Metastatic Colorectal Cancer: Is There One Standard Approach?

Review Article [1] | August 01, 2005
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Despite enormous advances in the treatment of colorectal cancer, there is no single standard treatment approach for all patients. However, there are general principles of management that can be used to guide therapy. The clinician who fails to individualize therapy for colorectal cancer is likely not taking full advantage of all therapeutic options available. Reviewing key clinical evidence that can help inform decision-making, this article addresses important questions in colorectal cancer management, including: Should bevacizumab (Avastin) be a component of most patients’ first-line treatment? Is there a role for continuing bevacizumab in subsequent regimens? Is there a role for cetuximab (Erbitux) in standard first-line chemotherapy? Are there practices in colorectal cancer that have become widely accepted without direct supportive data?

The past 10 years have seen enormous changes in the options available to patients with colorectal cancer. In 1995, there was one drug, fluorouracil (5-FU), approved for the treatment of this disease. In 2005, there are six drugs on the market for the management of colorectal cancer, not including leucovorin, which is a modifier of 5-FU but has no intrinsic anticancer activity of its own. Several other potentially useful agents are in the late phases of clinical development. With the availability of so many options, the efficacy of our treatment regimens has increased substantially. So too, however, has the complexity of the treatment decisions the oncologist must wrestle with when charting a course for his or her patient. Is there a simple standard treatment approach that can be adopted for all patients with colorectal cancer? No, not at this time. The progress that has been made has not proceeded in a neat, well-organized, linear fashion. Many different approaches and many different questions have been explored in parallel, rather than in series. Some of our more common practices are based on solid comparative data, while others are more appropriately characterized as widely accepted leaps of faith. However, there are certain principles of management that can be used to guide selections of therapy. Rather than an exhaustive review of all the data that support our current practices, this manuscript will instead address some of the more important questions that confront us in the area of colorectal cancer management, and will review key clinical evidence that can help inform our decision-making. When the evidence is strong, and evidence to the contrary is little or none, then clearly that evidence should dictate our practices. However, there are many circumstances in which the evidence is equivocal, with an important decision being either inadequately addressed by available data, or there being potentially conflicting data that muddy the waters. In these cases, we must critically consider which data might reasonably be extrapolated from to guide decision-making. With this caveat in mind, I will explore the data that address some of the more important questions that arise in selecting therapies for patients with metastatic colorectal cancer, bearing in mind that new data and options are arising frequently. The answers and opinions offered herein are based on available information at the time of this writing.

**Bevacizumab First-Line Treatment**

Should bevacizumab (Avastin) be a component of most patients’ first-line treatment regimen? Yes. Rarely in oncology have we had such compelling and unopposed data as we do on this topic. Bevacizumab is a humanized monoclonal antibody that targets a key substance known as vascular endothelial growth factor (VEGF).[1] How bevacizumab works in metastatic colorectal cancer is the subject of some debate. That it works is a clearly established clinical fact.
It is clear that bevacizumab binds to and thereby effectively neutralizes circulating VEGF. This may have several important effects that influence tumor growth and survival. VEGF is a centrally important component of the proangiogenic pathway. As such, new blood vessel formation necessary to support tumor progression is potentially inhibited by the decrease or absence of circulating VEGF levels. However, VEGF exerts other actions that may be even more critical to its therapeutic efficacy. Unlike mature, long-established vasculature, the newly formed blood vessels that support a growing tumor have relatively thin walls and are dependent on continued growth factor (including VEGF) for support and maintenance of integrity. In the absence of sufficient VEGF levels, these immature vessels become fragile and leaky, and ultimately are degraded, leading to a normalization of tumor vasculature.[2] These changes would be anticipated to deliver other, concurrently administered, chemotherapy more effectively to the tumor tissue. Additionally, bevacizumab has been demonstrated to lower intratumoral interstitial pressure, further facilitating transfer of other antineoplastic agents from the bloodstream to the tumor tissue.[3] To what degree each of these mechanisms contributes to the antitumor activity of bevacizumab is a matter of conjecture at this time.

### Key Clinical Trial

The pivotal trial that demonstrated the utility of bevacizumab in colorectal cancer was reported by Hurwitz et al.[4] In a randomized, double-blind, placebocontrolled trial of approximately 800 patients, half received the thenstandard IFL (irinotecan [Camptosar], 5-FU by weekly bolus, and leucovorin)[ 5] plus a placebo, and half received the same chemotherapy plus bevacizumab at a dose of 5 mg/kg every other week. The major efficacy parameters are shown in Table 1. Patients who received bevacizumab had a median survival that was almost 5 months longer than those who did not. Other supportive end points such as progression-free survival were increased as well. The subjective toxicity-that which the patient was overtly aware of-was essentially nil, such that a placebo control was realistically possible. That is not to say that side effects were not encountered: There was roughly a 10% increased risk of serious hypertension (which responded to oral medication), a 1.5% risk of gastrointestinal perforation, and a 2.5% increased risk of arterial thrombotic events. Clearly, these represent major and potentially lethal complications. But are these side effects reason enough to eschew routine use of frontline bevacizumab? No, in my opinion. Taken as a whole, side effects notwithstanding, patients who received bevacizumab responded better and lived longer than those who did not. In discussion of these risks with patients, I have likened the decision to add bevacizumab to their chemotherapy to the decision to use a seat belt. While there is a possibility that in an accident the seat belt might actually cause an injury, it is far more likely to prevent one. Likewise, bevacizumab may cause a complication, but it is more likely to benefit the patient. Older patients and patients with a history of significant cardiovascular or cerebrovascular disease appear to be at increased risk for arterial thrombotic complications from bevacizumab, and these factors should be considered when individualizing therapy.

**ECOG 3200** - Other data have corroborated the efficacy of bevacizumab in metastatic colorectal cancer. The pivotal trial that demonstrated the utility of bevacizumab in colorectal cancer was reported by Hurwitz et al.[4] In a randomized, double-blind, placebocontrolled trial of approximately 800 patients, half received the thenstandard IFL (irinotecan [Camptosar], 5-FU by weekly bolus, and leucovorin)[ 5] plus a placebo, and half received the same chemotherapy plus bevacizumab at a dose of 5 mg/kg every other week. The major efficacy parameters are shown in Table 1. Patients who received bevacizumab had a median survival that was almost 5 months longer than those who did not. Other supportive end points such as progression-free survival were increased as well. The subjective toxicity-that which the patient was overtly aware of-was essentially nil, such that a placebo control was realistically possible. That is not to say that side effects were not encountered: There was roughly a 10% increased risk of serious hypertension (which responded to oral medication), a 1.5% risk of gastrointestinal perforation, and a 2.5% increased risk of arterial thrombotic events. Clearly, these represent major and potentially lethal complications. But are these side effects reason enough to eschew routine use of frontline bevacizumab? No, in my opinion. Taken as a whole, side effects notwithstanding, patients who received bevacizumab responded better and lived longer than those who did not. In discussion of these risks with patients, I have likened the decision to add bevacizumab to their chemotherapy to the decision to use a seat belt. While there is a possibility that in an accident the seat belt might actually cause an injury, it is far more likely to prevent one. Likewise, bevacizumab may cause a complication, but it is more likely to benefit the patient. Older patients and patients with a history of significant cardiovascular or cerebrovascular disease appear to be at increased risk for arterial thrombotic complications from bevacizumab, and these factors should be considered when individualizing therapy.
colorectal cancer. The Eastern Cooperative Oncology Group (ECOG) 3200 study, recently reported in abstract form, randomized 829 bevacizumab-naive patients who had failed previous chemotherapy with both 5-FU and irinotecan (together or individually) to receive either bevacizumab, FOLFOX (biweekly infusional 5-FU, leucovorin, and oxaliplatin [Eloxatin]), or bevacizumab plus FOLFOX. The bevacizumab-alone arm was closed early due to concerns of inferior efficacy. The final data for this arm have not yet been reported at the time of this writing. The overall survival benefit for the bevacizumab-plus- FOLFOX arm over FOLFOX alone was 12.5 vs 10.7 months (P < .002).[6] Of note, the incidence of grade 3 neurotoxicity was increased in the bevacizumab/FOLFOX group compared to those receiving FOLFOX alone (14.9% vs 8.4%). While this may be simply a result of the greater time on therapy leading to increasing oxaliplatin exposure, the possibility of bevacizumab facilitating platinum entry into neurons and so exacerbating oxaliplatin neurotoxicity cannot be excluded at this time. It will be instructive, when data are available, to see if the neuropathy incidence over time is similar between the two arms, or if the neurotoxicity appears earlier in the bevacizumab-containing arm.

**Other Trials**—Three other studies thus far have provided supportive evidence of the efficacy of bevacizumab in colorectal cancer. A trial reported by Kabbinavar et al demonstrated improved response rates and progression-free survivals for bevacizumab in conjunction with 5-FU/leucovorin, as did a smaller randomized phase II trial.[7,8] Neither of these trials was designed or powered to detect a survival benefit. More recently, the preliminary results of a small randomized phase II trial adding bevacizumab to cetuximab (Erbitux) and to cetuximab plus irinotecan in bevacizumab-naive patients suggested a strong improvement in response rate and time to tumor progression as compared to historical controls.[9] In short, all of the data suggest that adding bevacizumab to active chemotherapy in bevacizumab-naive patients improves antitumor activity. Why then, are some oncologists choosing to routinely not use bevacizumab in the management of their patients? I do not know. One argument that has been offered is that the survival time on the IFL/bevacizumab trial (20.5 mo) did not differ substantially from the survival time in the FOLFOX arm of the recent intergroup N9741 trial.[10] This is a specious argument. First, it is a cross-study comparison of two trials conducted with different investigators and different patient populations, making the comparison inappropriate and invalid. Second, even if one wishes to explore the comparison, there is a marked imbalance in availability of second-line treatment that would negate the validity of the survival comparison, even if such a comparison were statistically valid. All of the patients who received FOLFOX in the N9741 intergroup trial had access to second-line irinotecan. Most of the patients who received IFL/bevacizumab in the Hurwitz trial did not have access to second-line oxaliplatin, since the drug had not received commercial approval in the United States at the time. Furthermore, of the limited number of patients who received oxaliplatin as second-line therapy in the Hurwitz trial, we do not have data as to what percentage received FOLFOX vs oxaliplatin alone. Oxaliplatin alone is now known to be substantially inferior to FOLFOX in second-line therapy,[11] although this was not known when the Hurwitz study was conducted.

**Subsequent Regimens**

Is there a role for continuing bevacizumab in subsequent regimens after progressing through a first-line bevacizumab-containing regimen? I don't think so. It should be emphasized that there are essentially no data at this time that specifically address this question. However, there are no data whatsoever that support the practice of continuing bevacizumab with subsequent regimens. In general, we require evidence that an intervention is useful before we adopt it as a standard practice. Until and unless we have evidence to support continuation of bevacizumab in serial regimens, I would consider such use inappropriate. Some clinicians have mistakenly interpreted the recently presented ECOG 3200 study as support for continuation of bevacizumab in second-line treatment. This study, as discussed above,[6] shows a modest but statistically significant survival advantage in patients who, after failing irinotecan and 5-FU, received FOLFOX plus bevacizumab vs FOLFOX alone. However, all of the patients who entered this trial were bevacizumab-naive when they started second-line therapy. These data therefore say nothing about the usefulness of second-line bevacizumab in patients who have already received the drug in first-line therapy. Since we have virtually no data on the mechanisms of bevacizumab resistance, we can hardly invoke a mechanistic rationale for continuation. We know that bevacizumab carries with it a risk of serious and even potentially fatal toxicities in the form of gastrointestinal perforation, heart attacks, and strokes. So I...
believe we must guard against being seduced by the very mild subjective toxicities of bevacizumab; just because the drug does not make patients feel unwell does not mean there is not a potentially serious downside to its continuation. It should be recalled that the once rhetorical question of "what harm could it do?" was used as a justification by some for routinely adding high doses of cyclooxygenase (COX)-2 inhibitors to chemotherapy regimens in the absence of clinical data to support this practice. The question of performing placebo-controlled trials to address the issue of continuation of bevacizumab has been raised. An argument made against this design is that the long half-life of bevacizumab would confound such trials, as residual drug in the placebo arm would influence the outcome. I do not believe, however, that this would pose a major impediment to addressing the issue. The question at hand is, does the patient benefit from the modest but real risk and the considerable expense of continuing bevacizumab administration? If a trial shows convincing evidence of a benefit for continuing bevacizumab, then let's do it. If a trial shows no benefit, then whether it is a negative trial because second-line repeat exposure to bevacizumab was inactive or because there was a carryover effect from first-line bevacizumab is an interesting but moot point; it would still be a negative trial indicating that continued administration of bevacizumab is not beneficial. To the argument that trastuzumab (Herceptin) treatment is often continued in multiple lines of therapy in HER2-positive breast cancer, it is appropriate to point out that (1) this is a different disease, (2) this is a different drug working on a different target by a different mechanism, and (3) there is a remarkable paucity of data supporting the practice of continued use of trastuzumab in serial regimens in breast cancer. **Cetuximab First-Line Treatment**

Is there a role for cetuximab in standard first-line chemotherapy? Perhaps there will be, but as of now, no. Cetuximab is a monoclonal antibody that binds to the epidermal growth factor receptor (EGFR) and blocks ligand from binding to the receptor, thereby blocking receptor activation.[12] Cetuximab has been convincingly and consistently shown to have activity as a single agent in irinotecan-refractory colorectal cancer[13-15] and to have a higher response rate and longer time to tumor progression when given concurrently with a continuation of irinotecan after irinotecan failure.[14,16] It is only in the irinotecan-refractory setting that definitive data for cetuximab are available. We have no randomized data to support the addition of cetuximab to first-line therapy of colorectal cancer. In the refractory setting, when there are no available active agents, activity in a nonrandomized phase II trial is meaningful. In the front-line setting, when given in conjunction with active chemotherapy regimens, there is little that can be determined other than the feasibility (or lack thereof) of the combination. A promising degree of activity in a small phase II trial does not establish that a combination is appropriate for routine use, nor does a less than outstanding response rate in a small phase II trial mean that a combination is without substantial merit. In the front-line setting, only a randomized trial can establish the relative safety and efficacy of the new combination. Several small phase II pilot trials have explored the feasibility of combining cetuximab with front-line regimens,[17-19] and the recent intriguing activity of cetuximab combined with bevacizumab in the salvage setting suggests that this double antibody combination in conjunction with front-line therapy should be investigated as well.[9] The preliminary data for cetuximab-based front-line combinations show encouraging response rates, especially with oxaliplatin-based combinations. These small phase II trials in well selected patients are not, however, a reason to adopt front-line cetuximab as part of routine practice. Rather, these studies support the conduct of randomized studies of these regimens to critically evaluate the appropriateness of incorporation of cetuximab into first-line regimens. Until the results of these studies are known, the benefits and risks of cetuximab in front-line therapy are unknown, both in terms of relative safety and efficacy, and routine use of these combinations in front-line care cannot be recommended.

**Immunohistochemical Testing**

Is immunohistochemical (IHC) testing of EGFR necessary or appropriate for the use of cetuximab? No. From a medical and scientific perspective, it is neither reasonable nor appropriate. The currently available tests for "determining" the EGFR status of a tumor have no clinical usefulness whatsoever. There is absolutely no prospective clinical evidence that supports the use of these tests in this setting. In the original report on cetuximab plus irinotecan,[16] the response rates for 1+, 2+, and 3+ positive patients, as determined by an independent response assessment committee, were virtually identical. The same was found to be true in a larger confirmatory trial.[14] In all of these studies, patients felt to be "negative" for the EGFR were excluded from treatment. Only two reports thus far have specifically explored the use of cetuximab-based therapy in EGFR-negative patients. Lenz et al reported a small series of nine EGFR-negative patients who were treated with single-agent cetuximab; two patients responded.[15] Independent radiology review of the nine patients confirmed one partial response and classified four patients as having achieved stable disease.
(Recall that up to a 49% regression is classified as stable disease from a regulatory perspective.) A somewhat larger set of patients was recently reported by Chung et al.,[20] who reviewed the experience with cetuximab at Memorial Sloan-Kettering Cancer Center for patients who initiated treatment with cetuximab during the first 3 months of its commercial availability. The computerized pharmacy records were used to eliminate recall bias in identifying all patients who received this drug. Records were then reviewed to identify patients who were negative for EGFR by IHC staining. Of 16 EGFR-negative patients, 14 had received cetuximab plus irinotecan and 2 had received single-agent irinotecan alone. (As would be expected, both patients who received cetuximab alone had indications of significant comorbidities and poor performance status, and one received only two doses of cetuximab.) A review of scans by a reference radiologist first confirmed that all 16 patients had demonstrated tumor growth on a prior irinotecan-based regimen. Further review then identified four confirmed partial responses to cetuximab-based therapy, all of which were durable at a 6-week (or later) follow-up scan. All four responders, as well as two additional minor responders, had received cetuximab plus irinotecan. Clearly, the idea that patients who lack IHC expression of EGFR are incapable of responding to cetuximab is overtly false (Table 2). This does not mean that EGFR is not the target for cetuximab. Rather, it means that the currently available IHC techniques are seriously flawed and are essentially useless from a clinical perspective. In truth, since it has been demonstrated that IHC expression of EGFR can vary over storage time and be influenced by the type of fixative used,[21] as well as vary from primary to metastasis, it is not reasonable to believe that these stains will be sufficiently sensitive and specific to allow for definitive selection or exclusion of patients. The implications of these findings are clear: Currently available IHC stains for EGFR have failed to show any predictive value in terms of the efficacy of cetuximab-based therapy; thus, no clinical decision should be made on the basis of these stains, and they should not be performed in routine practice. No patient who is felt to be otherwise appropriate for cetuximab-based therapy should be excluded from such therapy solely on the basis of a negative EGFR IHC stain. Similarly, a high degree of EGFR expression is meaningless in terms of predicting for cetuximab activity, in colorectal cancer or otherwise, and this should not be used as justification for use of the drug.

**Leaps of Faith** Are there practices in colorectal cancer that have become widely accepted without direct supportive data? Yes. We have, as a community, been willing to make certain leaps of faith. **FOLFOX Variations**

One of the most interesting of these leaps is the move from FOLFOX4, which is the US Food and Drug Administration (FDA)-approved schedule, to modified FOLFOX6, which is currently being investigated in the National Cancer Institute (NCI)-supported intergroup studies and is in widespread use in clinical practice. FOLFOX4 includes 85 mg/m² of oxaliplatin, with leucovorin and bolus 5-FU being given for 2 consecutive days. In FOLFOX6, the oxaliplatin dose was raised to 100 mg/m², and the leucovorin dose was doubled on day 1 and omitted on day 2. The bolus 5-FU was given on day 1 only, and the infusional 5-FU dose was doubled from 600 mg/m²/d to 1,200 mg/m²/d. In modified FOLFOX6, the dose of oxaliplatin was dropped to the 85 mg/m² dose of FOLFOX4. No head-to-head comparisons of any of these regimens have or will be done. That modified FOLFOX6 has become a de facto standard regimen at our institution and in the gastrointestinal intergroup studies is, in my opinion, quite reasonable, but it is not based directly on data.

<table>
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<th>Table 2</th>
<th>Response to Cetuximab Plus Irinotecan in Irinotecan-Refractory Colorectal Cancer</th>
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<tbody>
<tr>
<td>Study</td>
<td>Number of Patients</td>
</tr>
<tr>
<td>Saltz et al, 2001[16]</td>
<td>120</td>
</tr>
<tr>
<td>Cunningham et al, 2004[14]</td>
<td>218</td>
</tr>
<tr>
<td>Chung et al, 2005[20]</td>
<td>16³</td>
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</tbody>
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*Includes two patients treated with cetuximab alone (no concurrent irinotecan).

EGFR = epidermal growth factor receptor; IHC = immunohistochemistry.
Does it matter which cytotoxic - irinotecan or oxaliplatin - is used in front-line therapy? Probably not. There appears to be a popular perception among oncologists in the United States that oxaliplatin is superior to irinotecan as a front-line drug. This perception is not well supported by data. There are several reasons that this perception might exist. First, oxaliplatin was unavailable for many years in the United States, long after its efficacy had been convincingly demonstrated in the literature. Many patients who had the means were traveling to Europe or Central America to obtain the drug. This created an image of oxaliplatin as the "forbidden fruit" and contributed to an aura of its being a superior agent. Second, there was a perception that if oxaliplatin worked after irinotecan, then it must be an even better drug. (A similar misperception existed briefly for irinotecan over 5-FU when irinotecan was first introduced.) Lastly, the results of the intergroup N9741 trial, in which IFL was compared directly to FOLFOX4,[10] have been largely misinterpreted as an indication that oxaliplatin is a superior drug to irinotecan. This is an incorrect interpretation for several reasons. First, a large, well-done study by De Gramont et al, which is largely ignored in the United States, demonstrated that the biweekly infusional schedule of 5-FU/leucovorin had a better response rate, time to tumor progression, and toxicity profile than bolus 5-FU, with a strong trend toward a 5-week survival advantage that just barely missed statistical significance (Table 3).[22] In the N9741 trial, irinotecan was given with bolus 5-FU while oxaliplatin was given with biweekly infusional 5-FU. Second, the survival data from the study have been widely misunderstood. The group that received frontline FOLFOX did achieve an impressive 4.7-month median survival advantage over the group that got IFL. However, in addition to the potential for infusional 5-FU to account for some of that advantage, the availability of second-line therapy was markedly imbalanced between the arms, with all patients in the FOLFOX arm having full access to irinotecan for second-line treatment, while the patients in the IFL arm had very limited access to oxaliplatin, as it was not commercially available in the United States during the study.

### Table 3

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<tr>
<th></th>
<th>Bolus 5-FU/LV N = 216</th>
<th>Biweekly Infusional 5-FU/LV (n = 217)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate</td>
<td>14%</td>
<td>33%</td>
<td>.0004</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>22 wk</td>
<td>28 wk</td>
<td>.0012</td>
</tr>
<tr>
<td>Overall survival</td>
<td>57 wk</td>
<td>62 wk</td>
<td>.067</td>
</tr>
<tr>
<td>Grade 3/4 toxicity</td>
<td>24%</td>
<td>11%</td>
<td>.0004</td>
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5-FU = fluorouracil; LV = leucovorin.
Adapted from de Gramont et al.[22]
Furthermore, the definitive data that showed single-agent oxaliplatin to be inadequate in the second-line setting (only the FOLFOX regimen, not single-agent oxaliplatin showed a 9.9% response rate; single-agent oxaliplatin showed a 1% response rate)[11] were not available at the time during which N9741 was conducted. Thus, even for the limited number of patients who received second-line oxaliplatin on N9741, we do not know how many received it in an active combination regimen, as opposed to having received it as a virtually inactive single agent. For all practical purposes, the survival comparison of N9741 is a comparison of front-line oxaliplatin with biweekly infusional 5-FU followed by second-line irinotecan, vs front-line irinotecan with bolus 5-FU, with little or no effective second-line therapy. Two trials have compared frontline oxaliplatin to front-line irinotecan in a setting of identical infusional 5-FU schedules, and with the same access to active second-line agents (Table 4).[23,24] In these trials, the first-line efficacy of oxaliplatin vs irinotecan, in terms of response rate, progression-free survival, and overall survival, is essentially identical. It is therefore reasonable practice to use either oxaliplatin or irinotecan, in conjunction with infusional 5-FU/leucovorin, as front-line therapy. The agents have very different side-effect profiles—i.e., greater gastrointestinal toxicity and alopecia with irinotecan but greater peripheral neuropathy with oxaliplatin. It therefore seems reasonable to regard either oxaliplatin plus infusional 5-FU or irinotecan plus infusional 5-FU as appropriate regimens for combination with bevacizumab in first-line chemotherapy regimens.

### Second-Line Treatment

What is appropriate second-line therapy? This is a complicated question that depends to some degree on what chemotherapy is used in first-line therapy. If I use FOLFOX/bevacizumab as my initial therapy, then at the time of disease progression I switch to irinotecan. Data from the United Kingdom Medical Research Council FOCUS trial have addressed the issue of continuation of second-line 5-FU after failure of first-line 5-FU (i.e., using FOLFIRI second-line therapy instead of single-agent irinotecan) and suggest that this practice may be more appropriate.[25] As noted above, I do not feel that bevacizumab should be continued in this second-line setting, in the absence of data to support this. Once second-line irinotecan-based chemotherapy has failed, I would then continue the irinotecan, and would add cetuximab. At present, there are no data regarding the use of cetuximab in non-irinotecan-refractory colorectal cancer. Some have made the assumption that there would be benefit to adding cetuximab with initial irinotecan. A major potential concern, however, is that irinotecan is one active regimen, and irinotecan/cetuximab is another active regimen. By adding cetuximab to the initial dose of irinotecan, one may be excluding an active regimen (single-agent irinotecan) and so limiting long-term treatment options. For many patients—approximately half in my current practice—I favor first-line FOLFIRI (5-FU, leucovorin, irinotecan) plus bevacizumab. These are predominantly the patients for whom the neuropathy of oxaliplatin would be a potential problem. This is not just the occasional musician, surgeon, or calligrapher that requires therapy, but anyone who uses a computer keyboard to a large degree, or people for whom cold sensitivity would be a major problem, such as construction workers or other manual laborers who work outside in cold climates. If I use FOLFIRI/bevacizumab first, then I favor (albeit without solid data to support a preference) irinotecan/cetuximab second, and FOLFOX as a third-line regimen. Although the comparison is nonrandomized and based on cross-study data, the response rate of FOLFOX after irinotecan and 5-FU was 10%, whereas the response rate of irinotecan/cetuximab after failure of 5-FU, irinotecan, and oxaliplatin was 23%, suggesting that cetuximab may offer greater activity in the salvage setting.

**Table 4**

<table>
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<tr>
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<th>FOLFIRI (n = 109)</th>
<th>FOLFOX6 (n = 111)</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Response rate</td>
<td>56%</td>
<td>54%</td>
<td>.68</td>
</tr>
<tr>
<td>Time to tumor progress</td>
<td>8.5 mo</td>
<td>8.1 mo</td>
<td>.26</td>
</tr>
<tr>
<td>Overall survival</td>
<td>21.5 mo</td>
<td>20.6 mo</td>
<td>.99</td>
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FOLFIRI = fluorouracil, leucovorin, irinotecan; FOLFOX6 = oxaliplatin, leucovorin, fluorouracil.
than oxaliplatin. Furthermore, this approach permits the delay of neurotoxicity until very late in the patient's treatment course, although it does introduce the skin rash of cetuximab earlier. In general, my subjective, anecdotal impression is that the skin rash of cetuximab is less problematic to patients than the neurotoxicity of oxaliplatin. **Optimal Initial Therapy** Is either oxaliplatin or irinotecan required in first-line therapy for optimal long-term outcome? The answer to this question has been thrown into some doubt. The majority of evidence would indicate that combination chemotherapy with either irinotecan/5-FU or oxaliplatin/5-FU and concurrent bevacizumab is the most appropriate initial therapy for most medically fit, good performance status patients. Recently, however, two interesting observations have offered some evidence to challenge how universally applicable this assumption might be. The first is the observation that 5-FU/leucovorin plus bevacizumab had superior activity to 5-FU/leucovorin alone,[7,8] and appeared to have very similar activity to 5-FU plus irinotecan, suggesting that the more tolerable bevacizumab might be used with 5-FU up front, possibly instead of irinotecan, allowing both irinotecan and oxaliplatin to remain in reserve for second-line and salvage therapies. The recently reported FOCUS trial, thus far available only in preliminary abstract form, also challenges the assumption that combination cytotoxic therapy is superior to a sequential strategy for all patients.[25] In this trial, 2,135 patients were randomized to one of three arms: (1) biweekly infusional 5-FU/leucovorin followed at time of progression by irinotecan alone, (2) biweekly infusional 5-FU/leucovorin followed at progression by continuation of 5-FU/leucovorin and the addition of either irinotecan or oxaliplatin (ie, change to FOLFIRI or FOLFOX), or (3) initial treatment with either FOLFIRI or FOLFOX. The trial showed no benefit in terms of survival for combination therapy initially vs use of first-line 5-FU/leucovorin followed by FOLFOX or FOLFIRI in the second-line setting. This is one trial, and the results are not completely consistent with earlier evidence. It does not definitively settle the question, but certainly raises the possibility of incorporating sequential strategies into standard treatment paradigms for some patients. Patients with bulky symptomatic disease or those being treated with an eye toward subsequent curative resection would most likely not be good candidates for consideration of sequential therapy. **Conclusions** There is no one standard of care for metastatic colorectal cancer today. Some practices are solidly supported by consistent data, and others are based more on reasonable extrapolations than on direct evidence. No one therapeutic approach has demonstrated such outstanding superiority that it takes all others off of the table. For this reason, the clinician who uses one standard treatment approach for all of his or her colorectal cancer patients is quite likely failing to appropriately individualize therapy, and may be failing to take full advantage of all the therapeutic options now available. The risks and benefits of the many different treatment options should be openly and clearly discussed with patients, and the patient should be an active participant in the decision-making process when it comes to selection of therapy. The options for management of colorectal cancer have gotten substantially better over the past decade. They have also gotten substantially more complicated. As physicians, we must attempt to understand the nuances of the current and emerging clinical data, in order to maximize the likelihood of the best possible outcome for each of our patients.

**Disclosures:**
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