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-083 Fruquintinib

Stand: Juni 2024

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Fruquintinib [zur Behandlung des metastasierten Kolonkarzinoms] **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 „Zugelassene Arzneimittel im Anwendungsgebiet“ Arzneimittel zur Erstlinienbehandlung des metastasierten Kolonkarzinoms wurden entsprechend des geplanten Anwendungsgebiets nicht berücksichtigt.
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	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: - Trifluridin/Tipiracil (Kombination mit Bevacizumab): Beschluss vom 15. Februar 2024 - Pembrolizumab: Beschluss vom 19. Januar 2023 - Nivolumab: Beschluss vom 20. Januar 2022 - Encorafenib: Beschluss vom 17. Dezember 2020 - Trifluridin/Tipiracil (Monotherapie): Beschluss vom 1. Oktober 2020 - Ramucirumab: Beschluss vom 1. September 2016 - Regorafenib: Beschluss vom 17. März 2016 - Aflibercept: Beschluss vom 15. August 2013
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:	
Fruquintinib L01EK04 Fruzaqla	Anwendungsgebiet laut Zulassung: Fruzaqla als Monotherapie wird angewendet zur Behandlung von erwachsenen Patienten mit metastasierendem kolorektalem Karzinom (mCRC), die bereits früher mitverfügbaren Standardtherapien, einschließlich Fluoropyrimidin-, Oxaliplatin- und Irinotecan-basierten Chemotherapien, Anti-VEGF-Arzneimitteln und Anti-EGFR-Arzneimitteln, behandelt wurden und bei denen die Erkrankung nach der Behandlung mit Trifluridin/Tipiracil oder Regorafenib fortgeschritten ist, oder die diese Behandlung nicht vertragen.
Zytostatika	
5-Fluorouracil L01BC02 generisch	Fortgeschrittenes und/oder metastasiertes kolorektales Karzinom
Calciumfolinat V03AF03 generisch	Calciumfolinat ist indiziert: • in Kombination mit 5-Fluorouracil in der zytotoxischen Therapie ○ bei fortgeschrittenem oder metastasiertem kolorektalem Karzinom
Capecitabin L01BC06 generisch	Xeloda wird angewendet: • zur Behandlung des metastasierten Kolorektalkarzinoms
Irinotecan L01CE02 generisch	Irinomedac ist angezeigt zur Behandlung von Patienten mit fortgeschrittenem kolorektalen Karzinom: • als Monotherapie bei Patienten, die auf eine Vorbehandlung mit einem etablierten 5-Fluorouracil-haltigen Regime nicht angesprochen haben. In Kombination mit Cetuximab ist Irinomedac zur Behandlung von Patienten mit EGFR (epidermal growth factor receptor)-exprimierendem metastasierendem kolorektalem Karzinom mit KRAS-Wildtyp ohne vorherige Behandlung oder nach Versagen einer Irinomedac enthaltenden zytotoxische Therapie angezeigt.
Mitomycin	Mitomycin wird in der palliativen Tumortherapie eingesetzt.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
L01DC03 generisch	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 generisch	Oxaliplatin wird in Kombination mit 5-Fluorouracil (5-FU) und Folinsäure (FA) angewendet: • zur Behandlung des metastasierenden kolorektalen Karzinoms
Tegafur/ Gimeracil/ Oteracil L01BC53 Teysuno	Teysuno ist bei Erwachsenen indiziert: • als Monotherapie oder in Kombination mit Oxaliplatin oder Irinotecan, mit oder ohne Bevacizumab, für die Behandlung von Patienten mit metastasiertem kolorektalem Karzinom, bei denen die Behandlung mit einem anderen Fluoropyrimidin nicht fortgesetzt werden kann, weil sich in einem adjuvanten oder metastasierten Setting ein Hand-Fuß-Syndrom oder eine kardio-vaskuläre Toxizität entwickelt hat.
Trifluridin/ Tipiracil L01BC59 Lonsurf	<u>Kolorektales Karzinom</u> Lonsurf wird angewendet in Kombination mit Bevacizumab zur Behandlung von erwachsenen Patienten mit metastasiertem kolorektalem Karzinom (KRK), die zuvor bereits zwei Krebstherapien erhalten haben. Diese Therapien beinhalten Fluoropyrimidin-, Oxaliplatin- und Irinotecan-basierte Chemotherapien, Anti-VEGF- und/oder Anti-EGFR-Substanzen. Lonsurf wird angewendet als Monotherapie zur Behandlung von erwachsenen Patienten mit metastasiertem kolorektalem Karzinom (KRK), die bereits mit verfügbaren Therapien behandelt wurden oder die für diese nicht geeignet sind. Diese Therapien beinhalten Fluoropyrimidin-, Oxaliplatin- und Irinotecan-basierte Chemotherapien, Anti-VEGF- und Anti-EGFR-Substanzen.
Antikörper	
Bevacizumab L01FG01 Avastin	Bevacizumab wird in Kombination mit einer Chemotherapie auf Fluoropyrimidin-Basis zur Behandlung von erwachsenen Patienten mit metastasiertem Kolon- oder Rektumkarzinom angewendet.
Cetuximab L01FE01 Erbitux	Erbitux ist indiziert zur Behandlung des metastasierenden, EGFR (epidermalen Wachstumsfaktor-Rezeptor) exprimierenden Kolorektalkarzinoms mit Ras-Wildtyp • in Kombination mit einer Irinotecan-basierten Chemotherapie,

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	• […] • als Monotherapie bei Patienten, bei denen die Therapie mit Oxaliplatin und Irinotecan versagt hat und die Irinotecan nicht vertragen.
Ipilimumab L01FX04 Yervoy	Kolorektalkarzinom (colorectal cancer, CRC) mit Mismatch-Reparatur-Defizienz (Mismatch repair deficient, dMMR) oder hoher Mikrosatelliteninstabilität (microsatellite instability high, MSI-H) YERVOY ist in Kombination mit Nivolumab zur Behandlung des metastasierten Kolorektalkarzinoms mit Mismatch-Reparatur-Defizienz oder hoher Mikrosatelliteninstabilität bei Erwachsenen nach vorheriger fluoropyrimidinbasierter Kombinationschemotherapie indiziert
Nivolumab L01FF01 Opdivo	Kolorektalkarzinom (colorectal cancer, CRC) mit Mismatch-Reparatur-Defizienz (Mismatch repair deficient, dMMR) oder hoher Mikrosatelliteninstabilität (microsatellite instability high, MSI-H) Opdivo ist in Kombination mit Ipilimumab zur Behandlung des metastasierten Kolorektalkarzinoms mit Mismatch-Reparatur-Defizienz oder hoher Mikrosatelliteninstabilität bei Erwachsenen nach vorheriger fluoropyrimidinbasierter Kombinationschemotherapie indiziert
Panitumumab L01FE02 Vectibix	Vectibix ist indiziert zur Behandlung von erwachsenen Patienten mit metastasiertem kolorektalem Karzinom (mCRC, metastatic colorectal cancer) mit RAS-Wildtyp • […] • in der Zweitlinientherapie in Kombination mit FOLFIRI bei Patienten, die in der Erstlinientherapie eine Fluoropyrimidin-haltige Chemotherapie erhalten haben (ausgenommen Irinotecan). • als Monotherapie nach Versagen von Fluoropyrimidin-, Oxaliplatin- und Irinotecan-haltigen Chemotherapieregimen.
Pembrolizumab L01FF02 Keytruda	Tumoren mit hochfrequenter Mikrosatelliten-Instabilität (MSI-H) oder mit einer Mismatch-Reparatur-Defizienz (dMMR) Kolorektalkarzinom (colorectal cancer, CRC) Keytruda ist als Monotherapie des Kolorektalkarzinoms mit MSI-H oder mit einer dMMR wie folgt bei Erwachsenen angezeigt: • zur Behandlung des nicht resezierbaren oder metastasierenden Kolorektalkarzinoms nach vorheriger Fluoropyrimidin-basierter Kombinationstherapie.
Ramucirumab L01FG02 Cyramza	Cyramza ist in Kombination mit FOLFIRI (Irinotecan, Folinsäure und 5-Fluorouracil) indiziert zur Behandlung von erwachsenen Patienten mit einem metastasierten Kolorektalkarzinom (mKRK) mit Tumorprogress während oder nach vorausgegangener Therapie mit Bevacizumab, Oxaliplatin und einem Fluoropyrimidin.
Proteinkinase-Inhibitoren	
Encorafenib	Encorafenib ist angezeigt:

II. Zugelassene Arzneimittel im Anwendungsgebiet	
L01EC03 Braftovi	• in Kombination mit Cetuximab zur Behandlung von erwachsenen Patienten mit metastasiertem Kolorektalkarzinom (CRC) mit einer BRAF-V600E-Mutation, die eine systemische Vortherapie erhalten haben.
Fruquintinib L01EK04 Fruzaqla	Fruzaqla als Monotherapie wird angewendet zur Behandlung von erwachsenen Patienten mit metastasierendem kolorektalem Karzinom (mCRC), die bereits früher mitverfügbaren Standardtherapien, einschließlich Fluoropyrimidin-, Oxaliplatin- und Irinotecan-basierten Chemotherapien, Anti-VEGF-Arzneimitteln und Anti-EGFR-Arzneimitteln, behandelt wurden und bei denen die Erkrankung nach der Behandlung mit Trifluridin/Tipiracil oder Regorafenib fortgeschritten ist, oder die diese Behandlung nicht vertragen.
Regorafenib L01EX05 Stivarga[1]	Stivarga ist angezeigt als Monotherapie zur Behandlung von erwachsenen Patienten mit: • metastasiertem Kolorektalkarzinom (KRK), die zuvor mit verfügbaren Therapien behandelt wurden oder die für diese nicht geeignet sind. Diese Therapien umfassen Fluoropyrimidin-basierte Chemotherapie, eine Anti-VEGF-Therapie und eine Anti-EGFR-Therapie.
Weitere Antineoplastische Wirkstoffe	
Aflibercept L01XX44 Zaltrap	Zaltrap in Kombination mit einer Chemotherapie, bestehend aus Irinotecan/5-Fluorouracil/Folinsäure (FOLFIRI), wird angewendet bei Erwachsenen mit metastasiertem kolorektalem Karzinom (MCRC), das unter oder nach einem Oxaliplatin-haltigen Regime fortgeschritten ist.

Quellen: AMIce-Datenbank, Fachinformationen

[1] Derzeit nicht in Deutschland in Verkehr.

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2023-B-083 Fruquintinib

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	9. Mai 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
CIMP	CPG-island methylation phenotype
CR	Complete response
CT	Chemotherapy
DNA/DNS	Desoxyribonukleinsäure
DPD	Dihydropyrimidin-Dehydrogenase
DPYD	Dihydropyrimidin-Dehydrogenase Genotypisierung
ECOG	Eastern Cooperative Oncology Group
EGFR(i)	Epidermal growth factor receptor (inhibitor)
FACT-C	Functional Assessment of Cancer Therapy – Colorectal Cancer
FISH	Fluoreszenz-in-situ-Hybridisierung
FOLFIRI	Folinsäure + 5-Fluorouracil + Irinotecan
FOLFIRINOX	Folinsäure + 5-Fluorouracil + Irinotecan + Oxaliplatin
FOLFOX	Folinsäure + 5-Fluourouracil + Oxaliplatin
FOLFOXIRI	Folinsäure + 5-Fluourouracil + Oxaliplatin + Irinotecan
FP	Fluorpyrimidine/s
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
HIA	Hepatic intra-arterial chemotherapy
HIPEC	Hyperthermic intraperitoneal chemotherapy
HNPCC	Hereditäres Kolorektales Karzinom ohne Polyposis
HR	Hazard Ratio
HRAS	Harvey rat sarcoma viral oncogene homolog
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
LV	Lederfolin
MAb	Monoclonal Kolorektalkarzinom
mCRC	metastasierendes Kolorektalkarzinom
MDT	Multidisciplinary team
MEK	MP-Kinase MEK1 und MEK2 Inhibitor
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
MT	Mutant
NICE	National Institute for Health and Care Excellence
NRAS	Neuroblastoma RAS viral oncogene homolog
OR	Odds Ratio
ORR	Overall response rate
OS	Overall survival
PD	Programmed death
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
TKI	Tyrosine kinase inhibitor
TRIP	Turn Research into Practice Database
UGT1A1	UDP-Glucuronosyltransferase 1 Polypeptid A1
VEGF	Vascular endothelial growth factor
VEGFi	Vascular endothelial growth factor inhibitor
WHO	World Health Organization
WT	wild-type

1 Indikation

Behandlung von erwachsenen Patienten mit metastasiertem kolorektalem Karzinom, die bereits mit verfügbaren Therapien behandelt wurden oder die für diese nicht geeignet sind, einschließlich Fluoropyrimidin-, Oxaliplatin- und Irinotecan-basierter Chemotherapie, Anti-VEGF-Therapie, Anti-EGFR-Therapie (bei Patienten mit RAS-Wildtyp), sowie Trifluridin/Tipiracil (TAS-102) oder Regorafenib.

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 2599 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 drei 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

Chen D et al., 2018 [2].

Efficacy and safety of TAS-102 in refractory metastatic colorectal cancer: a meta-analysis

Fragestellung

This meta-analysis is designed to assess the efficacy and safety of TAS-102 in patients with mCRC.

Methodik

Population:

- Patients with refractory mCRC

Intervention:

- TAS-102 (Trifluridine/tipiracil)

Komparator:

- Standard Chemotherapy

Endpunkte:

- OS, PFS

Recherche/Suchzeitraum:

- Until 2018

Qualitätsbewertung der Studien:

- Cochrane Collaboration’s tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 3

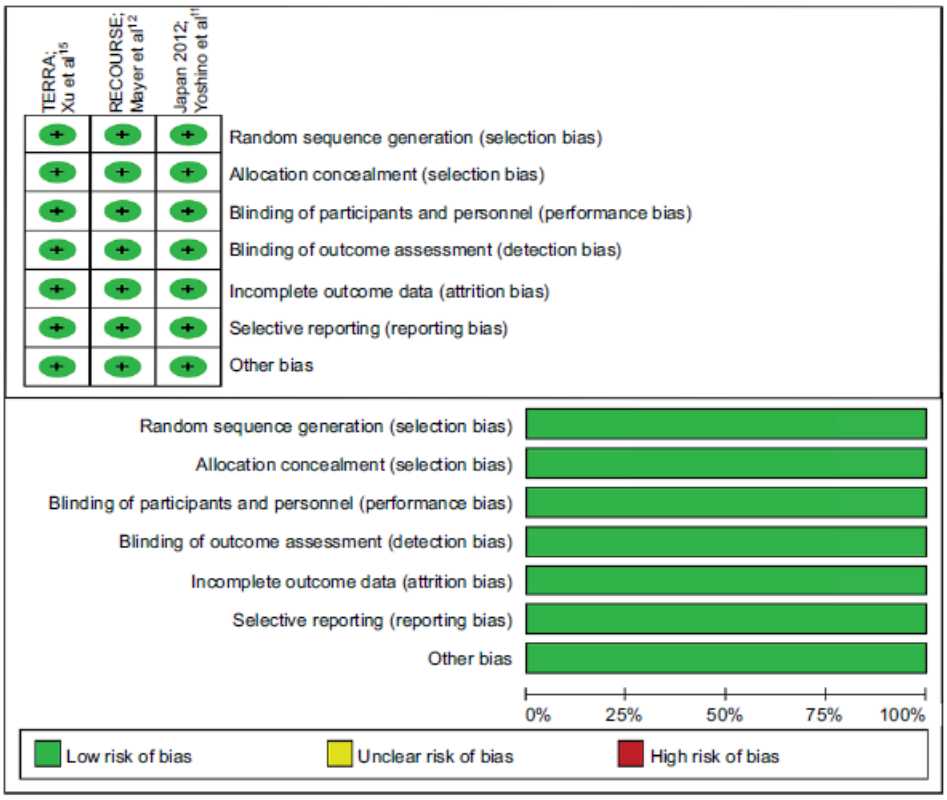
Charakteristika der Population:

Table 1 Characteristics of three RCTs

Trials	Arms	Study phase	Primary end point	Patients enrolled	ECOG PS	Sample size	Average age (years)	Histology	KRAS mutational status		Time since diagnosis of first metastasis (months)	
									Wild type	Mutant	<18	≥18
Japan 2012; Yoshino et al[11]	TAS-102	II	OS	Refractory or intolerant to standard chemotherapies[a]	0–2	112	63	Adenocarcinoma	54	45	NR	NR
	Placebo					57	62		24	26	NR	NR
RECOURSE; Mayer et al[12]	TAS-102	III	OS	Refractory or intolerant to standard chemotherapies[a]	0–1	534	63	Adenocarcinoma	262	272	111	423
	Placebo					266	63		131	135	55	211
TERRA; Xu et al[13]	TAS-102	III	OS	Refractory or intolerant to standard chemotherapies[a]	0–1	271	58	Adenocarcinoma	172	99	134	137
	Placebo					135	56		85	50	52	83

Notes: [a]Patients have received chemotherapy with each of the following agents: fluoropyrimidine, oxaliplatin and irinotecan. The blue shading highlights that the primary endpoint is critical to assessing the accuracy of RCTs results, and that the meta-analysis also considers the consistency of the primary endpoint for pooled outcomes.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; NR, not reported OS, overall survival; RCT, randomized controlled trial.

Qualität der Studien:



Studienergebnisse:

- OS
  - OS was the primary end point of three trials, and the pooled HR showed that TAS-102 decreased the risk of death by 30% compared with placebo (HR 0.70, 95% CI 0.62–0.79, I2=24%; Figure 3). The subgroup analyses were performed. Remarkably, TAS-102 had statistically significant OS benefits in patients with both KRAS mutation (HR 0.76, 95% CI 0.63–0.92, I2=44%) and wild-type KRAS (HR 0.66, 95% CI 0.55–0.79, I2=2%; Figure 4). TAS-102 prolonged OS in patients whether with one or two metastatic sites (HR 0.75, 95% CI 0.62–0.90, I2=20%) or more than three metastatic sites (HR 0.67, 95% CI 0.55–0.83, I2=0%). Interestingly, patients with >18 months since diagnosis of the first metastasis had OS improvement (HR 0.65, 95% CI 0.55–0.77, I2=0%), but the benefit was not observed in patients with <18 months since diagnosis of the first metastasis (HR 0.85, 95% CI 0.66–1.11, I2=0%).

- Progression-free survival (PFS)
  - PFS was significantly improved in patients who were treated with TAS-102 (HR 0.46, 95% CI 0.40–0.52, I_2=0%; Figure 5). No more relevant data were recorded about PFS
  - in the subgroup patients, so we could not perform deeper subgroup analysis.

Anmerkung/Fazit der Autoren

TAS-102 plays a significant role in improving OS and PFS with a favorable safety profile in mCRC patients who are refractory or intolerant to standard treatment including fluorouracil, irinotecan, oxaliplatin, anti-VEGF and anti-EGFR. According to subgroup analysis results, these effects are not related to KRAS gene status and the number of metastatic sites. However, patients who have been >18 months since the diagnosis of first metastases seem to have survival benefits, which requires further researches to explore. In a word, TAS- 102 is a viable option in salvage therapy.

Kommentare zum Review

- Limitation: Nur drei eingeschlossene Studien

3.3 Leitlinien

Morris, V. K. et al., 2022 [3].

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

Clinical Question 4

For patients with previously treated BRAF V600E–mutant mCRC, does treatment with encorafenib plus cetuximab result in better outcomes compared with chemotherapy plus targeted therapy?

Recommendation 4.1. Encorafenib plus cetuximab should be offered to patients with previously treated BRAF V600E–mutant mCRC that has progressed after at least one previous line of therapy (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

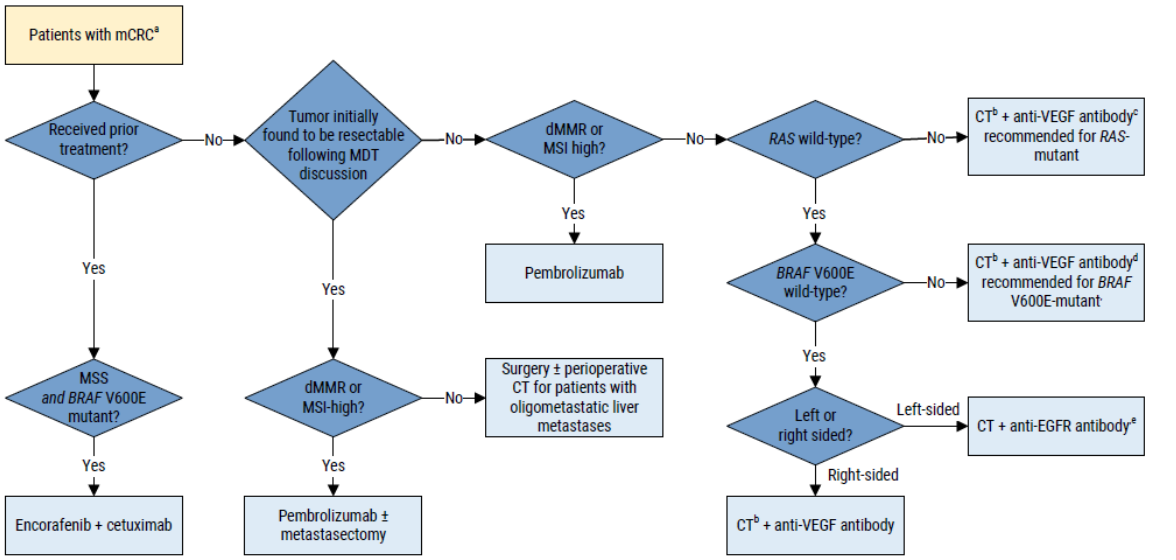
Literature review.

Approximately 8% of patients with mCRC have BRAF V600E mutations, and these patients have poorer prognoses compared with patients with wild-type disease.55 The BEACON phase III RCT with 441 patients met the inclusion criteria for treatment options for patients with previously treated BRAF V600E mCRC.56 In the encorafenib plus cetuximab group, 95% received prior oxaliplatin, and within the control group (cetuximab plus irinotecan-based chemotherapy), 91% received prior oxaliplatin.57 Nine percent and five percent within the encorafenib plus cetuximab group and the chemotherapy group were MSI-H, respectively. OS (HR, 0.61; 95% CI, 0.48 to 0.77), PFS (HR, 0.44; 95% CI, 0.35 to 0.55), and ORR (RR, 13.18; 95% CI, 4.64 to 37.42) were significantly improved in the encorafenib plus cetuximab group, compared with cetuximab plus chemotherapy. There were significantly fewer grade 3 or greater adverse events in the encorafenib plus cetuximab group, compared with the control group (Data Supplement).

Clinical interpretation.

On the basis of positive results from the BEACON trial, the Expert Panel agrees that the combination of BRAF inhibitor encorafenib plus anti-EGFR monoclonal antibodies cetuximab or panitumumab are recommended for patients with BRAF V600E–mutant mCRC previously treated with chemotherapy.

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.

55. Van Cutsem E, Huijberts S, Grothey A, et al: Binimetinib, encorafenib, and cetuximab triplet therapy for patients with BRAF V600E-mutant metastatic colorectal
cancer: Safety lead-in results from the phase III BEACON colorectal cancer study. J Clin Oncol 37:1460-1469, 2019
56. Kopetz S, Grothey A, Yaeger R, et al: Encorafenib, binimetinib, and cetuximab in BRAF V600E-mutated colorectal cancer. N Engl J Med 381:1632-1643, 2019
57. Scott Kopetz DA, Grothey A, Van Cutsem E, et al: Overall survival (OS) with encorafenib (enco) 1 cetuximab (cetux) in BEACON CRC: Effect of prior therapy for

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

Grundlage der Leitlinie

- 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.

Recherche/Suchzeitraum:

- PubMed and MEDLINE from 1990 forward

LoE/GoR

Levels of Evidence

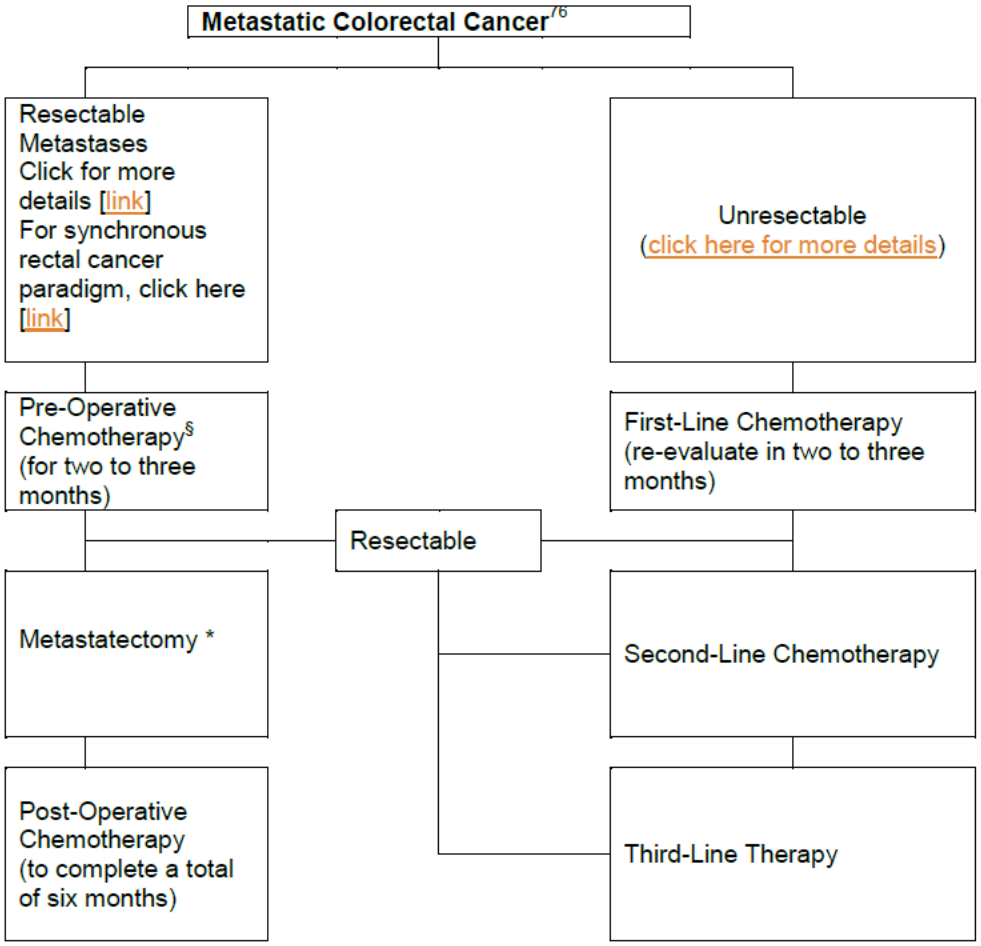
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) 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

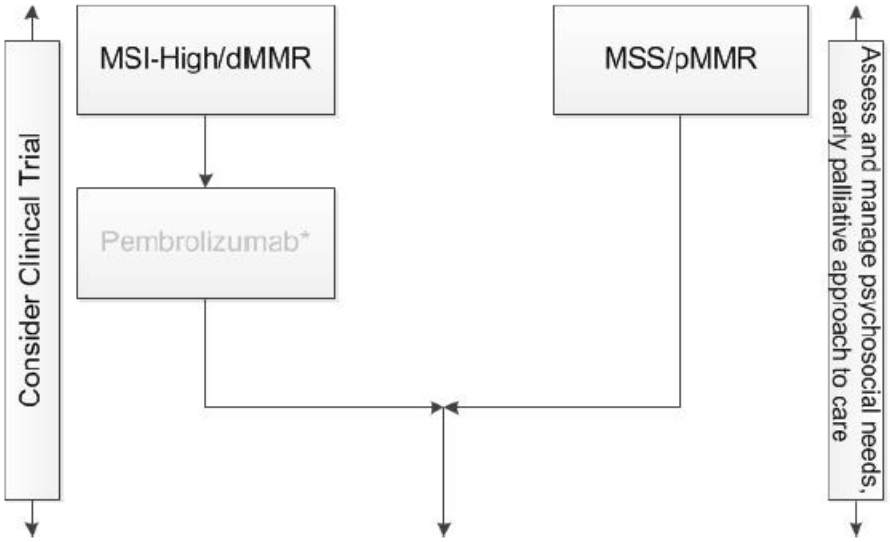
A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, 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/m^2 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/m^2 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/m^2 IV 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).</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/m^2</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. For patients who are not upfront resectable the addition of biological agents is controversial. The general approach for consideration of a biologic agent for non-liver limited mCRC should be used. Kras wild type, left sided primary, consider panitumumab85; Kras mutant, consider bevacizumab.86 For patients who have resection of liver metastases with no residual disease, give subsequent consideration to "adjuvant" chemotherapy to complete a total course of therapy equivalent to six months
- 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

Referenzen aus Leitlinien

1. Kanas GP, Taylor A, Primrose JN, Langeberg WJ, Kelsh MA, Mowat FS, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. Clin Epidemiol 2012;4:283-301.
6. Berber E, Pelley R, Siperstein AE. Predictors of survival after radiofrequency thermal ablation of colorectal cancer metastases to the liver: a prospective study. J Clin Oncol 2005 Mar 1;23(7):1358-1364.
12. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004 Jan 15;22(2):229-237.
13. Cassidy J, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol 2008 Apr 20;26(12):2006-2012.
14. Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2004 Jan 1;22(1):23-30.
15. Cremolini C, Loupakis F, Antoniotti C, Lupi C, Sensi E, Lonardi S, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. Lancet Oncol 2015 Oct;16(13):1306-1315.

16. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004 Jun 3;350(23):2335-2342.
17. Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 2007 Apr 20;25(12):1539-1544.
18. Saltz LB, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008 Apr 20;26(12):2013-2019.
19. Ranpura V, Hapani S, Chuang J, Wu S. Risk of cardiac ischemia and arterial thromboembolic events with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis of randomized controlled trials. Acta Oncol 2010 Apr;49(3):287-297.
20. Allegra CJ, Yothers G, O'Connell MJ, Sharif S, Colangelo LH, Lopa SH, et al. Initial safety report of NSABP C-08: A randomized phase III study of modified FOLFOX6 with or without bevacizumab for the adjuvant treatment of patients with stage II or III colon cancer. J Clin Oncol 2009 Jul 10;27(20):3385-3390.
21. Bose D, Meric-Bernstam F, Hofstetter W, Reardon DA, Flaherty KT, Ellis LM. Vascular endothelial growth factor targeted therapy in the perioperative setting: implications for patient care. Lancet Oncol 2010 Apr;11(4):373-382.
22. Zhu X, Wu S, Dahut WL, Parikh CR. Risks of proteinuria and hypertension with bevacizumab, an antibody against vascular endothelial growth factor: systematic review and meta-analysis. Am J Kidney Dis 2007 Feb;49(2):186-193.
23. Nalluri SR, Chu D, Keresztes R, Zhu X, Wu S. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. JAMA 2008 Nov 19;300(19):2277-2285.
24. Okines A, Puerto OD, Cunningham D, Chau I, Van Cutsem E, Saltz L, et al. Surgery with curative-intent in patients treated with first-line chemotherapy plus bevacizumab for metastatic colorectal cancer First BEAT and the randomised phase-III NO16966 trial. Br J Cancer 2009 Oct 6;101(7):1033-1038.
25. Hapani S, Chu D, Wu S. Risk of gastrointestinal perforation in patients with cancer treated with bevacizumab: a meta-analysis. Lancet Oncol 2009 Jun;10(6):559-568.
26. Hurwitz HI, Saltz LB, Van Cutsem E, Cassidy J, Wiedemann J, Sirzen F, et al. Venous thromboembolic events with chemotherapy plus bevacizumab: a pooled analysis of patients in randomized phase II and III studies. J Clin Oncol 2011 May 1;29(13):1757-1764.
27. Van Cutsem E, Kohne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009 Apr 2;360(14):1408-1417.
28. Douillard JY, Oliner KS, Siena S, Tabernero J, Burkes R, Barugel M, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med 2013 Sep 12;369(11):1023-1034.
29. Peeters M, Price TJ, Cervantes A, Sobrero AF, Ducreux M, Hotko Y, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol 2010 Nov 1;28(31):4706-4713.
30. Saltz L, Badarinath S, Dakhil S, Bienvenu B, Harker WG, Birchfield G, et al. Phase III trial of cetuximab, bevacizumab, and 5-fluorouracil/leucovorin vs. FOLFOX-bevacizumab in colorectal cancer. Clin Colorectal Cancer 2012 Jun;11(2):101-111.
31. Tol J, Koopman M, Cats A, Rodenburg CJ, Creemers GJ, Schrama JG, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med 2009 Feb 5;360(6):563-572.
32. Jonker DJ, O'Callaghan CJ, Karapetis CS, Zalcberg JR, Tu D, Au HJ, et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med 2007 Nov 15;357(20):2040-2048.
33. Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 2008 Oct 23;359(17):1757-1765.
34. Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 2007 May 1;25(13):1658-1664.
35. Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008 Apr 1;26(10):1626-1634.
36. Loupakis F, Cremolini C, Salvatore L, Masi G, Sensi E, Schirripa M, et al. FOLFOXIRI plus bevacizumab as first-line treatment in BRAF mutant metastatic colorectal cancer. Eur J Cancer 2014 Jan;50(1):57-63.
37. Kopetz S, Grothey A, Yaeger R, Van Cutsem E, Desai J, Yoshino T, et al. Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer. N Engl J Med 2019 Oct 24;381(17):1632-1643.

38. Corcoran RB, Andre T, Atreya CE, Schellens JHM, Yoshino T, Bendell JC, et al. Combined BRAF, EGFR, and MEK Inhibition in Patients with BRAF(V600E)-Mutant Colorectal Cancer. Cancer Discov 2018 Apr;8(4):428-443.
39. Vauthey JN, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol 2006 May 1;24(13):2065-2072.

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

Referenzen

1. **Alberta Health Services (AHS).** Metastatic colorectal cancer [online]. 02.2021. Edmonton (CAN): AHS; 2021. [Zugriff: 28.11.2022]. (Clinical practice guideline GI-003, Version 12). URL: https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-gi003-colorectal-metastatic.pdf.
2. **Chen D, Wu YS, Lin H, Wang Y, Li L, Zhang T.** Efficacy and safety of TAS-102 in refractory metastatic colorectal cancer: a meta-analysis. Cancer Manag Res 2018;10:2915-2924.
3. **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.

[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[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

Gemeinsamer Bundesausschuss

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

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO