Treatment Guidelines for Metastatic Colorectal Cancer
- NCCN -

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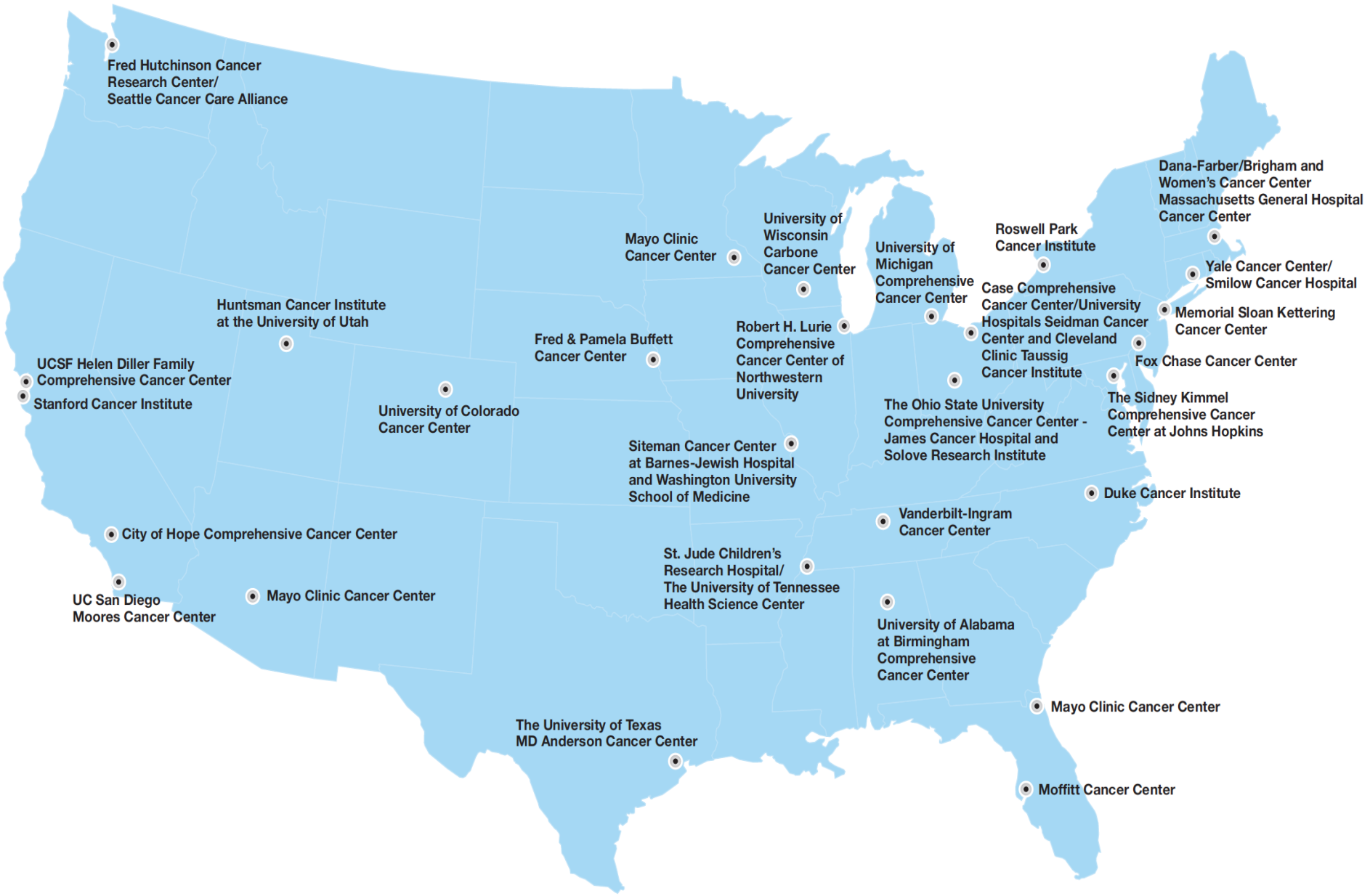
NCCN - Overview

- 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 Member Institutions



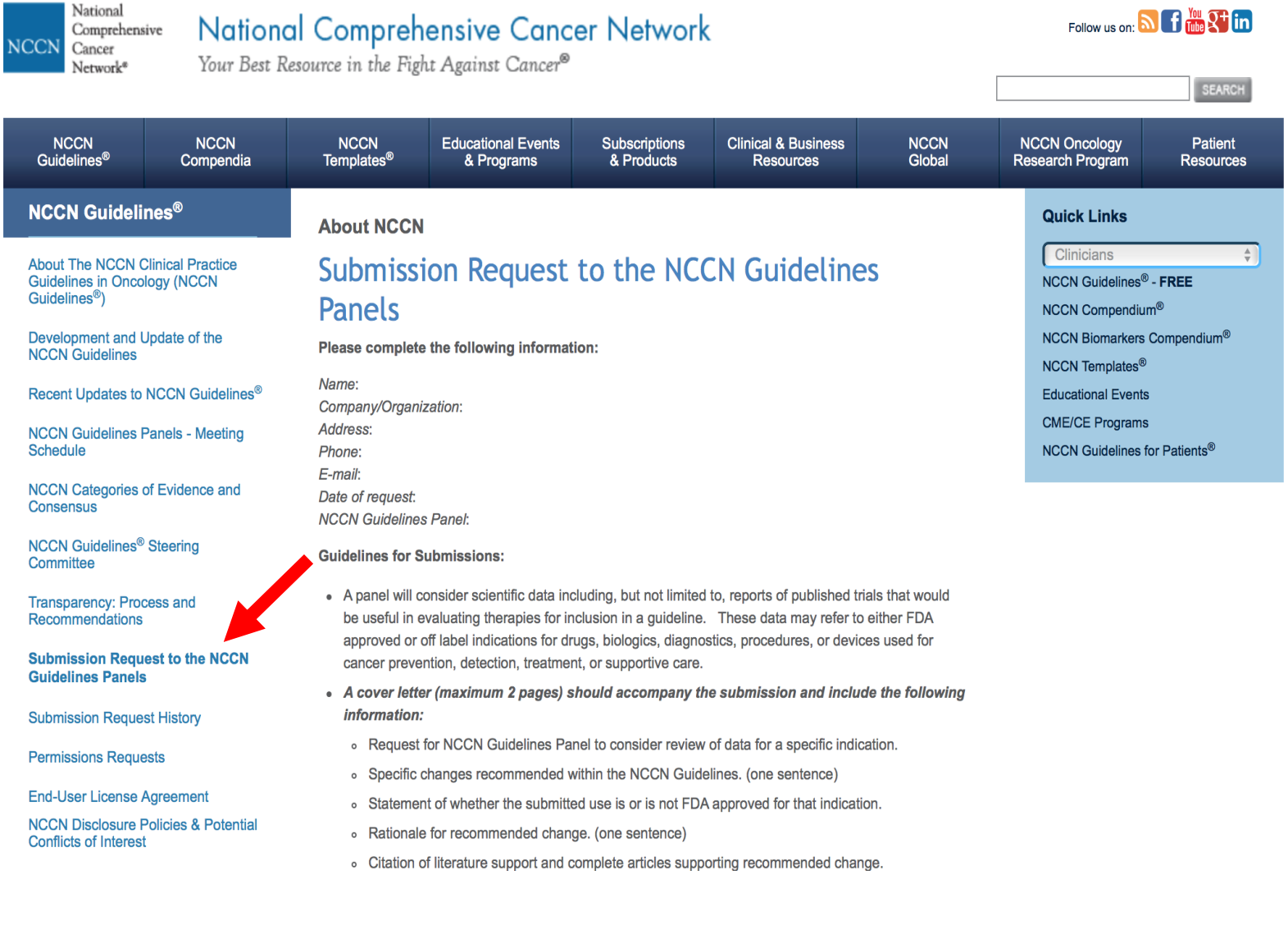
NCCN CRC Committee

- 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



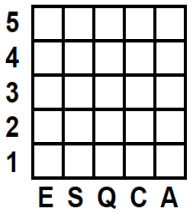
NCCN Guidelines Development Process

- 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

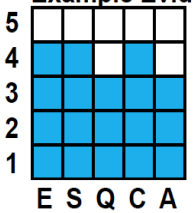
- **Category 1:** Based upon **high-level evidence**, there is **uniform** NCCN consensus that the intervention is appropriate.
- **Category 2A:** Based upon **lower-level evidence**, there is **uniform** NCCN consensus that the intervention is appropriate.
- **Category 2B:** Based upon **lower-level 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



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



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 om 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.

National Comprehensive Cancer Network®

Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Colon Cancer

NCCN Evidence Blocks™

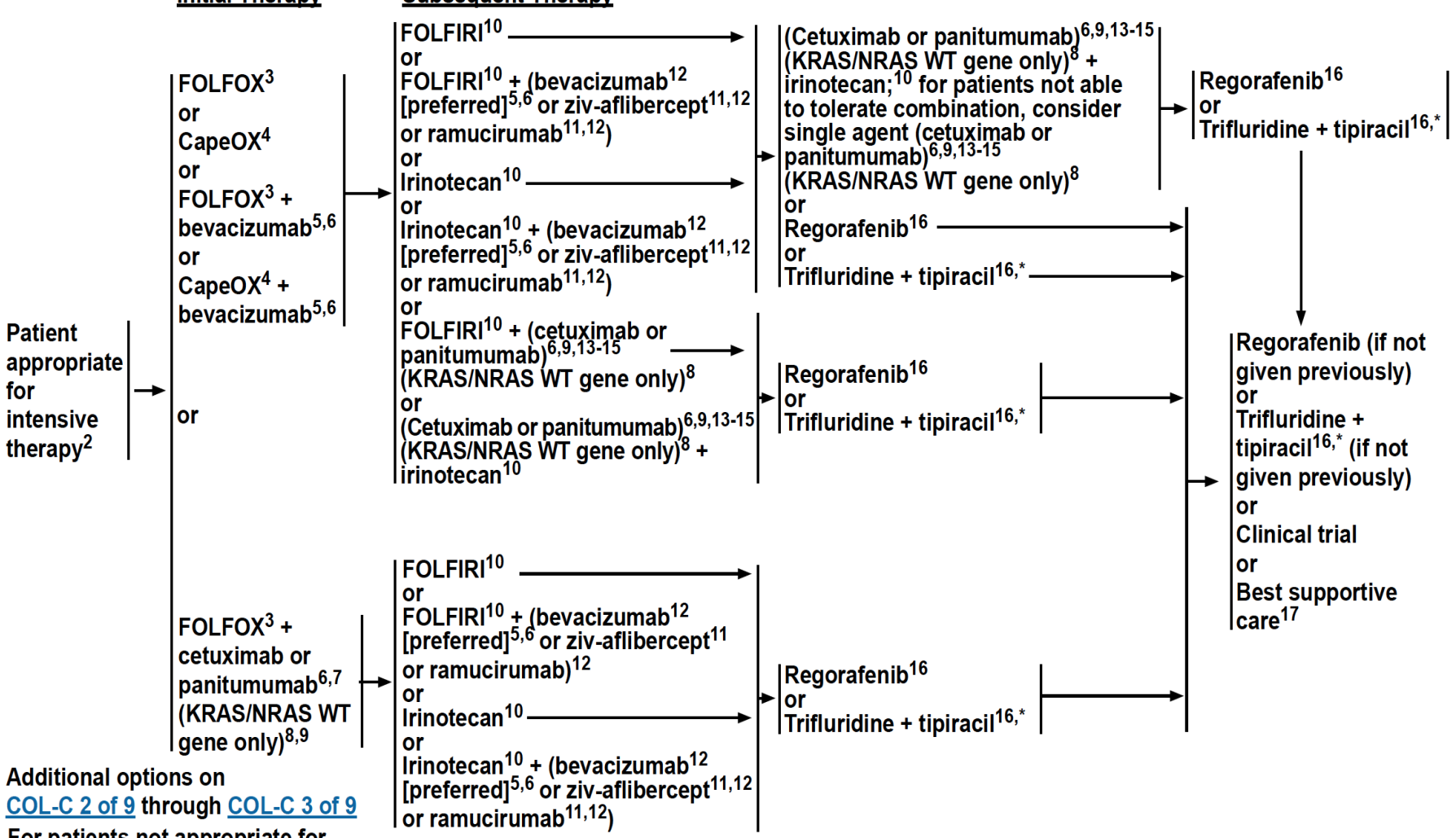
Version 2.2016

NCCN.org

Continue

Oxaliplatin first line

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



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

Oxaliplatin first line

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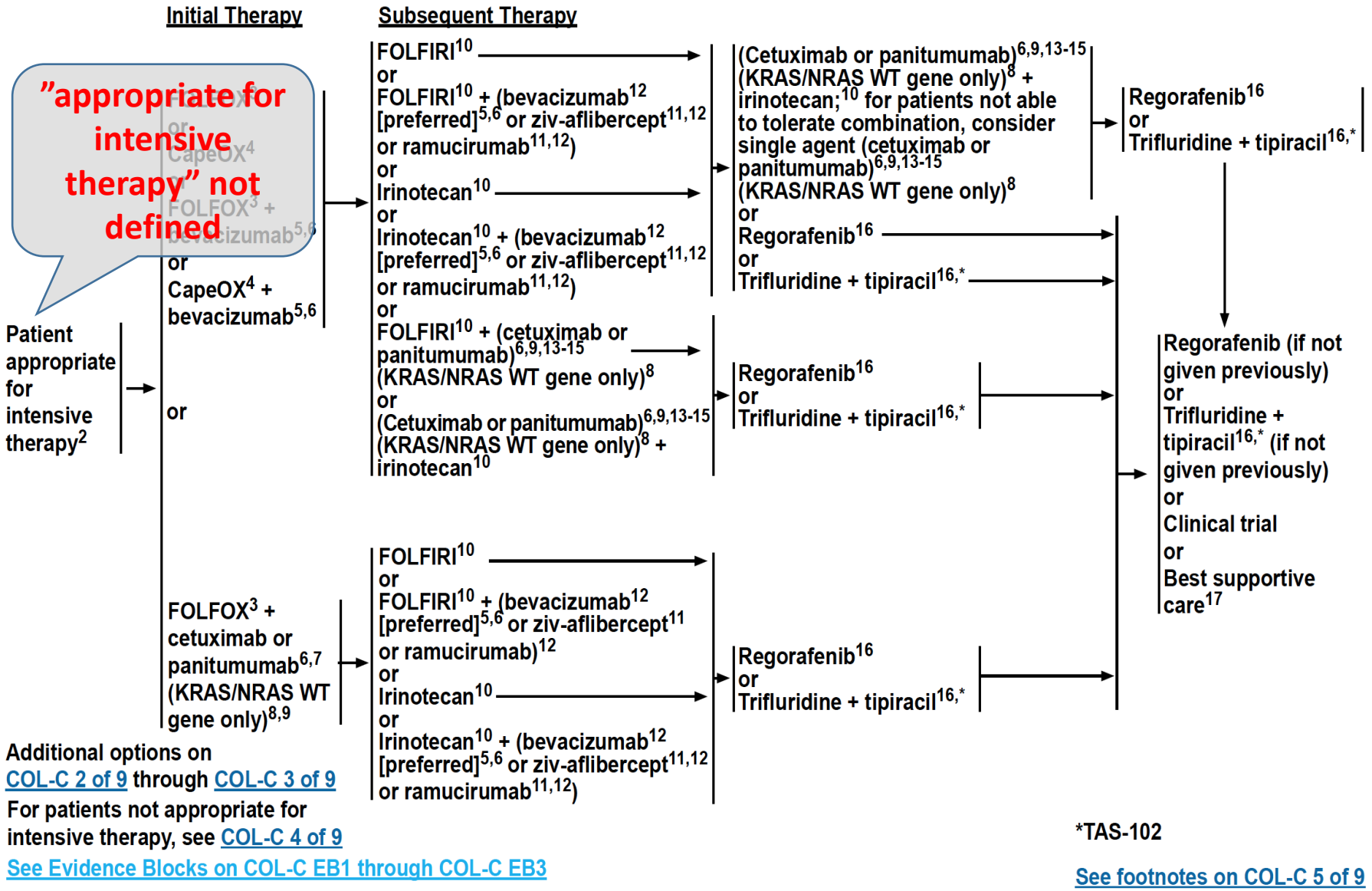

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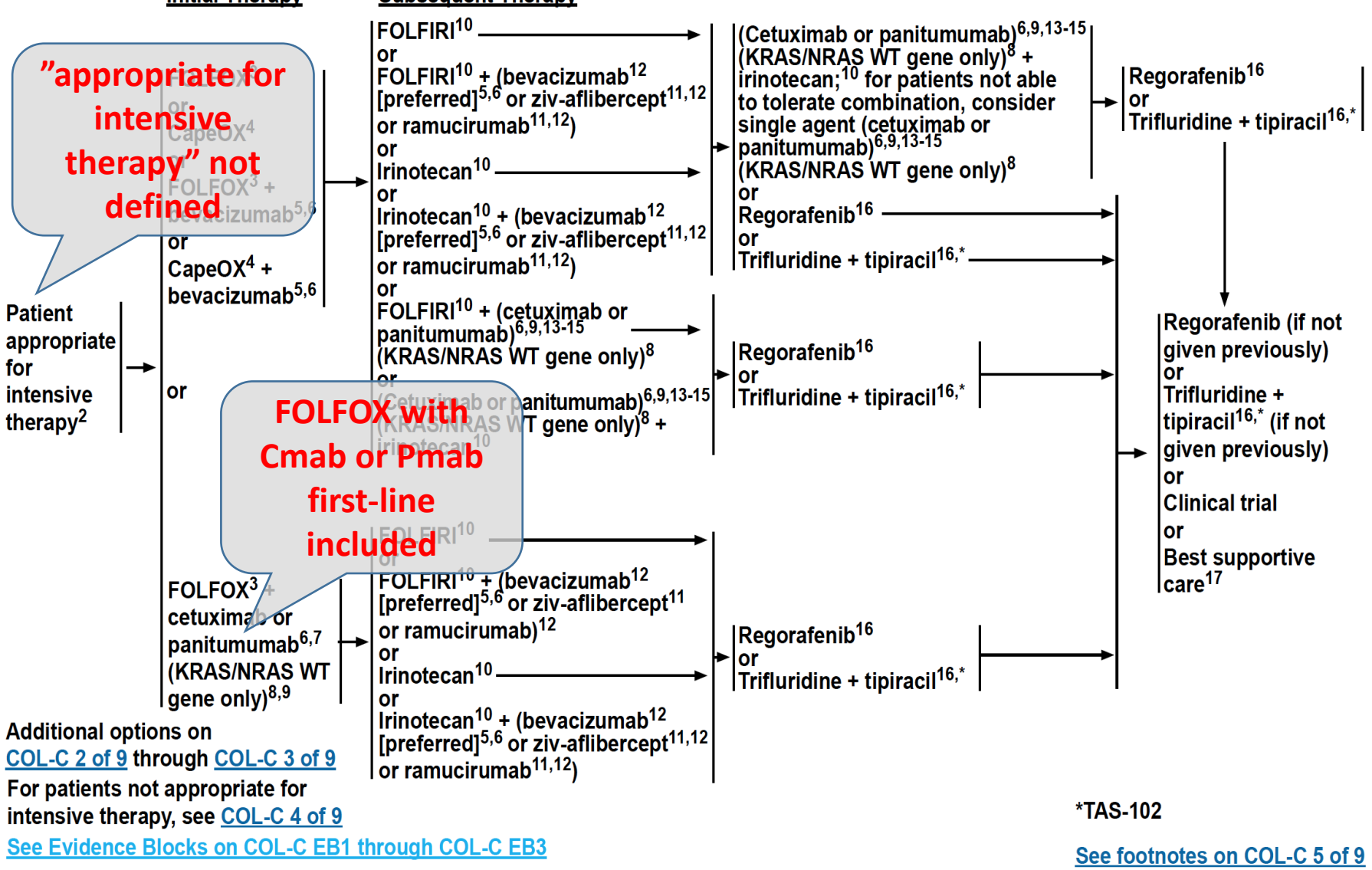

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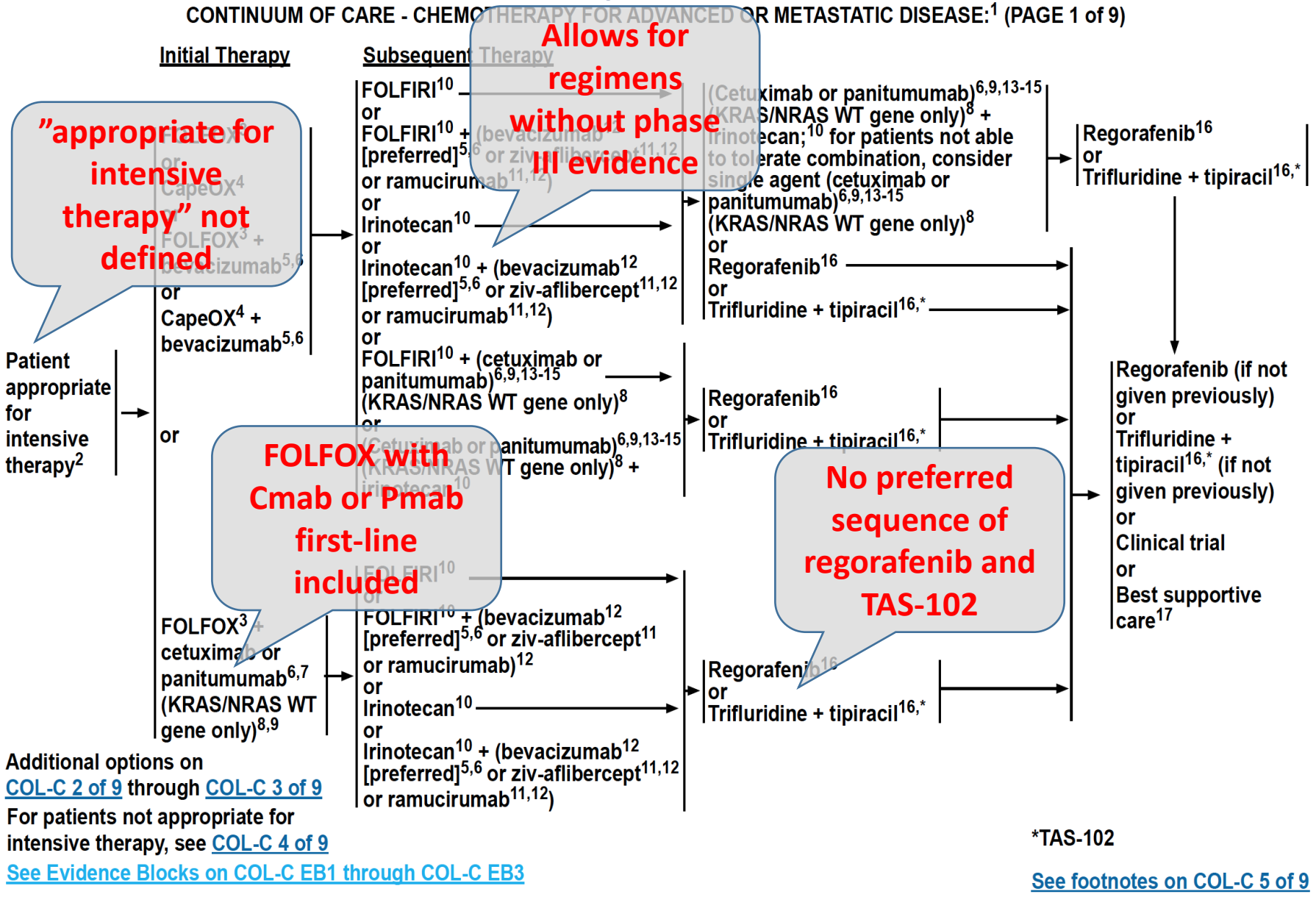

Irinotecan first line

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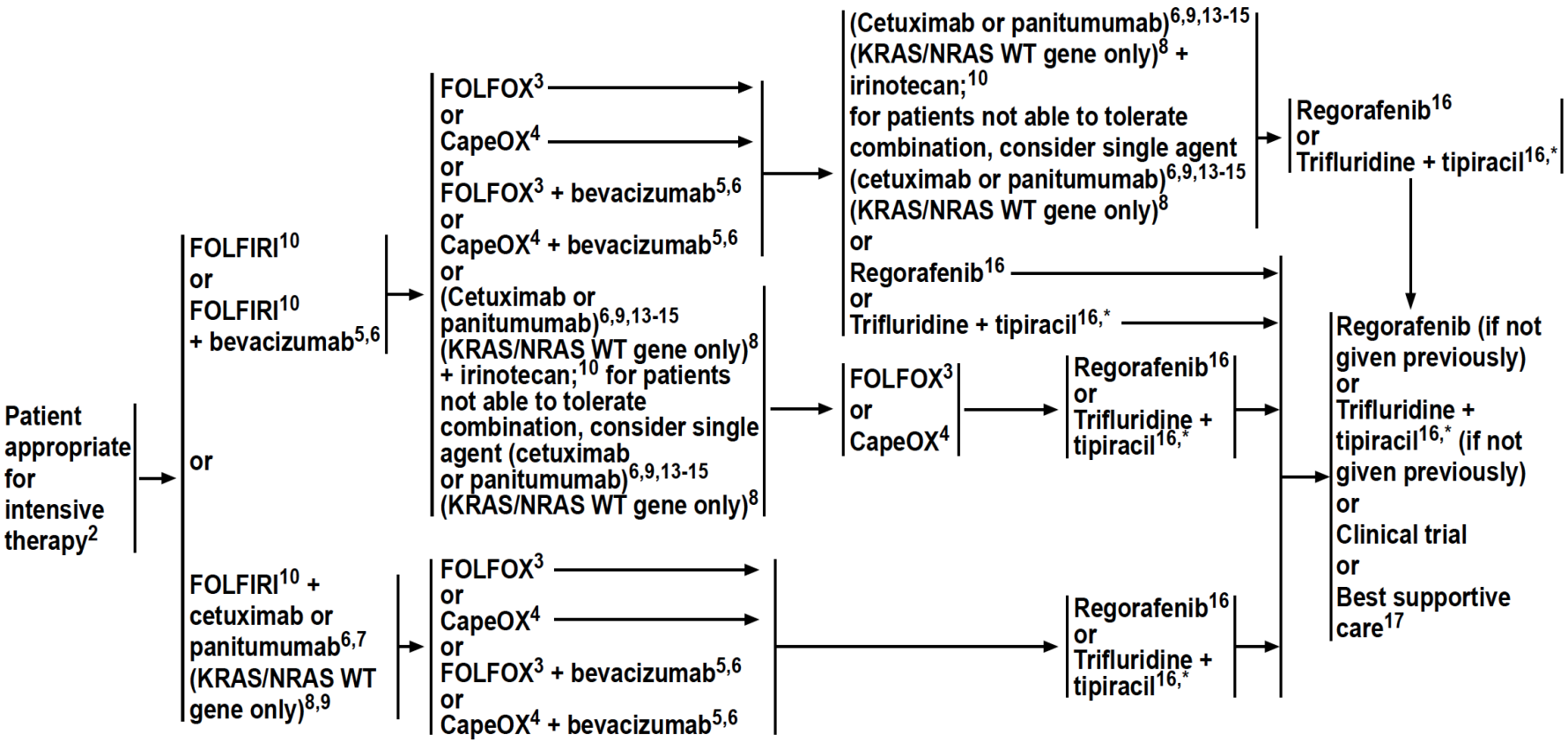

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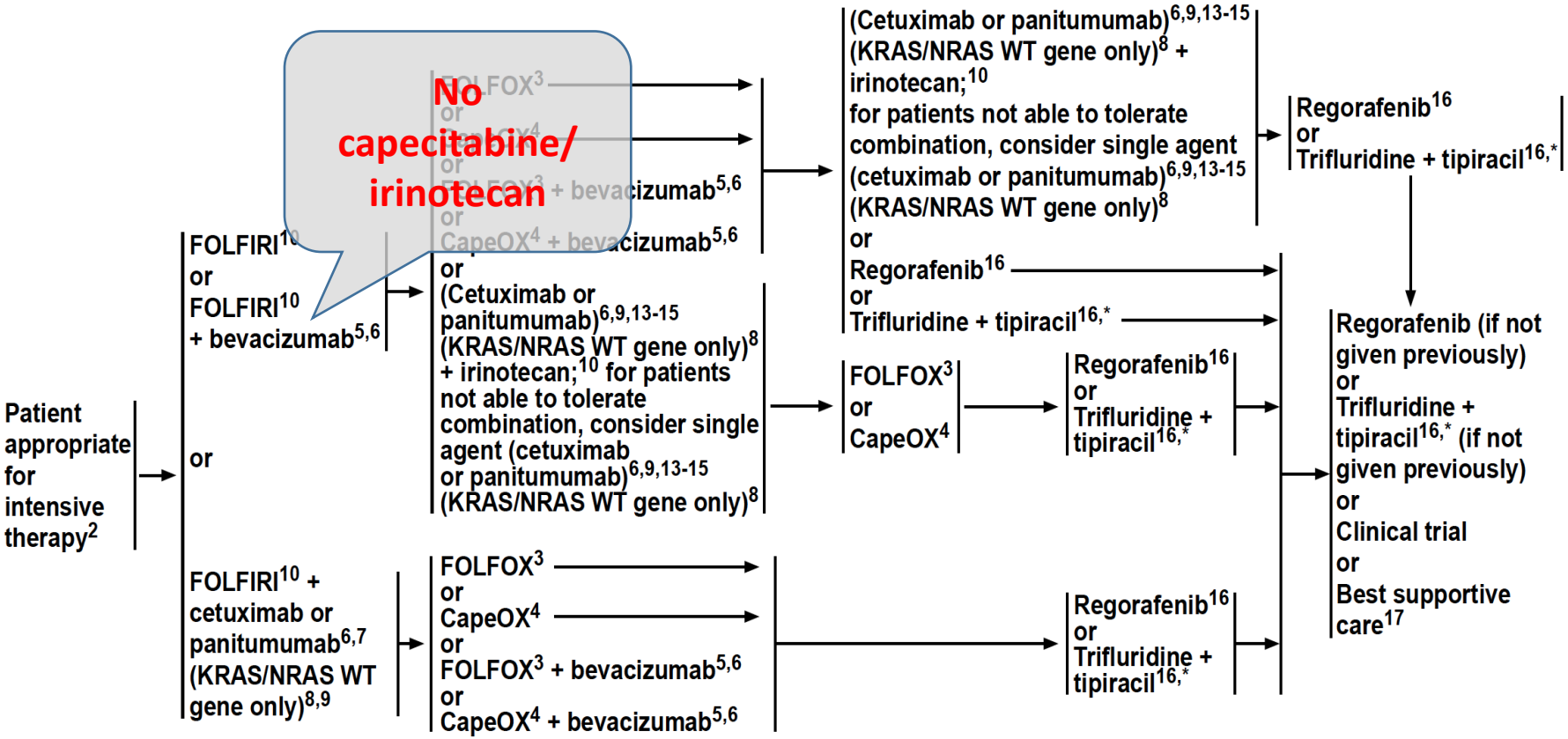

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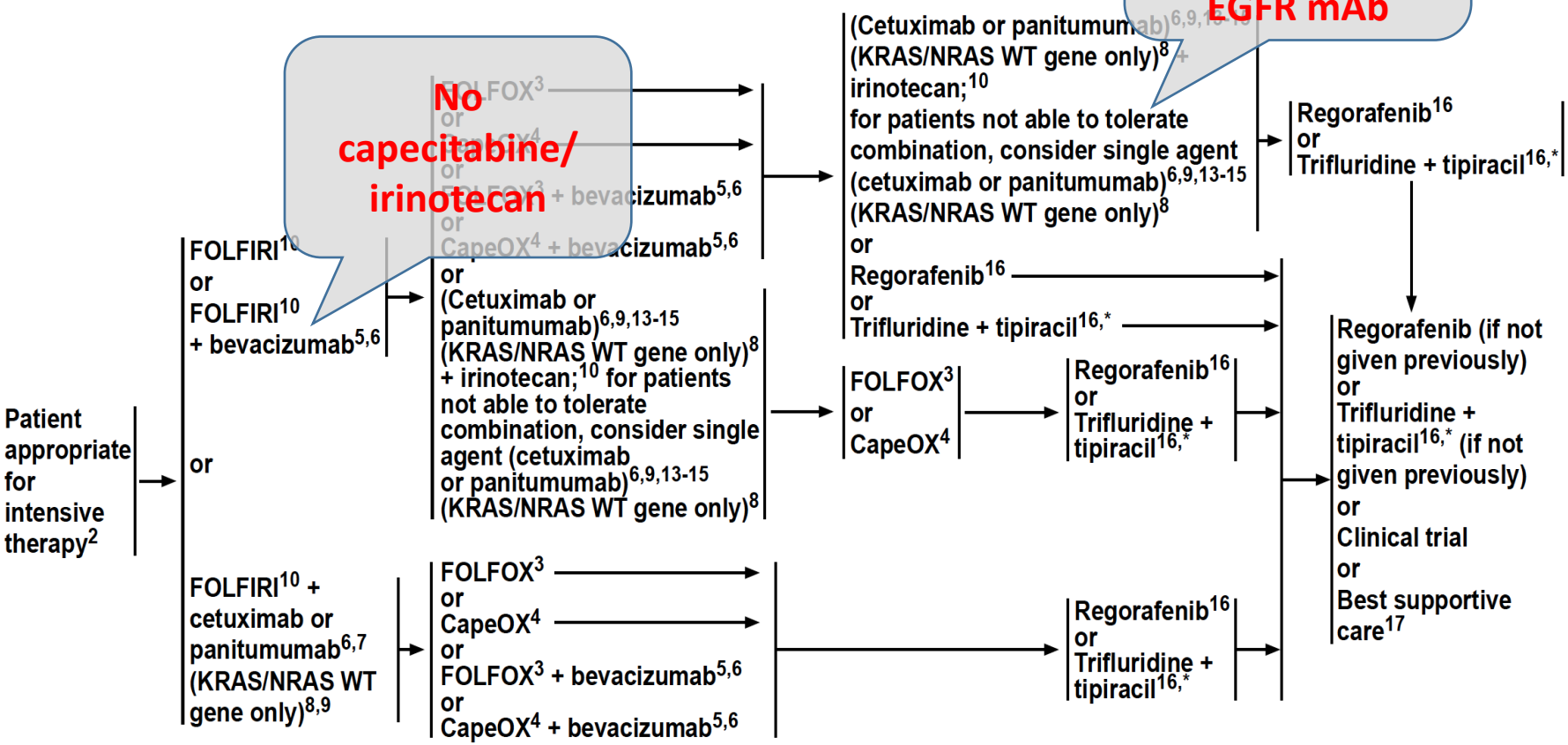

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Other first line regimens

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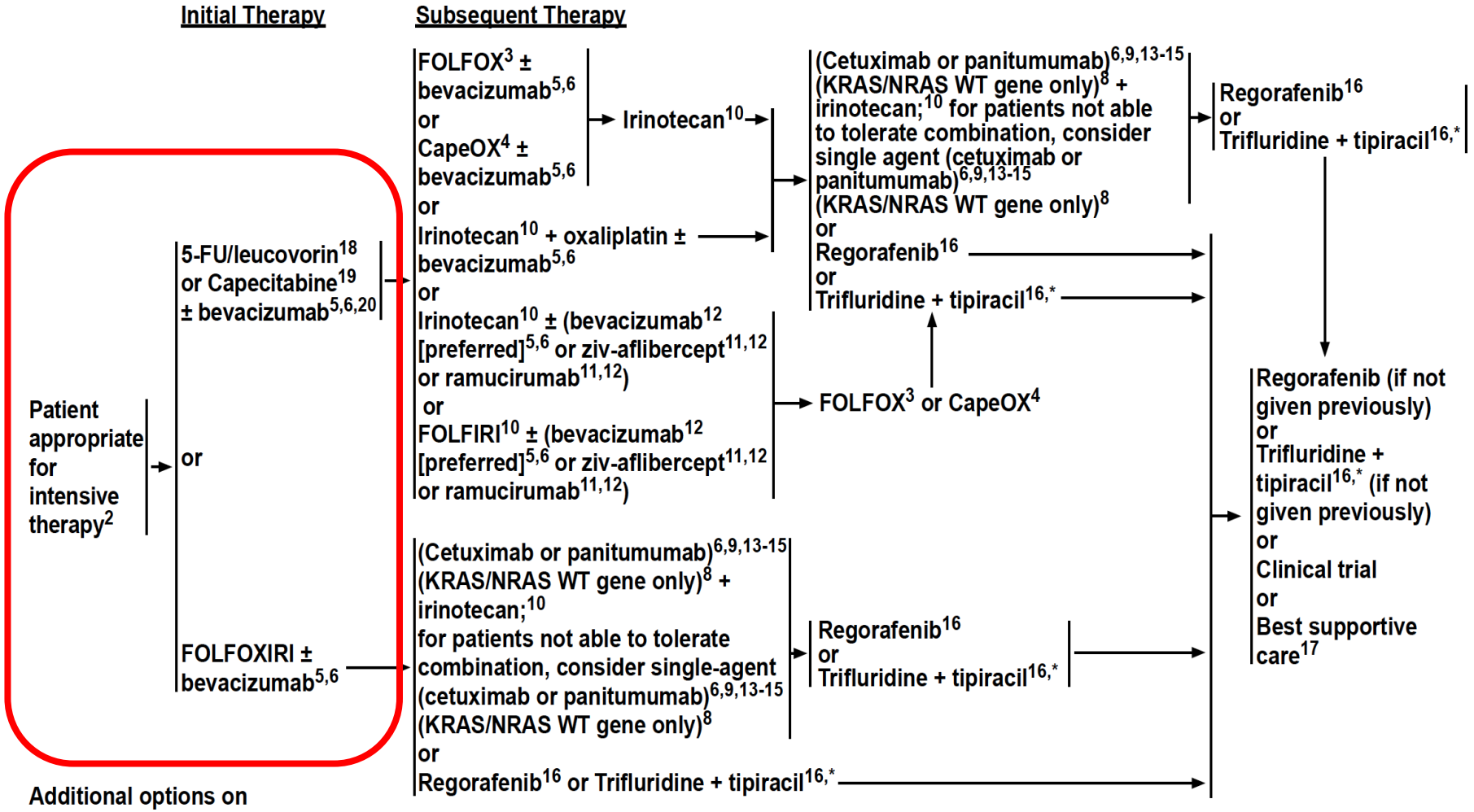

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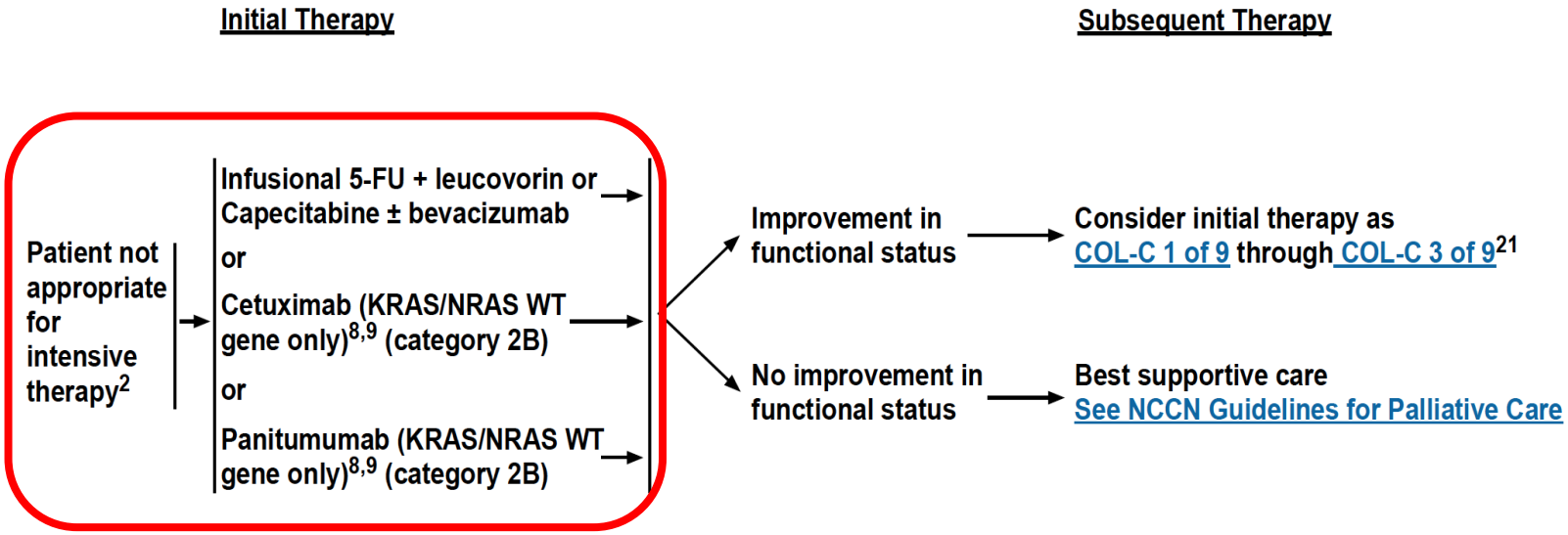

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NCCN Guidelines - Weaknesses

- 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