Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2023-B-037 Nivolumab

Stand: Mai 2023

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Nivolumab
[Erstlinienbehandlung des nicht resezierbaren oder metastasierten Kolorektalkarzinoms]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschluss über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: • Pembrolizumab: Beschluss vom 16. September 2021
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Nivolumab L01FF01 Opdivo	<u>Geplantes Anwendungsgebiet laut Beratungsanforderung:</u> Nivolumab ist in Kombination mit Ipilimumab zur Erstlinienbehandlung des nicht resezierbaren oder metastasierten Kolorektalkarzinoms mit Mismatch-Reparatur-Defizienz oder hoher Mikrosatelliteninstabilität bei Erwachsenen indiziert.
Zytostatika	
5-Fluorouracil L01BC02 5-FU medac	<u>Fortgeschrittenes oder metastasiertes kolorektales Karzinom</u>
Calciumfolinat V03AF03 Calciumfolinat-GRY	Calciumfolinat ist indiziert: – in Kombination mit 5-Fluorouracil in der zytotoxischen Therapie o bei fortgeschrittenem oder metastasiertem kolorektalem Karzinom
Capecitabin L01BC06 Capecitabin medac	Capecitabin medac wird angewendet: – zur Behandlung des metastasierten Kolorektalkarzinoms (siehe Abschnitt 5.1).
Irinotecan L01XX19 Irinotecan onkovis	Irinotecan onkovis ist indiziert zur Behandlung von Patienten mit fortgeschrittenem kolorektalem Karzinom: – in Kombination mit 5-Fluorouracil und Folinsäure bei Patienten ohne vorausgegangene Chemotherapie zur Behandlung der fortgeschrittenen Erkrankung Irinotecan onkovis ist in Kombination mit Cetuximab indiziert zur Behandlung von Patienten mit EGFR (epidermal growth factor receptor)-exprimierendem metastasierendem kolorektalem Karzinom vom KRAS Wildtyp, die zuvor keine Behandlung der metastasierten Erkrankung erhalten haben, oder nach Versagen einer Irinotecanhydrochlorid-haltigen zytotoxischen Therapie (siehe Abschnitt 5.1).

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	Irinotecan onkovis ist in Kombination mit 5-Fluorouracil, Folinsäure und Bevacizumab indiziert zur Erstlinientherapie bei Patienten mit metastasierendem Kolon- oder Rektumkarzinom. Irinotecan onkovis ist in Kombination mit Capecitabin mit oder ohne Bevacizumab indiziert zur Erstlinientherapie bei Patienten mit metastasierendem kolorektalem Karzinom.
Mitomycin L01DC03 Mitomycin medac	<u>Intravenöse Anwendung</u> Mitomycin wird in der palliativen Tumortherapie eingesetzt. Die intravenöse Anwendung von Mitomycin ist in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei Erwachsenen mit folgenden Erkrankungen angezeigt: – fortgeschrittenes kolorektales Karzinom
Oxaliplatin L01XA03 Oxaliplatin-GRY	Oxaliplatin wird in Kombination mit 5-Fluorouracil (5-FU) und Folinsäure (FA) angewendet: – zur Behandlung des metastasierenden kolorektalen Karzinoms.
Antikörper	
Bevacizumab L01XC07 Avastin	Bevacizumab wird in Kombination mit einer Chemotherapie auf Fluoropyrimidin-Basis zur Behandlung von erwachsenen Patienten mit metastasiertem Kolon- oder Rektumkarzinom angewendet.
Cetuximab L01XC06 Erbitux	Erbitux ist indiziert zur Behandlung des metastasierenden, EGFR (epidermalen Wachstumsfaktor-Rezeptor) exprimierenden Kolorektalkarzinoms mit Ras-Wildtyp – in Kombination mit einer Irinotecanbasierten Chemotherapie, – als Erstlinienbehandlung in Kombination mit FOLFOX
Panitumumab L01XC08 Vectibix	Vectibix ist indiziert zur Behandlung von erwachsenen Patienten mit metastasiertem kolorektalem Karzinom (mCRC, metastatic colorectal cancer) mit RAS-Wildtyp: – in der Erstlinientherapie in Kombination mit FOLFOX oder FOLFIRI.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Pembrolizumab L01XC18 Keytruda	<u>Kolorektalkarzinom (colorectal cancer, CRC)</u> KEYTRUDA ist als Monotherapie zur Erstlinienbehandlung des metastasierenden Kolorektalkarzinoms bei Tumoren mit hochfrequenter Mikrosatelliten-Instabilität (MSI-H) oder mit einer Mismatch-Reparatur-Defizienz (dMMR) bei Erwachsenen angezeigt.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2023-B-037 (Nivolumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	29. März 2023

Inhaltsverzeichnis

Abkürzungsverzeichnis

5-FU	5-Fluorouracil
AE	Adverse Event/s
AK	Antikörper
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BEV	Bevacizumab
CAPOX/XELOX	Capecitabine + Oxaliplatin
CI	Konfidenzintervall
CR	Complete response
CT	Chemotherapy
ECOG	Eastern Cooperative Oncology Group
EGFR(i)	Epidermal growth factor receptor (inhibitor)
FOLFIRI	Folinsäure + 5-Fluorouracil + Irinotecan
FOLFIRINOX	Folinsäure + 5-Fluorouracil + Irinotecan + Oxaliplatin
FOLFOX	Folinsäure + 5-Fluourouracil + Oxaliplatin
FOLFOXIRI	Folinsäure + 5-Fluourouracil + Oxaliplatin + Irinotecan
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HER2	Human epidermal growth factors receptor 2
HR	Hazard Ratio
HRQoL	Health-related Quality of Life
HTA	Health Technology Assessments
IFL	Irinotecan + Folinsäure + 5-Fluorouracil
IgG	Immunglobulin G
IHC	Immunhistochemische Untersuchung
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IV	Intravenös
KI	Konfidenzintervall
KRAS	Kirsten rat sarcoma viral oncogene homolog
LoE	Level of Evidence
MAb	Monoclonal Kolorektalkarzinom
mCRC	metastasierendes Kolorektalkarzinom
MDT	Multidisciplinary team

MERGE	Method for Evaluating Reserch and Guideline Evidence
MMR	Mismatch-repair Gen
MMRd	defekte Mismatch Reparatur
MMRp	profiziente Mismatch Reparatur
MRI	Magnetic resonance imaging
MSI	Mikrosatelliteninstabilität
MSS	Mikrosatellitenstabilität
NICE	National Institute for Health and Care Excellence
NRAS	Neuroblastoma RAS viral oncogene homolog
OR	Odds Ratio
ORR	Overall response rate
OS	Overall survival
PFS	Progression free survival
PR	Partial Response
QoL	Quality of Life
RCT	Randomisierte kontrollierte Studie/n
RR	Relatives Risiko
SD	Stable disease
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
VEGF	Vascular endothelial growth factor
VEGFi	Vascular endothelial growth factor inhibitor
WHO	World Health Organization
WT	wild-type

1 Indikation

Erstlinienbehandlung des nicht resezierbaren oder metastasierten Kolorektalkarzinoms.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Kolorektalkarzinom* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.startpage.com*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Die Erstrecherche wurde am 21.04.2022 durchgeführt, die folgende am 24.11.2022. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter ist am Ende der Synopse detailliert dargestellt. Die Recherchen ergaben insgesamt 2607 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt fünf Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten Reviews identifiziert.

3.2 Systematische Reviews

Cremolini C et al., 2020 [2].

Individual Patient Data Meta-Analysis of FOLFOXIRI Plus Bevacizumab Versus Doublets Plus Bevacizumab as Initial Therapy of Unresectable Metastatic Colorectal Cancer

Fragestellung

We conducted a systematic review followed by an individual patient data (IPD)–based meta-analysis aimed at providing a robust estimation of the added value of FOLFOXIRI + bevacizumab over conventional doublets + bevacizumab in terms of OS and at exploring the interaction of treatment effect with main patient and disease characteristics at baseline

Methodik

Population:

- patients with mCRC

Intervention:

- Triple-Therapie plus Bevacizumab: FOLFOXIRI

Komparator:

- Dublet-Therapie plus Bevacizumab: FOLFIRI, irinotecan and capecitabine [XELIRI], FOLFOX, capecitabine and oxaliplatin [XELOX])

Endpunkte:

- Primär: OS
- Sekundär: PFS, ORR, R0 resection rate, grade 3/4 adverse events

Recherche/Suchzeitraum:

- Jan. 2019 in PubMed, Embase, Medline, Cochrane Library, ASCO proceedings, and European Society of Medical Oncology (ESMO) proceedings

Qualitätsbewertung der Studien:

- Entsprechend Method for Evaluating Research and Guideline Evidence (MERGE) criteria (randomization, blinding, outcome measures, measure assessment, arm comparability, loss to follow-up, and intention-to-treat analysis)

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 RCTs [TRIBE, OLIVIA, CHARTA, STEAM, TRIBE2] (N=1.697)

Charakteristika der Population/Studien:

- The median age of the pooled population was 61 years (IQR, 53-67 years); most patients had an ECOG performance status of 0 (78.3%) and presented with synchronous

metastases (84.7%). Of the patients, 34.8% had a right-sided primary tumor, and 32.7% had liver-limited disease. Of 1,316 patients with available data, RAS and BRAF mutations were reported in 65% and 9%, respectively. No relevant differences between the 2 treatment groups were evident, except for a higher percentage of patients with a right-sided primary tumor (37.3% v 32.3%) and liver-only disease (35.6 v 29.9%) in the FOLFOXIRI + bevacizumab group

Qualität der Studien:

- all included studies were of sufficiently high quality to consider the risk of bias as low to moderate

Studienergebnisse:

- OS:
  - Medianes Gesamtüberleben: 28,9 vs. 24,5 Monate zugunsten FOLFOXIRI plus Bev.
  - 5-Jahres-Überleben: 22,3% vs. 10,7%
  - HR 0,81 (95%-CI 0,72;0,91), I^2=2%, p<0,001
- PFS:
  - Medianes PFS: 12,2 vs. 9,9 Monate zugunsten FOLFOXIRI plus Bev.
  - HR 0,74 (95%-CI 0,67;0,82), I^2=35%, p<0,001
- ORR
  - OR 1,57 (95%-CI 1,29;1,91, I^2=0%, p<0,001 zugunsten FOLFOXIRI plus Bev. gemäß RECIST
- Sicherheit:
  - Compared with doublets + bevacizumab, the administration of FOLFOXIRI + bevacizumab was associated with a significantly higher incidence of the following grade 3 or 4 adverse events:
    - neutropenia (45.8% v 21.5%; P < .001),
    - febrile neutropenia (6.3% v 3.7%; P = .019),
    - nausea (5.5% v 3.0%; P = .016),
    - mucositis (5.1% v 2.9%; P = .024),
    - diarrhea (17.8% v 8.4%; P < .001).
    - No significant increase in the rate of toxic deaths was reported

Anmerkung/Fazit der Autoren

In conclusion, on the basis of the results of our metaanalysis, FOLFOXIRI + bevacizumab is a valuable upfront option able to provide a clinically meaningful survival benefit to patients with unresectable mCRC with an ECOG performance status of 0 or 1.

Kommentare zum Review

Keine signifikanten Interaktionen in den Subgruppenanalysen

Dai J et al., 2019 [3].

The efficacy and safety of irinotecan +/- bevacizumab compared with oxaliplatin +/- bevacizumab for metastatic colorectal cancer: A meta-analysis

Fragestellung

This meta-analysis therefore aimed to compare the efficacy and safety between IRI±bevacizumab and OXA±bevacizumab in patients with mCRC

Methodik

Population:

- Patienten mit mCRC

Intervention:

- Irinotecan + Bevacizumab

Komparator:

- Oxaliplatin + Bevacizumab

Endpunkte:

- Primär: OS, TTP
- Sekundär: ORR, Toxizität

Recherche/Suchzeitraum:

- Dez. 2018 in PubMed, EMBASE, Cochrane Controlled Trials Register

Qualitätsbewertung der Studien:

- Cochrane RoB

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 RCTs (N=4.191)

Charakteristika der Population/Studien:

- No differences were found in the baseline characteristics between patients in the 2 groups in the selected studies

Qualität der Studien:

- Nicht berichtet

Studienergebnisse:

- Keine signifikanten Unterschiede zwischen den Gruppen für OS und TTP
- Marginaler Vorteil für Oxaliplatin + Bevacizumab für ORR
- Toxizität:
  - Höher im Irinotexan-Arm:
    - Nausea (RR=1.63, 95% CI: 1.28–2.07, P<.001),
    - vomiting (RR=1.40, 95% CI: 1.09–1.81, P=.009),
    - diarrhea (RR=1.44, 95% CI: 1.23–1.70, P<.001),
    - anemia (RR=4.13, 95% CI: 2.75–6.22, P<.001) were higher in the IRI arm. However, the
  - höher im Oxaliplatin-Arm:
    - neutropenia (RR=0.75, 95% CI: 0.68–0.83, P<.001),
    - thrombocytopenia (RR=0.43, 95% CI: 0.26–0.73, P=.002),

- paresthesia/neurological disturbances (RR=0.04, 95% CI: 0.02–0.07, P<.001) were higher in the OXA arm

Anmerkung/Fazit der Autoren

No statistically significant differences were observed in OS and TTP. However, the OXA group was superior to the IRI group in terms of ORR. Moreover, the 2 treatment regimens showed manageable toxicities. The results suggested the superior efficacy of OXA±bevacizumab therapy compared with IRI±bevacizumab therapy for mCRC patients

Kommentare zum Review

Schlussfolgerung nicht nachvollziehbar

SR mit ähnlicher Fragestellung: Ren et al. 2021 [5]

3.4 Leitlinien

Morris, V. K. et al., 2022 [4].

American Society of Clinical Oncology

Treatment of Metastatic Colorectal Cancer: ASCO Guideline

Zielsetzung/Fragestellung

This guideline provides a review of the evidence for areas of uncertainty in the treatment of mCRC, including indications for targeted therapy, and treatment options for oligometastatic and liver-limited disease.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Keine Konsensusprozesse angewendet, externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- PubMed and Cochrane Library until June 20, 2022.

LoE

TABLE A2. Recommendation Rating Definitions

Term	Definitions
Quality of evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

GoR

Strength of recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects All or almost all informed people would make the recommended choice for or against an intervention
Weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. Most informed people would choose the recommended course of action, but a substantial number would not

Empfehlungen

1. For patients with previously untreated, initially unresectable mCRC who are candidates for chemotherapy plus bevacizumab, is doublet (folinic acid, FU, and oxaliplatin [FOLFOX], or folinic acid, FU, and irinotecan [FOLFIRI]) or triplet (folinic acid, FU, oxaliplatin, and irinotecan [FOLFOXIRI]) cytotoxic chemotherapy recommended?

Recommendation 1.1. Doublet (folinic acid, fluorouracil [FU], and oxaliplatin [FOLFOX], or folinic acid, FU, and irinotecan [FOLFIRI]) backbone chemotherapy should be offered as first-line therapy to patients with initially unresectable microsatellite stable (MSS) or proficient mismatch repair (pMMR) mCRC (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).
Qualifying statement. Treatment with capecitabine plus oxaliplatin may be substituted for folinic acid, FU, and oxaliplatin (FOLFOX) at the clinical discretion of the treating provider, and in shared decision making with the patient.

Recommendation 1.2. Triplet (folinic acid, FU, oxaliplatin, and irinotecan [FOLFOXIRI]) backbone chemotherapy may be offered as first-line therapy to selected patients with initially unresectable MSS or pMMR mCRC (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak).
Qualifying statements for Recommendations 1.1 and 1.2.
• All patients included in the evidence-base for Recommendations 1.1 and 1.2 received anti–vascular endothelial growth factor (VEGF) antibody bevacizumab in addition to doublet or triplet chemotherapy backbone.
• Shared decision making is recommended, including a discussion of the potential for benefit and risk of harm; while survival and recurrence outcomes are improved, number of grade 3

or greater adverse events are more frequent with triplet chemotherapy, compared with doublet chemotherapy (Table 1).

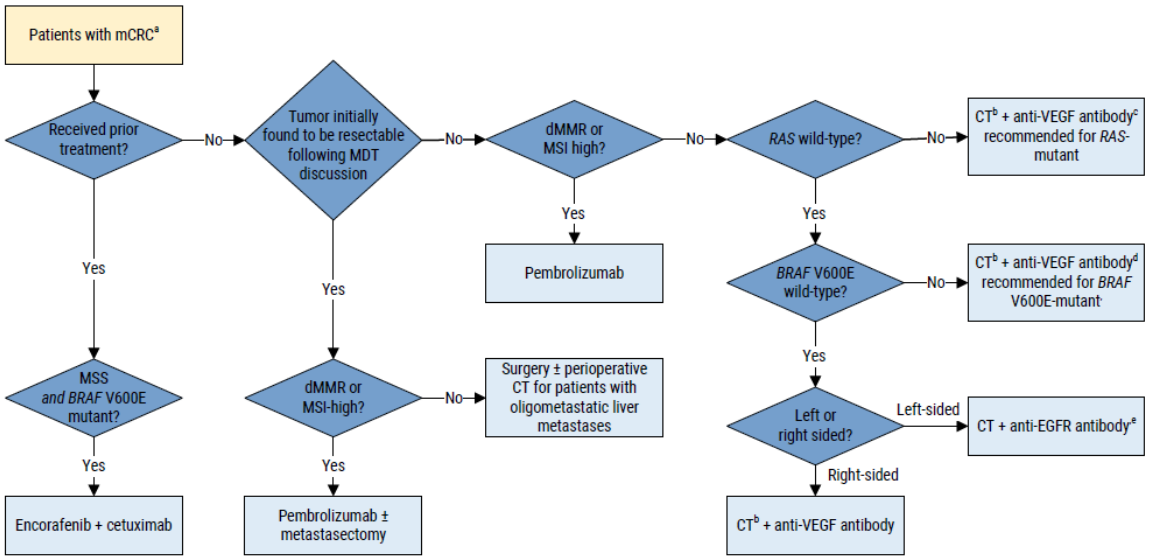
2a. In the first-line setting, are outcomes for patients with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) mCRC improved with pembrolizumab immunotherapy versus chemotherapy with or without bevacizumab or cetuximab?
2b. Is pembrolizumab recommended as later-line therapy for patients with microsatellite stable (MSS) or proficient mismatch repair (pMMR) mCRC and high tumor mutational burden (TMB $ 10 mutations/Mb)?

Recommendation 2.1. Pembrolizumab should be offered as first-line therapy to patients with microsatellite instability-high or deficient mismatch repair mCRC (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

3. For patients with treatment-naive RAS wild-type mCRC, are anti–epidermal growth factor receptor (EGFR) antibodies (ie, panitumumab and cetuximab) recommended for patients with right-sided or left-sided primary tumors?

Recommendation 3.1. Anti–epidermal growth factor receptor (EGFR) therapy plus doublet chemotherapy should be offered as first-line therapy to patients with MSS or pMMR left-sided RAS wild-type mCRC (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).
Qualifying statements.
• Anti-EGFR therapy is not recommended as first-line therapy for patients with right-sided RAS wild-type mCRC, and consistent with the qualifying statements to Recommendation 1.1 and 1.2, these patients should be offered chemotherapy and anti-VEGF therapy.
• Anti-EGFR therapy is not recommended for patients with RAS-mutant mCRC.
• Anti-EGFR therapy with triplet chemotherapy is not recommended.
• Although anti-EGFR therapy is preferred, anti-VEGF therapy remains an active treatment option for patients with left-sided treatment-naive RAS wild-type mCRC in the first-line setting.
• Shared decision making is recommended, including a discussion of potential for benefit and risk of harms, such as the increased risk of treatment-related rash with anti-EGFR agents (Table 3).

Systemic Therapy for Metastatic Colorectal Cancer (mCRC) Algorithm



[a] Decisions regarding treatment options and sequencing for all patients with mCRC should be made within the context of an MDT.
[b] Doublet CT should be offered, or triplet CT may be offered. Shared decision-making is recommended, including a discussion of the potential for benefit and risk of harm; while survival and recurrence outcomes are improved, grade 3 or greater adverse events are more frequent with triplet CT, compared to doublet CT.
[c] Anti-EGFR therapy is not recommended for patients with RAS-mutant mCRC.
[d] Anti-EGFR therapy is not recommended as a lone biologic agent for treatment-naïve patients with BRAF V600E-mutant mCRC.
[e] Although anti-EGFR therapy is preferred, anti-VEGF therapy remains an active treatment option for patients with left-sided treatment-naïve RAS wild-type mCRC.
Abbreviations: CT: chemotherapy; dMMR: deficient mismatch repair; Doublet CT: FOLFOX, CAPOX or FOLFIRI. MDT: multidisciplinary team; MSI: microsatellite instability; MSS: microsatellite stable; Triplet CT: FOLFOXIRI.

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Alberta Health Services, 2021 [1].

Alberta Health Services (AHS)

Metastatic colorectal cancer.

Zielsetzung/Fragestellung

What are the recommended treatment regimens for adult patients with metastatic colorectal cancer?

Methodik

<u>Grundlage der Leitlinie</u>

- Repräsentatives Gremium; trifft zu
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt; trifft zu
- Systematische Suche, Auswahl und Bewertung der Evidenz; trifft zu
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt; trifft zu
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt; trifft zu
- Regelmäßige Überprüfung der Aktualität gesichert.

<u>Recherche/Suchzeitraum:</u>

- PubMed and MEDLINE from 1990 forward

<u>LoE/GoR</u>

Levels of Evidence

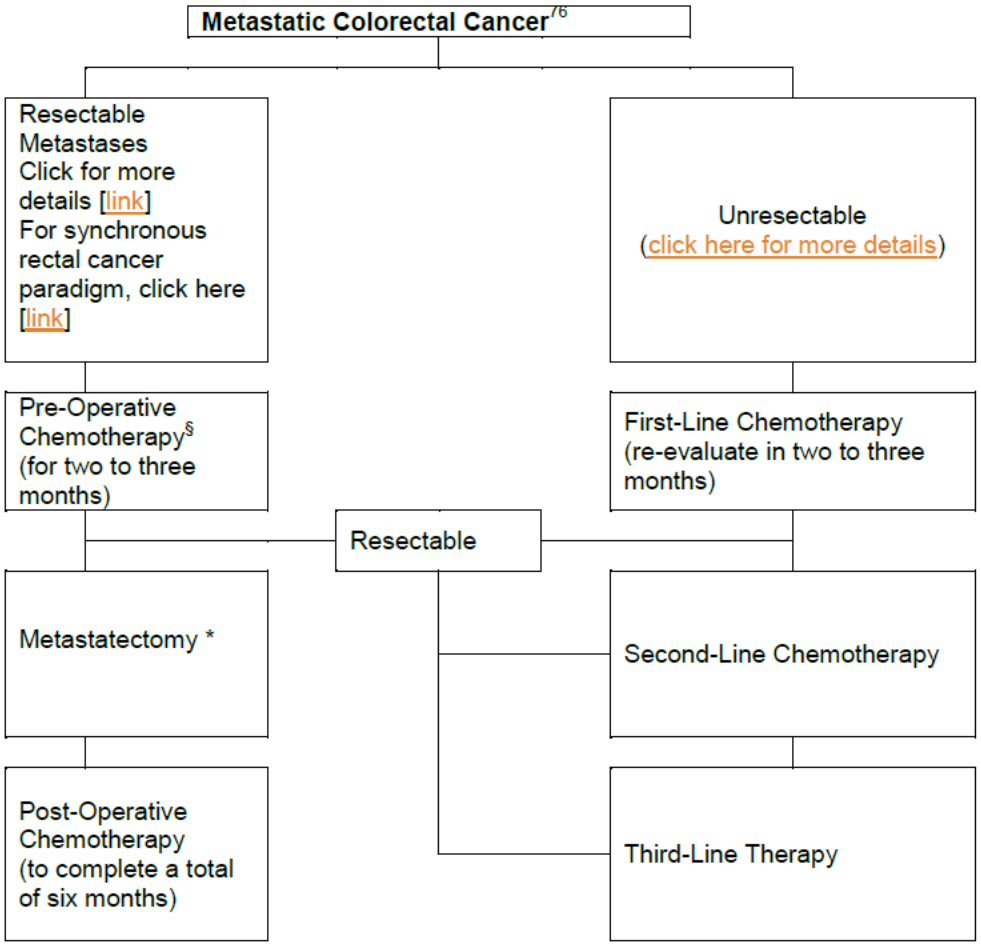
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

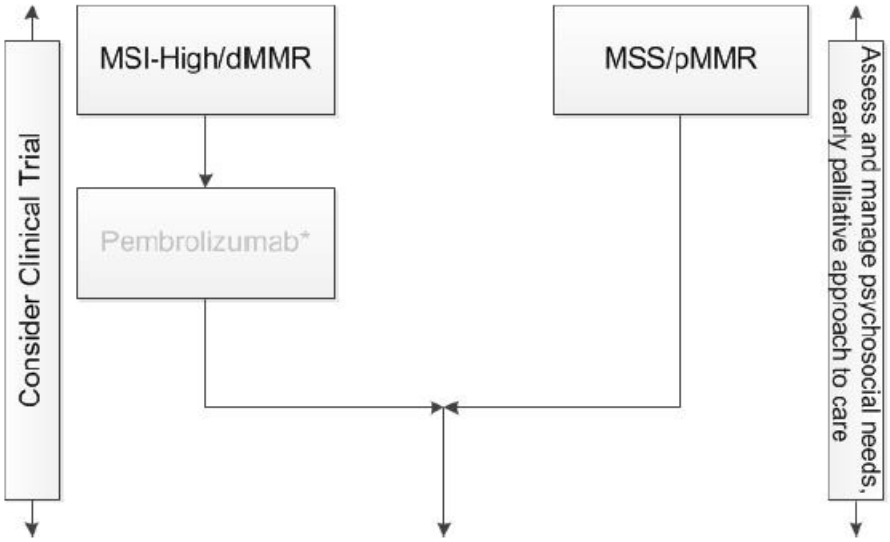
A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Recommendations

- Algorithm for metastatic cancer treatment



- Chemotherapy options for Unresectable Metastatic Colorectal Cancer Consider an Early Palliative Approach to Care



BRAF Mutant	RAS Wild Type - Left Sided Primary	RAS Wild Type - Right Sided Primary	RAS Mutant
Consider FOLFOXIRI Bevacizumab[1]	FOLFOX/CAPOX or FOLFIRI ± EGFRI[1]	FOLFOX/CAPOX or FOLFIRI ± Bevacizumab[1]	
Encorafenib + Cetuximab*	Alternative doublet ± Bevacizumab[1]	Alternative doublet ± Bevacizumab (if not used in the first line)[1]	
	Panitumumab if not used in the first line		
Trifluridine tipiracil* or Regorafenib* or Clinical Trial			

Subsequent lines of therapy

Or Alternative Chemotherapy Options Include:

Capecitabine/5FULV/Ralitrexed
Irinotecan
FOLFOX or CAPOX ± Bevacizumab[1]
Panitumumab if RAS wild type
Trifluridine tipiracil* or Regorafenib* or Clinical Trial

Subsequent lines of therapy

[1]If clinically appropriate
*Not available on provincial formulary

- 4. Standard palliative chemotherapy regimens to consider are described in Table 2.

Table 2. Palliative Chemotherapy Regimens for Patients with Metastatic Colorectal Cancer.

Regimen	Details
FOLFIRI[12]	• Involves the administration of Irinotecan (180 mg/m^2 IV) and Leucovorin (400 mg/m^2 IV) concurrently over two hours followed by 5-Fluorouracil (400 mg/m^2 IV bolus and then an IV infusion of 2,400 mg/m^2 over forty-six hours) in every two-week cycle. This regimen requires placement of a port, central venous catheter (CVC), or peripherally inserted central catheter (PICC). • For patients who have complications with, or contraindications to, placement of a port, CVC, or PICC along with the capacity to tolerate the potential for greater toxicity, consider CAPIRI (administers Irinotecan 200 mg/m^2 IV over ninety minutes followed by Capecitabine 800 mg/m^2 PO Q12h for fourteen days in every twenty-one day cycle).[78] • Supplement with Bevacizumab, where appropriate (see below). • Consider a switch to FOLFOX6 (or CAPOX) at progression, provided it is medically reasonable and the patient wishes further therapy. The sequence of FOLFIRI followed by FOLFOX6 is equivalent to the sequence of FOLFOX6 followed by FOLFIRI[12]. • Due to Oxaliplatin's propensity to cause a cumulative peripheral sensory neuropathy, consider a non–Oxaliplatin-containing regimen before an Oxaliplatin-based regimen. Irinotecan should be considered relatively contraindicated (or consider a dose modification) for patients with an elevated bilirubin due to metastatic disease or Gilbert's syndrome • **Gilbert's syndrome** results from impaired activity of uridine diphosphate glucuronyl-transferase isoform 1A1 (UGT_{1A1}). It delays the metabolism of Irinotecan and thereby increases the risk of severe toxicity.
CAPOX and FOLFOX6 [12-14]	• **CAPOX** involves the administration of Oxaliplatin (130 mg/m^2 IV over two hours) and Capecitabine 1,000 mg/m^2 PO Q12h for fourteen days in every twenty-one day cycle. • **FOLFOX6** involves the administration of Oxaliplatin (100 mg/m^2 IV) and Leucovorin (400 mg/m^2 IV) concurrently over two hours followed by 5-Fluorouracil (400 mg/m^2 IV bolus and then an intravenous infusion of 2,400 mg/m^2 over forty-six hours) in every two-week cycle. This regimen requires placement of a port, central venous catheter (CVC), or peripherally inserted central catheter (PICC). • Supplement with Bevacizumab, where appropriate (see below). • Consider a switch to FOLFIRI or Irinotecan at progression, provided it is medically reasonable and the patient wishes further therapy. The sequence of FOLFIRI followed by FOLFOX6 is equivalent to the sequence of FOLFOX6 followed by FOLFIRI[12]. • Due to Oxaliplatin's propensity to cause a cumulative peripheral sensory neuropathy, consider a non–Oxaliplatin-containing regimen before an Oxaliplatin-based regimen. • For patients with persistent grade ≥ 2 peripheral neuropathy, considering holding or reducing the doses of Oxaliplatin.
FOLFOXIRI[15]	• Involves the administration of a 90 minute infusion of Irinotecan (165 mg/m^2), a 120 minute infusion of Oxaliplatin (85 mg/m^2), and a concomitant 120 minute infusion of Leucovorin (400 mg/m^2), followed by a 48-hour continuous infusion 5-Fluorouracil (total dose 3200 mg/m^2) in every two-week cycle. This regimen requires placement of a port, central venous catheter (CVC), or peripherally inserted central catheter (PICC). • Supplement with Bevacizumab, where appropriate (see below). • FOLFOXIRI is usually reserved for patients with excellent performance status

<table>
<tr><th>Regimen</th><th>Details</th></tr>
<tr><td></td><td>as the progression free survival and overall survival improvement associated with FOLFOXIRI and Bevacizumab in the TRIBE study were accompanied with increased toxicity[15].</td></tr>
<tr><td>Capecitabine[16]</td><td>• Involves the administration of Capecitabine 1,250 mg/m² PO Q12h for fourteen days in every twenty-one day cycle. Refer to "Capecitabine: A Guide for Patient Care."
• Supplement with Bevacizumab, where appropriate (see below).</td></tr>
<tr><td>Irinotecan[17]</td><td>• Involves the administration of Irinotecan (350 mg/m² IV over ninety minutes) in every three-week cycle.
• Decrease the dose by 20% for patients over seventy years of age or for patients who have received prior radiotherapy to the pelvis.
Irinotecan should be considered relatively contraindicated (or consider a dose modification) for patients with an elevated bilirubin due to metastatic disease or Gilbert's syndrome
• Gilbert's syndrome results from impaired activity of uridine diphosphate glucuronyl-transferase isoform 1A1 (UGT_{1A1}). It delays the metabolism of Irinotecan and thereby increases the risk of severe toxicity.</td></tr>
<tr><td>5-Fluorouracil (simplified LV5FU2)</td><td>• Involves the administration of Leucovorin (400 mg/m² IV over two hours) followed by 5-Fluorouracil (400 mg/m² IV bolus and then an intravenous infusion of 2,400 mg/m² over forty-six hours) in every two-week cycle.
• This regimen requires placement of a port, central venous catheter (CVC), or peripherally inserted central catheter (PICC).
• Supplement with Bevacizumab, where appropriate (see below).</td></tr>
<tr><td>Raltitrexed[18]</td><td>• Considered for patients intolerant of 5-Fluorouracil
• Involves the administration of Raltitrexed IV at a dose and frequency that is based on the patient's creatinine clearance.
<table>
<tr><th>Creatinine Clearance</th><th>Dose as Percentage of 3 mg/m²</th><th>Interval</th></tr>
<tr><td>> 65 mL/minute</td><td>100%</td><td>Q3weeks</td></tr>
<tr><td>55 to 65 mL/minute</td><td>75%</td><td>Q4weeks</td></tr>
<tr><td>25 to 54 mL/minute</td><td>% Equivalent to Creatinine Clearance</td><td>Q4weeks</td></tr>
<tr><td>< 25 mL/minute</td><td>No therapy</td><td>Not applicable</td></tr>
</table></td></tr>
<tr><td>Bevacizumab[1] [6,19-23]</td><td>• Bevacizumab interrupts VEGF-mediated angiogenesis — a critical factor in tumor growth and progression. It is thought to decrease the interstitial pressure in tumors, to normalize tumor vasculature, and to improve the delivery of chemotherapy.
• Bevacizumab is contraindicated in patients with:
· Radiological or clinical evidence of invasion of the tumor into a major blood vessel;
· Major surgical procedure or significant trauma within preceding twenty-eight days;
· Major surgical procedure anticipated within forthcoming four to six weeks;</td></tr>
</table>

<table>
<tr><th>Regimen</th><th>Details</th></tr>
<tr><td></td><td>
· Uncontrolled hypertension;
· Clinically significant cardio- or cerebro-vascular disease (e.g.: myocardial infarction or cerebrovascular accident within six months, unstable angina, congestive heart failure, use of a thrombolytic agent within six months, serious dysrhythmia);
· Inherited bleeding diathesis, coagulopathy, or esophageal varices;
· Significant proteinuria or renal dysfunction;
· Non-healing wound, ulcer, or bone fracture;
· Metastases within central nervous system or ophthalmologic abnormalities; and
· Pregnancy, lactation, or childbearing potential without effective contraception.
• If the medical oncologist feels the benefits outweigh the risks, it may be combined with chemotherapy in patients with a good performance status (ECOG ≤2). It can be administered over ten minutes at 5 mg/kg IV (Q2week chemotherapy schedule) or over fifteen minutes at 7.5 mg/kg IV (Q3week chemotherapy schedule).

<table>
<tr><th rowspan="2">Toxicities</th><th colspan="2">Summary Incidence</th><th colspan="2">Relative Risk</th></tr>
<tr><th>All-Grade Events</th><th>High-Grade Events</th><th>All-Grade Events</th><th>High-Grade Events</th></tr>
<tr><td>Arterial Thromboembolic Events[19]
Cardiac Ischemia
Cerebrovascular Ischemia</td><td>3.3%</td><td>2.0%
1.5%
1.2%</td><td>HR 2.08</td><td>HR 1.29
HR 2.14
HR 1.37</td></tr>
<tr><td>Proteinuria[22]</td><td>—</td><td>1.0%</td><td>HR 1.40</td><td>—</td></tr>
<tr><td>Hypertension[22]</td><td>—</td><td>8.7%</td><td>—</td><td>HR 3.00</td></tr>
<tr><td>Wound Healing Complications[20,21,24]</td><td>4.9%</td><td>3.7%</td><td>—</td><td>—</td></tr>
<tr><td>Gastrointestinal Perforation[25]</td><td>—</td><td>0.9%</td><td>—</td><td>HR 2.15</td></tr>
</table>
• Discrepant results exist as to the risk of venous thromboembolic events[23,26]
• It is not indicated for monotherapy and it is currently not funded by the Alberta Health Services Cancer Drug Benefit Program for treatment beyond progression.
  • Refer to the Bevacizumab Administration Guidelines.
</td></tr>
<tr><td>EGFR inhibitor and chemotherapy [27-29]</td><td>
• First-line anti-EGFR therapies may include:
  a. Cetuximab with FOLFIRI[27]
  b. Panitumumab with FOLFOX[28]
  c. Panitumumab with FOLFIRI (based on extrapolation from data in second-line treatment)[29]
</td></tr>
<tr><td></td><td>
• EGFR inhibitors should not be given with bevacizumab as clinical trials with combinations of both EGFR inhibitor and bevacizumab give worse outcome[30,31].
• Refer to Panitumumab and Cetuximab: Toxicity Management Guidelines
</td></tr>
</table>

- 8. Whether treatment is with combination chemotherapy or sequential monotherapy (with or without Bevacizumab) depends upon the patient's goals, their physical status, and other life circumstances, as assessed by their treating oncologist. Sequences of therapy may include:

  a. FOLFIRI followed by CAPOX/FOLFOX6

  b. CAPOX/FOLFOX6 followed by FOLFIRI or Irinotecan

  c. Capecitabine followed by Irinotecan followed by CAPOX/FOLFOX6

- 9. In the situation where a liver metastatectomy would be facilitated by a reduction in the size of the liver metastasis, patients should only be treated with chemotherapy until optimal resectability rather than to maximal response or progression. Only a limited number of cycles of chemotherapy should be delivered so as to minimize the consequences to the liver and their adverse effects. Oxaliplatin-based therapy is less likely to impact on post-metastatectomy mortality than Irinotecan-based therapy39.
- 14. Patients who have progressed on all standard therapy should be encouraged to participate in clinical trials.
- The following trials have been conducted in patients who have progressed on or were intolerant to a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and an EGFR inhibitor (if KRAS/NRAS wild type):
- The phase III CORRECT trial randomized 760 patients who progressed on standard therapy to best supportive care with placebo or regorafenib.38 OS for patients on regorafenib was 6.4 months versus 5.0 months for the placebo arm (HR 0.77, 95% CI 0.64–0.94, p=0.005). PFS improved modestly but significantly (1.9 months versus 1.7 months; HR 0.49, 95% CI 0.42 – 0.58, p<0.000001). The most common adverse events observed in the trial were hand-foot skin reactions (17%), fatigue (10%), hypertension (7%), diarrhea (7%) and rash/desquamation (6%). Regorafenib is currently not funded by the Alberta Health Services Outpatient Cancer Drug Benefit Program.
- The phase III RECOURSE trial randomized 800 patients to trifluridine-tipiracil or placebo. Median OS was significantly prolonged in patients treated with trifluridine-tipiracil compared to placebo (7.1 versus 5.3 months, HR 0.68, 95% CI 0.58- 0.81; P<0.001), and this benefit was irrespective of prior regorafenib use. Trifluridine-tipiracil is currently not funded by the Alberta Health Services Outpatient Cancer Drug Benefit Program40

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 11 of 12, November 2022) am 24.11.2022

#	Suchfrage
1	[mh ^"colorectal neoplasms"]
2	(colon OR colorectal OR rectal):ti,ab,kw
3	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma*):ti,ab,kw
4	#1 OR (#2 AND #3)
5	#4 with Cochrane Library publication date from Nov 2017 to present

Systematic Reviews in Medline (PubMed) am 24.11.2022

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.01.2020.

#	Suchfrage
1	colorectal neoplasms/therapy[majr]
2	colon[tiab] OR colorectal[tiab] OR rectal[tiab]
3	tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR sarcoma*[tiab] OR cancer*[tiab]
4	#2 AND #3
5	(#4) AND ((treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab]))
6	#1 OR #5
7	neoplasm metastasis[mh] OR advanced[tiab] OR metastat*[tiab] OR metastas*[tiab] OR recurren*[tiab] OR unresectab*[tiab]
8	#6 AND #7
9	(#8) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR

#	Suchfrage
	validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
10	((#9) AND ("2017/11/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
11	(#10) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 24.11.2022

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	colorectal neoplasms[majr]
2	colon[ti] OR colorectal[ti] OR rectal[ti]
3	tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR sarcoma*[tiab] OR cancer*[tiab]
4	#1 OR (#2 AND #3)
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
6	(((#5) AND ("2017/11/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 24.11.2022

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- National Cancer Institute (NCI)

- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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4. **Morris VK, Kennedy EB, Baxter NN, Benson AB, 3rd, Cercek A, Cho M, et al.** Treatment of metastatic colorectal cancer: ASCO guideline. J Clin Oncol 2022:Jco2201690.

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[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.0

Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2023-B-037

Verfasser	
Arbeitsgemeinschaft Internistische Onkologie (AIO) der Deutschen Krebsgesellschaft (DKG) Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO) Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS)	
Datum der Erstellung	05.April 2023

Indikation
Erstlinienbehandlung des nicht resezierbaren oder metastasierten Kolorektalkarzinoms mit Mismatch-Reparatur-Defizienz oder hoher Mikrosatelliteninstabilität bei Erwachsenen
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*

Zusammenfassung

Standard in der Erstlinienbehandlung des nicht resezierbaren oder metastasierten, kolorektalen Karzinoms mit Mismatch-Reparatur-Defizienz oder hoher Mikrosatelliteninstabilität ist die Therapie mit einem Immuncheckpoint-Inhibitor. Zugelassen für die EU ist Pembrolizumab. Nach Fluoropyrimidin-haltiger Vortherapie ist Nivolumab/Ipilimumab hoch wirksam.

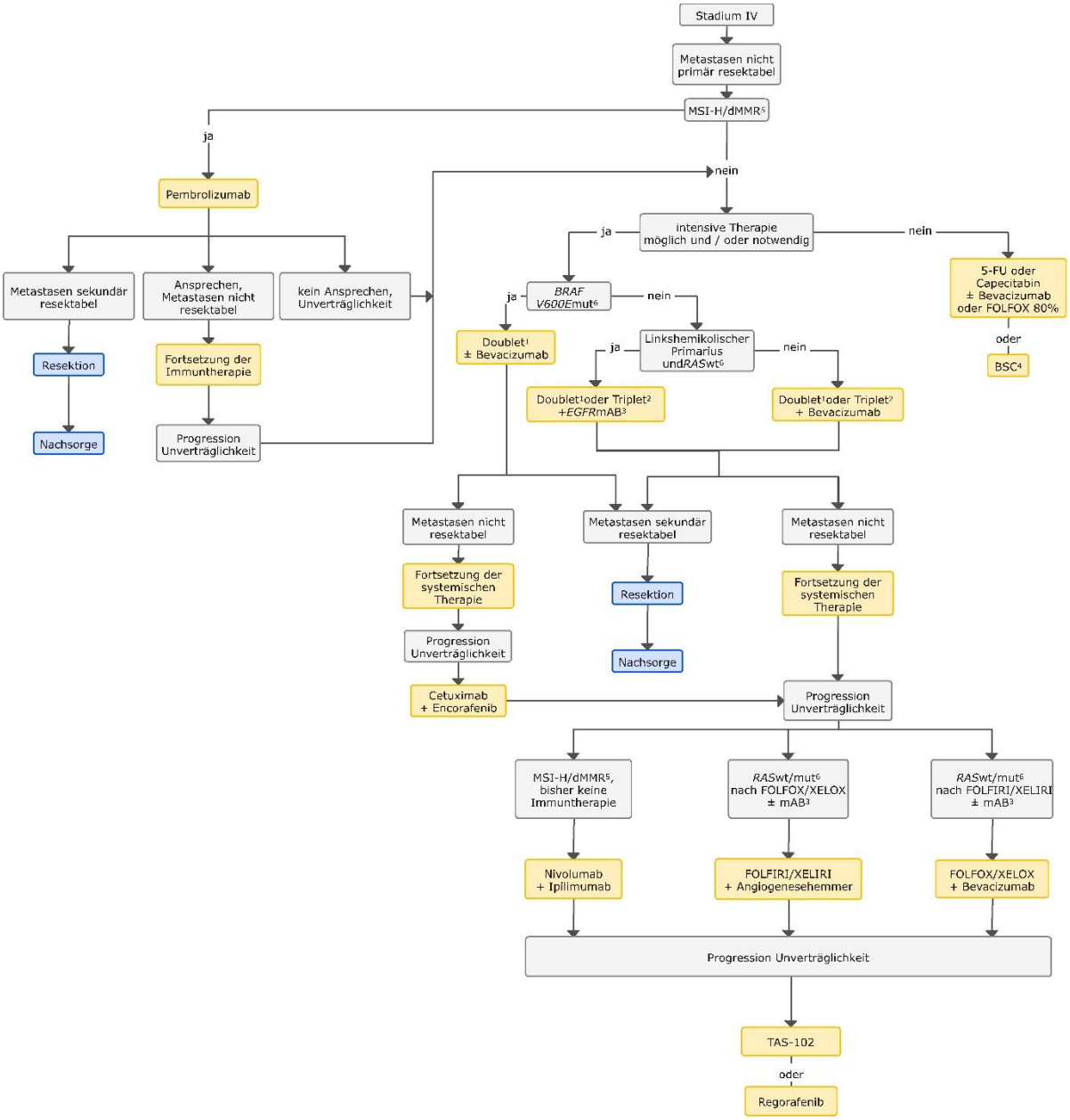
Stand des Wissens

Grundlage dieser Gutachterlichen Expertise sind die aktuellen Leitlinien zum kolorektalen Karzinom [1, 2].

Für Patientinnen und Patienten (Pat.), in deren Tumorgewebe eine Mikrosatelliteninstabilität vorliegt, wurde in der KEYNOTE-177 Studie Pembrolizumab mit verschiedenen „Standard of care“ Regimen verglichen [3]. Hierbei zeigte sich eine klinisch bedeutsame und signifikante Verlängerung des PFS (Hazard ratio 0.6 (0.45 – 0.80)) bei deutlich reduzierter Toxizität (22% statt 6% Grad 3-4 Nebenwirkungen). Die Gesamtüberlebenszeit wurde ebenfalls verlängert. Zum Zeitpunkt der finalen Analyse war der Median der Gesamtüberlebenszeit in Pembrolizumab-Arm nicht erreicht, im Kontrollarm lag er bei 38,7 Monaten (HR 0,74; p=0,036). Der in der Studienplanung präspezifizierte Wert von 0,025 wurde nicht erreicht. Bei dieser Auswertung muss die hohe Rate von „cross-over“ innerhalb und außerhalb der Studie berücksichtigt werden.

Der aktuelle Algorithmus ist in Abbildung 1 dargestellt [2].

Abbildung 1: Therapiestruktur im Stadium IV bei primär nicht resektablen Metastasen [2]



Legende:

[1] Doublet – Kombination von Fluoropyrimidin plus entweder Oxaliplatin oder Irinotecan;
[2] Triplet – Kombination von Fluoropyrimidin plus Oxaliplatin und Irinotecan;
[3] mAB – monoklonarer Antikörper,
[4] BSC – Best Supportive Care
[5] MSI-H/dMMR – microsatellite instability-high/deficient DNA mismatch repair;
[6] mut - mutiert; wt - Wildtyp (unmutiert)

Eine Alternative ist die Therapie mit Nivolumab/Ipilimumab. Nivolumab ist zugelassen in Kombination mit Ipilimumab zur Behandlung des metastasierten Kolorektalkarzinoms mit dMMR/MSI-H bei Pat. nach vorheriger Fluoropyrimidin-basierter Kombinationschemotherapie. Nivolumab + Ipilimumab führte zu einer Remissionsrate von 65% sowie nach 52 Monaten zu einer Rate der progressionsfreien Überlebenszeit von etwa 50% und der Gesamtüberlebensrate von etwa 70%. Diese Ergebnisse liegen weit oberhalb der erwarteten Überlebensraten in diesem Kollektiv [4]. Aufgrund seiner hohen Wirksamkeit wird Nivolumab + Ipilimumab wird bei Pat. mit Rezidiv nach adjuvanter Fluoropyrimidin-basierter Kombinationschemotherapie eingesetzt.

Das Therapieziel von Pat. im Stadium IV galt früher ausschließlich als palliativ. In den letzten 20 Jahren ist deutlich geworden, dass bei bis zu 25 % der Pat. mit synchron hepatisch metastasiertem, kolorektalem Karzinom ein kurativ Potential besteht [5, 6]. Ein kurativ Potential besteht auch bei Pat. mit hepatischem Rezidiv oder isolierter pulmonaler Metastasierung.

Das ist auch bei Pat. mit Nachweis einer Mikrosatelliteninstabilität zu berücksichtigen. Deshalb wird bei Erreichen einer sekundären Resektabilität eine Metastasenresektion empfohlen.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?
(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)

Bei Kontraindikationen gegen Immuncheckpoint-Inhibitoren oder bei Auftreten intolerabler Nebenwirkungen ist der Wechsel auf ein Zytostatika-basiertes Regime indiziert.

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