

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.

Principles of Adjuvant Therapy¹

- Consists of regimens that also include both concurrent chemotherapy and radiotherapy and adjuvant chemotherapy.
- Six months of perioperative therapy is preferred.
- In response to the shortage of leucovorin over the last few years, the FDA recently approved levoleucovorin in combination with 5-FU for the palliative treatment of patients with advanced metastatic colorectal cancer. Levoleucovorin 200mg/m² is the equivalent of leucovorin 400mg/m².

Postoperative Adjuvant Therapy for Patients Not Receiving Preoperative Therapy¹

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

REGIMEN	DOSING
mFOLFOX6 (oxaliplatin + leucovorin + 5-fluorouracil [5-FU])²⁻⁴	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.
Capecitabine⁵	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 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)⁸	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 + leucovorin⁹	Days 1, 8, 15, 22, 29 and 36: Leucovorin 500mg/m ² IV, followed by 5-FU 500mg/m ² IV bolus. Repeat cycle every 8 weeks for 6 months perioperative therapy.

Concurrent Chemotherapy + Radiotherapy¹

External beam radiotherapy [XRT] + 5-FU¹⁰	Days 1–5 OR 1–7: 5-FU 225mg/m ² IV over 24 hours during XRT.
XRT + 5-FU + leucovorin¹¹	Days 1–4: Leucovorin 20mg/m ² IV bolus, followed by 5-FU 400g/m ² IV bolus during XRT. Repeat cycle during weeks 1 and 5 of XRT.
XRT + capecitabine^{12,13}	Days 1–5 OR 1–7: Capecitabine 825mg/m ² twice daily + XRT. Repeat cycle weekly for 5 weeks.

Chemotherapy for Advanced or Metastatic Disease¹

mFOLFOX6²⁻⁴	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^{3,14†}	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.

continued

RECTAL CANCER TREATMENT REGIMENS (Part 2 of 4)

Chemotherapy for Advanced or Metastatic Disease¹ (continued)

REGIMEN	DOSING
mFOLFOX6 + panitumumab ^{3,15}	<p>Day 1: Oxaliplatin 85mg/m² IV over 2 hours + leucovorin 400mg/m² IV over 2 hours, followed by 5-FU 400mg/m² IV bolus, followed by 5-FU 1,200mg/m²/day IV x 2 days (total 2,400mg/m²) as a 46–48-hour continuous infusion.</p> <p>Day 1: Panitumumab 6mg/kg IV over 1 hour.</p> <p>Repeat cycle every 2 weeks.</p>
FOLFOX + cetuximab ^{2,16}	<p>Day 1: Oxaliplatin 85mg/m² IV over 2 hours + leucovorin 400mg/m² IV over 2 hours, followed by 5-FU 400mg/m² IV bolus, followed by 5-FU 1,200mg/m²/day IV x 2 days (total 2,400mg/m²) as a 46–48-hour continuous infusion</p> <p>PLUS</p> <p>Day 1: Cetuximab 400mg/m² IV over 2 hours first infusion, then 250mg/m² IV over 60 minutes weekly.</p> <p>OR</p> <p>Day 1: Cetuximab 500mg/m² IV over 2 hours every 2 weeks.</p>
CapeOX ^{6,7*}	<p>Day 1: Oxaliplatin 130mg/m² IV</p> <p>Days 1–14: Capecitabine 850–1,000mg/m² orally twice daily.</p> <p>Repeat cycle every 3 weeks.</p>
CapeOX + bevacizumab ^{5,7,17*†}	<p>Day 1: Oxaliplatin 130mg/m² IV.</p> <p>Days 1–14: Capecitabine 850–1,000mg/m² orally twice daily.</p> <p>Day 1: Bevacizumab 7.5mg/kg IV. Repeat cycle every 3 weeks.</p>
FOLFIRI ¹⁸	<p>Day 1: Irinotecan 180mg/m² IV + leucovorin 400mg/m² IV, followed by 5-FU 400mg/m² IV bolus, followed by 5-FU 1,200mg/m²/day IV x 2 days (total 2,400mg/m²) as a 46–48 hour continuous infusion.</p> <p>Repeat cycle every 2 weeks.</p>
FOLFIRI + bevacizumab ^{18,19}	<p>Day 1: Irinotecan 180mg/m² IV + leucovorin 400mg/m² IV, followed by 5-FU 400mg/m² IV bolus, followed by 5-FU 1,200mg/m²/day IV x 2 days (total 2,400mg/m²) as a 46–48 hour continuous infusion.</p> <p>Day 1: Bevacizumab 7.5mg/kg IV.</p> <p>Repeat cycle every 3 weeks.</p>
FOLFIRI + cetuximab ^{18,20,21}	<p>Day 1: Irinotecan 180mg/m² IV + leucovorin 400mg/m² IV, to match duration off irinotecan infusion followed by 5-FU 400mg/m² IV bolus, followed by 5-FU 1,200mg/m²/day IV x 2 days (total 2,400mg/m²) as a 46–48 hour continuous infusion.</p> <p>Repeat cycle every 2 weeks.</p> <p>PLUS</p> <p>Day 1: Cetuximab 400mg/m² IV over 2 hours first infusion, then 250mg/m² IV over 60 minutes weekly.</p> <p>OR</p> <p>Day 1: Cetuximab 500mg/m² IV over 2 hours every 2 weeks.</p>
FOLFIRI + panitumumab ^{17,22}	<p>Day 1: Irinotecan 180mg/m² IV + bevacizumab 5mg/kg IV + leucovorin 400mg/m² IV, followed by 5-FU 400mg/m² IV bolus, followed by 5-FU 1,200mg/m²/day IV x 2 days (total 2,400mg/m²) as a 46–48-hour continuous infusion.</p> <p>Repeat cycle every 2 weeks.</p>
FOLFIRI + ziv-aflibercept ²³	<p>Day 1: Irinotecan 180mg/m² IV + leucovorin 400mg/m² IV, followed by 5-FU 400mg/m² IV bolus, followed by 5-FU 1,200mg/m²/day IV x 2 days (total 2,400mg/m²) as a 46–48-hour continuous infusion</p> <p>Day 1: Ziv-aflibercept 4mg/kg IV.</p> <p>Repeat cycle every 2 weeks.</p>
Capecitabine ²⁴	<p>Days 1–14: Capecitabine 1,250mg/m² orally twice daily.</p> <p>Repeat cycle every 3 weeks.</p>
Capecitabine + bevacizumab ^{17,24†}	<p>Days 1–14: Capecitabine 850–1,250mg/m² orally twice daily</p> <p>Day 1: Bevacizumab 7.5mg/kg IV.</p> <p>Repeat cycle every 3 weeks.</p>
Bolus or infusional 5-FU/leucovorin (Roswell-Park Regimen) ²⁵	<p>Days 1, 8, 15, 22, 29 and 36: Leucovorin 500mg/m² IV, followed by 5-FU 500mg/m² IV bolus.</p> <p>Repeat cycle every 8 weeks.</p>

continued

RECTAL CANCER TREATMENT REGIMENS (Part 3 of 4)

Chemotherapy for Advanced or Metastatic Disease¹ (continued)

REGIMEN	DOSING
Simplified biweekly infusional 5-FU/LV (sLV5FU2) ¹⁸	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.
Weekly 5-FU + leucovorin ^{26,27}	Day 1: Leucovorin 20mg/m ² IV, followed by 5-FU 500mg/m ² IV bolus. 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. Repeat cycle every 3 weeks.
FOLFOXIRI ^{29,30}	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 (total 5-FU=3,200mg/m ²) ± Day 1: Bevacizumab 5mg/kg IV. Repeat cycle every 2 weeks.
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 300–350mg/m ² IV over 30–90 minutes. Repeat cycle every 3 weeks.
Cetuximab ± irinotecan ²¹	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 every 3 weeks. OR Day 1: Irinotecan 180mg/m ² IV every 2 weeks. OR Days 1 and 8: Irinotecan 125mg/m ² IV. Repeat cycle every 3 weeks.
Cetuximab (KRAS/NRAS wild-type gene only) ^{21,33}	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 (KRAS/NRAS wide-type gene only) ³⁴	Day 1: Panitumumab 6mg/kg IV administered over 60 minutes. Repeat cycle every 2 weeks.
Regorafenib ³⁵	Days 1–21: Regorafenib 160mg orally once daily. Repeat cycle every 28 days.

Principles of Chemotherapy for Advanced or Metastatic Disease:

*The majority of safety and efficacy data for this regimen have been developed in Europe, where capecitabine starting dose of 1,000mg/m² twice a day 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.

¹Bevacizumab may be safely given at a rate of 0.5mg/kg/minute (5mg/kg over 10 minutes and 7.5mg/kg over 15 minutes).

References

- NCCN Clinical Practice Guidelines in Oncology™. Rectal Cancer. v 2.2015. Available at: http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed May 6, 2015.
- deGramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced rectal cancer. *J Clin Oncol*. 2000;18:2938–2947.
- Cheeseman SL, Joel SP, Chester JD, et al. A “modified deGramont” regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. *Br J Cancer*. 2002;87:393–399.
- Maindault-Goebel F, deGramont A, Louvet C, et al. Evaluation of oxaliplatin dose intensity in bimonthly leucovorin and 48-hour 5-fluorouracil continuous infusion regimens (FOLFOX) in pretreated metastatic colorectal cancer. *Ann Oncol*. 2000; 11:1477–1483.
- Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med*. 2005;352: 2696–2704.

continued

References (continued)

6. Schmolli HJ, Cartwright T, Tabernero J, et al. Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: a planned safety analysis in 1,864 patients. *J Clin Oncol.* 2007;25:102-109.
7. Haller DG, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. *J Clin Oncol.* 2011;29:1465-1471.
8. Andre T, Boni C, Mounedji-Bouafif L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med.* 2004;350:2343-2351.
9. Petrelli N, Dougllass HO Jr, Herrare L, et al. The modulation of fluorouracil with leucovorin in metastatic colorectal carcinoma: a prospective randomized phase III trial. Gastrointestinal Tumor Study Group. *J Clin Oncol.* 1989;7:1419-1426.
10. O'Connell MJ, Martenson JA, Wieand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. *N Engl J Med.* 1994;331:502-507.
11. Tepper JE, O'Connell M, Niedzwiecki D, et al. Adjuvant therapy in rectal cancer: analysis of stage, sex, and local control—final report of intergroup 0114. *J Clin Oncol.* 2002;20:1744-1750.
12. Roh MS, Yothers GA, O'Connell MJ, et al. The impact of capecitabine and oxaliplatin in the preoperative multimodality treatment in patients with carcinoma of the rectum: NSABP R-04 [abstract]. *J Clin Oncol.* 2011;29(suppl):3503.
13. Hofheinz R, Wenz FK, Post S et al. Capecitabine (Cape) versus 5-fluorouracil (5-FU)-based (neo)adjuvant chemotherapy (CRT) for locally advanced rectal cancer (LARC): long-term results of a randomized, phase III trial [abstract]. *J Clin Oncol.* 2011;29(suppl):3504.
14. Emmanouilides C, Sfakiotiaki G, Androulakis N, et al. Front-line bevacizumab in combination with oxaliplatin, leucovorin and 5-fluorouracil (FOLFOX) in patients with metastatic colorectal cancer: a multicenter phase II study. *BMC Cancer.* 2007;7:91
15. Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol.* 2010;28:4697-4705.
16. Venook AP, Niedzwiecki D, Lenz H-J, et al. CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab or cetuximab for patients with KRAS wild-type untreated metastatic adenocarcinoma of the colon or rectum [abstract]. ASCO Meeting Abstracts 2014;32:LBA3. Available at: http://meeting.ascpubs.org/cgi/content/abstract/32/15_suppl/LBA3.
17. Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. *J Clin Oncol.* 2008;26:2013-2019.
18. Andre T, Louvet C, Maindrault-Goebel F, et al. CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. *Eur J Cancer.* 1999;35:1343-1347.
19. Fuchs CS, Marshall J, Mitchell E, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. *J Clin Oncol.* 2007;25:4779-4786.
20. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med.* 2004;351:337-345.
21. Martin-Martorell P, Roselló S, Rodríguez-Braun, et al. Biweekly cetuximab and irinotecan in advanced colorectal cancer patients progressing after at least one previous line of chemotherapy: results of a phase II single institution trial. *Br J Cancer.* 2008; 99:455-458.
22. Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *J Clin Oncol.* 2010;28:4706-4713.
23. Van Cutsem E, Tejpar S, Vanbeckevoort D, et al. Inpatient cetuximab dose escalation in metastatic colorectal cancer according to the grade of early skin reactions: the randomized EVEREST study. *J Clin Oncol.* 2012;30:2861-2868.
24. Van Cutsem E, Twelves C, Cassidy J, et al; Xeloda Colorectal Cancer Study Group. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. *J Clin Oncol.* 2001;19:4097-4106.
25. Wolmark N, Rockette H, Fisher B, et al. The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Protocol C-03. *J Clin Oncol.* 1993;11: 1879-1887.
26. Jager E, Heike M, Bernhard H, et al. Weekly high-dose leucovorin versus low-dose leucovorin combined with fluorouracil in advanced colorectal cancer: results of a randomized multicenter trial. Study Group for Palliative Treatment of Metastatic Colorectal Cancer Study Protocol 1. *J Clin Oncol.* 1996;14: 2274-2279.
27. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet.* 2000;355:1041-1047.
28. Haller DG, Rothenberg ML, Wong AO, et al. Oxaliplatin plus irinotecan compared with irinotecan alone as second-line treatment after single-agent fluoropyrimidine therapy for metastatic colorectal carcinoma. *J Clin Oncol.* 2008 Oct 1;26(28):4544-50.
29. Loupakis F, Cremonlini C, Masi G et al. FOLFIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of metastatic colorectal cancer: Results of the phase III randomized TRIBE trial. *J Clin Oncol.* 2013;31(suppl 4): abstract 336.
30. Falcone A, Ricci S, Brunetti I, et al. Gruppo Oncologico Nord Ovest. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol.* 2007;25:1670-1676.
31. Cunningham D, Pyrhönen S, James RD, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet.* 1998;352:1413-1418.
32. Fuchs CS, Moore MR, Harker G, Villa L, Rinaldi D, Hecht JR. Phase III comparison of two irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer. *J Clin Oncol.* 2003;21:807-814.
33. Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol.* 2012;30:3499-3506.
34. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol.* 2007; 25:1658-1664.
35. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; 381: 303-12.