Rectal Cancer Treatment Regimens

Clinical Trials: The National Comprehensive Cancer Network 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 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 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])[2–4,a]	**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 × 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[6,d]	**Days 1–14:** Capecitabine 1,000–1,250mg/m^2 orally twice daily. Repeat cycle every 3 weeks for 6 months perioperative therapy.
CapeOX (oxaliplatin + capecitabine)[7,8,a,d]	**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)[5]	**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 × 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 × 6 + leucovorin 500mg/m^2 IV weekly × 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[11,b]	**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,d]	**Days 1–5:** Capecitabine 825mg/m^2 twice daily + XRT. Repeat cycle weekly for 5 weeks.

▶Systemic Therapy for Advanced or Metastatic Disease[1]

mFOLFOX6[3,4,14,a,c]	**Day 1:** Oxaliplatin 85mg/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 × 2 days (total 2,400mg/m^2) as a 46–48-hour continuous infusion. Repeat cycle every 2 weeks.
mFOLFOX7[15,a]	**Day 1:** Oxaliplatin 85mg/m^2 IV + leucovorin 400mg/m^2 IV **Days 1-2:** 5-FU 1200mg/m^2/day IV (total 2400mg/m^2) as 46-48 continuous infusion. Repeat cycle every 2 weeks.
FOLFOX6 + bevacizumab[16,a]	**Day 1:** Oxaliplatin 85mg/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 × 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.
FOLFOX + panitumumab[17,a] **(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 × 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.

continued

Rectal Cancer Treatment Regimens

▶Systemic Therapy for Advanced or Metastatic Disease[1] (continued)

REGIMEN	DOSING
FOLFOX + cetuximab[18,a] (KRAS/NRAS wild-type gene only)	**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 × 2 days (total 2,400mg/m²) as a 46–48-hour continuous infusion **PLUS** **Day 1:** Cetuximab 400mg/m² IV over 2 hours first infusion, then 250mg/m² IV over 60 minutes weekly. **OR** **Day 1:** Cetuximab 500mg/m² IV over 2 hours every 2 weeks.
CapeOX[19,a,d]	**Day 1:** Oxaliplatin 130mg/m² IV **Days 1–14:** Capecitabine 1,000mg/m² orally twice daily. Repeat cycle every 3 weeks.
CapeOX + bevacizumab[19,a,c,d]	**Day 1:** Oxaliplatin 130mg/m² IV **Days 1–14:** Capecitabine 1,000mg/m² orally twice daily **Day 1:** Bevacizumab 7.5mg/kg IV. Repeat cycle every 3 weeks.
FOLFIRI[5,20]	**Day 1:** Irinotecan 180mg/m² IV over 30–90 minutes + leucovorin 400mg/m² IV, to match duration of irinotecan infusion, **followed by** 5-FU 400mg/m² IV bolus, **followed by** 5-FU 1,200mg/m²/day IV × 2 days (total 2,400mg/m²) as a 46–48-hour continuous infusion. Repeat cycle every 2 weeks.
FOLFIRI + bevacizumab[21,c]	**Day 1:** Irinotecan 180mg/m² IV over 30–90 minutes + leucovorin 400mg/m² IV, to match duration of irinotecan infusion, **followed by** 5-FU 400mg/m² IV bolus, **followed by** 5-FU 1,200mg/m²/day IV × 2 days (total 2,400mg/m²) as a 46–48-hour continuous infusion **Day 1:** Bevacizumab 5mg/kg IV. Repeat cycle every 2 weeks.
FOLFIRI + cetuximab[22,23] (KRAS/NRAS wild-type gene only)	**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 × 2 days (total 2,400mg/m²) as a 46–48-hour continuous infusion. Repeat cycle every 2 weeks. **PLUS** **Day 1:** Cetuximab 400mg/m² IV over 2 hours first infusion, then 250mg/m² IV over 60 minutes weekly. **OR** **Day 1:** Cetuximab 500mg/m² IV over 2 hours every 2 weeks.
FOLFIRI + panitumumab[24] (KRAS/NRAS wild-type gene only)	**Day 1:** Irinotecan 180mg/m² IV over 30–90 minutes + leucovorin 400mg/m² IV, to match duration of irinotecan infusion, **followed by** 5-FU 400mg/m² IV bolus, **followed by** 5-FU 1,200mg/m²/day IV × 2 days (total 2,400mg/m²) as a 46–48-hour continuous infusion. **Day 1:** Panitumumab 6mg/kg IV over 1 hour. Repeat cycle every 2 weeks.
FOLFIRI + ziv-aflibercept[25]	**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 × 2 days (total 2,400mg/m²) as a 46–48-hour continuous infusion **Day 1:** Ziv-aflibercept 4mg/kg IV. Repeat cycle every 2 weeks.
FOLFIRI + ramucirumab[26]	**Day 1:** Irinotecan 180mg/m² IV over 30–90 minutes + leucovorin 400mg/m² IV, to match duration of irinotecan infusion, **followed by** 5-FU 400mg/m² IV bolus, **followed by** 5-FU 1,200mg/m²/day IV × 2 days (total 2,400mg/m²) as a 46–48-hour continuous infusion. **Day 1:** Ramucirumab 8mg/kg over 1 hour. Repeat cycle every 2 weeks.
FOLFOXIRI ± bevacizumab[27,28,a,c]	**Day 1:** Irinotecan 165mg/m² IV + oxaliplatin 85mg/m² IV + leucovorin 400mg/m² IV **Days 1 and 2:** 5-FU 1,600mg/m²/day continuous infusion IV over 48 hours ± **Day 1:** Bevacizumab 5mg/kg IV. Repeat cycle every 2 weeks.
IROX[29,a]	**Day 1:** Oxaliplatin 85mg/m² IV + irinotecan 200mg/m² IV over 30–90 minutes. Repeat cycle every 3 weeks.
Bolus or infusional 5-FU/ leucovorin (Roswell-Park Regimen)[30]	**Days 1, 8, 15, 22, 29, and 36:** Leucovorin 500mg/m² IV over 2 hours, **followed by** 5-FU 500mg/m² IV bolus 1 hour after start of leucovorin. Repeat cycle every 8 weeks.
Simplified biweekly infusional 5-FU/LV (sLV5FU2)[5]	**Day 1:** Leucovorin 400mg/m² IV over 2 hours, **followed by** 5-FU 400mg/m² IV bolus, **followed by** 5-FU 1,200mg/m²/day IV × 2 days (total 2,400mg/m²) as a 46–48-hour continuous infusion. Repeat cycle every 2 weeks.

continued

Rectal Cancer Treatment Regimens

▶Systemic Therapy for Advanced or Metastatic Disease[1] (continued)

REGIMEN	DOSING
Weekly 5-FU + leucovorin[31]	**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.
Capecitabine[19]	**Days 1–14:** Capecitabine 850–1,250mg/m^2 orally twice daily. Repeat cycle every 3 weeks.
Capecitabine + bevacizumab[32,c]	**Days 1–14:** Capecitabine 850–1,250mg/m^2 orally twice daily **Day 1:** Bevacizumab 7.5mg/kg IV. Repeat cycle every 3 weeks.
Irinotecan[33,34]	**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[23,35] **(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.
Irinotecan + cetuximab + vemurafenib (KRAS/NRAS wild-type gene only)[36]	**Day 1:** Irinotecan 180mg/m^2 IV + cetuximab 500mg/m^2 IV **Days 1-14:** Vemurafenib 960mg orally twice daily Repeat cycle every 2 weeks.
Irinotecan + panitumumab + vemurafenib (BRAF V600E mutation positive)[1]	**Day 1:** Irinotecan 180mg/m^2 IV + panitumumab 6mg/kg IV over 60 minutes **Days 1-14:** Vemurafenib 960mg orally twice daily Repeat cycle every 2 weeks.
Cetuximab[23,35] **(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[37] **(KRAS/NRAS wild-type gene only)**	**Day 1:** Panitumumab 6mg/kg IV over 60 minutes. Repeat cycle every 2 weeks.
Regorafenib[38,39,e,f]	**Days 1–21:** Regorafenib 160mg orally once daily. Repeat cycle every 28 days **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[40]	**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.
Pembrolizumab[41]	**Day 1:** Pembrolizumab 2mg/kg. Repeat cycle every 3 weeks.
Nivolumab[42]	**Day 1:** Nivolumab 3mg/kg. Repeat cycle every 2 weeks. **OR** Day 1: Nivolumab 240mg IV. Repeat cycle every 2 weeks.

continued

Rectal Cancer Treatment Regimens

[a] Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1mg/m^2/min. Leucovorin infusion should match time of oxaliplatin. Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1mg/m^2/min. *J Oncol Pract*. 2016;12:e548-553.

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

[c] 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).

[d] 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.

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

[f] Regorafenib or trifluridine + tipiracil are treatment options for patients who have progressed through all available regimens.

References

1. NCCN Clinical Practice Guidelines in Oncology™. Rectal Cancer. v 1.2018. Available at: http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed July 11, 2018.
2. Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med*. 2004;350:2343-2351.
3. Cheeseman SL, Joel SP, Chester JD, et al. A 'modified de Gramont' regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. *Br J Cancer*. 2002;87:393-399.
4. Maindrault-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.
5. Andre T, Louvet C, Maindrault-Goebel F, et al. CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. *Eur J Cancer*. 1999;35(9):1343-1347.
6. Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med*. 2005;352(26):2696-2704.
7. Schmoll 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.
8. 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.
9. Petrelli N, Douglass Jr HO, Herrare L, et al. The modulation of fluorouracil with leucovorin in metastatic colorectal carcinoma: a prospective randomized phase III trial. *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. O'Connell MJ, Colangelo LH, Beart RW, et al. Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from National Surgical Adjuvant Breast and Bowel Project trial R-04. *J Clin Oncol*. 2014;32:1927-1934.
13. Hofheinz R, Wenz FK, Post S, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: A randomized, multicentre, noninferiority, phase 3 trial. *Lancet Oncol*. 2012;13:579-588.
14. 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.
15. Hochster HS, Grothey A, Hart L, et al. Improved time to treatment failure with an intermittent oxaliplatin strategy: results of CONcePT. *Ann Oncol*. 2014;25:1172-1178.
16. Emmanouilides C, Sfakiotaki 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.
17. 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.
18. 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.
19. 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.
20. 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.
21. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomized, open-label, phase 3 trial. *Lancet Oncol*. 2014.
22. 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.
23. Martín-Martorell P, Roselló S, Rodríguez-Braun E, 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.
24. 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.
25. 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.
26. Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomized, double-blind, multicentre, phase 3 study. *Lancet Oncol*. 2015;16:499-508.
27. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) 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(13):1670-1676.
28. Cremolini C, Loupakis F, Antoniotti C, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. *Lancet Oncol*. 2015;16:1306-1315.
29. 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;26:4544-4550.
30. 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.
31. Jäger 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. *J Clin Oncol*. 1996;14:2274-2279.
32. Cunningham D, Lang I, Marcuello E, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2013;14:1077-1085.
33. Cunningham D, Pyrhonen S, James R, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *The Lancet*. 1998;352:1413-1418.
34. Fuchs CS, Moore MR, Harker G, et al. Phase III comparison of two irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer. *J Clin Oncol*. 2003;21:807-814.
35. Van Cutsem E, Tejpar S, Vanbeckevoort D, et al. Intrapatient 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.
36. Kopetz S, McDonough SL, Lenz, H-J, et al. Randomized trial of irinotecan and cetuximab with or without vemurafenib in BRAF-mutant metastatic colorectal cancer (SWOG S1406). *J Clin Oncol*. 2017;35(suppl; abstr 3505).
37. Van Custem 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.
38. 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;381:303-312.
39. Bekaii-Saab, TS, Ou F-S, Anderson DM, et al. Regorafenib dose optimization study (ReDOS): Randomized phase II trial to evaluate dosing strategies for regorafenib in refractory metastatic colorectal cancer (mCRC)—An ACCRU Network study. *J Clin Oncol*. 2018;36(suppl 4S;abstr 611).
40. Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer (RECOURSE). *N Engl J Med*. 2015;372:1909-1919.
41. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372:2509-2520.
42. Overman MJ, Kopetz S, McDermott RS, et al. Nivolumab {+/-} ipilimumab in treatment of patients with metastatic colorectal cancer (mCRC) with and without high microsatellite instability (MSI-H): CheckMate-142 interim results [abstract]. ASCO Meeting Abstracts. 2016;34:3501.

(Revised 7/2018)