CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE.¹ (PAGE 3 of 10)

Subsequent Therapy

Previous irinotecan-based therapy without oxaliplatin

FOLFOX ± bevacizumab

or

CAPEOX ± bevacizumab

or

Irinotecan⁶ + (cetuximab or panitumumab)³,⁴,¹¹ (KRAS/NRAS WT only)

or

Regorafenib¹²

or

Trifluridine + tipiracil¹²

or

(Nivolumab or pembrolizumab)* (dMMR/MSI-H only)

See Subsequent therapy

FOLFOX or CAPEOX

or

Irinotecan⁶ + (cetuximab or panitumumab)³,⁴,¹¹ (KRAS/NRAS WT only)

or

(Nivolumab or pembrolizumab)* (dMMR/MSI-H only)

See Subsequent therapy

See Subsequent therapy

Ref: 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.

See footnotes COL-C 6 of 10

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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:¹ (PAGE 4 of 10)

Subsequent Therapy

Previous FOLFOXIRI

Irinotecan⁶ + (cetuximab or panitumumab)³,⁴,¹¹ (KRAS/NRAS WT only) or Regorafenib¹² or Trifluridine + tipiracil¹² or (Nivolumab* or pembrolizumab)* (dMMR/MSI-H only)

Regorafenib¹² or Trifluridine + tipiracil¹² or (Nivolumab or pembrolizumab)* (dMMR/MSI-H only)

See Subsequent therapy

Regorafenib**¹² or Trifluridine + tipiracil**¹² or Clinical trial or Best supportive care

See Subsequent therapy

*if neither previously given
**if not previously given

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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE: ¹ (PAGE 5 of 10)

### Subsequent Therapy

| Previous fluoropyrimidine without irinotecan or oxaliplatin | FOLFOX ± bevacizumab or CAPEOX ± bevacizumab or FOLFIRI⁶ ± (bevacizumab⁹ [preferred] or ziv-aflibercept⁹,¹⁰ or ramucirumab⁹,¹⁰) or Irinotecan⁶ ± bevacizumab or (Nivolumab or pembrolizumab)* (dMMR/MSI-H only) | See Subsequent therapy |
| | Irinotecan⁶ ± (cetuximab or panitumumab)*+³,⁴,¹¹ (KRAS/NRAS WT only) or (Nivolumab or pembrolizumab)* (dMMR/MSI-H only) | See Subsequent therapy |
| | Regorafenib¹² or Trifluridine + tipiracil¹² | Regorafenib**¹² or Trifluridine + tipiracil**¹² or Clinical trial or Best supportive care |
| | (Nivolumab or pembrolizumab)* (dMMR/MSI-H only) | (Nivolumab or pembrolizumab)* (dMMR/MSI-H only) |
| | | See Subsequent therapy |

*If neither previously given
**If not previously given

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*See footnotes COL-C 6 of 10*
SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 6 of 10)

1. For chemotherapy references, see Chemotherapy Regimens and References (COL-C 7-10).
2. Chest/Abdominal/Pelvic CT with contrast or Chest CT and Abdominal/Pelvic MRI with contrast to monitor progress of therapy. PET/CT should not be used.
4. BRAF V600E mutation makes response to panitumumab or cetuximab highly unlikely.
5. 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.
6. Irinotecan should be used with caution in patients with Gilbert's disease or elevated serum bilirubin. There is a commercially available test for UGT1A1. Guidelines for use in clinical practice have not been established.
7. A treatment option for patients not able to tolerate oxaliplatin or irinotecan.
8. The use of single-agent capecitabine after progression on a fluoropyrimidine-containing regimen has been shown to be ineffective; therefore, this is not recommended.
9. Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.
10. 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.
11. Ziv-aflibercept and ramucirumab have only shown activity when given in conjunction with FOLFIRI in FOLFIRI-naïve patients.
12. Cetuximab or panitumumab are recommended in combination with irinotecan-based therapy or as single-agent therapy for patients who cannot tolerate irinotecan.
13. Regorafenib or trifluridine + tipiracil are treatment options for patients who have progressed through all available regimens.

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Bolus or infusional 5-FU/leucovorin  
Roswell Park regimen\(^{20}\)  
Leucovorin 500 mg/m\(^2\) IV over 2 hours, days 1, 8, 15, 22, 29, and 36  
5-FU 500 mg/m\(^2\) IV bolus 1 hour after start of leucovorin, days 1, 8, 15, 22, 29, and 36  
Repeat every 8 weeks

Simplified biweekly infusional 5-FU/LV (sLV5FU2)\(^{9}\)  
Leucovorin\(^{**}\) 400 mg/m\(^2\) IV over 2 hours on day 1, followed by 5-FU bolus 400 mg/m\(^2\) and then 1200 mg/m\(^2\)/d \(\times\) 2 days (total 2400 mg/m\(^2\) over 46–48 hours) continuous infusion  
Repeat every 2 weeks

Weekly  
Leucovorin 20 mg/m\(^2\) IV over 2 hours on day 1, 5-FU 500 mg/m\(^2\) IV bolus injection 1 hour after the start of leucovorin. Repeat weekly.\(^{21}\)  
5-FU 2600 mg/m\(^2\) by 24-hour infusion plus leucovorin 500 mg/m\(^2\)  
Repeat every week\(^{21}\)

Capecitabine\(^{8}\)  
Capecitabine 850–1250 mg/m\(^2\) PO twice daily, days 1–14  
Repeat every 3 weeks

Capecitabine + Bevacizumab\(^{22,\dagger}\)  
Bevacizumab 7.5 mg/kg IV, day 1  
Repeat every 3 weeks

Irinotecan  
Irinotecan 125 mg/m\(^2\) IV over 30–90 minutes, days 1 and 8  
Repeat every 3 weeks\(^{23,24}\)  
or Irinotecan 180 mg/m\(^2\) IV over 30–90 minutes, day 1  
Repeat every 2 weeks  
or Irinotecan 300–350 mg/m\(^2\) IV over 30–90 minutes, day 1  
Repeat every 3 weeks

Irinotecan + cetuximab (KRAS/NRAS WT only)  
Cetuximab 400 mg/m\(^2\) first infusion, then 250 mg/m\(^2\) IV weekly\(^{25}\)  
or Cetuximab 500 mg/m\(^2\) IV over 2 hours, day 1, every 2 weeks\(^{13}\)

Cetuximab (KRAS/NRAS WT only)  
Cetuximab 400 mg/m\(^2\) first infusion, then 250 mg/m\(^2\) IV weekly\(^{25}\)  
or Cetuximab 500 mg/m\(^2\) IV over 2 hours, day 1, every 2 weeks\(^{13}\)

Panitumumab\(^{26}\) (KRAS/NRAS WT only)  
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

Regorafenib\(^{27}\)  
Regorafenib 160 mg\(^{\S}\) PO daily days 1–21  
Repeat every 28 days

Trifluridine + tipiracil\(^{28}\)  
Trifluridine + tipiracil 35 mg/m\(^2\) up to a maximum dose of 80 mg per dose (based on the trifluoruridine component)  
PO twice daily days 1–5 and 8–12  
Repeat every 28 days

Pembrolizumab\(^{29}\)  
Pembrolizumab 2 mg/kg every 3 weeks

Nivolumab\(^{30}\)  
Nivolumab 3 mg/kg every 2 weeks  
or Nivolumab 240 mg IV every 4 weeks

**Leucovorin 400 mg/m\(^2\) is the equivalent of levoleucovorin 200 mg/m\(^2\).

\(^{\dagger}\)Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

\(^{\S}\)It is common practice to start at a lower dose of regorafenib (80 or 120 mg) and escalate, as tolerated.

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