, cetuximab, and panitumumab). Recent guidelines recommend the use of a combination of these agents as the standard of care for patients with mCRC. The improved outcome associated with bevacizumab has led to its addition to all current first-line regimens for patients who can tolerate intensive therapy, with the option of including it in first-line therapy for patients who cannot tolerate intensive treatment. Additionally, increasing evidence indicates that exposure to irinotecan, oxaliplatin, and a fluoropyrimidine over the course of treatment can improve survival. Given the wide variety of options, the challenge lies in developing a treatment plan that includes the best integration and sequencing of agents for each patient.

Approximately 40% of patients with colorectal cancer (CRC) develop metastatic disease. The standard management of patients with metastatic CRC (mCRC) involves the use of chemotherapy agents. For approximately 4 decades, 5-fluorouracil (5-FU) administered alone or in combination with leucovorin (LV) has been the therapeutic mainstay in these patients. Compared with best supportive care, 5-FU/LV-based chemotherapy produces objective tumor response rates (RRs) of approximately 20% and prolongs median overall survival (OS) by 4–6 months (from approximately 6–8 months to approximately 10–12 months).¹

Although 5-FU/LV remains the backbone of most current chemotherapy protocols, the armamentarium of therapeutic agents for mCRC has expanded substantially in recent years to include both cytotoxic agents (irinotecan [Camptosar], oxaliplatin [Eloxatin], and capecitabine [Xeloda]) and biologic ones (bevacizumab [Avastin], cetuximab [Erbiximab], and panitumumab [Vectibix]). These agents offer new hope for longer survival, increased time to disease progression (TTP), and potentially enhanced quality of life.^{2,3}

The availability of a variety of therapeutic options

presents the challenge of how best to use these options for the benefit of the patient. This article summarizes the current approach for managing mCRC given the efficacy of the newly available options.

Greater benefit of irinotecan, oxaliplatin, and capecitabine

Irinotecan

Irinotecan is a semisynthetic derivative of camptothecin that on conversion to SN-38 is a potent inhibitor of topoisomerase I.⁴ Two major studies have indicated that irinotecan in combination with 5-FU/LV in the first-line setting is associated with a better RR, TTP or progression-free survival (PFS), and OS than 5-FU/LV alone. In one study, combining irinotecan with bolus 5-FU/LV (IFL regimen) produced a significantly longer PFS (7.0 months vs 4.3 months; $P = 0.004$), a higher RR (39% vs 21%; $P < 0.001$), and a longer OS (14.8 months vs 12.6 months; $P = 0.04$) than 5-FU/LV.⁵ In the second study, combining irinotecan with infusional 5-FU/LV (FOLFIRI) yielded

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TABLE 1

Addition of bevacizumab to IFL improves outcomes in metastatic colorectal cancer

Outcome	IFL + placebo	IFL + bevacizumab	P value
Median overall survival, months	15.6	20.3	< 0.001
1-year survival rate, %	63.4	74.3	< 0.001
Progression-free survival, months	6.2	10.6	< 0.001
Overall response rate, %	34.8	44.8	0.004
Complete response, %	2.2	3.7	
Partial response, %	32.6	41.0	
Median duration of response, months	7.1	10.4	0.001

IFL = irinotecan/bolus 5-fluorouracil/leucovorin
Adapted from Hurwitz et al⁶

a significantly higher RR (49% vs 31%; $P < 0.001$), longer TTP (6.7 months vs 4.4 months; $P < 0.001$), and longer OS (17.4 months vs 14.1 months; $P = 0.031$) than infusional 5-FU/LV alone.⁶

Based on the better outcome with infusional 5-FU/LV, the National Comprehensive Cancer Network (NCCN) has recommended the infusional FOLFIRI regimen over the bolus IFL regimen, considering the latter to be inferior.⁷ A direct comparison of the FOLFIRI and IFL regimens in period 1 of the BICC-C study supports this recommendation. In this study, 430 patients were randomized to receive treatment with FOLFIRI, a modified IFL regimen (mIFL), or capecitabine and irinotecan (CapeIRI). FOLFIRI achieved a superior PFS compared with CapeIRI or mIFL (7.6 months vs 5.5 months and 5.8 months, respectively). OS also favored FOLFIRI over the other two regimens, but the improvement did not reach statistical significance.⁸

Oxaliplatin

Oxaliplatin is the first cisplatin derivative shown to be effective in CRC. Various combination protocols of oxaliplatin with different schedules of 5-FU/LV have been developed in recent years. In three phase III trials, combination protocols of infusional 5-FU/LV plus oxaliplatin (FOLFOX or FUFOX) were compared with 5-FU/LV as first-line therapy in advanced CRC.⁹⁻¹¹ Across all

three studies, a significantly higher antitumor activity was noted consistently with the combination regimens, with an RR of approximately 50% and a PFS in the range of 8–9 months. In these studies, the median OS achieved with 5-FU/LV/oxaliplatin was in the range of 17.5–20 months.

Direct comparison between FOLFIRI and FOLFOX has shown that the addition of irinotecan or oxaliplatin to infusional 5-FU/LV is equally effective in terms of RR, TTP, and OS.^{12,13}

Capecitabine

Capecitabine is an oral prodrug of 5-FU that undergoes a three-step enzymatic conversion to 5-FU. The final conversion is catalyzed by the enzyme thymidine phosphorylase, which is preferentially expressed in tumor cells and has angiogenic properties. Clinical trials demonstrated that capecitabine produces outcomes comparable with those of bolus and continuous-infusion 5-FU/LV but is less toxic.¹⁴

Data from the NO16966 trial have shown that capecitabine plus oxaliplatin (XELOX) is noninferior to FOLFOX4 as first-line treatment for mCRC. Originally a two-arm trial comparing XELOX and FOLFOX4, the trial was amended to a four-arm study—XELOX plus placebo, XELOX plus bevacizumab, FOLFOX4 plus placebo, and FOLFOX4 plus bevacizumab—after phase III bevacizumab data became available. In the two-arm part of this study, XE-

LOX and FOLFOX4 achieved equivalent OS (hazard ratio [HR], 0.89; 97.5% confidence interval [CI], 0.72–1.11, in the intent-to-treat population). Discontinuation rates due to adverse events were comparable: 24.8% for XELOX-treated patients and 26.0% for FOLFOX4-treated patients.¹⁵

Targeted therapies for mCRC: additional improvements in outcome

Bevacizumab

Bevacizumab, a humanized monoclonal antibody (mAb), targets vascular endothelial growth factor (VEGF), which is markedly upregulated in mCRC and other malignant tumors. The mechanism of action of bevacizumab is not completely understood, but it may exert antitumor activity via a direct antiangiogenic mechanism or by altering tumor vasculature and vascular permeability. The latter effect could reduce tumor interstitial pressure and thereby may enhance delivery of chemotherapy to the tumor. A pivotal phase III trial showed that the addition of bevacizumab to IFL as first-line therapy in patients with mCRC results in statistically significant and clinically meaningful improvement in all endpoints studied (Table 1).¹⁶

Because FOLFIRI is now considered superior to the IFL regimen, adding bevacizumab to FOLFIRI is anticipated to achieve additional improvements in outcome. The BICC-C study is addressing this. In period 2 of this study, 117 patients were randomized to receive treatment with bevacizumab and either FOLFIRI or mIFL as first-line therapy. Preliminary results show that patients in the bevacizumab-plus-FOLFIRI arm have a significantly prolonged OS compared with patients in the bevacizumab-plus-mIFL arm. At the time of reporting, the patients receiving FOLFIRI and bevacizumab had not yet reached their median OS; patients in the mIFL-plus-bevacizumab arm had a median OS of 19.2 months.¹⁷

The addition of bevacizumab to FOLFOX has resulted in an overall RR of 53%, compared with 43% among patients who received FOLFOX alone.¹⁸ The recently reported results from the four-arm part of the NO16966 study (n = 1,400) also showed the benefit of bevacizumab.¹⁹ Chemotherapy plus bevacizumab conferred a significant improvement in PFS compared with chemotherapy alone (9.4 months vs 8.0 months; $P = 0.0023$). In the subgroup analyses, PFS was 9.3 months in the XELOX/bevacizumab group versus 7.4 months in the XELOX/placebo group ($P = 0.0026$) and 9.4 months in the FOLFOX4/bevacizumab group versus 8.6 months in the FOLFOX4/placebo group ($P = 0.1871$). The NCCN guidelines now recommend including bevacizumab in all first-line combination therapies for patients with advanced or metastatic disease who can tolerate intensive therapy.⁷

In the Eastern Cooperative Oncology Group (ECOG) E3200 study, bevacizumab was shown to be efficacious when used as second-line therapy in combination with FOLFOX in bevacizumab-naïve patients. There was a small improvement in OS in this study.²⁰ The benefit of continued use of bevacizumab after first-line therapy is not clear.

Cetuximab

Cetuximab is a recombinant mAb that binds with high specificity to the extracellular domain of the epidermal growth factor receptor (EGFR), which is overexpressed in many cancers. Binding of cetuximab to the EGFR blocks ligand-induced receptor autophosphorylation and activation of receptor-associated kinases, which, in turn, inhibits cell growth and induces apoptosis. Cetuximab appears to be beneficial in patients whose disease is refractory to irinotecan, allowing some patients to overcome resistance to irinotecan.

Cetuximab monotherapy appears to be comparable to oxaliplatin-based combinations for treating mCRC resistant to irinotecan. In a phase II open-

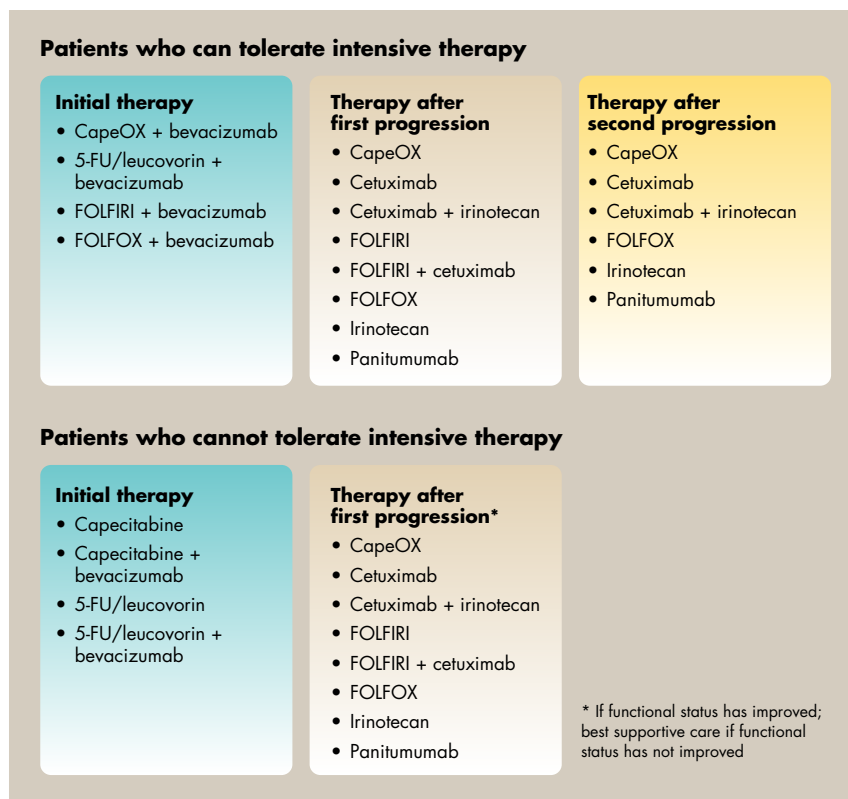


FIGURE 1 Chemotherapy options for patients with metastatic colorectal cancer who can and cannot tolerate intensive therapy. CapeOX = capecitabine/oxaliplatin; 5-FU = 5-fluorouracil; FOLFIRI = irinotecan/leucovorin/continuous infusion 5-FU; FOLFOX = oxaliplatin/leucovorin/continuous infusion 5-FU. Adapted, with permission, from the National Comprehensive Cancer Network⁷

label clinical trial of weekly cetuximab monotherapy in patients with irinotecan-refractory mCRC, the RR was 10.5% (95% CI, 4%–22%), ie, equivalent to the level of activity seen in similarly refractory patients with mCRC who subsequently received standard FOLFOX combination therapy.²¹ The median PFS of 1.4 months, however, was somewhat shorter than that reported for FOLFOX.²²

In the Bowel Oncology with Cetuximab Antibody 007 (BOND-1) trial, patients whose disease progressed on an irinotecan-containing regimen were randomized to receive therapy with cetuximab alone or cetuximab plus the previous irinotecan regimen.²³ Patients who received cetuximab plus an irinotecan-containing regimen had a significantly higher RR than patients who received cetuximab alone (22.9% vs

10.8%; $P = 0.007$). Of the patients in the cetuximab monotherapy arm who received irinotecan at disease progression, 3.6% had a partial response and 37.5% had stable disease after crossing over from cetuximab alone.

Panitumumab

Panitumumab is a fully human mAb directed against the EGFR. Results from a phase III study indicate that single-agent panitumumab is beneficial in mCRC patients with refractory disease. Patients who received panitumumab and best supportive care had a 46% lower relative progression rate than those receiving best supportive care alone (HR = 0.54; 95% CI, 0.44–0.66).²⁴ The efficacy of panitumumab also is being investigated in the first-line setting. Preliminary results indicate a

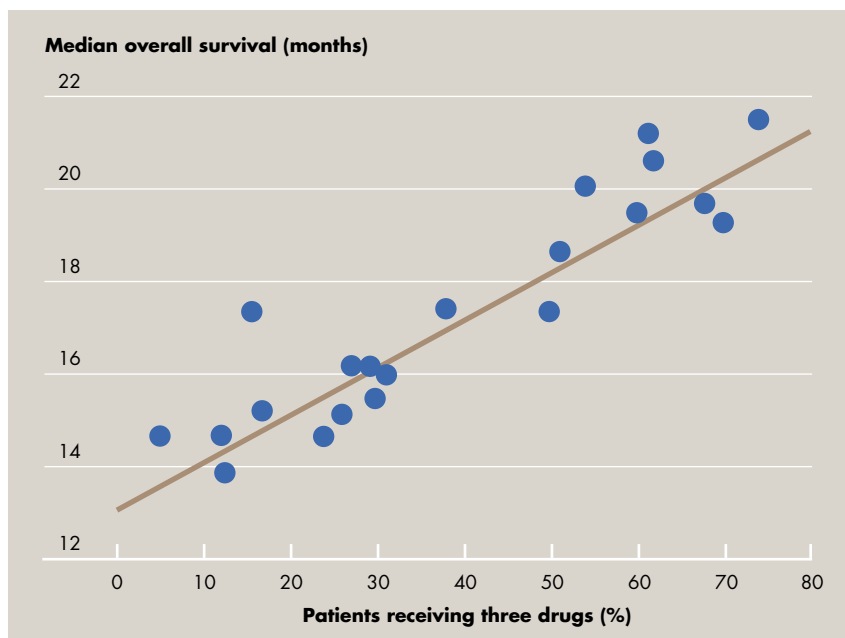


FIGURE 2 Use of all three cytotoxic agents (irinotecan, oxaliplatin, and a fluoropyrimidine) over the course of treatment improves survival rates in metastatic colorectal cancer. Adapted, with permission, from Grothey and Sargent²⁶

median PFS of 10.9 months and 5.6 months when panitumumab was added to FOLFIRI and IFL, respectively.²⁵ The ongoing Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) study, which compares first-line treatment with chemotherapy and bevacizumab with or without panitumumab, will elucidate the role of panitumumab in combination with chemotherapy. [Editor's note: Panitumumab treatment recently has been discontinued in the PACCE study, based on analysis of preliminary results that showed superiority of the control arm in terms of PFS and OS and higher toxicity rates on the combination-therapy arm.]

Current approach for managing mCRC

First-line therapy

Based on the efficacy data discussed previously, a combination chemotherapy regimen as first-line therapy currently is considered the standard of care for patients with mCRC. For patients who can tolerate intensive ther-

apy, the 2007 NCCN guidelines recommend combination therapy with FOLFOX, CapeOX (capecitabine/oxaliplatin), FOLFIRI, or 5-FU/LV, plus bevacizumab as first-line therapy (Figure 1).⁷ The choice of which combination therapy to use up front should be based on consideration of the type and timing of prior therapy and the differing toxicity profiles of the constituent drugs. Using all three cytotoxic agents (irinotecan, oxaliplatin, and a fluoropyrimidine) during the course of treatment significantly improves OS (Figure 2).²⁶

Although bevacizumab is recommended in all first-line combination therapies, insufficient data exist to support its use in second- or third-line regimens after progression on a first-line bevacizumab-containing regimen. In addition, monotherapy with bevacizumab or the addition of bevacizumab to a regimen that has failed has not been shown to be effective in mCRC.⁷

Second-line therapy

The recommended second-line therapy for patients who have re-

ceived prior 5-FU/LV includes irinotecan as a single agent or in combination with cetuximab, FOLFIRI, or FOLFOX.⁷ Cetuximab in combination with irinotecan also is indicated for patients whose disease is refractory to irinotecan-based chemotherapy. Cetuximab and panitumumab appear to have similar single-agent activity in advanced, refractory CRC and are recommended as second- or later-line therapies.

Less-intensive therapy

For patients with mCRC who cannot tolerate intensive therapy, the NCCN guidelines recommend either capecitabine or 5-FU/LV, with or without bevacizumab as first-line therapy (Figure 1).⁷ The guidelines also recommend consideration of second-line therapy for these patients based on functional status. Patients with no improvement in functional status should receive best supportive care.

Roundtable discussion

The roundtable discussion on key issues in expanded treatment options in metastatic disease was moderated by Dr. Charles S. Fuchs. Participants included Drs. Al Benson III, Charles Blanke, and Axel Grothey.

What are the key considerations in choosing treatment options for a patient? What factors impact the choice of first-line therapy?

Dr. Grothey: When we look at recent trial data, an issue that we face is that we cannot push first-line PFS beyond approximately 10–12 months. We have “maxed out” our first-line potential. We have also seen OSs way beyond 2 years, which reassures us that we are doing something right. However, it also highlights the importance of focusing on the sequence of therapies rather than on maximizing, in pileup fashion, the efficacy of first-line treatment.

Dr. Fuchs: Perhaps we just haven't gotten to all the right targets.

Clinical commentary

Outcomes with FOLFOX or FOLFIRI are the same. Whether FOLFOXIRI should be used more often is a complex question. The study by Falcone et al²⁷ did show a survival advantage, but a phase III trial from the Hellenic Oncology Research Group showed no advantage of FOLFOXIRI over FOLFIRI.²⁸ In addition, we do not know how FOLFOXIRI should be combined with biologics.

I am uncomfortable interchanging FOLFOX with CapeOX because of the dosing issues in the patient population in the United States and the hint from NO16966 that bevacizumab may not add as much to oxaliplatin regimens as expected.¹⁹ Although further analysis is needed, these data raise the possibility that FOLFOX plus bevacizumab may not be the optimal regimen, even though it is the most common initial regimen.

Although we have theoretical reasons for continuing bevacizumab into second-line therapy, the iBET trial will evaluate whether this approach is beneficial. In this trial, patients whose disease has progressed on FOLFOX plus bevacizumab will be randomized to one of three treatment arms: irinotecan-based chemotherapy plus cetuximab alone or this regimen with the addition of either 5 mg or 10 mg of bevacizumab.

—Alan P. Venook, MD

Dr. Grothey: Recently released data from the PACCE trial indicate that the addition of panitumumab to FOLFOX/bevacizumab does not increase the RR. Without the advent of a new drug with amazing efficacy in first-line therapy, the emphasis has to be on long-term treatment planning. I would like to have a new drug that changes tumor biology completely—a drug that has a big impact from the moment we start treating a patient.

Why is FOLFOXIRI not used more often?

Dr. Blanke: We have two phase II trials with a 70% RR. We have a phase III study against FOLFIRI that shows FOLFOXIRI is better. However, I don't know anybody who is using it outside the setting of liver metastasis.

Dr. Grothey: The FOLFOXIRI data on patients exposed to all three drugs show a median OS of 22.6 months, which is more or less in line with the prediction of the mathematical model that Dan Sargent and I put forth.^{26,27} I don't see any rationale for using all three drugs in first-line therapy, except in the neoadjuvant setting, where the

goal is to move patients to liver resection. Otherwise, I would like to go beyond 2 years in median OS.

Dr. Blanke: However, why save something for later, when you may never have the chance to use it?

Dr. Fuchs: If combining all three agents into a first-line regimen does not improve survival, it is less clear to me that all agents should be administered at once outside the scenario of potentially bringing a patient to a curative resection.

In the first-line treatment of mCRC, is single-agent therapy ever an option?

Dr. Benson: Using only a single agent is a concern if first-line therapy is the best opportunity to have an impact on response. At least in the trials, there is a significant dropout rate among patients going on to second- or third-line therapy. Care should be exercised in defining the treatment goal. Patients who have a compromised performance status because of their cancer may be served best by combination therapy, given the hope of effecting a more rapid and better response. However, perhaps a less-aggressive treatment approach would be appropriate in some patients because

nothing may have the desired impact.

What we have referred to as the continuum of care requires carefully assessing up front what the treatment goals are and what can be accomplished. For example, for the patient who is a potential candidate for liver resection, you may want to be aggressive to give that patient the best opportunity for resection. The same may be true for the patient whose performance status is compromised by the disease. You may want to push harder with the hope that you will achieve a better goal.

Dr. Grothey: Patients may have an ECOG grade 2 performance status because of an aggressive tumor, comorbidities, or advanced age. Each case requires a different approach. For a patient who has a poor performance status because of a rapidly progressing tumor, I do not use single-agent therapy.

Dr. Blanke: We know patients do remarkably well with 5-FU, LV, and bevacizumab, if they do not have some bleeding diathesis, perforation, or other contraindication to bevacizumab. We rarely use pure single-agent therapy.

Dr. Grothey: The acute toxicity of FOLFOX is not much higher than the toxicity of 5-FU/LV. The problem with oxaliplatin comes later. It is a relatively safe regimen. I sometimes omit the bolus 5-FU, and patients don't have myelosuppression.

What is your approach to treating a patient with a poor performance status due to comorbid disease?

Dr. Grothey: This is a different issue. Such patients would not necessarily be candidates for bevacizumab because the comorbidities often are cardiovascular. Patients with a history of coronary artery disease or transient ischemic attacks should not be given bevacizumab, and some patients are not candidates for any chemotherapy.

As first-line therapy, how do FOLFOX and FOLFIRI compare?

Dr. Blanke: We have two randomized trials suggesting that FOLFOX

and FOLFIRI are identical in terms of efficacy.^{12,13} I think it is purely a toxicity question, unless a biologic agent is being added and the interaction with one regimen is considered better than with the other one.

Dr. Grothey: We have data on combining bevacizumab with an oxaliplatin- or irinotecan-based regimen. The data on FOLFIRI/bevacizumab in BICC-C were convincing.¹⁷ FOLFIRI/bevacizumab and FOLFOX/bevacizumab should each be considered the standard of care in that setting.

In combination, is capecitabine equivalent to infusional 5-FU?

Dr. Blanke: We now have a European trial suggesting capecitabine's noninferiority to 5-FU/LV.¹⁴ I think it is equivalent, but reimbursement for the oral fluoropyrimidine-with-bevacizumab regimen can be a problem in this country. I have no significant reservations, but the dosing sometimes is difficult.

Dr. Fuchs: Although the trial does suggest noninferiority between CapeOX and FOLFOX, I'm uncertain about the tolerability of full-dose CapeOX relative to FOLFOX in a North American patient population.

Dr. Blanke: I agree. I certainly worry about their equivalence in the adjuvant setting, barring additional data. However, in the metastatic setting, if there is a difference, it is very, very small.

Dr. Grothey: Regarding dosing, the NO16966 study used 1,000 mg/m² bid, whereas in the United States we use 850 mg/m² bid. The difference in PFS when CapeOX and FOLFOX are compared is minor. In trials, however, the CapeOX curve consistently has trailed a bit under the FOLFOX curve for PFS.

What is your opinion on continuing bevacizumab as second-line therapy after disease progression has occurred with it as part of first-line therapy?

Dr. Blanke: Theoretically, it may be beneficial. If it is enhancing chemotherapy delivery and if patients are not

truly refractory to the bevacizumab, it makes some sense. However, we have no data to support this approach. I have not been doing it. The upcoming SWOG/NCCTG (Southwest Oncology Group/North Central Cancer Treatment Group) trial will be a randomized study looking at that exact question.

Dr. Grothey: This question is important not only for CRC but also for other diseases treated with bevacizumab. I would not like to see bevacizumab carried from first- to second- to third-line therapy without any clinical data because financial and toxicity implications might be prohibitive.

Dr. Benson: This is an example of where we need to come down hard on an empirical approach, which so many oncologists use. When we have no understanding of how an agent is behaving in the human model, it is difficult to defend. So much of what is happening is extrapolation. If these research efforts were supported, we would obtain the answers to the questions more readily.

Do you combine cetuximab with irinotecan or give them sequentially?

Dr. Grothey: It will be interesting to see what the reaction of the oncology audience is when the data from the EPIC (Eribitux Plus Irinotecan in Colorectal Cancer) study are presented, because it is not only survival but PFS and RR that count. How active is irinotecan without cetuximab after oxaliplatin therapy? We don't have much data on that. We have the data of Tournigand et al,¹² suggesting a 4% RR with second-line FOLFIRI after FOLFOX. According to a press release on EPIC,²⁹ the RR and PFS increase when cetuximab is added to irinotecan, but OS does not increase because, presumably, many patients are crossing over. So in EPIC, it's not a now-or-never but a now-or-later situation for cetuximab.

Dr. Fuchs: The data we have from EPIC suggest that there may be no difference in survival with cetuximab and

irinotecan given as second-line therapy versus irinotecan followed by cetuximab. It is nice to have a longer PFS. But, do we need to expose patients to cetuximab therapy earlier and potentially longer without a survival benefit? I think EPIC suggests that there is no compelling reason to give cetuximab initially in second-line therapy.

Dr. Blanke: I still give these agents separately. However, I know other experts who give both agents right away. Cetuximab does have some toxicity that patients do not like.

Do you think cetuximab and panitumumab should be considered in first-line therapy?

Dr. Benson: I would not use them up front off trial.

Dr. Grothey: I have been running a clinical trial in NCCTG, looking at FOLFOX plus cetuximab as neoadjuvant therapy for nonoptimally resectable, liver-limited disease. However, this usage clearly is experimental.

Dr. Fuchs: The results of PACCE lead to questions about whether any better outcomes will be achieved, but we need to see the final results with more follow-up.

Are you using panitumumab as a single agent or in combination with irinotecan?

Dr. Grothey: I use it in combination. Panitumumab integrates well into even a FOLFOX or FOLFIRI regimen. We just don't have much data, which is why, again, the PACCE data are so important.

Dr. Fuchs: I have also used it in combination.

Dr. Grothey: This year at AACR (the American Association for Cancer Research's annual meeting) and at ASCO (the American Society of Clinical Oncology's annual meeting), we will see much of the data on EGFR inhibition in CRC, including NCIC (National Cancer Institute of Canada) data (last-line cetuximab versus best supportive care), EPIC data, PACCE data, and

CRYSTAL (Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer) data. We have only bits and pieces of information about each of those trials, but we are talking about them as if we already know. We really don't know what's happening.

Dr. Blanke: It will be a subject of a clinical science symposium at ASCO 2007.

Dr. Fuchs: However, the hints from these trials are consistent with the notion that, at least in first-line therapy, we may be hitting a wall. It may be that we just need some effective target other than angiogenesis and the EGFR to move to the next level in first-line therapy.

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