

Treatment Guidelines for Metastatic Colorectal Cancer - NCCN -

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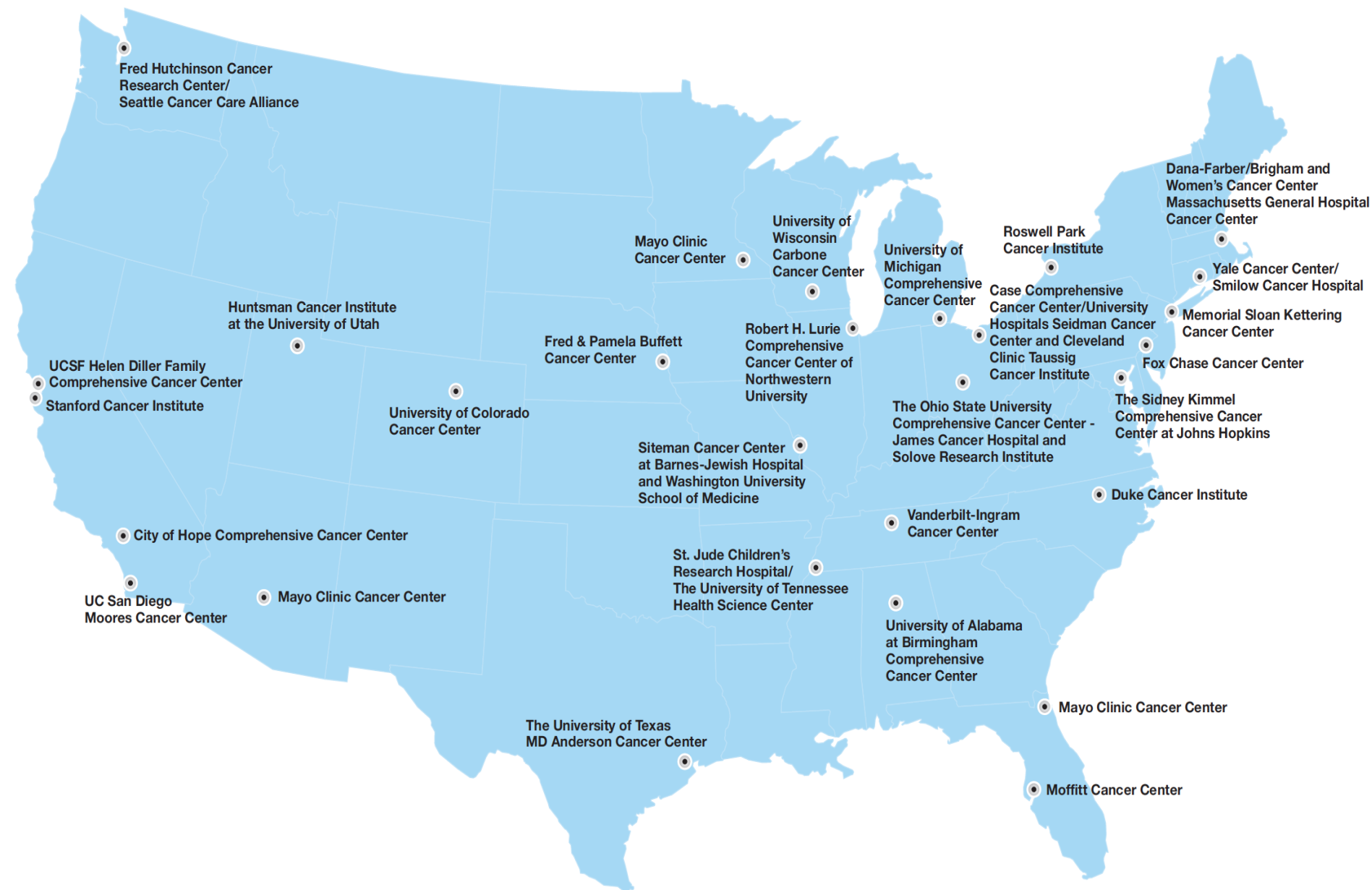
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NCCN - Overview

- 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 Member Institutions



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

NCCN Guidelines Development Process



National Comprehensive Cancer Network
Your Best Resource in the Fight Against Cancer®

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NCCN Guidelines®

About The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Development and Update of the NCCN Guidelines

Recent Updates to NCCN Guidelines®

NCCN Guidelines Panels - Meeting Schedule

NCCN Categories of Evidence and Consensus

NCCN Guidelines® Steering Committee

Transparency: Process and Recommendations

Submission Request to the NCCN Guidelines Panels

Submission Request History

Permissions Requests

End-User License Agreement

NCCN Disclosure Policies & Potential Conflicts of Interest

About NCCN

Submission Request to the NCCN Guidelines Panels

Please complete the following information:

Name:

Company/Organization:

Address:

Phone:

E-mail:

Date of request:

NCCN Guidelines Panel:

Guidelines for Submissions:

- A panel will consider scientific data including, but not limited to, reports of published trials that would be useful in evaluating therapies for inclusion in a guideline. These data may refer to either FDA approved or off label indications for drugs, biologics, diagnostics, procedures, or devices used for cancer prevention, detection, treatment, or supportive care.
- **A cover letter (maximum 2 pages) should accompany the submission and include the following information:**
 - Request for NCCN Guidelines Panel to consider review of data for a specific indication.
 - Specific changes recommended within the NCCN Guidelines. (one sentence)
 - Statement of whether the submitted use is or is not FDA approved for that indication.
 - Rationale for recommended change. (one sentence)
 - Citation of literature support and complete articles supporting recommended change.

Quick Links

Clinicians

NCCN Guidelines® - FREE

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NCCN Biomarkers Compendium®

NCCN Templates®

Educational Events

CME/CE Programs

NCCN Guidelines for Patients®

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.

NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS

5					
4					
3					
2					
1					
	E	S	Q	C	A

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

Example Evidence Block					
5					
4					
3					
2					
1					
	E	S	Q	C	A

E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	Highly effective: Often provides long-term survival advantage or has curative potential
4	Very effective: Sometimes provides long-term survival advantage or has curative potential
3	Moderately effective: Modest, no, or unknown impact on survival but often provides control of disease
2	Minimally effective: Modest, no, or unknown impact on survival and sometimes provides control of disease
1	Palliative: Provides symptomatic benefit only

Safety of Regimen/Agent

5	Usually no meaningful toxicity: Uncommon or minimal side effects. No interference with activities of daily living (ADLs)
4	Occasionally toxic: Rare significant toxicities or low-grade toxicities only. Little interference with ADLs
3	Mildly toxic: Mild toxicity that interferes with ADLs is common
2	Moderately toxic: Significant toxicities often occur; life threatening/fatal toxicity is uncommon. Interference with ADLs is usual
1	Highly toxic: Usually severe, significant toxicities or life threatening/fatal toxicity often observed. Interference with ADLs is usual and/or severe

Quality of Evidence

5	High quality: Multiple well-designed randomized trials and/or meta-analyses
4	Good quality: Several well-designed randomized trials
3	Average quality: Low quality randomized trials or well-designed non-randomized trials
2	Low quality: Case reports or clinical experience only
1	Poor quality: Little or no evidence

Consistency of Evidence

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

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

5	Very inexpensive
4	Inexpensive
3	Moderately expensive
2	Expensive
1	Very expensive

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

NCCN CRC Guidelines – Key Footnotes

- 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 fluoropyrimidine-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.



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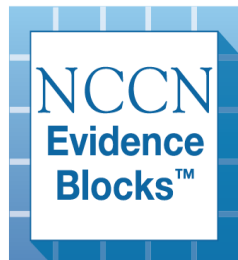
Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Colon Cancer

NCCN Evidence Blocks™

Version 2.2016

NCCN.org



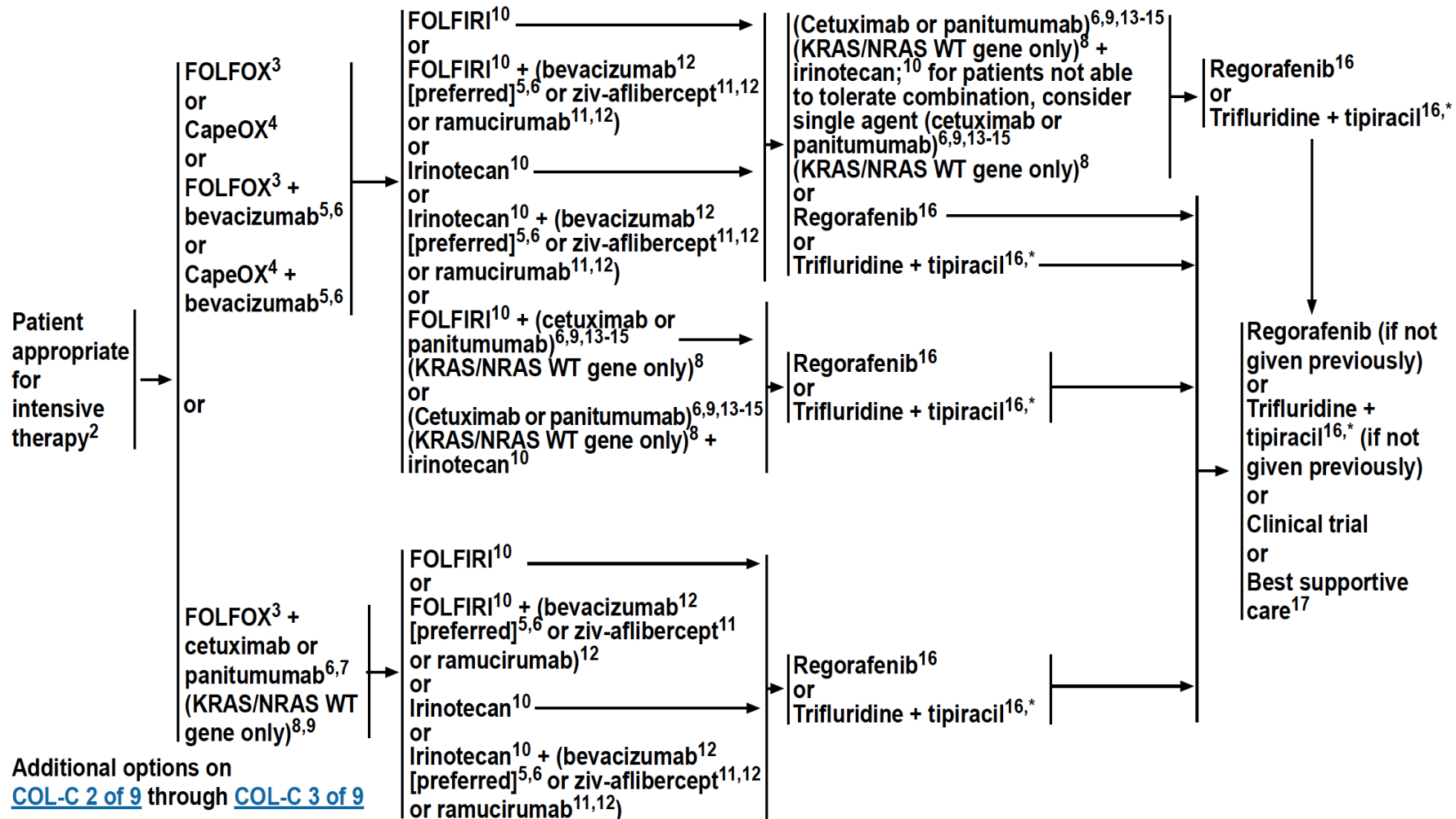
Continue

Oxaliplatin first line

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

Initial Therapy

Subsequent Therapy



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](#)

*TAS-102

[See footnotes on COL-C 5 of 9](#)

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



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

See footnotes on COL-C 5 of 9

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

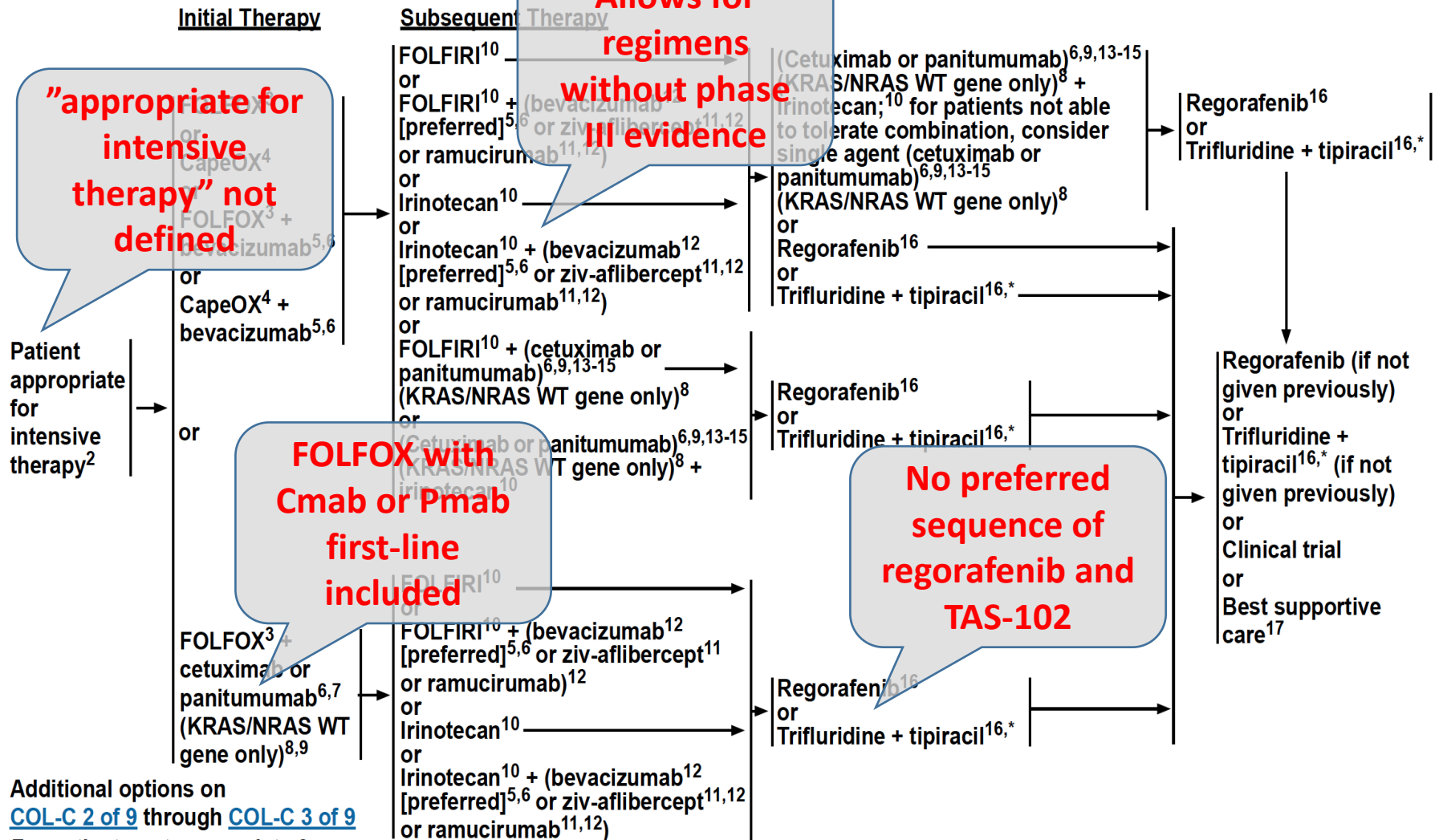


See Evidence Blocks on COL-C EB1 through COL-C EB3

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)



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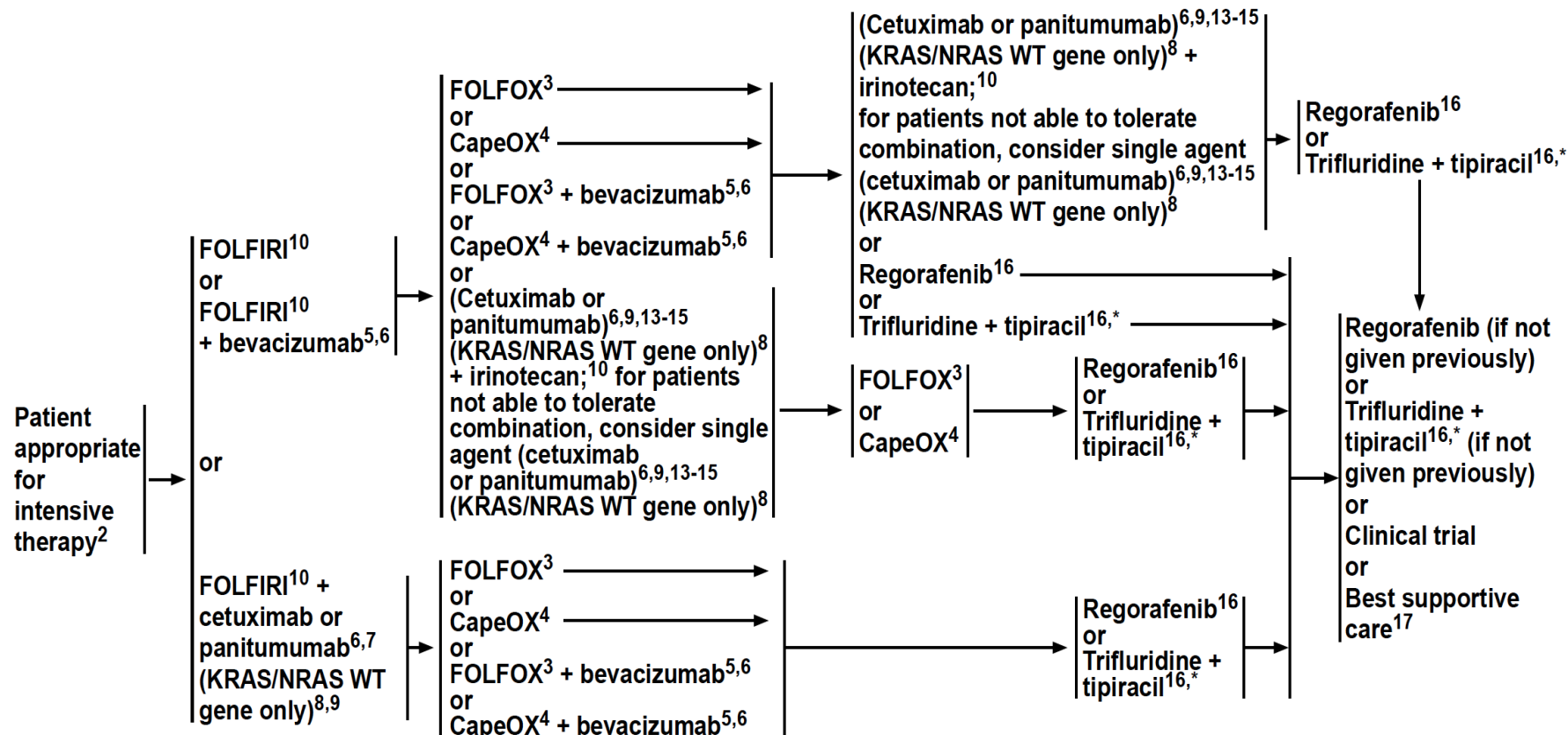
See footnotes on COL-C 5 of 9

Irinotecan first line

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

Initial Therapy

Subsequent Therapy



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](#)

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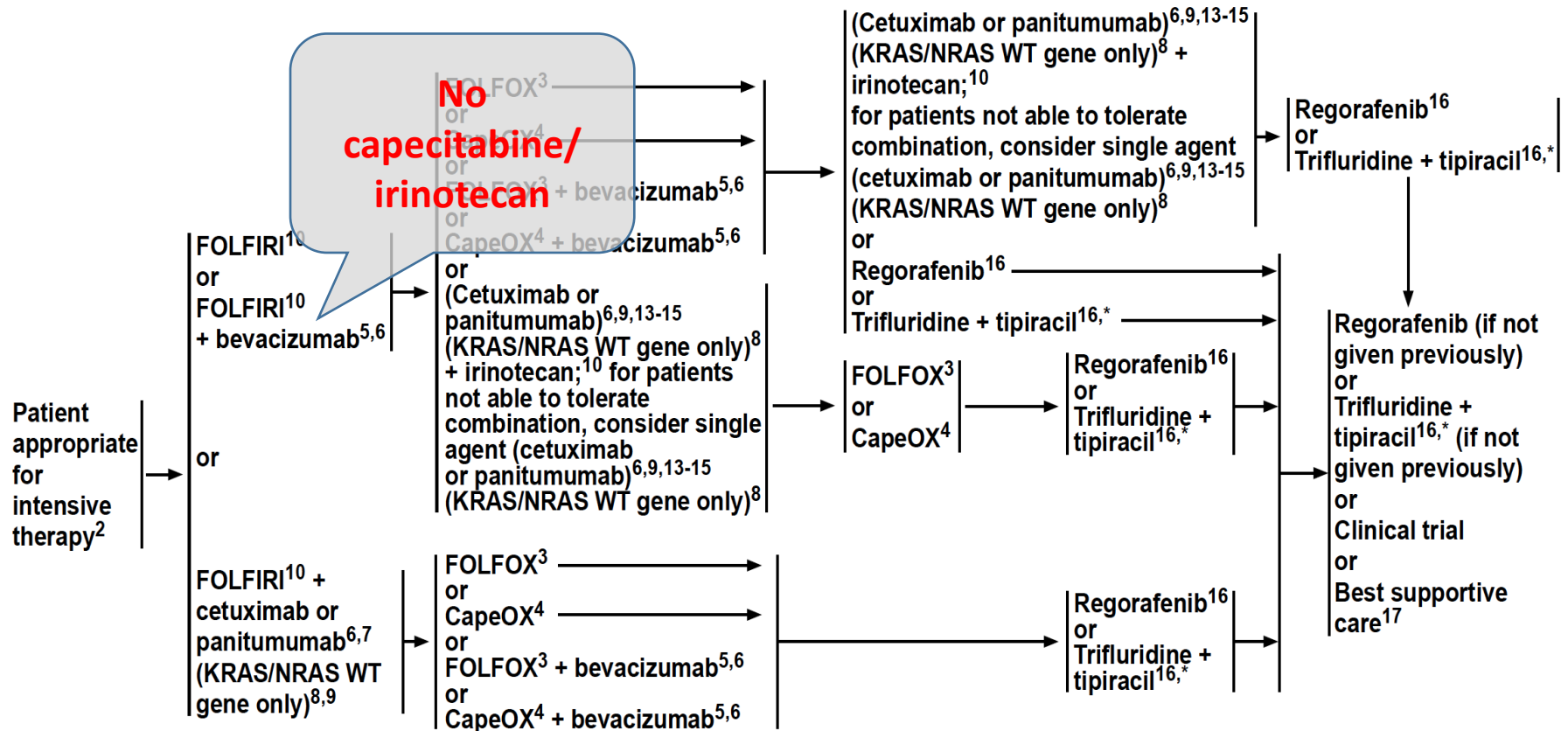
[See footnotes on COL-C 5 of 9](#)

Irinotecan first line

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

Initial Therapy

Subsequent Therapy



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](#)

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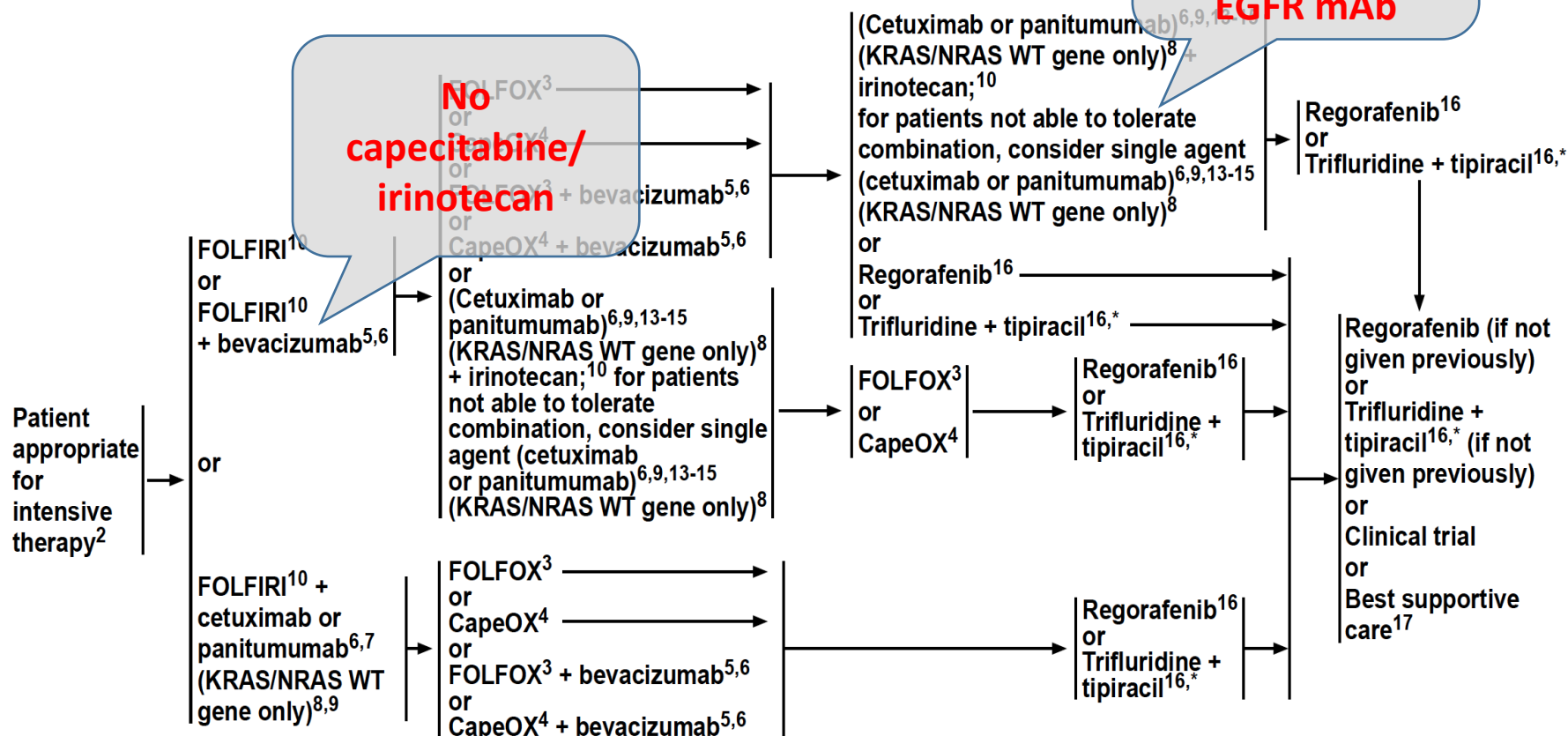
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Irinotecan first line

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

Initial Therapy

Subsequent Therapy



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

Subsequent Therapy

Patient appropriate for intensive therapy²

5-FU/leucovorin¹⁸
or Capecitabine¹⁹
± bevacizumab^{5,6,20}

FOLFOXIRI ±
bevacizumab^{5,6}

FOLFOX³ ±
bevacizumab^{5,6}
or
CapeOX⁴ ±
bevacizumab^{5,6}

Irinotecan¹⁰ + oxaliplatin ±
bevacizumab^{5,6}

Irinotecan¹⁰ ± (bevacizumab¹²
[preferred]^{5,6} or ziv-aflibercept^{11,12}
or ramucirumab^{11,12})
or
FOLFIRI¹⁰ ± (bevacizumab¹²
[preferred]^{5,6} or ziv-aflibercept^{11,12}
or ramucirumab^{11,12})

(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 + tipiracil^{16,*}

Irinotecan¹⁰

(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 + tipiracil^{16,*}

FOLFOX³ or CapeOX⁴

Regorafenib¹⁶
or
Trifluridine + tipiracil^{16,*}

Regorafenib¹⁶
or
Trifluridine + tipiracil^{16,*}

Regorafenib (if not
given previously)
or
Trifluridine +
tipiracil^{16,*} (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](#)

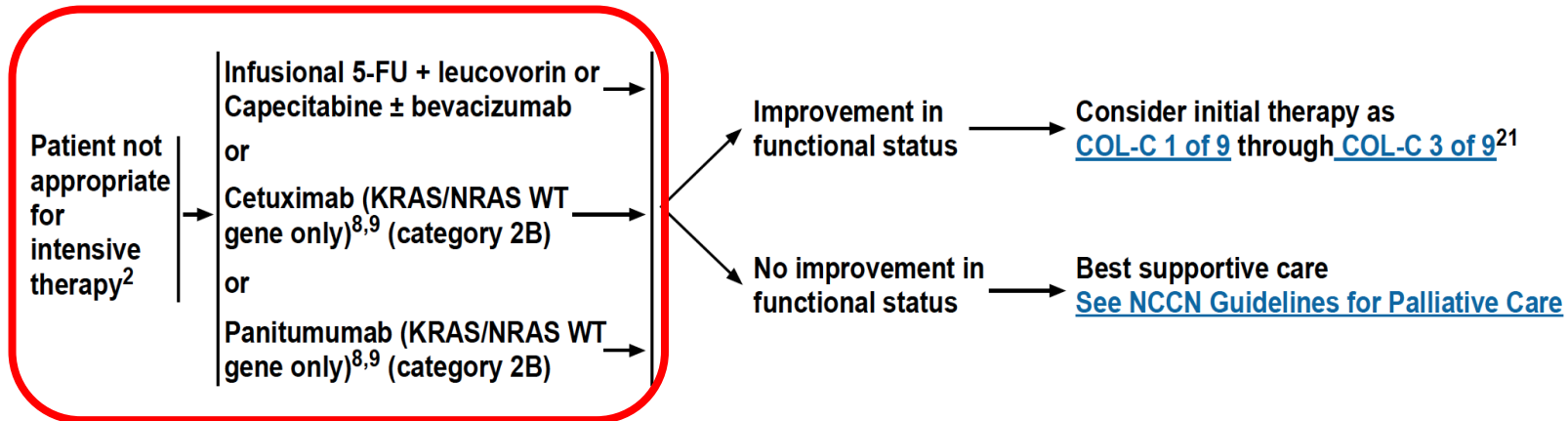
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[See footnotes on COL-C 5 of 9](#)

CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:¹ (PAGE 4 of 9)

Initial Therapy

Subsequent Therapy



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 1st, 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