Treatment Guidelines for Metastatic Colorectal Cancer
- NCCN -

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NCCN - Overview

• NCCN = National Comprehensive Cancer Network
• US-based alliance of 27 cancer centers combined in a non-profit organization
• Founded in 1995
• Mission: to advance the quality, effectiveness, and efficiency of cancer care
• Publishes guidelines for diagnosis, monitoring, and treatment of cancer patients which routinely serve as compendia for reimbursement of diagnostic tests and cancer therapies in the US
NCCN CRC Committee

• 32 members which represent
  • Medical oncology,
  • Radiation oncology,
  • Surgical oncology,
  • Gastroenterology,
  • Interventional radiology,
  • Pathology, and
  • Patient advocacy

• Committee members are appointed by member institutions
NCCN Guidelines Development Process

• Committee reviews guidelines and proposed changes via TC every 3 months
  • Proposed changes can come from within the committee, member institutions, but also from outside the NCCN network
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NCCN Guidelines Development Process

• Committee reviews guidelines and proposed changes via TC every 3 months
  • Proposed changes can come from within the committee, member institutions, but also from outside the NCCN network
  • Every 3 months, members of the NCCN institutions are solicited to bring forward input and change requests from their internal departments
  • Ad hoc TCs and F2F meetings can be set up as needed

• Recommendations are being categorized based on evidence and consensus in 4 separate categories
NCCN Evidence and Consensus Categories

- **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.

## Colon Cancer

### NCCN Evidence Blocks™

#### NCCN Evidence Blocks Categories and Definitions

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>Efficacy of Regimen/Agent</td>
</tr>
<tr>
<td>S</td>
<td>Safety of Regimen/Agent</td>
</tr>
<tr>
<td>Q</td>
<td>Quality of Evidence</td>
</tr>
<tr>
<td>C</td>
<td>Consistency of Evidence</td>
</tr>
<tr>
<td>A</td>
<td>Affordability of Regimen/Agent</td>
</tr>
</tbody>
</table>

#### Example Evidence Block

- **E = Efficacy of Regimen/Agent**
- **S = Safety of Regimen/Agent**
- **Q = Quality of Evidence**
- **C = Consistency of Evidence**
- **A = Affordability of Regimen/Agent**

#### Efficacy of Regimen/Agent

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Highly effective: Often provides long-term survival advantage or has curative potential</td>
</tr>
<tr>
<td>4</td>
<td>Very effective: Sometimes provides long-term survival advantage or has curative potential</td>
</tr>
<tr>
<td>3</td>
<td>Moderately effective: Modest, no, or unknown impact on survival but often provides control of disease</td>
</tr>
<tr>
<td>2</td>
<td>Minimally effective: Modest, no, or unknown impact on survival and sometimes provides control of disease</td>
</tr>
<tr>
<td>1</td>
<td>Palliative: Provides symptomatic benefit only</td>
</tr>
</tbody>
</table>

#### Quality of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>High quality: Multiple well-designed randomized trials and/or meta-analyses</td>
</tr>
<tr>
<td>4</td>
<td>Good quality: Several well-designed randomized trials</td>
</tr>
<tr>
<td>3</td>
<td>Average quality: Low quality randomized trials or well-designed non-randomized trials</td>
</tr>
<tr>
<td>2</td>
<td>Low quality: Case reports or clinical experience only</td>
</tr>
<tr>
<td>1</td>
<td>Poor quality: Little or no evidence</td>
</tr>
</tbody>
</table>

#### Consistency of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Highly consistent: Multiple trials with similar outcomes</td>
</tr>
<tr>
<td>4</td>
<td>Mainly consistent: Multiple trials with some variability in outcome</td>
</tr>
<tr>
<td>3</td>
<td>May be consistent: Few trials or only trials with few patients; lower quality trials whether randomized or not</td>
</tr>
<tr>
<td>2</td>
<td>Inconsistent: Meaningful differences in direction of outcome between quality trials</td>
</tr>
<tr>
<td>1</td>
<td>Anecdotal evidence only: Evidence in humans based upon anecdotal experience</td>
</tr>
</tbody>
</table>

#### Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Very inexpensive</td>
</tr>
<tr>
<td>4</td>
<td>Inexpensive</td>
</tr>
<tr>
<td>3</td>
<td>Moderately expensive</td>
</tr>
<tr>
<td>2</td>
<td>Expensive</td>
</tr>
<tr>
<td>1</td>
<td>Very expensive</td>
</tr>
</tbody>
</table>
Key Strengths of NCCN Guidelines

- Frequent update cycle (3-4 times a year)
  - Ability to react to breakthrough events
- Rapid online publication with free access to the public
  - Annotated algorithms are a “living document”
- Participation of a large, standing committee of experts in various fields related to the diagnosis and management of CRC
- Involvement of patient advocates
- Allows input from outside sources
- Consensus classification available in areas where phase III level of evidence is lacking
- In the US, most important guideline for treatment decision in oncology and reimbursement by government and private payers
NCCN CRC Guidelines – Key Footnotes

• PET/CT scans should NOT be used to monitor response to therapy

• If an oxaliplatin-based first-line regimen is used, discontinuation of oxaliplatin after 3-4 months should be strongly considered
  • Oxaliplatin can be reintroduced later if discontinued for side-effects, but not because of PD on therapy

• All patients with mCRC should have their tumor tissue genotyped for RAS (KRAS/ NRAS) and BRAF mutations.
  • Patients with known KRAS or NRAS mutations (exon 2 or non-exon 2) should not be treated with either cetuximab or panitumumab
  • There is increasing evidence that BRAF V600E mutations makes response to EGFR mAbs, as single agent or in combination with cytotoxic chemotherapy, highly unlikely

• MMR or MSI testing should be performed for all patients with mCRC
• There are no data to suggest activity of FOLFIRI- aflibercept or FOLFIRI-ramucirumab in a patient who has progressed on FOLFIRI-bevacizumab, or vice versa.

• Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.

• There are no data, nor is there a compelling rationale, to support the use of panitumumab after clinical failure on cetuximab, or vice versa.

• The use of single-agent capecitabine as salvage therapy after failure on a fluoropyrimididine-containing regimen has shown to be ineffective and is therefore not recommended.

• The combination of capecitabine plus irinotecan is not recommended due to toxicity concerns.
Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Colon Cancer

NCCN Evidence Blocks™


NCCN.org

Continue
Oxaliplatin first line

CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:¹ (PAGE 1 of 9)

**Initial Therapy**

- FOLFOX³ or CapeOX⁴
- FOLFOX³ + bevacizumab⁵,⁶ or CapeOX⁴ + bevacizumab⁵,⁶

**Subsequent Therapy**

- FOLFIRI¹⁰ or FOLFIRI¹⁰ + bevacizumab¹² (preferred)⁵,⁶ or ziv-aflibercept¹¹,¹² or ramucirumab¹¹,¹² or irinotecan¹⁰
- FOLFIRI¹⁰ + (bevacizumab¹² or ziv-aflibercept¹¹,¹² or ramucirumab¹¹,¹²) or irinotecan¹⁰
- FOLFIRI¹⁰ + (bevacizumab¹² or ziv-aflibercept¹¹,¹² or ramucirumab¹¹,¹²) or irinotecan¹⁰

**Continued on next page**
"appropriate for intensive therapy" not defined

Patient appropriate for intensive therapy^2

FOLFOX^3 + cetuximab or panitumumab^6,7 (KRAS/NRAS WT gene only)^8,9

Additional options on COL-C 2 of 9 through COL-C 3 of 9
For patients not appropriate for intensive therapy, see COL-C 4 of 9
See Evidence Blocks on COL-C EB1 through COL-C EB3

See footnotes on COL-C 5 of 9
Oxaliplatin first line

CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:1 (PAGE 1 of 9)

"appropriate for intensive therapy" not defined

FOLFOX with Cmab or Pmab first-line included

Additional options on COL-C 2 of 9 through COL-C 3 of 9
For patients not appropriate for intensive therapy, see COL-C 4 of 9
See Evidence Blocks on COL-C EB1 through COL-C EB3

See footnotes on COL-C 5 of 9
Oxaliplatin first line

CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:¹ (PAGE 1 of 9)

**Initial Therapy**
- FOLFOX³ or CapeOX⁴ with bevazcizumab⁵,⁶
- Patient appropriate for intensive therapy²

**Subsequent Therapy**
- FOLFOX³ or CapeOX⁴ with bevazcizumab⁵,⁶
- Allows for regimens without phase III evidence
- "appropriate for intensive therapy" not defined

- FOLFOX⁴ with Cmab or Pmab first-line included
- FOLFOX³ with cetuximab or panitumumab⁶,⁷ (KRAS/NRAS WT gene only)⁸,⁹
- No preferred sequence of regorafenib and TAS-102

For patients not appropriate for intensive therapy, see COL-C 4 of 9
See Evidence Blocks on COL-C EB1 through COL-C EB3

*TAS-102
See footnotes on COL-C 5 of 9
IRINOTECAN FIRST LINE

CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:1 (PAGE 2 of 9)

**Initial Therapy**

**FOLFIRI**
- or
- **FOLFOX**
  - or
  - **CapeOx**
- or
- **FOLFOX** + bevacizumab
  - or
  - **CapeOx** + bevacizumab
- or
- (Cetuximab or panitumumab) (KRAS/NRAS WT gene only) + irinotecan; for patients not able to tolerate combination, consider single agent (cetuximab or panitumumab) (KRAS/NRAS WT gene only)

**Patient appropriate for intensive therapy**

**FOLFIRI**
- or
- **FOLFOX**
- or
- **CapeOx**
- or
- **FOLFOX** + bevacizumab
  - or
  - **CapeOx** + bevacizumab

**Subsequent Therapy**

<table>
<thead>
<tr>
<th>(Cetuximab or panitumumab) (KRAS/NRAS WT gene only) + irinotecan; for patients not able to tolerate combination, consider single agent (cetuximab or panitumumab) (KRAS/NRAS WT gene only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regorafenib; Trifluridine + tipiracil</td>
</tr>
<tr>
<td>Regorafenib (if not given previously) or Trifluridine + tipiracil (if not given previously) or Clinical trial or Best supportive care</td>
</tr>
</tbody>
</table>

Additional options on
- COL-C 1 of 9 through COL-C 3 of 9
- For patients not appropriate for intensive therapy, see COL-C 4 of 9

See Evidence Blocks on COL-C EB1 through COL-C EB3

*TAS-102
See footnotes on COL-C 5 of 9
Irinotecan first line

CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE

**Initial Therapy**

- **No capecitabine/irinotecan**
  - FOLFIRI\(^{10}\) or FOLFIRI\(^{10}\) + bevacizumab\(^{5,6}\)
  - or (Cetuximab or panitumumab)\(^{6,9,13-15}\) (KRAS/NRAS WT gene only)\(^8\) + irinotecan;\(^{10}\) for patients not able to tolerate combination, consider single agent (cetuximab or panitumumab)\(^{6,9,13-15}\) (KRAS/NRAS WT gene only)\(^8\)

**Subsequent Therapy**

- (Cetuximab or panitumumab)\(^{6,9,13-15}\) (KRAS/NRAS WT gene only)\(^8\) + irinotecan;\(^{10}\) for patients not able to tolerate combination, consider single agent (cetuximab or panitumumab)\(^{6,9,13-15}\) (KRAS/NRAS WT gene only)\(^8\)
  - FOLFOX\(^3\)
  - or CapeOX\(^4\)
  - or Regorafenib\(^{16}\)
  - or Trifluridine + tipiracil\(^{16,*}\)

- Regorafenib (if not given previously)
  - or Trifluridine + tipiracil\(^{16,*}\) (if not given previously)
  - or Clinical trial
  - or Best supportive care\(^{17}\)

Additional options on
**COL-C 1 of 9 through COL-C 3 of 9**

For patients not appropriate for intensive therapy, see **COL-C 4 of 9**

*See Evidence Blocks on COL-C EB1 through COL-C EB3*

*TAS-102

See footnotes on COL-C 5 of 9*
Other first line regimens

CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:¹ (PAGE 3 of 9)

**Initial Therapy**

- 5-FU/leucovorin¹⁸ or Capecitabine¹⁹ or bevacizumab⁵,⁶,20
- or Irinotecan¹⁰ ± oxaliplatin ± bevacizumab⁵,⁶
- or Irinotecan¹⁰ ± bevacizumab¹² [preferred]⁵,⁶ or ziv-aflibercept¹¹,¹² or ramucirumab¹¹,¹²
- or FOLFIRI¹⁰ ± bevacizumab¹² [preferred]⁵,⁶ or ziv-aflibercept¹¹,¹² or ramucirumab¹¹,¹²

**Patient appropriate for intensive therapy²**

- or FOLFOXIRI ± bevacizumab⁵,⁶

**Subsequent Therapy**

- FOLFOX³ ± bevacizumab⁵,⁶ or CapeOX⁴ ± bevacizumab⁵,⁶
- or Irinotecan¹⁰ → Irinotecan¹⁰ → Regorafenib¹⁶ or Trifluridine + tipiracil¹⁶,*
- or (Cetuximab or panitumumab)⁶,⁹,¹³-¹⁵ (KRAS/NRAS WT gene only)⁸ + irinotecan;¹⁰ for patients not able to tolerate combination, consider single agent (cetuximab or panitumumab)⁶,⁹,¹³-¹⁵ (KRAS/NRAS WT gene only)⁸ or Regorafenib¹⁶ or Trifluridine + tipiracil¹⁶,*
- or FOLFOX³ or CapeOX⁴ → Regorafenib (if not given previously) or Trifluridine + tipiracil¹⁶,* (if not given previously) or Clinical trial or Best supportive care¹⁷

**Additional options on** COL-C 1 of 9 through COL-C 2 of 9
For patients not appropriate for intensive therapy, see COL-C 4 of 9
See Evidence Blocks on COL-C EB1 through COL-C EB3

*TAS-102
See footnotes on COL-C 5 of 9
CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:

**Initial Therapy**

- Patient not appropriate for intensive therapy
  - Infusional 5-FU + leucovorin or Capecitabine ± bevacizumab
  - Cetuximab (KRAS/NRAS WT gene only) (category 2B)
  - Panitumumab (KRAS/NRAS WT gene only) (category 2B)

**Subsequent Therapy**

- Improvement in functional status
  - Consider initial therapy as COL-C 1 of 9 through COL-C 3 of 9
- No improvement in functional status
  - Best supportive care
    - See NCCN Guidelines for Palliative Care

See Evidence Blocks on COL-C EB1 through COL-C EB3

See footnotes on COL-C 5 of 9
NCCN Guidelines - Weaknesses

• Some of the regimens with level 2A recommendation have very little or no supporting clinical trial data
  • Recommendation based on CONSENSUS
• Too few “preferred” choices, a potpourri of options included, lack of guidance
• Goal of therapy not used to select initial therapy
• Assessment of (unexpected) resectability not included in the palliative algorithm
• Maintenance therapy not in flow algorithm, but in supporting text
NCCN Guidelines – Upcoming Discussion (August 1\textsuperscript{st}, F2F meeting)

- Role of sidedness for initial treatment selection
- Role of immunotherapy in MSI-H/ MMR-D CRC
- HER-2 testing?
- Refinement of Evaluation Blocks
Conclusions

• NCCN guidelines in CRC provide comprehensive recommendations for diagnosis, treatment, and surveillance of CRC

• Frequent updates assure up-to-date information

• Consensus model allows recommendation in areas with lack of clinical trial data (which comes at the price of reduced level of evidence)

• Role of NCCN guidelines for reimbursement in part drives the more inclusive nature of treatment recommendations

• Value assessment in form of “Evaluation Blocks” across all NCCN guidelines is being developed