
Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced health care team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are provided only to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data become available. The NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Systemic Therapy for Advanced or Metastatic Disease - Chemotherapy Regimens

NOTE: All recommendations are category 2A unless otherwise indicated.

<table>
<thead>
<tr>
<th>REGIMEN</th>
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<tbody>
<tr>
<td>mFOLFOX6-5,6,13</td>
<td>Day 1: Oxaliplatin 85mg/m² IV over 2 hours</td>
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<td>Day 1: Leucovorin 400mg/m² IV over 2 hours</td>
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<td>Days 1–2: 5-FU 400mg/m² IV bolus on day 1, then 1,200mg/m²/day × 2 days (total 2,400mg/m² over 46–48 hours) IV continuous infusion</td>
<td>Repeat cycle every 2 weeks.</td>
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<tr>
<td>mFOLFOX7-5,9</td>
<td>Day 1: Oxaliplatin 85mg/m² IV + leucovorin 400mg/m² IV followed by</td>
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<td>Days 1–2: 5-FU 1,200mg/m²/day (total 2,400mg/m² over 46–48 hours) IV continuous infusion</td>
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<tr>
<td>FOLFOX + bevacizumab5</td>
<td>Day 1: Oxaliplatin 85mg/m² IV over 2 hours</td>
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<td>Day 1: Bevacizumab 5mg/kg IV. Repeat cycle every 2 weeks.</td>
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<td>FOLFOX + panitumumab3</td>
<td>Day 1: Oxaliplatin 85mg/m² IV over 2 hours</td>
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<td>(KRAS/NRAS WT gene only)13</td>
<td>Day 1: Leucovorin 400mg/m² IV over 2 hours</td>
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<td>Days 1–2: 5-FU 400mg/m² IV bolus on day 1, then 1,200mg/m²/day × 2 days (total 2,400mg/m² over 46–48 hours) IV continuous infusion</td>
<td>Day 1: Panitumumab 6mg/kg IV over 60 minutes. Repeat cycle every 2 weeks.</td>
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<tr>
<td>FOLFOX + cetuximab3</td>
<td>Day 1: Oxaliplatin 85mg/m² IV over 2 hours</td>
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<td>Day 1: Leucovorin 400mg/m² IV over 2 hours</td>
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<td>Days 1–3: 5-FU 400mg/m² IV bolus on day 1, then 1,200mg/m²/day × 2 days (total 2,400mg/m² over 46–48 hours) IV continuous infusion</td>
<td>Day 1: Cetuximab 500mg/m² IV over 2 days every 2 weeks.</td>
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<tr>
<td>CapeOX6</td>
<td>Day 1: Oxaliplatin 130mg/m² IV over 2 hours</td>
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<td>Days 1–14: Capetebicine 850–1,000mg/m² orally twice daily. Repeat cycle every 3 weeks.</td>
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<tr>
<td>CapeOX + bevacizumab2</td>
<td>Day 1: Oxaliplatin 130mg/m² IV over 2 hours</td>
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<td>Days 1–14: Capetebicine 850–1,000mg/m² orally twice daily. Repeat cycle every 3 weeks.</td>
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<tr>
<td>FOLFIRI10,11,14</td>
<td>Day 1: Irinotecan 180mg/m² IV over 30–90 minutes</td>
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<td>Day 1: Leucovorin 400mg/m² IV infusion to match duration of irinotecan infusion</td>
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<td>Days 1–2: 5-FU 400mg/m² IV bolus day 1, then 1,200mg/m²/day × 2 days (total 2,400mg/m² over 46–48 hours) continuous infusion</td>
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<td>FOLFIRI + bevacizumab12</td>
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<td>Day 1: Bevacizumab 5mg/kg IV. Repeat cycle every 2 weeks.</td>
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<td>FOLFIRI + cetuximab13</td>
<td>Day 1: Irinotecan 180mg/m² IV over 30–90 minutes</td>
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<td>(KRAS/NRAS WT gene only)13,14</td>
<td>Day 1: Leucovorin 400mg/m² IV infusion to match duration of irinotecan infusion</td>
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<td>Days 1–2: 5-FU 400mg/m² IV bolus day 1, then 1,200mg/m²/day × 2 days (total 2,400mg/m² over 46–48 hours) continuous infusion</td>
<td>Day 1 and 8: Cetuximab 400mg/m² IV over 2 hours first infusion, then 250mg/m² IV over 60 minutes. Repeat cycle every 2 weeks.</td>
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<td>OR Day 1: Cetuximab 500mg/m² IV over 2 hours. Repeat cycle every 2 weeks.</td>
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| **FOLFIRI + panitumumab (KRAS/NRAS WT gene only)**<sup>15</sup> | **Day 1:** 1: Irinotecan 180mg/m<sup>2</sup> IV over 30–90 minutes  
**Days 1 and 8:** 1: Leucovorin 400mg/m<sup>2</sup> IV infusion to match duration of irinotecan infusion  
**Days 1–2:** 5-FU 400mg/m<sup>2</sup> IV bolus day 1, then 1,200mg/m<sup>2</sup>/day × 2 days (total 2,400mg/m<sup>2</sup> over 46–48 hours) IV continuous infusion  
**Day 1:** Panitumumab 6mg/kg IV over 60 minutes. Repeat cycle every 2 weeks. |
| **FOLFIRI + ziv-aflibercept**<sup>16</sup> | **Day 1:** 1: Irinotecan 180mg/m<sup>2</sup> IV over 30–90 minutes  
**Day 1:** Leucovorin 400mg/m<sup>2</sup> IV infusion to match duration of irinotecan infusion  
**Days 1–2:** 5-FU 400mg/m<sup>2</sup> IV bolus day 1, then 1,200mg/m<sup>2</sup>/day × 2 days (total 2,400mg/m<sup>2</sup> over 46–48 hours) continuous infusion  
**Day 1:** Ziv-aflibercept 4mg/kg IV over 1 hour. Repeat cycle every 2 weeks. |
| **FOLFIRI + ramucirumab**<sup>17</sup> | **Day 1:** 1: Irinotecan 180mg/m<sup>2</sup> IV over 30–90 minutes  
**Day 1:** Leucovorin 400mg/m<sup>2</sup> IV infusion to match duration of irinotecan infusion  
**Days 1–2:** 5-FU 400mg/m<sup>2</sup> IV bolus day 1, then 1,200mg/m<sup>2</sup>/day × 2 days (total 2,400mg/m<sup>2</sup> over 46–48 hours) IV continuous infusion  
**Day 1:** Ramucirumab 8mg/kg IV over 60 minutes. Repeat cycle every 2 weeks. |
| **FOLFOXIRI**<sup>18,a</sup> | **Day 1:** 1: Irinotecan 165mg/m<sup>2</sup> over 30 to 90 minutes + oxaliplatin 85mg/m<sup>2</sup> over 2 hours  
**Day 1:** Leucovorin 400mg/m<sup>2</sup> over 2 hours  
**Days 1–2:** Fluorouracil 1,200mg/m<sup>2</sup> (2,400mg/m<sup>2</sup> over 48 hours) IV continuous infusion. Repeat cycle every 2 weeks. |
| **FOLFOXIRI + bevacizumab**<sup>19</sup> | **Day 1:** 1: Irinotecan 165mg/m<sup>2</sup> IV + oxaliplatin 85mg/m<sup>2</sup> IV  
**Day 1:** Leucovorin 400mg/m<sup>2</sup> IV  
**Days 1–3:** Fluorouracil 1,600mg/m<sup>2</sup>/day × 2 days (total 3,200mg/m<sup>2</sup> over 48 hours) continuous infusion starting on day 1, ±  
**Day 1:** Bevacizumab 5mg/kg IV. Repeat cycle every 2 weeks. |
| **IROX**<sup>20</sup> | **Day 1:** Oxaliplatin 85mg/m<sup>2</sup> IV over 2 hours, followed by irinotecan 200mg/m<sup>2</sup> IV over 30–90 minutes. Repeat cycle every 3 weeks. |
| **Bolus or infusional 5-FU/-leucovorin Roswell Park regimen**<sup>21</sup> | **Days 1, 8, 15, 22, 29, and 36:** Leucovorin 500mg/m<sup>2</sup> IV over 2 hours  
**Days 1, 8, 15, 22, 29, and 36:** 5-FU 500mg/m<sup>2</sup> IV bolus 1 hour after start of leucovorin. Repeat cycle every 8 weeks. |
| **Simplified biweekly infusional 5-FU/LV (sLV5FU2)**<sup>10,a</sup> | **Day 1:** Leucovorin 400mg/m<sup>2</sup> IV over 2 hours  
**Days 1–3:** 5-FU bolus 400mg/m<sup>2</sup> and then 1,200mg/m<sup>2</sup>/day × 2 days (total 2,400mg/m<sup>2</sup> over 46–48 hours) continuous infusion. Repeat cycle every 2 weeks. |
| **Weekly infusional LV5FU2**<sup>22</sup> | **Day 1:** Leucovorin 20mg/m<sup>2</sup> IV over 2 hours  
**Day 1:** 5-FU 500mg/m<sup>2</sup> IV bolus injection 1 hour after the start of leucovorin. Repeat cycle every week  
**OR**  
**Day 1:** 5-FU 2,600mg/m<sup>2</sup> by 24-hour infusion plus leucovorin 500mg/m<sup>2</sup> IV. Repeat cycle every week. |
| **Capecitabine**<sup>23</sup> | **Days 1–14:** Capecitabine 850–1,250mg/m<sup>2</sup> orally twice daily. Repeat cycle every 3 weeks. |
| **Capecitabine + bevacizumab**<sup>24</sup> | **Day 1:** Bevacizumab 7.5mg/kg IV  
**Days 1–14:** Capecitabine 850–1,250mg/m<sup>2</sup> orally twice daily. Repeat cycle every 3 weeks. |
| **Irinotecan**<sup>24,25</sup> | **Days 1 and 8:** Irinotecan 125mg/m<sup>2</sup> IV over 30–90 minutes. Repeat cycle every 3 weeks.  
**OR**  
**Day 1:** Irinotecan 300–350mg/m<sup>2</sup> IV over 30–90 minutes. Repeat cycle every 3 weeks.  
**OR**  
**Day 1:** Irinotecan 180mg/m<sup>2</sup> IV over 30–90 minutes. Repeat cycle every 2 weeks. |
| **Cetuximab (KRAS/NRAS WT gene only) + irinotecan**<sup>14,26</sup> | Cetuximab 400mg/m<sup>2</sup> first infusion, then 250mg/m<sup>2</sup>/IV weekly OR cetuximab 500mg/m<sup>2</sup>/IV every 2 weeks, +  
Irinotecan 300–350mg/m<sup>2</sup>/IV every 3 weeks OR irinotecan 180mg/m<sup>2</sup>/IV every 2 weeks OR irinotecan 125mg/m<sup>2</sup> on days 1 and 8 and repeat every 3 weeks. |
| **Irinotecan + cetuximab + vemurafenib (BRAF V600E mutation positive)**<sup>27</sup> | **Day 1:** Irinotecan 180mg/m<sup>2</sup> IV over 30–90 minutes + cetuximab 500mg/m<sup>2</sup>/IV  
**Days 1–14:** Vemurafenib 960mg orally twice daily. Repeat cycle every 2 weeks. |

<sup>continued</sup>
### COLON CANCER TREATMENT REGIMENS (Part 3 of 4)

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| Irinotecan + panitumumab + vemurafenib (BRAF V600E mutation positive) | **Day 1:** Irinotecan 180mg/m² IV over 30–90 minutes + panitumumab 6mg/kg IV over 60 minutes  
**Days 1–14:** Vemurafenib 960mg orally twice daily.  
Repeat cycle every 2 weeks. |
| Cetuximab (KRAS/NRAS WT gene only) | **Day 1:** Cetuximab 400mg/m² first infusion, then 250mg/m² IV weekly  
**OR**  
**Day 1:** Cetuximab 500mg/m² IV over 2 hours every 2 weeks  
Repeat cycle every 2 weeks. |
| Panitumumab (KRAS/NRAS WT gene only) | **Day 1:** Panitumumab 6mg/kg IV over 60 minutes.  
Repeat cycle every 2 weeks. |
| Regorafenib | **Days 1–21:** Regorafenib 160mg orally daily.  
**OR**  
**First Cycle:**  
**Days 1–7:** Regorafenib 80mg orally daily  
**Days 8–14:** Regorafenib 120mg orally daily  
**Days 15–21:** Regorafenib 160mg orally daily  
**Subsequent Cycles:**  
**Days 1–21:** Regorafenib 160mg orally daily  
Repeat cycle every 4 weeks. |
| Trifluridine + tipiracil | **Days 1–5 and 8–12:** Trifluridine + tipiracil 35mg/m² up to a maximum dose of 80mg/dose (based on the trifluridine component) orally twice daily.  
Repeat cycle every 28 days. |
| Pembrolizumab | **Day 1:** Pembrolizumab 2mg/kg IV  
**OR**  
**Day 1:** Pembrolizumab 200mg IV.  
Repeat every 3 weeks. |
| Nivolumab | **Day 1:** Nivolumab 3mg/kg IV  
**OR**  
**Day 1:** Nivolumab 240mg IV.  
Repeat every 2 weeks. |

#### Adjuvant Chemotherapy Regimens

- **Principals of Adjuvant Therapy:**
  - FOLFOX is superior to 5-FU/leucovorin for patients with stage III colon cancer.
  - Capecitabine/oxaliplatin is superior to bolus 5-FU/leucovorin for patients with stage III colon cancer.
  - Capecitabine appears to be equivalent to bolus 5-FU/leucovorin in patients with stage III colon cancer.
  - A survival benefit has not been demonstrated for the addition of oxaliplatin to 5-FU/leucovorin in stage II colon cancer. FOLFOX is reasonable for high-risk stage II patients and is not indicated for good- or average-risk patients with stage II colon cancer.
  - A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients age 70 and older has not been proven.
  - In patients staged as T1-3, N1 (low-risk stage III), 3 months of CapeOX is non-inferior to 6 months of CapeOX for disease-free survival; non-inferiority of 3 vs 6 months of FOLFOX has not been proven. In patients staged as T4, N1-2 or T any, N2 (high-risk stage III), 3 months of FOLFOX is inferior to 6 months of FOLFOX for disease-free survival, whereas non-inferiority of 3 vs 6 months of CapeOX has not been proven. Grade 3+ neurotoxicity rates are lower for patients who receive 3 months vs 6 months of treatment (3% vs 16% for FOLFOX; 3% vs 9% for CapeOX).  
  - **mFOLFOX6**  
    **Day 1:** Leucovorin 400mg/m² IV over 2 hours  
    **Days 1–2:** 5-FU 400mg/m² IV bolus on day 1, then 1,200mg/m²/day × 2 days (total 2,400mg/m² over 46–48 hours) continuous infusion.  
    Repeat cycle every 2 weeks.  
  - **Capecitabine**  
    **Days 1–14:** Capecitabine 1,000-1,250mg/m² orally twice daily.  
    Repeat cycle every 3 weeks for 24 weeks.  
  - **CapeOx**  
    **Day 1:** Oxaliplatin 130mg/m² IV over 2 hours  
    **Days 1–14:** Capecitabine 1,000mg/m² orally twice daily.  
    Repeat cycle every 3 weeks for 24 weeks.  
  - **5-FU/leucovorin**  
    Leucovorin 500mg/m² given as a 2-hour infusion and repeated weekly × 6 weeks, plus 5-FU 500mg/m² given IV bolus 1 hour after the start of leucovorin and repeated weekly × 6 weeks.  
    Repeat cycle every 8 weeks for 4 cycles.  
    **OR**  
    **Simplified biweekly infusional 5-FU/LV** (sLV5FU2)  
    Leucovorin 400mg/m² IV over 2 hours on day 1, followed by 5-FU bolus 400mg/m² and then 1,200mg/m²/day × 2 days (total 2,400mg/m² over 46-48 hours) continuous infusion.  
    Repeat cycle every 2 weeks.  

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*a* Leucovorin 400mg/m² is the equivalent of levoleucovorin 200mg/m².  
*b* The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1,000mg/m² twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine.

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*continued*