COLON CANCER TREATMENT REGIMENS (Part 1 of 4)

Clinical Trials: The NCCN recommends cancer patient participation in clinical trials as the gold standard for treatment.

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 Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network 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.

Advanced or Metastatic Disease[1]

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

REGIMEN	DOSING
mFOLFOX6[2-4ab]	**Day 1:** Oxaliplatin 85mg/m² IV over 2 hours **Day 1:** Leucovorin 400mg/m² IV over 2 hours **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. Repeat cycle every 2 weeks.
mFOLFOX6 + Bevacizumab[3,5ab]	**Day 1:** Oxaliplatin 85mg/m² IV over 2 hours **Day 1:** Leucovorin 400mg/m² IV over 2 hours **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 **Day 1:** Bevacizumab 5mg/kg IV. Repeat cycle every 2 weeks.
mFOLFOX6 + Panitumumab (*KRAS/NRAS* WT gene only)[3,6ab]	**Day 1:** Oxaliplatin 85mg/m² IV over 2 hours **Day 1:** Leucovorin 400mg/m² IV over 2 hours **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 **Day 1:** Panitumumab 6mg/kg IV over 60 minutes. Repeat cycle every 2 weeks.
FOLFOX + Cetuximab (*KRAS/NRAS* WT gene only)[3,7ab]	**Day 1:** Oxaliplatin 85mg/m² IV over 2 hours **Day 1:** Leucovorin 400mg/m² IV over 2 hours **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. Repeat cycle every 2 weeks, **plus** Cetuximab 400mg/m² IV over 2 hours for the first infusion, then 250mg/m² IV over 60 minutes weekly. **OR** **Day 1:** Cetuximab 500mg/m² IV over 2 hours every 2 weeks.
CapeOX[2c]	**Day 1:** Oxaliplatin 130mg/m² IV over 2 hours **Days 1–14:** Capecitabine 850–1,000mg/m² orally twice daily. Repeat cycle every 3 weeks.
CapeOX + Bevacizumab[2,8c]	**Day 1:** Oxaliplatin 130mg/m² IV over 2 hours **Days 1–14:** Capecitabine 850–1,000mg/m² orally twice daily **Day 1:** Bevacizumab 7.5mg/kg IV. Repeat cycle every 3 weeks.
FOLFIRI[9ab]	**Day 1:** Irinotecan 180mg/m² IV over 30–90 minutes **Day 1:** Leucovorin 400mg/m² IV infusion to match duration of irinotecan infusion **Days 1–3:** 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. Repeat cycle every 2 weeks.
FOLFIRI + Bevacizumab[9,10ab]	**Day 1:** Irinotecan 180mg/m² IV over 30–90 minutes **Day 1:** Leucovorin 400mg/m² IV infusion to match duration of irinotecan infusion **Days 1–3:** 5-FU 400mg/m² IV bolus day 1, then 1,200mg/m²/day × 2 days (total 2,400mg/m² over 46–48 hours) IV continuous infusion **Day 1:** Bevacizumab 5mg/kg IV. Repeat cycle every 2 weeks.
FOLFIRI + Cetuximab (*KRAS/NRAS* WT gene only)[9,10,12ab]	**Day 1:** Irinotecan 180mg/m² IV over 30–90 minutes **Day 1:** Leucovorin 400mg/m² IV infusion to match duration of irinotecan infusion **Days 1–3:** 5-FU 400mg/m² IV bolus day 1, then 1,200mg/m²/day × 2 days (total 2,400mg/m² over 46–48 hours) IV continuous infusion, **plus** **Days 1 and 8:** Cetuximab 400mg/m² IV over 2 hours first infusion, then 250mg/m² IV over 60 minutes. **OR** **Day 1:** Cetuximab 500mg/m² IV over 2 hours. Repeat cycle every 2 weeks

continued

COLON CANCER TREATMENT REGIMENS (Part 2 of 4)

Advanced or Metastatic Disease (continued)

REGIMEN	DOSING
FOLFIRI + Panitumumab (*KRAS/NRAS* WT gene only)[9,13a]	**Day 1:** Irinotecan 180mg/m² IV over 30–90 minutes **Day 1:** Leucovorin 400mg/m² IV infusion to match duration of irinotecan infusion **Days 1–3:** 5-FU 400mg/m² IV bolus day 1, then 1,200mg/m²/day × 2 days (total 2,400mg/m² over 46–48 hours) IV continuous infusion **Day 1:** Panitumumab 6mg/kg IV over 60 minutes. Repeat cycle every 2 weeks.
FOLFIRI + ziv-aflibercept[14ab]	**Day 1:** Irinotecan 180mg/m² IV over 30–90 minutes **Day 1:** Leucovorin 400mg/m² IV infusion to match duration of irinotecan infusion **Days 1–3:** 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 **Day 1:** Ziv-aflibercept 4mg/kg IV over 1 hour. Repeat cycle every 2 weeks.
FOLFIRI + Ramucirumab[15ab]	**Day 1:** Irinotecan 180mg/m² IV over 30–90 minutes **Day 1:** Leucovorin 400mg/m² IV infusion to match duration of irinotecan infusion **Days 1–3:** 5-FU 400mg/m² IV bolus day 1, then 1,200mg/m²/day × 2 day (total 2,400mg/m² over 46–48 hours) IV continuous infusion **Day 1:** Ramucirumab 8mg/kg IV over 60 minutes. Repeat cycle every 2 weeks.
Capecitabine[16]	**Days 1–14:** Capecitabine 850–1,250mg/m² orally twice daily. Repeat cycle every 3 weeks.
Capecitabine + Bevacizumab[8,16]	**Day 1:** Bevacizumab 7.5mg/kg IV **Days 1–14:** Capecitabine 850–1,250mg/m² orally twice daily. Repeat cycle every 3 weeks.
Bolus or infusional 5-FU/leucovorin Roswell Park regimen[17]	**Days 1, 8, 15, 22, 29, and 36:** Leucovorin 500mg/m² IV over 2 hours **Days 1, 8, 15, 22, 29, and 36:** 5-FU 500mg/m² IV bolus 1 hour after start of leucovorin. Repeat cycle every 8 weeks.
Simplified biweekly infusional 5-FU/LV (sLV5FU2)[9ab]	**Day 1:** Leucovorin 400mg/m² IV over 2 hours **Days 1–3:** 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.
Weekly infusional LV5FU2[18,19]	**Day 1:** Leucovorin 20mg/m² IV over 2 hours **Day 1:** 5-FU 500mg/m² IV bolus injection 1 hour after the start of leucovorin **Day 1:** 5-FU 2,600mg/m² by 24-hour infusion plus leucovorin 500mg/m² IV. Repeat cycle every week.
IROX[20]	**Day 1:** Oxaliplatin 85mg/m² IV over 2 hours, followed by irinotecan 200mg/m² IV over 30–90 minutes. Repeat cycle every 3 weeks.
FOLFOXIRI ± bevacizumab[21,22]	**Day 1:** Irinotecan 165mg/m² IV + oxaliplatin 85mg/m² IV **Day 1:** Leucovorin 400mg/m² IV **Days 1–3:** Fluorouracil 1,600mg/m²/day × 2 days (total 3,200mg/m² over 48 hours) continuous infusion starting on day 1, **±** **Day 1:** Bevacizumab 5mg/kg IV. Repeat cycle every 2 weeks.
Irinotecan[23,24]	**Days 1 and 8:** Irinotecan 125mg/m² IV over 30–90 minutes. Repeat cycle every 3 weeks. **OR** **Day 1:** Irinotecan 300–350mg/m² IV over 30–90 minutes. Repeat cycle every 3 weeks. **OR** **Day 1:** Irinotecan 180mg/m² IV over 30–90 minutes. Repeat cycle every 2 weeks.
Cetuximab (*KRAS/NRAS* WT gene only) + irinotecan[12,25]	Cetuximab 400mg/m² first infusion, then 250mg/m² IV weekly **OR** cetuximab 500mg/m² IV every 2 weeks, **±** Irinotecan 300–350mg/m² IV every 3 weeks **OR** irinotecan 180mg/m² IV every 2 weeks **OR** irinotecan 125mg/m² on days 1 and 8 and repeat every 3 weeks.
Cetuximab (*KRAS/NRAS* WT gene only)[12,23]	**Day 1:** Cetuximab 400mg/m² first infusion, then 250mg/m² IV weekly **OR** 500mg/m² IV over 2 hours. Repeat cycle every 2 weeks.
Panitumumab (*KRAS/NRAS* WT gene only)[26]	Panitumumab 6mg/kg IV over 60 minutes every 2 weeks.
Regorafenib[27]	**Days 1–21:** Regorafenib 160mg orally daily. Repeat cycle every 28 days.
Trifluridine + tipiracil[28]	**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.

continued

COLON CANCER TREATMENT REGIMENS (Part 3 of 4)

Adjuvant Chemotherapy Regimens

Principals of Adjuvant Therapy[1]

FOLFOX is superior to 5-FU/leucovorin for patients with stage III colon cancer.[29,30]

Capecitabine/oxaliplatin is superior to bolus 5-FU/ leucovorin for patients with stage III colon cancer. FLOX is an alternative to FOLFOX or CapeOx but FOLFOX or CapeOx is preferred.[31]

Capecitabine appears to be equivalent to bolus 5-FU/leucovorin in patients with stage III colon cancer.[32]

A survival benefit has not been demonstrated for the addition of oxaliplatin to 5-FU/leucovorin in stage II colon cancer.[33] 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.[33]

Bevacizumab, cetuximab, panitumumab, irinotecan, ziv-aflibercept, ramucirumab, regorafenib, or trifluridine + tipiracil should not be used in the adjuvant setting for patients with stage II or III colon cancer outside the setting of a clinical trial.

REGIMEN	DOSING
mFOLFOX6[34-36ab]	**Day 1:** Oxaliplatin 85mg/m² IV over 2 hours **Day 1:** Leucovorin 400mg/m² IV over 2 hours **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) continuous infusion. Repeat cycle every 2 weeks.
FLOX[37]	5-FU 500mg/m² IV bolus weekly × 6 + leucovorin 500mg/m² IV weekly × 6, each 8-week cycle × 3 with oxaliplatin 85mg/m² IV administered on weeks 1, 3, and 5 of each 8-week cycle × 3.
Capecitabine[38]	**Days 1–14:** Capecitabine 1,250mg/m² orally twice daily. Repeat cycle every 3 weeks for 24 weeks.
CapeOx[39,40]	**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[41,42ab]	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.

a Leucovorin 400mg/m² is the equivalent of levoleucovorin 200mg/m².

b NCCN recommends limiting chemotherapy orders to 24-hour units (i.e., 1,200mg/m²/day NOT 2,400mg/m² over 48 hours) to minimize medication errors.

c 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. The relative efficacy of CapeOx with lower starting doses of capecitabine has not been addressed in large-scale randomized trials.

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