Sequencing of Treatment in Advanced Unresectable Colorectal Cancer

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Abstract
This article reviews the various systemic therapy options for patients with metastatic colorectal cancer (CRC) that is judged to be noncurable. The choice of initial therapy depends on patient preferences, treatment goals, performance status, and presence of comorbid conditions. Whether surgical resection of the primary tumor should be considered in patients who present with metastatic CRC is a matter of controversy. The components of the initial systemic regimen influence the options for second- and third-line options when disease progression occurs during therapy. The standard of practice is often to continue chemotherapy until progression, unacceptable side effects, or death. In patients with incurable CRC, the balance between efficacy, toxicity, and repeated hospital or clinic visits must be discussed with the patient. Although continuous treatment may be appropriate for some patients, intermittent treatment strategies or maintenance with the least toxic agents may be preferable for others. If disease progression occurs during a chemotherapy break or while the patient is on maintenance therapy, previously used agents may be reintroduced provided that preexisting toxicities have resolved. (JNCCN 2013;11[Suppl 4]:S28–S37)
A variety of options for systemic therapy exist for patients with advanced colorectal cancer (CRC). This article focuses on patients in whom surgical resection of metastatic disease is not considered feasible. A multidisciplinary consultation is strongly recommended to identify patients who are definitely unresectable and those with potentially resectable disease who may benefit from multimodality therapy to convert them to a resectable status.

Management of the Primary Tumor in Metastatic Disease

Prophylactic surgery to remove the primary tumor has been performed to prevent subsequent complications of perforation, obstruction, or bleeding. Analysis of the SEER database from 1988 and 2000 indicated that 66% of patients presenting with metastatic CRC underwent primary tumor resection; these patients had higher median and 1-year survival rates (eg, colon primary, 11 vs 2 months; 45% vs 12%). The impact of surgical resection versus patient selection on survival differences is not known. A review of the literature from 1980 to 2010 identified 21 nonrandomized studies comparing palliative resection in stage IV CRC with other treatment modalities. Most studies showed a survival benefit for patients who underwent palliative resection. Multivariate analysis indicated that tumor burden and performance status were major independent prognostic variables.

If the patient is asymptomatic from the primary tumor, any potential benefit must be balanced by the risk of morbidity and mortality from resection. Delay in initiating systemic therapy is another important consideration. Some authors argue that resection of the primary tumor in asymptomatic patients with metastatic CRC is unnecessary. Multiagent regimens including targeted biologic agents have resulted in improved local and distant tumor control, reducing the need for surgical intervention for late primary-related complications.

If the patient has significant bleeding, perforation, or complete or near total obstruction, resection of the primary tumor results in rapid control of these symptoms. The decision to proceed with primary tumor resection in patients with a high metastatic disease burden is more problematic, because greater potential exists for disease progression during the recovery period. In some patients with an unresectable obstructing primary tumor, resection with primary anastomosis may not be feasible because of comorbid illness or locally extensive disease; a diverting end colostomy with creation of a mucous fistula is reasonable. In either case, a laparoscopic approach is preferred to reduce the risk of postoperative complications and decrease recovery time.

In selected patients with an obstructing primary tumor, placement of an endoluminal colonic stent may result in palliation. However, the procedure may be technically challenging in distal rectal or very proximal colon tumors, and can be associated with complications, including migration, occlusion from tumor ingrowth, and perforation. Radiation therapy with sensitizing doses of a fluoropyrimidine may also be used for palliation in the setting of obstruction or bleeding.

A concern has been the risk of perforation of the primary tumor with the use of bevacizumab-containing therapy. National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol C-10 evaluated bolus and infusional 5-FU, leucovorin, and oxaliplatin (FOLFOX6) plus bevacizumab for patients with unresectable stage IV colon cancer and a synchronous asymptomatic primary tumor. The results indicated that patients with surgically unresectable...
metastatic colon cancer and an intact asymptomatic primary tumor can be spared initial noncurative resection of the primary.

Options for First-Line Therapy

Patients with metastatic CRC should have analysis of KRAS mutational status in a Clinical Laboratory Improvement Amendments (CLIA)–accredited laboratory.\textsuperscript{12} Retrospective analysis indicates that patients with mutations in the KRAS gene do not benefit from anti–epidermal growth factor receptor (EGFR) antibody therapy. This will determine up front whether anti-EGFR antibody therapy will be a possibility. Different assays are available to detect mutations in the KRAS gene.\textsuperscript{13,14} False-negatives or -positives may occur because of the presence of rare polymorphisms; mutations outside of exon 2; heterogeneity of the tumor; poor specimen selection, such as one exposed to prior chemoradiation before tumor sampling; inadequate amount of tumor tissue; improper tissue preservation; or technical error.

Several commercial entities offer molecular profiling of metastatic tumor tissue as a means of selecting therapy for patients with metastatic CRC. The ability of these markers to predict sensitivity to chemotherapy has largely been derived from retrospective data. Until data from prospective clinical trials indicate an improved outcome when tumor profiling is used to direct therapy, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon and Rectal Cancers do not recommend the routine use of these assays (to view the most recent version of these guidelines, visit NCCN.org).\textsuperscript{15,16}

FOLFOX, capecitabine, and oxaliplatin (CapeOX) and irinotecan given with leucovorin-modulated bolus and infusional 5-FU (FOLFIRI) are considered to be equally effective, but have different toxicity profiles.\textsuperscript{17–27} Several iterations of FOLFOX have not been directly compared. The assumption that each schedule has comparable efficacy is based on similar outcomes in sequential trials. Modified FOLFOX6 is the most commonly used schedule in clinical trials. Some oncologists prefer a modified FOLFOX7 regimen that omits bolus 5-FU to reduce potential toxicities.\textsuperscript{28,29}

There may be regional differences in tolerability to capecitabine, possibly based on differences in reduced folate supplementation in foods in North America.\textsuperscript{30–32} The most commonly used dose of capecitabine monotherapy in European studies is 1250 mg/m\textsuperscript{2} by mouth twice daily for 14 of 21 days.\textsuperscript{22} NCCN Guidelines recommend capecitabine at 850 to 1250 mg/m\textsuperscript{2} by mouth twice daily for 14 of 21 days.\textsuperscript{15} Dose reduction of capecitabine by 25\% is recommended on the product label for patients with moderately impaired renal function (creatinine clearance, 30–50 mL/min), and its use is not recommended in patients with creatinine clearance less than 30 mL/min.

In patients who have received prior adjuvant therapy with an oxaliplatin-fluoropyrimidine regimen, selection of an irinotecan-based treatment plan is reasonable. If an oxaliplatin-fluoropyrimidine therapy is selected in a treatment-naïve patient, then careful attention should be given to persistent sensory neuropathy that is delayed in onset and generally continues to worsen even after reduction or discontinuation. Calcium and magnesium infusions given before and after oxaliplatin do not ameliorate acute cold-related or cumulative sensory neuropathy.\textsuperscript{33} Some experts advocate that oxaliplatin be discontinued after 6 to 8 doses, and allowing the patient to continue on maintenance therapy with the other agents in the regimen.\textsuperscript{28} Oxaliplatin can then be reintroduced on disease progression (partial stop and go).\textsuperscript{28} Clinical trials mandate oxaliplatin dose reductions or discontinuation based on the severity of neurologic symptoms. Even if the patient does not complain of persistent neuropathy, oxaliplatin treatment should not typically be continued beyond 6 months. Chronic oxaliplatin-associated neuropathy is thought to result from the dose-dependent accumulation of platinum within the dorsal root ganglia, causing neuronal atrophy.\textsuperscript{34,35} The sensory neuropathy usually affects the extremities, but disabling sensorimotor polyneuropathy has also been reported.\textsuperscript{34,26,27,34–37} Although gradual improvement in the sensory neuropathy occurs in some patients, others will have permanent, disabling symptoms.\textsuperscript{34–37}

The Optimox 2 trial randomized 220 patients to 6 cycles of modified FOLFOX7 (oxaliplatin, 100 mg/m\textsuperscript{2}; leucovorin, 400 mg/m\textsuperscript{2}; and 5-FU infusion, 3000 mg/m\textsuperscript{2} given over 46 hours) followed by maintenance leucovorin and bolus and infusional 5-FU given until progression versus a complete stop of chemotherapy.\textsuperscript{38} Reintroduction of FOLFOX7 was planned after tumor progression in both arms.
unless this progression occurred during the initial 3 months of therapy. The primary end point was duration of disease control (DDC), defined as the sum of progression-free survival (PFS) in patients whose disease progressed on initial therapy, or the sum of the PFS for the initial chemotherapy and PFS after reintroduction of chemotherapy. The median DDC was 13.1 months in patients randomized to maintenance therapy versus 9.2 months in those randomized to complete stop. In contrast, another study evaluated intermittent versus continuous palliative chemotherapy in 354 patients with advanced CRC receiving either leucovorin, 200 mg/m², followed by bolus 5-FU, 400 mg/m², then infusional 5-FU, 600 mg/m² over 22 hours on days 1 and 2 every other week, continuous 5-FU, 300 mg/m² per 24 hours, or raltrexed, 3 mg/m² given intravenously over 15 minutes every 3 weeks.¹⁹ No clear survival benefit was seen in continuing therapy indefinitely until disease progression (hazard ratio [HR], 0.87 in favor of intermittent therapy; P=.23), and fewer adverse effects were seen with intermittent therapy.

FOLFOXIRI, which combines folinic acid, bolus and infusional 5-FU, oxaliplatin, and irinotecan, can be used in first-line therapy for metastatic CRC.²⁵ Because of the toxicities, this may represent overly aggressive treatment for patients with incurable stage IV disease.

Some patients with incurable stage IV CRC may wish to avoid the potential toxicity of either oxaliplatin or irinotecan, and initial therapy with a fluoropyrimidine is reasonable.⁴⁰–⁴² Table 1 summarizes clinical results of chemotherapy-only options for metastatic CRC. Time to progression is defined as time from randomization to time of documented disease progression. PFS duration is defined as the time from randomization to objective tumor progression or death, and is generally preferred as an end point.⁴¹ Bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor (VEGF) A, may be combined with chemotherapy.⁴⁴–⁴⁸ Relative contraindications to the use of bevacizumab include active bleeding, a pathologic condition associated with a high risk of bleeding; a history of transient ischemic attack, cerebrovascular disease, myocardial infarction, or unstable angina within the prior 6 months; uncontrolled hypertension; significant proteinuria (>1000 mg per 24 hours); a major surgical procedure within the prior 4 to 6 weeks; and a nonhealing wound or fistula. The results of bevacizumab combined with chemotherapy are summarized in Table 2.

For patients whose tumors contain a wild-type KRAS gene, some randomized clinical trials demonstrated a benefit of anti-EGFR antibodies when combined with chemotherapy.⁴⁹–⁵² Table 3 shows the various treatment arms from phase III trials involving anti-EGFR antibody plus chemotherapy. Randomized trial data show a benefit of cetuximab, a chimeric antibody, in combination with FOLFIRI, and panitumumab, a fully human antibody, in combination with either FOLFOX (first-line) or FOLFIRI (second-line). Randomized trials evaluating cetuximab plus oxaliplatin–fluoropyrimidine regimens have not shown a significant improvement in survival.⁵¹–⁵⁴ No direct comparisons of panitumumab and cetuximab exist; when the results of studies of similar design are compared, the benefit of either antibody seems comparable. Most clinical trials of cetuximab involved a loading dose of 400 mg/m² given intravenously over 2 hours for week 1 followed by 250 mg/m² given intravenously over 1 hour weekly. An every-other-week schedule of cetuximab uses 500 mg/m² given intravenously over 2 hours. The standard schedule of panitumumab is 6 mg/kg given intravenously every 2 weeks. The impact of anti-EGFR–associated toxicities on quality of life should be considered when deciding whether to use either cetuximab or panitumumab in the initial therapy of patients with incurable metastatic CRC whose tumors contain a wild-type KRAS gene.

Three randomized trials indicate a worse outcome when either panitumumab or cetuximab are combined with bevacizumab and 5-FU–based therapy; such combination therapy is not currently recommended for metastatic CRC outside of a clinical trial.⁵⁵–⁵⁷

**Options for Second-Line Therapy**

If a fluoropyrimidine was selected as initial treatment for metastatic CRC, oxaliplatin or irinotecan can be introduced as part of a combination regimen. If the patient received prior oxaliplatin-based therapy as initial treatment for metastatic CRC, then an irinotecan-based regimen is reasonable. If an irinotecan-based regimen was used, then second-line therapy with oxaliplatin plus fluoropyrimidine is reasonable.²⁵,⁵⁸,⁵⁹ Bevacizumab can be used with second-line therapy.⁶⁰
A prospective phase III trial compared the worth of continued use of bevacizumab (either 5 mg/kg every other week or 7.5 mg/kg every 3 weeks) or no additional bevacizumab with either oxaliplatin or irinotecan plus a fluoropyrimidine in 820 patients with metastatic CRC who experienced disease progression within 3 months of prior therapy with bevacizumab plus standard first-line therapy. The choice of fluoropyrimidine was discretionary. Patients who received prior irinotecan switched to oxaliplatin, and vice versa. The intent-to-treat population was 819 patients. Patients who received

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>n</th>
<th>RR</th>
<th>TTP or PFS (mo)</th>
<th>Median Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>LV, 200 mg/m² over 2 h, bolus 5-FU, 400 mg/m² then 5-FU, 600 mg/m² over 24 h, days 1 and 2 q2wk</td>
<td>217</td>
<td>32.6%</td>
<td>6.4a</td>
<td>14.3</td>
</tr>
<tr>
<td>18</td>
<td>LV, 200 mg/m² over 2 h, bolus 5-FU, 400 mg/m² then 5-FU, 600 mg/m² over 24 h, days 1 and 2 q2wk</td>
<td>210</td>
<td>22.3%</td>
<td>6.2a</td>
<td>14.7</td>
</tr>
<tr>
<td>19</td>
<td>LV, 500 mg/m² over 2 h, 5-FU, 2600 mg/m² over 24 h weekly for 6 of 8 wk</td>
<td>91</td>
<td>44.0%</td>
<td>7.1a</td>
<td>16.6</td>
</tr>
<tr>
<td>20</td>
<td>LV, 500 mg/m² over 2 h, 5-FU, 2600 mg/m² over 24 h weekly for 6 of 8 wk</td>
<td>213</td>
<td>34.4%</td>
<td>6.4a</td>
<td>16.9</td>
</tr>
<tr>
<td>21</td>
<td>Cape, 1250 mg/m² twice daily for 14 of 21 d</td>
<td>301</td>
<td>24.8%</td>
<td>4.3a</td>
<td>12.5</td>
</tr>
<tr>
<td>22</td>
<td>Cape, 1250 mg/m² twice daily for 14 of 21 d</td>
<td>302</td>
<td>19.9%</td>
<td>5.2a</td>
<td>13.2</td>
</tr>
<tr>
<td>23</td>
<td>Investigator choice: IRI, 180 mg/m² + l-LV, 100 mg/m² over 2 h, bolus 5-FU, 400 mg/m² then 5-FU, 600 mg/m² over 22 h, days 1 and 2 q2wk OR IRI, 80 mg/m² + LV, 500 mg/m² over 2 h + 5-FU, 2300 mg/m² over 24 h qwk for 6 of 8 wk</td>
<td>198</td>
<td>35.0%</td>
<td>6.7a</td>
<td>17.4</td>
</tr>
<tr>
<td>24</td>
<td>IRI, 180 mg/m² + l-LV, 100 mg/m² over 2 h, bolus 5-FU, 400 mg/m² then 5-FU, 600 mg/m² over 22 h, days 1 and 2 q2wk</td>
<td>164</td>
<td>31.0%</td>
<td>7.0b</td>
<td>14.0</td>
</tr>
<tr>
<td>25</td>
<td>IRI, 180 mg/m² + l-LV, 100 mg/m² over 2 h, bolus 5-FU, 400 mg/m² then 5-FU, 600 mg/m² over 22 h, days 1 and 2 q2wk</td>
<td>122</td>
<td>41.0%</td>
<td>6.9b</td>
<td>16.7</td>
</tr>
<tr>
<td>20</td>
<td>IRI, 80 mg/m² + LV, 500 mg/m² over 2 h, 5-FU, 2000 mg/m² over 24 h weekly for 6 of 8 wk</td>
<td>213</td>
<td>62.2%</td>
<td>8.5a</td>
<td>20.1</td>
</tr>
<tr>
<td>26</td>
<td>Ox, 85 mg/m² + LV, 200 mg/m² over 2 h, bolus 5-FU, 400 mg/m² then 5-FU, 600 mg/m² over 22 h, days 1 and 2 q2wk</td>
<td>210</td>
<td>50.7%</td>
<td>9.0a</td>
<td>16.2</td>
</tr>
<tr>
<td>24</td>
<td>Ox, 85 mg/m² + LV, 200 mg/m² over 2 h, bolus 5-FU, 400 mg/m² then 5-FU, 600 mg/m² over 22 h, days 1 and 2 q2wk</td>
<td>267</td>
<td>45.0%</td>
<td>8.7a</td>
<td>19.5</td>
</tr>
<tr>
<td>27</td>
<td>Ox, 85 mg/m² + LV, 200 mg/m² over 2 h, bolus 5-FU, 400 mg/m² then 5-FU, 600 mg/m² over 22 h, days 1 and 2 q2wk</td>
<td>172</td>
<td>34.0%</td>
<td>7.0a</td>
<td>15.0</td>
</tr>
<tr>
<td>27</td>
<td>Ox, 130 mg/m² day 1, Cape, 1000 mg/m² twice daily from day 1 evening to day 15 morning q3wk alone OR with placebo q2wk OR with bevacizumab, 5 mg/kg q2wk</td>
<td>1017</td>
<td>48.0%</td>
<td>8.5b</td>
<td>19.5</td>
</tr>
<tr>
<td>25</td>
<td>IRI, 165 mg/m², Ox, 85 mg/m² + l-LV, 200 mg/m², 5-FU, 2300 mg/m² over 48 h q2wk for 6 mo as “induction therapy”</td>
<td>122</td>
<td>66.0%</td>
<td>9.8b</td>
<td>22.6</td>
</tr>
</tbody>
</table>

Abbreviations: Cape, capecitabine; l-LV, infusional leucovorin; IRI, irinotecan; LV, leucovorin; Ox, oxaliplatin; PFS, median progression-free survival; RR, response rate; TTP, median time to progression.

aMedian time to progression.
bProgression-free survival.
Treatments for Metastatic Colorectal Cancer

Table 2 Clinical Results From Randomized Phase III Trials Involving Chemotherapy Plus Bevacizumab Regimens in First-Line Treatment for Metastatic Colorectal Cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>n</th>
<th>RR</th>
<th>PFS (mo)</th>
<th>Median Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>44</td>
<td>IRI, 125 mg/m², LV, 20 mg/m², bolus 5-FU, 500 mg/m² qwk x 4 of 6 wk + Bev, 5 mg/kg q2wk</td>
<td>402</td>
<td>44.7%</td>
<td>10.6</td>
<td>20.3</td>
</tr>
<tr>
<td>45</td>
<td>LV, 500 mg/m², bolus 5-FU, 500 mg/m² qwk x 6 of 8 wk + Bev, 5 mg/kg q2wk</td>
<td>110</td>
<td>40.0%</td>
<td>8.8</td>
<td>18.3</td>
</tr>
<tr>
<td>46</td>
<td>Ox, 130 mg/m² day 1 + Cape, 1000 mg/m² twice daily days 1–14 + Bev, 7.5 mg/kg day 1 q3wk</td>
<td>350</td>
<td>47.0%</td>
<td>9.4</td>
<td>21.3</td>
</tr>
<tr>
<td></td>
<td>Ox, 85 mg/m² + LV, 200 mg/m² over 2 h, bolus 5-FU, 400 mg/m² then 5-FU, 600 mg/m² over 24 h days 1 and 2 + Bev, 5 mg/kg q2wk</td>
<td>349</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>Investigator choice: Bev q2wk + Ox-FU/LV</td>
<td>410</td>
<td>48.0%</td>
<td>10.5</td>
<td>24.5</td>
</tr>
<tr>
<td>48</td>
<td>Investigator choice: Bev q2wk + IRI-FU/LV</td>
<td>115</td>
<td>40.0%</td>
<td>11.9</td>
<td>20.5</td>
</tr>
<tr>
<td>48</td>
<td>Cape, 1250 mg/m² twice daily for 14 of 21 days + Bev, 7.5 mg/kg on day 1</td>
<td>157</td>
<td>38.1%</td>
<td>8.5</td>
<td>18.9</td>
</tr>
</tbody>
</table>

Abbreviations: Bev, bevacizumab; Cape, capecitabine; IRI, irinotecan; LV, leucovorin; Ox, oxaliplatin; PFS, median progression-free survival; RR, response rate.

continuation bevacizumab had a superior overall survival (11.2 vs 9.8 months; HR, 0.81; P=0.0062). Grades 3 through 5 toxicities of the following types were more common in the bevacizumab-plus-chemotherapy group: bleeding or hemorrhage (2.0% vs 0.2%), gastrointestinal perforation (1.7% vs 0.7%), venous thromboembolism (4.7% vs 2.9%), neutropenia (16.2% vs 12.7%), mucositis (3.2% vs 1.0%), and diarrhea (10.0% vs 8.3%).

Another option is ziv-aflibercept (also known as VEGF Trap), a recombinant fusion protein that contains VEGF-binding portions from the extracellular domains of human VEGF receptors 1 and 2, fused to the Fc portion of human immunoglobulin (Ig)G1. Ziv-aflibercept targets VEGF-A, VEGF-B, and placental growth factor. A phase III trial compared ziv-aflibercept or placebo given every 2 weeks with FOLFI R1 in 1226 patients with metastatic CRC who had prior oxaliplatin-based therapy.62 Patients receiving ziv-aflibercept/FOLFI R1 had an improvement in overall survival (13.5 vs 12.1 months; HR, 0.82; P=0.0032). In addition to anticipated anti-VEGF treatment-related adverse effects, common side effects associated with FOLFI R1 were also increased. Grades 3 through 4 toxicities were as follows: hypertension (19.3% vs 15.0%), proteinuria (7.8% vs 12.2%), hemorrhage (3.0% vs 1.7%), arterial thromboembolism (1.8% vs 0.5%), diarrhea (19.3% vs 7.8%), stomatitis (13.8% vs 5.0%), infection (12.3% vs 6.9%), neutropenia (36.7% vs 29.5%), and neutropenic complications (5.7% vs 2.9%). The selection of either bevacizumab or ziv-aflibercept may depend on physician preference, cost, and formulary considerations.

Second-line therapy in patients who receive initial FOLFOXIRI is limited, particularly if bevacizumab was used. If the tumor contains a wild-type KRAS gene, anti-EGFR therapy would be reasonable. If the tumor has a mutation in the KRAS gene, then treatment with regorafenib (discussed in the next section) can be considered.

Options for Third-Line Therapy

If a patient whose tumor has a normal KRAS gene has not received a prior anti-EGFR antibody, then either cetuximab or panitumumab may be used as monotherapy.63,64 The combination of cetuximab or panitumumab with irinotecan is also reasonable, because the response rate and PFS seem to be superior compared with anti-EGFR antibody alone.65 Retrospective analyses suggest that patients with wild-type KRAS, but whose tumor contains a mutation in codon 600 of the BRAF gene, are unlikely to benefit from anti-EGFR antibody in the third-line setting.66 If the patient experienced disease progression on prior anti-EGFR therapy, there is no reason to retry the same anti-EGFR antibody, and there is no reason to expect that the alternate anti-EGFR antibody will have efficacy.
Warning that severe and sometimes fatal hepatotoxicity may occur. Hepatic function must be monitored before and during treatment. Hepatotoxicity is manifested through elevated liver function tests, and liver biopsies will show hepatocellular necrosis. Regorafenib should be interrupted and then either reduced or discontinued in these cases.

There may be patients who have received prior oxaliplatin or irinotecan in whom these treatments were discontinued for reasons other than disease progression (eg, to allow a treatment break, maintenance therapy without these drugs, toxicity). In selected cases, oxaliplatin or irinotecan may be reintroduced. The reintroduction of cytotoxic agents should rely on best clinical judgement regarding toxicities, prior treatment response, and duration of prior response. If oxaliplatin was discontinued previously because of cumulative sensory neuropathy, this symptom should have resolved to grade 1 or less before oxaliplatin reintroduction. A small randomized study reported that oral L-glutamine, 15 g

**Table 3 Clinical Results From Randomized Phase III Trials Involving Chemotherapy Plus Anti-EGFR Antibody Regimens in First-Line Treatment for Wild-Type KRAS Metastatic Colorectal Cancer**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>n</th>
<th>RR</th>
<th>PFS (mo)</th>
<th>Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>49</td>
<td>IRI, 180 mg/m², LV, 400 mg/m², bolus 5-FU, 400 mg/m² then 5-FU, 2400 mg/m² over 46 h q2wk alone</td>
<td>350</td>
<td>39.7%</td>
<td>8.4</td>
<td>20.0</td>
</tr>
<tr>
<td>OR</td>
<td>+ CETUX, 400 mg/m² over 2 h wk 1 then 250 mg/m² over 1 h qwk</td>
<td>316</td>
<td>57.3%</td>
<td>9.9</td>
<td>23.5</td>
</tr>
<tr>
<td>50</td>
<td>Ox, 85 mg/m² + LV, 200 mg/m² over 2 h, bolus 5-FU, 400 mg/m² then 5-FU, 600 mg/m² over 22 h days 1 and 2 q2wk alone</td>
<td>331</td>
<td>48.0%</td>
<td>8.0</td>
<td>19.3</td>
</tr>
<tr>
<td>OR</td>
<td>+ PANITUM, 6 mg/kg</td>
<td>325</td>
<td>55.0%</td>
<td>9.6</td>
<td>23.0</td>
</tr>
<tr>
<td>51</td>
<td>Investigator choice: Ox, 130 mg/m² day 1 + Cape, 850–1000 mg/m² twice daily days 1–14 q3wk</td>
<td>367</td>
<td>57.0%</td>
<td>8.6</td>
<td>17.9</td>
</tr>
<tr>
<td>OR</td>
<td>Ox, 85 mg/m² + LV, 350 mg/m² over 2 h, bolus 5-FU, 400 mg/m² then 5-FU, 2400 mg/m² over 46 h q2wk alone</td>
<td>362</td>
<td>64.0%</td>
<td>8.6</td>
<td>17.0</td>
</tr>
<tr>
<td>OR</td>
<td>+ CETUX, 400 mg/m² over 2 h wk 1 then 250 mg/m² over 1 h qwk</td>
<td>97</td>
<td>47.0%</td>
<td>8.7</td>
<td>22.0</td>
</tr>
<tr>
<td>52</td>
<td>Ox, 85 mg/m² over 0.5–1.5 h day 1 + bolus 5-FU, 500 mg/m² + bolus LV, 60 mg/m² 30 min later alone</td>
<td>97</td>
<td>46.0%</td>
<td>7.9</td>
<td>20.1</td>
</tr>
<tr>
<td>OR</td>
<td>+ CETUX, 400 mg/m² over 2 h wk 1 then 250 mg/m² over 1 h qwk</td>
<td>109</td>
<td>51.0%</td>
<td>7.5</td>
<td>21.4</td>
</tr>
</tbody>
</table>

Abbreviations: Cape, capecitabine; CETUX, cetuximab; EGFR, epidermal growth factor receptor; IRI, irinotecan; LV, leucovorin; Ox, oxaliplatin; PANITUM, panitumumab; PFS, median progression-free survival; RR, response rate.

If the patient’s tumor has a KRAS-mutant gene, and has progressed on prior oxaliplatin- and irinotecan-based therapy, regorafenib can be introduced. Regorafenib is an oral multikinase inhibitor that blocks the activity of VEGFR1, VEGFR2, VEGFR3, TIE2 (regulation of tumor angiogenesis), KIT, RET, RAF1, BRAF, and mutant BRAF (v600e; regulation of oncogenesis), and PDGFR and FGFR (regulation of the tumor microenvironment). A phase III trial randomized 760 patients with progressive disease during or within 3 months after the last of all approved standard therapies (2:1) to either regorafenib, 160 mg by mouth daily for 21 of 28 days, or placebo. Overall survival was improved in the regorafenib arm (6.4 vs 5.0 months; HR, 0.77). The most common grade 3 or higher toxicities associated with regorafenib included hand-foot skin reaction (17.0%), fatigue (10.0%), diarrhea (36.7%), hypertension (36.7%), and rash or desquamation (29.6%). The approved label includes a black box warning that severe and sometimes fatal hepatotoxicity may occur. Hepatic function must be monitored before and during treatment. Hepatotoxicity is manifested through elevated liver function tests, and liver biopsies will show hepatocellular necrosis. Regorafenib should be interrupted and then either reduced or discontinued in these cases. There may be patients who have received prior oxaliplatin or irinotecan in whom these treatments were discontinued for reasons other than disease progression (eg, to allow a treatment break, maintenance therapy without these drugs, toxicity). In selected cases, oxaliplatin or irinotecan may be reintroduced. The reintroduction of cytotoxic agents should rely on best clinical judgement regarding toxicities, prior treatment response, and duration of prior response. If oxaliplatin was discontinued previously because of cumulative sensory neuropathy, this symptom should have resolved to grade 1 or less before oxaliplatin reintroduction. A small randomized study reported that oral L-glutamine, 15 g
twice daily on days 1 through 7, significantly reduced the incidence and severity of oxaliplatin-associated neuropathy in patients with metastatic CRC receiving oxaliplatin, 85 mg/m² every 2 weeks with bolus 5-FU/leucovorin, with no significant difference in overall response rate or survival. Another small randomized study reported that oxcarbazepine, 600 mg by mouth twice daily, reduced oxaliplatin-induced neuropathy in patients receiving FOLFOX4.

Patients experiencing disease progression while on available options can be considered for participation in clinical trials evaluating investigational new strategies if their performance status is adequate. Otherwise, the focus should be on best supportive care.

References


5. Poultsides GA, Paty PB. Reassessing the need for primary tumor resection in clinical trials evaluating investigational new strategies if their performance status is adequate. Otherwise, the focus should be on best supportive care.


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