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: 2026-B-127-z Encorafenib

Stand: Juli 2026

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Encorafenib+Cetuximab **[Erstlinienbehandlung des metastasierten Kolorektalkarzinoms, BRAF-V600E Mutation]** **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 • Nivolumab: Beschluss vom 18. Dezember 2025
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:	
Encorafenib L01EC03 Braftovi	<u>Anwendungsgebiet:</u> Encorafenib in Kombination mit Cetuximab und FOLFOX ist angezeigt für die Erstlinienbehandlung von erwachsenen Patienten mit metastasiertem kolorektalem Karzinom mit einer BRAF V600E-Mutation.
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 5-Fluorouracil, Folinsäure und Bevacizumab indiziert zur Erstlinientherapie bei Patienten mit metastasierendem Kolon- oder Rektumkarzinom.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	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.
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 kardiovaskuläre Toxizität entwickelt hat.
Antikörper	
Bevacizumab S01LA08 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 Irinotecan-basierten Chemotherapie, - als Erstlinienbehandlung in Kombination mit FOLFOX [...]
Nivolumab L01FF01	Opdivo ist in Kombination mit Ipilimumab zur Behandlung des Kolorektalkarzinoms mit Mismatch-Reparatur-Defizienz oder hoher Mikrosatelliteninstabilität bei Erwachsenen in den folgenden Fällen indiziert:

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Opdivo	- Erstlinientherapie des nicht resezierbaren oder metastasierten Kolorektalkarzinoms
Panitumumab L01FE02 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.
Pembrolizumab L01FF02 Keytruda	Kolorektalkarzinom (colorectal cancer, CRC) 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

Vorgang: 2026-B-127z (Beratung nach § 35a SGB V) Encorafenib+Cetuximab

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	6. Juli 2026

Inhaltsverzeichnis

Abkürzungsverzeichnis

5-FU	5-Fluorouracil
AE	Adverse Event/s
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BEV	Bevacizumab
CAPOX/XELOX	Capecitabine + Oxaliplatin
CT	Chemotherapy
DCR	Disease Control Rate
dMMR	Defiziente Mismatch-Reparatur
ECOG	Eastern Cooperative Oncology Group
ECRI	Emergency Care Research Institute
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
FU	Fluorouracil
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HR	Hazard Ratio
HRQoL	Health-related Quality of Life
IFL	Irinotecan + Folinsäure + 5-Fluorouracil
IHC	Immunhistochemische Untersuchung
KI	Konfidenzintervall
KRAS	Kirsten rat sarcoma viral oncogene homolog
LoE	Level of Evidence
mCRC	metastasierendes Kolorektalkarzinom
MDT	Multidisciplinary team
MERGE	Method for Evaluating Reserch and Guideline Evidence
MMR	Mismatch-repair Gen
MoAb	Monoclonal Antibodies
MSI-H	Hohe Mikrosatelliten-Instabilität
MSS	microsatellite stable

pMMR	proficient mismatch repair
RAS	rat sarcoma
WT	wild-type

1 Indikation

Erstlinienbehandlung bei Patientinnen und Patienten mit metastasiertem Kolorektalkarzinom mit BRAF-600E-Mutation.

Hinweis zur Synopse: „Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt“.

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.

Der Suchzeitraum der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 06.02.2026 abgeschlossen. Am 08.06.2026 erfolgte eine Überprüfung der iterativen Handsuche. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 2758 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. Dabei wurde für systematische Reviews, inkl. Meta-Analysen, ein Publikationszeitraum von 2 Jahren und für Leitlinien von 5 Jahren betrachtet. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Alle eingeschlossenen Referenzen wurden im Volltext beschafft. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen im Volltext 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 9 Referenzen eingeschlossen. Es erfolgt eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews im Anwendungsgebiet identifiziert.

3.2 Systematische Reviews

Alhamzani AI et al., 2025 [2].

Efficacy and Safety Comparison of S-1 and Capecitabine in Metastatic Colorectal Carcinoma: A Systematic Review and Meta-Analysis

Fragestellung

S-1 and capecitabine are both oral chemotherapy options often used to treat metastatic colorectal cancer (mCRC). Their effectiveness and side effects have generated clinical interest, particularly in deciding which one to use. This review aimed to directly compare the two regimens in terms of outcomes and tolerability.

Methodik

Population:

- patients histologically or cytologically diagnosed with metastatic colorectal carcinoma (mCRC, stage IV) as the population

Intervention/ Komparator:

- All studies compared S-1-based and capecitabine-based chemotherapy regimens, frequently in combination with oxaliplatin and/or bevacizumab.

Endpunkte:

- ORR, DCR, PFS, OS, and AEs.

Recherche/Suchzeitraum:

- We systematically searched PubMed, Web of Science, and Google Scholar from inception to August 1, 2024.

Qualitätsbewertung der Studien:

- RoB 2

Ergebnisse

Anzahl eingeschlossener Studien:

- Five studies 1,414 patients.

Charakteristika der Population/Studien:

The total number of patients across the included studies was 1,414 (sample size ranged from 86 to 487). The reported age range across the studies was 22 to 87 years, with an estimated mean age of 61.0±10.0 years. Across all studies, a total of 970 patients were reported with a sex breakdown: of these, 512 (52.7%) were male and 458 (47.3%) were female. All included studies reported baseline ECOG performance status, with four studies including patients with scores of 0-2, and one study limiting inclusion to patients with scores of 0 or 1.

Study (Author, Year)	Country	Name of Journal Published	Study Design	Sample Size	Age Range (Years)	Male (%)	ECOG Performance Status
Hong et al. (2012) [5]	South Korea	The Lancet Oncology	Randomized, non-inferiority phase III trial	340	N/A	109 (32.1%)	0-2
Kwakman et al. (2017) [6]	Netherlands	Annals of Oncology	Randomized phase III trial	161	66-79	56 (34.8%)	0-2
Kim et al. (2014) [10]	South Korea	Journal of Cancer	Randomized phase II study	86	29-83	28 (32.6%)	0-2
Kim et al. (2015) [11]	South Korea	BMC Cancer	Randomized, non-inferiority phase III trial	340	N/A	109 (32.1%)	0-2
Yamada et al. (2018) [12]	Japan	Annals of Oncology	Randomized, open-label, phase III trial	487	22-87	143 (59.1%)	0-2

Qualität der Studien:

- The overall RoB 2 assessment indicated that three of the five studies were labeled as 'low risk' of bias, while two studies raised 'some concerns'.

Studienergebnisse:

- Objective Response Rate (ORR)
  - A meta-analysis was conducted to compare ORR between patients treated with S-1 and those receiving capecitabine. Four studies were included, encompassing a total of 629 patients (S-1: n = 314; capecitabine: n = 315). The pooled RR for ORR was 1.14 (95% CI: 0.99-1.32; p = 0.07), favoring S-1, although the result did not reach statistical significance. The test for heterogeneity showed no significant heterogeneity across studies (I^2 = 0%, p = 0.80), indicating consistency among the included trials.
- Disease Control Rate (DCR)
  - DCR was reported in three studies and pooled using a random-effects model. The combined RR was 0.91 (95% CI: 0.46-1.83; p = 0.80), indicating no significant difference between the S-1 and capecitabine groups. Substantial heterogeneity was observed (I^2 = 66%), suggesting variability in study outcomes. Overall, the data do not support a clear superiority of either regimen in terms of DCR.
- Progression-Free Survival (PFS)
  - Median PFS was reported in all five studies. In the largest study, the three-week and four-week S1/irinotecan plus bevacizumab regimens achieved median PFS values of 13.2 months and 14.3 months, respectively, while the mFOLFOX6 and CapeOX arms showed 11.4 and 10.4 months, respectively [12]. Another trial reported a median PFS of 8.4 months in the S-1 group versus 8.2 months in the capecitabine group (HR 0.99, p = 0.93). In a third study, the SOX group had a longer median PFS than the CapeOX group in both the intention-to-treat (8.5 vs. 6.7 months) and per-protocol (8.5 vs. 6.6 months) populations [5]. A fourth study showed a median PFS of 7.1 months (SOX) vs. 6.3 months (CapeOX) (p = 0.10) [10]. The fifth study found a median PFS of 6.1 months (S-1) vs. 7.4 months (capecitabine) (p = 0.599) [11].
- Overall Survival (OS)
  - Median OS was reported in four of the five studies [5,6,10,11]. The highest median OS was observed in the S1/irinotecan plus bevacizumab group (34.9 months; 95% CI: 31.9-42.4), compared to 33.6 months (95% CI: 29.8-40.1) in the mFOLFOX6 or CapeOX group [12]. One study reported 12- and 18-month OS rates of 67% and 50% for

capecitabine, and 62% and 41% for S-1 (HR 1.23; p = 0.32) [6]. In a third study, median OS was 21.2 months for SOX and 20.5 months for CapeOX in the intention-to-treat population [5]. Another trial showed similar OS: 19.0 vs. 18.5 months (HR 0.86; p = 0.19) [10].

- Hematological Complications
  - Three studies reported hematologic AEs, including anemia, leukopenia, and thrombocytopenia. Metaanalysis showed no statistically significant difference in overall hematologic toxicities between the S-1 and capecitabine groups (RR: 1.00, 95% CI: 0.78-1.28; I^2 = 88%). Subgroup analysis revealed a non-significant trend toward higher anemia risk with S-1 (RR: 1.24, 95% CI: 0.97-1.59), while thrombocytopenia appeared less frequent in S-1 arms, but with substantial heterogeneity (I^2 = 95%) (Figure 5).

Anmerkung/Fazit der Autoren

This systematic review and meta-analysis found that S-1-based regimens are comparable in efficacy to capecitabine-based regimens for the treatment of mCRC. Additionally, S-1 was associated with a lower incidence of HFS. With additional research to support these findings, S-1 may serve as an effective alternative to capecitabine, particularly for patients who are unable to tolerate capecitabine or who are at higher risk for adverse events such as HFS.

Zhang QJ et al., 2025 [9].

The efficacy and safety of chemoimmunotherapy in patients with MSI-L/MSS/pMMR status metastatic colorectal cancer: a systematic review and meta-analysis of randomized controlled trials

Fragestellung

This study aimed to comprehensively evaluate the efficacy and safety of chemoimmunotherapy in metastatic CRC (mCRC) patients with MSI-L/ MSS/pMMR status.

Methodik

Population:

- patients with MSI-L/MSS/pMMR status metastatic colorectal cancer

Intervention:

- In the experimental arms, all studies combined an ICI with chemotherapy.

Komparator:

- In the control arms used standard chemotherapy.

Endpunkte:

- progression-free survival (PFS), overall survival (OS), adverse events (AE)

Recherche/Suchzeitraum:

- PubMed, EMBASE, ScienceDirect, and Cochrane Library databases to systematically filter published studies from December 2020 to April 2024 for present research.
- The search terms and keywords were “metastatic” OR “advanced” AND “colorectal neoplasm” OR “colorectal tumor” AND “immunotherapy” OR “immune checkpoint inhibitor” OR “nivolumab” OR “ipilimumab” OR “sintilimab” OR “durvalumab” OR “atezolizumab” OR “pembrolizumab” OR “avelumab” OR “camrelizumab” OR “tislelizumab” OR “tremelimumab” OR “toripalimab”. All entries that met these criteria were manually searched for.

Qualitätsbewertung der Studien:

- Ris of bias tool 2

Ergebnisse

Anzahl eingeschlossener Studien:

- Four studies encompassing 934 patients with mCRC.

Charakteristika der Population/Studien:

- A total of 934 patients were included in the four studies, with publication years ranging from 2022 to 2024. In these studies, the vast majority or all patients had MSI-L/MSS/pMMR status. The median follow-up was reported in three studies, ranging from 20.3 months to 45.2 months.

Qualität der Studien:

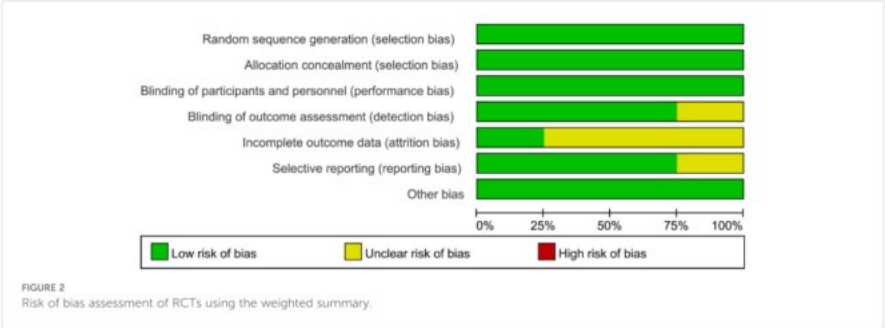


FIGURE 2
Risk of bias assessment of RCTs using the weighted summary.

Studienergebnisse:

- The comparison of PFS and OS with chemoimmunotherapy versus standard chemotherapy
  - In the pooled analysis of four studies, the use of ICIs was associated with a 18% reduction in the risk of progression or death compared with standard chemotherapy (HR: 0.82, 95% CI: 0.70– 0.97, P = 0.02) (Figure 4). The included studies exhibited a low degree of heterogeneity (I^2 = 0%, P = 0.65).
  - Data regarding OS were available from three studies. The use of ICIs was associated with a relatively lower risk of death than chemotherapy (HR: 0.85, 95% CI: 0.65–1.11) (Figure 5). The included studies had a low degree of heterogeneity (I^2 = 0%, P = 0.58).
- The comparison of adverse events with chemoimmunotherapy versus standard chemotherapy
  - In the pooled data of the three studies, all-grade adverse events in the ICIs groups (95.9%) were slightly higher than those in the standard chemotherapy groups (91.7%). The difference was of conspicuous significance (OR: 2.16, 95% CI: 1.18–3.96, P = 0.01). The result showed low heterogeneity (P=0.70, I2 = 0%) for all-grade adverse events
- Subgroup analyses based on sex (male vs. female) and ECOG status consistently demonstrated a significant benefit of chemoimmunotherapy in MSI-L/MSS/pMMR tumors.

Anmerkung/Fazit der Autoren

Existing evidence indicates a statistically significant and clinically meaningful benefit in PFS with chemoimmunotherapy, albeit with a slight increase in all-grade and high-grade toxicities compared to chemotherapy. Future research focusing on biomarkers and innovative treatments is essential for enhancing patient outcomes.

Yoshino T et al., 2024 [8].

A meta-analysis of efficacy and safety data from head-to-head first-line trials of epidermal growth factor receptor inhibitors versus bevacizumab in adult patients with RAS wild-type metastatic colorectal cancer by sidedness

Fragestellung

The primary objective of this systematic literature review and Meta-analysis was to assess the published literature reporting relative efficacy and safety of first-line EGFRIs (cetuximab or panitumumab) plus doublet chemotherapy versus bevacizumab plus doublet chemotherapy among patients with RAS WT left-sided mCRC. We also reviewed the relative efficacy and safety data of these first-line regimens by tumor sidedness (left-sided vs right-sided vs all-sided tumor) among patients with RAS WT mCRC.

Methodik

Population:

- adult (18 + years of age) RAS WT mCRC patients, with no geographic restrictions
- first-line

Intervention:

- cetuximab or panitumumab plus chemotherapy (FOLFOX or FOLFIRI)

Komparator:

- bevacizumab plus chemotherapy (FOLFOX or FOLFIRI)

Endpunkte:

- OS, PFS, ORR, overall or complete resection rate (RR), early tumor shrinkage (ETS), and/or safety (grade 3/4 adverse events [AEs] or deaths). ORR was defined as the percentage of patients whose disease decreases (partial response, at least 30% reduction in size), or disappears (complete response, disappearance of all clinical evidence of disease after treatment).

Recherche/Suchzeitraum:

- Eligible studies consisted of trials included in the Heinemann et al., 2016 meta-analysis [2], and additional phase II/III RCTs published in the English language from 01 July 2015 through 20 January 2024, the date of the present literature search.
- This date was selected to capture additional literature from the previous meta-analysis conducted by Heinemann et al., 2016 [2].
- Studies published as either peer-reviewed journal articles or conference abstracts in the preceding 3 years were included (from January 2021 to January 2024). Trials must have been registered in a publicly available database to be included.

Qualitätsbewertung der Studien:

- Cochrane Collaboration's 'Risk of Bias' tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Thus, 10 studies, representative of 8 unique trials, were included in the abstraction database

Charakteristika der Population/Studien:

Table 1
Summary of baseline characteristics and demographics for RAS wild-type metastatic colorectal cancer patients treated with first-line cetuximab or panitumumab plus chemotherapy or first-line bevacizumab plus chemotherapy (N = 8).

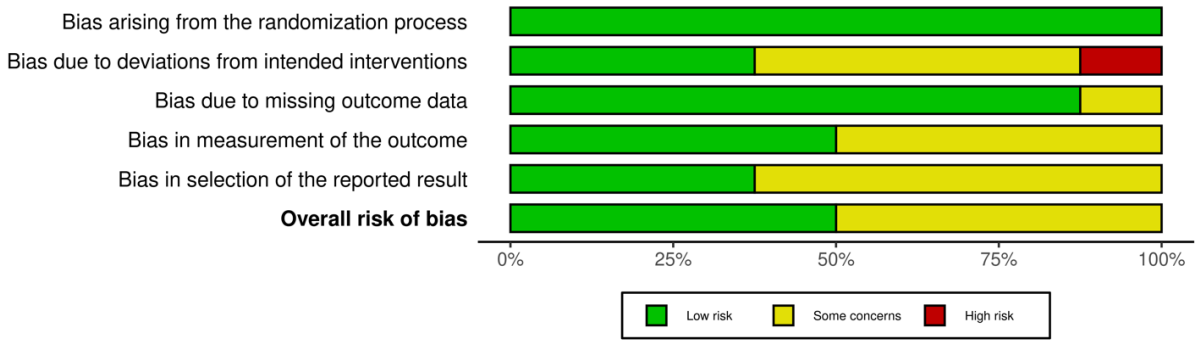
Author (Year): Trial Name	First-line Treatment	Study Type	RAS Assessable/Evaluable Population*									
			n	Median Age, Years (Range)	Male (%)	ECOG PS 0/1 (%)	Left- Sided Tumor (%)	Primary Colon Cancer (%)	Prior Radiotherapy (%)	Prior Adjuvant Chemotherapy (%)	≥ 2 Metastatic Sites (%)	Liver Metastases Only (%)
Oki (2019)[17]: ATOM	Cetuximab + FOLFOX	Phase II trial	59	65 (42–79)	57.6	100	76.3	NR	NR	3.4	69.5	100
	Bevacizumab + FOLFOX		57	64 (32–80)	59.6	100	84.2	NR	NR	5.3	73.7	100
Bond(2023)[14]: CAIRO5	Panitumumab + FOLFIRI or FOLFOX	Phase III trial	116	60 (52–69)	63	99	100	NR	12	3	NR	100
	Bevacizumab + FOLFIRI or FOLFOX		114	59 (53–67)	61	100	100	NR	16	4	NR	100
Venook (2017)[5]: CALGB/ SWOG 80405^	Cetuximab + FOLFIRI or FOLFOX	Phase III trial	346	59 (21–90)	62	NR	NR	NR	9	14	NR	36
	Bevacizumab + FOLFIRI or FOLFOX		324	60 (23–84)	64	NR	NR	NR	9	15	NR	33
Heinemann (2021) [15]: FIRE-3	Cetuximab + FOLFIRI	Phase III trial	199	64 (41–76)	74	98	60	79	9	19	57	36
	Bevacizumab + FOLFIRI		201	64 (31–76)	66	98	63	74	14	19	58	31
Janssens (2020)1[6]: PANIB	Panitumumab + FOLFOX	Phase II trial	20	68 (47–81)	70	NR	NR	NR	NR	NR	NR	NR
	Bevacizumab + FOLFOX		20	67 (47–86)	70	NR	NR	NR	NR	NR	NR	NR
Watanabe(2023)[18]: PARADIGM	Panitumumab + FOLFOX	Phase III trial	400	66.0 (32–79)	63.0	99.7	78.0	NR	0.5	5.5	51.0	26.3
	Bevacizumab + FOLFOX		402	66.0 (28–79)	66.7	100	72.6	NR	0.7	5.0	51.7	28.1
Rivera (2017)[4]: PEAK^	Panitumumab + FOLFOX	Phase II trial	88	62 (23–82)	66	100	NR	73	NR	NR	64	26
	Bevacizumab + FOLFOX		82	60 (39–82)	68	99	NR	70	NR	NR	59	27
Sastre (2021)[13]: VISNU-2	Cetuximab + FOLFIRI	Phase II trial	94	60 (32–70)	68	99	84.0	60	5	12	50	38
	Bevacizumab + FOLFIRI		102				81.4					

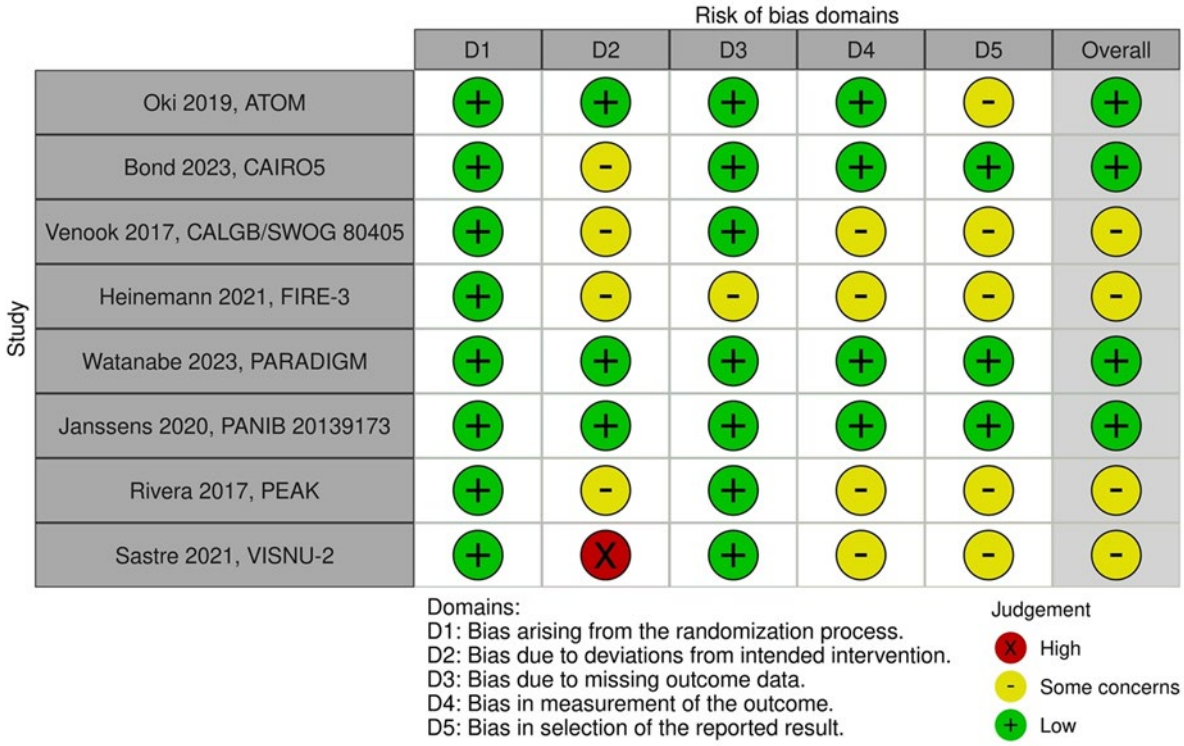
ECOG PS: Eastern Cooperative Oncology Group Performance Score; FOLFIRI: Combination chemotherapy of leucovorin calcium (folinic acid), fluorouracil, and irinotecan hydrochloride; FOLFOX: Combination chemotherapy of leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin; NR: Not reported

*Study information abstracted for patients with RAS status data. BRAF wild-type patients were selected, if outcome reported by mutational status.

^Arnold et al. (2017) [6] provided left-sided tumor data for these trials

Qualität der Studien:





Studienergebnisse:

Table 2
Summary of efficacy data comparing first-line cetuximab or panitumumab plus chemotherapy versus first-line bevacizumab plus chemotherapy: Patients with (A) left-sided (N = 5); (B) right-sided (N = 4); (C) all-sided RAS wild-type metastatic colorectal cancer (N = 7).

(A) Left-sided

Author (Year): Trial Name	First-Line Therapy	Primary Endpoint	RAS Wild-Type Metastatic Colorectal Cancer Patients						
			n	Median OS, Months (95% CI)	Median PFS, Months (95% CI)	RR, % (95% CI)	Objective Response Rate, % (95% CI)	ETS, % (95% CI)	Median DpR, %, (95% CI)
Bond (2023)[14]: CAIRO5	Panitumumab + FOLFIRI or FOLFOX	PFS	116	38.3 (NR-NR)^	10.4 (9.8–13.0)	58 (NR)	80	NR	49
	Bevacizumab + FOLFIRI or FOLFOX		114	40.4 (NR-NR)^	10.8 (9.9–12.6)	58 (NR)	53	NR	33
	HR or OR (95% CI)			HR: 1.02 (0.72–1.46), p = 0.89^	HR: 1.11 (0.84–1.48), p = 0.46	HR: NR, p = 1	OR: NR, p <0.0001	NR	OR: NR, p < 0.0001
Arnold (2017)[6]: CALGB/SWOG 80405	Cetuximab + FOLFIRI or FOLFOX	OS	173	39.3 (NR)	12.7 (NR)	NR	69.4 (NR)	NR	NR
	Bevacizumab + FOLFIRI or FOLFOX		152	32.6 (NR)	11.2 (NR)	NR	57.9 (NR)	NR	NR
	HR or OR (95% CI)			HR: 0.77 (0.59-0.99), p = 0.05	HR: 0.84 (0.66–1.06), p = 0.15	NR	OR: 1.65 (1.16–2.34), p = 0.005	NR	NR
Heinemann (2021) [15]: FIRE-3	Cetuximab + FOLFIRI	Objective response rate	158	36 (30-41)	11 (10–12)	NR	69 (61–76)	71 (NR)	50 (NR)
	Bevacizumab + FOLFIRI		149	28 (25-31)	11 (10–12)	NR	62 (53–70)	50 (NR)	33 (NR)
	HR or OR (95% CI)			HR: 0.70 (0.55-0.89), p = 0.004	HR: 0.90 (0.71–1.14), p = 0.38	NR	OR: 1.37 (0.85-2.20), p = 0.19	NR	NR
Watanabe (2023) [18]: PARADIGM	Panitumumab + FOLFOX	OS	312	37.9 (34.1–42.6)	13.1 (11.6–14.5)	18.3 (14.1–23.0)	80.2 (75.3–84.5)	76.3 (71.2–80.9)	85.8
	Bevacizumab + FOLFOX		292	34.3 (30.9–40.3)	11.9 (11.3–13.5)	11.6 (8.2–15.9)	68.6 (62.9–74.0)	62.3 (56.5–67.9)	74.3
	HR or OR (95% CI)			HR: 0.82 (0.68–0.99), p = 0.031	HR: 1.00 (0.83–1.20), p = NR	NR	1.85 (1.27–2.69),p = 0.001	NR	NR
Arnold (2017)[6]: PEAK	Panitumumab + FOLFOX	PFS	53	43.4 (NR)	14.6 (NR)	NR	64.1 (NR)	NR	NR
	Bevacizumab + FOLFOX		54	32.0 (NR)	11.5 (NR)	NR	57.4 (NR)	NR	NR
	HR or OR (95% CI)			HR: 0.77 (0.46–1.28), p = 0.31	HR: 0.68 (0.45–1.04), p = 0.07	NR	OR: 1.33 (0.72-2.46), p = 0.37	NR	NR

(B) Right-sided

Author (Year): Trial Name	First-Line Therapy	Primary Endpoint	RAS Wild-Type Metastatic Colorectal Cancer Patients						
			n	Median OS, Months(95% CI)	Median PFS, Months(95% CI)	RR, % (95% CI)	Objective Response Rate, % (95% CI)	ETS, % (95% CI)	Median DpR, %, (95% CI)
Arnold (2017)[6]: CALGB/SWOG 80405	Cetuximab + FOLFIRI or FOLFOX	OS	71	13.7 (NR)	7.5 (NR)	NR	42.3 (NR)	NR	NR
	Bevacizumab + FOLFIRI or FOLFOX		78	29.2 (NR)	10.2 (NR)	NR	39.7 (NR)	NR	NR
	HR or OR (95% CI)			1.36 (0.93–1.99), p = 0.11	1.64 (1.15–2.36), p = 0.007	NR	1.11 (0.61–2.01), p = 0.73	NR	NR
Heinemann (2021) [15]: FIRE-3	Cetuximab + FOLFIRI	Objective response rate	38	18 (12–25)	8 (6-9)	NR	53 (36–69)	57 (NR)	38 (NR)
	Bevacizumab + FOLFIRI		50	23 (19-26)	9 (7-12)	NR	50 (36–65)	41 (NR)	29 (NR)
	HR or OR (95% CI)			1.27 (0.81–1.98), p = 0.29	1.41 (0.91–2.19), p = 0.13	NR	1.11 (0.48-2.59), p = 0.83	NR	NR
Watanabe (2023) [18]: PARADIGM	Panitumumab + FOLFOX	OS	84	20.2 (15.2–32.0)	7.2 (6.6–9.9)	10.7 (5-19.4)	54.9 (43.5–65.9)	60.2 (50.1–69.7)	65.8
	Bevacizumab + FOLFOX		103	23.2 (18.5–29.1)	9.4 (7.6–13)	9.7 (4.8-17.1)	63.1 (53-72.4)	52.4 (41.2–63.4)	69.1
	HR or OR (95% CI)			1.09 (0.79–1.51), p = NR	1.43 (1.03–1.97),p = NR	NR	0.71 (0.39, 1.28), p = 0.249	NR	NR

(A) Left-sided

Author (Year): Trial Name	First-Line Therapy	Primary Endpoint	RAS Wild-Type Metastatic Colorectal Cancer Patients						
			n	Median OS, Months (95% CI)	Median PFS, Months (95% CI)	RR, % (95% CI)	Objective Response Rate, % (95% CI)	ETS, % (95% CI)	Median DpR, %, (95% CI)
Arnold (2017)[6]: PEAK	Panitumumab + FOLFOX	PFS	22	17.4 (NR)	8.7 (NR)	NR	63.6 (NR)	NR	NR
	Bevacizumab + FOLFOX		14	21.04 (NR)	12.6 (NR)	NR	50 (NR)	NR	NR
	HR or OR (95% CI)			0.67 (0.30–1.50), p = 0.32	1.04 (0.50–2.18), p = 0.91	NR	1.75 (0.57, 5.41), p = 0.33	NR	NR

(C) All-sided

Author (Year): Trial Name	First-Line Therapy	Primary End-Point	RAS Wild-Type Metastatic Colorectal Cancer Patients						
			n	Median OS, Months (95% CI)	Median PFS, Months (95% CI)	RR. % (95% CI)	Objective Response Rate, % (95% CI)	ETS, % (95% CI)	Median DpR, %, (95% CI)
Oki (2019)[17]: ATOM	Cetuximab + FOLFOX	PFS	59	Not achieved yet	14.8 (9.7–17.3)	49.2 (NR)	84.7 (73.0–92.8)	Median tumor shrinkage rates at 8 weeks: 37.8 (NR)	NR
	Bevacizumab + FOLFOX		57	30.4 (NR)	11.5 (9.2–13,3)	56.1 (NR)	68.4 (54.8–80.1)	Median tumor shrinkage rates at 8 weeks: 25.3 (NR)	NR
	HR or OR (95% CI)			HR: 0.83 (0.44–1.56), p = 0.56	HR: 0.80 (0.51–1.26), p = 0.33	NR	NR, p = 0.05	NR	NR
Venook (2017)[5]: CALGB/ SWOG 80405	Cetuximab + FOLFIRI or FOLFOX	OS	578	30 (NR)	10.5 (5.8–17.7)	NR	59.6 (NR)	NR	NR
	Bevacizumab + FOLFIRI or FOLFOX		539	29 (NR)	10.6 (6.4–16.6)	NR	55.2 (NR)	NR	NR
	HR or OR (95% CI)			HR: 0.88 (0.77–1.01), p = 0.08	HR: 0.95 (0.84–1.08), p = 0.45	NR	1.2 (0.95, 1.52), p = 0.13	NR	NR
Heinemann (2021) [15]: FIRE-3	Cetuximab + FOLFIRI	ORR	199	31 (25–36)	10 (9–12)	NR	66 (59–72)	20% cut-off at 6 weeks: 68 (NR)	49 (NR)
	Bevacizumab + FOLFIRI		201	26 (23–29)	10 (10–12)	NR	59 (52–66)	20% cut-off at 6 weeks: 49 (NR)	32 (NR)
	HR or OR (95% CI)			HR: 0.76 (0.62–0.94), p = 0.012	HR: 0.96 (0.79–1.18), p = 0.71	NR	OR: 1.36 (0.90–2.03), p = 0.15	OR: 2.26 (1.45–3.54), p = 0.0004	OR = NR, p < 0.0001
Janssens (2020) [16]: PANIB	Panitumumab + FOLFOX	PFS	20	29.5 (19.6–39.4)	13.6 (5.9–21.3)	15 (NR)	84 (NR)	Cut-off % NR: 88 (NR)	NR
	Bevacizumab + FOLFOX		20	31.2 (14.7–47.6)	9.3 (0–20.3)	5 (NR)	55 (NR)	Cut-off % NR: 50 (NR)	NR
	HR or OR (95% CI)			HR: 0.67 (0.28–1.6), p = 0.371	HR: 0.79 (0.24–3.63), p = 0.7	NR	NR	NR	NR
Watanabe (2023) [18]: PARADIGM	Panitumumab+ FOLFOX	OS	400	36.2 (32.0–39.0)	12.2 (10.8–13.2)	16.5 (13.0–20.5)	74.9 (70.3–79.1)	20% cut-off at 8 weeks: 71.3 (66.5-75.6)	81.9 (NR)
	Bevacizumab + FOLFOX		402	31.3 (29.3–34.1)	11.4 (11.2–13.2)	10.9 (8.1–14.4)	67.3 (62.4–1.9)	20% cut-off at 8 weeks: 61.7 (56.7-66.5)	72.8 (NR)
	HR or OR (95% CI)			HR: 0.84 (0.72–0.98), p = 0.03	HR: 1.05 (0.9–1.24), p = NR	NR	1.45 (1.06-1.98),p = 0.0196	1.54 (1.15, 2.07), p = 0.004	NR
Rivera (2017)[4]: PEAK	Panitumumab + FOLFOX	PFS	88	36.9 (27.9–46.1)	12.8 (10.7–15.1)	10 (NR)	65 (54-75)	20% cut-off at 8 weeks: 75 (NR)	65.0 (45.7-89.5)
	Bevacizumab + FOLFOX		82	28.9 (23.3–32.0)	10.1 (9.0–12.7)	9 (NR)	60 (49-71)	20% cut-off at 8 weeks: 62 (NR)	46.3 (29.5-63.3)
	HR or OR (95% CI)			HR: 0.76 (0.53–1.11), p = 0.15	HR: 0.68 (0.48–0.96), p = 0.029	NR	OR: 1.12 (0.56-2.22), p = 0.86	OR: 1.67 (0.78, 3.58),p = 0.21	NR, p = 0.0018
Sastre (2021)[13]: VISNU-2	Cetuximab + FOLFIRI	PFS	94	34.1 (29.9–42.1)	12.5 (10.5–16.1)	NR	78 (NR)	NR	NR
	Bevacizumab + FOLFIRI		102	36.0 (28.3–43.7)	12.9 (10.3–14.9)	NR	67 (NR)	NR	NR
	HR or OR (95% CI)			0.91 (0.63, 1.33), p = 0.63	0.99 (0.67, 1.45), p = 0.95	NR	NR	NR	NR

3.5. Efficacy

From the 5 trials (CAIRO5, CALGB/SWOG 80405, FIRE-3, PARADIGM, and PEAK), meta-analysis for OS in the left-sided RAS WT population favored EGFRI plus chemotherapy versus bevacizumab plus chemotherapy (HR=0.80, 95% CI: 0.71–0.90; Fig. 2B). This association was attenuated in the meta-analysis for OS in the all-sided RAS WT populations of the 7 trials, which also favored EGFRI plus chemotherapy versus bevacizumab plus

chemotherapy but to a lesser extent (HR=0.85, 95% CI: 0.78–0.93; Fig. 2A). This association remained unchanged in a sensitivity analysis that excluded VISNU-2 (Supplemental Figure 2). Meta-analysis for OS in the right-sided RAS WT population showed no difference between EGFRI plus chemotherapy versus bevacizumab plus chemotherapy (HR=1.17, 95% CI: 0.95–1.44; Supplementary Figure 3A).

Meta-analysis for PFS in the left-sided RAS WT population was not statistically significantly different for EGFRI plus chemotherapy versus bevacizumab plus chemotherapy (HR=0.93, 95% CI: 0.84–1.04; Fig. 3B). Further, no significant association was observed in the all-sided RAS WT population (HR=0.97, 95% CI: 0.89–1.05; Fig. 3A). Meta-analysis of four trials (CALGB/SWOG 80405, FIRE-3, PARADIGM, PEAK) for PFS in the right-sided RAS WT population favored bevacizumab plus chemotherapy versus EGFRI plus chemotherapy (HR=1.45, 95% CI: 1.19–1.78; Supplementary Figure 3B).

Seven trials reported ORR for patients with all-sided tumors (ATOM, CALGB/SWOG 80405, FIRE-3, PANIB, PARADIGM, PEAK, VISNU-2); however only 3 studies reported measures of association (CALGB/ SWOG 80405, FIRE-3, PEAK). The measures of association (odds ratio) for left-sided and all-sided tumors in the PARADIGM trial were calculated given available data by treatment. However, the limited data of the remaining 3 trials (ATOM, PANIB, VISNU-2) precluded inclusion of these trials into the all-sided analysis. Meta-analysis for ORR in the left-sided and all-sided RAS WT population favored EGFRI plus chemotherapy versus bevacizumab plus chemotherapy (OR = 1.61; 95% CI: 1.30–1.99 for left-sided tumors; Fig. 4B, OR = 1.29; 95% CI: 1.09–1.52 for all-sided tumors; Fig. 4A). No significant association was observed for the right-sided RAS WT population (HR = 0.99, 95% CI: 0.69–1.41; Supplementary Figure 3C).

Five trials reported ETS for patients with all-sided tumors (FIRE-3, PEAK, PANIB, ATOM, PARADIGM); however only 2 studies reported measures of association (FIRE-3, PEAK) (Table 2). The measure of association (odds ratio) for all-sided tumors in the PARADIGM trial were calculated given available data by treatment. However, the limited data of the remaining two trials (PANIB, ATOM) precluded inclusion of these trials in the all-sided analysis. Meta-analysis of early tumor shrinkage of ≥ 20% at week 6 or 8 for all-sided tumors favored EGFRI plus chemotherapy vs. bevacizumab plus chemotherapy (OR 1.72; 95% CI: 1.36, 2.17; Supplementary Figure 4). There were two trials that reported ETS by tumor sidedness, therefore further summary analysis could not be performed. Resection data for the left-sided RAS WT population were available from PARADIGM and CAIRO5 (Table 2). In the PARADIGM trial, RR was 18.3% (95% CI: 14.1–23.0) in the panitumumab arm compared to 11.6% (95% CI: 8.2–15.9) in the bevacizumab arm. There was no measure of association reported; however, this was not expected to be different given the overlapping confidence intervals. In CAIRO5, RR was 58% for both panitumumab and bevacizumab arms in patients with left-sided tumors and indicated no statistical difference (p = 1.00). Right-sided RAS WT population data came from PARADIGM, and RR was 10.7% (95% CI: 5.0%−19.4%) and 9.7% (95% CI: 4.8%−17.1%) in the panitumumab and bevacizumab arms, respectively, also showing no statistical difference. No association measures for RR were reported for all-sided data. Resection details for all-sided population were available from PEAK, PANIB, PARADIGM, and ATOM trials. RR in PEAK was 10% with panitumumab and 9% with bevacizumab. In PANIB, RR was 15% with panitumumab and 5% with bevacizumab. ATOM trial showed RR of 49.2% with cetuximab and 56.1% with bevacizumab. PARADIGM demonstrated RR of 16.5% (95% CI: 13.0%−20.5%) with panitumumab and 10.9% (95% CI: 8.1%−14.4%) with bevacizumab, with no significant difference observed.

OS

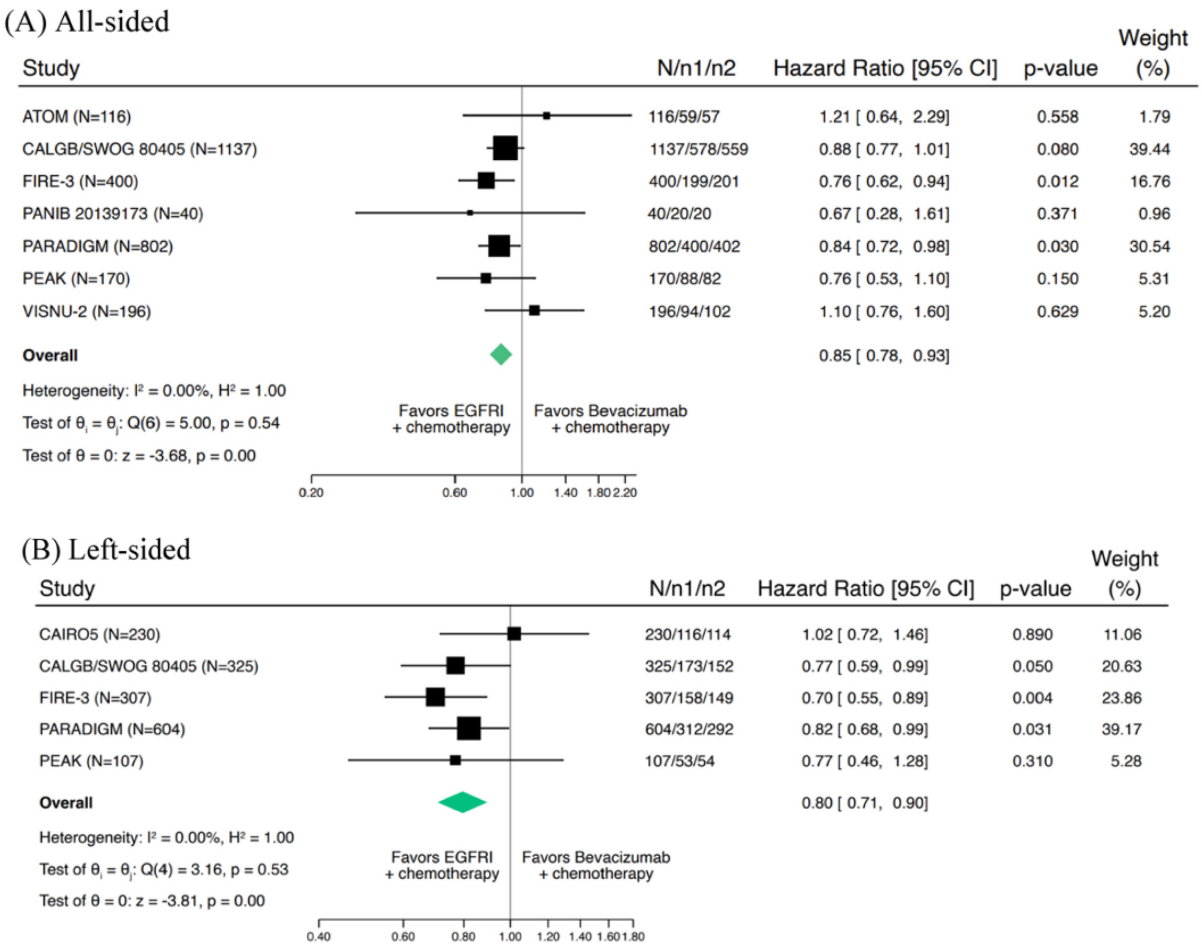
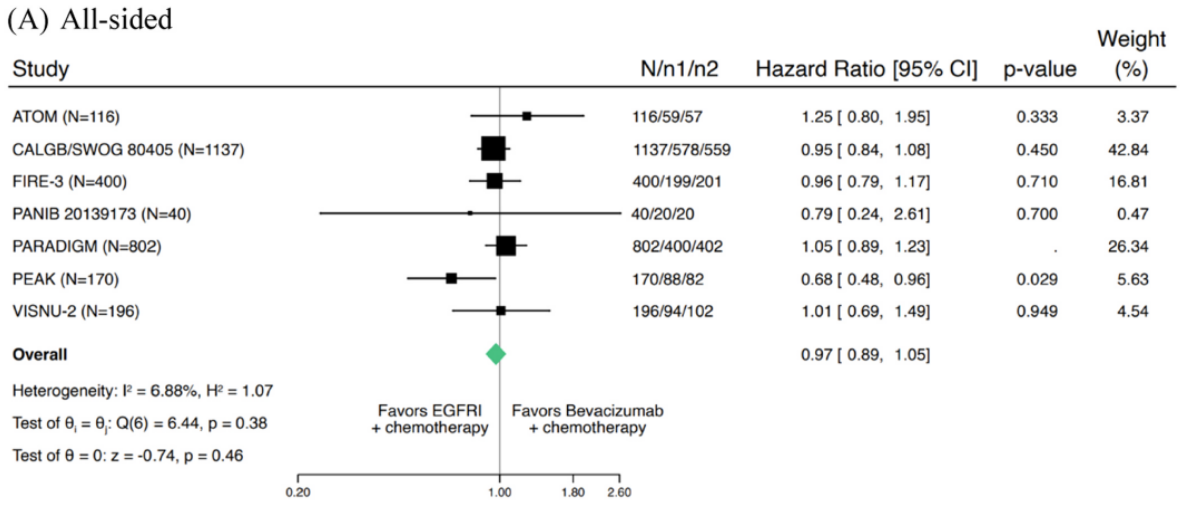


Fig. 2. Forest plots for overall survival in (A) all-sided and (B) left-sided RAS wild-type metastatic cancer patients. Weight is relative weight (%) from the fixed-effects model. p-value is two sided. CI, confidence interval; EGFRI, epidermal growth factor receptor inhibitor (cetuximab or panitumumab); HR, hazard ratio; N, total study size, n, total number evaluable; n1, number evaluable in the EGFRI arm; n2, number evaluable in the bevacizumab arm.

PFS



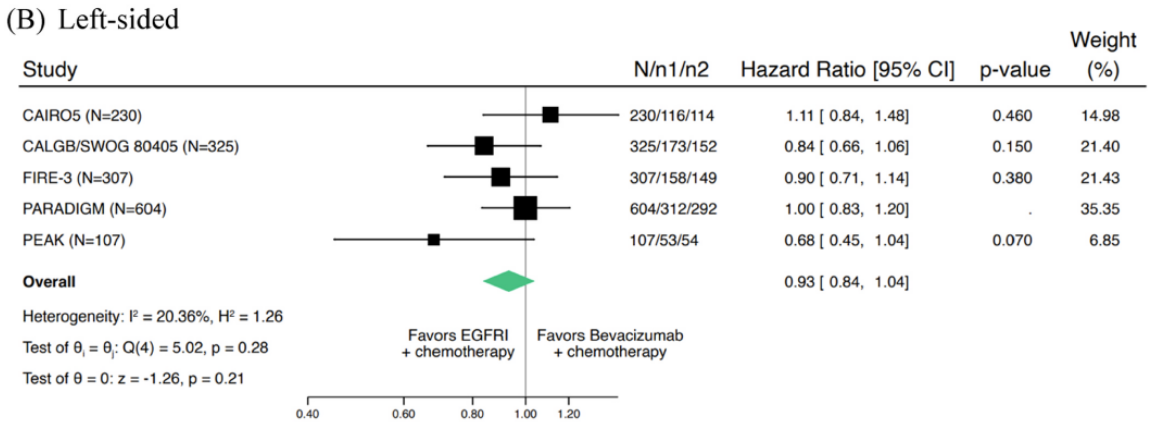


Fig. 3. Forest plots for progression-free survival in (A) all-sided and (B) left-sided RAS wild-type metastatic colorectal cancer patients). Weight is relative weight (%) from the fixed-effects model. p-value is two sided. CI, confidence interval; EGFRI, epidermal growth factor receptor inhibitor (cetuximab or panitumumab); HR, hazard ratio; N, total study size, n, total number evaluable; n1, number evaluable in the EGFRI arm; n2, number evaluable in the bevacizumab arm.

ORR

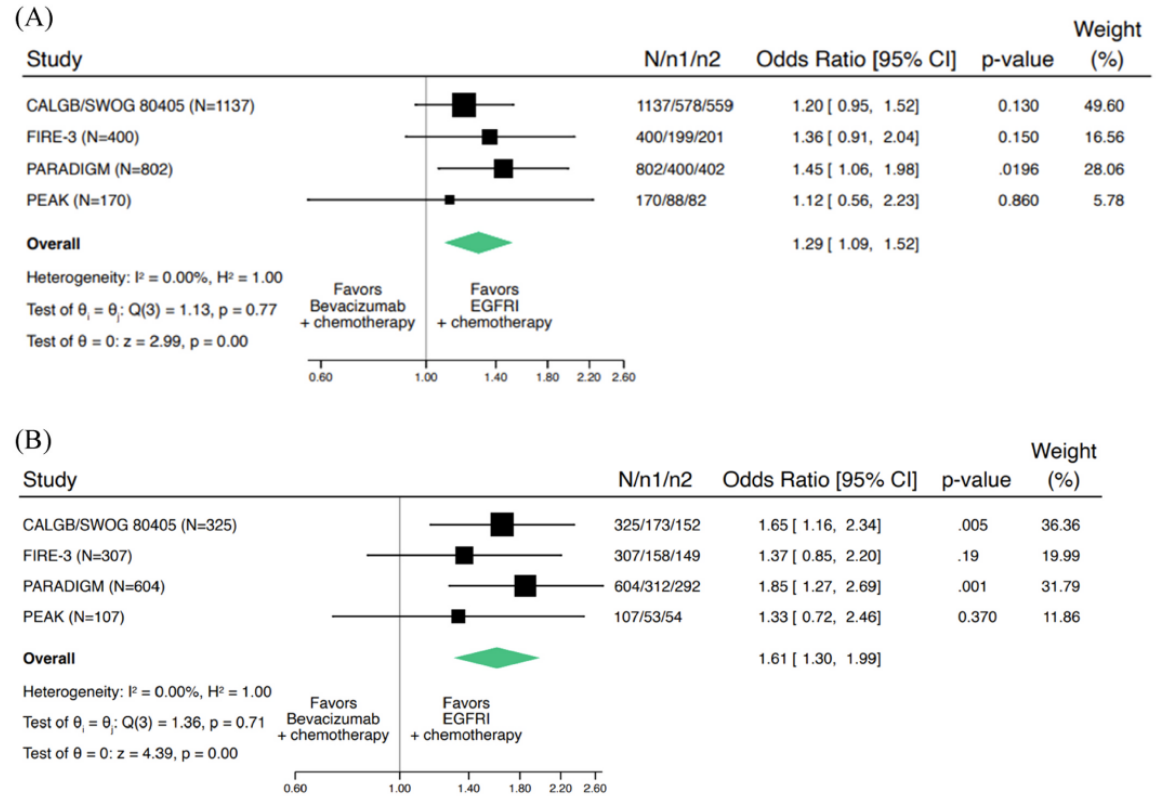


Fig. 4. Forest plots for objective response rate in (A) all-sided and (B) left-sided RAS wild-type metastatic colorectal cancer patients. Weight is relative weight (%) from the fixed-effects model. p-value is two sided. CI, confidence interval; EGFRI, epidermal growth factor receptor inhibitor (cetuximab or panitumumab); OR, odds ratio; N, total study size, n, total number evaluable; n1, number evaluable in the EGFRI arm; n2, number evaluable in the bevacizumab arm.

Table 3
Summary of safety/tolerability data comparing first-line cetuximab or panitumumab plus chemotherapy versus first-line bevacizumab plus chemotherapy among patients with RAS wild-type metastatic colorectal cancer in: (a) ATOM; (B) CAIRO5; (C) FIRE-3; (D) PANIB; (E) PARADIGM; (F) PEAK; (G) VISNU-2 (d) PANIB; (e) PEAK; (F) PARADIGM; (G) VISNU-2 (N = 7).

(A) ATOM (Oki 2019)[17]		
Safety/Tolerability Outcome	Cetuximab + FOLFOX	Bevacizumab + FOLFOX
	n (%)	n (%)
Discontinuation due to AEs	6 (9.8)	8 (13.1)
Worst grade ≥ 3 AEs	NR (52.5)	NR (40.4)
Selected grade ≥ 3 AEs of interest occurring in ≥ 5% of patients / ≥ 2% difference between treatment arms	Neutropenia: (50.8) Mucositis: (5.1) Fatigue: (6.8) Peripheral neuropathy: (10.2) Paronychia: (15.3) Dermatitis acneiform: (15.3)	Neutropenia: (36.8) Peripheral neuropathy: (7.0) Hypertension: (15.8)
Deaths	0	0
(B) CAIRO5 (Bond 2023)[14]		
Safety/Tolerability Outcome	Panitumumab + FOLFOX or FOLFIRI n (%)	Bevacizumab + FOLFOX or FOLFIRI n (%)
Discontinuation due to AEs	5 (4)	3 (3)
Worst grade ≥ 3 AEs	80 (69)	61 (54)
Selected grade ≥ 3 AEs of interest occurring in ≥ 5% of patients / ≥ 2% difference between groups	Neutropenia: 24 (21) Skin toxicity: 29 (25) Hypertension: 8 (7) Diarrhea: 18 (16) Mucositis/stomatitis: 11 (9) Thromboembolic events: 3 (3) Peripheral sensory neuropathy: 5 (4) Fatigue: 8 (6)	Neutropenia: 29 (25) Skin toxicity: 1 (1) Hypertension: 20 (18) Diarrhea: 5 (4) Mucositis/stomatitis: 4 (4) Thromboembolic events: 5 (5) Peripheral sensory neuropathy: 11 (10) Fatigue: 3 (3)
Deaths	6	1
(C) FIRE-3 (Heinemann 2021)[15]		
Safety/Tolerability Outcome,	Cetuximab + FOLFIRI n (%)	Bevacizumab + FOLFIRI n (%)
Discontinuation due to AEs	NR (15)	NR (8)
Worst grade ≥ 3 AEs,	127 (64)	103 (51)
Selected grade ≥ 3 AEs of interest occurring in ≥ 5% of patients and ≥ 2% difference between treatment arms	Rash/acne, acneiform: 36 (18.1) Rash/desquamation 15 (7.5) Paronychia: 14 (7.0) Hypomagnesemia: 9 (4.5)	Hypomagnesemia: 14 (0.7)
Treatment-related Deaths	0 (0)	3 (1.5)
(D) PANIB (Janssens 2020)[16]		
Safety/Tolerability Outcome	Panitumumab + FOLFOX n (%)	Bevacizumab + FOLFOX n (%)
Discontinuation due to AEs	4 (20)	1 (5)
Worst grade ≥ 3 AEs	15 (75)	6 (30)
Selected grade ≥ 3 AEs of interest occurring in ≥ 5% of patients / ≥ 2% difference between groups	Skin: 5 (25)	
Deaths	NR	NR
(E)PARADIGM (Watanabe 2023)[18]		
Safety/Tolerability Outcome	Panitumumab + FOLFOX n (%)	Bevacizumab + FOLFOX n (%)
Discontinuation due to AEs	96 (23.8)	75 (18.4)
Worst grade ≥ 3 AEs	290 (71.8)	264 (64.9)
Selected grade ≥ 3 AEs of interest occurring in ≥ 5% of patients / ≥ 2% difference between groups	Acne-like dermatitis: (17) Stomatits: (7) Decreased appetite: (8)	Acne-like dermatitis: 0 (0) Stomatits: (2) Decreased appetite: (4)

Table 3 (*continued*)

(A) ATOM (Oki 2019)[17]		
Safety/Tolerability Outcome	Cetuximab + FOLFOX	Bevacizumab + FOLFOX
	n (%)	n (%)
	Paronychia: (9) Dry skin: (8) Diarrhea: (6) Hypomagnesemia (8)	Paronychia: (<1) Dry skin: (<1) Diarrhea: (3) Hypomagnesemia: 0 (0)
Deaths	10	2
(F) PEAK (Rivera 2017)[4]		
Safety/Tolerability Outcome	Panitumumab + FOLFOX n (%)	Bevacizumab + FOLFOX n (%)
Discontinuation due to AEs	25 (29)	24 (30)
Worst grade ≥ 3 AEs	NR	NR
Selected grade ≥ 3 AEs of interest occurring in ≥ 5% of patients and ≥ 2% difference between treatment arms	Rash: 13 (15) Hypomagnesaemia: 7 (8) Stomatitis: 6 (7) Decreased appetite: 5 (6) Dehydration: 5 (6) Acne: 4 (5) Dermatitis acneiform: 4 (5) Deep vein thrombosis: 2 (2) Hypertension: 0 (0)	Rash: 0 (0) Hypomagnesaemia: 0 (0) Stomatitis: 0 (0) Decreased appetite: 1 (1) Dehydration: 1 (1) Acne: 0 (0) Dermatitis acneiform: 0 (0) Deep vein thrombosis: 6 (8) Hypertension: 6 (8)
Deaths	NR	NR
(G) VISNU-2 (Sastre 2021)[13]		
Safety/Tolerability Outcome	Cetuximab + FOLFIRI n (%)	Bevacizumab + FOLFIRI n (%)
Discontinuation due to AEs	NR (15)	NR (8)
Worst grade ≥ 3 AEs	64 (68.8)	59 (57.8)
Selected grade ≥ 3 AEs of interest occurring in ≥ 5% of patients / ≥ 2% difference between treatment arms	Diarrhea: 12 (12.9) Asthenia: 8 (8.6) Neutropenia: 11 (11.8) Skin toxicity dermatitis-like:16 (17.2) Pulmonary embolism: 4 (4.3)	Diarrhea: 8 (7.8) Asthenia: 4 (3.9) Neutropenia: 23 (22.6) Pulmonary embolism: 2 (2)
Deaths	2 (2)	6 (5)

AE: Adverse event
NR: Not reported

Anmerkung/Fazit der Autoren

In conclusion, the findings of this study support the use of first-line EGFRIs plus chemotherapy as a first-line treatment option for patients with left-sided RAS WT mCRC. These findings are consistent with recent guidelines that have implicated tumor sidedness in treatment decision- making. It is essential to consider the appropriate sequence of biologics and the distinct safety profiles when making treatment choices. Individualized treatment decisions should be made in collaboration with patients, considering the tumor characteristics, RAS mutation status, and safety. Further research and well-designed clinical trials studies with efficacy and safety outcomes reported by sidedness with larger sample sizes and standardized cutoff values for ETS assessment are warranted to validate these findings and refine treatment recommendations for this specific patient population.

3.3 Leitlinien

Leitlinienprogramm Onkologie, 2025 [4].

Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS)

Kolorektales Karzinom. Version 3.0. [3, 5]

Zielsetzung/Fragestellung

Ziel der Leitlinie ist es, evidenzbasierte Empfehlungen zu allen Aspekten von Darmkrebs von der Prävention über das Screening, zur Therapie bis zur Nachsorge zu geben, um hierdurch die Versorgung von Darmkrebspatienten im Erwachsenenalter in Deutschland zu verbessern.

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: Trifft zu.

Recherche/Suchzeitraum:

- Bereits bestehende Leitlinien mit Bezug zum Thema Kolorektales Karzinom wurden in den Leitlinienregistern des Guidelines International Networks (www.g-i-n.net), des National Institute for Health and Care Excellence (www.nice.org), des Scottish Intercollegiate Guidelines Network (https://www.sign.ac.uk/), der European Society For Medical Oncology (https://www.esmo.org/) sowie in der Datenbank PubMed für den Zeitraum 2022 bis 2023 recherchiert. Die Suche erfolgte am 22.03.2023 unter Verwendung des Suchbegriffes „Colorectal cancer“.
- In Absprache mit der Leitliniengruppe erfolgte initial eine gemeinsame systematische Literaturrecherche nach aktuellen Übersichtsarbeiten (Systematische Reviews und Meta-Analysen) für alle de-novo Schlüsselfragen sowie für die Aktualisierung der bestehenden evidenzbasierten Empfehlungen.Die Recherchen wurden in der Medline Datenbank über die PubMed Suchoberfläche https://pubmed.ncbi.nlm.nih.gov/ sowie in der Cochrane Library https://www.cochranelibrary.com/ durchgeführt. Der Suchzeitraum erstreckte sich vom 01.01.2022 bis zum Zeitpunkt der Suche (18.06.2023).
- Nach Aufarbeitung der Übersichtsarbeiten erfolgte eine Recherche nach Einzelstudien für die de-novo Schlüsselfragen, für welche keine aggregierte Evidenz identifiziert werden konnte bzw. für welche die aggregierte Evidenz allein nicht ausreichend zur Beantwortung der Fragestellungen war. Die Suche erfolgte in der Medline Datenbank über die PubMed Suchoberfläche. Zusätzlich wurde eine Recherche in Cochrane CENTRAL trials database https://www.cochranelibrary.com/ durchgeführt. Für die Schlüsselfragen 1 und 4, für welche keine geeignete aggregierte Evidenz gefunden wurde, wurde ein Suchzeitraum von 5 Jahren gewählt (01.01.2018 bis 14.09.2023), um möglichst aktuelle Einzelstudien zu identifizieren. Für die Schlüsselfragen 6 bis 9 wurde

in Ergänzung zu der vorliegenden aggregierten Evidenz eine Suche nach Einzelstudien der letzten drei Jahre durchgeführt (01.01.2021 bis 14.09.2023), in Anschluss an den Suchzeitraum der Übersichtsarbeiten.

- Es wurde für alle evidenzbasierten Empfehlungen zur Überarbeitung, für welche keine aggregierte Evidenz identifiziert werden konnte, eine Updaterecherche nach Einzelstudien durchgeführt. Eine Übersicht zu diesen Empfehlungen lässt sich dem Appendix entnehmen. Die Suche erfolgte in der Medline Datenbank über die PubMed Suchoberfläche. Zusätzlich wurde eine Recherche in Cochrane CENTRAL trials database https://www.cochranelibrary.com/ durchgeführt. Der Suchzeitraum erstreckte sich vom Zeitpunkt der letzten Leitlinienveröffentlichung (v2.0) im Januar 2019 bis zum Zeitpunkt der Suche (19.10.2023).

LoE

- Die Literaturbewertung wurde nach der Evidenzklassifizierung des Oxford Centre for Evidence-Based Medicine 2011 für Interventions- und diagnostische Studien durchgeführt.
- Die methodische Qualität der Literaturstelle wurde mit Hilfe von Checklisten überprüft und die gefundenen Mängel im „Notes“ Bereich der Evidenztabellen festgehalten. Studien mit bedeutenden methodischen Schwächen und/ oder bedeutsamer Heterogenität wurden um eine Note abgewertet.
- Vorgehensweise: Das Evidenzlevel kann herabgestuft werden auf Grund der Studienqualität, Ungenauigkeit, Indirektheit (Studien PICO passt nicht genau zur Frage PICO), Inkonsistenz zwischen Studien, oder weil die absolute Effektgröße sehr klein ist. Das Evidenzlevel kann hochgestuft werden, wenn der beobachtete Effekt groß oder sehr groß ist.
- Die Beurteilung der Qualität von Übersichtsarbeiten erfolgte mit AMSTAR II; für randomisierte kontrollierte Studien fand das Risk-of-Bias (RoB) Tool der Cochrane Collaboration-2 Anwendung.

  (*Hinweis*: Eine Evidenzgraduierung nach GRADE als Evidenzbewertungs- und -graduierungssystem wurde nicht konkret benannt.)

GoR

Tabelle 4: Verwendete Empfehlungsgrade

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll
B	Empfehlung	sollte
0	Empfehlung offen	kann

Sonstige methodische Hinweise

- Die Gültigkeitsdauer der Leitlinie beträgt 3 Jahre bis zum 31. Mai 2028. Im Sinne einer "living guideline" sind regelmäßige Aktualisierungen der gesamten Leitlinie vorgesehen. Unmittelbar im Anschluss an die Veröffentlichung der v3.01 wird noch 2025 ein 2. Aktualisierungszyklus gestartet.

10 Therapie bei Metastasierung und in der Palliation

Der folgende Teil der S3-Leitlinie enthält 2024 aktualisierte Empfehlungen zur Tu-mortherapie beim metastasierten Kolorektalkarzinom (mKRK), die vor allem Erkennt-nisse

aus Studien der Jahre 2003-2023 Jahre widerspiegeln. Auf die primär resektab-len/lokal abladierbaren Metastasen wird ebenso eingegangen wie auf die besondere Situation einer sekundären Resektion/lokalen Therapie in einem primär palliativen Therapiekonzept. Die Entscheidung über das therapeutische Vorgehen bei Nachweis einer Metastasierung beginnt mit der Beurteilung der Resektabilität der Metastasie-rung und ggf. des Primärtumors unter Berücksichtigung des Allgemeinzustandes des Patienten.

Bei resektablen Tumormanifestationen und günstiger Risikokonstellation soll primär die Metastasenresektion angestrebt werden. Für Patienten, für die primär keine chirur-gische Interventionsmöglichkeit besteht, sollten andere lokaltherapeutische Verfahren geprüft werde. Besteht keine Möglichkeit der lokalen Therapie sollte eine möglichst effektive medikamentöse Therapie mit dem Ziel der maximale Tumorreduktion ange-strebt werden. Die Wahl des Therapieregimes hängt entscheidend von dem molekular-pathologischen Profil des Tumors ab. Bei Patienten mit RAS-Wildtyp Tumoren kommt als weitere Entscheidungsgrundlage die Lokalisation des Primärtumors hinzu.

10.1 Allgemeine Behandlungsstrategie

10.1	Konsensbasierte Empfehlung	neu 2025
EK	Grundsätzlich sollen Patienten im Laufe ihrer Erkrankung Zugang zu allen Therapiemodalitäten haben und die Therapiestrategie soll in einem interdisziplinären Tumorboard festgelegt werden, vorzugsweise in zertifizierten Zentren.	
	Starker Konsens	

10.2	Konsensbasierte Empfehlung	neu 2025
EK	Das Tumorboard soll bei jedem Patienten initial sowie unter laufender Behandlung prüfen, ob lokale Therapieverfahren in kurativer Intention in die Therapiestrategie integriert werden können. Hier kommen die Metastasenresektion und andere lokale Therapieverfahren (SRBT, thermoablative Verfahren, TACE, intraarterielle CTx) in Frage.	
	Starker Konsens	

10.3	Konsensbasierte Empfehlung	neu 2025
EK	Eine Tumortherapie soll zum Zeitpunkt des Nachweises von Metastasen unabhängig von metastasenbezogenen Symptomen eingeleitet werden.	
	Starker Konsens	

10.4	Konsensbasierte Empfehlung	neu 2025
EK	Die Intensität der Tumortherapie soll an den Allgemeinzustand des Patienten und das molekulare Tumorprofil angepasst werden. Hierbei ist zu berücksichtigen, ob der AZ vorrangig tumorbedingt reduziert ist. Grundsätzlich sollen Patienten Zugang zu der effektivsten und noch tolerablen Therapie haben. Alter per se stellt keine Kontraindikation dar. Bei der Therapieentscheidung sollen die Patienten mit einbezogen werden.	
	Starker Konsens	

10.5	Evidenzbasierte Empfehlung	neu 2025
Empfehlungsgrad A	Vor Einleitung einer Erstlinientherapie soll die Bestimmung des molekularen Tumorprofils (dMMR/MSI, RAS- und BRAF-Mutationen) erfolgen (siehe Kapitel 8).	
Level of Evidence 1a	[679]	
	Starker Konsens	

10.6	Evidenzbasierte Empfehlung	neu 2025
Empfehlungsgrad A	Vor Einsatz einer Fluoropyrimidinhaltigen (FP) Therapie soll eine Mutation in den 4 wichtigsten DPD-Loci ausgeschlossen werden. Die FP Dosis ist bei einem DPD Mangel entsprechend anzupassen.	
Level of Evidence 2a	[918], [919]	
	Starker Konsens	

10.7	Konsensbasierte Empfehlung	neu 2025
EK	Vor Beginn einer CTx mit Irinotecan kann eine UGT1A1-Genotypisierung hilfreich sein, um Patienten mit einem erhöhten Risiko für schwere Neutropenien und Durchfälle zu identifizieren, z. B. bei v.a. Morbus Meulengracht oder anderen Bilirubin-Konjugationsstörungen.	
	Starker Konsens	

Hintergrund

Die therapeutische Strategie wird auf dem Boden patientenspezifischer und tumorspezifischer Eigenschaften festgelegt. Die Behandlung von Patienten im Stadium IV eines kolorektalen Karzinoms verfolgt nicht mehr lediglich palliative Ziele. Die Resektion von Metastasen ist zentraler Bestandteil des kurativen Konzeptes, da für bis zu 25 % der Patienten mit hepatischen und oder pulmonale Metastasen die Möglichkeit einer kurativen Behandlung durch Operation (R0-Resektion) oder andere lokale Therapieverfahren besteht. Patienten mit operablen Leber- oder Lungenmetastasen erreichen in bis zu 50

% der Fälle ein krankheitsfreies Fünfjahresüberleben. In Einzelfällen profitieren auch Patienten mit anderen Metastasenlokalisationen von lokalen Therapieansätzen.

Zu den lokalen Therapieverfahren zählen neben der Operation:

- Radiofrequenzablation (RFA) [920], [921]
- Selective interne Radiotherapie (SIRT) [922]
- Transarterielle Radioembolisation (TARE) [923]
- Sterotaktische Body Radio-Therapie (SRBT) [924]
- Transarterielle Chemoembolisation (TACE) [925]
- Hepatisch Intraarterielle Chemotherapie (HIA) [926]

Setzt man den Behandlungswillen (partizipative Entscheidungsfindung) des Patienten voraus, sind die patientenbezogenen Parameter (wie Allgemeinzustand, Komorbiditäten, Lebenserwartung) für die Auswahl der Therapiekonzepte und -intensität entscheidend. Unter den tumorbezogenen Charakteristika kommt der molekularen Markerkonstellation und der Lokalisation des Primärtumors die größte Bedeutung zu. Vor diesem Hintergrund der Patienten- und tumorspezifischen Faktoren sollten Patienten in der Erstlinientherapie die möglichst effektivste Therapie erhalten. Da pro Therapielinie 25 – 30 % der Patienten die nächste Therapielinien nicht mehr erreichen können, sollten wirksame Medikamente in der Erstlinientherapie nicht zurückgehalten werden.

Fluorouracil (FU)-haltige Therapieschemata sind die Grundlage für die Behandlung des kolorektalen Karzinoms. Das Risiko schwerer Nebenwirkungen unter einer FU-haltigen Therapie liegt in bis zu 9 % der kaukasischen Patienten an genetischen Varianten der Dihydropyrimidin-Dehydrogenase (DPD), einem für den Abbau von FU verantwortlichen Enzym. Eine Testung auf das Vorliegen der vier häufigsten, genetischen DPYD Varianten (DPYD*2A, DPYD*13, Polymorphismus c.2846A>T (rs67376798) und HaplotypB3) ist obligat. Das Ergebnis der genetischen Analyse ist Basis eines differenzierte Dosisanpassung des FU [919].

Eine UGT1A1-Genotypisierung kann hilfreich sein, um Patienten mit einem erhöhten Risiko für schwere Neutropenien und Durchfälle unter Irinotecan zu identifizieren. Patienten, die langsame UGT1A1-Metabolisierer sind (z. B. homozygot für UGT1A1*28-oder *6-Varianten, wie beim Gilbert-Syndrom), haben nach einer Behandlung mit Irinotecan ein erhöhtes Risiko für schwere Neutropenie und Durchfall. Dieses Risiko steigt mit der Dosis von Irinotecan. Eine geringere Irinotecan-Anfangsdosis sollte bei Patienten mit verringerter UGT1A1-Aktivität in Betracht gezogen werden. Dies gilt insbesondere für Patienten, denen Dosen von über 180 mg/m2 verabreicht werden, oder die geschwächt sind. Bei guter Verträglichkeit können nachfolgende Dosen erhöht werden [927].

Aktuelle Versorgungsstudien haben gezeigt, dass eine Behandlung in zertifizierten Zentren zu einer besseren Überlebensrate beitragen kann [928].

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10.2 Resektable Metastasierung

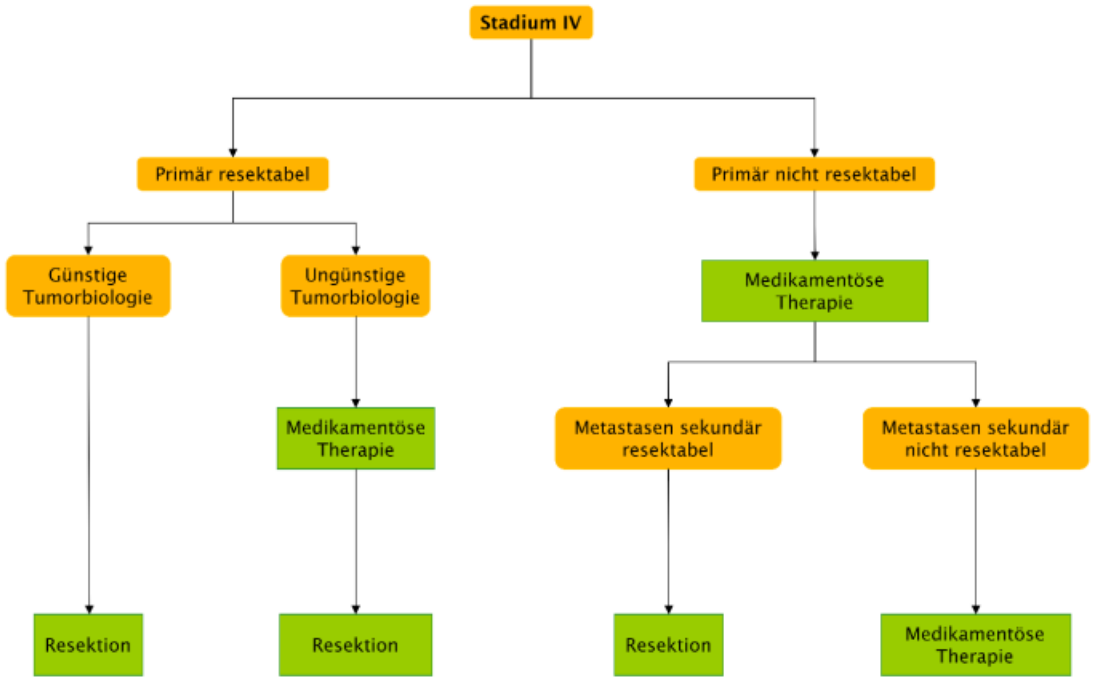

Abbildung 8: Flowchart zu Kapitel 10.2 Resektable Metastasierung

10.8	Konsensbasiertes Statement	neu 2025
EK	Bei primär resektabler Metastasierung (inklusive Oligometastasierung) ist die Anwendung lokaler Therapieverfahren zu prüfen. Neben einer Operation sind andere lokalen Therapieverfahren zu berücksichtigen.	
	Starker Konsens	

10.9	Konsensbasierte Empfehlung	neu 2025
EK	Die Beurteilung der Resektabilität oder des Einsatzes anderer lokaler Therapieverfahren soll unter Beteiligung eines in der Metastasenchirurgie erfahrenen Chirurgen bzw. in der Anwendung lokaler Therapieverfahren (SRBT, thermoablative Verfahren, TACE, intraarterielle CTx) erfahrenen Therapeuten erfolgen.	
	Starker Konsens	

10.10	Konsensbasierte Empfehlung	neu 2025
EK	Eine neoadjuvante Therapie von primär resektablen Lebermetastasen kann insbesondere bei prognostisch ungünstiger Tumorbiologie (z. B. kurzes krankheitsfreies Intervall oder synchrone Metastasierung, Anzahl und Lokalisation der Metastasen etc.) erfolgen. Kann durch diese systemische Therapie eine Stabilisierung der Erkrankung erreicht werden, so sollte die Resektion möglichst zeitnah (d. h. nach 2 – 3 Monaten Therapie) angestrebt werden.	
	Starker Konsens	

10.11	Konsensbasierte Empfehlung	neu 2025
EK	Der Stellenwert einer adjuvanten/additiven medikamentösen Therapie nach Lebermetastastenresektion/-ablation ist nicht gesichert.	
	Starker Konsens	

10.3 Nicht resektable Metastasen

10.12	Evidenzbasierte Empfehlung	neu 2025
Empfehlungsgrad A	Die Resektion eines asymptomatischen Primärtumors (keine Stenosesymptomatik, keine klinisch relevanten Blutungen) bei Patienten mit inoperabler metastasierter Erkrankung soll nicht erfolgen.	
Level of Evidence 1b	[638]	
	Starker Konsens	

Hintergrund

Im Rahmen der kombinierten Analyse der Synchronous und der CCRe-IV Studie wurden insgesamt 393 Patienten mit nicht synchronen resektablen Metastasen randomisiert. Die Patienten erhielten entweder primär eine Chemotherapie (n=206) oder eine

Resektion des Primärtumors gefolgt von einer medikamentösen Therapie. Die Resektion des Primärtumors konnte das Gesamtüberleben nicht verbessern. Eine Ausnahme stellen blutende Primärtumoren dar. Bei

mechanischem Ileus kann neben der Resektion des Primärtumors auch die Anlage eines Stomas sinnvoll sein [638].

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10.3.1 Patienten in gutem Allgemeinzustand

10.13	Evidenzbasierte Empfehlung	geprüft 2026
Empfehlungsgrad **A**	Patienten mit metastasierter Erkrankung und dMMR/MSI-H-Status sollen eine Checkpoint-Inhibitor-Therapie erhalten.	
Level of Evidence **2**	[658], [935], [936], [937]	
	Starker Konsens	

10.14	Konsensbasierte Empfehlung	modifiziert 2025
EK	Patienten mit RAS-Wildtyp (RAS-wt) und BRAF-wt Erkrankung und linksseitiger Lokalisation des Primärtumors sollen in der Erstlinientherapie mit einer Chemotherapie-Doublette plus anti-EGFR-Therapie behandelt werden. Eine Triplette plus EGFR-AK sollte nicht gegeben werden. *Leitlinienadaptation* ASCO Guideline 2022, *siehe auch* Abbildung 9	
	Starker Konsens	

10.15	Evidenzbasierte Empfehlung	neu 2025
Empfehlungsgrad **A/B**	Patienten mit RAS-Wildtyp (RAS-wt), BRAFwt Erkrankung und rechtsseitiger Lokalisation des Primärtumors sollen in der Erstlinientherapie präferentiell mit einer Chemotherapie-Doublette plus anti-VEGF Therapie behandelt werden. Eine Doublette oder Triplette plus EGFR-AK sollte nicht gegeben werden. In Einzelfällen kann eine Triplette plus anti-VEGF Therapie zum Einsatz kommen. Leitlinienadaptation ASCO Guideline 2022	
Level of Evidence ⊕⊕⊕⊖	[938]	
	Starker Konsens	

10.16	Evidenzbasierte Empfehlung	neu 2025
Empfehlungsgrad A	Patienten mit RAS-mutierter (RAS-mut) Erkrankung unabhängig von der Lokalisation des Primärtumors sollen in der Erstlinientherapie präferentiell mit einer Chemotherapie-Doublette oder Triplette +/- Bevacizumab behandelt werden. *Leitlinienadaptation* ASCO Guideline 2022	
Level of Evidence ⊕⊕⊕⊖	[938]	
	Starker Konsens	

10.17	Evidenzbasierte Empfehlung	modifiziert 2026
Empfehlungsgrad B	Patienten mit BRAF-V600E-Mutation sollten in der Erstlinie eine Therapie mit FOLFOX + Encorafenib + Cetuximab erhalten.	
Level of Evidence 2	[939]	
	Starker Konsens	

Hintergrund

Empfehlung 10.13: MSI-H bzw. dMMR mKRK

MSI-H oder dMMR ist bei etwa 4 % der Patienten mit fortgeschrittenem kolorektalem Karzinom (KRK) vorhanden.

In der Keynote-177 (randomisierte kontrollierte Studie) wurde in der Erstlinie Pembrolizumab im Vergleich zu FOLFOX mit oder ohne Bevacizumab oder FOLFIRI mit oder ohne Bevacizumab oder Cetuximab bei 307 Patienten mit MSI-H oder dMMR mKRK untersucht. Das progressionsfreie Überleben (PFS) verbesserte sich nach einer medianen Nachbeobachtung von 32,4 Monaten signifikant mit Pembrolizumab (medianes PFS 16,5 vs. 8,2 Monate, HR, HR, 0,60, 95% KI, 0,45 bis 0,80) [658]. Allerdings betrug die Rate der initialen Krankheitsprogression im Pembrolizumab-Arm 29 %, verglichen mit 12 % im Chemotherapie-Arm.

Nach einer medianen Nachbeobachtung von 73,3 Monaten war die mediane Überlebenszeit unter Pembrolizumab verdoppelt (77,5 vs. 36,7 Monate, OS nach 5 Jahren 54,8 % mit Pembrolizumab vs. 44,2 % mit Chemotherapie, HR, 0,73, 95% KI, 0,53 bis 0,99) trotz eines Cross-over zu Pembrolizumab 62,3 % nach Progress im Kontrollarm. Die Toxizität war unter Pembrolizumab deutlich geringer (Grad 3-5 21,6 % vs. 67,1 %). Die häufigsten Nebenwirkungen unter Pembrolizumab waren Diarrhoen (alle Schweregrade 24,8 %) und Fatigue (20,3 %) und die häufigsten immunologischen Nebenwirkungen Hypothyreose (10,5 %) und Colitis (5,2 %) [936],

Die Pembrolizumab-Monotherapie führte zu klinisch bedeutsamen Verbesserungen der gesundheitsbezogenen Lebensqualität im Vergleich zur Chemotherapie [658].

Günstige Ergebnisse für Checkpoint-Inhibitoren bei MSI-H bzw. dMMR mKRK zeigte auch die Phase-2-CheckMate-142-Studie für Nivolumab plus niedrig dosiertes Ipilimumab bei 45 Patienten in der Erstlinie. Die Ansprechrate betrug 69 %, die CR-Rate 13 % und 74 % der Responder waren nach einer medianen Nachbeobachtung von 29 Monaten noch rezidivfrei. [659].

In der nachfolgenden 3-armigen Phase 3-Studie CheckMate 8HW wurde bei Patienten mit MSI-H bzw. dMMR mKRK Nivolumab (240 mg alle 3 Wochen, ab der 5. Dosis 480 mg alle 4 Wochen) plus Ipilimumab (1 mg/kg alle 3 Wochen für 4 Dosen) vs. Nivolumab mono (240 mg alle 2 Wochen für 6 Dosen, danach 480 mg alle 4 Wochen) vs. Chemotherapie mit oder ohne EGFR- oder VGFR-Antikörper 2:2:1 verglichen. Primärer Endpunkt war das PFS. Eine Besonderheit der Studie war, dass der MSI-H bzw. dMMR-Status zentral nachuntersucht wurde. Die erste publizierte Auswertung betraf den Ver-gleich von Nivolumab/Ipilimumab (n=354) vs. Nivolumab mono (n=353) und beinhaltete sowohl Patienten ohne als auch mit Vortherapien. Bei 18 % der Patienten konnte der MSI-H bzw. dMMR-Status zentral nicht bestätigt werden. Nach einer medianen Nachbeobachtung von 47,0 Monaten zeigte die Kombination mit Ipilimumab ein längeres PFS im Vergleich zu Nivolumab mono (alle randomisierten Patienten: medianes PFS 54,1 vs. 18,4 Monate, HR 0,64 (95%KI 0,52-0,79), nur zentral bestätigte MSI-H bzw. dMMR-Status: medianes PFS nicht erreicht vs. 39,3 Monate, HR 0,62 (95%KI 0,48 – 0,81)). Der Unterschied war aber nur für letztere signifikant (p=0,0003). Die Toxizität war höher im Kombinationsarm (Grad 3-4 22 % vs. 14 %) [935].

Zusätzlich wurde im Rahmen der CheckMate 8HW in der Erstlinientherapie die Kombi-nation aus Nivolumab und Ipilimumab mit einer primären Chemotherapie untersucht [940]. 303 Patienten wurden randomisiert, von denen bei 255 Patienten (84 %) der MSI-H bzw. dMMR-Status zentral bestätigt wurde. In der Gruppe mit zentral bestätigter MSI-H bzw. dMMR-Status betrug nach einem medianen Follow-up von 31,5 Monaten das mediane PFS in der Kombinationstherapiegruppe nicht erreicht vs. 5,9 Monate in der Chemotherapiegruppe, p<0,001. Das mediane PFS nach 1 Jahr betrug 79 % (95%KI 72-84) vs. 21 % (95 KI 11-32), nach 2 Jahren 72 % (95% KI 64-79) vs. 14 (95% KI 6-25). Die Grad 3-4 Toxizität betrug 23 % in der Immuntherapiegruppe vs. 48 % in der Chemotherapiegruppe. In der Immuntherapiegruppe zeigte die Lebensqualität ab Woche 13 eine Verbesserung, in der Chemotherapie blieb die Lebensqualität stabil bis Woche 29 und nahmen dann ab.

Somit zeigen sowohl die Keynote-177 als auch die Checkmate 8HW-Studie eindrucks-voll eine klare Überlegenheit für die Immuntherapie im Vergleich zur Chemotherapie für metastasierte KRK Patienten mit MSI-H bzw. dMMR-Tumoren. Die Kombination aus Nivolumab und Ipilimumab scheint der Monotherapie mit Nivolumab überlegen, geht aber mit einer höheren Nebenwirkungsrate einher. Gleichzeitig zeigt die 8HW-Studie, wie wichtig eine qualitätsgesicherte Untersuchung des MSI-H bzw. dMMR-Status ist. Empfehlung 10.14 und 10.15: mKRK mit RAS-wt und BRAF-wt

Patienten mit linksseitigen Primärtumoren und RAS-wt profitieren signifikant von einer Erstlinientherapie mit Anti-EGFR-Antikörpern und Kombinationschemotherapie, während bei Patienten mit rechtsseitigen Primärtumoren und RAS-wt kein Vorteil dieser Therapie festgestellt wurde.

Für die Erstlinientherapie bei Patienten mit RAS-Wildtyp (RASwt) zeigen die Metaanalyse von Ciliberto et al. und die in den Einzelstudien erzielten Ergebnissen den signifikanten Nutzen von Anti-EGFR-Antikörpern (Panitumumab und Cetuximab) in Kombination mit Doublet-Chemotherapie im Vergleich zur alleinigen Doublet-Chemotherapie oder der Kombination mit Anti-VEGF-Antikörpern (Bevacizumab). Dies trifft insbesondere für linksseitige Tumoren zu. Diese Therapie führt zu einem verbesserten Ge-samtüberleben (OS) (HR, 0,71; 95% KI, 0,58 bis 0,85). Bei rechtsseitigen Tumoren ergab sich hingegen kein signifikanter Vorteil für das OS (HR 1,35; 95% KI, 1,0 bis 1,8) [941].

<u>Empfehlung 10.16: mKRK mit aktivierender RAS-Mutation</u>

Patienten mit nachgewiesenen Mutationen in den RAS-Genen (KRAS Exon 2-4 und NRAS Exon 2 – 4) sollten nicht mit Anti-EGFR-Antikörpern behandelt werden, da sie keinen Nutzen daraus ziehen. Der Stellenwert der Hinzunahme von Bevacizumab zu einer Doublette oder Triplette bei Vorliegen einen RAS Mutation ist nicht eindeutig klar, da die meisten Studien bei einem Mischkollektiv von Patienten mit oder ohne RAS Mutation durchgeführt wurden. Diese Studien hatten zwar einen Vorteil im PFS, aber keinen im OS ergeben [942].

Die einzige randomisierte Studie zu diesem Thema ist die BECOME Phase 2 Studie aus China, in der 241 Patienten mit RAS mutierter Erkrankung und isolierten Lebermeta-stasen mit FOLFOX allein oder in Kombination mit Bevacizumab behandelt wurden. Die RR der mit Bevacizumab behandelten Pateinten war signifikant höher (55 vs. 37 %, p<0.001), das PFS mit 9.5 vs. 5.6 Monaten (Median p<0-001) und auch das OS mit 26 vs. 21 Monaten (Median, p= 0.03). Außerdem war die R0 Resektionsrate mit 22 vs. 6 % signifikant (P<0.001) erhöht [943].

Zusammenfassend zeigen diese Ergebnisse und Analysen, dass die Behandlung von mKRK unter Berücksichtigung des RAS-Status des Patienten und der Tumorlokalisation personalisiert werden muss, um den größtmöglichen Nutzen zu erzielen. Die Verwendung von Anti-EGFR-Antikörpern in der Erstlinientherapie bietet signifikante Vorteile für Patienten mit linksseitigen RASwt mKRK.

Empfehlung 10.17: mKRK und aktivierende BRAF-Mutation

Die Empfehlung zur Erstlinientherapie bei Patienten mit BRAF-Mutation leitet sich aus den Ergebnissen der BREAKWATER-Studie ab [939]. In dieser randomisierten Studie wurde bei Patienten mit BRAF-V600E-Mutation als Erstlinientherapie eine Kombination aus mFOLFOX6 mit Encorafenib und Cetuximab mit einer Standardtherapie bestehend aus Chemotherapie +/- Bevacizumab verglichen. Das mediane progressionsfreie Über-leben betrug nach einem medianen Follow-up von 16,8 Monate in der Gruppe mit mFOFOLX6, Encorafenib und Cetuximab 12,8 Monate (95%KI 11,2-15,9) versus 7,1 Monate (95% KI 6,8-8,5) in der Standardtherapiegruppe mit einer Hazard-Ratio von 0,53 (95% KI 0,41-0,68; p<0,001). Das mediane Gesamtüberleben betrug 30,3 Monate (95%KI 21,7-nicht erreicht) vs. 15,1 Monate (95%KI 13,7-17,7) mit einer Hazard-Ratio von 0,49 (95%KI 0,38-0,63; p<0,001). Höhergradige Nebenwirkungen (Grad 3/4) traten bei 46,1 % der Patienten unter mFOLFOX6 mit Encorafenib und Cetuximab und 38,9 % in der Standardtherapiegruppe auf. Die Ergebnisse zeigten somit eine hoch signifikante Verbesserung sowohl für das progressionsfreie als auch das Gesamtüber-leben für die Kombination aus mFOLFOX6 mit Encorafenib und Cetuximab im Ver-gleich zu dem bisherigen Standard in Form einer Chemotherapie +/- Bevacizumab.

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10.3.2 Patienten in reduziertem Allgemeinzustand

10.18	Konsensbasierte Empfehlung	modifiziert 2025
EK	Bei herabgesetztem Allgemeinzustand können in Abwägung zu Best-Supportiv-Care Fluoropyrimidine als Monotherapie (5-Fluorouracil/Folinsäure oder Capecitabine) oder in Kombination mit Bevacizumab eingesetzt werden. Bei RAS-wt Patienten können auch EGFR-AK als Monotherapie zum Einsatz kommen. Auch Doubletten in reduzierter Dosis können eingesetzt werden.	
	Starker Konsens	

Hintergrund

Ein herabgesetzter Allgemeinzustand ist nicht klar definiert, es sei denn, man orientiert sich ausschließlich am ECOG oder Karnofsky-Index. Grundsätzlich sollte man zwischen einem (ausschließlich) durch die Tumorerkrankung reduziertem und einem überwiegend durch Ko-Morbiditäten reduziertem AZ unterscheiden. Dadurch ist dies auch in hohem Maße eine klinische Entscheidung. Bei überwiegend (auschließlich) durch die Tumorerkrankung reduziertem AZ kann auch (gerade) bei einem ECOG 3 eine intensive medikamentöse Therapie indiziert sein.

Die AVEX-Studie evaluierte die Effektivität einer Kombination aus Capecitabin plus Bevacizumab bei älteren Patienten (≥ 70 Jahre) und verglich diese im Rahmen eines Phase III Designs mit einer Capecitabin Monotherapie. Überwiegend wurden Patienten mit einem Performance Status ECOG 0 (45 %) und ECOG 1 (45 %) eingeschlossen. Die Häufigkeit von Patienten mit ECOG ≥2 betrug unter 10 %. Als primärer Endpunkt wurde das PFS untersucht. Unter der Behandlung mit Capecitabin plus Bevacizumab wurde eine signifikante Verlängerung des PFS (9,1 vs. 5,1 Monate; HR 0,53, p<0,0001; primärer Studienendpunkt) sowie eine Steigerung der ORR (19 % vs. 10 %; p=0,04) erreicht. Das Gesamtüberleben (sekundärer Endpunkt) betrug 16,8 Monate im Kontrollarm und 20,7 Monate in der mit Capecitabin und Bevacizumab behandelten Gruppe ((HR 0,79, 95% KI 0,57–1,09; p=0,18), dieser Unterschied war nicht signifikant. Die Behandlung kann grundsätzlich als gut verträglich eingestuft werden. Die Häufigkeit schwerwiegender Nebenwirkungen (SAEs) lag unter der Capecitabin-Monotherapie bei 31 %, unter der Kombination von Capecitabin und Bevacizumab bei 30 %. Analysen der Lebensqualität wurden nicht durchgeführt.

Diese Daten werden durch eine randomisierte Phase II Studie unterstützt, die bei Patienten durchgeführt wurde, die für eine Erstlinientherapie mit Irinotecan nicht in Betracht kamen. Auch in dieser Studie lag die Häufigkeit der Patienten mit ECOG 2 unterhalb von 10 %. In dieser Population wurde Bevacizumab plus 5-FU/LV mit einer alleinigen 5-FU/LV-Behandlung verglichen. Die Zugabe von Bevacizumab zu 5-FU/LV induzierte eine signifikante Steigerung des PFS (9,2 vs. 5,5 Monate; HR 0.50, p=0.0002) sowie eine nicht signifikante Steigerung des OS (16,6 vs. 12,9 Monate; HR 0.79, p=0.16) und der ORR (26,0 % vs. 15,2 %, p=0.055). Die Evaluation des FACT-C Scores zeigte keinen negativen Effekt von Bevacizumab auf die Lebensqualität (QOL). Die mediane Zeit bis zur Verschlechterung der Lebensqualität lag im Bevacizumab-Arm bei 3,2 Monaten und im Placebo-Arm bei 2,3 Monaten (HR 0,66; p=0,016) [944].

Kleinere Phase II Studien ergaben eine Ansprechrate von 10 % und eine stabile Erkrankung von 34 – 58 % auf eine Cetuximab Monotherapie in zum Teil unselektioniertem Kollektiv [945].

Zusammengefasst weisen diese Studienergebnisse darauf hin, dass die Erstlinien-Chemotherapie mit einem Fluoropyrimidin und Bevcizumab bei älteren Patienten und solchen, die für eine initiale Irinotecan-basierte Therapie nicht geeignet waren, effektiv ist und damit für diese Patientenpopulation eine sinnvolle Behandlungsoption darstellt. Außerdem scheint eine Cetuximab Monotherapie in Einzelfällen eine Option darzustellen.

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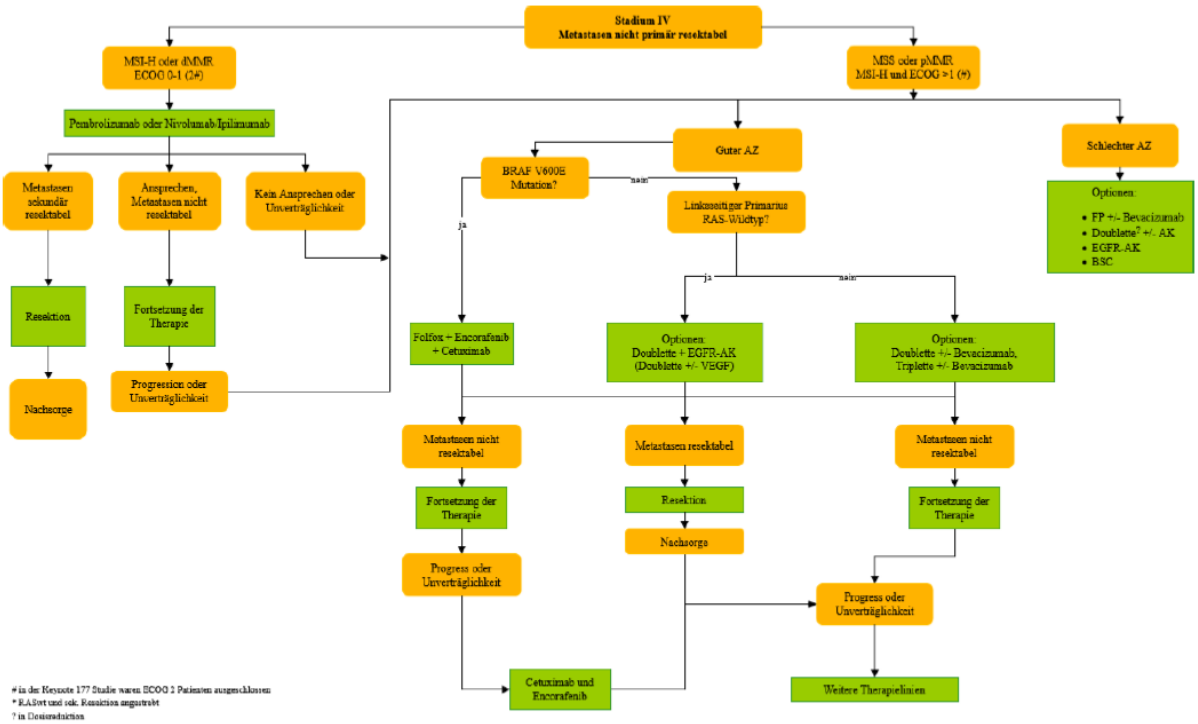

Abbildung 9: Flowchart zu Kapitel 10.3 Nicht resektable Metastasen

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Morris VK et al., 2023 [6].

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

<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
- Keine Konsensusprozesse angewendet, 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, trifft zu.

<u>Recherche/Suchzeitraum:</u>

- 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

Question 1:

For patients with previously untreated, initially unresectable mCRC who are candidates for chemotherapy plus bevacizumab, is doublet (FOLFOX or FOLFIRI) or triplet (FOLFOXIRI) cytotoxic chemotherapy recommended?

Recommendation 1.1.—Doublet (FOLFOX or FOLFIRI) backbone chemotherapy should be offered as first-line therapy to patients with initially unresectable MSS or 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 FOLFOX at the clinical discretion of the treating provider, and in shared decision making with the patient.

Recommendation 1.2.—Triplet (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.

Hintergrund Question 1: Literature review and analysis

One systematic review with meta-analysis of five phase II or III RCTs[25-30] comparing doublet chemotherapy (FOLFIRI or FOLFOX) to triplet chemotherapy (FOLFOXIRI) met the inclusion criteria.[7] In four of five studies and 74% of patients, doublet chemotherapy consisted of FOLFOX, with the remaining control arm patients receiving FOLFIRI. The duration of induction chemotherapy ranged from 4 to 6 months, and was followed by maintenance with a fluoropyrimidine (FU or capecitabine) plus bevacizumab until disease progression, patient refusal, unacceptable adverse events, or withdrawal of consent. OS (HR, 0.81; 95% CI, 0.72 to 0.91), PFS (HR, 0.74; 95% CI, 0.67 to 0.82), and objective response rate (ORR; odds ratio, 1.57; 95% CI, 1.29 to 1.91) were significantly improved in the triplet chemotherapy group, compared with doublet chemotherapy. Adverse events including diarrhea, neurotoxicity, and neutropenia were significantly more likely with triplet chemotherapy, although in a subgroup analysis, the rate of neurotoxicity did not differ between groups of patients treated with FOLFOXIRI versus FOLFOX.

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Question 2:

a. In the first-line setting, are outcomes for patients with MSI-H or dMMR mCRC improved with pembrolizumab immunotherapy versus chemotherapy with or without bevacizumab or cetuximab?

b. […]

Recommendation 2.1. Pembrolizumab should be offered as first-line therapy to patients with MSI-H or dMMR mCRC (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Hintergrund Question 2:

Literature review and analysis. Keynote-177 is a phase III RCT of pembrolizumab compared with FOLFOX with or without bevacizumab, or FOLFIRI with or without bevacizumab or cetuximab, in patients with MSI-H or dMMR mCRC. PFS was significantly improved with pembrolizumab (HR, 0.60; 95% CI, 0.45 to 0.80), while there was no significant difference between arms for overall response rate (RR, 1.32; 95% CI, 0.99 to 1.76). Grade 3 or greater adverse events were significantly lower in the pembrolizumab arm (Table 2).[12] OS results reported in a subsequent abstract showed no significant difference between treatment and control groups (HR, 0.74; 95% CI, 0.53 to 1.03).[34]

Referenzen

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Question 3:

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

Recommendation 3.1.—Anti-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).

Hintergrund Question 3: Literature review and analysis

Anti-EGFR antibodies plus doublet chemotherapy compared with doublet chemotherapy in RAS wild-type right-sided or left-sided mCRC.

The meta-analysis by Ciliberto et al found a significant benefit in terms of OS and PFS for anti-EGFR antibodies (ie, panitumumab and cetuximab) plus chemotherapy compared with chemotherapy alone as first-line therapy for RAS wildtype mCRC (Data Supplement).[13] When the results were stratified by tumor side in post hoc subgroup analyses, the OS and PFS results remained significant for left-sided tumors only. Grade 3-4 adverse events, including skin toxicity and rash, were more likely with anti-EGFR antibodies plus doublet chemotherapy versus chemotherapy alone (Table 3).

Anti-EGFR antibodies plus doublet chemotherapy compared with anti-VEGF antibodies plus doublet chemotherapy in RAS wild-type right-sided or left-sided mCRC.

In the included meta-analysis,[13] anti-EGFR antibodies significantly improved OS, compared with chemotherapy plus bevacizumab for left-sided and right-sided patients combined. For PFS, there was considerable heterogeneity, which was potentially attributable to the variety of agents used in the treatment and control groups (Data Supplement).

In patients with left-sided tumors, treatment with anti-EGFR therapy resulted in a significantly better OS (HR, 0.71; 95% CI, 0.58 to 0.85), while the HR for OS in rightsided tumors was 1.35 (95% CI, 1.0 to 1.8). PFS for leftsided tumors nonsignificantly favored chemotherapy plus anti-EGFR, compared with chemotherapy plus bevacizumab (HR, 0.86; 95% CI, 0.73 to 1.02), while PFS for right-sided tumors was more favorable with the chemotherapy plus bevacizumab combination (HR, 1.53; 95% CI, 1.16 to 2.01; Table 4).

There was a similar likelihood of grade 3-4 adverse events in the chemotherapy plus anti-EGFR versus chemotherapy plus bevacizumab groups (Table 4). In a network meta-analysis, Ciliberto et al[13] found that the combination of chemotherapy plus cetuximab was most likely to induce a grade 3-4 adverse event, compared with other treatment combinations.

In the PARADIGM trial, authors reported a significant benefit for OS (HR, 0.82; 95.798% CI, 0.68 to 0.99) and ORR (HR, 1.17; 95% CI, 1.06 to 1.29), although no benefit in PFS (HR, 0.98; 95% CI, 0.82 to 1.17), and no difference in rate of grade 3 or greater adverse with panitumumab plus FOLFOX versus bevacizumab plus FOLFOX in patients with left-sided primary tumors (Data Supplement). In an exploratory analysis, the HR for OS in the right-sided RAS wild-type population of PARADIGM was 1.09 (95% CI, 0.79 to 1.51).[52]

Anti-EGFR antibodies plus triplet chemotherapy compared with triplet chemotherapy in RAS wild-type mCRC. In a small phase II RCT, investigators found a significantly improved investigator-assessed ORR for patients treated with panitumumab plus triplet chemotherapy, compared with triplet chemotherapy alone; however, there was no significant difference in PFS or OS, and a higher incidence of grade 3 or greater adverse events in the panitumumab plus triplet chemotherapy group (Data Supplement).[14]

Anti-EGFR antibodies plus triplet chemotherapy compared with anti-EGFR antibodies plus doublet chemotherapy in RAS wild-type mCRC.

Data from a phase III RCT of triplet chemotherapy plus panitumumab versus doublet chemotherapy plus panitumumab showed that the ORR and PFS were not significantly different between groups, and the triplet chemotherapy group experienced more gastrointestinal adverse events (Data Supplement).[15]

Referenzen

13 Ciliberto D, Staropoli N, Caglioti F, et al: The best strategy for RAS wild-type metastatic colorectal cancer patients in first-line treatment: A classic and Bayesian meta-analysis. Crit Rev Oncol Hematol 125:69-77, 2018

14 Modest DP, Martens UM, Riera-Knorrenschild J, et al: FOLFOXIRI plus panitumumab as first-line treatment of RAS wild-type metastatic colorectal cancer: The randomized, open-label, phase II VOLFI study (AIO KRK0109). J Clin Oncol 37:3401-3411, 2019

15 Rossini D, Antoniotti C, Lonardi S, et al: Upfront modified fluorouracil, leucovorin, oxaliplatin, and irinotecan plus panitumumab versus fluorouracil, leucovorin, and oxaliplatin plus panitumumab for patients

with RAS/BRAF wild-type metastatic colorectal cancer: The phase III TRIPLETE study by GONO. J Clin Oncol 40: 2878-2888, 2022
52 Muro K, Watanabe J, Shitara K, et al: LBA 0-10; First Line Panitumumab Versus Bevacizumab in Combination With mFOLFOX6 for RAS Wild Type Metastatic Colorectal Cancer: PARADIGM Trial Results. Barcelona, Spain, European Society for Medical Oncology World Congress on Gastrointestinal Cancer, 2022

Question 5:

For patients with colorectal peritoneal metastases, are outcomes improved with CRS with or without HIPEC plus chemotherapy, compared with chemotherapy alone?

Recommendation 5.1.—CRS plus systemic chemotherapy may be recommended for selected patients with colorectal peritoneal metastases (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak).

Qualifying statements.

- In the PRODIGE 7 trial, 15% of patients with isolated colorectal peritoneal metastases experienced no disease progression in the 5 years following surgery, indicating that CRS may be a curative option for an appropriately selected subgroup of patients.
- This recommendation applies to patients who have been deemed amenable to complete resection of colorectal peritoneal metastases, regardless of previous treatment, and who have no extraperitoneal metastases.
- Complete macroscopic cytoreduction was achieved in 91% of patients in the PRODIGE 7 trial, which is attributed to the majority of patients undergoing CRS at centers with substantial clinical experience.[8] CRS should be considered as a treatment option only within these specialized centers.
- Multidisciplinary team (MDT) management is recommended for patients with mCRC who are considered candidates for CRS. The MDT should include expertise in medical oncology, surgical oncology, radiology, and pathology.
- Shared decision making should include a discussion of the potential impact on quality of life and rate of adverse events associated with CRS (Table 5).

Referenzen

8 Quénet F, Elias D, Roca L, et al: Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal
peritoneal metastases (PRODIGE 7): A multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 22:256-266, 2021

Recommendation 5.2.—Oxaliplatin-based HIPEC is not recommended as an addition to CRS for treatment of patients with colorectal peritoneal metastases (Type: Evidence-based, harms outweigh benefits; Evidence quality: Moderate; Strength of recommendation: Strong).

Question 6

For patients with unresectable liver-limited mCRC, are liver-directed therapies SBRT and SIRT recommended?

Recommendation 6.1.—SBRT may be recommended following systemic therapy for patients with oligometastases of the liver who are not considered candidates for resection (Type:

Evidence-based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Recommendation 6.2.—SIRT is not routinely recommended for patients with mCRC and unilobar or bilobar metastases of the liver (Type: Evidence-based, harms outweigh benefits; Evidence quality: Low; Strength of recommendation: Weak).

Qualifying statement for Recommendations 6.1 and 6.2.: MDT management is required for patients with mCRC who are considered candidates for SBRT or SIRT. The MDT should include expertise in medical oncology, radiation oncology, hepatobiliary surgery, and radiology.

Question 7

For patients with mCRC and potentially curable oligometastatic liver metastases, is perioperative chemotherapy recommended?

Recommendation 7.1.—Surgery with or without perioperative chemotherapy should be offered to patients with mCRC who are candidates for potentially curative resection of liver metastases (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak).

Qualifying statements.

- Perioperative chemotherapy may be more likely to be recommended over surgery alone in patients with a greater number of metastases or with larger tumors. Shared decision making, including discussion of the potential for benefits and risks of harm outlined in Table 10, is recommended.
- The choice of perioperative chemotherapy or surgery alone, and coordination of treatment sequencing, should be discussed within a MDT that includes expertise in medical oncology and hepatobiliary surgery.
- Perioperative chemotherapy is recommended for a total preoperative and postoperative duration of 6 months, on the basis of total duration of chemotherapy in the EORTC 40983 trial.[64]

Referenzen

64 Nordlinger B, Sorbye H, Glimelius B, et al: Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases fromcolorectal cancer (EORTC 40983): Long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol 14:1208-1215, 2013

Hintergrund Question 7: Literature review and analysis

[…]

Perioperative chemotherapy compared with surgery alone.

In the 364-person EORTC study, 94% and 79% of randomly assigned patients started and completed six cycles of preoperative chemotherapy, respectively. PFS was not significantly different for perioperative chemotherapy versus surgery alone in the intention-to-treat study population (HR, 0.79; 95% CI, 0.62 to 1.02); however, in an exploratory analysis of the 83% of randomly assigned patients who ultimately underwent surgery, the HR for PFS favored the perioperative chemotherapy group (HR, 0.73; 95%CI, 0.55 to 0.97). There was no significant difference in OS between groups, and reversible postoperative complications were more likely in the perioperative chemotherapy group (Table 10). The definition of reversible postoperative complications was not provided.

Hepatectomy plus postoperative FOLFOX compared with hepatectomy alone.

In the JCOG0603 study, OS was not significantly different for patients who received hepatectomy

plus postoperative FOLFOX, or hepatectomy alone (HR, 1.25; 95%CI, 0.78 to 2.0); however, for the primary outcome DFS, the HR was 0.67 (95% CI, 0.50 to 0.92), favoring the postoperative chemotherapy group.[23] Adverse events were more likely in the group that received FOLFOX, compared with surgery alone (Table 11). In this trial, there was an imbalance in postrecurrence interventions; the proportion of patients receiving oxaliplatin-based therapy was higher in the hepatectomy-only arm, and the proportion receiving irinotecanwas higher in the chemotherapy arm.

Single-agent chemotherapy (FU plus folinic acid) after potentially curative resection of metastases from CRC versus resection alone. There were no significant differences found in DFS or OS in a pooled univariate analysis of two trials of FU plus folinic acid following potentially curative resection of CRC metastases, compared with resection alone.[24] In a multivariate analysis controlling for number of metastases, previous adjuvant chemotherapy, and maximum size of metastases, DFS showed a significant benefit in favor of postoperative FU plus folinic acid (HR, 0.72; P 5 .026; Cis not provided). In a multivariate analysis controlling for number of metastases, disease-free interval, maximum size of metastases, andWHO performance status, the estimate of

the association of treatment group for OS also showed a significant benefit in favor of postoperative chemotherapy (HR, 0.72; P5.046; CIs not provided). Risk of recurrence or death was significantly elevated in patients with two or more metastases, compared with one metastasis

Referenzen

23 Kanemitsu Y, Shimizu Y, Mizusawa J, et al: Hepatectomy followed by mFOLFOX6 versus hepatectomy alone for liver-only metastatic colorectal cancer (JCOG0603): A phase II or III randomized controlled trial. J Clin Oncol 39:3789-3799, 2021

24 Mitry E, Fields AL, Bleiberg H, et al: Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: A pooled analysis of two randomized trials. J Clin Oncol 26:4906-4911, 2008

National Institute for Health and Care Excellence (NICE), 2021 [7].

Colorectal Cancer (NG151)

Zielsetzung/Fragestellung

This guideline covers managing colorectal (bowel) cancer in people aged 18 and over. It aims to improve quality of life and survival for adults with colorectal cancer through management of local disease and secondary tumours (metastatic disease).

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: Trifft zu (*Hinweis*: Last reviewed 27 August 2025 […] This guideline will be reviewed if there is new evidence that is likely to change the recommendations.).

Recherche/Suchzeitraum:

- 2025 exceptional surveillance of ovarian cancer: recognition and initial management, colorectal cancer, and oesophago-gastric cancer: assessment and management in adults (NICE guidelines CG122, NG151 and NG83): The study authors searched MEDLINE, EMBASE, Cochrane library, and the Science Citation Index, ClinicalTrials.gov, and WHO ICTRP trial registers up to 14 April 2022.
- 2020: Systematic literature searches were undertaken to identify published clinical evidence relevant to each review question. All searches were conducted in the following databases: Medline, Medline-in-Process, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessments (HTA) and Embase. For review questions related to information provision, PsycInfo, CINAHL and Web of Science were also searched. Web of Science was also used for the question about prevention of colorectal cancer; Searches were updated 6 to 8 weeks in advance of the final committee meetings

LoE/GoR

- GRADE

1.5 Management of advanced or metastatic colorectal cancer

Systemic anticancer therapy for untreated advanced or metastatic colorectal cancer

High MSI or MMR deficiency disease

1.5.1 Nivolumab with ipilimumab is recommended as an option in NICE technology appraisal guidance for untreated unresectable or metastatic colorectal cancer with high

microsatellite instability (MSI) or mismatch repair (MMR) deficiency. For full details, see the guidance on nivolumab plus ipilimumab (TA1065, 2025).

1.5.2 Pembrolizumab is recommended as an option in NICE technology appraisal guidance for untreated metastatic colorectal cancer with high MSI or MMR deficiency. It should be stopped after 2 years or earlier if disease progresses. For full details, see the guidance on pembrolizumab (TA709, 2021).

EGFR-expressing, RAS wild-type disease

1.5.3 Cetuximab is recommended as an option in NICE technology appraisal guidance for untreated epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer in combination with:

- 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX) or
- 5-fluorouracil, folinic acid and irinotecan (FOLFIRI).
- For full details, see the guidance on cetuximab (TA439, 2017).

RAS wild-type disease

1.5.4 Panitumumab is recommended as an option in NICE technology appraisal guidance for untreated RAS wild-type metastatic colorectal cancer in combination with:

- FOLFOX or
- FOLFIRI.

For full details, see the guidance on panitumumab (TA439, 2017).

Other systemic anticancer therapy for untreated disease

1.5.5 Bevacizumab (originator and biosimilars) with fluoropyrimidine-based chemotherapy is recommended as an option for untreated metastatic colorectal cancer when targeted treatments or immunotherapy are unsuitable, and chemotherapy would otherwise be offered. For full details, see NICE's technology appraisal guidance on bevacizumab (TA1136, 2026).

1.5.6 For medicines not recommended in NICE technology appraisal guidance for untreated metastatic colorectal cancer, see the guidance on:

- bevacizumab in combination with 5-fluorouracil plus folinic acid (TA118, 2012)
- bevacizumab in combination with oxaliplatin and either fluorouracil plus
- folinic acid or capecitabine (TA212, 2010).

People with an asymptomatic primary tumour

1.5.13 Consider surgical resection of the primary tumour for people with incurable metastatic colorectal cancer who are receiving systemic anticancer therapy and have an asymptomatic primary tumour. Discuss the implications of the treatment options with the person before making a shared decision (see table 2).

People with metastatic colorectal cancer in the liver

1.5.14 Consider resection, either simultaneous or sequential, after discussion by a multidisciplinary team with expertise in resection of disease in all involved sites.

1.5.15 Consider perioperative systemic anticancer therapy if liver resection is a suitable treatment.

1.5.16 Consider chemotherapy with local ablative techniques for people with colorectal liver metastases that are unsuitable for liver resection after discussion by a specialist multidisciplinary team.

1.5.17 Do not offer selective internal radiation therapy (SIRT) as first-line treatment for people with colorectal liver metastases that are unsuitable for local treatment. See the NICE interventional procedures guidance on selective internal radiation therapy for unresectable colorectal metastases in the liver, which recommends that SIRT should only be offered:

- with special arrangements for clinical governance, consent, and audit or research to people who are chemotherapy intolerant or who have liver metastases that are refractory to chemotherapy
- in the context of research to people who can have chemotherapy

People with metastatic colorectal cancer in the lung

1.5.18 Consider metastasectomy, ablation or stereotactic body radiation therapy for eople with lung metastases that are suitable for local treatment, after discussion by a multidisciplinary team that includes a thoracic surgeon and a specialist in non-surgical ablation.

1.5.19 Consider biopsy for people with a single lung lesion to exclude primary lung cancer.

People with metastatic colorectal cancer in the peritoneum

1.5.20 For people with colorectal cancer metastases limited to the peritoneum:

- offer systemic anticancer therapy, and
- within a multidisciplinary team, discuss referral to a nationally commissioned specialist centre to consider cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC).
- See also NICE's interventional procedures guidance on cytoreductive surgery with HIPEC for peritoneal carcinomatosis.

Alberta Health Services, 2021 [1].

Alberta Health Services (AHS)

Metastatic Colorectal Cancer, Version 14

Zielsetzung/Fragestellung

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

Methodik

Grundlage der Leitlinie

Update Version 14 (Juli 2025)

- Repräsentatives Gremium; trifft teilweise zu (*Hinweis*: Einbindung einer PV nicht klar dargestellt.).
- 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. (*Hinweis*: A formal review of the guideline will be conducted in 2026. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.)

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

Empfehlungen

1. Consider treatment on a clinical trial, if available.

2. Patients with a new diagnosis of metastatic disease (stage IV diagnosis) should receive testing for activating mutations of Ras (Kras and Nras), BRAF, and evaluation of microsatellite instability or mismatch repair deficiency in tumour tissue.

3. In the absence of relevant comorbid medical problems, patients with metastatic colorectal cancer and a performance status of ECOG 0, 1, or 2 should be offered palliative chemotherapy.

[…]

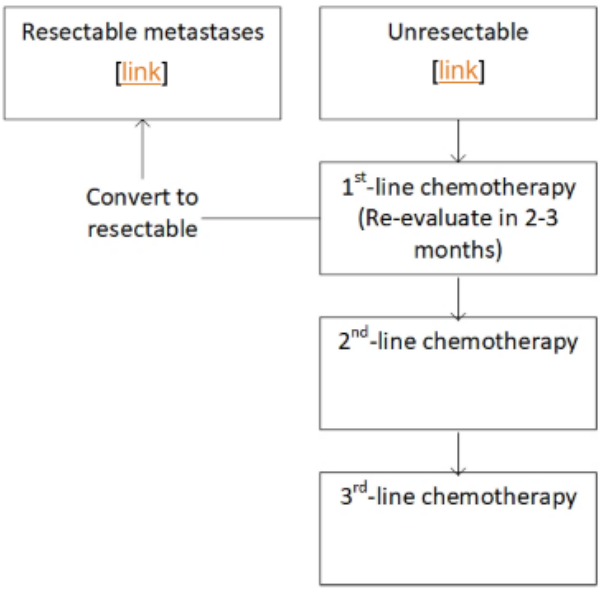

Figure 1. Algorithm for Metastatic Colorectal Cancer Treatment
Multidisciplinary discussion is encouraged. Resection may require multiple procedures. Liver resection may require portal vein embolization. SBRT may be considered.

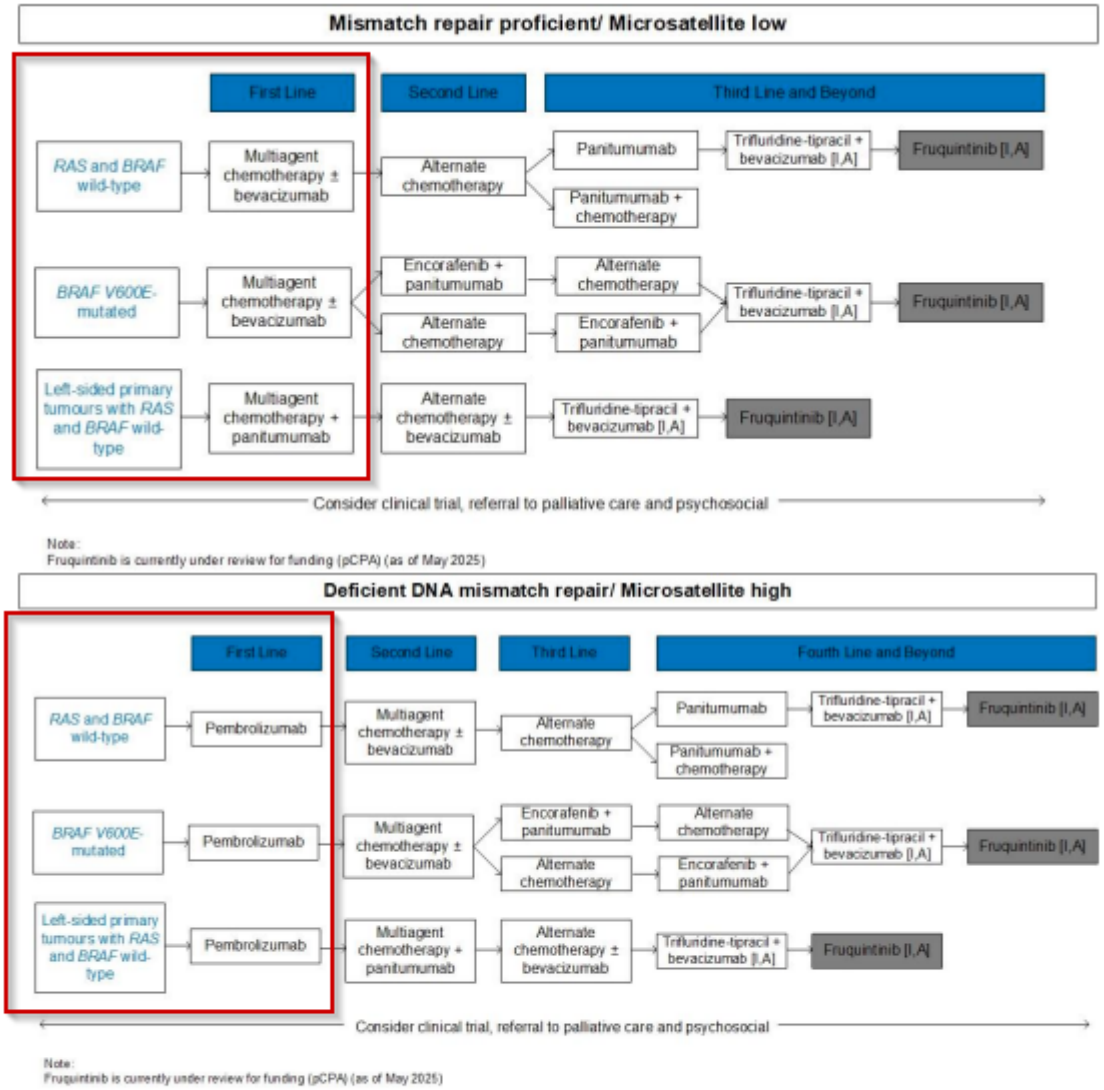

Figure 2. Systemic therapy options for Unresectable Metastatic Colorectal Cancer Consider an Early Palliative Approach to Care, More information: [Link]. Levels of evidence in square brackets defined [here]. For patients who are not suitable for multiagent chemotherapy, consider single agent fluoropyrimidine ± bevacizumab [link].

5. Standard palliative chemotherapy regimens to consider are described in **Table 2.**

6. Patients who present with resectable lung or liver metastasis should be discussed in multidisciplinary rounds (Refer to **Appendix A**). Patients that may proceed directly to metastatectomy for liver metastasis can be considered for perioperative FOLFOX4 chemotherapy delivered 3 months pre-hepatic resection and 3 months post-hepatic resection. The EORTC Intergroup trial 40983 demonstrated an improvement in PFS, but not necessarily overall survival. The 5-year OS in this trial was approximately 50%.[7] The addition of cetuximab to FOLFOX in this setting is not appropriate. For patients who have resection of liver metastases with no residual disease, the role of adjuvant chemotherapy is unclear. Postoperative oxaliplatin based chemotherapy for 6 months improved disease-free survival HR 0.67, 95% CI (0.50-0.92, one sided p = 0.006) but not overall survival HR 1.25 (0.78-2.00) two sided P=0.42 in JCOG 0603.[8]

7 Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a

randomised controlled trial. Lancet (London, England). 2008;371(9617):1007-1016. doi:10.1016/S0140-6736(08)60455-9 [doi]
8 Kanemitsu Y, Shimizu Y, Mizusawa J, et al. Hepatectomy Followed by mFOLFOX6 Versus Hepatectomy Alone for Liver-Only Metastatic Colorectal Cancer (JCOG0603): A Phase II or III Randomized Controlled Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 12/01/2021 2021;39(34)doi:10.1200/JCO.21.01032

The location of the tumour within the colon (proximal/distal) appears to be important. A multivariate analysis of 1,437,846 patients in sixty-six trials published between 1995 and 2016 demonstrated that the location of the primary tumor site in the distal (left-sided) (versus proximal or right-sided) colon is associated with a better survival (HR 0.82, CI95% 0.79-0.84, p < 0.001).[9] Beyond outcome, differences in epidemiology, pathogenesis, genetic and epigenetic alterations, and molecular pathways are now recognized between proximal and distal primary tumor sites:[10]

9 Petrelli F, Tomasello G, Borgonovo K, et al. Prognostic Survival Associated With Left-Sided vs Right-Sided Colon Cancer: A Systematic Review and Meta-analysis. JAMA oncology. 2017;3(2):211-219. doi:10.1001/jamaoncol.2016.4227 [doi]
10 Lee GH, Malietzis G, Askari A, Bernardo D, Al-Hassi HO, Clark SK. Is right-sided colon cancer different to left-sided colorectal cancer? - a systematic review. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2015;41(3):300-308. doi:10.1016/j.ejso.2014.11.001 [doi]

8. The PARADIGM trial demonstrated the superiority of panitumab versus bevacizumab in combination with FOLFOX in patients with left sided, advanced RAS wild type colorectal cancer (median OS 37.9 vs 34.3 months, HR = 0.82, 95.798% CI 0.68-0.99, p = 0.031).[11] Pooled retrospective analyses establish the predictive and prognostic value of primary tumor site using Cetuximab and Panitumumab.[12,13] In a retrospective evaluation of 38% of the 5,760 patients enrolled in the CRYSTAL, FIRE-3, PEAK, PRIME, 181, and CALGB 80405 studies (trials with different populations, control arms, treatments, etc.), primary tumor location confers both prognostic effect (outcomes are worse for disease that arises from the proximal colon, regardless of the treatment received) and predictive effect (first-line use of anti-EGFR therapy improves outcomes in RAS wild-type disease that arises from the distal colon but offers no benefit when disease arises from the proximal colon).[14] The Alberta Provincial Gastrointestinal Tumour Team supports the use of EGFR inhibitors in first-line treatment for patients with Ras wild-type, MSS/MMR proficient metastatic colorectal cancer (i.e. non-mutated Kras or Nras) with left sided primary tumors. Selection of first-line therapy should now consider the results of a rigorous molecular analysis as well as reference to the primary tumor location (in addition to patient preferences, extent of cancer, goals of care, mutations in RAS, medical comorbidities, performance status, etc.).

11 Yoshino T, Watanabe J, Shitara K, et al. Panitumumab (PAN) plus mFOLFOX6 versus bevacizumab (BEV) plus mFOLFOX6 as first-line treatment in patients with RAS wild-type (WT) metastatic colorectal cancer (mCRC): Results from the phase 3 PARADIGM trial. meeting-report. J Clin Oncol. 2022-06-08 2022;40(17_suppl)
12 Boeckx N, Koukakis R, Op de Beeck K, et al. Primary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer: results from two randomized first-line panitumumab studies. Annals of oncology : official journal of the European Society for Medical Oncology. 2017;28(8):1862-1868. doi:10.1093/annonc/mdx119 [doi]
13 Tejpar S, Stintzing S, Ciardiello F, et al. Prognostic and Predictive Relevance of Primary Tumor Location in Patients With RAS Wild-Type Metastatic Colorectal Cancer: Retrospective Analyses of the CRYSTAL and FIRE-3 Trials. JAMA oncology. 2017;3(2):194-201. doi:10.1001/jamaoncol.2016.3797 [doi]
14 Arnold D, Lueza B, Douillard JY, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Annals of oncology : official journal of the European Society for Medical Oncology. 2017;28(8):1713-1729. doi:10.1093/annonc/mdx175 [doi]

9. Mutations in Kras and Nras predict a lack of response in anti-Epidermal Growth Factor Receptor (EGFR) therapy in patients with metastatic colorectal cancer.[15] **Patients with known RAS mutations should not be treated with either cetuximab or panitumumab**.

> *a. Note:* The recommendation for RAS testing should not necessarily indicate a preference regarding regimen selection in the first-line setting. Rather, early identification of Ras status is intended to plan for the treatment continuum. […]

15 Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. The New England journal of medicine. 2013;369(11):1023-1034. doi:10.1056/NEJMoa1305275; 10.1056/NEJMoa1305275

10. Patients with BRAF V600E mutated metastatic colorectal cancer represent a distinct group of patients who have a poor prognosis and are typically resistant to traditional doublet chemotherapy regimens. The individual patient data meta-analysis of 5 trials compared FOLFOXIRI + bevacizumab versus doublet chemotherapy + bevacizumab, including n=115 patients with BRAF mutations. FOLFOXIRI + bevacizumab had increased response rates for patients with BRAF mutations. This regimen is associated with increased neutropenia, febrile neutropenia, and diarrhea. There was no significant improvement in OS or PFS with FOLFOXIRI + bevacizumab compared to doublet chemotherapy + bevacizumab.[18] In select patients with BRAF mutations, FOLFOXIRI + bevacizumab may be considered. For patients who have progressed on first or second line treatments (i.e. those that have been exposed to both irinotecan and oxaliplatin), the combination of BRAF, MEK and EGFR inhibition appears to be effective. The phase III open-label BEACON trial studied 665 patients with BRAF V600E mutated metastatic colorectal cancer [Level I]. Patients had progressed on 1 or 2 prior treatments.[19] They were randomized to encorafenib, binimetinib and cetuximab, encorafenib and cetuximab or dealer's choice of irinotecan+ cetuximab or FOLFIRI plus cetuximab (argued to be the standard treatment). The analysis was powered to compare the triplet regimen against the standard treatment arm. In an updated overall survival analysis, median OS was similar in patients treated with encorafenib + cetuximab with or without binimetinib (9.3 mo and 9.3 mo, respectively). Median OS in the standard treatment arm was 5.9 mo. Treatment with encorafenib + cetuximab with or without binimetinib was associated with longer maintenance of quality of life across different QOL assessment tools compared to the standard arm.[19] In Alberta, encorafenib is administered with panitumumab. pERC and clinical experts noted that concurrent administration with panitumumab instead of cetuximab would lead to less frequent chemotherapy sessions, and it is expected that patients who receive encorafenib in combination with panitumumab would respond similarly to patients treated with cetuximab.

18 Cremolini C, Loupakis F, Antoniotti C, 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. The LancetOncology. 2015;16(13):1306-1315. doi:10.1016/S1470-2045(15)00122-9 [doi]

19 Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer. The New England journal of medicine. 2019;381(17):1632-1643. doi:10.1056/NEJMoa1908075 [doi]

11. 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
- d. Consideration of EGFR inhibitors for patients with RAS wild-type disease

For patients with MSI-high or dMMR metastatic colorectal cancer (approximately 3.5% of cases[20]), pembrolizumab improves progression-free survival compared to standard chemotherapy (median 16.5 months vs. 8.2 mo, HR: 0.60; 95%CI: 0.45-0.80, p=0.0002), with a lower incidence of grade 3 or higher adverse events (22% vs. 66%) and delays time to deterioration in quality of life [Level I].[21] Patients with a deletion in MLH1 and a BRAF mutation likely have a sporadic mutation and do not necessarily need a referral to genetics. A referral to genetics should be offered for all other patients that are MSI-high or dMMR.

20 Koopman M, Kortman G, Mekenkamp L, et al. Deficient mismatch repair system in patients with sporadic advanced colorectal cancer. British journal of cancer. 01/27/2009 2009;100(2)doi:10.1038/sj.bjc.6604867
21 Diaz L, Shiu K, Kim T, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. The Lancet Oncology. 2022 May 2022;23(5)doi:10.1016/S1470-2045(22)00197-8

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).[25] • 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.[26] • 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 mFOLFOX6 [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. • **mFOLFOX6** involves the administration of Oxaliplatin (85 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.[26] • 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).

Regimen	Details
	• Supplement with Bevacizumab, where appropriate (see below). • FOLFOXIRI is usually reserved for patients with excellent performance status as the progression free survival and overall survival improvement associated with FOLFOXIRI and Bevacizumab in the TRIBE study were accompanied with increased toxicity.[18]
Capecitabine[16]	• 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).
Irinotecan[17]	• 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.
5-Fluorouracil (simplified LV5FU2)	• 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).
Raltitrexed[18]	• 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.

Creatinine Clearance	Dose as Percentage of 3 mg/m^2	Interval
> 65 mL/minute	100%	Q3weeks
55 to 65 mL/minute	75%	Q4weeks
25 to 54 mL/minute	% Equivalent to Creatinine Clearance	Q4weeks
< 25 mL/minute	No therapy	Not applicable

Bevacizumab[16, 19-23]	• 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; · 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.

<table>
<tr><th>Regimen</th><th>Details</th></tr>
<tr><td></td><td>
• 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[27]
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[28]</td><td>—</td><td>1.0%</td><td>HR 1.40</td><td>—</td></tr>
<tr><td>Hypertension[28]</td><td>—</td><td>8.7%</td><td>—</td><td>HR 3.00</td></tr>
<tr><td>Wound Healing Complications[29-31]</td><td>4.9%</td><td>3.7%</td><td>—</td><td>—</td></tr>
<tr><td>Gastrointestinal Perforation[32]</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[33,34]
• 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[15,35,36]</td><td>
• First-line anti-EGFR therapies may include:
  a. Cetuximab with FOLFIRI[35]
  b. Panitumumab with FOLFOX[15]
  c. Panitumumab with FOLFIRI (based on extrapolation from data in second-line treatment)[36]
• EGFR inhibitors should not be given with bevacizumab as clinical trials with combinations of both EGFR inhibitor and bevacizumab give worse outcome.[37,38]
• Refer to Panitumumab and Cetuximab: Toxicity Management Guidelines
</td></tr>
<tr><td>Trifluridine-tipiracil and Bevacizumab[22]</td><td>Bevacizumab is administered at a dose of 5 mg/kg IV on days 1 and 15. Trifluridine-tipiracil is an oral medication administered at a dose of 35 mg/m2 bid on days 1 to 5 and 8 to 12 every 28 days</td></tr>
<tr><td>Fruquintinib</td><td>Fruquintinib is administered at 5 mg on days 1-21 every 28 days</td></tr>
</table>

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Appendix A: Approach to Metastatic Colorectal Cancer

<table>
<tr>
<td>Resectable lung or liver metastases</td>
<td>

Consider upfront resection especially for patients with favorable criteria: metachronous, fewer lesions, unilobar disease, no extra-hepatic disease.[40]

Perioperative oxaliplatin based chemotherapy, with 3 months pre-hepatic resection and 3 months post-hepatic resection can be considered for patients with resectable liver metastases, especially when the prognosis is unclear or for downstaging to reduce the magnitude of liver resection. This strategy improved three-year progression-free survival (423.4% versus 33.2% in resected patients, HR=0.73;95%CI: 0.55-0.97; p=00.025) in EORTC 40983, however, overall survival was not improved (Level II).[7,41]
The optimal role of adjuvant chemotherapy after upfront resection is unclear. Post-operative oxaliplatin based chemotherapy for 6 months improved disease-free survival HR 0.67, 95% CI (0.50-0.92, one sided p = 0.006) but not overall survival HR 1.25 (0.78-2.00) two sided P=0.42.[8]

The use of chemotherapy in this setting may be influenced by the clinical presentation: synchronous versus metachronous presentation, technical criteria for resectability, and/or number and size of metastases.[40]
For patients with metastatic colorectal cancer, optimal palliative chemotherapy offers two-year survivals under 40% and five-year survivals under 5% whereas resection of liver metastases offers two-year survivals of 60% to 70% and five-year survivals of 30%.
Resection of lung metastases offers a five-year overall survival of 48% (39.6% for R_0 and 0% for R_1 or R_2 resections).[3]
Assigning one point to each factor (node-positive primary, disease-free interval under twelve months, two or more hepatic metastases, largest metastasis over 5 cm, and CEA level over 200 µg/L) to generate a clinical risk ("Fong") score; it is highly predictive of outcome.[2]

<table>
<tr><th rowspan="2">"Fong Score"</th><th colspan="6">Survival</th></tr>
<tr><th>One-Year</th><th>Two-Year</th><th>Three-Year</th><th>Four-Year</th><th>Five-Year</th><th>Median</th></tr>
<tr><td>0</td><td>93%</td><td>79%</td><td>72%</td><td>60%</td><td>60%</td><td>6.2 Years</td></tr>
<tr><td>1</td><td>91%</td><td>76%</td><td>66%</td><td>54%</td><td>44%</td><td>4.3 Years</td></tr>
<tr><td>2</td><td>89%</td><td>73%</td><td>60%</td><td>51%</td><td>40%</td><td>3.9 Years</td></tr>
<tr><td>3</td><td>86%</td><td>67%</td><td>42%</td><td>25%</td><td>20%</td><td>2.8 Years</td></tr>
<tr><td>4</td><td>70%</td><td>45%</td><td>38%</td><td>29%</td><td>25%</td><td>1.7 Years</td></tr>
<tr><td>5</td><td>71%</td><td>45%</td><td>27%</td><td>14%</td><td>14%</td><td>1.8 Years</td></tr>
</table>

The definition of resectable liver metastases continues to evolve. Currently, resection is considered possible if both an R_0 resection and an adequate* future liver remnant are anticipated, and two contiguous liver segments can be preserved.
For patients with a normal liver, hepatic insufficiency is rare when the future liver remnant exceeds 20% of the total liver volume.[39] For patients extensively pre-treated with chemotherapy, a future liver remnant that exceeds 30% of the total liver volume is required. For patients with underlying liver disease (e.g.: cirrhosis), a future liver remnant that exceeds 40% of the total liver volume is necessary to avoid cholestasis, fluid retention, and liver failure.
The use of EGFR inhibitors for resectable colorectal liver metastases is not recommended. The New EPOC trial randomized operable metastatic patients with KRAS wild-type metastatic colorectal cancer to FOLFOX with or without cetuximab. The addition of cetuximab was associated with significantly worse PFS (median 15.5 mo vs. 22.2 mo) and OS (median 81.0 mo vs. 55.4 mo; HR: 1.45; 95%CI: 1.02-2.05; p=0.036).[42]

</td>
</tr>
</table>

Marginally resectable liver metastases	• Pre-operative chemotherapy can downsize tumors,[43,44] identify responders (progression predicts for a poor outcome),[44] and improve three-year progression-free survival (42.4% *versus* 33.2% in resected patients, HR 0.73, $CI_{95\%}$ 0.55-0.97, $p = 0.025$).[7] • In the situation where a liver metastatectomy could be facilitated by reduction in the size of the liver metastasis, patients should be treated with Oxaliplatin-based chemotherapy to optimal resectability rather than to maximal response or progression. The general approach for consideration of a biologic agent for non-liver limited mCRC should be used. Kras wild type, left sided primary, consider panitumumab;[45] Kras mutant, consider bevacizumab.[46] • As the post-operative morbidity increases with the number of cycles of chemotherapy administered pre-operatively, only a limited number of cycles of chemotherapy should be delivered.[47] The type of hepatic injury is regimen specific:[48] · 5-Fluorouracil predisposes to steatosis, a typically indolent manifestation of non-alcoholic fatty liver disease (NAFLD) that can increase the risks of post-operative infectious complications. · Irinotecan predisposes to non-alcoholic steatohepatitis (NASH), a serious complication of non-alcoholic fatty liver disease that includes fatty infiltration, inflammation, and hepatocyte damage. This can affect the hepatic reserve and increase morbidity and mortality after partial hepatectomy (ninety-day mortality of 1.6% *versus* 14.7%, $p = 0.001$).[49] · Oxaliplatin predisposes to sinusoidal obstruction (characterized by peri-sinusoidal inflammation, congestion, fibrosis, and venous occlusion). Some studies[49] suggest that it fails to increase the risk of peri-operative death while others[50] suggest that it increases morbidity (from 6.3% to 40.0%, $p < 0.026$) and prolongs length-of-stay (from 10.9 days to 17.0 days, $p < 0.006$) after hepatectomy. · Bevacizumab reduces the sinusoidal dilation induced by Oxaliplatin (all grades: from 53.5% to 27.4%; moderate or severe grades: from 27.9% to 8.1%, $p < 0.01$) as well as the degree of tumor viability when used in combination with 5-Fluorouracil and Leucovorin (32.9% *versus* 45.3%, $p = 0.02$).[51] Bevacizumab fails to impair liver regeneration after portal vein embolization.[52] • In a retrospective analysis of patients with initially unresectable metastatic disease,[53] 12.5% became resectable after pre-operative FOLFOX. This was associated with a five-year survival of 33% — similar to the results achieved in "initially operable" patients. • In a retrospective analysis of patients who underwent pre-operative chemotherapy and resection of colorectal liver metastases, the degree of pathologic response correlated with outcome (five-year survival of 75% for complete response, 56% for major response, and 33% for minor response). The predictors for complete or major response were CEA ≤ 5 µg/L, tumor size ≤ 3 cm, and chemotherapy with fluoropyrimidine, Oxaliplatin, and Bevacizumab.[54] • Portal vein occlusion by pre-operative embolization or intra-operative ligation can increase the volume of the left lobe by 30 to 40%. Metastases in the future liver remnant should be resected before portal vein embolization.[55] • The addition of Oxaliplatin[56,57] but not Irinotecan[58-60] to 5-Fluorouracil and Leucovorin in the adjuvant treatment of stage III colon cancer improves outcomes. Therefore, if the metastatic disease is resected, give subsequent consideration to "adjuvant" chemotherapy to complete a total course of therapy equivalent to six months (see Clinical Practice Guidelines for Early Stage Colon Cancer).[61]
BRAF wild type, unresectable colorectal liver metastases with no extra hepatic disease	In the TRANSMET trial, liver transplantation plus chemotherapy significantly improved survival versus chemotherapy alone (insert hazard ratio and reference). Patients were highly selected, responsive to chemotherapy, and had their primary tumor resected. Potential patients should be discussed with a hepatobiliary surgery.

Radiofrequency ablation [Level II]	• Radiofrequency ablation applies multiple four- to six-minute cycles of current to create irreversible damage and protein coagulation around a percutaneously-placed needle. It can be applied to liver metastases under 5 cm (preferably under 3 cm) that are located away from large blood vessels ("heat sinks"). Although hemorrhage, bile leak, and infection can occur, major complications arise in only about 2% of patients treated. Incomplete ablation is identified in 20 to 30% of cases. While needle-track recurrences occur, this is reduced by ablation upon withdrawal. Retrospective studies[62-64] suggest that radiofrequency ablation is associated with a higher local recurrence rate and a lower recurrence-free and overall survival when compared to resection of a hepatic metastasis.
Peritoneal carcinomatosis	• Cytoreductive surgery in combination with heated intra-peritoneal chemotherapy (HIPEC) followed by systemic 5-Fluorouracil and Leucovorin provides superior outcomes when compared to the same systemic chemotherapy regimen with or without palliative surgery (median survival 22.3 months *versus* 12.6 months, HR 0.55, $CI_{95\%}$ 0.32-0.95, $p = 0.032$).[4] Patients with involvement of zero to five of the seven regions of the abdominal cavity have a significantly better survival than patients with six or seven affected regions. Macroscopically complete cytoreduction (R_1) confers a significantly superior survival than patients with residual disease (R_2). • Cytoreductive surgery[65] involves the complete removal of macroscopic disease (e.g.: peritonectomy, omentectomy, cholecystectomy, splenectomy, abdominal organs involved with tumor), lysis of intra-abdominal adhesions (to permit optimal exposure to heated intra-peritoneal chemotherapy), and reconstitution of the gastrointestinal tract. Hyperthermia exerts a direct cytotoxic effect that impairs DNA repair, denatures proteins, induces heat-shock proteins, induces apoptosis, inhibits angiogenesis, and blocks oxidative metabolism[64]. Hyperthermia is synergistic with cytotoxic agents.[66] The process is associated with a reported morbidity and mortality rates of 22.9% and 4%, respectively.[67]
Unresectable disease	• Consider palliative chemotherapy. click here for more details • Resection of an asymptomatic primary colorectal cancer provides only minimal palliative benefit, risks morbidity and mortality, and delays initiation of systemic therapy.[68,69] Obstruction and bleeding complicate only 13.9% and 3.0% of cases treated with palliative chemotherapy when the primary tumor is left *in situ*. Therefore, when a patient presents with an unequivocally unresectable metastatic disease and an asymptomatic primary colorectal cancer, palliative chemotherapy can be initiated; resection of the primary tumor can be reserved for the small proportion of patients who develop a complication related to the primary tumor. Resection, diversion, placement of a stent, or radiation is indicated for a symptomatic primary colorectal cancer.
Stereotactic Body Radiotherapy (SBRT) [Level III]	• Liver SBRT is used to deliver high doses of radiation accurately to ablate and destroy all normal and tumour cells within a small geographic area. SBRT can provide moderate rates of local control for patients with liver metastases (50-100% at 1 year, 45-80% at 2 years), however, literature is limited to single institution retrospective studies.[70-76] • Patients should be discussed at multidisciplinary rounds. SBRT can be considered for unresectable disease when alternative therapies have failed or are contraindicated. • Liver SBRT is currently under investigation in Phase II clinical trials open at the TBCC and CCI. Consider referral of patients with good liver function (Child Pugh A, B) and a limited number of metastases of an amenable size for participation in these studies. • Continued clinical trials in the use of liver SBRT are recommended. Enrollment of patients into clinical trials or investigational protocols should be encouraged.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 02 of 12, February 2026) am 06.02.2026

#	Suchschritt
1	[mh "colorectal neoplasms"]
2	(colon* OR colo-rect* OR colorect* OR rect*):ti,ab,kw
3	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesion* OR malignan*):ti,ab,kw
4	#1 OR (#2 AND #3)
5	#4 with Cochrane Library publication date from Feb 2021 to present, in Cochrane Reviews
6	#4 with Cochrane Library publication date from Feb 2024 to present, in Cochrane Reviews
7	#5 NOT #6

Leitlinien und systematische Reviews in PubMed am 06.02.2026

verwendete Suchfilter für Leitlinien:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.02.2026

verwendeter Suchfilter für systematische Reviews:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 01.01.2026.

#	Suchschritt
	Leitlinien
1	colorectal neoplasms[majr]
2	colon[ti] OR colonic[ti] OR colo-rect*[ti] OR colorect*[ti] OR rectal[ti] OR rectum[ti]
3	tumor[ti] OR tumors[ti] OR tumour*[ti] OR carcinoma*[ti] OR adenocarcinoma*[ti] OR neoplas*[ti] OR sarcoma*[ti] OR cancer*[ti] OR lesion*[ti] OR malignan*[ti]
4	#1 OR (#2 AND #3)
5	(#4) AND (Guideline[pt] OR Practice Guideline[pt] OR guideline*[ti] OR Consensus Statement[pt] OR Consensus Development Conference, NIH[pt] OR recommendation*[ti])
6	(#5) AND ("2021/02/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews
8	colorectal neoplasms/therapy[majr]
9	colon[tiab] OR colonic[tiab] OR colo-rect*[tiab] OR colorect*[tiab] OR rectal[tiab] OR rectum[tiab]

#	Suchschritt
10	(tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR sarcoma*[tiab] OR cancer*[tiab] OR lesion*[tiab] OR malignan*[tiab])
11	(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])
12	#9 AND #10 AND #11
13	(#8 OR #12) AND (neoplasm metastasis[mh] OR advanced[tiab] OR metastat*[tiab] OR metastas*[tiab] OR recurren*[tiab])
14	(#13) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[pt] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR (("evidence-based medicine"[mh] OR evidence synthes*[tiab]) AND "review"[pt]) OR ((("evidence based"[tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR "technical report"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
15	(#14) AND ("2021/02/01"[PDAT] : "3000"[PDAT])
16	(#15) NOT "The Cochrane database of systematic reviews"[Journal]
17	(#16) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews ohne Leitlinien
18	(#17) NOT (#7)
19	(#18) AND ("2024/02/01"[PDAT] : "3000"[PDAT])
20	#18 NOT #19

Iterative Handsuche nach grauer Literatur, abgeschlossen am 06.02.2026, überprüft am 08.06.2026

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- American Society of Clinical Oncology (ASCO)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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5. **Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft (DKG), Deutsche Krebshilfe (DKH), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)).** Kolorektales Karzinom; S3-Leitlinie, Leitlinienreport, Vers.. 3.2 [online]. AWMF-Registrierungsnummer 021-007OL. last update: 04.2026. Berlin (GER): Leitlinienprogramm Onkologie; 2025. [Zugriff: 08.06.2026]. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Kolorektales_Karzinom/Version_3/LL_KRK_v3.2_Leitlinienreport_09.04.2026.pdf.

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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