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NCCN Clinical Practice Guidelines in Oncology
(NCCN Guidelines®)

Colon Cancer

Overall management of Colon Cancer is described in the full NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer. Visit NCCN.org to view the complete library of NCCN Guidelines®.

NCCN National Comprehensive Cancer Network®

CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,o]

pMMR/MSS (or dMMR/MSI-H or *POLE/POLD1* mutation that is ineligible for or progressed on checkpoint inhibitor immunotherapy)

SECOND-LINE AND SUBSEQUENT THERAPY OPTIONS (if not previously given)[c,p]

Previous oxaliplatin-based therapy without irinotecan	Previous therapy with oxaliplatin and irinotecan	Biomarker-directed therapy
• FOLFIRI[i] or irinotecan[i] • FOLFIRI[i] + (bevacizumab[e,q] [preferred] or ziv-aflibercept[q,r] or ramucirumab[q,r]) • Irinotecan[i] + (bevacizumab[e,q] [preferred] or ziv-aflibercept[q,r] or ramucirumab[q,r]) • If *KRAS/NRAS/BRAF* WT[h]: ▸ FOLFIRI[i] + (cetuximab or panitumumab)[f,s] ▸ (Cetuximab or panitumumab)[f,s] ± irinotecan[i] • Biomarker-directed therapy (see Biomarker-directed therapy)	• If *KRAS/NRAS/BRAF* WT[h]: ▸ (Cetuximab or panitumumab)[f,s] ± irinotecan[i] • Biomarker-directed therapy (see Biomarker-directed therapy) • For disease that has progressed through all available regimens: ▸ Fruquintinib ▸ Regorafenib ▸ Trifluridine + tipiracil ± bevacizumab[e] (bevacizumab combo preferred) • Best supportive care (NCCN Guidelines for Palliative Care)	• *BRAF* V600E mutation positive[f] ▸ Encorafenib + (cetuximab or panitumumab)[t] • HER2-amplified and *RAS* and *BRAF* WT[f] ▸ (Trastuzumab[l] + [pertuzumab or lapatinib or tucatinib])[m] • HER2-amplified ▸ Fam-trastuzumab deruxtecan-nxki[u] • *KRAS* G12C mutation positive[f] ▸ (Sotorasib or adagrasib)[v] + (cetuximab or panitumumab) • *NTRK* gene fusion-positive ▸ Entrectinib or larotrectinib • *RET* gene fusion-positive ▸ Selpercatinib
Previous irinotecan-based therapy without oxaliplatin	**Previous therapy without oxaliplatin or irinotecan**	
• FOLFOX[d] or CAPEOX[d] • FOLFOX[d] + bevacizumab[e] • CAPEOX[d] + bevacizumab[e] • If *KRAS/NRAS/BRAF* WT[h]: ▸ FOLFOX[d] + (cetuximab or panitumumab)[f] ▸ CAPEOX[d] + (cetuximab or panitumumab)[f] ▸ (Cetuximab or panitumumab)[f,s] ± irinotecan[i] • Biomarker-directed therapy (see Biomarker-directed therapy)	• FOLFOX[d] or CAPEOX[d] • (FOLFOX or CAPEOX)[d] + bevacizumab[e] • FOLFIRI[i] or irinotecan[i] • (FOLFIRI or irinotecan)[i] + (bevacizumab[e,q] [preferred] or ziv-aflibercept[q,r] or ramucirumab[q,r]) • Irinotecan[i] + oxaliplatin[d] ± bevacizumab[e] • FOLFIRINOX[d,k] ± bevacizumab[e] • If *KRAS/NRAS/BRAF* WT[h]: ▸ FOLFIRI[h] + (cetuximab or panitumumab)[f,s] ▸ (Cetuximab or panitumumab)[f,s] ± irinotecan[i] • Biomarker-directed therapy (see Biomarker-directed therapy)	

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Footnotes
COL-D 4 of 11

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – FOOTNOTES

[a] For chemotherapy references, see Chemotherapy Regimens and References (COL-D [5 of 11]).
[b] For infection risk, monitoring, and prophylaxis recommendations for targeted therapies, see INF-A in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
[c] C/A/P CT with contrast or chest CT and abdomen/pelvis MRI with contrast to monitor progress of therapy. FDG-PET/CT should not be used. See Principles of Imaging (COL-A).
[d] Discontinuation of oxaliplatin should be strongly considered after 3 to 4 months of therapy (or sooner for unacceptable neurotoxicity) while maintaining other agents until time of progression. Oxaliplatin may be reintroduced if it was discontinued for neurotoxicity rather than for disease progression.
[e] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[f] Principles of Pathologic Review (COL-B 4 of 10).
[g] The panel defines the left side of the colon as splenic flexure to rectum. Evidence suggests that patients with tumors originating on the right side of the colon (hepatic flexure through cecum) are unlikely to respond to cetuximab and panitumumab in first-line therapy for metastatic disease. Data on the response to cetuximab and panitumumab in patients with primary tumors originating in the transverse colon (hepatic flexure to splenic flexure) are lacking.
[h] Patients with *BRAF* mutations other than V600E may be considered for anti-EGFR therapy.
[i] Irinotecan should be used with caution in patients with Gilbert syndrome or elevated serum bilirubin. There is a commercially available test for *UGT1A1*. Guidelines for use in clinical practice have not been established.
[j] FOLFIRINOX should be strongly considered for patients with excellent performance status.
[k] FOLFIRINOX is recommended instead of FOLFOXIRI because FOLFOXIRI uses a high dose of 5-FU (3,200 mg/m² over 48 hours). Patients in the United States have been shown to have greater toxicity with 5-FU. The dose of 5-FU (2,400 mg/m² over 46 hours) is a starting dose consistent with the dose recommended in FOLFOX or FOLFIRI and should be strongly considered for U.S. patients.
[l] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[m] If no previous treatment with HER2 inhibitor.
[n] The use of single-agent capecitabine after progression on a fluoropyrimidine-containing regimen has been shown to be ineffective; therefore, this is not recommended.
[o] Arterially directed catheter therapy, and in particular yttrium-90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases. See Principles of Surgery (COL-C).
[p] If patients had therapy stopped for reasons other than progression (eg, cumulative toxicity, elective treatment break, patient preference), rechallenge is an option at time of progression.
[q] Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.
[r] There are no data to suggest activity of FOLFIRI-ziv-aflibercept or FOLFIRI-ramucirumab in a patient who has progressed on FOLFIRI-bevacizumab, or vice versa. Ziv-aflibercept and ramucirumab have only shown activity when given in conjunction with FOLFIRI in FOLFIRI-naïve patients.
[s] Cetuximab or panitumumab are recommended in combination with irinotecan-based therapy or as single-agent therapy for patients who cannot tolerate irinotecan.
[t] In the second-line setting for *BRAF* V600E mutation-positive tumors, there is phase 3 evidence for better efficacy with targeted therapies over FOLFIRI.
[u] Some activity was seen after a previous HER2-targeted regimen. May not be indicated in patients with underlying lung issues due to lung toxicity (2.6% report of deaths from interstitial lung disease).
[v] If patient is unable to tolerate EGFR inhibitor due to toxicity, single-agent adagrasib or sotorasib can be considered.
[w] Checkpoint inhibitor therapy options include: nivolumab ± ipilimumab, pembrolizumab, or dostarlimab-gxly. Nivolumab + ipilimumab combination is category 2B when intensive therapy is not recommended due to toxicity concerns.
[x] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[y] If disease response, consider discontinuing checkpoint inhibitor after 2 years of treatment.

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Continued

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.