RECTAL 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 healthcare 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 only provided to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data becomes 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.

General Treatment Notes[1]

- Consists of regimens that include both concurrent chemotherapy and radiotherapy and adjuvant chemotherapy.
- Six months of perioperative therapy is preferred in the adjuvant therapy setting.
- Following a shortage of leucovorin, the FDA approved levoleucovorin in combination with 5-FU for the palliative treatment of patients with advanced metastatic colorectal cancer. Levoleucovorin 200mg/m^2 is the equivalent of leucovorin 400mg/m^2.

Postoperative Adjuvant Therapy for Patients Not Receiving Preoperative Therapy[1]

Note: All recommendations are Category 2A unless otherwise indicated.

REGIMEN	DOSING
mFOLFOX6 (oxaliplatin + leucovorin + 5-fluorouracil [5-FU])[2–4a]	**Day 1:** Oxaliplatin 85mg/m^2 IV over 2 hours + leucovorin 400mg/m^2 IV over 2 hours, **followed by** 5-FU 400mg/m^2 IV bolus, **followed by** 5-FU 1,200mg/m^2/day IV x 2 days (total 2,400mg/m^2) as a 46–48-hour continuous infusion. Repeat cycle every 2 weeks for a total of 6 months perioperative therapy.
Capecitabine[5]	**Days 1–14:** Capecitabine 1,250mg/m^2 orally twice daily. Repeat cycle every 3 weeks for 6 months perioperative therapy.
CapeOX (oxaliplatin + capecitabine)[6,7]	**Day 1:** Oxaliplatin 130mg/m^2 IV over 2 hours **Days 1–14:** Capecitabine 1,000mg/m^2 orally twice daily. Repeat cycle every 3 weeks for 6 months perioperative therapy.
Simplified biweekly infusional 5-FU/LV (sLV5FU2)[8b]	**Day 1:** Leucovorin 400mg/m^2 IV, **followed by** 5-FU 400mg/m^2 IV bolus, **followed by** 5-FU 1,200mg/m^2/day IV x 2 days (total 2,400mg/m^2) as a 46–48 hour continuous infusion. Repeat cycle every 2 weeks for 6 months perioperative therapy.
5-FU + leucovorin[9]	5-FU 500mg/m^2 IV bolus weekly x 6 + leucovorin 500mg/m^2 IV weekly x 6, each 8-week cycle. Repeat cycle every 8 weeks for 6 months perioperative therapy.

Concurrent Chemotherapy + Radiotherapy[1]

External beam radiotherapy [XRT] + 5-FU[10]	**Days 1–5 OR 1–7:** 5-FU 225mg/m^2 IV over 24 hours during XRT.
XRT + 5-FU + leucovorin[11c]	**Days 1–4:** 5-FU 400mg/m^2 IV bolus + leucovorin 20mg/m^2 IV bolus. Repeat cycle during weeks 1 and 5 of XRT.
XRT + capecitabine[12,13]	**Days 1–5:** Capecitabine 825mg/m^2 twice daily + XRT. Repeat cycle weekly for 5 weeks.

Chemotherapy for Advanced or Metastatic Disease[1]

mFOLFOX6[2–4ab]	**Day 1:** Oxaliplatin 85mg/m^2 IV over 2 hours + leucovorin 400mg/m^2 IV over 2 hours **followed by** 5-FU 400mg/m^2 IV bolus, **followed by** 5-FU 1,200mg/m^2/day IV x 2 days (total 2,400mg/m^2) as a 46–48-hour continuous infusion. Repeat cycle every 2 weeks.
mFOLFOX6 + bevacizumab[3,14abd]	**Day 1:** Oxaliplatin 85mg/m^2 IV over 2 hours + leucovorin 400mg/m^2 IV over 2 hours, **followed by** 5-FU 400mg/m^2 IV bolus, **followed by** 5-FU 1,200mg/m^2/day IV x 2 days (total 2,400mg/m^2) as a 46–48-hour continuous infusion **Day 1:** Bevacizumab 5mg/kg IV. Repeat cycle every 2 weeks.
mFOLFOX6 + panitumumab[3,15ab] **(KRAS/NRAS wild-type gene only)**	**Day 1:** Oxaliplatin 85mg/m^2 IV over 2 hours + leucovorin 400mg/m^2 IV over 2 hours, **followed by** 5-FU 400mg/m^2 IV bolus, **followed by** 5-FU 1,200mg/m^2/day IV x 2 days (total 2,400mg/m^2) as a 46–48-hour continuous infusion **Day 1:** Panitumumab 6mg/kg IV over 1 hour. Repeat cycle every 2 weeks.
FOLFOX + cetuximab[2,16ab] **(KRAS/NRAS wild-type gene only)**	**Day 1:** Oxaliplatin 85mg/m^2 IV over 2 hours + leucovorin 400mg/m^2 IV over 2 hours, **followed by** 5-FU 400mg/m^2 IV bolus, **followed by** 5-FU 1,200mg/m^2/day IV x 2 days (total 2,400mg/m^2) as a 46–48-hour continuous infusion **PLUS** **Day 1:** Cetuximab 400mg/m^2 IV over 2 hours first infusion, then 250mg/m^2 IV over 60 minutes weekly. **OR** **Day 1:** Cetuximab 500mg/m^2 IV over 2 hours every 2 weeks.

continued

RECTAL CANCER TREATMENT REGIMENS (Part 2 of 4)

Chemotherapy for Advanced or Metastatic Disease[1] (continued)

REGIMEN	DOSING
CapeOX[6,7e]	**Day 1:** Oxaliplatin 130mg/m^2 IV **Days 1–14:** Capecitabine 850–1,000mg/m^2 orally twice daily. Repeat cycle every 3 weeks.
CapeOX + bevacizumab[6,7,17de]	**Day 1:** Oxaliplatin 130mg/m^2 IV **Days 1–14:** Capecitabine 850–1,000mg/m^2 orally twice daily **Day 1:** Bevacizumab 7.5mg/kg IV. Repeat cycle every 3 weeks.
FOLFIRI[18b]	**Day 1:** Irinotecan 180mg/m^2 IV over 30–90 minutes + leucovorin 400mg/m^2 IV, to match duration of irinotecan infusion, **followed by** 5-FU 400mg/m^2 IV bolus, **followed by** 5-FU 1,200mg/m^2/day IV x 2 days (total 2,400mg/m^2) as a 46–48-hour continuous infusion. Repeat cycle every 2 weeks.
FOLFIRI + bevacizumab[18,19bd]	**Day 1:** Irinotecan 180mg/m^2 IV over 30–90 minutes + leucovorin 400mg/m^2 IV, to match duration of irinotecan infusion, **followed by** 5-FU 400mg/m^2 IV bolus, **followed by** 5-FU 1,200mg/m^2/day IV x 2 days (total 2,400mg/m^2) as a 46–48-hour continuous infusion **Day 1:** Bevacizumab 5mg/kg IV. Repeat cycle every 2 weeks.
FOLFIRI + cetuximab[18, 20,21b] **(KRAS/NRAS wild-type gene only)**	**Day 1:** Irinotecan 180mg/m^2 IV + leucovorin 400mg/m^2 IV, to match duration off irinotecan infusion, **followed by** 5-FU 400mg/m^2 IV bolus, **followed by** 5-FU 1,200mg/m^2/day IV x 2 days (total 2,400mg/m^2) as a 46–48-hour continuous infusion. Repeat cycle every 2 weeks. **PLUS** **Day 1:** Cetuximab 400mg/m^2 IV over 2 hours first infusion, then 250mg/m^2 IV over 60 minutes weekly. **OR** **Day 1:** Cetuximab 500mg/m^2 IV over 2 hours every 2 weeks.
FOLFIRI + panitumumab[17,22b] **(KRAS/NRAS wild-type gene only)**	**Day 1:** Irinotecan 180mg/m^2 IV over 30–90 minutes + leucovorin 400mg/m^2 IV, to match duration of irinotecan infusion, **followed by** 5-FU 400mg/m^2 IV bolus, **followed by** 5-FU 1,200mg/m^2/day IV x 2 days (total 2,400mg/m^2) as a 46–48-hour continuous infusion. **Day 1:** Panitumumab 6mg/kg IV over 1 hour. Repeat cycle every 2 weeks.
FOLFIRI + ziv-aflibercept[23b]	**Day 1:** Irinotecan 180mg/m^2 IV + leucovorin 400mg/m^2 IV, **followed by** 5-FU 400mg/m^2 IV bolus, **followed by** 5-FU 1,200mg/m^2/day IV x 2 days (total 2,400mg/m^2) as a 46–48-hour continuous infusion **Day 1:** Ziv-aflibercept 4mg/kg IV. Repeat cycle every 2 weeks.
Capecitabine[24]	**Days 1–14:** Capecitabine 850–1,250mg/m^2 orally twice daily. Repeat cycle every 3 weeks.
Capecitabine + bevacizumab[17,24d]	**Days 1–14:** Capecitabine 850–1,250mg/m^2 orally twice daily **Day 1:** Bevacizumab 7.5mg/kg IV. Repeat cycle every 3 weeks.
Bolus or infusional 5-FU/ leucovorin (Roswell-Park Regimen)[25]	**Days 1, 8, 15, 22, 29, and 36:** Leucovorin 500mg/m^2 IV over 2 hours, **followed by** 5-FU 500mg/m^2 IV bolus 1 hour after start of leucovorin. Repeat cycle every 8 weeks.
Simplified biweekly infusional 5-FU/LV (sLV5FU2)[18]	**Day 1:** Leucovorin 400mg/m^2 IV over 2 hours, **followed by** 5-FU 400mg/m^2 IV bolus, **followed by** 5-FU 1,200mg/m^2/day IV x 2 days (total 2,400mg/m^2) as a 46–48-hour continuous infusion. Repeat cycle every 2 weeks.
Weekly 5-FU + leucovorin[26,27]	**Day 1:** Leucovorin 20mg/m^2 IV over 2 hours, **followed by** 5-FU 500mg/m^2 IV bolus 1 hour after start of leucovorin. Repeat cycle weekly. **OR** **Day 1:** Leucovorin 500mg/m^2 IV, **followed by** 5-FU 2,600mg/m^2 continuous infusion. Repeat cycle weekly.
IROX[28]	**Day 1:** Oxaliplatin 85mg/m^2 IV + irinotecan 200mg/m^2 IV over 30–90 minutes. Repeat cycle every 3 weeks.
FOLFOXIRI ± bevacizumab[29,30bd]	**Day 1:** Irinotecan 165mg/m^2 IV + oxaliplatin 85mg/m^2 IV + leucovorin 400mg/m^2 IV **Days 1 and 2:** 5-FU 1,600mg/m^2/day continuous infusion IV over 48 hours **±** **Day 1:** Bevacizumab 5mg/kg IV. Repeat cycle every 2 weeks.

continued

RECTAL CANCER TREATMENT REGIMENS (Part 3 of 4)

Chemotherapy for Advanced or Metastatic Disease[1] (continued)

REGIMEN	DOSING
Irinotecan[31,32]	**Days 1 and 8:** Irinotecan 125mg/m^2 IV over 30–90 minutes. Repeat cycle every 3 weeks. **OR** **Day 1:** Irinotecan 180mg/m^2 IV over 30–90 minutes. Repeat cycle every 2 weeks. **OR** **Day 1:** Irinotecan 300–350mg/m^2 IV over 30–90 minutes. Repeat cycle every 3 weeks.
Cetuximab + irinotecan[21] **(KRAS/NRAS wild-type gene only)**	**Day 1:** Cetuximab 400mg/m^2 IV first infusion, then 250mg/m^2 IV every 7 days **OR** **Day 1:** Cetuximab 500mg/m^2 IV every 2 weeks **+** **Day 1:** Irinotecan 300–350mg/m^2 IV over 30–90 minutes every 3 weeks. **OR** **Day 1:** Irinotecan 180mg/m^2 IV over 30–90 minutes every 2 weeks. **OR** **Days 1 and 8:** Irinotecan 125mg/m^2 IV over 30–90 minutes every 3 weeks.
Cetuximab[21,33] **(KRAS/NRAS wild-type gene only)**	Cetuximab 400mg/m^2 first infusion, then 250mg/m^2 IV weekly. **OR** Cetuximab 500mg/m^2 IV over 2 hours every 2 weeks.
Panitumumab[34] **(KRAS/NRAS wild-type gene only)**	**Day 1:** Panitumumab 6mg/kg IV over 60 minutes. Repeat cycle every 2 weeks.
Regorafenib[35f]	**Days 1–21:** Regorafenib 160mg orally once daily. Repeat cycle every 28 days.
Trifluridine/tipiracil[36]	**Days 1–5 and 8–12:** Trifluridine/tipiracil 35mg/m^2 up to a maximum of 80mg/m^2 per dose (based on the trifluridine component) orally twice daily. Repeat every 28 days.

[a] Oxaliplatin may instead be infused at 1mg/m^2/min, a shorter time rate than 2 hours. If this shorter infusion time is used, leucovorin infusion time should be matched to the oxaliplatin infusion time.

[b] NCCN recommends limiting chemotherapy orders to 24-hour units (ie, 1,200mg/m^2/day NOT 2,400mg/m^2 over 48 hours) to minimize medical errors.

[c] Bolus 5-FU/leucovorin/XRT is an option for patients not able to tolerate capecitabine or infusional 5-FU.

[d] Bevacizumab may be safely given at a rate of 0.5mg/kg/minute (5mg/kg over 10 minutes and 7.5mg/kg over 15 minutes).

[e] Most of the safety and efficacy data for this regimen have come from Europe, where a capecitabine starting dose of 1,000mg/m^2 twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, necessitating the use of 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.

[f] It is common practice to start at a lower dose of regorafenib (80 or 120mg) and escalate, as tolerated.

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