



# NCCN Guidelines: Systemic Therapy for mCRC

## Second-line and subsequent therapy options<sup>a</sup> *pMMR/MSS mCRC or dMMR/MSI-H or POLE/POLD1 mutation<sup>b</sup>*

| Previous oxaliplatin-based therapy without irinotecan                                                                                                                                                                                                                                                                                                                                                                                                     | Previous therapy with oxaliplatin and irinotecan                                                                                                                                                                                                                                                                                                                                                                                                       | Previous irinotecan-based therapy without oxaliplatin                                                                                                                                                                                                                                                                                                                                               | Previous therapy without oxaliplatin or irinotecan                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| <ul style="list-style-type: none"> <li>FOLFIRI or irinotecan</li> <li>FOLFIRI + bevacizumab (preferred) or ziv-aflibercept or ramucirumab</li> <li>Irinotecan + bevacizumab (preferred) or ziv-aflibercept or ramucirumab</li> <li>If <i>KRAS/NRAS/BRAF</i> wt: <ul style="list-style-type: none"> <li>➤ FOLFIRI + (cetuximab or panitumumab)</li> <li>➤ Cetuximab or panitumumab ± irinotecan</li> </ul> </li> <li>Biomarker-directed therapy</li> </ul> | <ul style="list-style-type: none"> <li>If <i>KRAS/NRAS/BRAF</i> wt: <ul style="list-style-type: none"> <li>➤ Cetuximab or panitumumab ± irinotecan</li> </ul> </li> <li>Biomarker-directed therapy</li> <li>For disease that has progressed through all regimens: <ul style="list-style-type: none"> <li>➤ Fruquintinib</li> <li>➤ Regorafenib</li> <li>➤ Trifluridine + tipiracil + bevacizumab (combo preferred)</li> </ul> </li> <li>BSC</li> </ul> | <ul style="list-style-type: none"> <li>FOLFOX or CAPEOX</li> <li>FOLFOX + bevacizumab</li> <li>CAPEOX + bevacizumab</li> <li>If <i>KRAS/NRAS/BRAF</i> wt: <ul style="list-style-type: none"> <li>➤ FOLFOX + (cetuximab or panitumumab)</li> <li>➤ CAPEOX + (cetuximab or panitumumab)</li> <li>➤ (Cetuximab or panitumumab) ± irinotecan</li> </ul> </li> <li>Biomarker-directed therapy</li> </ul> | <ul style="list-style-type: none"> <li>FOLFOX or CAPEOX</li> <li>(FOLFOX or CAPEOX) + bevacizumab</li> <li>FOLFIRI or irinotecan</li> <li>(FOLFIRI + irinotecan) + (bevacizumab [preferred] or ziv-aflibercept or ramucirumab)</li> <li>Irinotecan + oxaliplatin + bevacizumab</li> <li>FOLFIRINOX ± bevacizumab</li> <li>If <i>KRAS/NRAS/BRAF</i> wt: <ul style="list-style-type: none"> <li>➤ FOLFIRI + (cetuximab or panitumumab)</li> <li>➤ (Cetuximab or panitumumab) ± irinotecan</li> </ul> </li> <li>Biomarker-directed therapy</li> </ul> |

<sup>a</sup> If not previously given; see NCCN guidelines for complete therapeutic recommendations, including biomarker-directed therapy and BSC for this disease setting. <sup>b</sup> Patients with *POLE/POLD1* mutation who are ineligible for, or progressed on, ICI.

Colon Cancer, NCCN Guidelines Version 1.2025. National Comprehensive Cancer Network. Updated February 7, 2025. Accessed March 7, 2025.

BSC: best supportive care; CAPEOX: capecitabine + oxaliplatin; dMMR: deficient mismatch repair (MMR); FOLFOX: leucovorin calcium (folinic acid), fluorouracil, oxaliplatin; FOLFIRI: leucovorin calcium (folinic acid), fluorouracil, and irinotecan; FOLFIRINOX: leucovorin calcium (folinic acid), fluorouracil, irinotecan, oxaliplatin; ICI: immune checkpoint inhibitor; mCRC: metastatic colorectal cancer; MSI-H: microsatellite instability-high; MSS: microsatellite stable; NCCN: National Comprehensive Cancer Network; pMMR: proficient MMR.

The information presented here is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment included here should not be used by clinicians without evaluation of their patients' conditions and possible contraindications, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities. No endorsement of any products or uses is made or implied by coverage of such in our materials. No responsibility is taken for errors or omissions in our materials.



# NCCN Guidelines: Biomarker-Directed Therapy for mCRC

**Second-line and subsequent therapy options<sup>a</sup>**  
*pMMR/MSS mCRC or dMMR/MSI-H or POLE/POLD1 mutation<sup>b</sup>*

## Biomarker-directed therapy

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| <ul style="list-style-type: none"> <li>• <i>BRAF</i> V600E mutation positive               <ul style="list-style-type: none"> <li>➤ Encorafenib + (cetuximab or panitumumab)</li> <li>➤ (Encorafenib + [cetuximab or panitumumab] + FOLFOX) (category 2B)</li> </ul> </li> <li>• HER2-amplified and <i>RAS</i> and <i>BRAF</i> wt               <ul style="list-style-type: none"> <li>➤ (Trastuzumab + [pertuzumab or lapatinib or tucatinib])</li> </ul> </li> <li>• HER2-amplified (IHC 3+)               <ul style="list-style-type: none"> <li>➤ Fam-trastuzumab deruxtecan-nxki</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>• <i>KRAS</i> G12C mutation positive               <ul style="list-style-type: none"> <li>➤ (Sotorasib or adagrasib) + (cetuximab or panitumumab)</li> </ul> </li> <li>• <i>NTRK</i> gene fusion-positive               <ul style="list-style-type: none"> <li>➤ Entrectinib</li> <li>➤ Larotrectinib</li> <li>➤ Repotrectinib</li> </ul> </li> <li>• <i>RET</i> gene fusion-positive               <ul style="list-style-type: none"> <li>➤ Selpercatinib</li> </ul> </li> </ul> |
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IHC: immunohistochemistry; mCRC: metastatic colorectal cancer; MSI-H: microsatellite instability-high; MSS: microsatellite stable; NCCN: National Comprehensive Cancer Network; pMMR: proficient MMR; wt: wild type.

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