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April 7, 2026

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®

PRINCIPLES OF SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE

General
- An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
- For chemotherapy dosing and references, see Chemotherapy Regimens and References (COL-D [8 of 17]).

Continuum of Care
- 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.
- A single-agent fluoropyrimidine is not recommended after progression on a fluoropyrimidine-containing regimen.
- Bevacizumab is the preferred anti-angiogenic agent and can be continued into the second line of therapy and beyond.
- EGFR inhibitors include cetuximab and panitumumab. An EGFR inhibitor should not be continued beyond progression of disease. There is no efficacy benefit in changing the EGFR inhibitor at the time of progression.
- Ziv-aflibercept and ramucirumab have only shown activity when given in conjunction with FOLFIRI in FOLFIRI-naïve patients. There are no data to suggest activity of FOLFIRI-ziv-aflibercept or FOLFIRI-ramucirumab in a patient whose disease has progressed on FOLFIRI-bevacizumab, or vice versa.
- Arterially directed catheter therapy, and in particular Y-90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy resistant/-refractory disease and with predominant hepatic metastases.[a]
- C/A/P CT with contrast or chest CT and abdomen/pelvis MRI with contrast are recommended to monitor progress of therapy. FDG-PET/CT should not be used. See Principles of Imaging (COL-A).
- 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.

Toxicity Risk Assessment
- The FDA added a Boxed warning recommending to test patients for genetic variants of *DPYD* prior to initiating capecitabine or fluorouracil unless immediate treatment is necessary. Furthermore, use should be avoided in patients with certain homozygous or compound heterozygous *DPYD* variants that result in complete DPD deficiency. However, no specific test is recommended and there are insufficient data to inform dose adjustments for many of the *DPYD* variants.[b]
- 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.
- Anti-angiogenic therapy should be held for at least 28 days prior to elective surgery; do not administer for 28 days following major surgery and until adequate wound healing.
- 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.

Checkpoint Inhibitor Immunotherapy[c]
- Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.
- Pembrolizumab and berahyaluronidase alfa-pmph subcutaneous injection may be substituted for IV pembrolizumab. Pembrolizumab and berahyaluronidase alfa-pmph has different dosing and administration instructions compared to IV pembrolizumab.
- Atezolizumab and hyaluronidase-tqjs subcutaneous injection may be substituted for IV atezolizumab. Atezolizumab and hyaluronidase-tqjs has different dosing and administration instructions compared to IV atezolizumab.
- If disease response on checkpoint inhibitor, consider discontinuing checkpoint inhibitor after 2 years of treatment.

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

PRINCIPLES OF SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE

pMMR/MSS (or dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB >50 mut/Mb] that is ineligible for or progressed on checkpoint inhibitor immunotherapy)

<table>
<tr><th colspan="2">*KRAS* WT/*NRAS* WT/*BRAF* WT[d,e]</th></tr>
<tr><th>Initial Therapy</th><th>Less Intensive Therapy (any line of therapy, if not previously given)</th></tr>
<tr><td>• CAPEOX (Capecitabine/Oxaliplatin) ± Bevacizumab
• CAPEOX + (Cetuximab or Panitumumab) (left-sided tumors only)[f]
• FOLFIRI (Leucovorin/Fluorouracil/Irinotecan) ± Bevacizumab
• FOLFIRI + (Cetuximab or Panitumumab) (left-sided tumors only)[f]
• FOLFIRINOX (Leucovorin/Fluorouracil/Irinotecan/Oxaliplatin) ± Bevacizumab
• FOLFOX (Leucovorin/Fluorouracil/Oxaliplatin) ± Bevacizumab
• FOLFOX + (Cetuximab or Panitumumab) (left-sided tumors only)[f]</td><td>• Capecitabine ± Bevacizumab
• Cetuximab or Panitumumab (left-sided tumors only, if first-line therapy)[f,g]
• Fluorouracil/Leucovorin ± Bevacizumab
• (Pertuzumab or Tucatinib) + Trastuzumab (HER2 (ERBB2) overexpression/amplification)[e,h]
• Tumor-Agnostic therapy (COL-D 6 of 17)
• Best supportive care[i]</td></tr>
<tr><th colspan="2">Subsequent Therapy (if not previously given)</th></tr>
<tr><th>Prior Oxaliplatin</th><th>Prior Oxaliplatin and Irinotecan or Beyond Second Line</th></tr>
<tr><td>• FOLFIRI + (Cetuximab or Panitumumab)
• FOLFIRI ± (Bevacizumab [preferred] or Ziv-aflibercept or Ramucirumab)
• Irinotecan + (Cetuximab or Panitumumab)
• Irinotecan ± (Bevacizumab [preferred] or Ziv-aflibercept or Ramucirumab)</td><td rowspan="3">• Fam-trastuzumab deruxtecan-nxki (HER2 overexpression [IHC 3+])[e,j]
• (Pertuzumab or Tucatinib) + Trastuzumab (HER2 [ERBB2] overexpression/amplification)[e,h]
• Tumor-Agnostic therapy (COL-D 6 of 17)
• For disease that has progressed through all available regimens:
▸ Trifluridine and Tipiracil ± Bevacizumab (Bevacizumab combo preferred)
▸ Fruquintinib
▸ Regorafenib
• Best supportive care[i]</td></tr>
<tr><th>Prior Irinotecan</th></tr>
<tr><td>• CAPEOX ± Bevacizumab
• CAPEOX + (Cetuximab or Panitumumab)
• FOLFOX ± Bevacizumab
• FOLFOX + (Cetuximab or Panitumumab)
• Irinotecan + (Cetuximab or Panitumumab)</td></tr>
</table>

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Footnotes

PRINCIPLES OF SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE

pMMR/MSS (or dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB >50 mut/Mb] that is ineligible for or progressed on checkpoint inhibitor immunotherapy)

<table>
<tr><th colspan="2">(KRAS mutation or NRAS mutation) and BRAF WT[d,e]</th></tr>
<tr><th>Initial Therapy</th><th>Less Intensive Therapy (any line of therapy, if not previously given)</th></tr>
<tr><td>• CAPEOX ± Bevacizumab
• FOLFIRI ± Bevacizumab
• FOLFIRINOX ± Bevacizumab
• FOLFOX ± Bevacizumab</td><td>• Capecitabine ± Bevacizumab
• Fluorouracil/Leucovorin ± Bevacizumab
• Adagrasib or Sotorasib monotherapy (KRAS G12C mutation)
• Tumor-Agnostic therapy (COL-D 6 of 17)
• Best supportive care[i]</td></tr>
<tr><th colspan="2">Subsequent Therapy (if not previously given)</th></tr>
<tr><th>Prior Oxaliplatin</th><th>Prior Oxaliplatin and Irinotecan or Beyond Second Line</th></tr>
<tr><td>• FOLFIRI ± (Bevacizumab [preferred] or Ziv-aflibercept or Ramucirumab)
• Irinotecan ± (Bevacizumab [preferred] or Ziv-aflibercept or Ramucirumab)</td><td rowspan="3">• Fam-trastuzumab deruxtecan-nxki (HER2 overexpression [IHC 3+])[e,j]
• (Adagrasib or Sotorasib) + (Cetuximab or Panitumumab) (KRAS G12C mutation)
• Tumor-Agnostic therapy (COL-D 6 of 17)
• For disease that has progressed through all available regimens:
▸ Trifluridine and Tipiracil ± Bevacizumab (Bevacizumab combo preferred)
▸ Fruquintinib
▸ Regorafenib
• Best supportive care[i]</td></tr>
<tr><th>Prior Irinotecan</th></tr>
<tr><td>• FOLFOX ± Bevacizumab
• CAPEOX ± Bevacizumab</td></tr>
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Footnotes

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pMMR/MSS (or dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB >50 mut/Mb] that is ineligible for or progressed on checkpoint inhibitor immunotherapy)

<table>
<tr><th colspan="2">*KRAS* WT/*NRAS* WT/*BRAF* V600E Mutation[d,e,k]</th></tr>
<tr><th>Initial Therapy</th><th>Less Intensive Therapy (any line of therapy, if not previously given)</th></tr>
<tr><td>Preferred
• FOLFIRI/Encorafenib + (Cetuximab or Panitumumab)
• FOLFOX/Encorafenib + (Cetuximab or Panitumumab)[l]

Other Recommended
• CAPEOX ± Bevacizumab
• CAPEOX/Encorafenib + (Cetuximab or Panitumumab)
• FOLFIRI ± Bevacizumab
• FOLFIRINOX ± Bevacizumab
• FOLFOX ± Bevacizumab</td><td>• Capecitabine ± Bevacizumab
• Encorafenib + (Cetuximab or Panitumumab)
• Fluorouracil/Leucovorin ± Bevacizumab
• Tumor-Agnostic therapy (COL-D 6 of 17)
• Best supportive care[i]</td></tr>
<tr><th colspan="2">Subsequent Therapy (if not previously given)</th></tr>
<tr><th>Prior Oxaliplatin</th><th>Prior Oxaliplatin and Irinotecan or Beyond Second Line</th></tr>
<tr><td>• FOLFIRI ± (Bevacizumab [preferred] or Ziv-aflibercept or Ramucirumab)
• Irinotecan ± (Bevacizumab [preferred] or Ziv-aflibercept or Ramucirumab)</td><td rowspan="2">• Fam-trastuzumab deruxtecan-nxki (HER2 overexpression [IHC 3+])[e,j]
• Tumor-Agnostic therapy (COL-D 6 of 17)
• For disease that has progressed through all available regimens:
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▸ Fruquintinib
▸ Regorafenib
• Best supportive care[i]</td></tr>
<tr><th>Prior Irinotecan</th></tr>
<tr><td>• CAPEOX ± Bevacizumab
• FOLFOX ± Bevacizumab</td></tr>
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Footnotes

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