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: 2021-B-231-z Nivolumab

Stand: August 2021

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

Nivolumab
indiziert in Kombination mit Ipilimumab zur Behandlung des metastasierten Kolorektalkarzinoms mit Mismatch-Reparatur-Defizienz oder hoher Mikrosatelliteninstabilität bei Erwachsenen nach vorheriger fluoropyrimidinbasierter Kombinationschemotherapie

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	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: - Trifluridin/Tipiracil: Beschluss vom 1. Oktober 2020 - Ramucirumab (neues Anwendungsgebiet): Beschluss vom 1. September 2016 - Regorafenib (Neubewertung nach Fristablauf): Beschluss vom 17. März 2016 - Aflibercept: Beschluss vom 15. August 2013 - Encorafenib: Beschluss vom 17.12.2020
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Nivolumab	Anwendungsgebiet laut Zulassung: indiziert in Kombination mit Ipilimumab zur Behandlung des metastasierten Kolorektalkarzinoms mit Mismatch-Reparatur-Defizienz oder hoher Mikrosatelliteninstabilität bei Erwachsenen nach vorheriger fluoropyrimidinbasierter Kombinationschemotherapie.
Aflibercept L01XX44 ZALTRAP®	ZALTRAP in Kombination mit einer Chemotherapie, bestehend aus Irinotecan/5-Fluorouracil/Folinsäure (FOLFIRI), wird angewendet bei Erwachsenen mit metastasiertem kolorektalem Karzinom (MCRC), das unter oder nach einem Oxaliplatin-haltigen Regime fortgeschritten ist.
Bevacizumab L01X C07 Avastin®	Bevacizumab wird in Kombination mit einer Chemotherapie auf Fluoropyrimidin-Basis zur Behandlung von erwachsenen Patienten mit metastasiertem Kolon- oder Rektumkarzinom angewendet.
Calciumfolinat V03AF03 Calciumfolinat-GRY®	Calciumfolinat ist indiziert: - in Kombination mit 5-Fluorouracil in der zytotoxischen Therapie - bei fortgeschrittenem oder metastasiertem kolorektalem Karzinom
Capecitabin L01BC06 Xeloda®	Xeloda wird angewendet: - zur Behandlung des metastasierten Kolorektalkarzinoms (siehe Abschnitt 5.1).
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, - als Monotherapie bei Patienten, bei denen die Therapie mit Oxaliplatin und Irinotecan versagt hat und die Irinotecan nicht vertragen.

Encorafenib L01XE46 Braftovi®	- in Kombination mit Cetuximab zur Behandlung von erwachsenen Patienten mit metastasiertem Kolorektalkarzinom (CRC) mit einer BRAF-V600E-Mutation, die eine systemische Vortherapie erhalten haben (siehe Abschnitte 4.4 und 5.1)
5-Fluorouracil L01BC02 Benda-5 FU	- Fortgeschrittenes oder metastasiertes kolorektales Karzinom
Irinotecan L01XX19 Irinotecan Fresenius	Irinotecan ist indiziert zur Behandlung von Patienten mit fortgeschrittenem kolorektalem Karzinom: - In Kombination mit 5-Fluorouracil und Folinsäure bei Patienten ohne vorausgegangene Chemotherapie einer fortgeschrittenen Erkrankung, - Als Monotherapie bei Patienten, die auf eine Vorbehandlung mit einem etablierten 5-Fluorouracil-haltigen Regime nicht angesprochen haben.
Mitomycin L01DC03 Mitomycin medac	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
Panitumumab L01XC08 Vectibix®	Vectibix ist indiziert zur Behandlung von erwachsenen Patienten mit metastasiertem kolorektalem Karzinom (mCRC, metastatic colorectal cancer) mit *RAS*-Wildtyp - in der Erstlinientherapie in Kombination mit FOLFOX oder FOLFIRI. - in der Zweitlinientherapie in Kombination mit FOLFIRI bei Patienten, die in der Erstlinientherapie eine Fluoropyrimidin-haltige Chemotherapie erhalten haben (ausgenommen Irinotecan). - als Monotherapie nach Versagen von Fluoropyrimidin-, Oxaliplatin- und Irinotecan-haltigen Chemotherapieregimen.
Ramucirumab L01XC21 Cyramza®	Cyramza ist in Kombination mit FOLFIRI (Irinotecan, Folinsäure und 5-Fluorouracil) indiziert zur Behandlung von erwachsenen Patienten mit einem metastasierten Kolorektalkarzinom (mKRK) mit Tumorprogress während oder nach vorausgegangener Therapie mit Bevacizumab, Oxaliplatin und einem Fluoropyrimidin.
Regorafenib L01XE21 Stivarga®	Stivarga ist angezeigt zur Behandlung von erwachsenen Patienten mit: - metastasiertem Kolorektalkarzinom (KRK), die zuvor mit verfügbaren Therapien behandelt wurden oder die für diese nicht geeignet sind. Diese Therapien umfassen Fluoropyrimidin-basierte Chemotherapie, eine Anti-VEGF-Therapie und eine Anti-EGFR-Therapie (siehe Abschnitt 5.1).

Trifluridin/ Tipiracil L01BC59 Lonsurf®	Lonsurf wird angewendet zur Behandlung von erwachsenen Patienten mit metastasiertem kolorektalem Karzinom (KRK), die bereits mit verfügbaren Therapien behandelt wurden oder die für diese nicht geeignet sind. Diese Therapien beinhalten Fluoropyrimidin-, Oxaliplatin- und Irinotecan-basierte Chemotherapien, Anti-VEGF- und Anti-EGFR-Substanzen.

Quellen: AMIS-Datenbank, AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2021-B-231-z (Nivolumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	14. Januar 2021

Inhaltsverzeichnis

Abkürzungsverzeichnis

5-FU	5-Fluorouracil
AE	Adverse Events
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BSC	Best supportive Care
CTC	Chemotherpie
dMMR	Deficient mismatch repair
EGFR	Epidermal growth factor receptor
EGFR MAB	EGFR monoclonal antibodies
EGFR TKI	EGFR tyrosine kinase inhibitors
FOLFOX	luorouracil + oxaliplatin + leucovorin
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IRI	Irinotecan
KI	Konfidenzintervall
KRAS	Kirsten rat sarcoma viral oncogene homolog
LoE	Level of Evidence
LV	Leucovorin
mCRC/KRK	Metastasiertes Kolorektales-Karzinom
MSI	Mikrosatelliteninstabilität
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
ORR	overall response rate
OS	Overall Survival (dt. Gesamtüberleben)
PFS	progression-free survival
RR	Relatives Risiko

SAE	severe adverse events
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
TTP	time to progression
WHO	World Health Organization

1 Indikation

Indikation der Synopse: zur Behandlung des metastasierten Kolorektalkarzinoms nach vorheriger Fluoropyrimidin-basierter Kombinationstherapie.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *metastasiertes Kolorektalkarzinom* durchgeführt. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, SIGN, TRIP, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien.

Die Erstrecherche wurde am 29.06.2020 durchgeführt, die Folgerecherche am 07.01.2021. Die Recherchestrategie der Erstrecherche wurde für die Folgerecherche übernommen und der Suchzeitraum jeweils auf die letzten 5 Jahre eingeschränkt. Die letzte Suchstrategie ist am Ende der Synopse detailliert dargestellt.

Die Recherchen ergaben insgesamt 2211 Quellen, die in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Es wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen und nur die Quellen der letzten 5 Jahre berücksichtigt. 37 Quellen wurden in die synoptische Evidenz-Übersicht aufgenommen.

3 Ergebnisse

3.1 G-BA-Beschlüsse/IQWiG-Berichte

G-BA, 2013 [14].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. August 2013 – Aflibercept

Anwendungsgebiet

Zaltrap® in Kombination mit einer Chemotherapie bestehend aus Irinotecan/ 5-Fluorouracil/Folinsäure (FOLFIRI) wird angewendet bei Erwachsenen mit metastasiertem kolorektalem Karzinom (MCRC), das unter oder nach einem Oxaliplatin-haltigen Regime fortgeschritten ist.

Zweckmäßige Vergleichstherapie

Die zweckmäßige Vergleichstherapie zur Behandlung von Patienten mit metastasiertem kolorektalem Karzinom, die mit einem Oxaliplatin-haltigen Regime vorbehandelt sind, ist die Kombinations-Chemotherapie aus 5-Fluorouracil, Folinsäure und Irinotecan.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der Kombinations-Chemotherapie aus 5-Fluorouracil, Folinsäure und Irinotecan:

Hinweis für einen geringen Zusatznutzen.

G-BA, 2016 [12].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 1. September 2016 – Ramucirumab (neues Anwendungsgebiet)

Anwendungsgebiet

„Ramucirumab (Cyramza®) ist in Kombination mit FOLFIRI (Irinotecan, Folinsäure und 5-Fluorouracil) indiziert zur Behandlung von erwachsenen Patienten mit einem metastasierten Kolorektalkarzinom (mKRK) mit Tumorprogress während oder nach vorausgegangener Therapie mit Bevacizumab, Oxaliplatin und einem Fluoropyrimidin.“

Vergleichstherapie

Kombinations-Chemotherapie aus 5-Fluorouracil + Folinsäure + Irinotecan

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der Kombinations-Chemotherapie aus 5-Fluorouracil + Folinsäure + Irinotecan:

Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [15].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 17. März 2016 – Regorafenib

Anwendungsgebiet

Stivarga® ist angezeigt zur Behandlung von erwachsenen Patienten mit metastasiertem Kolorektalkarzinom (KRK), die zuvor mit verfügbaren Therapien behandelt wurden oder die für diese nicht geeignet sind. Diese Therapien umfassen Fluoropyrimidin-basierte Chemotherapie, eine Anti-VEGF-Therapie und eine Anti-EGFR-Therapie.

Vergleichstherapie

Die zweckmäßige Vergleichstherapie für Regorafenib zur Behandlung von Patienten mit metastasiertem kolorektalen Karzinom, die eine vorangegangene Fluoropyrimidin-basierte Chemotherapie, eine Anti-VEGF-basierte Therapie, und, sofern ein kras-Wildtyp vorliegt, eine Anti-EGFR-basierte Therapie gehabt haben, oder für eine solche Therapie nicht infrage kommen, ist Best-Supportive-Care.

Als Best-Supportive-Care wird die Therapie verstanden, die eine bestmögliche, Patienten-individuell optimierte, unterstützende Behandlung zur Linderung von Symptomen und Verbesserung der Lebensqualität gewährleistet.

Dabei wird in Bezug auf das vorliegende Anwendungsgebiet von einem fortgeschrittenen Behandlungsstadium ausgegangen, in dem die derzeit empfohlenen und zugelassenen Standardtherapien für die Behandlung im metastasierten Stadium bereits ausgeschöpft worden sind und für das weitere anti-neoplastische Therapien nicht regelhaft infrage kommen. Mit der Bestimmung von Best-Supportive-Care als zweckmäßige Vergleichstherapie wird von einer ausschließlich palliativen Zielsetzung der Behandlung ausgegangen.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive-Care:

Ein Zusatznutzen ist nicht belegt.

G-BA, 2017 [13].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 02. Februar 2017 - Trifluridin/Tipiracil.

Anwendungsgebiet

Lonsurf wird angewendet zur Behandlung von erwachsenen Patienten mit metastasiertem kolorektalem Karzinom (KRK), die bereits mit verfügbaren Therapien behandelt wurden oder die für diese nicht geeignet sind. Diese Therapien beinhalten Fluoropyrimidin-, Oxaliplatin- und Irinotecan-basierte Chemotherapien, Anti-VEGF- und Anti-EGFR-Substanzen.

Vergleichstherapie

Best Supportive Care

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:

Anhaltspunkt für einen geringen Zusatznutzen.

3.2 Cochrane Reviews

Chan DLH et al., 2017 [6].

Epidermal growth factor receptor (EGFR) inhibitors for metastatic colorectal cancer.

Fragestellung

To determine the efficacy, safety profile, and potential harms of EGFR inhibitors in the treatment of people with metastatic colorectal cancer when given alone, in combination with chemotherapy, or with other biological agents.

Methodik

Population:

- People with a histological diagnosis of colorectal carcinoma and confirmed evidence of unresectable, metastatic disease.

Intervention/ Komperator:

- EGFR MAb
  - first-line treatment with chemotherapy and an EGFR inhibitor compared to chemotherapy alone;
  - second-line treatment with chemotherapy and an
  - EGFR inhibitor compared to chemotherapy alone;
  - third-line treatment (> 2 prior chemotherapy regimens) with an EGFR inhibitor alone compared to best supportive care.

• EGFR TKI
  - treatment with chemotherapy and EGFR TKI compared to chemotherapy alone;
  - treatment with EGFR TKI compared to best supportive care.

Different EGFR inhibitor regimens
  - treatment with one EGFR inhibitor compared to treatment with another EGFR inhibitor;
  - treatment with one regimen of an EGFR inhibitor compared to treatment with another regimen of the same EGFR inhibitor.

• EGFR inhibitors in combination with chemotherapy and anti-angiogenic agents
  - treatment with chemotherapy and anti-angiogenic agent compared to chemotherapy and EGFR inhibitor;
  - treatment with chemotherapy and anti-angiogenic agent compared to treatment with chemotherapy, antiangiogenic agent, and EGFR inhibitor.

Endpunkte:

- PFS, OS, Response, AE, QoL

Recherche/Suchzeitraum:

- September 2016
  - Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, Issue 9, 2016)

- Ovid MEDLINE (from 1950)
- Ovid Embase (from 1974)

- Hand-searches for meeting proceedings of major conferences (European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), and ASCO GI) from 2012 toMarch 2016 on 14-15 January 2016

Qualitätsbewertung der Studien:

- Cochrane 'Risk of bias' tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 33 Studien (N=15.025 Patienten)
- In total, 7948 participants were enrolled and KRAS status was assessable in 6969 participants: 4402 were KRAS exon 2 WT and 2567 were KRAS exon 2 mutant (MT).

Charakteristika der Population:

1. Twelve studies examined the effect of adding EGFR MAbs to either chemotherapy (10 studies) or best supportive care (2 studies) on progression-free survival (PFS) in the KRAS exon 2 wild-type (WT) setting. Ten studies compared the combination of EGFR MAb and chemotherapy (8 with cetuximab, 2 with panitumumab) to the same chemotherapy alone with KRAS status available. *(Adams COIN 2011; Bokemeyer OPUS 2009; Ciardiello CAPRI-GOIM 2016; Douillard PRIME 2010; Passardi ITACA 2015; Peeters 2010; Seymour PICCOLO 2013;Tveit NORDIC VII 2012; Van Cutsem CRYSTAL 2009; Ye 2013)***. Two studies (one with cetuximab and one with panitumumab) examined the effect of EGFR MAb as monotherapy *(Amado 2008; Karapetis CO17 2008 – 3.Therapielinie).*** In total, 7948 participants were enrolled and KRAS status was assessable in 6969 participants: 4402 were KRAS exon 2 WT and 2567 were KRAS exon 2 mutant (MT).

2. Three studies examined the effect of adding EGFR MAb to chemotherapy in the KRAS unselected setting; this involved 1483 KRAS unselected participants *(Borner 2008; Polikoff EXPLORE 2005; Sobrero EPIC 2008).*

3. One study involving 42 participants solely examined the effect of adding EGFR MAb to chemotherapy in the KRAS mutant setting *(Siena 2013);* we considered this trial in combination with the KRAS mutant cohorts of the studies in 1).

4. Four studies examined the effect of adding EGFR MAb to chemotherapy on progression-free survival compared to adding another (non-EGFR) biological agent to chemotherapy in 2189 KRAS exon 2 WT participants. All trials used bevacizumab as the second biological agent, which permitted its use as the comparator. All four trials compared the combination of chemotherapy with EGFR MAb to the combination of the same chemotherapy with bevacizumab. The chemotherapy backbone was an investigator's choice of mFOLFOX6 or FOLFIRI in Venook CALGB 80405 2014; FOLFIRI in Hecht SPIRITT 2015; mFOLFOX6 in Schwartzberg PEAK 2014; and FOLFIRI in Heinemann FIRE-3 2014.

5. Six studies examined the effect of using one EGFR inhibitor (whether MAb or TKI) compared to another EGFR inhibitor in 1708 participants. Imgatuzumab (GA201) was compared to cetuximab in KRAS exon 2 WT participants, with FOLFIRI being the chemotherapy backbone (Bridgewater GAIN-C 2015). Afatinib was compared to cetuximab in KRAS exon 2 WT participants in the second trial, both of which were given as monotherapy (Hickish 2014).

Brodowicz 2013 compared two different regimens of cetuximab in combination with first-line FOLFOX chemotherapy. Ma 2013 compared the combination of continuous erlotinib and CAPOX chemotherapy to intermittent erlotinib with CAPOX therapy. Price ASPECCT 2014 compared cetuximab and panitumumab as monotherapies. Finally, Wasan COIN-B 2014 compared a strategy of intermittent mFOLFOX6 with cetuximab (with mFOLFOX6 with cetuximab ceased after 12 weeks, and assuming stable disease or better with initial treatment, re-introduction of the same treatment on progression) with the same strategy of intermittent mFOLFOX6 with cetuximab, but with maintenance cetuximab in between these treatments.

6. Two studies examined the effect of adding EGFR TKI to chemotherapy on progression-free survival in the KRAS unselected setting in 195 participants. Santoro 2008 investigated gefitinib with initiation of FOLFIRI chemotherapy, which was continued until progression. Vincent 2011 studied erlotinib plus capecitabine in people unsuitable for usual first-line combination chemotherapy.

7. Six studies examined the effect of adding EGFR inhibitor (whether MAb or TKI) to a combination of chemotherapy and anti-angiogenic agent on progression-free survival compared to chemotherapy and anti-angiogenic agent only in 1571 participants. (Hagman ACT2 2014; Hecht PACCE 2009; Johnsson Nordic ACT 2013; Passardi ITACA 2015; Tol CAIRO2 2008; Tournigand DREAM 2015). Two studies investigated EGFR TKI (erlotinib in Hagman ACT2 2014 and gefitinib in Tournigand DREAM 2015) added to bevacizumab in the maintenance setting commenced after stable disease or better with bevacizumab-containing induction chemotherapy. The other three studies investigated EGFR MAb (panitumumab in Hecht PACCE 2009 and cetuximab in Passardi ITACA 2015 and Tol CAIRO2 2008) commenced at the start of first-line chemotherapy together with bevacizumab in both arms. We note that Passardi ITACA 2015 was also mentioned in section 1) above.

Qualität der Studien:

The evidence we identified was generally of moderate to high quality. Our main reason fornot judging the evidence for all outcomes as high quality was that in some studies the treating doctors assessed their patients' scans for tumour shrinkage or growth, and their knowledge of what treatment the patient received resulted in a higher risk of bias. Another reason for our judging of the evidence as lower quality was that there were differences between the studies grouped in the meta-analyses calculations (heterogeneity).

Studienergebnisse:

Hinweis: berichtet werden ausschließlich die Ergebnisse ab 2. Therapielinie

The addition of EGFR MAb to standard therapy in *KRAS* exon 2WT populations

- PFS
  - Pooled analysis of second-line trials in KRAS exon 2 WT populations (4 RCTs, 1258 participants) showed that adding EGFR MAb to chemotherapy reduced the risk of disease progression by 24% (HR 0.76, 95% CI 0.67 to 0.86; P < 0.001)
  - Pooled analysis of third-line trials in KRAS exon 2 WT populations (2 RCTs, 473 participants) showed that compared to placebo, EGFR MAb reduced the risk of disease progression by 57% (HR 0.43, 95% CI 0.35 to 0.54; P < 0.001)
- **OS**
  - Pooled analysis of second-line trials (4 RCTs, 1258 participants) in KRAS exon 2WT populations showed that adding EGFRMAb to second-line chemotherapy did not

significantly decrease the risk of death (HR 0.93, 95% CI 0.82 to 1.05; P = 0.25; Analysis 1.2.2). No important heterogeneity was present (Chi2 = 2.36, df = 3, P = 0.50, I2 = 0%).

- Pooled analysis of third-line trials (2 RCTs, 473 participants) in KRAS exon 2WT populations showed that compared to placebo, EGFR MAb did not significantly decrease the risk of death (HR 0.79, 95% CI 0.50 to 1.24; P = 0.31). Substantial statistical heterogeneity was present (Chi2 = 4.35, df = 1, P = 0.04, I2 = 77%), likely attributable to the differential cross-over in the two included studies.

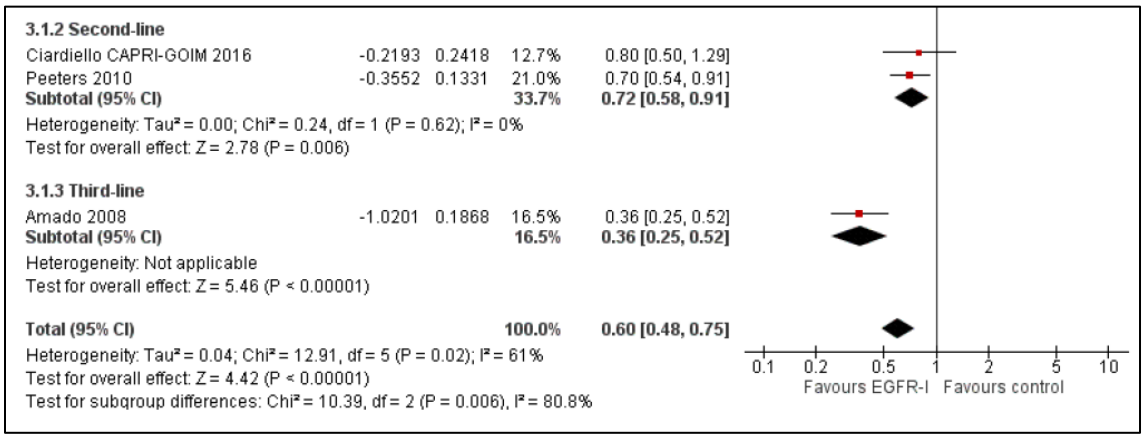
- **Tumour response rate**
  - Pooled analysis of second-line trials (4 RCTs, 1243 participants) in KRAS exon 2WT populations showed that adding EGFRMAb to second-line chemotherapy increased the rate of response by 21.8% from 11.3% (70/618) to 33.1% (206/625) (OR 3.60, 95% CI 2.45 to 5.30; P < 0.001), with no important heterogeneity (Chi2 = 4.18, df = 3, P = 0.24, I2 = 28%).
  - Pooled analysis of third-line trials (2 RCTs, 457 participants) in KRAS exon 2 WT populations showed that using EGFR Mab compared to placebo increased the rate of response from 0% (0/216) to 14.9% (36/241) (OR 38.44, 95% CI 5.22 to 282.91; P = 0.0003). No important heterogeneity was present (Chi2 = 0.01, df = 1, P = 0.91, I2 = 0%).

EGFR MAb in KRAS exon 2 mutant participants

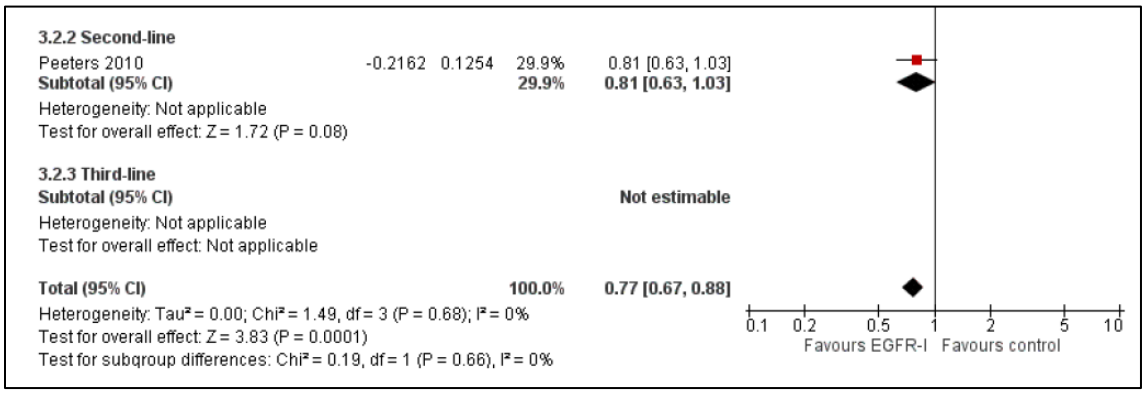
- **PFS**
  - The only second-line trial reporting PFS outcomes in KRAS exon 2 MT populations was Peeters 2010 (1 RCT, 486 participants). The risk of progression did not significantly decrease (HR 0.85, 95% CI 0.68 to 1.06; P = 0.15)
  - Pooled analysis of third-line trials (2 RCTs, 348 participants) showed that using EGFR MAb compared to best supportive care in KRAS exon 2 MT participants did not decrease the risk of progression (HR0.99, 95%CI 0.80 to 1.24; P = 0.96). No important heterogeneity was present (Chi2 = 0.00, df = 1, P = 0.99, I2 = 0%).
- **OS**
  - The one second-line study, Peeters 2010, reported no reduction in risk of death (HR 0.93, 95% CI 0.76 to 1.15; P = 0.52). No important heterogeneity was present in these subgroup analyses (First-line: Chi2 = 3.53, df = 4, P = 0.47, I2 = 0%; third-line: Chi2 = 0, df = 1, P = 0.98, I2 = 0%).
  - Pooled analysis by line of therapy also showed no significant reduction in risk of death in the third-line (HR 0.98, 95% CI 0.80 to 1.21; P = 0.87)

EGFR MAb in extended RASWT participants

- **PFS**



- **OS**



EGFR MAb in extended RAS mutant participants

- **PFS**
  - Pooled analysis of second-line trials (2 RCTs, 616 participants) in extended RAS MT populations showed that adding EGFR Mab in the second-line setting did not significantly decrease the risk of progression (HR 1.05, 95%CI 0.62 to 1.79; Analysis 4.1.2). Substantial heterogeneity was present in this analysis (Chi2 = 2.64, df = 1, P = 0.10, I2 = 62%). This was potentially due to the inclusion of different populations in the trials: Peeters 2010 enrolled participants all with KRAS genotypes, and thus their population in this analysis comprises both participants with KRAS exon 2 mutations as well as other KRAS or NRAS mutations; in contrast, Ciardiello CAPRI-GOIM 2016 restricted enrolment to people with KRAS exon 2 WT tumours, and thus their population in this analysis would not have had KRAS exon 2mutations, but rather mutations in other exons of KRAS or NRAS. Interpretation of this subgroup analysis should therefore be interpreted with caution.
  - The only third-line trial reporting PFS outcomes in this population was Amado 2008 (1 RCT, 213 participants), which reported no significant decrease in risk of progression with HR 0.97 (95% CI 0.73 to 1.29).
- **OS**
  - The one secondline study, Peeters 2010, (574 participants) reported no reduction in risk of death (HR 0.91, 95% CI 0.76 to 1.10; P = 0.34).

Anmerkung/Fazit der Autoren

Our main finding was that the addition of EGFR MAb drugs to standard treatment in people whose tumours were KRAS wild type reduces the risk of disease progression by 30%. The risk of death is reduced by 12% (i.e. patients live longer overall), and the chance of tumour shrinkage is increased from 31% to 46%. In people who are both KRAS and NRAS (extended RAS) wild type, the risk of disease progression is reduced by 40%; risk of death is reduced by 23%; and the rate of tumour shrinkage increases from 21% to 48%.

There was no evidence of any difference in outcome between the combination of EGFRMAb plus chemotherapy and the combination of bevacizumab (another targeted drug) plus chemotherapy.

There was no evidence that the use of EGFR TKI improved outcomes, although the number of studied participants (and trials) was too small for a formal analysis.

There was no evidence that adding EGFR MAb to both chemotherapy and bevacizumab improved outcomes, and in fact was found to increase toxicity.

The addition of EGFR MAb to standard therapy in KRAS exon 2 WT participants increased the likelihood of tumour response with an odds ratio of 2.41. Significant heterogeneity was again present, likely attributable to varying lines of therapy where different degrees of benefit were observed (OR 1.73 in first-line compared to OR 38.44 in third-line settings), which was probably due to the fact that placebo was used as the control arm in third-line trials, whereas combination chemotherapy was the control in first- and second-line trials.

Kommentare zum Review

- 4 Studien für Second-Line
- 2 Studien für Third-Line – Placebovergleich

Amado 2008	
Methods	Phase III open-label RCT; n = 572
Participants	Advanced colorectal cancer; prior treatment with fluorouracil, irinotecan, and oxaliplatin
Interventions	Panitumumab vs best supportive care
Outcomes	Primary endpoint: OS. Secondary endpoints: PFS, TRR, QoL (EORTC QLQ-C30), safety
Notes	Funded by Amgen. Median follow-up 14.1 months for participants still alive. Amado: employment/leadership position (Amgen), stock ownership (Amgen). Chang: employment/leadership position (Amgen), stock ownership (Amgen)

Karapetis CO17 2008	
Methods	Phase III RCT; n = 572
Participants	People with mCRC, prior treatment with fluoropyrimidine, irinotecan, and oxaliplatin
Interventions	Cetuximab vs best supportive care
Outcomes	Primary outcome: OS. Secondary outcomes: PFS, TRR, quality of life
Notes	Supported by National Cancer Institute of Canada, ImClone Systems, and Bristol-Myers Squibb. Karapetis: consulting fees (Merck Serono), Zalcberg: research grants (Amgen, Merck Serono, Bristol-Myers Squibb, Alphapharm)

Mocellin S et al., 2017 [22].

Second-line systemic therapy for metastatic colorectal cancer (Review) determine the efficacy and toxicity of second-line.

Fragestellung

To determine the efficacy and toxicity of second-line systemic therapy in people with metastatic CRC.

Methodik

Population:

People with distant metastatic or locally advanced unresectable CRC (that is, TNMstage IV disease) that had progressed, recurred or did not respond to first-line systemic therapy.

Intervention/ Komperator:

Any second-line systemic therapy regimen (single agent or combinatory regimen). We considered the following comparisons:

- second-line systemic therapy versus control (placebo or best supportive care);
- comparisons of different second-line systemic therapy regimens.

Endpunkte:

OS, PFS, ORR, SAE, QoL

Recherche/Suchzeitraum:

- Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library 2016, Issue 4)
- Ovid MEDLINE (1950 to May 2016)
- Ovid MEDLINE In-process & Other Non-Indexed Citations (1946 to May 2016)
- Ovid EMBASE (1974 to May 2016)
- Searching in other resources

Qualitätsbewertung der Studien:

- Cochrane 'Risk of bias' tool

Ergebnisse

Anzahl eingeschlossener Studien:

34 Studien (N=13.787)

Charakteristika der Population:

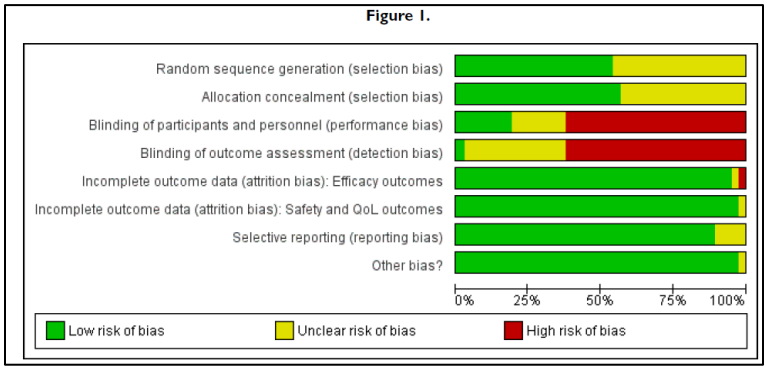
The main features of each of the 34 included trials (overall enrolling 13,787 participants; range: 55 to 1298; median: 247) are reported in the Characteristics of included studies table.

One trial compared four arms (Bendell 2013˙folfiri), four trials compared three arms (Cohn 2013˙conat; Élez 2015; O'Neil 2014; Rothenberg 2003˙folfox), and the remaining 27 trials compared two arms. Only one trial compared a second-line chemotherapy regimen with best

supportive care (Cunningham1998). The other included studies compared two ormore different second-line treatments.

Qualität der Studien:

Considering the risk of single biases across trials, a high risk was present in a significant proportion (greater than 50%) of trials only for performance and detection bias (Figure 1). However, it should be noted that performance biaswas unavoidable in some circumstances (e.g. chemotherapy compared to best supportive care); moreover, it is unlikely that this type of bias had a significant impact on the trial results and ultimately on the findings of the meta-analysis. While evaluating the risk of bias we did not find any difference between different outcomes; therefore, the risk assessment across domains is reported as a single assessment for all outcomes.



Studienergebnisse:

1. Chemotherapy (irinotecan) was more effective than best supportive care (HR for OS: 0.58, 95% CI 0.43 to 0.80; 1 RCT; moderate quality evidence);

2. modern chemotherapy (FOLFOX (5-fluorouracil plus leucovorin plus oxaliplatin), irinotecan) is more effective than outdated chemotherapy (5-fluorouracil) (HR for PFS: 0.59, 95% CI 0.49 to 0.73; 2 RCTs; high-quality evidence) (HR for OS: 0.69, 95% CI 0.51 to 0.94; 1 RCT; moderate-quality evidence);

3. irinotecan-based combinations were more effective than irinotecan alone (HR for PFS: 0.68, 95% CI 0.60 to 0.76; 6 RCTs; moderate-quality evidence);

4. targeted agents improved the efficacy of conventional chemotherapy both when considered together (HR for OS: 0.84, 95% CI 0.77 to 0.91; 6 RCTs; high-quality evidence) and when bevacizumab was used alone (HR for PFS: 0.67, 95% CI 0.60 to 0.75; 4 RCTs; high-quality evidence).

Patient or population: people with metastatic CRC
Settings: second-line treatment
Intervention: modern CTX (FOLFOX or irinotecan)
Comparison: 5FU

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	5FU	Modern CTX				
Overall survival	800 per 1000	671 per 1000 (560 to 780)	HR 0.69 (0.51 to 0.94)	167 (1 RCT)	+ + + - Moderate	Reason for downgrading: only 1 trial available
Progression-free survival	900 per 1000	749 per 1000 (669 to 818)	HR 0.59 (0.49 to 0.73)	470 (2 RCTs)	+ + + + High	-
Overall tumour response	34 per 1000	99 per 1000 (50 to 197)	RR 2.96 (1.66 to 5.27)	866 (3 RCTs)	+ + + + High	-
Severe adverse effects	450 per 1000	621 per 1000 (481 to 801)	RR 1.39 (1.22 to 1.58)	843 (3 RCTs)	+ + + - Moderate	Reason for downgrading: between-study heterogeneity

*The basis for the **assumed risk** (median control group risk across studies) for survival outcomes is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
5FU: 5-fluorouracil; **CI:** confidence interval; **CRC:** colorectal cancer; **CTX:** chemotherapy; **FOLFOX:** fluorouracil + oxaliplatin + leucovorin; **HR:** hazard ratio; **RCT:** randomized controlled trial; **RR:** risk ratio.

Anmerkung/Fazit der Autoren

Systemic therapy offers a survival benefit to people with metastatic CRC who did not respond to first-line treatment, especially when targeted agents are combined with conventional chemotherapeutic drugs. Further research is needed to define the optimal regimen and to identify people who most benefit from each treatment.

We could not draw any conclusions on other debated aspects in this field of oncology, such as ranking of treatments (not all possible comparisons have been tested and many comparisons were based on single trials enrolling a small number of participants) and quality of life (virtually no data available).

Kommentare zum Review

- Fokus auf 2. Therapielinie

Wulaningsih W et al., 2016 [35].

Irinotecan chemotherapy combined with fluoropyrimidines versus irinotecan alone for overall survival and progression free survival in patients with advanced and/or metastatic colorectal cancer (Review)

Fragestellung

To compare the efficacy and safety of two chemotherapeutic regimens, irinotecan monotherapy or irinotecan in combination with fluoropyrimidines, for patients with advanced CRC when administered in the first or second-line settings.

Methodik

Population:

patients diagnosed histologically or cytologically with locally advanced and/or metastatic CRC

Intervention:

IRI with fluoropyrimidines administered intravenously or orally

Komperator:

single agent IRI

Endpunkte:

OS, TTP, PFS, QoL, AE, CR, PR

Recherche/Suchzeitraum:

Bis Dezember 2014; update Januar 2016

Qualitätsbewertung der Studien:

Cochrane 'Risk of bias' tool

Ergebnisse

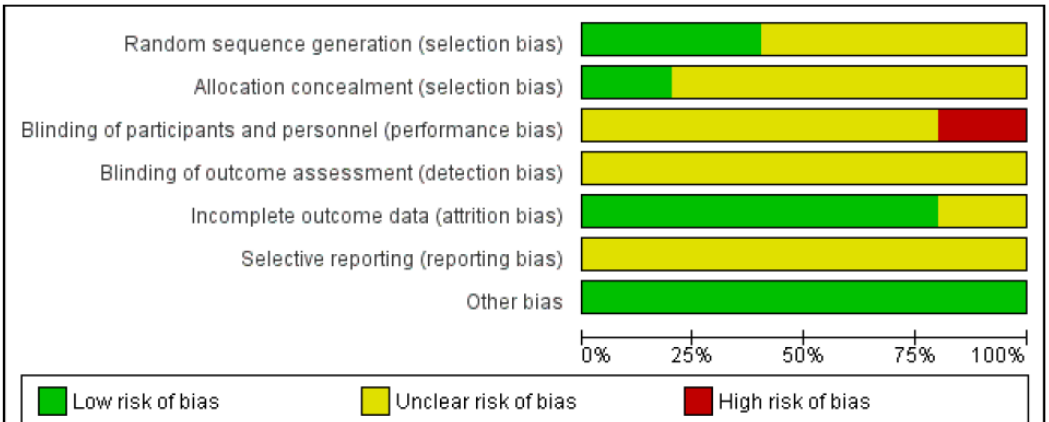
Anzahl eingeschlossener Studien:

Charakteristika der Population:

A total of 1,726 patients were randomised: 686 in the IRI-fluoropyrimidine combination group and 1,040 in the control group. Four of the studies administered IRI and the combination of IRI with fluoropyrimidine as a second-line treatment (Bécouarn 2001; Clarke 2011; Graeven 2007; Seymour 2007) and one study as a first-line treatment (Saltz 2000)

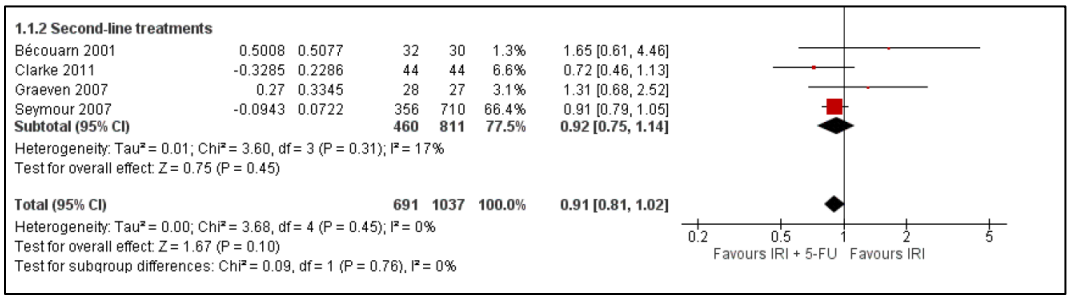
Qualität der Studien:

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

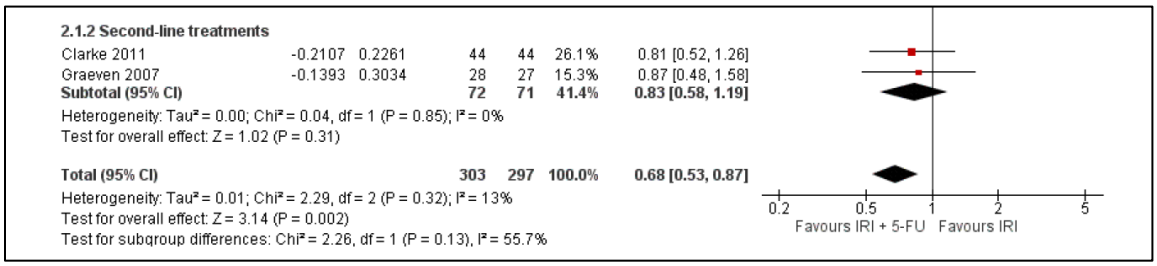


Studienergebnisse:

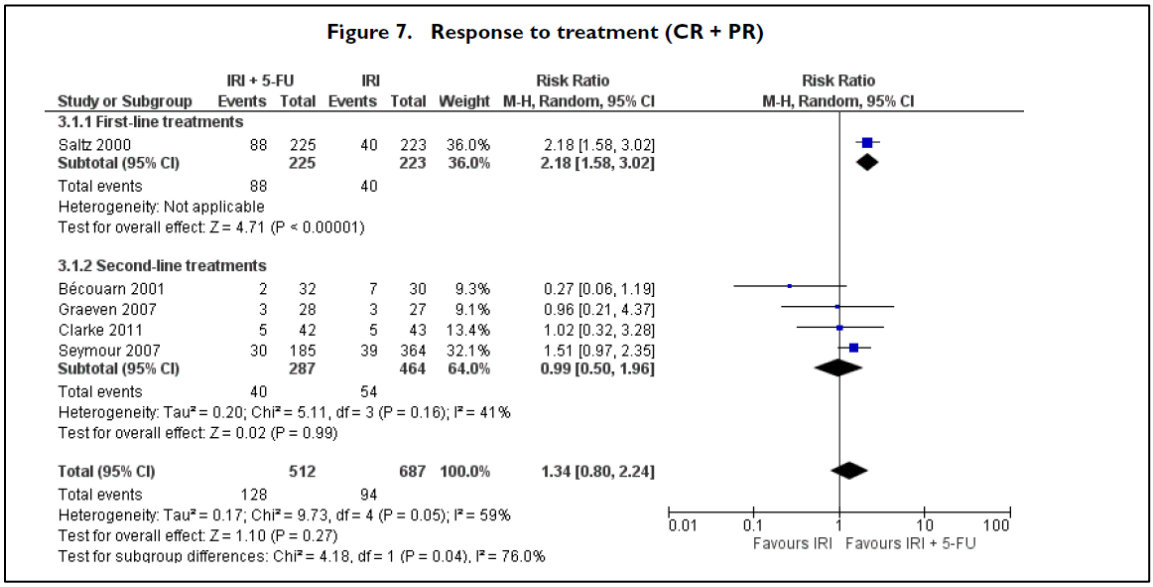
- **OS**



- **PFS**



- **Response to treatment (CR + PR)**



- **Adverse events**

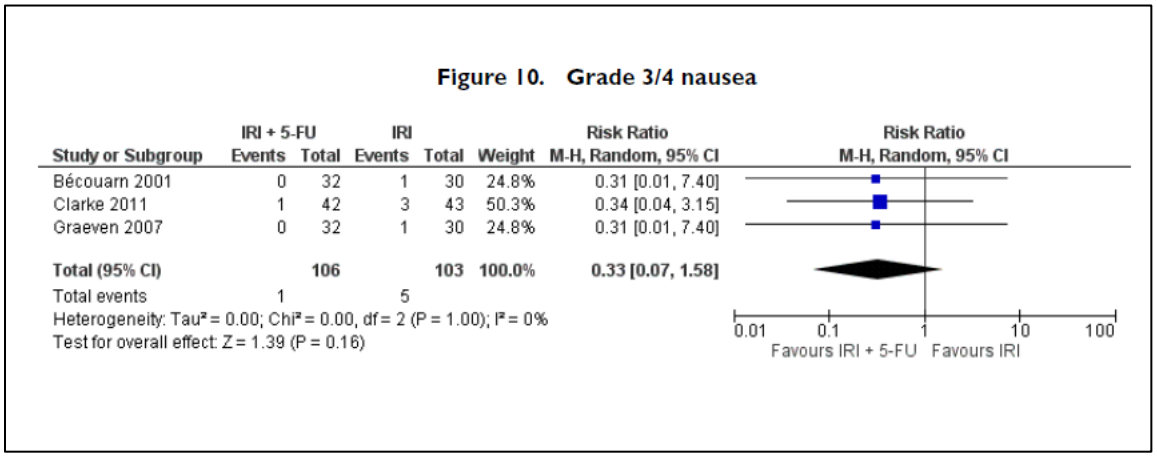


Figure 14. Grade 1/2 alopecia

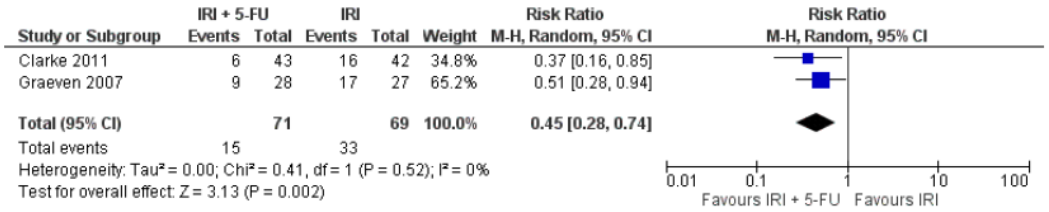
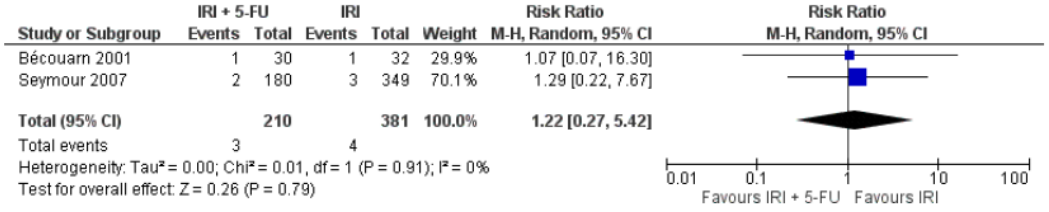


Figure 15. Neuropathy



Anmerkung/Fazit der Autoren

There was no overall survival benefit of the irinotecan and fluoropyrimidine treatment over irinotecan alone, thus both regimens remain reasonable options in treating patients with advanced or metastatic CRC. Given the low and moderate quality of the evidence, future studies with sufficient numbers of patients in each treatment arms are needed to clarify the benefit observed in progression-free survival with combination irinotecan and fluoropyrimidines.

Kommentare zum Review

- Pat. mit fortgeschrittenen und/ oder metastasierten CRC umfasst
- Fokus auf 2. Therapielinie

3.3 Systematische Reviews

Su GL et al., 2020 [30].

A meta-analysis comparing regorafenib with TAS-102 for treating refractory metastatic colorectal cancer.

Fragestellung

to compare the efficacy and toxicity of regorafenib and TAS-102.

Methodik

Population:

- patients with treatment-refractory mCRC

Intervention:

- regorafenib

Komparator:

- TAS-102

Endpunkte:

- OS, PFS, toxicity (incidence of severe adverse effects)

Recherche/Suchzeitraum:

- PubMed, EMBASE, and Cochrane Library through December 2018

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 3 trials were included in the analysis

Charakteristika der Population:

Table 1. The primary characteristics of the eligible studies.

			Number of patients		Mean patient age		Number of male patients		
First author	Year	Country	Regorafenib	TAS-102	Regorafenib	TAS-102	Regorafenib	TAS-102	Reference
Toshinori Sueda	2016	Japan	23	14	59	66	12	10	19
Toshikazu Moriwaki	2018	Japan	146	54	Not report	Not report	126	197	20
Toshiki Masuishi	2016	Japan	223	327	64	64	90	30	21

Qualität der Studien:

- All studies included in this study were based on moderate- to high-quality evidence.

Studienergebnisse:

- Regorafenib was significantly associated with disease progression (odds ratio [OR]= 0.33, 95% confidence interval [CI]= 0.21–0.50) and adverse events (OR= 4.38, 95% CI= 2.69–7.13).
- However, overall (OR= 0.97, 95% CI= 0.81–1.17) and progression-free survival (OR= 1.01, 95% CI= 0.86–1.18) did not significantly differ between the groups.
- The most common treatment-related adverse events in the regorafenib group were neutropenia (OR= 0.06, 95% CI= 0.03–0.11), hand–foot syndrome (OR= 50.34, 95% CI= 10.44–242.84), and liver dysfunction (OR= 34.51, 95% CI= 8.30–143.43). Conversely, the incidence of thrombocytopenia did not differ between the two groups.

Anmerkung/Fazit der Autoren

Our meta-analysis found that regorafenib and TAS-102 have similar efficacy but different adverse event profiles in patients with mCRC who are refractory to standard chemotherapy. To our knowledge, patient comorbidities and the safety profiles of the drugs are the major drivers of the selection of regorafenib or TAS-102. Further analyses of biomarkers, assessments of initial dose reduction, or the use of combination therapy may aid in further tailoring the treatment for chemotherapy-resistant mCRC to obtain maximal clinical benefits.

He S et al., 2020 [17].

Efficacy of immunotherapy with PD-1 inhibitor in colorectal cancer: a meta-analysis.

Fragestellung

a meta-analysis on the effects of the monotherapy anti-PD-1 inhibitors in treating metastatic colorectal cancer (mCRC).

Methodik

Population:

- patients with diagnostic CRC

Intervention/Komparator:

- anti-PD-1 inhibitors: pembrolizumab or nivolumab

Endpunkte:

- overall survival rate (OS), progression-free survival rate (PFS), disease control rate (DCR) and objective response rate (ORR)

Recherche/Suchzeitraum:

- PubMed, Web of science, Elsevier, Cochrane Library, Embase and CNKI (China National Knowledge Infrastructure) before 22 May 2020

Qualitätsbewertung der Studien:

- Cochrane Collaboration tool. Risk ofbias for each item was graded as ’low’, ’unclear’ and ’high’

Ergebnisse

Anzahl eingeschlossener Studien:

- six studies were included with a total of 297 participants
- Among the five studies evaluating immunotherapy with PD-1 inhibition, two studies were conducted to evaluate the performance ofnivolumab and four studies described the performance of pembrolizumab

Charakteristika der Population:

- All the eligible patients had progressed on or after, at least one previous line of treatment, including chemotherapy, monoclonal antibody or targeted therapy

Table 1. Characteristics of included studies for programmed cell death protein-1 inhibitor on colorectal cancer.

Study	Year	n	Age (years)	M/F	Anti-PD-1 inhibitor	OS rate at 1 year (%)	DCR	PFS rate 1 year (%)	ORR (%)	Dose	Molecular pheno-types	Ref.
Keynote 164	2018	63	59 (23–83)	33/30	Pembrolizumab	76	95%	41	33	200 mg every 3 weeks	dMMR	[11]
Le *et al.*	2015	11	46 (24–65)	6/5	Pembrolizumab	-	90%	-	40	10 mg/kg	dMMR	[13]
		21	61 (32–79)	13/8	Pembrolizumab	-	11%	-	0	10 mg/kg	pMMR	
O'Neil *et al.*	2017	23	57 (40–78)	13/10	Pembrolizumab	29.8	-	4.3	4	10 mg/kg	pMMR	[14]
Overman *et al.*	2017	74	52.5 (44–64)	44/30	Nivolumab	73	69%	50	31.1	3 mg/kg	dMMR	[9]
T. Le *et al.*	2017	86	57 (24–92)	44/42	Pembrolizumab	76	-	64	52	-	dMMR	[12]
Topalian *et al.*	2012	19	63 (29–85)	-	Nivolumab	-	-	-	0	0.3 mg/kg	pMMR	[10]

-: Non declared; DCR: Disease control rate; dMMR: DNA mismatch repair deficient; mCRC: Metastatic colorectal cancer; MSI-H: Microsatellite instability-high; MSS: Microsatellite-stable; ORR: Objective respose rate; OS: Overall survival; PD-1: Programmed cell death protein-1; PFS: Progression-free survival; pMMR: DNA mismatch repair proficient.

Qualität der Studien:

Figure 1. Flow diagram of the literature search in this meta-analysis.

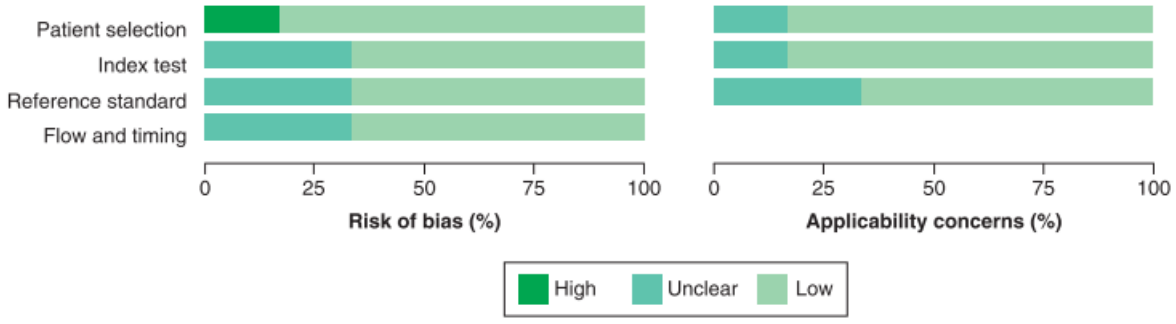


Figure 2. Risk of bias summary of six included studies.

Studienergebnisse:

- The overall survival rate at 1-year was 64.2% (95% CI: 0.46–0.83).
- Disease control rate was 56.5% (CI: 0.27–0.86) and the objective response rate as 19.7% (CI: 0.08–0.32).
- The 1-year-progression-free survival rate was 38.4% (CI: 0.12–0.66).

Anmerkung/Fazit der Autoren

The efficacy of monotherapy anti-PD-1 inhibitor is encouraging with prolonged survival related to patients with dMMR/MSI-H mCRC. Still, treatments like surgical operation, radiotherapy or chemotherapy are still the main treatments modality. The result ofcurrent study shows a promising future ofPD-1 inhibitor on treatment ofCRC. We encourage more attention on the exploration ofPD-1 inhibitor in the treatment ofCRC patients and with the results showing that PD-1 inhibitors are effective in dMMR CRC and MSI-H mCRC, additional information is needed for a further evaluation on it.

Fan Q et al., 2020 [10].

Selective Vascular Endothelial Growth Factor Receptor Inhibitors Provide Limited Benefits for Metastatic Colorectal Cancer: A Meta-Analysis.

Fragestellung

To demonstrate the efficacy and safety of selective VEGFR inhibitors in the management of mCRC.

Methodik

Population:

- mCRC patients

Intervention:

- chemotherapy + VEGFR

Komparator:

- Chemotherapy without VEGFR

Endpunkte:

- progression-free survival (PFS) rates, overall survival (OS) rates, complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), objective response rates (ORRs), disease control rates (DCRs) and adverse effect (AE) rates

Recherche/Suchzeitraum:

- PubMed, EMBASE, Web of Science, Ovid MEDLINE, Google Scholar, Springer and Cochrane Central databases from the inception of the database to January 15, 2020

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 22 studies with a total of 9362 patients

Charakteristika der Population:

Table 1. Characteristics of the included studies.

First Author	Publication Year	Location of Study	Patients	Number of Patients in VEGFR Inhibitor Group/Control Group	Number of male Patients In VEGFR Inhibitor Group/Control Group	Median Age of VEGFR Inhibitor Group/Control Group	Intervention Method	VEGFR Targets
Axel Grothey	2013	Multiple nations	Previously treated mCRC	505/255	311/153	61/61	Regorafenib (160 mg/dfor 3 weeks on/1 week off)/placebo	VEGFR-1, VEGFR-2,VEGFR-3
Jin Li	2015	Multiple nations	Previously treated mCRC	136/68	85/33	57.5/55.5	Regorafenib (160 mg/d for 3 weeks on/1 week off)/placebo	VEGFR-1, VEGFR-2,VEGFR-3
Rui-Hua Xu	2017	China	Previously treated mCRC	47/24	35/17	50/54	Fruquintinib (5 mg/d for 3 weeks on/1 week off)/placebo	VEGFR-1, VEGFR-2,VEGFR-3
Cristina Grávalos	2018	Spain	Previously treated mCRC	25/24	16/17	69/67	Axitinib (5 mg/d in cycles of 4 weeks)/placebo	VEGFR-1, VEGFR-2,VEGFR-3
Jin Li	2018	China	Previously treated mCRC	278/138	158/97	55/57	Fruquintinib (5 mg/d for 3 weeks on/1 week off)/placebo	VEGFR-1, VEGFR-2,VEGFR-3
Xiaoli Liao	2018	China	Previously treated advanced CRC	27/26	20/16	51/58.5	Apatinib (500 mg/d)/none	VEGFR-2
E. Van Cutsem	2018	Multiple nations	Previously treated mCRC	386/382	236/218	62/62	Nintedanib (400 mg/d for 3 weeks on/1 week off)/placebo	VEGFR-1, VEGFR-2,VEGFR-3
J. Randolph Hecht	2011	Multiple nations	Previously untreated mCRC	585/583	368/352	59.1/59.69(Mean)	FOL-FOX4+vatalanib(1250 mg/d)/FOLFOX4+placebo	VEGFR-1, VEGFR-2,VEGFR-3
T. Kato(20 mg)	2012	Japan	Previously untreated mCRC	58/58	38/39	63.5/64(Mean)	mFOL-FOX4+cediranib(20 mg/d)/mFOL-FOX4+placebo	VEGFR-1, VEGFR-2,VEGFR-3
T. Kato(30 mg)	2012	Japan	Previously untreated mCRC	56/58	30/39	53.6/64(Mean)	mFOL-FOX4+cediranib(30 mg/d)/mFOL-FOX4+placebo	VEGFR-1, VEGFR-2,VEGFR-3
Alfredo Carrato	2013	Multiple nations	Previously untreated mCRC	386/382	222/203	59/58	FOLFIR+sunitinib(37.5mg/d)/FOLFIR+placebo	VEGFR-2
Josep Tabernero	2013	Multiple nations	Previously untreated mCRC	97/101	42/63	59.2/60.3(Mean)	FOL-FOX4+sorafenib(800 mg/d)/FOLFOX4+placebo	VEGFR-3
Eric Van Cutsem	2011	Multiple nations	Previously treated mCRC	426/429	264/268	60.5/59.2(Mean)	FOL-FOX4+vatalanib（1250 mg/d）/FOL-FOX4+placebo	VEGFR-1, VEGFR-2,VEGFR-3

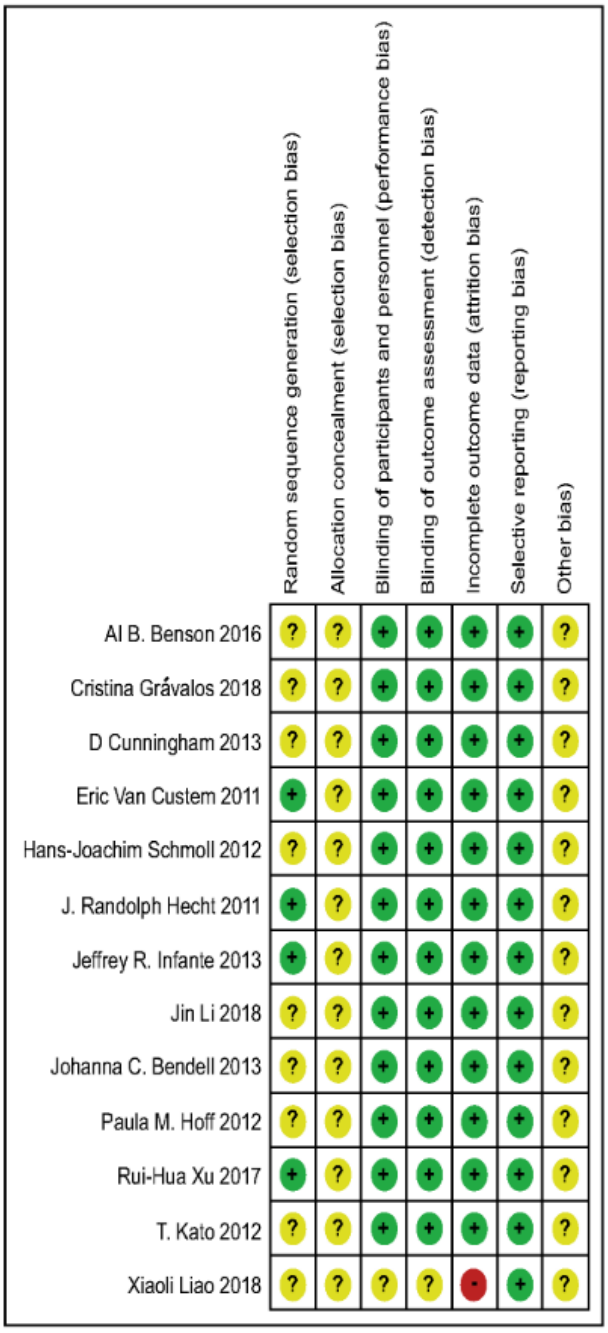
Table 1 contd...

Paulo M. Hoff	2012	Multiple nations	Previously untreated mCRC	502/358	299/212	58/59	FOL-FOX4/mFOLFOX4/CAPOX+cediranib(20 mg/d)/mFOL-FOX4+placebo	VEGFR-1, VEGFR-2,VEGFR-3
Hanna K. Sanoff	2018	United States and Ireland	Previously treated mCRC	120/61	68/30	62/62	FOLFIRi+regorafenib (160 mg/d)/FOLFIRI+placebo	VEGFR-1, VEGFR-2,VEGFR-3
Hans-Joachim Schmoll	2012	Multiple nations	Previously untreated mCRC	709/713	412/414	59/60	Cediranib(20 mg/d)+mFOL-FOX4/bevacizumab (5 mg/kg every 14 d)+mFOLFOX4	VEGFR-1, VEGFR-2,VEGFR-3
Johanna C. Bendell	2013	Multiple nations	Previously treated mCRC	36/35	16/24	58.5/60	Axitinib(5 mg/d)+mFOL-FOX4/FOLFIRI/bevacizumab(5 mg/kg every 14 d)+ mFOL-FOX4/FOLFIRI	VEGFR-1, VEGFR-2,VEGFR-3
D Cunningham(20 mg)	2013	Multiple nations	Previously treated mCRC	71/66	49/39	-	Cediranib(20 mg/d)+mFOL-FOX4/bevacizumab (10 mg/kg every 14 d)+mFOLFOX4	VEGFR-1, VEGFR-2,VEGFR-3
D Cunningham (30 mg)	2013	Multiple nations	Previously treated mCRC	73/66	47/39	-	Cediranib (30 mg/d)+mFOL-FOX4/bevacizumab (10 mg/kg every 14 d)+mFOLFOX4	VEGFR-1, VEGFR-2,VEGFR-3
Jeffrey R. Infante	2013	United States	Previously untreated mCRC	42/43	25/28	61/64	Axitinib (5 mg/d) +mFOL-FOX4/bevacizumab (5 mg/kg every 14 d)+mFOLFOX4	VEGFR-1, VEGFR-2,VEGFR-3
Bert H. O'Neil (7.5mg)	2014	Multiple nations	Previously treated mCRC	50/49	30/29	62/57	Linifanib (7.5 mg/d)+mFOL-FOX4/bevacizumab (10 mg/kg every 14 d)+mFOLFOX4	VEGFR-1, VEGFR-2
Bert H. O'Neil (12.5mg)	2014	Multiple nations	Previously treated mCRC	49/49	26/29	59/57	Linifanib (12.5 mg/d)+mFOL-FOX4/bevacizumab (10 mg/kg every 14 d)+mFOLFOX4	VEGFR-1, VEGFR-3
Al B. Benson	2016	Multiple nations	Previously untreated mCRC	177/88	118/55	61.9/62.6(Mean)	Tivozanib(5 mg/d)+mFOL-FOX4/bevacizumab (5 mg/kg every 14 d)+mFOLFOX4	VEGFR-1, VEGFR-2,VEGFR-3

Table 1 contd....

Galal KM	2011	Saudi Arabia	Previously treated mCRC	18/17	11/11	57/58	Sorafenib (800mg/d)+cetuximab(1100mg/m^2 in a month)/cetuximab (1100mg/m^2 in a month)	VEGFR-2
Lillian L. Siu	2013	Multiple nations	Previously treated mCRC	376/374	247/234	64.1/63.4	Brivanib (800mg/d)+cetuximab (1100mg/m^2 in a month)/cetuximab(1100mg/m^2 in a month)+placebo	VEGFR-2

Qualität der Studien:



Studienergebnisse:

- Compared with placebo, selective VEGFR inhibitors significantly increased the PFS rate, SD, PR and DCR, reduced PD, caused more treatment-emergent adverse events (TEAEs), hypertension, hand-foot skin reaction, diarrhoea, fatigue, and thrombocytopaenia and increased aspartate aminotransferase(AST) concentration.
- There was no significant difference between selective VEGFR inhibitors and placebo regarding OS rate, CR, ORR, proteinuria, hyperbilirubinaemia or alkaline phosphatase(ALP) concentration.

Table 2. Results of forest plots for the PFS rate and OS rate.

	Comparisons	Number of Included Studies	OR	95% CI	P Value	X^2	I^2
PFS rate							
-	Selective VEGFR inhibitors *vs* placebo at 7 months	6	4.96	1.77,13.91	0.002	0.004	71%
-	FOLFOX4+selective VEGFR inhibitors *vs* FOLFOX4+placebo at 18 months	6	1.11	0.76,1.61	0.59	0.008	68%
-	FOLFOX4+selective VEGFR inhibitors *vs* FOLFOX4+bevacizumab at 10 months	8	0.83	0.57,1.21	0.34	0.01	61%
-	Selective VEGFR inhibitors +cetuximab *vs* cetuximab at 7 months	2	1.49	1.07,2.07	0.02	0.60	0%
OS rate							
-	Selective VEGFR inhibitors *vs* placebo at 15 months	6	1.28	0.75,2.20	0.37	0.001	75%
-	FOLFOX4+selective VEGFR inhibitors *vs* FOLFOX4+placebo at 12 months	8	0.94	0.78,1.13	0.51	0.23	25%
-	FOLFOX4+selective VEGFR inhibitors *vs* FOLFOX4+bevacizumab at 20 months	7	0.76	0.54,1.07	0.12	0.09	45%
-	Selective VEGFR inhibitors +cetuximab *vs* cetuximab at 12 months	2	1.21	0.90,1.64	0.21	0.69	0%

- Additionally, compared with FOLFOX4+placebo, FOLFOX4+ selective VEGFR inhibitors, clearly reduced PD, and caused more 3-4 AEs, serious AEs, hypertension, hand-foot syndrome, diarrhoea, nausea, vomiting, decreased appetite, dehydration, fatigue, dizziness, neutropaenia and thrombocytopaenia.
- For PFS rate, OS rate, CR, PR, SD, ORR, abdominal pain, peripheral sensory neuropathy, asthaenia, anaemia and hypokalaemia rates, there was no significant difference between FOLFOX4+ selective VEGFR inhibitors and FOLFOX4+placebo.
- However, compared with FOLFOX4+bevacizumab, FOLFOX4+selective VEGFR inhibitors, led to increased hypertension, neutropaenia, fatigue, thrombocytopaenia and asthaenia. There is no clear difference between FOLFOX4+selective VEGFR inhibitors and FOLFOX4+ bevacizumab with regard to PFS rate, OS rate, CR, PR, SD, PD, ORR, diarrhoea, nausea, vomiting, peripheral neuropathy and abdominal pain rates.
- Selective VEGFR inhibitors+cetuximab increased PFS and PR and reduced PD compared to cetuximab, but there was no statistical difference between the two groups for OS and SD.

Table 3. Results of forest plots for CR, PR, SD, PD, ORR and DCR.

-	Comparisons	Number of Included Studies	OR	95% CI	P value	X^2	I^2
CR							
-	Selective VEGFR inhibitors *vs* placebo	6	1.50	0.06,36.99	0.81	-	-
-	FOLFOX4+selective VEGFR inhibitors *vs* FOLFOX4+placebo	6	0.91	0.39,2.10	0.83	0.60	0%
-	FOLFOX4+selective VEGFR inhibitors *vs* FOLFOX4+bevacizumab	6	1.09	0.52,2.28	0.81	0.71	0%
PR							
-	Selective VEGFR inhibitors *vs* placebo	7	3.84	1.21,12.23	0.02	0.92	0%
-	FOLFOX4+selective VEGFR inhibitors *vs* FOLFOX4+placebo	5	1.00	0.74,1.37	0.98	0.05	57%
-	FOLFOX4+selective VEGFR inhibitors *vs* FOLFOX4+bevacizumab	6	0.90	0.75,1.07	0.23	0.47	0%
-	Selective VEGFR inhibitors +cetuximab *vs* cetuximab	2	2.04	1.28,3.26	0.003	0.86	0%
SD							
-	Selective VEGFR inhibitors *vs* placebo	3	4.65	2.37,9.11	<0.00001	0.42	0%
-	FOLFOX4+selective VEGFR inhibitors *vs* FOLFOX4+placebo	5	1.07	0.89,1.28	0.49	0.42	0%
-	FOLFOX4+selective VEGFR inhibitors *vs* FOLFOX4+bevacizumab	6	0.95	0.80,1.14	0.59	0.83	0%
-	Selective VEGFR inhibitors +cetuximab *vs* cetuximab	2	1.27	0.96,1.69	0.10	0.42	0%
PD							
-	Selective VEGFR inhibitors *vs* placebo	2	0.15	0.07,0.33	<0.00001	0.91	0%
-	FOLFOX4+selective VEGFR inhibitors *vs* FOLFOX4+placebo	5	0.62	0.45,0.85	0.003	0.55	0%
-	FOLFOX4+selective VEGFR inhibitors *vs* FOLFOX4+bevacizumab	6	1.09	0.83,1.43	0.54	0.46	0%
-	Selective VEGFR inhibitors +cetuximab *vs* cetuximab	2	0.46	0.34,0.63	0.54	<0.00001	0%
ORR							
-	Selective VEGFR inhibitors *vs* placebo	3	3.74	0.82,17.00	0.09	0.49	0%
-	FOLFOX4+selective VEGFR inhibitors *vs* FOLFOX4+placebo	5	0.97	0.74,1.28	0.84	0.13	44%
-	FOLFOX4+selective VEGFR inhibitors *vs* FOLFOX4+bevacizumab	5	0.74	0.51,1.09	0.13	0.34	12%
DCR							
-	Selective VEGFR inhibitors *vs* placebo	5	6.23	3.33,11.65	<0.00001	0.0001	82%

Anmerkung/Fazit der Autoren

Compared with placebo or cetuximab, selective VEGFR inhibitors alone or combined with cetuximab seemed to be more efficacious for mCRC respectively; however, the effects were not better than FOLFOX4 alone or when combined with bevacizumab for mCRC. Additionally,

selective VEGFR inhibitors were not as safe as placebo or FOLFOX4 alone or in combination with bevacizumab in mCRC.

Kommentare zum Review

- Therapielinien gemischt.

Cao M et al., 2020 [4].

Comparison of efficacy and safety for patients with beyond second line treated metastatic colorectal cancer: a network meta-analysis of randomized controlled trials.

Fragestellung

We performed this systematic review and network meta-analysis to evaluate the efficacy and safety of regorafenib, TAS-102, fruquintinib, cetuximab and panitumumab in mCRC patients beyond second line treatment in randomized controlled trials (RCTs).

Methodik

Population:

- patients with previously treated mCRC (had previously received at least two regimens or were unable to tolerate standard treatments)

Intervention/Komparator:

- compare different drugs with control (placebo or best supportive care [BSC])

Endpunkte:

- OS, progression-free survival [PFS], adverse events

Recherche/Suchzeitraum:

- PubMed in March 2019

Qualitätsbewertung der Studien:

- Cochrane collaboration risk bias tool

Ergebnisse

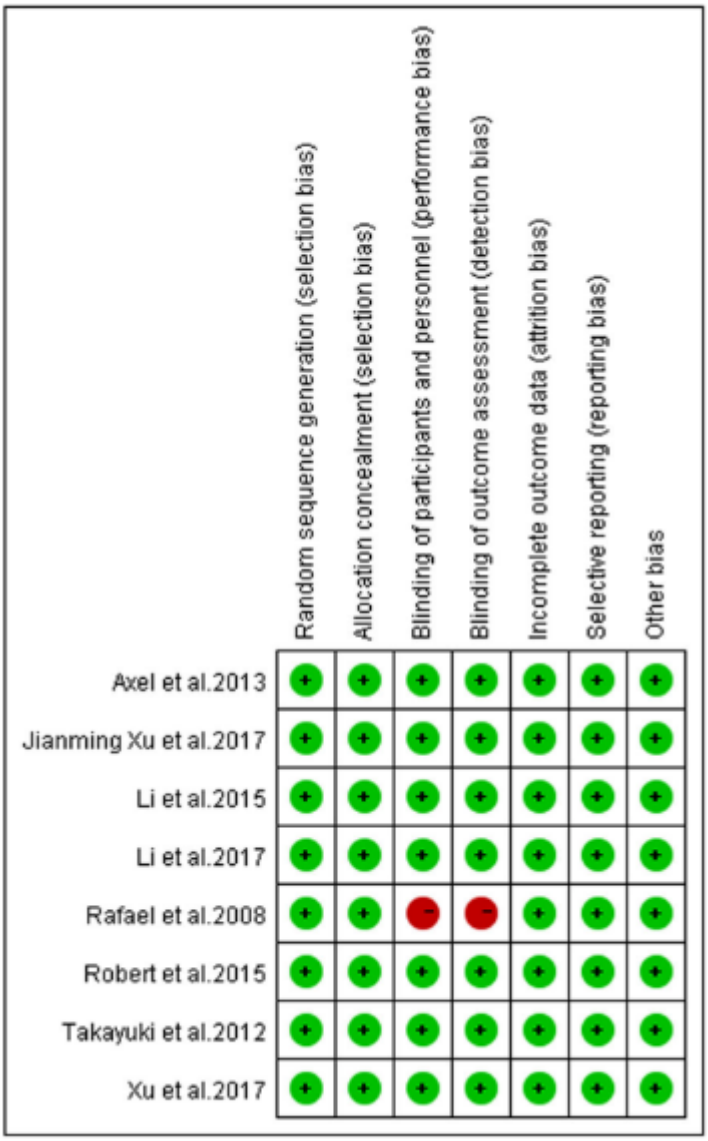
Anzahl eingeschlossener Studien:

- 8 studies
- All of the eight studies compared these different drugs (one drug per study) as single agents versus placebo.

Charakteristika der Population:

- There were 3,289 patients (regorafenib, n=641; TAS102, n=917; fruquintinib, n=325; panitumumab, n=231; control, n=1,175) from eight RCTs in this network meta-analysis.

Qualität der Studien:



Studienergebnisse:

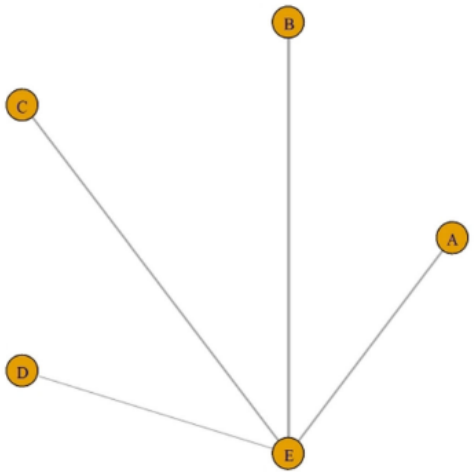


Figure 3. Network of the comparisons for the network meta-analysis (A: regorafenib; B: TAS-102; C: fruquintinib; D: panitumumab; E: placebo).

- Indirect comparisons showed that OS was not significantly different among the four drugs, but regorafenib (HR = 0.68, 95% CI, 0.46–0.95) and TAS-102 (HR = 0.69, 95% CI, 0.51–0.91) showed better OS than the placebo group. Fruquintinib (HR = 0.27, 95% CI, 0.17–0.45), regorafenib (HR = 0.43, 95% CI, 0.26–0.62) and TAS-102 (HR = 0.45, 95% CI, 0.31–0.63) showed better PFS than the placebo group, but there were no significant differences in PFS among the four drugs.
- When considering KRAS status, indirect comparison showed that OS and PFS for mutant KRAS patients was not significantly different mong the four drugs and placebo.
- Patients with wild-type KRAS who received one of the four drugs exhibited significantly better OS and PFS than the placebo group, with the exception of OS for patients treated with panitumumab (HR = 1, 95% CI, 0.77–1.3). Panitumumab also performed worse for OS than fruquintinib (HR = 1.8, 95% CI, 1.2–2.8), regorafenib (HR = 1.6, 95% CI, 1.1–2.3) and TAS-102 (HR = 1.5, 95% CI, 1.1–2.1).
- There was no significant difference in OS among fruquintinib, regorafenib or TAS-102 treated patients. Fruquintinib exhibited significantly better PFS compared with regorafenib (HR = 0.38, 95% CI, 0.25–0.59), TAS-102(HR = 0.39, 95% CI, 0.26–0.58) and panitumumab (HR = 0.4, 95% CI, 0.26–0.62).
- Indirect comparison showed that the incidence of grade 3–5 toxicity reaction for regorafenib and fruquintinib were significantly higher than the placebo group (regorafenib: RR = 3.7, 95% CI, 1.8–7.8; fruquintinib: RR = 3.2, 95% CI, 1.2–8.8); regorafenib exhibited a higher toxicity profile than TAS-102 (RR = 3.1, 95% CI, 1.2–9.2). In addition, the incidence of all grades toxicity reaction for regorafenib was higher than placebo (RR = 1.8, 95% CI, 1–3.1), but no significant differences with TAS-102, fruquintinib and panitumumab.
- Subgroup analysis of specific toxicity types showed the most common non-hematological toxicity, which occurred in at least 10% of patients taking any of the four drugs, was diarrhea. There was no significant difference among the all grade diarrhea for these four drugs. Regorafenib and TAS-102 represented significantly higher gastrointestinal adverse effects than fruquintinib, but no differences between each other (TAS-102: diarrhea, RR = 0.62, 95% CI, 0.38–1; vomiting, RR = 1.5, 95% CI, 0.2–12). Regorafenib and fruquintinib were associated with higher rates of hand-foot skin reaction (HFSR) and hypertension compared

with TAS-102. Skin-related toxicities were the most common cause of panitumumab related toxicity reactions, which occurred in 90% of patients.

Anmerkung/Fazit der Autoren

In summary, regorafenib, TAS-102 and fruquintinib all showed positive effects on OS and PFS, though there was no evidence to indicate that any one treatment had better efficacy than the others. Clinicians should consider potential adverse events as they relate to each individual patient's condition when making treatment choices. For patients with wild-type KRAS, fruquintinib exhibited significantly better PFS and was well tolerated, with reduced gastrointestinal adverse effects compared with the other drugs, making it a promising agent for treatment of patients with wild-type KRAS mCRC beyond second line.

Casadei-Gardini A et al., 2020 [5].

Is There an Optimal Choice in Refractory Colorectal Cancer? A Network Meta-Analysis.

Fragestellung

Network meta-analysis (NMA) evaluated and compared the efficacy of these 4 therapeutic alternatives in the setting of patients with chemorefractory CRC.

Methodik

Population:

- patients with chemorefractory CRC

Intervention/Komparator:

- drugs used in the third-line treatment of advanced colon cancer.

Endpunkte:

- OS

Recherche/Suchzeitraum:

- PubMed database until November 1, 2018

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien/Charakteristika der Population:

- The NMA between TAS-102 and regorafenib included data from 2170 individual patients with CRC fulfilling the eligibility criteria. Of these patients, 641 had received regorafenib (29.5%), 805 had received TAS-102 (37.1%), and 724 had (33.4%) received placebo.
- The NMA of all drugs approved for refractory and/or mCRC included data from 3739 patients fulfilling the eligibility criteria. Of these, 641 had received regorafenib (17.1%), 805 had received TAS-102 (21.5%), 787 had received cetuximab (21.0%), 499 had received panitumumab (13.3%), and 1009 (27.0%) had received placebo or BSC.

Supplemental Table 10 Characteristic of Studies Selected for Network Meta-analysis

Variable	TERRA[1]	RECOURSE[2]	CONCUR[3]	CORRECT[4]	NCT00079066[5]	ASPECCT[6]
Primary outcome	OS	OS	OS	OS	OS	OS
Trial type	Superiority	Superiority	Superiority	Superiority	Superiority	No inferiority
Treatment	TAS-102 versus PBO	TAS-102 versus PBO	Rfen versus PBO	Rfen versus PBO	Cmab versus BSC	Pmab versus Cmab

Abbreviations: BSC = best supportive care; Cmab = cetuximab; OS = overall survival; PBO = placebo; Pmab = panitumumab; Rfen = regorafenib.

Qualität der Studien:

Supplemental Table 11 Possible Sources of Bias From Randomized Controlled Trials Included in Network Meta-analysis

Variable	TERRA[1]	RECOURSE[2]	CONCUR[3]	CORRECT[4]	NCT00079066[5]	ASPECCT[6]
Random sequence generation (selection bias)	Low	Low	Low	Low	Low	Low
Allocation concealment (selection bias)	Low	Low	Low	Low	Low	Low
Blinding of participants and personnel (performance bias)	Double	Double	Double	Double	Impossible	Impossible
Blinding of outcome assessment (detection bias)	High (due to double blinding)	High (due to double blinding)	High (due to double blinding)	High (due to double blinding)	High (outcome not influenced by lack of blinding)	High (outcome not influenced by lack of blinding)
Incomplete outcome data (attrition bias)	Low	Low	Low	Low	Low	Low
Selective reporting (reporting bias)	Low	Low	Low	Low	Low	Low
Other bias	NA	NA	NA	NA	NA	NA

Abbreviation: NA = not available.

Studienergebnisse:

- No difference in OS was found between regorafenib and TAS-102.
- For a rectal primary location, TAS-102 conferred benefit versus placebo (hazard ratio [HR], 0.671), but regorafenib did not (HR, 0.950).
- For patients aged > 65 years, TAS-102 showed benefit versus placebo (HR, 0.579) but regorafenib did not (HR, 0.816).
- For patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 in the indirect comparison, regorafenib showed benefit versus placebo (HR, 0.687), as did TAS-102 (HR, 0.756) but with a lower advantage.
- For patients with RAS wild type not previously treated with anti-EGFR antibodies, panitumumab was the optimal choice for OS.

Anmerkung/Fazit der Autoren

Our NMAs were unable to identify a difference in term of OS between regorafenib and TAS-102. However, the clinical efficacy of TAS-102 appears to be improved compared with regorafenib for patients with a primary rectal location, ECOG PS > 0, and age > 65 years. In contrast, regorafenib was associated with improved clinical efficacy for patients with ECOG PS 0 and age < 65 years. In the RAS WT population, anti-EGFR antibody therapy was clearly superior with respect to clinical activity compared with regorafenib and TAS-102. These findings should be viewed as exploratory, and further prospective studies are warranted to validate these data.

Petrelli F et al., 2020 [25].

A systematic review of salvage therapies in refractory metastatic colorectal cancer.

Fragestellung

a systematic review of all the published phase 2–3 trials, with the scope to evaluate the benefit of any later-line regimens in refractory metastatic CRC.

Methodik

Population:

- patients with mCRC

Intervention/Komparator:

- third-line treatments or beyond

Endpunkte:

- overall survival (OS), progression-free survival (PFS), response rate (ORR), stable disease rate (SD), and 6-month and 1-year OS

Recherche/Suchzeitraum:

- Pubmed, EMBASE, and Cochrane Library from January 2008 to May 5, 2019

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool for assessing the risk of bias nd the Risk ofBias in Nonrandomized Studies ofInterventions (ROBINS I) tool

Ergebnisse

Anzahl eingeschlossener Studien/Charakteristika der Population/Qualität der Studien:

- Overall, 7556 patients were included from 67 studies (n = 70 arms)

Table 1 Characteristics of included studies

Author/year	Type of study	Pts n°	Median age (years) /PS 0–1 (%)	CT schedule (%)	Biologic-1 (%)	Biologic-2 (%)	ORR %	SD %	PFS (months)	OS (months)	6 m OS %	12 m OS %	Risk of bias
Altomare/2011	Phase 2	50 (50% ≥ 5 L)	56/NR	–	BEV (100)	EVE (100)	0 (*n* = 49)	46	2.3	8.1	60	34	Moderate
Andre/1999	Phase 2	33	60.8/94 (WHO)	FOLFIRI (100)	–	–	6	61	4.5	5.75	80	50	
Andre/2012	Phase 2	41°	62/89.3 (WHO)	CPT-11 (100)	PANI (100)	–	46.3	34.1	8.7	15.8	80	60	Moderate
Baratelli/2017	Phase 2	42 (47% ≥ 4 L)	67.8/100	MMC + UFT + FA (100)	–	–	2.3 (*n* = 29)	23.9	3.3	6.9	–	–	Moderate
Becerra/2014	Phase 2	168 (76% ≥ 4 L)	60/97	–	Figitumumab 20 & 30 mg/kg	–	0	–	1.4	5.7	35	25	Low
Bouche/2011	Phase 2	46 (86% ≥ 4 L)	83/NR	–	BIBF 1120 (100)	Afatinib (100)	0	43.5	1.9	5.5	45	–	Moderate
Calegari/2017	Phase 2	41 (63% ≥ 4 L)	66/85	Temozolamide (100)	–	–	10	22	1.9	5.1	41	16.2	Moderate
Cascinu/2017	Phase 3	70 (31 + 39)	61/100 (FOLFOX), 64/100 (CPT-11 + CET)	FOLFOX (44)	CPT-11 + CET (56)	–	23/21	–	4/4.7	–	–	–	Moderate
Chen Y/2019	Phase 2	46 (4.3% 4 L)	57/93.5	S-1 + raltitrexed (100)	–	–	13	41.3	3.82	13.3	82	55	Moderate
Chen X/2019	Phase 2	26 (100% ≥ 4 L)	57/77	–	Apatinib (100)	–	0	23	3.9	7.9	–	–	Low
Choi/2015	Phase 2	25	61/40	CAPE + oral FA (100)	–	–	12	44	2.8 (TTP)	7.1	80	36	Moderate
Chong/2005	Phase 2	36 (50% ≥ 5 L)	64/78	CAPE + MMC (100)	–	–	15.2 (*n* = 33)	48.5	5.4	9.3	70	30.6	Moderate
Cremolini/2018	Phase 2	28	69/64 (PS 0)	CPT-11 (100)	CET (100)	–	21	32	3.4	9.8	–	–	Low
Chung/2010	Phase 2	47 (100% ≥ 3 L)	62/100	–	Tremelimumab (100)	–	2	2	2.3	4.8	40	10.7	Moderate
Ducreux/2017	Phase 2	37	62/100	NAB-paclitaxel (100)	–	–	0	16	2	–	–	–	Moderate
Eng/2019	Phase 3	267 (77% ≥ 5 L)	57.6/100	ATEZO+COBI (A 50)	ATEZO (B 25)	REGO (C 25)	A 3; B 2 C 2	A 23; B 19 C 32	A 1.91; B 1.94 C 2	A 8.87; B 7.10; C 8.51	A 63, B 61, C 60	A 40; B 38; C 29	Low
Fakih/2012	Phase 2	58 (100% ≥ 3 L)	60/93	5-FU + FA (100)	Vorinostat 800 mg ×3 days (100)	Vorinostat 1400 mg ×3 days (100)	1.7	27.5	2.65	6.6	50	20	Moderate
Grothey/2013	Phase 3	500 (75% ≥4 L)	61/100	–	REGO (100)	–	1	40	1.9	6.4	52.5	24.3	Low
Hecht/2007	Phase 2	148	59.5/100	–	PANI (100)	–	9	29	3.5	9	60	25	Low
Hickish/2017	Randomized phase 2	207 (60% ≥4 L)	64/82	–	MABp1 (100)	–	0	17	–	6.1	50	15	Moderate
Hsu/2018	Phase 2	41 (93% ≥4 L)	62/95	S-1 + FA (100)	–	–	0 (*n* = 36)	61.1	2.5	7.63	70	27	Moderate
Huang/2013	Phase 4	269 (36% ≥ 4 L)	60/94	OXA- or IRI-based CT (100)	CET (100)	–	20.1	20.5	3.37	17.57	82	59	Moderate
Jonker/2018	Phase 3	138 (41% ≥ 4 L)	64/100	–	Napabucasin (100)	–	0	12	1.8	4.4	32	10	Moderate
Kemeny/2004	Randomized phase 2	209 (101 + 108)	63	LV5FU2 (48.3) FOLFOX-4 (51.7)	–	–	2 13	48 66	2.4 (TTP) 4.8 (TTP)	11.4 9.9	74/74	48/35	Low
Kopetz/2015	Phase 2	21 (71% ≥4 L)	65/100	–	VEMU (100)	–	5	33.3	2.1	7.7	60	30	Low
Lee/2014	Phase 2	41 (65% ≥ 4 L)	62/100	GEM + UFT (100)	–	–	2.4	34.1	1.7	9.2	60	39	Serious
Li/2018	Phase 3	278 (31.6% ≥ 4 L)	55/72.3	–	Fruquintinib (100)	–	4.7	57.5	3.7	9.3	70	31	Low
Li/2015	Phase 3	136 (65% ≥ 4 L)	57.5/100	–	REGO (100)	–	4	47	3.2	8.8	68	35	Low
Matsuda/2015	Phase 2	45 (42% > 4 L)	NR/97.8	XELOX (100)	–	–	46.7	48.9	3.8	10.7	78	35	Moderate
Mayer/2015	Phase 3	534 (83% ≥ 4 L)	63/	TAS-102	–	–	1.6	42.4	2	7.1	58	27	Low
Meric-Benstam/2019	Phase 2	57 (70% ≥ 4 L)	55/98	–	TRAST (100)	PERT (100)	32	44	2.9	11.5	70	50	Low
Miranda/2016	Phase 2	50 (68% ≥ 4 L)	57/96	5-FU + FA (100)	Metformin (100)	–	0	22	1.8	7.9	53	35	Moderate
Moorcraft/2013	Phase 2	29 (62% ≥ 4 L)	66/100	Patupilone (100)	–	–	0	13.7	2.6	6.1	50	27	Low
Morano/2018	Phase 2	25 (78% ≥ 4 L)	62/100	Temozolomide + CPT-11 (100)	–	–	24	44	4.4	13.8	72	60	Low
Muro/2009	Phase 2	52 (48% ≥ 4 L)	59/100	–	PANI (100)	–	13.5	33	2	9.3	–	–	Serious
Ng/2013	Phase 2	199	61/97.5	–	EVE (100) (70 mg/w or 10 mg/day)	–	0	31.7	1.7	5.9	48	22	Low
Osumi/2018	Phase 2	40	59/100	CPT-11 (100)	CET (100)	.	25.0	47.5	5.7	15.1	88	60	Moderate
Overman/2017	Phase 2	74 (54% ≥ 4 L)	52.5/100	–	NIVO (100)	–	31.1	37.8	Not reached	Not reached	84	73.4	Moderate
Overman/2018	Phase 2	119 (40% ≥ 4 L)	58/100	–	NIVO (100)	IPI (100)	54	31	Not reached	Not reached	90	85	Moderate
Pishvaian/2018	Phase 2	75 (50% ≥ 4 L)	56/97	Temozolomide (100)	Veliparib (100)	–	2.6	21.3	1.8	6.6	50	20	Moderate
Ramanthan/2008	Phase 2	45 (22% ≥ 4 L)	59/98	Milataxel (100)	–	–	0	6.6	1.4 (TTP)	–	–	–	Moderate
Reidy/2010	Randomized phase 2	64	61/100	–	IMC-A12 + CET (50)	IMC-A12 (50)	1.5^	–	1.78	6.8	48	27	Moderate
Santoro/2010	Phase 2	33 (50% ≥ 4 L)	65/100	–	NGR-hTNF (100)	–	3	36	2.5	13.1	73	50	Low
Sartore Bianchi/2016	Phase 2	27 (100% > 5 L)	62/100	–	TRAST (100)	LAP (100)	30	44	5.25	11.5	84	45	Low
Shitara/2011	Phase 2	30 (70% ≥ 4 L)	60/98	CPT-11 (100)	CET (100)	–	30	50	5.8	Not reached	83	60	Moderate
Siu/2013	Phase 3	750 (100% ≥ 4 L)	63.7/90	–	CET + brivanib (50)	CET (50)	10.4	47	4.2	8.45	62	33	Low
Skougaard/2016	Phase 2	66	63/88	CPT-11 (100)	CET (100)	–	21.2	66.7	NR	12	90	55	Moderate
Soeda/2014	Phase 2	41	68/100	CPT-11 (100)	CET (100)	–	12	26.8	2.65	8.9	68	25	Moderate
Spindler/2014	Phase 2	49	63/96	GEM (100)	CAPE (100)	–	0	30	2.7	6.8	50	10	Moderate
Spindler/2015	Phase 2	107	62/90.7	CPT-11 (100)	CET (100)		20	34	3.5	7.2	–	–	Moderate
Stec/2014	Phase 2	74 (62% ≥ 4 L)	62/100	MMC + 5FU + AF (100)	–	–	3.2	53.2	4.9	9.7	74	38	Moderate
Strosberg/2012	Phase 2	37 (89% ≥ 4 L)	60/81	–	RO4929097 (100)	–	0 (n = 33)	18	1.8	6	50	–	Moderate
Tahara/2008	Phase 2	39 (64% ≥ 4 L)	58/100	CPT-11 (100)	CET (100)	–	38.8	33.3	4.1 (TTP)	8.8	66	45	Moderate
Takajashi/2016	Phase 2	23 (27% ≥ 4 L)	64/100	S-1 (100)	CET (100)		29.7	27	5.5	13.5			Serious
Tanioka/2019	Phase 2	41 (63% ≥ 4 L)	67/97.5	S-1 + OXA (100)	BEVA (70.7%)		10	54%	3.3	10.1	80	40	Low
Trarbach/2010	Phase 2	38 (54% > 4 L)	63/100	–	Mapatumumab (100)	–	0 (*n* = 35)	32	1.2	–	–	–	Moderate
Van Cutsem/2014	Randomized phase 2	142 (29.5% > 4 L)	59.6/100	–	PANI (100)	Rilotumumab or ganitumumab (66)	24.6	38	4.7	12	80	52	Low
Vincenzi/2009	Phase 2	48 (100% ≥ 4 L)	68/75	5FU + AF (100)	BEV (100)	–	6.5	30.4	3.5 (TTP)	7.7	–	–	Moderate
Wilke/2008	Phase 2	1147 (46.5% ≥ 4 L)	62/100	CPT-11 (100)	CET (100)	–	20.1	25.1	3.2	9.2	68	40	Moderate
Wolpin/2013	Phase 2	40	56/97.5	–	Tivozanib (100)	EVE (100)	0	50	3	5.6	49	31	Moderate
Wu/2013	Phase 2	24	57/–	PEM (100)	–	–	3.45	20.7	2.5 (TTP)	9.1	–	–	Moderate
Xu RH/2017		47 (74.5% ≥ 4 L)	50/100	–		–	2.1 (*n* = 45)	66	4.73	7.72	73	24	Moderate

	Randomized phase 2				Fruquintinib (100)								
Xu RH/2017	Phase 2	99 (61% ≥ 4 L))	55/100	–	Famitinib (100)	–	2.2	57.6	2.1	7.4	60	30	Moderate
Yamaguchi/2015	Phase 2	31 (81% ≥ 4 L)	69/94	S-1 + LV (100)	BEV (100)	–	7 (*n* = 28)	58	5.3	9.9	74	41	Moderate
Yoshida/2016	Phase 2	30	68/92	S-1 (100)	BEV (100)	–	0	63	3.7	8.6	70	33	Moderate
Yoshino/2012	Randomized phase 2	112 (77% ≥ 4 L)	64/97	TAS-102	–	–	1	43	2	9	70	37	Low

PS, performance status; *CT*, chemotherapy; *ORR*, overall response rate; *SD*, stable disease; *PFS*, progression-free survival; *OS*, overall survival; *NR*, not reported; *BEV*, bevacizumab; *EVE*, everolimus; *FOLFIRI*, FU + FA + irinotecan; *CPT-11*, irinotecan; *PANI*, panitumumab; *MMC*, mitomycin C; *UFT*, tegafur + uracil; *AF*, folinic acid; *FOLFOX*, FU + FA + oxaliplatin; *CET*, cetuximab; *CAPE*, capecitabine; *ATEZO*, atezolimumab; *COBI*, cobimetinib; *REGO*, regorafenib; *5-FU*, fluorouracil; *OXA*, oxaliplatin; *IRI*, irinotecan; *VEMU*, vemurafenib; *GEM*, gemcitabine; *XELOX*, capecitabine + oxaliplatin; *TRAST*, trastuzumab; *PERT*, pertuzumab; *NIVO*, nivolumab; *IPI*, ipilimumab; *LAP*, lapatinib; *PEM*, pembrolizumab; *LV*, leucovorin; *, all wild type patients; *LCRC*, left colorectal cancer; *RCRC*, right colorectal cancer; ^, cumulative for all arms

Studienergebnisse:

- Overall, the pooled ORR and SD were 15.4% (95% CI 13–18%) and 36.9% (95% CI 33.5–40.6%). Median PFS, 6-month and 1-year OS, and median OS were 3.2 (95% CI 2.9–3.3) months, 65.4% (95% CI 61.9–68.8%), 36% (95% CI 32.3–39.9%) and 8.8 (95% CI 8.3–9.2) months.
- Overall survival was different in the monochemotherapy, polychemotherapy, chemotherapy + targeted therapy, and targeted therapy alone arms (7.6, 9.5, 10.3, and 7.9 months, respectively, P for difference = 0.01).
- Median PFS were respectively 2.3, 3.9, 3.8, and 2.6, respectively (P for difference < 0.01).

Anmerkung/Fazit der Autoren

Based on the results of the present systematic review, and despite the lack of definitive prospective data suggesting a benefit of one strategy over another (single agent vs. polychemotherapy, targeted therapies alone or in combination), the combination of two or more agents is associated with a higher ORR, median PFS and OS than single agents alone. Individual treatment decisions should be customized for each patient based on specific factors such as performance status, comorbid conditions, renal and hepatic function, treatment compliance, and preference. Prospective trials are needed in which approved single agents (e.g., regorafenib and trifluoridine/ tipiracil) for refractory CRC are introduced earlier during the course of disease. Molecular selection (e.g., MSI and HER-2) of treatment, active multiagent combinations, anti-EGFR rechallenge, or reintroduction of previous chemotherapy regimens are potential strategies to implement in clinical practice.

Galvano A et al., 2019 [11].

How to Deal with Second Line Dilemma in Metastatic Colorectal Cancer? A Systematic Review and Meta-Analysis.

Fragestellung

To analyze and compare the efficacy and safety of treatment using anti-VEGF (bevacizumab, aflibercept and ramucirumab) or anti-EGFR (cetuximab and panitumumab) agents in second-line in RAS wt mCRC patients, through a systematic review of data reported in the literature.

Methodik

Population:

- patients with histologically proven diagnosis of advanced colorectal cancer in progression after first-line chemotherapy

Intervention/Komparator:

- argeted therapies (anti-VEGF or anti-EGFR) associated with backbone chemotherapy (CT) regimen (FOLFOX/4 or 6, FOLFIRI, CAPOX) versus CT alone

Endpunkte:

- objective response rate (ORR), disease control rate (DCR), PFS, OS AEs–adverse events and SAEs–serious adverse events

Recherche/Suchzeitraum:

- Data available up to March 2019 on Medline (PubMed), EMBASE databases and Cochrane-Library

Qualitätsbewertung der Studien:

- The overall quality assessment was evaluated according to the CONSORT checklist statement / Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- a total of eight studies

Qualität der Studien:

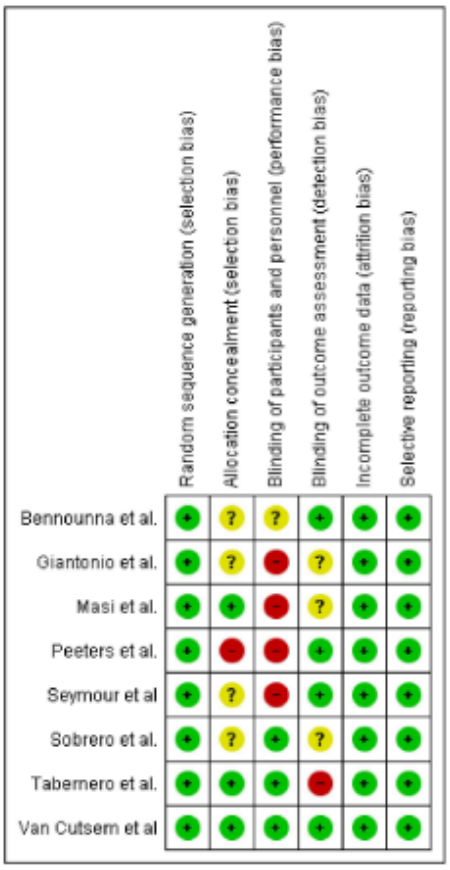


Figure 5. Bias summary: Review authors' judgements about each risk of bias item for each included study.

Studienergebnisse:

Direct Comparisons

- Anti-VEGF + CT vs CT alone
  - Five RCTs enrolling 3879 patients evaluated Anti-VEGF (bevacizumab, aflibercept or ramucirumab) + CT vs CT in second line mCRC settings.
  - Pooled results showed statistically significant differences in terms of DCR (RR 1.15, 95% CI 1.07–1.23; p = 0.0001), PFS (HR 0.73, 95% CI 0.68–0.78; p < 0.00001) and OS (HR 0.81, 95% CI 0.75–0.87; p < 0.00001) favouring anti-VEGF combinations.
  - Our analysis reported also a significant trend towards ORR for anti-VEGF combinations (RR 1.46, 95% CI 1.00–2.12; p = 0.05).
  - Subgroup analysis concerning RAS/BRAF status showed statistical significance of anti-VEGF combinationx in RAS WT or RAS mutated patients both in term of PFS and OS (only a trend for RAS mutated OS).
  - As regards safety endpoints, in our pooled analysis anti-VEGF combinations have been shown to significantly increase drug-related risk of bleeding (RR 2.40, 95% CI 1.11–5.23; p = 0.03), arterial hypertension (RR 4.07, 95% CI 1.82–9.09; p = 0.0006), neutropenia (RR 1.34, 95% CI 1.07–1.61; p = 0.002), venous thromboembolism (RR 1.40, 95% CI 1.02–1.92; p = 0.03) and proteinuria (RR 8.48, 95% CI 4.20–17.13; p≤ 0.00001). Grade 3–5 serious adverse events (SAEs) risk was associated to anti-VEGF strategy (RR 1.23, 95% CI 1.14–1.33; p ≤ 0.00001). As for most common AEs, anti-VEGF addition did affect diarrhea, vomiting, asthenia and neutropenia risk (RR 1.43, 95% CI 1.31–1.56; p < 0.00001).
- Anti-EGFR + CT vs EGFR Alone
  - Three randomized phase III controlled trials (RCTs) enrolling a total of 2944 patients investigated the addition of an anti-EGFR agent (cetuximab or panitumumab) in the same mCRC setting (second line).
  - Our pooled results showed a statistically significant anti-EGFR combination benefit in terms of ORR (RR 2.85, 95% CI 2.01–4.06; p < 0.00001), DCR (RR 1.20, 95% CI 1.06–1.36; p = 0.005) and PFS (HR 0.71, 95% CI 0.64–0.80; p < 0.00001) but not for OS (HR 0.98, 95% CI 0.88–1.10; p = 0.31), if compared with CT alone.
  - Considering RAS, our analysis confirmed mutated RAS status as a negative predictive factor for anti-EGFR efficacy both in all the above mentioned endpoints.
  - For safety analysis, EGFR drug-related skin toxicities (RR 24.12, 95% CI 13.11–44.36; p < 0.00001) and hypomagnesaemia (RR 13.49, 95% CI 3.20–56.81; p = 0.0004) were more associated with anti-EGFR combination regimen. Diarrhea (RR 1.77, 95% CI 1.50–2.09; p < 0.00001) risk was significantly related to anti-EGFR strategy. We also registered a trend over neutropenia (RR 1.15, 95% CI 1.00–1.32; p = 0.05) and asthenia (RR 1.15, 95% CI 0.99–1.35; p = 0.07) while no significant difference was observed for vomiting. Grade 3–5 SAEs were mostly related to anti-EGFR strategy (RR 1.40, 95% CI 1.31–1.50; p < 0.00001).

Indirect Comparisons

- Anti-VEGF vs Anti-EGFR
  - For clinical endpoints in the overall population, we obtained significant differences favoring anti-VEGF combination in OS (HR 0.83, 95% CI 0.72–0.94) and DCR (RR 1.27,

95% CI 1.04–1.54) while anti-EGFR showed superiority in terms of ORR (RR 0.54, 95% CI 0.31–0.96).

- No statistical difference in PFS was registered. Comparisons in the RAS wild type subgroup showed a greater benefit for anti-VEGF agents in terms of OS while Anti-EGFR demonstrated benefit over anti-VEGF in ORR (RR 0.63, 95% CI 0.31–0.96), although they did not reach a statistical relevance.
- As regards most common safety events, anti-VEGF strategies increased the risk for asthenia (RR 1.34, 95% CI 1.03–1.75), with a trend for neutropenia (RR 1.17 95% CI 0.98–1.40) and vomiting (RR 1.37, 95% CI 0.94–2.00). No difference in terms of diarrhea.

Anmerkung/Fazit der Autoren

To our knowledge, our meta-analysis results support, for the first time, a trend towards improved OS and DCR for anti-VEGF combinations in second line mCRC and thus providing to clinicians a robust and encouraging scientific evidence to select the best strategy for every patient according to mutational status, clinical conditions and toxicities. Moreover, this scenario should change with the improvement of immunotherapy. Nonetheless, prospective phase III studies are needed to evaluate the optimal treatment sequencing of biological therapies.

Duan KF et al., 2019 [9].

The efficacy of panitumumab in refractory metastatic colorectal cancer: A meta-analysis.

Fragestellung

to clarify and evaluate the effectiveness of panitumumab in patients with refractory mCRC.

Methodik

Population:

- mCRC patients who had received prior chemotherapy

Intervention:

- panitumumab

Komparator:

- chemotherapy

Endpunkte:

- OS, PFS, and ORR

Recherche/Suchzeitraum:

- PubMed, Cochrane and Embase were searched up to October 2018

Qualitätsbewertung der Studien:

- Cochrane Collaboration’s “Risk of bias” tool

Ergebnisse

Anzahl eingeschlossener Studien:

- a total of 7 RCTs

Charakteristika der Population:

Table 1. Detailed information of included studies

Study,Year	*Treatment regimen*		*Patients number*		*Age(years)*	
	Study arm	*Comparative arm*	*Study arm*	*Comparative arm*	*Study arm*	*Comparative arm*
Shitara, 2016	FOLFIRI plus panitumumab	FOLFIRI plus bevacizumab	59	58	62	64
Jerzak, 2017	panitumumab monotherapy	cetuximab plus irinotecan	803	278	64	61
Hecht 2014	FOLFIRI plus panitumumab	FOLFIRI plus bevacizumab	91	91	62	58
Kim 2016	panitumumab plus best supportive care	best supportive care	189	188	62	60
Hayashi, 2018	panitumumab	cetuximab	44	178	/	/
Peeters, 2015	FOLFIRI plus panitumumab	FOLFIRI alone	208	213	60	60
Yamaguchi, 2016	Panitumumab plus irinotecan	Cetuximab plus irinotecan	42	107	62	63

Qualität der Studien:

- All included studies were based on moderate to high quality evidence.

Studienergebnisse:

- PFS
  - the pooled results from 6 studies showed that the PFS of the chemotherapy group was comparable with the panitumumab group
- OS
  - no significant difference in OS between the panitumumab group and the chemotherapy group
- ORR
  - The pooled ORR data showed a significant difference between the two groups (OR=3.71, 95% CI 1.34-10.31; p=0.01) i.e. significantly increased ORR was found in the panitumumab group
- Subgroup analysis of patients treated with panitumumab plus irinotecan-based chemotherapy
  - patients treated with panitumumab plus irinotecan-based chemotherapy did not differ significantly in PFS versus the controls and OS
- Subgroup analysis of patients treated with panitumumab-based chemotherapy vs cetuximab-based chemotherapy
  - pooled data showed no significant difference in PFS and OS between panitumumab and cetuximab for pretreated advanced mCRC patients

Anmerkung/Fazit der Autoren

In summary, the current study indicates that panitumumab was not associated with either OS or PFS benefit, but significantly increased ORR among pre-treated mCRC patients. Development in the therapy of mCRC patients who have disease progression after failure of initial therapy have led to a paradigm of “personalized” medicine in oncology, at least in selected patients with driver gene mutations such as EGFR mutations, which need to be explored in the future.

Sun H et al., 2019 [31].

Efficacy and safety of anti-EGFR monoclonal antibodies combined with different chemotherapy regimens in patients with RAS wild-type metastatic colorectal cancer: A meta-analysis.

Fragestellung

To investigate the efficacy and safety of adding anti-epidermal growth factor receptor [EGFR] MoAbs to various chemotherapy regimens in patients with RAS wild-type metastasized colorectal cancer (RASWTmetastatic colorectal cancer [mCRC]) and to identify the optimal combination regimens.

Methodik

Population:

- patients with KRAS, NRAS, or HRAS WT mCRC

Intervention/Komparator:

- intervention included multiple chemotherapy regimens, with or without anti-EGFR MoAbs, antiEGFR MoAbs monotherapy versus best supportive care (BSC), and cetuximab

Endpunkte:

- progression-free survival (PFS), overall survival (OS), overall response rate (ORR), and grade 3 or higher adverse events (AEs)

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, and CENTRAL from the inception date to 20th May 2019

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 18 RCTs

Charakteristika der Population:

- A total of 8848 patients aged from 21 to 86 years. 4278 patients received anti-EGFR MoAbs plus chemotherapy, 4340 patients received chemotherapy alone
- nine studies for anti-EGFR MoAbs plus oxaliplatin-based chemotherapy (6 FOLFOX, 2 CapeOX, 1 Nordic FLOX; n = 5859 patients), four studies for anti-EGFR MoAbs plus irinotecan-based chemotherapy (3FOLFIRI, 1 irinotecan; n=1818 patients), three studies for

anti-EGFR MoAbs monotherapy (n = 850 patients), and two studies for cetuximab weekly or biweekly regimen (n = 321 patients). RAS WT was the main genotype of the patients included in the study, while BRAF or PIK3CA WT was less common. Data of the WT gene were obtained from four RCTs and the subgroup analysis of 14 RCTs study, while BRAF or PIK3CA WT was less common. Data of the WT gene were obtained from four RCTs and the subgroup analysis of 14 RCTs.

Qualität der Studien:

- Fourteen studies described the process of generating random sequences, while the remaining four only mentioned randomization. Seven studies described the methods of allocation concealment. Although all studies were open label, the risk of bias was low using OS or PFS as the primary endpoint and was not influenced by no blinding. All studies reported loss of follow-up or had complete outcome data and were free of other sources of bias except for one study with funders involved in the study design.

Studienergebnisse:

- Adding anti-EGFRMoAbs to oxaliplatin-based chemotherapy
  - Seven RCTs involving 2307 participants with RASWTmCRC reported the PFS data. There was significant heterogeneity among included studies (I2 = 56%, P = 0.03). Meta-analysis with random-effects model revealed that adding anti-EGFR MoAbs to oxaliplatin-based chemotherapy significantly prolonged PFS (HR= 0.80, 95% CI: 0.67 to 0.94, P = 0.008).
  - Nine RCTs involving 5772 participants with RAS WT mCRC reported the OS data. The random-effects model was applied because of significant heterogeneity among studies (I2 = 43%, P= 0.08). Pooled analysis revealed that adding anti-EGFR MoAbs to oxaliplatin-based chemotherapy did not prolong OS.
  - Six RCTs involving 1651 participants with RASWT mCRC reported the ORR data. The random-effects model meta-analysis revealed that adding anti-EGFR MoAbs to oxaliplatin-based chemotherapy significantly increased ORR in WT mCRC participants (OR = 2.09, 95% CI: 1.33 to 3.29, P = .001), with significant heterogeneity (I2 = 73%, P = .002).
  - Sensitivity analysis were performed based on adding anti-EGFR MoAbs to oxaliplatin-based chemotherapy as first-line treatment. Whereas, the benefit revealed only in PFS (HR = 0.82, 95% CI: 0.69 to 0.98, P = .03), but not in OS, and the heterogeneity among studies had not eliminated (PFS P = .02, I2 = 64%). For the first-line treatment, the chemotherapeutic regimen was FOLFOX in three studies, CapeOX in two studies, and Nordic FLOX in one study.
  - Sensitivity analysis based on adding antiEGFR MoAbs to FOLFOX as first-line treatment indicated a PFS and OS benefits (PFS HR = 0.74, 95% CI: 0.64 to 0.84, P < .0001; OS HR= 0.83, 95% CI: 0.73 to 0.95, P = .008, respectively), without significant heterogeneity (PFS P = .28, I2 = 23%;OS P = .64, I2 = 0%, respectively).
- Adding anti-EGFRMoAbs to irinotecan-based chemotherapy
  - The PFS, OS, and ORR of patients with RAS WT status were available from three studies (1723 participants), four studies (1818 participants), and three studies (1709 participants), respectively. There was no significant heterogeneity for PFS (I2 = 0%, P = .52), OS (I2 = 25%, P = .26), while significant heterogeneity for ORR (I2 = 84%, P = .002) among studies.

- Compared with irinotecan-based regimens alone, adding anti-EGFR MoAbs to irinotecan-based regimens significantly reduced the risk of disease progression (HR = 0.77, 95% CI: 0.69 to 0.86, P < .00001) and death (HR = 0.89, 95% CI: 0.80 to 0.98, P= .02) (Figure 5B), while significantly increased the rate of overall response (OR= 3.39, 95% CI: 1.86 to 6.21, P < .0001).

- Anti-EGFRMoAbs monotherapy
  - Three studies (835 participants) compared anti-EGFR MoAbs monotherapy with BSC in patients with RAS WT mCRC and there was no significant heterogeneity (PFS: I2 = 0%, P = .42; ORR: I2 = 0%, P = .87).
  - The pooled results suggested that PFS and ORR were significantly improved with anti-EGFR MoAbs monotherapy (HR = 0.46, 95% CI: 0.40 to 0.54, P < .00001; ORR = 27.79, 95% CI: 10.00 to 77.25, P < .00001, respectively). Study by Amado et al24 used a crossover design and patients with BSC received panitumumab treatment after disease progression.
  - Sensitivity analysis after excluding this study showed that there were significant OS benefit with anti-EGFRMoAbs monotherapy (HR= 0.65, 95% CI: 0.54 to 0.78, P < .00001).

- Cetuximab weekly plus FOLFOX4 versus cetuximab every second week plus FOLFOX4
  - Two trials (321 participants): We could not pool the results as study by Wasan et al did not provide aggregated data HR. Brodowicz et al demonstrated that there was no statistically significant differences in PFS and OS and Wasan et al showed similar results.

    ORR data were available from these two trials and the pooled result revealed that there were no statistically significant differences in ORR between the two regimens.

- Adverse events

TABLE 2 Meta-analysis results of grade ≥3 adverse events

Adverse events	No. of trials	No. of participants	Statistical method	Events, OR (95% CI)	*P* Value
A.Oxaliplatin-based chemotherapy					
(Acneiform or acne-like) Rash	5	4716	M-H, Fixed, 95% CI	86.66 (43.95, 170.87)	<.00001
Skin toxicity	3	1221	M-H, Fixed, 95% CI	36.51 (17.61, 75.67)	<.00001
Nail toxicity	4	4793	M-H, Fixed, 95% CI	18.22 (7.08, 46.93)	<.00001
Diarrhea	7	5518	M-H, Fixed, 95% CI	1.86 (1.58, 2.20)	<.00001
Nausea	4	4279	M-H, Fixed, 95% CI	1.07 (0.78, 1.47)	.91
Vomiting	3	4144	M-H, Random, 95% CI	1.65 (0.85, 3.18)	.14
Hypomagnesemia	4	3596	M-H, Fixed, 95% CI	11.80 (5.28, 26.37)	<.00001
Peripheral neuropathy	5	3300	M-H, Fixed, 95% CI	0.84 (0.69, 1.01)	.07
Stomatitis or mucositis	5	4716	M-H, Fixed, 95% CI	4.54 (3.14, 6.55)	<.00001
B. Irinotecan-based chemotherapy					
(Acneiform or acne-like) Rash	1	667	M-H, Fixed, 95% CI	69.01 (4.20, 1135.24)	.003
Skin toxicity	3	1683	M-H, Fixed, 95% CI	39.84 (19.56, 81.12)	<.00001
Nail toxicity	3	1683	M-H, Fixed, 95% CI	37.38 (9.44, 147.98)	<.00001
Neutropenia	3	1683	M-H, Random, 95% CI	1.29 (0.78, 2.13)	.32
Diarrhea	3	1683	M-H, Fixed, 95% CI	1.77 (1.35, 2.32)	<.0001
C. Cet q1w + FOLFOX4 versus Cet q2w + FOLFOX4					
(Acneiform or acne-like) Rash	2	321	M-H, Fixed, 95% CI	0.73 (0.45, 1.118)	.20
Neutropenia	2	321	M-H, Fixed, 95% CI	0.99 (0.62, 1.58)	.97
Diarrhea	2	321	M-H, Fixed, 95% CI	1.23 (0.67, 2.28)	.50
Peripheral neuropathy	2	321	M-H, Fixed, 95% CI	0.81 (0.29, 2.29)	.69

FOLFOX4, fluorouracil, leucovorin, and oxaliplatin; OR, odds risk; CI, confidence interval.

Anmerkung/Fazit der Autoren

In conclusion, anti-EGFR MoAbs as a monotherapy or in combination with irinotecan-based chemotherapy has better response and survival outcome in the treatment of patients with RAS WT mCRC; however, there is no clear benefit in oxaliplatin-based chemotherapy, except for the combination of anti-EGFR MoAbs with FOLFOX as first-line treatment. Anti-EGFR MoAbs have a significantly higher risk of AEs in all treatment. For the weekly and biweekly regimens for cetuximab, efficacy and safety of both arms were comparable. Due to the limited number of studies and RAS WT data derived from subgroup analysis, higher-quality RCTs for RAS WT are needed to evaluate the optimal combination of anti-EGFR MoAbs and different chemotherapy regimens.

Wisselink DD et al., 2019 [34].

Systematic review of published literature on oxaliplatin and mitomycin C as chemotherapeutic agents for hyperthermic intraperitoneal chemotherapy in patients with peritoneal metastases from colorectal cancer.

Fragestellung

to evaluate published literature on CRS/HIPEC for PMCRC with either MMC- or OX-based regimens, regarding patient selection, use of perioperative systemic therapy, procedural characteristics, morbidity, disease-free survival (DFS) and overall survival (OS).

Methodik

Population:

- patients with PMCRC

Intervention/Komparator:

- CRS/HIPEC for PMCRC with either MMC- or OX-based regimens

Endpunkte:

- Main outcome measures of this study were severe postoperative complication rate, DFS and OS

Recherche/Suchzeitraum:

- PubMed, Embase and Cochrane Library databases. Latest search was performed on March 2nd 2018.

Qualitätsbewertung der Studien:

- Joanna Briggs Institute (JBI) Critical Appraisal Checklist. A study was considered to be of high quality if a minimum of six out of the 11 questions that make up this checklist were answered with ‘yes’.

Ergebnisse

Anzahl eingeschlossener Studien:

- A total of 46 studies qualified for data-extraction

- Six out of 46 studies were prospective cohort studies and the remaining 40 studies had a retrospective design. Of all studies included, six were comparative cohort studies on MMC versus OX, 28 were cohort studies on MMC and 12 on OX. Common exclusion criteria were ‘distant metastases’ or ‘extra-abdominal metastases’, ‘incomplete cytoreduction’, ‘poor performance status’ and ‘unresectable disease’.
- A total of 3516 patients were included in the final analysis, of whom 2768 patients received MMC and 748 received OX. Median follow-up ranged from 10 months to 63 months. Median follow-up could not be extracted for 25 studies, due to median follow-up times concerning multiple different subgroups.

Qualität der Studien:

- Assessment of methodological quality showed 41 studies to be of high quality. Of the five studies deemed to be of lower quality, one was a comparative study, three reported on MMC only and one on OX only. This leads to five/six comparative studies being considered to be of high quality and 25/28 studies on MMC and 11/12 of the studies on OX being of high quality.

Studienergebnisse:

- Severe postoperative complication rate: In the meta-analysis on severe postoperative complication rate 17 articles on MMC and 10 articles on OX were included. A proportion of 21% in the cohort receiving MMC developed severe postoperative complications, versus a proportion of 30% in the cohort treated with OX. Significant heterogeneity was observed in both groups. Comparability of the MMC and OX studies was assessed for three of four predefined criteria.
  - Synchronous / metachronous PMCRC: Nine out of the 17 MMC articles and five out of the 10 OX articles reported this characteristic. Of the five articles in which OX was used, one study did not differentiate between the included subgroups. The MMC cohort seems to have a higher percentage of synchronous PM when compared to the OX cohort, with a pooled percentage of 56% versus 45%, respectively.
  - Extent of peritoneal metastases: Thirteen of the 17 articles on MMC and eight of the 10 articles on OX reported data on this clinico-histopathological characteristic. As the extent of PM was noted in a variety of ways between the studies, exact percentages of a PCI-score below or above a certain cut-off value could not be calculated. For this reason, comparison was performed through observation and discussion between two reviewers. The MMC and OX cohorts appeared to be comparable in terms of extensiveness of PM, with the median PCI ranging from 8 to 12 and 7.58 to 12, respectively.
  - Optimal cytoreduction: Sixteen out of the 17 MMC studies and nine out of the 10 OX studies reported data on the completeness of cytoreduction. However, one study could not be used for comparison, as no distinction was made between the CC-scores of zero, one and two. Hence, ultimately 15 articles on MMC versus nine articles on OX were included in this comparison. Optimal cytoreduction appears to have been reached in a higher percentage of the OX group compared to the MMC group, with pooled percentages of 99% and 88%, respectively. Despite the fact that the MMC cohort seemed to be at a slight disadvantage when compared to the OX cohort, it was decided that formal statistical comparison was justified. Comparing the 30% severe complication risk after OX with the corresponding 21% after MMC resulted in a p-value of 0.046. This suggests an overall

higher risk of developing severe postoperative complications when treated with OX compared to MMC.

- OS: Pooled proportions and heterogeneity of the outcomes were calculated for the one-, three-, and five-year OS for both the MMC and OX studies. One-year OS proportions were 73% (11 studies) and 92% (4 studies) for MMC and OX, respectively. Two-year OS proportions were 38% for MMC (13 studies) and 54% for OX (3 studies). Proportions for the five-year OS were 25% for MMC (9 studies) and 47% for OX (5 studies) (Figs. 6 and 7). Heterogeneity in OS outcomes was high (> 50%) in all plots concerning MMC and low (< 50%) for those of OX. Comparability between the MMC and OX studies that reported on 5-year OS was assessed for the predefined criteria.
  - Synchronous / metachronous PMCRC Data on the ratio of synchronous to metachronous PMCRC could be extracted from only four out of nine articles on MMC which were included for meta-analysis. Out of the five articles on OX, only two reported on this characteristic. This concerned the entire cohort instead of our specific subgroup of colorectal patients in one of these two. The percentage of synchronous PM calculated from these articles amounted to 50% in the MMC studies versus 14% in the OX studies. Based on these numbers, the MMC studies seem to be at a great disadvantage.
  - Extent of peritoneal metastases: Five out of the total of nine articles on MMC and five out of the total of 10 articles on OX reported data on this clinico-histopathological characteristic. Data extracted from two of the articles on MMC and from one on OX, referred to the entire study population consisting of multiple subgroups. Another article on MMC only reported on an incomplete amount of patients. The MMC and OX cohorts appeared to be comparable in terms of extensiveness of PM after comparison performed through observation and discussion between two reviewers. The reported median PCI scores ranged from 9.4 to 12 and 9.6 to 12, respectively.
  - Optimal cytoreduction: All nine articles on MMC reported on the completeness of cytoreduction. One of these articles did not differentiate between any scores higher than zero and could therefore not be used for this particular comparison. Data from three of the remaining eight articles concerned the total study population rather than the specific subgroup we aimed to compare. Likewise, all five articles on OX reported this characteristic. One study did not report data for our specific subgroup of colorectal patients separately. Pooled proportions of optimal cytoreduction were 84% of patients in the MMC studies versus 98% of patients in the OX studies. Hence, the MMC cohort appears to be at a slight disadvantage. Overall, the MMC cohort appeared to be at a disadvantage compared to the OX cohort when looking at the comparisons of prognostic factors above. For this reason, it was concluded that MMC and OX studies were not comparable regarding the endpoint OS, and no statistical comparison was performed.
- DFS: Pooled proportions and heterogeneity of the outcomes within a cohort were calculated for the one-, three- and five-year DFS. One-year DFS proportions were 46% (3 studies) and 76% (2 studies) for MMC and OX, respectively. For the three-year DFS, these numbers were 28% (2 studies) and 34% (2 studies). Proportions for the five-year DFS were 21% for the MMC cohort (3 studies) and 22% for the OX cohort (3 studies). Heterogeneity was high for the one-year outcomes in both cohorts, but low for the three- and five-year intervals. The studies included in the meta-analysis of five-year DFS rates were assessed for comparability.
  - Synchronous / metachronous: PMCRC None of the three MMC articles that were included in meta-analysis for DFS rates reported on this characteristic. This information could be

extracted from two out of three articles on OX. However, since no data was available for the MMC cohort, a comparison could not be made.

- Extent of peritoneal metastases: Data on the extent of PM was extracted from two out of the three articles included for analysis for MMC and from all three included for analysis for OX. Comparison was again performed by educated observation and discussion between two reviewers. Ultimately, the MMC and OX cohorts were deemed comparable in terms of extensiveness of PM median PCI ranging from 9.4 to 12 and 9.6 to 12, respectively.
- Optimal cytoreduction: Three articles for both chemotherapeutical agents reported on the completeness of cytoreduction. For two of the articles on MMC, this data concerned the entire cohort. This was the case for one of the articles on OX. One article did not differentiate between any cytoreduction scores from one onwards and was left out of the comparison. Optimal cytoreduction was reached in 94% and 97% for the MMC and OX studies, respectively. Overall, MMC and OX studies were deemed comparable in terms of the ratio of synchronous to metachronous presentation, extent of PMCRC, and optimal cytoreduction. However, the MMC cohort appeared to be at a considerable disadvantage where the administration of neo-adjuvant therapy is concerned. For this reason, no formal statistical comparison was performed between the pooled proportions of the MMC and OX studies.

Anmerkung/Fazit der Autoren

In conclusion, this systematic review showed a higher proportion of severe complications following OX based CRS/HIPEC. No meaningful comparison, however, could be made regarding DFS and OS, especially because induction systemic therapy was mostly given in OX studies, while studies on MMC mainly included patients who underwent upfront CRS/HIPEC. In Prodige 7, 30 min OX based HIPEC did not improve survival in comparison with CRS alone in patients after months of oxaliplatin-based neoadjuvant chemotherapy. In our view this regimen should be discouraged in the latter patient category. For upfront CRS/ HIPEC, the data are insufficient to abandon OX based HIPEC, but caution is warranted because of a potentially higher complication rate.

Ruan WC et al., 2018 [28].

Efficacy and Toxicity of Addition of Bevacizumab to Chemotherapy in Patients with Metastatic Colorectal Cancer

Fragestellung

We aimed to evaluate the efficacy and toxicity of bevacizumab plus chemotherapy compared with bevacizumab-naive based chemotherapy as second-line treatment in people with metastatic CRC

Methodik

Population:

- Second-line systemic therapy in people harboring treatment-refractory mCRC that progressed

Intervention:

- bevacizumab plus chemotherapy

Komparator:

- bevacizumab-naive based chemotherapy

Endpunkte:

- efficacy and toxicity

Recherche/Suchzeitraum:

- Systematische Recherche in PubMed, Embase und Cochrane Datenbank bis März 2018

Qualitätsbewertung der Studien:

- RoB Cochrane

Ergebnisse

Anzahl eingeschlossener Studien:

- N=5 RCTs

Charakteristika der Population:

Table 1. The primary characteristics of the eligible studies.

Author (year)	Country	Number of Patients (E/C)	Median Age, Year (E/C)	Regimen (E/C)
Giantonio (2007)	Multi-country	286/291	62.0 (21-85)/60.8 (25-84)	Bevacizumab + FOLFOX *vs* FOL- FOX
Hecht (2011)	America	91/91	60 (25-80)/60 (27-84)	Bevacizumab+ FOLFIRI *vs* Panitumumab + FOLFIRI
Bennouna (2013)	Multi-country	409/411	63 (27-84)/63 (21-84)	Bevacizumab + che- motherapy *vs* che- motherapy
Cao (2015)	China	65/77	62(30-79)/61 (24-81)	Bevacizumab + FOLFIRI *vs* FOLFIRI
Masi (2015)	Italian	92/92	62 (38-75)/66.5 (38-75)	Bevacizumab + che- motherapy *vs* che- motherapy

Qualität der Studien:

- k.A.

Studienergebnisse:

- **Gesamtüberleben**

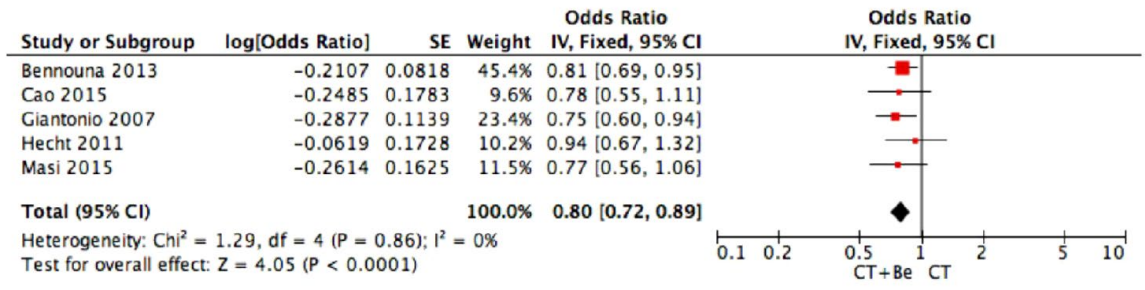


Fig. (2). Pooled analysis of OS between bevacizumab-based and bevacizumab-naive treatment.

- **PFS und ORR**

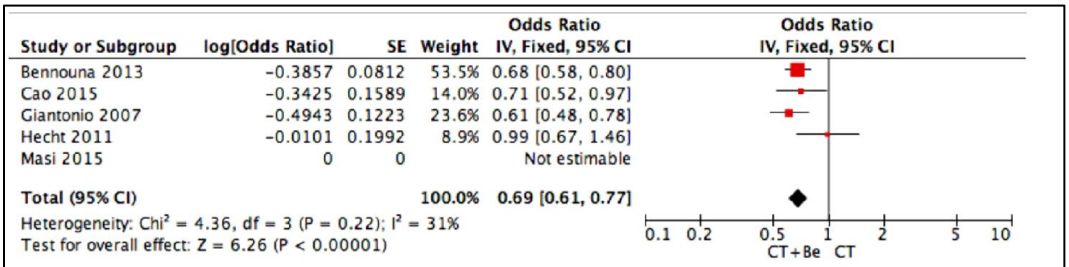


Fig. (3). Pooled analysis of PFS between bevacizumab-based and bevacizumab-naive treatment.

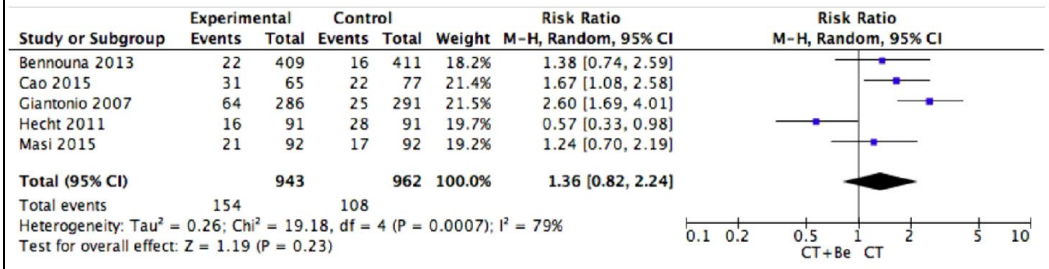


Fig. (4). Pooled analysis of ORR between bevacizumab-based and bevacizumab-naive treatment.

- **SAE**

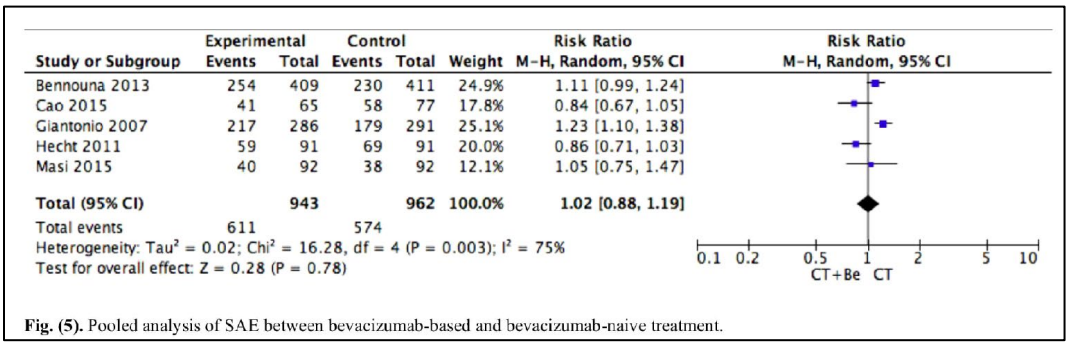


Fig. (5). Pooled analysis of SAE between bevacizumab-based and bevacizumab-naive treatment.

Anmerkung/Fazit der Autoren

Result: Five trials were eligible in the meta-analysis. Patients who received the combined bevacizumab and chemotherapy treatment in MCRC as second-line therapy showed a longer overall survival (OS) (OR=0.80,95%CI=0.72-0.89, P<0.0001) and progression-free survival (PFS) (OR=0.69,95%CI=0.61-0.77, P<0.00001). In addition, there was no significant difference in objective response rate (ORR) (RR=1.36,95%CI=0.82-2.24, P=0.23) or severe adverse event (SAE) (RR=1.02,95%CI=0.88-1.19, P=0.78) between bevacizumab-based chemotherapy and bevacizumab-naive based chemotherapy.

Conclusion: Our results suggest that the addition of bevacizumab to the chemotherapy therapy could be an efficient and safe treatment option for patients with metastatic colorectal cancer as second-line therapy and without increasing the risk of an adverse event.

Kommentare zum Review

- Qualitätsbewertung der Studien war geplant, wurde jedoch nicht durchgeführt.
- Fokus auf 2. Therapielinie

Xue WS et al., 2018 [37].

A meta-analysis of safety and efficacy of regorafenib for refractory metastatic colorectal Cancer

Fragestellung

In order to make a more rational choice of treatment for treatment-refractory mCRC patients, we performed the current meta-analysis to pool controlled trials with regorafenib and analyze both the efficacy and toxicity of regorafenib.

Methodik

Population:

- patients harboring treatment-refractory mCRC

Intervention:

- regorafenib

Komparator:

- k.A.

Endpunkte:

- (PFS and OS) and toxicity (incidence of severe adverse effects), and ORs

Recherche/Suchzeitraum:

- updated to November 2017 (PubMed, Embase, and the Cochrane library)

Qualitätsbewertung der Studien:

- risk of bias items (ROBI) recommended by The Cochrane Handbook for Systematic Reviews of Interventions

Ergebnisse

Anzahl eingeschlossener Studien:

- 4 RCTs

Charakteristika der Population:

Table 1

the primary characteristics of the eligible studies in more detail.

Author	Year	Trail	Study design	Regorafenib	The control	The control arm
Jin Li	2015	CONCUR	RCT	136	68	Placebo
Axel Grothey	2012	CORRECT	RCT	505	255	Placebo
Takayuki Yoshino	2015	CORRECT (1)	RCT	67	33	Placebo
	2015	CORRECT (2)	RCT	438	222	Placebo
Moriwaki T	2017	REGOTAS	PSM	174	174	Trifluridine/tipiracil

CORRECT (1): in Japanese subpopulations.
CORRECT (2): in non-Japanese subpopulations.

Qualität der Studien:

- All the mentioned studies were based on moderate-to-high quality evidence.

Studienergebnisse:

- **PFS/ OS**

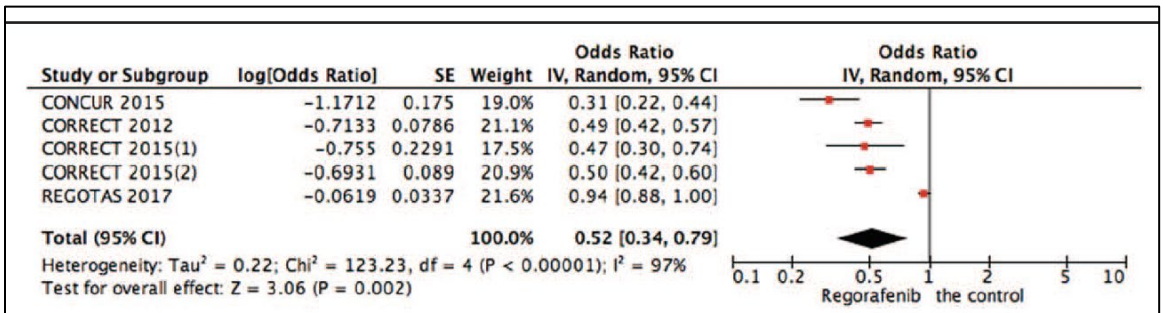


Figure 2. Pooled analysis of PFS comparing regorafenib with the control group. PFS = progression-free survival.

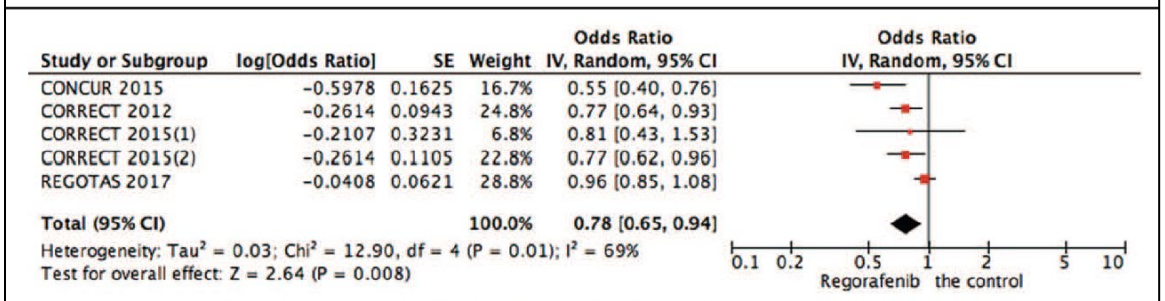


Figure 3. Pooled analysis of OS comparing regorafenib with the control group. OS = overall survival.

[15] Li J, Qin S, Xu R, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, doubleblind, placebo-controlled, phase 3 trial. Lancet Oncol 2015;16:619–29.
[16] Yoshino T, Komatsu Y, Yamada Y, et al. Randomized phase III trial of regorafenib in metastatic colorectal cancer: analysis of the CORRECT Japanese and non-Japanese subpopulations. Invest New Drugs 2015;33:740–50.
[17] Moriwaki T, Fukuoka S, Taniguchi H, et al. Propensity score analysis of regorafenib versus trifluridine/tipiracil in patients with metastatic colorectal cancer refractory to standard chemotherapy (REGOTAS): a Japanese Society for Cancer of the Colon and Rectum Multicenter Observational Study. Oncologist 2017;23:7–15.

- **AE**
  - Pooled analysis of AEs comparing regorafenib with the control group.
  - The most common toxicities occurred significantly more frequently in the regorafenib group than in the placebo group (OR=3.73,95%CI=1.68–8.28, P=.001)
  - The most common treatment-emergent AEs were diarrhea (OR=7.12,95%CI=2.99–16.99, P<.00001), fatigue (OR=1.96,95%CI=1.27–3.04, P=.003), hand-foot skin reaction (OR=38.60,95%CI=12.23–121.80, P<.00001), thrombocytopenia (OR= 5.72,95%CI=1.74–18.75, P=.004) and hypertension (OR=7.34, 95%CI=3.28–16.41, P<.00001).

- **SAE**
  - The pooled data showed that the SAEs were more commonly reported in the regorafenib group. The AEs had no statistical significance only in anorexia with exclusion of the regorafenib group (OR=1.17; 95% CI, 0.63–2.19; P=.62)

Anmerkung/Fazit der Autoren

In conclusion, the current evidence indicated that regorafenib conferred a survival benefit mCRC patients not responding to standard treatments. The AEs associated with regorafenib treatment frequently occurred. Considering the safety profile of regorafenib, further studies and clinical trials to investigate the dosing of regorafenib and alternative approaches are needed to explore molecular biomarkers for therapy selection.

Jiang W et al., 2018 [18].

Efficacy of bevacizumab versus epidermal growth factor receptor inhibitors for wild-type *RAS* metastatic colorectal cancer: a meta-analysis.

Fragestellung

Here, we performed this meta-analysis to review available clinical trial data to evaluate the efficacy of chemotherapy in combination with a VEGF inhibitor versus EGFR inhibitors in patients with wild-type RAS mCRC, including wild-type KRAS mCRC.

Methodik

Population:

- mCRC patients regardless of the study regimen and number of previous treatments

Intervention/ Komperator:

- VEGF inhibitor (bevacizumab) and EGFR inhibitors (cetuximab or panitumumab)

Endpunkte:

- ORR, PFS und OS

Recherche/Suchzeitraum:

- PubMed, Embase, and the Cochrane databases) from inception until January 2018

Qualitätsbewertung der Studien:

- Jadad quality score

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 RCTs (nur 2 Studien relevant, da Second-Line)

16. Hecht JR, Cohn A, Dakhil S, et al. SPIRITT: a randomized, multicenter, phase II study of panitumumab with FOLFIRI and bevacizumab with FOLFIRI as second-line treatment in patients with unresectable wild type KRAS metastatic colorectal cancer. Clin Colorectal Cancer. 2015;14(2):72–80.
17. Shitara K, Yonesaka K, Denda T, et al. Randomized study of FOLFIRI plus either panitumumab or bevacizumab for wild-type KRAS colorectal cancer-WJOG 6210G. Cancer Sci. 2016;107(12):1843–1850.

Charakteristika der Population:

Table 1 Characteristics of the 5 included studies comparing chemotherapy combined with VEGF inhibitor versus EGFR inhibitors

Study	Phase	Treatment line	Year of study	Treatment regimen	Response assessment	Quality scores	References
CALGB/ SWOG 80405	III	First line	2017	CT (either mFOLFOX6 or FOLFIRI) + Cet vs CT + Bev	RECIST 1.0	3	11
FIRE-3	III	First line	2014	FOLFIRI + Cet vs FOLFIRI + Bev	RECIST 1.0	3	12, 13
PEAK	II	First line	2014	mFOLFOX + Pan vs mFOLFOX + Bev	RECIST 1.0	3	14, 15
SPIRITT	II	Second line	2014	FOLFIRI + Pan vs FOLFIRI + Bev	RECIST 1.0	3	16
WJOG 6210G	II	Second line	2016	FOLFIRI + Pan vs FOLFIRI + Bev	RECIST 1.1	3	17

Abbreviations: VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor; CT, chemotherapy; FOLFIRI, folinate, fluorouracil, and irinotecan; Cet, cetuximab; Bev, bevacizumab; RECIST, The Response Evaluation Criteria in Solid Tumors; mFOLFOX, modified folinic acid-fluorouracil-oxaliplatin; Pan, panitumumab.

Qualität der Studien:

2 relevanten Studien (jeweils Quality Score von 3)

Studienergebnisse:

Es werden nur die Subgruppenergebnisse für die 2 relevanten Studien (Second-line Therapie) berichtet:

- Für OS und PFS zeigten sich keine statistisch signifikanten Unterschiede
  - OS (HR: 1.10; 95% CI: 0.84, 1.43; *p*=0.49)
  - PFS (HR: 1.08; 95% CI: 0.82, 1.41; *p*=0.66)
- Keine Analysen zu ORR

Anmerkung/Fazit der Autoren

This meta-analysis suggests the superiority of anti-EGFR therapy compared with anti-VEGF therapy for mCRC with wild-type RAS. Primary tumor location should be taken into account in target drug selection. Further research is still needed to confirm which inhibitor may be a better choice when combined with different chemotherapy regimens.

Kommentare zum Review

- nur 2 Studien relevant – Fokus 2. Therapielinie
- Qualität der Studien moderat

Chen D et al., 2018 [7].

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

Fragestellung

In this review, we will focus on angiogenesis blockade in the second-line treatment of mCRC, and summarize the data that can help in making clinical decisions

Methodik

Population:

- patients with mCRC

Intervention:

- TAS-102 alone

Komparator:

Chemotherapy or placebo alone

Endpunkte:

- OS, progressionfree survival (PFS), disease control rate (DCR) and adverse events

Recherche/Suchzeitraum:

- Bis März 2018 (PubMed, Embase, Web of Science and Cochrane, as well as clinicaltrial.gov)

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool

Ergebnisse

Anzahl eingeschlossener Studien:

N=3 RCTs (n=1318 Patienten)

Charakteristika der Population:

Table 1 Characteristics of three RCTs

Trials	Arms	Study phase	Primary end point	Patients enrolled	ECOG PS	Sample size	Average age (years)	Histology	KRAS mutational status		Time since diagnosis of first metastasis (months)	
									Wild type	Mutant	<18	≥18
Japan 2012; Yoshino et al[11]	TAS-102	II	OS	Refractory or intolerant to standard chemotherapies[a]	0–2	112	63	Adenocarcinoma	54	45	NR	NR
	Placebo					57	62		24	26	NR	NR
RECOURSE; Mayer et al[12]	TAS-102	III	OS	Refractory or intolerant to standard chemotherapies[a]	0–1	534	63	Adenocarcinoma	262	272	111	423
	Placebo					266	63		131	135	55	211
TERRA; Xu et al[15]	TAS-102	III	OS	Refractory or intolerant to standard chemotherapies[a]	0–1	271	58	Adenocarcinoma	172	99	134	137
	Placebo					135	56		85	50	52	83

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

Qualität der Studien:

- risk of bias was low

Studienergebnisse:

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

- PFS
  - PFS was significantly improved in patients who were treated with TAS-102 (HR 0.46, 95% CI 0.40–0.52, I2=0%).
  - No subgroup analysis
- DCR
  - Based on the published DCR in three trials, the pooled odds ratio of DCR was 4.15 (95% CI 3.18–5.43, I2=0%). This result indicated the superiority of TAS-102 in improving DCR compared with placebo.
- Adverse Events
  - Consistent with previous reports, the application of TAS-102 would strikingly induce adverse events, including neutropenia RR 116.51, 95% CI 23.51–577.33, I2=0%), leucopenia (RR 67.70, 95% CI 13.63–336.29, I2=0%), anemia (RR 4.28, 95% CI 2.70–6.79, I2=3%) and diarrhea (RR 5.10, 95% CI 1.40–18.61, I2=3%).

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

- ausschließlich Placebo-Vergleichende Primärstudien

Abrahao ABK et al., 2018 [1].

A Comparison of Regorafenib and TAS-102 for Metastatic Colorectal Cancer: A Systematic Review and Network Meta-analysis.

Siehe auch: Røed Skårderud M et al., 2018 [27].

Fragestellung

We have performed a systematic review and network-meta-analysis designed to assess the efficacy and safety of Regorafinib vs. TAS-102

Methodik

Population:

- Patienten mit mCRC

Intervention/ Komparator:

- Regorafinib, TA-102, Placebo

Endpunkte:

- OS, PFS, ORR, disease control, toxicity

Recherche/Suchzeitraum:

- Bis November 2015 (Pubmed, Ovid, Medline)

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- N=3 RCTs

Charakteristika der Population:

- Alle Patienten hatten refraktären mCRC, nach Behandlung mit
- Three randomized controlled trials fulfilled eligibility criteria (regorafenib monotherapy for previously treated metastatic colorectal cancer [CORRECT]: an international, multicentre, randomised, pacebo-controlled, phase 3 trial, regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer [CONCUR]: a randomised, double-blind, placebo-controlled, phase 3 trial, and randomized trial of TAS-102 for refractory metastatic colorectal cancer [RECOURSE] trials) involving 1764 patients (regorafenib, 641; TAS-102, 534; placebo, 589).

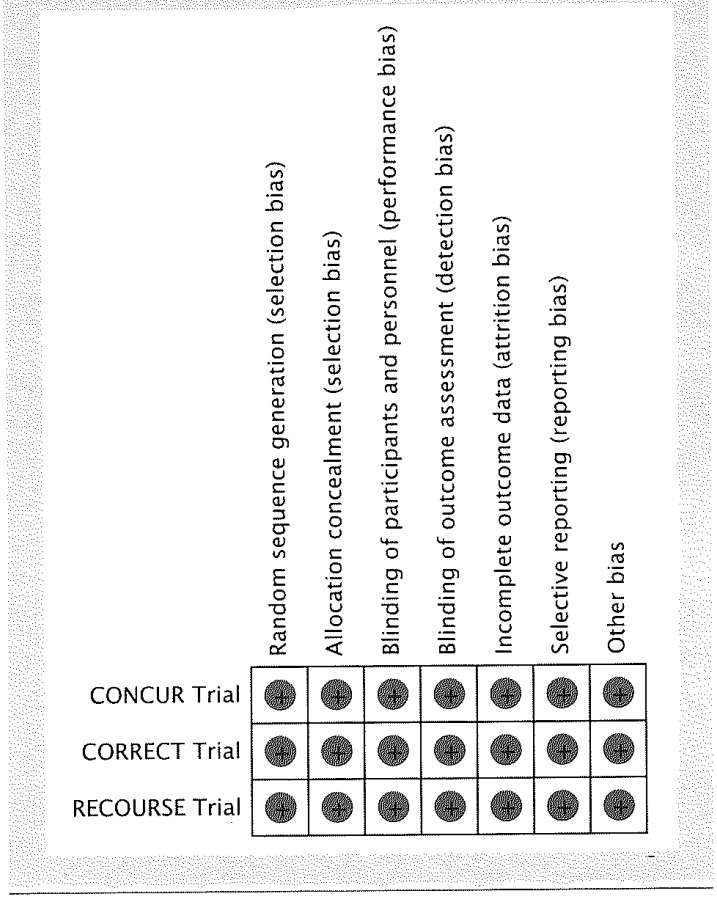
Table 1 Characteristics of Identified Randomized, Controlled Trials

Trial	Primary Outcome	Type of Trial	Treatment	Randomized Patients
CORRECT	Overall survival	Superiority	Regorafenib[a]	505
			Placebo	255
CONCUR	Overall survival	Superiority	Regorafenib[a]	136
			Placebo	68
RECOURSE	Overall survival	Superiority	TAS-102[b]	534
			Placebo	266

Abbreviations: CONCUR = regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer: a randomised, double-blind, placebo-controlled, phase 3 trial; CORRECT = regorafenib monotherapy for previously treated metastatic colorectal cancer: an international, multicentre, randomised, pacebo-controlled, phase 3 trial; RECOURSE = randomized trial of TAS-102 for refractory metastatic colorectal cancer.
[a]Regorafenib 160 mg daily on days 1 to 21 of each 28-day cycle.
[b]TAS-102 35 mg/m^2 twice daily administered in 28-day cycles, each comprising 5 days of treatment followed by a 2-day rest period each week for 2 weeks, and then a 14-day rest period.

Qualität der Studien:

Figure 3 Study Selection



Abbreviations: CONCUR = regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer: a randomised, double-blind, placebo-controlled, phase 3 trial; CORRECT = regorafenib monotherapy for previously treated metastatic colorectal cancer: an international, multicentre, randomised, pacebo-controlled, phase 3 trial; RECOURSE = randomized trial of TAS-102 for refractory metastatic colorectal cancer.

Studienergebnisse:

Gesamtüberleben – direct comparison	PFS-direct comparison
For OS in the direct meta-analysis, regorafenib showed benefit when compared with placebo (HR, 0.67; 95% CI, 0.48-0.93). A similar magnitude of benefit was observed with TAS-102 when compared with placebo (HR, 0.69; 95% CI, 0.57-0.83)	In an analysis of PFS in the direct pairwise meta-analysis, regorafenib demonstrated superiority when compared with placebo (HR, 0.40; 95% CI, 0.26-0.63) as well as TAS-102 compared with placebo (HR, 0.47; 95% CI, 0.39-0.56) (Figure 5).

- In the indirect comparison, no statistically significant differences were observed between regorafenib and TAS-102 in overall survival (hazard ratio, 0.96; 95% confidence interval [CI], 0.57-1.66; P = .91) or progression-free survival (hazard ratio, 0.85; 95% CI, 0.40-1.81; P = .67).
- However, regorafenib has statistically more all grade any toxicity (risk difference, 0.31; 95% CI, 0.25-0.38; P = .001) compared with TAS-102. Subgroup analysis of adverse events showed a different toxicity profile between both drugs

Anmerkung/Fazit der Autoren

In this indirect comparison, regorafenib and TAS-102 appeared to have similar efficacy. However, regorafenib was associated with more toxicity compared with TAS-102.

Clinical Practice Points

- Regorafenib and TAS-102 are superior to placebo in refractory mCRC.
- Regorafenib and TAS-102 demonstrated similar efficacy with comparable OS, PFS, objective response rate, and disease control rate.
- Regorafenib and TAS-102 have different toxicity profiles. Regorafenib showed significantly higher all-grade toxicities and grade 3 to 5 toxicities mainly owing to nonhematologic toxicities.
- The differences in the toxicity profile between the 2 drugs, in addition to patient comorbidities and history of toxicity with prior treatments, may guide clinical decision-making.

Kommentare zum Review

A moderate to high heterogeneity was present in the meta-analysis. While the patient group in the CONCUR trial was all Asian, the CORRECT trial presented patients originating from several continents. Secondly, all patients in the CORRECT trial had received prior VEGF therapy, compared to the CONCUR trial in which 41% and 38% of the patients in the regorafenib and placebo group, respectively, had never received any targeted biological treatment.

In terms of mutation status, there was a higher proportion of patients having a KRAS-mutation in the CORRECT trial, but the amount of patients with unknown mutation status was rather high in the CONCUR trial (29%), and complicates the attempt on a comparison.

Xiong XY et al., 2017 [36].

The role of angiogenesis inhibitors re-challenge in colorectal cancer previously treated with bevacizumab: a meta-analysis of randomized controlled trials.

Fragestellung

we assess the effect on OS and PFS of angiogenesis inhibitors (AIs) rechallenge in advanced CRC patients, who had previously been given bevacizumab-containing regimens.

Methodik

Population:

- Patients were pathologically confirmed of colorectal cancer

Intervention/ Komparator:

- therapies with or without AIs (bevacizumab, aflibercept, sorafenib, sunitinib, vandetanib, pazopanib, axitinib, regorafenib, apatinib, cediranib, ramucirumab, nintedanib, thalidomide, lenalidomide)

Endpunkte:

- OS, PFS

Recherche/Suchzeitraum:

- Bis Oktober 2016 (PubMed, Embase and the Cochrane Library

Qualitätsbewertung der Studien:

- 5-item Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- N=6 (n=2.686 Patienten)

Charakteristika der Population:

Table I. Baseline characteristic of the six trials included for analysis.

Authors	Total patients	No. of patients who received AIs already	Treatment arms	Primary endpoint	Median follow-up	Jadad score
Van cutsem et al/2012	1226	373	Aflibercept + FOLFIRI Placebo + FOLFIRI	OS	22.28	5
Bennouna et al/2013	820	820	Bevacizumab +chemotherapy chemotherapy	OS	9.6	3
Grothey et al/2013	760	760	Regorafenib placebo	OS	NR	5
Siu et al/2013	750	152	Brivanib + cetuximab Placebo + cetuximab	OS	18.7	5
Li et al/2015	204	45	Regorafenib Placebo	OS	7.4	5
Tabernero et al/2015	1072	1072	Ramucirumab + FOLFIRI Placebo + FOLFIRI	OS	21.7	5

Qualität der Studien:

- The quality of each included study was roughly assessed according to Jadad scale, and five trials had Jadad score of 5, and one trial had Jadad scores of 3

Studienergebnisse:

- Gesamtüberleben
  - Six trials reported OS data of AIs re-challenge in CRC patients
  - AIs re-challenge significantly improved OS in comparison with non-AIs containing therapies (HR 0.82, 95% CI: 0.76-0.89, $p < 0.001$, Figure 2) using a fixed-effects model ($I2= 0\%$, $p = 0.96$).
- PFS
  - Six trials reported PFS data
  - AIs re-challenge also significantly improved PFS giving HR 0.63 (95% CI: 0.52-0.76, $p < 0.001$, Figure 3), compared with non-AIs containing regimens. There was significant heterogeneity between trials ($I2 = 79.6\%$, $p < 0.001$), and the pooled HR for PFS was performed by using a random-effects model.

Anmerkung/Fazit der Autoren

Our results indicate that AIs re-challenge offers an improved PFS and OS in metastatic CRC patients when compared to non-AIs containing regimens. Thus, AIs could be recommended for metastatic CRC patients who previously treated with bevacizumab.

Van Helden EJ et al., 2017 [32].

Optimal use of anti-EGFR monoclonal antibodies for patients with advanced colorectal cancer: a meta-analysis.

Fragestellung

We pooled efficacy data to objectify and compare overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) for each treatment line. With meta-regression, the influence of the chemotherapeutic backbone and type of anti-EGFR mAb were analyzed. Furthermore, we evaluated whether the addition of anti-EGFR mAb is superior to anti-VEGF mAb in first-line treatment.

Methodik

Population:

- Included patients must be KRAS WT (at least exon 2), or the KRAS status was retrospectively determined and ORR, PFS and OS was specified for this selected subgroup.

Intervention/ Komparator:

- anti-EGFR

Endpunkte:

- OS, PFS, and ORR

Recherche/Suchzeitraum:

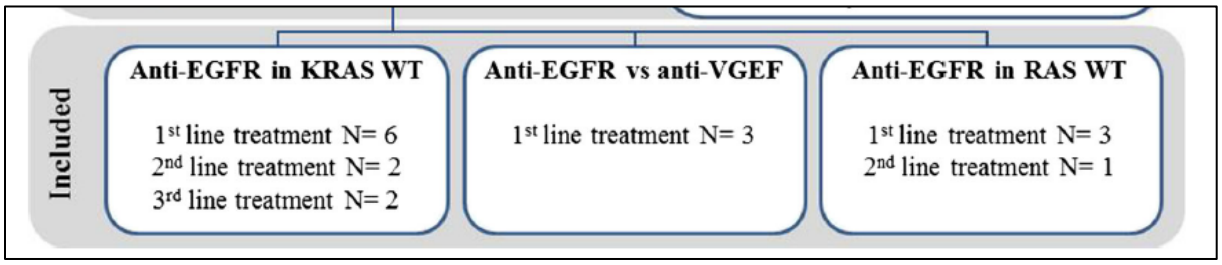
- Februar 2016 (PubMed, Embase, and Wiley/Cochrane Library)

Qualitätsbewertung der Studien:

- Cochrane collaboration's tool

Ergebnisse

Anzahl eingeschlossener Studien:



Charakteristika der Population:

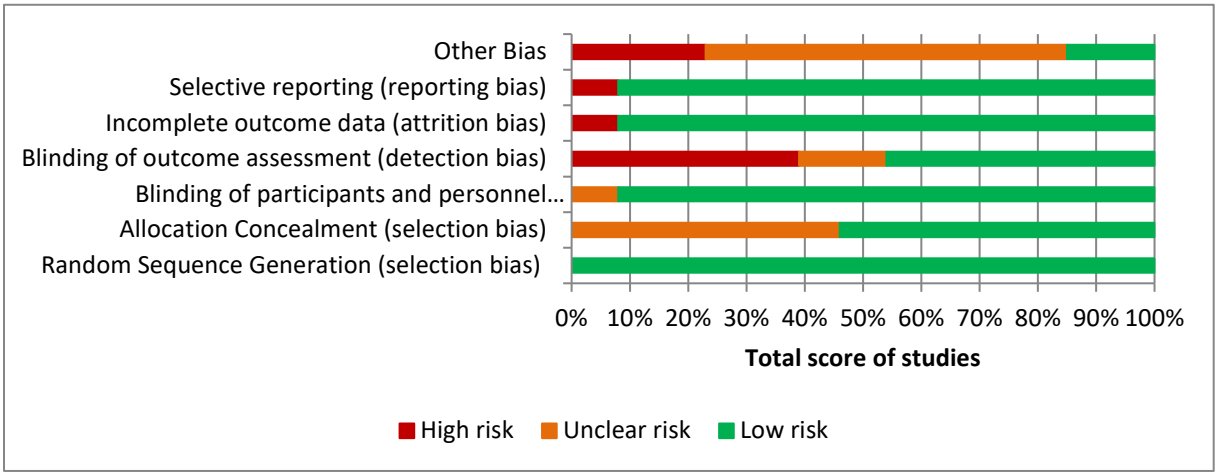
C. The addition of an anti-EGFR mAb to the second-line treatment of mCRC					
20,050,181 (Peeters)	Pani + FOLFIRI (303)	FOLFIRI (294)	36 *versus* 10 (5.5, 3.3–8.9, <0.001)	6.7 *versus* 4.9 (0.82, 0.7–1.0, 0.02)	14.5 *versus* 12.5 (0.92, 0.8–1.1, 0.37)
PICCOLO (Seymour)	Pani + irinotecan (230)	Irinotecan (230)	34 *versus* 12 (4.1, 2.5–6.8, <0.001)	5.5 *versus* 4.7 (0.78, 0.6–1.0, 0.02)	10.4 *versus* 10.9 (1.01, 0.83–1.23, 0.91)
D. The addition of an anti-EGFR mAb to the third-line treatment of mCRC					
20,020,408 (Amado)	Pani + BSC (115)	BSC (114)	17 *versus* 0	3.1 *versus* 1.8 (0.45, 0.3–0.6, <0.001)	8.1 *versus* 7.6 (0.99, 0.8–1.3)[a]
CO.17 (Karapetis)	Cetux +BSC (110)	BSC (105)	13 *versus* 0	3.7 *versus* 1.9 (0.4, 0.3–0.5, <0.001)	9.5 *versus* 4.8 (0.55, 0.4–0.7, <0.001)

mAb monoclonal antibodies, *mCRC* metastatic colorectal cancer, *Cetux* cetuximab, *Pani* panitumumab, *Beva* bevacizumab, *BSC* best supportive care, *OR* odds ratio, *CI* confidence interval, *HR* hazard ratio, *OS* overall survival, *PFS* progression-free survival

[a] Crossover design

Pooled analyses were done for six first-line studies (n = 2580 patients), two second-line studies (n = 1057), and two third-line studies (n = 444).

Qualität der Studien:



Studienergebnisse:

- In two studies, second-line chemotherapy with or without anti-EGFR mAb was compared [18, 19]. Comparable to first-line studies, ORR and PFS were significantly improved in the arms that included anti-EGFR mAb (OR 4.78, CI 3.39–6.75; HR 0.80, CI 0.71–0.91).
- OS remained unaffected (HR 0.96, CI 0.84–1.10). In the [19] study, 45.5% of the patients in the FOLFIRI alone arm received anti-EGFR mAb therapy after progression; this could reduce the observed benefit in OS in the combination arm [19]. In the PICCOLO study, only 6% of the control group received subsequent anti-EGFR mAb therapy and data concerning other subsequent therapies were not collected [18].

18. Seymour, M. T., Brown, S. R., Middleton, G., Maughan, T., Richman, S., Gwyther, S., et al. (2013). Panitumumab and irinotecan versus irinotecan alone for patients with KRAS wildtype, fluorouracil-resistant advanced colorectal cancer (PICCOLO): a prospectively stratified randomised trial. The Lancet Oncology, 14(8), 749–759.
19. Peeters,M., Price, T. J., Cervantes, A., Sobrero, A. F., Ducreux,M., Hotko, Y., et al. (2014). Final results from a randomized phase 3 study of FOLFIRI {+/–} panitumumab for second-line treatment of metastatic colorectal cancer. Annals of Oncology, 25(1), 107–116.

- Two third-line anti-EGFR mAb monotherapy studies revealed an improved PFS and OS (HR 0.44, CI 0.35–0.52; HR 0.55, CI 0.41–0.74).

Differences in (progression-free) survival between treatment lines

- The addition of anti-EGFR mAb in first- or second-line treatment renders the same beneficiary effect (first-line HR 0.79 versus second-line HR 0.80). The HR of PFS in the third line is not comparable to first or second line as it is compared to BSC.
- OS in first and second line for the KRAS WT population was similar between the combination arm versus the control arm. Yet, in the RAS WT group, a significant improvement was seen in first-line treatment (HR of 0.77, CI 0.67–0.89). Only one second-line study, 20,050,181, reported survival in RAS WT data, with a non-significantly different survival between the two arms (median OS combination 16.2 versus 13.9 months, HR of 0.80, p = 0.08) [20]. OS in the third line was only evaluable in the CO.17, which revealed an improved OS with a HR of 0.55 ($p < 0.001$).

Differences in efficacy data due to the chemotherapeutic backbones

- Between the included first- and second-line studies, ORR, PFS, and OS for combinations with irinotecan versus oxaliplatin were compared using meta-regression. ORR was significantly different, with an OR of 3.41 in the irinotecan combinations versus an OR of 1.45 in the oxaliplatin combinations (p = 0.0016). However, this benefit for irinotecan combinations was not reflected by PFS and OS gain (p = 0.10 and p = 0.51, respectively).

Differences in toxicity between treatment lines

- In all treatment lines, there was an added absolute incidence of grade ≥3 adverse events of approximately 20% with the addition of anti-EGFR mAb. The total incidence of any grade ≥3 adverse events was 82% in the first-line combination therapy group, while this was 58% in third-line setting.

Anmerkung/Fazit der Autoren

Based on our meta-analysis, we conclude that the anti-EGFR treatment significantly improves response and survival outcome of patients with (K)RAS wild-type mCRC, regardless of treatment line or chemotherapeutic backbone. It is a sensible treatment strategy to save anti-EGFR mAb as third-line monotherapy for patients with mCRC in a true non-curative setting, as combination therapy is more toxic and has no clinically significant benefit compared to sequential therapy. For patients with limited disease, first-line combination therapy with anti-EGFR mAb can be considered, if local radical treatment may still be an option upon downstaging. As sound data to support this last consideration are lacking, further research is necessary.

Jiang Y et al., 2017 [19].

Efficacy and safety of FOLFIRI and biotherapy versus FOLFIRI alone for metastatic colorectal cancer patients.

Fragestellung

This meta-analysis was designed to investigate whether the biological therapy combined with FOLFIRI regimen is effective for mCRC patients

Methodik

Population:

- Patients histologically or cytologically diagnosed as mCRC
- chemotherapy that confined to the FOLFIRI regimen and the treatment that confined to the second-line therapy
- no previous treatment of irinotecan

Intervention:

- FOLFIRI combined with biological therapy

Komparator:

- FOLFIRI alone

Endpunkte:

- PFS, OS, overall response rate (ORR), and Grade 3/4 adverse effects (AEs)

Recherche/Suchzeitraum:

- Zwischen Januar 2000 und Dezember 2015

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- N=7 RCTs → nur 2 Studien relevant

Charakteristika der Population:

Table 2

Basic patient characteristics.

Ref.	Study type	Comparison	Cases, n	Male sex, %	Median PFS, mo	Median OS, mo	ORR, %	Grade3/4 AEs, %
Tabernero et al[11]	Phase III RCT	Folfiri ± Ramucirumab	536 and 536	54.0%, vs 61.0%	5.7 vs 4.5	13.3, vs 11.7	13.4%, vs 12.5%	79%, vs 62%
Peeters et al[8]	Phase II RCT	Folfiri ± trebananib	95 and 49	63.0%, vs 49.0%	3.5, vs 5.2	11.9, versus 8.8	14%, vs 0	55.3%, vs 59.2%
Cohn et al[9]	Phase II RCT	Folfiri ± conatumumab	51 and 52	53.0%, vs 44.0%	6.5, vs 4.6	12.3, vs 12.0	14%, vs 2%	72%, vs 47%
Cohn et al[9]	Phase II RCT	Folfiri ± Ganitumab	52 and 52	46.0%, vs 44.0%	4.5, vs 4.6	12.4, vs 12.0	8%, vs 2%	55%, vs 47%
Cutsem et al[10]	Phase III RCT	Folfiri ± Aflibercept	612 and 614	59.6%, vs 57.5%	6.90, vs 4.67	13.50, vs 12.06	19.8%, vs 11.1%	83.5%, vs 62.5%
Peeters et al[7]	Phase III RCT	Folfiri ± panitumumab	303 and 294	62.0% vs 65.0%	5.9, vs 3.9	14.5, vs 12.5	35%, vs 10%	73%, vs 52%
Xie et al[14]	Phase II RCT	Folfiri ± panitumumab or bevacizumab	137 and 155	59.1%, vs 63.2%	5.5, vs 4.2	13.9, vs 10.7	40.1%, vs 30.1%	52.6%, vs 80.0%
Cao et al[15]	Phase II RCT	Folfiri ± bevacizumab	65 and 77	61.5%, vs 62.3%	8.5, vs 5.1	15.2, vs 11.3	9.2%, vs 6.5%	63.1%, vs 75.3%

AE = adverse effect, Folfiri = 5-fluorouracil, leucovorin, and irinotecan, NA = not available, ORR = overall response rate, OS = overall survival, PFS = progression-free survival, RCT = randomized controlled trials.

Table 1 Characteristics of the 5 included studies comparing chemotherapy combined with VEGF inhibitor versus EGFR inhibitors

Study	Phase	Treatment line	Year of study	Treatment regimen	Response assessment	Quality scores	References
CALGB/ SWOG 80405	III	First line	2017	CT (either mFOLFOX6 or FOLFIRI) + Cet vs CT + Bev	RECIST 1.0	3	11
FIRE-3	III	First line	2014	FOLFIRI + Cet vs FOLFIRI + Bev	RECIST 1.0	3	12, 13
PEAK	II	First line	2014	mFOLFOX + Pan vs mFOLFOX + Bev	RECIST 1.0	3	14, 15
SPIRITT	II	Second line	2014	FOLFIRI + Pan vs FOLFIRI + Bev	RECIST 1.0	3	16
WJOG 6210G	II	Second line	2016	FOLFIRI + Pan vs FOLFIRI + Bev	RECIST 1.1	3	17

Abbreviations: VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor; CT, chemotherapy; FOLFIRI, folinate, fluorouracil, and irinotecan; Cet, cetuximab; Bev, bevacizumab; RECIST, The Response Evaluation Criteria in Solid Tumors; mFOLFOX, modified folinic acid-fluorouracil-oxaliplatin; Pan, panitumumab.

Qualität der Studien:

Table 1

Risk of bias among included studies.

Source	Sequence generation	Allocation concealment	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data addressed	Free of selective reporting	Other bias
Tabernero et al [11]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Peeters et al [8]	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear	Low risk
Cohn et al [9]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Cohn et al [9]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Cutsem et al [10]	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear	Low risk
Peeters et al [7]	Low risk	Unclear	Low risk	Unclear	Low risk	Unclear	Low risk
Xie et al [14]	Low risk	Unclear	High risk	Unclear	Low risk	Unclear	Low risk
Cao et al [15]	Low risk	High risk	High risk	High risk	Low risk	Unclear	Low risk

Studienergebnisse:

In subgroup analyses, OS remained prolonged for wild-type KRAS patients treated with EGFR inhibitors as first-line therapy (HR: 0.82; 95% CI: 0.74, 0.92; p=0.0005). However, this survival benefit disappeared in second-line therapy (HR: 1.10; 95% CI: 0.84, 1.43; p=0.49). Neither first-line nor second-line studies revealed significant differences in PFS, with HRs equal to 0.97 (95% CI: 0.88, 1.07; p=0.56) and 1.08 (95% CI: 0.82, 1.41; p=0.60), respectively.

Anmerkung/Fazit der Autoren

A clear OS advantage was demonstrated in first-line therapy favoring EGFR inhibitors, but this improvement was not noted in second-line therapy, with an increased ORR and no significant effect on PFS.

Kommentare zum Review

- Ergebnisse basieren auf Subgruppenanalysen (2 Studien)

Wang H et al., 2016 [33].

Efficacy and safety of anti-epidermal growth factor receptor therapy compared with anti-vascular endothelial growth factor therapy for metastatic colorectal cancer in first-line and second-line therapies: a meta-analysis.

Fragestellung

we conducted this meta-analysis including randomized clinical trials and retrospective studies so as to give an overview of the results comparing anti-EGFR and anti-VEGF therapies as first- and second-line therapies based on survival outcomes, toxicity, and conversion rate in conversion therapy in patients with KRAS exon 2 wild-type (KRAS-WT) mCRC.

Methodik

Population:

- patients diagnosed with KRAS-WT mCRC

Intervention:

- anti-EGFR therapy

Komparator:

- anti-VEGF therapy in association with combination chemotherapy as first-line or second-line chemotherapy

Endpunkte:

- OS, PFS, ORR, toxicity, and conversion therapy

Recherche/Suchzeitraum:

- Bis Januar 2016 (PubMed, EMBASE, and the Cochrane databases)

Qualitätsbewertung der Studien:

- Jadad scale to assess the methodological quality of all eligible randomized controlled trials (RCTs) and the Newcastle–Ottawa Scale to evaluate the quality of the nonrandomized studies

Ergebnisse

Anzahl eingeschlossener Studien:

- N=7 Studien

- Two articles (including one meeting abstract) containing 160 patients in the anti-EGFR group and 147 patients in the anti-VEGF group, respectively, were eligible for our study in the second-line setting

Charakteristika der Population:

Table 1 Characteristics of studies included in this meta-analysis

Study	Year	Country	Study design	Treatment groups	No of patients	Regimen	Age	PS
Heinemann et al[12]	2014	Germany	Randomized Phase III study	Group A	A=297	A: FOLFIRI + cetuximab	64 (38–79)	0–2
				Group B	B=295	B: FOLFIRI + bevacizumab	65 (27–76)	0–2
Schwartzberg et al[14]	2014	Spain	Randomized Phase II study	Group A	A=142	A: mFOLFOX6 + panitumumab	63 (23–82)	0–1
				Group B	B=143	B: mFOLFOX6 + bevacizumab	61 (28–82)	0–1
CALGB/ SWOG80405[13,15,24,26]	2014	USA	Randomized Phase III study	Group A	A=578	A: FOLFIRI/mFOLFOX6 + cetuximab	59 (NA)	0–1
				Group B	B=559	B: FOLFIRI/mFOLFOX6 + bevacizumab	59 (NA)	0–1
Stremitzer et al[25]	2015	Austria	Retrospective	Group A	A=37	A: Fluoropyrimidine only/irinotecan/oxaliplatin + cetuximab	63 (31–80)	NA
				Group B	B=101	B: irinotecan/irinotecan + oxaliplatin/oxaliplatin + bevacizumab	63 (31–80)	NA
Yang et al[27]	2014	Taiwan	Retrospective	Group A	A=63	A: irinotecan-based/oxaliplatin-based + cetuximab	NA	NA
				Group B	B=95	B: irinotecan-based/oxaliplatin-based + bevacizumab	NA	NA
Heinemann et al[29]	2015	Germany	Randomized Phase III study	Group A	A=69	A: FOLFIRI + cetuximab	NA	0–1
				Group B	B=56	B: FOLFIRI + bevacizumab	NA	0–1
Hecht et al[28]	2015	USA	Randomized Phase II study	Group A	A=91	A: FOLFIRI + panitumumab	60 (27–84)	0–1
				Group B	B=91	B: FOLFIRI + bevacizumab	60 (25–80)	0–1

Abbreviations: Irinotecan-based, irinotecan-based combination therapy; Oxaliplatin-based, oxaliplatin-based combination therapy; NA, not applicable; FOLFIRI, fluorouracil, folinic acid, and irinotecan; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; PS, performance status; mFOLFOX, modified, 5-fluorouracil, leucovorin, oxaliplatin.

Qualität der Studien:

- All the RCTs had Jadad scores of ≥3 and were considered to be high-quality studies. All the retrospective studies had Newcastle–Ottawa Scale score of 6 and were considered to be moderate-quality studies

Studienergebnisse:

- Two articles (including one meeting abstract) provided data on the comparison between anti-EGFR and anti-VEGF therapies in combination with FOLFIRI for KRAS-WT mCRC when the disease progressed during oxaliplatin-based chemotherapy.
- There was no significant difference in OS (HR =1.17, 95% CI: 0.88–1.56, P=0.29, n=2) (Figure 5A) and PFS (HR =1.12, 95% CI: 0.88–1.43, P=0.36, n=2) between the two therapies.
- However, there was a significant improvement in ORR in the anti-EGFR group when it was used as the second-line therapy (OR =1.91, 95% CI: 1.16–3.16, P=0.01, n=2)

Referenzen:
28. Hecht JR, Cohn A, Dakhil S, et al. SPIRITT: a randomized, multicenter, Phase II study of panitumumab with FOLFIRI and bevacizumab with FOLFIRI as second-line treatment in patients with unresectable wild type KRAS metastatic colorectal cancer. *Clin Colorectal Cancer*. 2015;14(2):72–80.
29. Heinemann V, Niedzwiecki D, Rachel V, et al. Outcomes for FOLFIRI plus bevacizumab (BEV) or cetuximab (CET) in patients previously treated with oxaliplatin-based adjuvant therapy: a combined analysis of data from FIRE-3 and CALGB 80405. *J Clin Oncol*. 2015;33:(Suppl; abstract 3585).

Anmerkung/Fazit der Autoren

Our results indicate that anti-EGFR therapy improved OS and ORR and caused the toxicity expected compared with anti-VEGF therapy as a first-line therapy for KRAS-WT and all RAS-WT mCRC. Furthermore, we found a clear tendency for conversion therapy in the anti-EGFR group. There was a significant improvement in ORR in the second-line setting in the anti-EGFR group. Therefore, more high-quality and well-designed studies are needed to provide further evidence.

Pei X et al., 2016 [24].

Outcome of Molecular Targeted Agents Plus Chemotherapy for Second-Line Therapy of Metastatic Colorectal Cancer: A Meta-Analysis of Randomized Trials.

Fragestellung

we conducted this meta-analysis to evaluate and further understand the efficacy and safety of molecular targeted agents in combination with chemotherapy for second-line therapy in patients with mCRC.

Methodik

Population:

- histologically or pathologically confirmed CRC (secondline treatment)

Intervention/ Komparator:

- Molecular Targeted Agents Plus Chemotherapy

Endpunkte:

PFS, OS, ORR, rate of grade ≥ 3 adverse effects

Recherche/Suchzeitraum:

- January 2000 to September 2015 (PubMed and Embase)

Qualitätsbewertung der Studien:

- Jadad score

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 RCTs (N=7.440 Patienten)

Charakteristika der Population:

Among them, the types of molecular targeted agents include anti-VEGF agent,[4,12,21,22,25,26] EGFR inhibitor, [13,20,24] DR5 inhibitor,[14] IGF1R inhibitor,14 and Ang-Tie2 inhibitor.[23]

First Author and Reference	Year	Phase	Median Age, Year (E/C)	Regimen (E/C)	Number of Patients (E/C)	Jadad Score
Tabernero[25]	2015	III	62 (21-83)/62 (33-87)	FOLFIRI + ramucirumab FOLFIRI + placebo	536/536	5
Masi[22]	2015	III	62 (38-75)/66.5 (38-75)	FOLFIRI/mFOLFOX-6 + bevacizumab FOLFIRI/mFOLFOX-6	92/92	3
Bennouna[12]	2013	III	63 (27-84)/63 (21-84)	CT + bevacizumab CT	409/411	3
Cohn(a)[14]	2013	II	59 (37-79)/59 (32-80)	FOLFIRI + conatumumab FOLFIRI + placebo	51/52	5
Cohn(b)[14]	2013	II	58 (28-81)/59 (32-80)	FOLFIRI + ganitumab FOLFIRI + placebo	52/52	5
Peeters[23]	2013	II	56 (23-79)/55 (29-79)	FOLFIRI + trebananib FOLFIRI + placebo	95/49	4
Seymour[24]	2013	NR	64 (57-70)/63 (56-69)	Irinotecan + panitumumab Irinotecan	230/230	3
Van Cutsem[4]	2012	III	61 (21-82)/61 (19-86)	FOLFIRI + aflibercept FOLFIRI + placebo	612/614	5
Van Cutsem[26]	2011	III	60.5 (21-85)/59.2 (18-81)	FOLFOX4 + PTK/ZK FOLFOX4 + placebo	426/429	5
Peeters[13]	2010	III	60 (28-84)/61 (29-86)	FOLFIRI + panitumumab FOLFIRI	303/294	3
Sobrero[20]	2008	III	61 (23-85)/62 (21-90)	Irinotecan + cetuximab Irinotecan	648/650	3
Giantonio[21]	2007	III	62.0 (21-85)/60.8 (25-84)	FOLFOX4 + bevacizumab FOLFOX4	286/291	3

Cohn (a) and Cohn (b) came from the same article.
Abbreviations: C = control arm; CT = chemotherapy; E = experimental arm; FOLFIRI = 5-fluorouracil, leucovorin, and irinotecan; FOLFOX = infusional fluorouracil, leucovorin, and oxaliplatin; NR = not reported.

Qualität der Studien:

- Siehe Tabelle

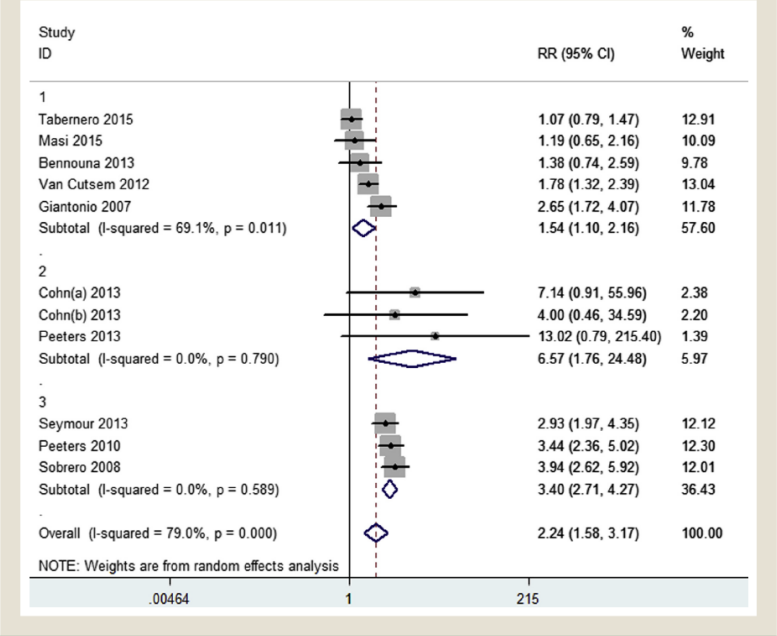
Studienergebnisse:

- PFS (11 Studien)
  - No significant heterogeneity between trials was detected (I2 = 39.3%; P = .079). Thus, the pooled HR for PFS was conducted using a fixed-effects model. The pooled data showed that a targeted agent plus chemotherapy significantly improved PFS (HR, 0.74; 95% CI, 0.70-0.78) more than chemotherapy alone in second-line treatment
  - In accordance with the type of molecular targeted agents, we divided the 11 trials into 3 subgroups: (1) VEGF inhibitor; (2) other pathway inhibitor, and (3) EGFR inhibitor. The addition of a VEGF or an EGFR inhibitor evidently prolonged PFS (HR, 0.74; 95% CI, 0.69-0.79; HR, 0.72; 95% CI, 0.65-0.78, respectively) compared with monotherapy. However, the regimen of another pathway inhibitor plus chemotherapy did not significantly improve PFS (HR, 0.99; 95% CI, 0.75-1.29). There was no significant publication bias (Begg test, Z = 0.75; P =.451 and Egger test, Z =1.27; P = 0.233.

- OS (11 Studien)
  - A fixed-effects model was used to pool the data, since the heterogeneity across the 11 studies was not significant (I2 = 30.4%; P = 0,149). The result indicated that combination therapy significantly prolonged OS compared with monotherapy (HR, 0.88; 95% CI, 0.83-0.93) (Figure 3). However, in the subgroup analysis, it was seen that EGFR or another pathway inhibitor combined with chemotherapy did not significantly improve the OS of mCRC patients (HR, 0.95; 95% CI, 0.86-1.05; HR, 1.01; 95% CI, 0.75-1.36, respectively). The addition of VEGF inhibitor provided a significant OS benefit for patients (HR, 0.84; 95% CI, 0.79-0.90). We also show that no significant publication bias existed (Begg test, Z = 0.21; P = 0.837 and Egger test, Z = 0.28; P = 0.787).

- OS (10 Studien)
  - The pooled analysis showed that there was a high heterogeneity among the 10 trials (I2=79.0%; P=0.000).Therefore, a random-effects model was conducted. As Figure 4 illustrates, the patients with mCRC treated with combined therapy had a higher RR than those treated with chemotherapy alone (RR, 2.24; 95% CI, 1.58-3.17).
  - Subgroup analysis revealed that there was a significant difference for each subgroup when comparing the combination arm with the chemotherapy-alone arm (Figure 4).

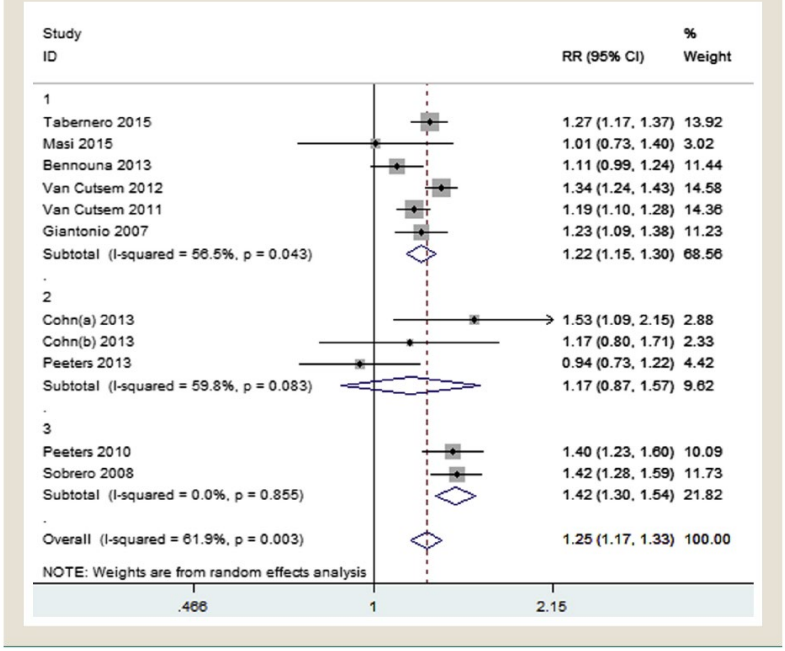
Figure 4 The Forest Plot of ORR Comparing Chemotherapy Plus Molecular Targeted Agent With Chemotherapy Alone. Subgroup 1: Anti-VEGF Agents; 2: Other Pathway Inhibitors; 3: EGFR Inhibitors



Abbreviations: CI = confidence interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; ORR = objective response rate; VEGF = vascular endothelial growth factor.

- Adverse Events (10 Studien)
  - A moderate heterogeneity was detected (I2 = 61.9%; P = 0.003), and the random-effects model was used to analyze this. A higher RR was observed in the arm of chemotherapy plus a targeted agent compared with the control arm (RR, 1.25; 95% CI, 1.17-1.33) (Figure 5). A subgroup analysis suggested that the addition of EGFR inhibitor and VEGF inhibitor to chemotherapy induced a higher RR (Figure 5).

Figure 5 The Forest Plot of Grade ≥ 3 Adverse Events Comparing Chemotherapy Plus Molecular Targeted Agent With Chemotherapy Alone. Subgroup 1: Anti-VEGF Agents; 2: Other Pathway Inhibitors; 3: EGFR Inhibitors



Abbreviations: CI = confidence interval; EGFR = epidermal growth factor receptor; RR = relative risk; VEGF = vascular endothelial growth factor.

Anmerkung/Fazit der Autoren

In conclusion, our meta-analysis showed that an available molecular targeted agent plus chemotherapy improved PFS, OS, and ORR as second-line therapy for mCRC, compared with the chemotherapy-alone group; however, the drug-related toxicities also increased. In addition, further subgroup analyses indicated that VEGF inhibitor in combination with chemotherapy was the most valid treatment option out of those studied on the whole as a second-line therapy for these patients. However, more RCTs on a larger scale are needed to determine valid results for EGFR and other pathway inhibitors.

3.4 Leitlinien

NICE, 2020 [23].

National Institute for Health and Care Excellence (NICE)

Colorectal cancer.

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 management of secondary tumours (metastatic disease).

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- Update Januar 2020

LoE/GoR

- Formulierungen im Text**.**

Sonstige methodische Hinweise

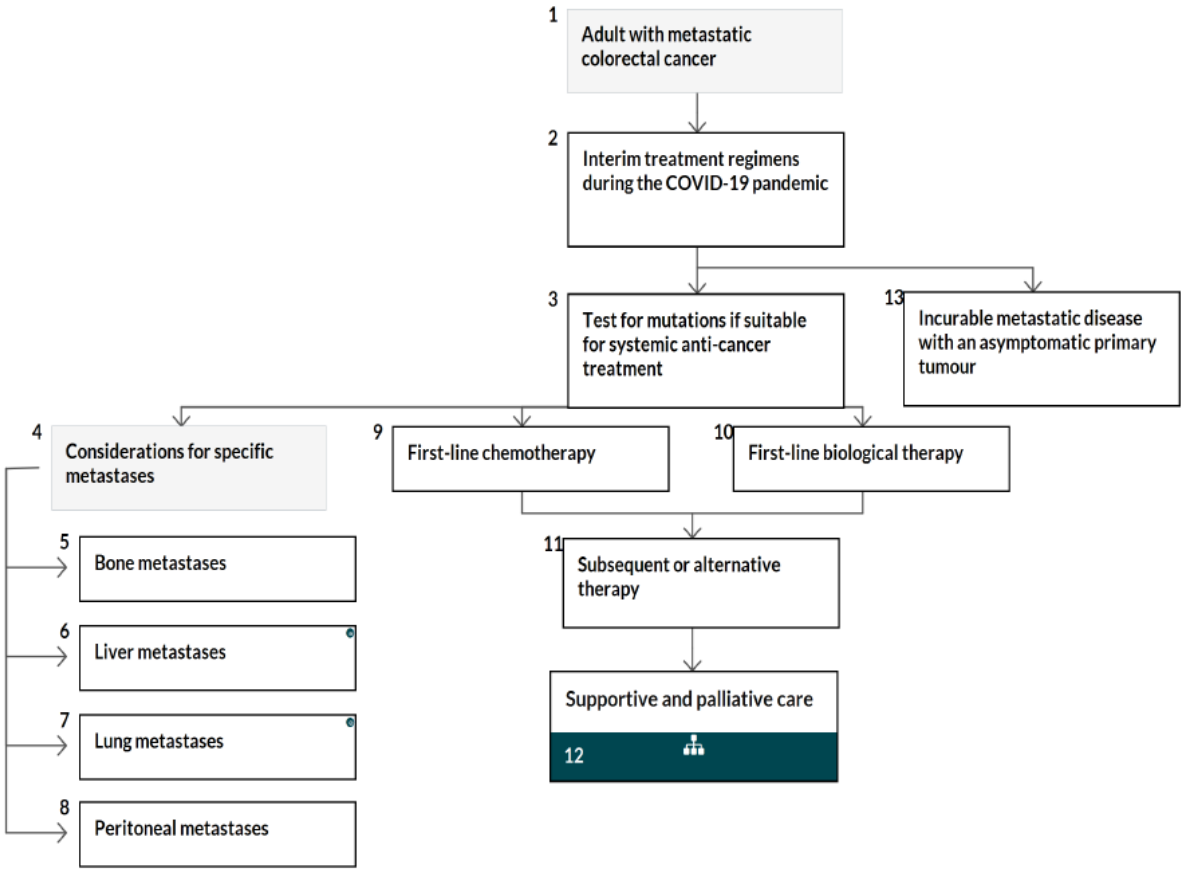
- This guideline is an update of NICE guideline CG131 (published November 2011) and NICE guideline CSG5 (published June 2004) and has replaced them.

Recommendations

Management of metastatic disease

- Consider surgical resection of the primary tumour for people with incurable metastatic colorectal cancer who are receiving systemic anti-cancer therapy and have an asymptomatic primary tumour. Discuss the implications of the treatment options with the person before making a shared decision.

Systemic anti-cancer therapy for people with metastatic colorectal cancer



- Subsequent or alternative therapy
  - *Trifluridine–tipiracil*: The following recommendation is from NICE technology appraisal guidance on trifluridine–tipiracil for previously treated metastatic colorectal cancer.

    Trifluridine–tipiracil is recommended, within its marketing authorisation, as an option for treating metastatic colorectal cancer, that is:

    in adults who have had previous treatment with available therapies including fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies, anti-vascular endothelial growth factor agents and anti-epidermal growth factor receptor agents, or when these therapies are not suitable, and

    only when the company provides trifluridine–tipiracil with the discount agreed in the patient access scheme.
  - *Aflibercept*: The following recommendations are from NICE technology appraisal guidance on aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy.

    Aflibercept in combination with irinotecan and fluorouracil-based therapy is not recommended within its marketing authorisation for treating metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin-containing regimen.

    People currently receiving aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that is resistant to or has

progressed after an oxaliplatin-containing regimen should be able to continue treatment until they and their clinician consider it appropriate to stop.

- *Cetuximab, bevacizumab and panitumumab*: The following recommendations are from NICE technology appraisal guidance on cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy.

  Cetuximab monotherapy or combination chemotherapy is not recommended for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy.

  Bevacizumab in combination with non-oxaliplatin (fluoropyrimidine-based) chemotherapy is not recommended for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy.

  Panitumumab monotherapy is not recommended for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy.

  People currently receiving cetuximab monotherapy or combination chemotherapy, bevacizumab in combination with non-oxaliplatin chemotherapy, or panitumumab monotherapy for the treatment of metastatic colorectal cancer that has progressed after first-line chemotherapy should have the option to continue treatment until they and their clinician consider it appropriate to stop.
- *Panitumumab in combination with chemotherapy*: NICE is unable to recommend panitumumab with 5 fluorouracil, folinic acid and irinotecan for previously treated metastatic colorectal cancer in adults because no evidence submission was received from the manufacturer or sponsor of the technology.

  Since the publication of TA240, the population covered by the marketing authorisation for panitumumab has changed from 'patients with wild-type KRAS metastatic colorectal cancer' to 'patients with wild-type RAS metastatic colorectal cancer'.
- *Regorafenib*: The NICE technology appraisal of regorafenib for metastatic colorectal cancer after treatment for metastatic disease was terminated because no evidence submission was received from Bayer for the technology. Therefore NICE is unable to make a recommendation about the use in the NHS of regorafenib for metastatic colorectal cancer after treatment for metastatic disease.
- *Genomic biomarker-based treatment for solid tumours*: The point at which to use genomic biomarker-based therapy in solid tumour treatment pathways is uncertain. See the NICE Pathway on genomic biomarker-based treatment for solid tumours for guidance on specific treatments.

Phelip JM et al., 2019 [26].

Siehe auch: Gerard JP et al., 2017 [16] & Lakkis Z et al., 2016 [20].

Metastatic colorectal cancer (mCRC): French intergroup clinical practice guidelines for diagnosis, treatments and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SFR).

Leitlinienorganisation/Fragestellung

Up-to-date comprehensive overview of pre-therapeutic exams, medico-surgical therapeutic strategies, the best chemotherapiesand targeted therapy choices according to patients’ and

tumors'characteristics, somatic molecular alterations, the site of localizedtherapies and new drugs available.

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- up until December 2018

LoE/GoR

- Recommendations based on the level of evidence were scored in 3 categories graded A, B and C), withonly expert opinion (agreement or not, grade D) when no scientific evidence was validated

Table 1
Grade of recommendations.

Grade	Quality of evidence	Definition
A	High	Strongly recommended based on robust scientific evidence (e.g., several randomized controlled trials/meta-analyses) Further research is very unlikely to change our confidence in the estimate of effect
B	Moderate	Usually recommended based on scientific presumption (e.g., one randomized controlled trial) Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
C	Low	Option based on weak scientific evidence (e.g., one or several non-randomized trials) Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
D	Very low	Expert opinion (agreement or not) Any estimate of effect is very uncertain

Empfehlungen

2. Pre-therapeutic assessment *(Hinweis FBMed → zusätzlich als Hintergrund zum Biomarker extrahiert)*

2.1. Recommendations

- RAS status (KRAS, NRAS) as a predictor of EGFRi (Epidermal Growth Factor Receptor Inhibitor) resistance (recommendation: grade A);
- BRAF V600E status as a poor prognosis factor (recommendation: grade B);
- MSI phenotyping (by immunochemistry of MMR proteins or microsatellite testing on tumor DNA) as a poor prognosis factor and predictor of immune checkpoint inhibitors' efficacy in mCRC (recommendation: grade C);
- DPD phenotyping (by measuring plasma uracil concentration): fluoropyrimidine dose adjustment in case of partial DPD deficiency and fluoropyrimidine contraindication in case of complete DPD deficiency (expert agreement);
- Thoraco-abdominopelvic CT scan at baseline ± liver MRI to assess for resectability of liver metastases.

2.2. Options

- UGT1A1 genotyping (for irinotecan dose adjustment in case of Gilbert's syndrome);
- DPYD Genotyping in patients with abnormal plasma uracil con-centration (expert agreement);
- TEP-scan when surgery of metastases (especially in the liver) is considered (recommendation: grade B).

What to do after a first-line chemotherapy?

4.1. Recommendations

- Recent data indicate that the L1–L2 therapy sequence may impact treatment efficacy. Given the relevance of continuous angiogene-sis blockade in 3 phase III trials [11,65,66] and biological rationale[71], the work group recommends:
  - Maintaining angiogenesis blockade in L2 when bevacizumab was used in L1, including cases of RAS WT tumors (Expert agreement); as phase II and retrospective data indicate a non-optimal efficacy of EGFRi in L2 following bevacizumab treatment [68,69].
  - Conversely, in case of L1 with EGFRi therapy, an antiangiogenic should be prescribed in L2.
  - Progression and/or intolerance during cytotoxic chemotherapy(5FU, irinotecan and oxaliplatin), EGFRi antibodies (if RAS WT) therapy and VEGFi antibodies therapies:

    2 systemic treatments are available for patients with good performance status (0–1): regorafenib and trifluridine/tipiracil (recommendation: grade A).
  - SIR-Spheres®(Y-90 resin microspheres) in case of exclusive orpredominant liver metastases with maintained liver function (rec-ommendation: grade B) [72,73]
  - Palliative care (ECOG PS > 2) or clinical trial (expert agreement)

4.2. Options

- Oxaliplatin re-introduction [74] if no previous progression on oxalipatin-based chemotherapy and/or if the neurotoxicity that justified interruption has regressed (recommendation: grade C)
- Re-introduction of EGFRi if no previous progression on EGFRi-based chemotherapy, the toxicities that justified interruption has regressed and for patients who underwent an interval chemotherapy without anti-EGFR and no evidence of RAS mutation when re-introduced (expert agreement)
- Hepatic intra-arterial chemotherapy (oxaliplatin + LV5FU2) (recommendation: grade C) in experienced care centers.

Referenzen:

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[65] Bennouna J, Sastre J, Arnold D, et al. Continuation of bevacizumab after firstprogression in metastatic colorectal cancer (ML18147): a randomised phase 3trial. Lancet Oncol 2013;14:29–37.
[66] Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combina-tion with second-line FOLFIRI in patients with metastatic colorectal carcinomathat progressed during or after first-line therapy with bevacizumab, oxaliplatin,and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre,phase 3 study. Lancet Oncol 2015;16:499–508.
[68] Hiret S, Borg C, Bertaut A, et al. Bevacizumab or cetuximab plus chemother-apy after progression with bevacizumab plus chemotherapy in patients withwtKRAS metastatic colorectal cancer: a randomized phase II study (prodige18—UNICANCER GI). J Clin Oncol 2016;34:3514.
[69] Taniguchi H, Komori A, Narita Y, et al. A short interval between bevacizumaband anti-epithelial growth factor receptor therapy interferes with efficacy ofsubsequent anti-EGFR therapy for refractory colorectal cancer. Jpn J Clin Oncol2016;46:228–33.

[72] Hendlisz A, Van den Eynde M, Peeters M, et al. Phase III trial comparingprotracted intravenous fluorouracil infusion alone or with yttrium-90 resinmicrospheres radioembolization for liver-limited metastatic colorectal cancerrefractory to standard chemotherapy. J Clin Oncol 2010;28:3687–94.
[73] Bester L, Meteling B, Pocock N, et al. Radioembolization versus standardcare of hepatic metastases: comparative retrospective cohort study of sur-vival outcomes and adverse events in salvage patients. J Vasc Interv Radiol2012;23:96–105.

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)), 2019 [21].

S3-Leitlinie Kolorektales Karzinom, Langversion 2.1, 2019, AWMF-Registrierungsnummer 021-007OL

Leitlinienorganisation/Fragestellung

Therapieempfehlungen für das kolorektale Karzinom.

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- Für die Aktualsierung der Leitlinie erfolgten eine Recherche in der GIN- Library nach Leitlinien sowie mehrere spezifische Literaturrecherchen zu priorisierten Schlüsselfragen. Eine separate Suche nach systematischen Übersichtsarbeiten und Meta-Analysen (wie für Version 1) erfolgte nicht. Reviews und Meta-Analysen wurden im Rahmen der spezifischen Suchen identifiziert.
- Zum Thema „Einsatz von Angiogenesehemmern und anti-EGFR-Antikörpern bei Patienten mit metastasiertem kolorektalem Karzinom“ wurde eine externe Evidenzaufarbeitung in Auftrag gegeben.
- Die Literaturercherchen wurden in MEDLINE (über Pubmed) durchgeführt. Ergänzend wurden Handsuchen in den Datenbanken Cochrane Clinical Trials Database sowie in den Literaturverzeichnissen der identifizierten Leitlinien und Sekundärliteratur durchgeführt.
- Die Literatursuche, Evidenzbewertung und Erstellung von Evidenztabellen fand zwischen zwischen August 2015 und April 2016 statt.

LoE

Tabelle 4: Schema der Empfehlungsgraduierung

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll/soll nicht
B	Empfehlung	sollte/sollte nicht
0	Empfehlung offen	kann/kann verzichtet werden

GoR

Tabelle 5: Klassifikation der Konsensusstärke

Konsensusstärke	Prozentuale Übereinstimmung
Starker Konsens	Zustimmung von > 95% der Teilnehmer
Konsens	Zustimmung von > 75-95% der Teilnehmer
Mehrheitliche Zustimmung	Zustimmung von >50-75% der Teilnehmer
Kein Konsens	Zustimmung von < 50% der Teilnehmer

Sonstige methodische Hinweise

- gültig bis 29.11.2022; 9.1.2019 aktualisierte Kurz- und Langfassung
- In den Empfehlungskästen ist jeweils das Datum der letzten Überarbeitung (2008, 2013 oder 2017) aufgeführt

Empfehlungen

Systemische Therapie in Abhängigkeit von der molekularpathologischen Subgruppe und der Tumorlokalisation

9.8.4. BRAF Mutation

9.23.	Evidenzbasierte Empfehlung	2017
Empfehlungsgrad **B**	Liegt eine BRAF-Mutation vor, sollte primär eine möglichst effektive Chemotherapie z. B. mit einer Triplette oder der Einschluss in eine klinische Studie erfolgen.	
Level of Evidence **4**	Quellen: [1062, 1119]	
	Konsens	

Hintergrund

Eine BRAF V600 Mutation wird bei 8-12% der mKRK Patienten beobachtet. Häufiger sind Frauen betroffen, das Erkankungsalter ist meist höher. Bei etwa zwei Dritteln der Betroffenen ist der Tumor im rechten Kolon lokalisiert; histologisch werden vermehrt muzinöse Subtypen beobachtet.

Klinisch fällt eine höhere Rate an Lymphknotenmetastasierung und Peritonealkarzinose auf. Molekularpathologisch stehen Mikrosatelliteninstabilität und ein „Methylator Phänotyp“ im Vordergrund [1120], [1057]. Die Prognose der Patienten mit BRAF-V600-Mutation ist außerordentlich schlecht, so dass in zahlreichen Studien mediane PFS-Zeiten von weniger als 6 Monaten und mediane Überlebenszeiten von weniger als einem Jahr berichtet werden [1059].

Derzeit wird bei Vorliegen einer BRAF-V600-Mutation eine Chemotherapie-Triplette, mit dem FOLFOXIRI-Regime, empfohlen. Diese Empfehlung gründet sich allerdings auf eine Subgruppenanalyse von nur 28 Patienten mit BRAF-Mutation, die im Rahmen der TRIBE-Studie behandelt wurden. Diese erzielten unter einer Behandlung mit FOLFOXIRI plus Bevacizumab (n=16) im Vergleich zu FOLFIRI plus Bevacizumab (n=12) deutlich günstigere Outcomedaten: Ein deutlich längeres OS (19,0 vs. 10,7 Monate; HR 0,54), ein längeres PFS (7,5 vs 5,5 Monate; HR 0,57) und eine höhere Remissionsrate (56 % vs 42 %; OR 1,87) [1062]. Einerseits können die Ergebnisse dieser Analyse aufgrund der geringen Fallzahl nur als hypothesengenerierend betrachtet werden, andererseits liegen weitere Untersuchungen derselben Arbeitsgruppe vor, welche die Effektivität von FOLFOXIRI plus Bevacizumab bei Vorliegen einer BRAF-Mutation unterstützen [1119].

Ob anti-EGFR-Substanzen bei Vorliegen einer BRAF-Mutation effektiv sind, ist Gegen-stand einer kontroversen Debatte. Zwei Meta-Analysen kommen hier zu unter-schiedlichen Bewertungen. In der Analyse von Pietrantonio et al. wird duch Gabe von anti-EGFR-Antikörpern keine signifikante Verlängerung von PFS (HR 0,88, p=0,33) oder OS (HR 0,91, p=0,63) gefunden [1059]. Dagegen argumentieren Rowland und Mitarbeiter, dass die Evidenz nicht ausreicht, um definitiv auszuschließen, dass anti-EGFR-Antikörper bei BRAF-Mutation einen anderen Behandlungseffekt haben als bei BRAF Wildtyp [1121].

Letztlich sind die vorliegenden Analysen durch kleine Fallzahlen charakterisiert, die weder für sich genommen noch in der gemeinsamen meta-analytischen Betrachtung definitive Schlussfolgerungen erlauben.

Die Frage nach dem Stellenwert einer Bevacizumab-basierten im Vergleich zu einer Cetuximab-basierten Therapie wurde in einer Subgruppenanalyse der FIRE-3-Studie adressiert. Bei 48 evaluierbaren Patienten mit RAS-wt/BRAF-mut mKRK, war das OS in beiden Therapiearmen kurz und vergleichbar (Median 12.3 vs 13.7 Monate) unab-hängig davon, ob Cetuximab oder Bevacizumab zusammen mit FOLFIRI gegeben worden war [1122]. Diese Analyse führte zu der Hypothese, dass gleichermaßen, weder eine anti-EGFR- noch eine anti-VEGF Strategie, in der Lage sind, das therapeutische Ergebnis zu verbessern.

Aufgrund der schlechten Prognose BRAF-mutierter Tumoren können in der Zweitlinientherapie individuelle (derzeit nicht zugelassene) Therapieansätze, z. B. mit einem BRAF-Inhibitor, MEK-Inhibitor und Anti-EGFR-Antikörper oder wenn möglich die Behandlung im Rahmen einer klinischen Studie in Betracht gezogen werden [1123].

Referenzen:

1062. Cremolini, C., et al., BRAF codons 594 and 596 mutations identify a new molecular subtype of metastatic colorectal cancer at favorable prognosis. Ann Oncol, 2015. **26**(10): p. 2092-7.
1119. Loupakis, F., et al., FOLFOXIRI plus bevacizumab as first-line treatment in BRAF mutant metastatic colorectal cancer. Eur J Cancer, 2014. **50**(1): p. 57-63.

Empfehlungen zur Zweitlinientherapie

Empfehlung 1 (GoR: B; LoE: 1b)

9.33.	Evidenzbasierte Empfehlung	2017
Empfehlungsgrad **B**	Die Effektivität der Zweitlinientherapie ist gewöhnlich deutlich geringer als die der Erstlinientherapie. Die Wahl einer Zweitlinientherapie sollte sich im Rahmen des sequenziellen Einsatzes aktiver Substanzen in erster Linie nach der Effektivität und den Nebenwirkungen der Vortherapie richten.	
Level of Evidence **1b**	Quellen: [1157-1159]	
	starker Konsens	

Referenzen:
1157. Rothenberg, M.L., et al., *Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial.* J Clin Oncol, 2003. **21**(11): p. 2059-69.
1158. Rougier, P., et al., *Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer.* Lancet, 1998. **352**(9138): p. 1407-12.
1159. Cunningham, D., et al., *Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer.* Lancet, 1998. **352**(9138): p. 1413-8.

Zweitlinientherapie mit anti-VEGF- bzw. anti-VEGFR-Substanzen

Mehrere randomisierte Studien belegen den Nutzen von Bevacizumab (E3200, TML, BEBYP), Aflibercept (VELOUR) und Ramucirumab (RAISE) in der Zweitlinientherapie. Die Therapieeffekte sind in hohem Maße konsistent. Die evaluierbaren Studien zeigen einheitlich, dass eine signifikante Verlängerung von PFS und OS erreicht werden kann, wenn die anti-VEGF Substanzen Bevacizumab oder Aflibercept bzw. der anti-VEGFR-Antikörper Ramucirumab zu einer Zweitlinienchemotherapie hinzugegeben werden. Einschränkend muss darauf hingewiesen werden, dass die absoluten Überlebens-zeitgewinne im Vergleich der medianen OS-Zeiten durchwegs moderat sind und überwiegend in einem Bereich von 1-2 Monaten liegen.

Die antiangiogene Therapie ist mit den für sie charakteristischen Nebenwirkungen verbunden. So wurden z.B. bei Zugabe von Aflibercept zu FOLFIRI im Vergleich zur alleinigen Behandlung mit FOLFIRI folgende Grad 3-4 Nebenwirkungen beobachtet: Hypertonie (19,3% vs 1,5%), Blutungen (2,9% v 1,7%), arterielle thromboembolische Ereignisse (1,8% v 0,5%), und venöse thromboembolische Ereignisse (7,9% v 6,3%). Darüber hinaus wurde z.T. aber auch eine Verstärkung von chemotherapieassoziierten Toxizitäten wie Diarrhoe oder Stomatitis beobachtet [1161].

In ähnlicher Weise wurde auch bei der Kombination des VEGFR-Inhibitors Ramucirumab mit FOLFIRI im Vergleich zur FOLFIRI-Chemotherapie eine Steigerung der Nebenwirkungen festgestellt. Diese betraf insbesondere Grad 3-4 Nebenwirkungen wie Neutropenie (38% vs 23%), Hypertonie (11% vs 3%), Blutungen (1,9% vs 1,5%) oder gastrointestinale Perforationen (1,5% vs 0,6%) [1162].

Tabelle 17: Randomisierte Studien zur Zweitlinientherapie mit anti-VEGF Substanzen

Studie	Vor-behandlung	Regime	N Pat.	ORR (%)	OR (P-Wert)	PFS (Mo)	HR PFS (P-Wert)	OS (Mo)	HR OS (P-Wert)
E3200 (Phase III) [1163]	Fluoropyrimidne and irinotecan (0% Bev)	FOFOX4 + Bev	286	22,7		7.3	0.61	12.9	0.75
		FOLFOX4	291	8.6	(<0.0001)	4.7	(<0.0001)	10.8	(0.0011)
TML (Phase III) [1164]	Chemotherapy (100% Bev)	Chemo-therapy + Bev	409	5		5.7	0.68	11.2	0.81
		Chemo-therapy	411	4	(n.s)	4.1	(<0.0001)	9.8	(0.0062)
BEBYP (Phase III) [1165]	Chemotherapy (100 % Bev)	Chemo-therapy + Bev	92	21		6.8	0.70	15.5	0.77
		Chemo-therapy	92	17	(0.573)	5.0	(0.010)	14.1	(0.043)
Chinese (Phase II) [1166]	Oxaliplatin-based (0 % Bev)	FOLFIRI + BEV	65	47.7		8.5	NR	15.2	NR
		FOLFIRI	77	28.5	(<0.001)	5.1		11.3	
VELOUR (Phase III) [1161]	Oxaliplatin-based (30.4% Bev)	FOLFIR + Afliberce pt	612	19.8		6.9	0.76	13.5	0.82
		FOLFIRI + Placebo	614	11.1	(0.0001)	4.7	(<0.0001)	12.1	(0.0032)
RAISE (Phase III) [1162]	Fluoropyrimidine and oxaliplatin (100% Bev)	FOLFIRI + Ramu-cirumab	536	13.4		5.7	0.79	13.3	0.84
		FOLFIRI + Placebo	536	12.5	(0.63)	4.5	(0.0005)	11.7	(0.0219)

Legende: Cape, Capecitabin; Bev, Bevacizumab; OR, Odds Ratio; ORR, objektive Responserate; PFS, progressionsfreies Überleben; OS Gesamtüberleben;

Referenzen aus Leitlinien:
1161. Van Cutsem, E., et al., Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol, 2012. 30(28): p. 3499-506.
1162. Tabernero, J., et al., Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. Lancet Oncol, 2015. 16(5): p. 499-508.
1163. Giantonio, B.J., et al., Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol, 2007. 25(12): p. 1539-44.
1164. Bennouna, J., et al., Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol, 2013. 14(1): p. 29-37.
1165. Masi, G., et al., Continuation or reintroduction of bevacizumab beyond progression to first-line therapy in metastatic colorectal cancer: final results of the randomized BEBYP trial. Ann Oncol, 2015. 26(4): p. 724-30.
1166. Cao, R., et al., A multi-center randomized phase II clinical study of bevacizumab plus irinotecan, 5-fluorouracil, and leucovorin (FOLFIRI) compared with FOLFIRI alone as second-line treatment for Chinese patients with metastatic colorectal cancer. Med Oncol, 2015. 32(1): p. 325.

Zweitlinientherapie mit anti-EGFR Substanzen

Randomisierte Studien belegen den Nutzen von Panitumumab und Cetuximab in der Zweitlinientherapie. Diese Medikamente können daher entsprechend ihrer Zulassung nach Durchlaufen der Erstlinientherapie eingesetzt werden.

Zwei randomisierte Studien (EPIC und 181-Studie) belegen die Effektivität der anti-EGFR Substanzen Cetuximab und Panitumumab in der. Beide Studien zeigen eine signifikante Steigerung von ORR und PFS, wenn anti-EGFR Substanzen in der Zweitlinientherapie zu einer FOLFIRI-Chemotherapie hinzugefügt werden. Allerdings wurde in keiner der Studien ein signifikanter Überlebensgewinn erreicht (Tabelle 18).

Eine typische Nebenwirkung der anti-EGFR Therapie ist das akneiforme Exanthem, welches z.B. in der EPIC-Studie in einer Gesamthäufigkeit von 81,2% und einer Grad 3-4 Inzidenz von 8,2 % auftrat. Auch bei Gabe von anti-EGFR-Substanzen wird eine Steigerung der chemotherapieassoziierten Toxizität z. B. der Diarrhoe (28,4 % vs 15,7 %) beobachtet [1167]. In der EPIC-Studie war die Gabe von Cetuximab mit einer signifikanten Steigerung des "global health" Scores verbunden. Kritisch muss allerdings angemerkt werden, dass die üblichen Instrumente zur Analyse der Lebensqualität, wie der EORTC QLQ-C30 Fragebogen, keinen exanthemrelvanten Score beinhalten und daher nicht geeignet sind, diesbezügliche Bewertungen zu untersuchen [1167].

Tabelle 18: Randomisierte Studien zur Zweitlinientherapie mit anti-EGFR Substanzen

Studie	Vor-behandlung	Regime	N Pat.	ORR	OR (P-Wert)	PFS	HR PFS (P)	OS	HR OS (P)
EPIC [1167]	Fluoropyrimidin + Oxaliplatin	FOLFIRI + Cet FOLFIRI	648 650	16.4 4.2	NR (<0.0001)	4.0 2.6	0.692 (<0.0001)	10.7 10.0	0.975 (0.71)
191** [1168]	Fluoropyrimidin-basierte Therapie (66% Oxaliplatin 19 % Bev)	FOLFIRI + Pani FOLFIRI	303 294	35 10	(<0.001)	5.9 3.9	0.73 (0.004)	14.5 12.5	0.85 (0.12)

Legende: *unselektierte Patienten; **KRAS Wildtyp; Cet, Cetuximab; Bev, Bevacizumab; OR, Odds Ratio; ORR, objektive Responserate; PFS, progressionsfreies Überleben; OS Gesamtüberleben

Referenzen aus Leitlinien:
1167. Sobrero AF, F.L., Rivera F, et al. , Phase III trial of Cetuximab plus Irinotecan after Fluoropyrimidine and Oxaliplatin Failure in Patients with Metastatic Colorectal Cancer J Clin Oncol 26: 2311-2319, 2008.
1168. Peeters, M., et al., Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol, 2010. 28(31): p. 4706-13.

9.11. Therapiesequenz

9.34.	Evidenzbasierte Empfehlung	2017
Empfehlungsgrad B	Bei Patienten mit RAS Wildtyptumoren ist die Lokalisation des Primärtumors eine wichtige Determinante in der Beurteilung der optimalen Therapiesequenz (siehe 9.8.2.). Bei Patienten mit linksseitigem mKRK und RAS Wildtyp sollte in der Erstlinientherapie ein anti-EGFR-AK in Kombination mit einer Chemotherapie zum Einsatz kommen. In dieser Konstellation kommt eine anti-VEGF Therapie erst ab der Zweitlinie in Betracht.	
Level of Evidence 2b	Quellen: [1130][1131]	
	Konsens	

9.35.	Evidenzbasierte Empfehlung	2017
Empfehlungsgrad B	Bei Patienten mit rechtseitigem mKRK und RAS Wildtyp sollten in der Erstlinientherapie keine anti-EGFR-AK in Kombination mit einer Chemotherapie zum Einsatz kommen.	
Level of Evidence 2b	Quellen: [1130][1131]	
	Starker Konsens	

Hintergrund

Abgesehen von der Lokalisation des Primärtumors (siehe 9.8.2) gibt es derzeit keine konkret belastbare Evidenz, die eine optimale Sequenz molekularbiologisch gezielter Substanzen zwingend belegt. Die bisher verfügbaren Daten kommen überwiegend (I) von theoretischen molekularbiologischen Abhandlungen / Erwägungen, (II) von mehr oder minder ungeplanten Erfassungen von Zweitlinientherapien nach Erstlinien-randomisation (FIRE-3, CALGB, PEAK) oder (III) von ebenso ungeplanten retrospektiven Erfassungen der Erstliniensituation in randomisierten Zweitlinientherapien (TML, VELOUR; PRIME, PEAK).

Referenzen aus Leitlinien:

1130. Gruenberger, T., et al., Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: the OLIVIA multinational randomised phase II trial. Ann Oncol, 2015. 26(4): p. 702-8.
1131. Maughan, T.S., et al., Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet, 2011. 377(9783): p. 2103-14.1167.
Sobrero AF, F.L., Rivera F, et al. , Phase III trial of Cetuximab plus Irinotecan after Fluoropyrimidine and Oxaliplatin Failure in Patients with Metastatic Colorectal Cancer J Clin Oncol 26: 2311-2319, 2008.

Fortführung der anti-VEGF Therapie in der Zweitlinienbehandlung

Die klinischen Daten der TML-Studie belegen, dass bei unselektierten mKRK Patienten die Fortführung einer anti-VEGF-Therapie mit Bevacizumab nach Progression unter einer Bevacizumab-basierten Erstlinientherapie eine effektive Behandlungsstrategie darstellt. Patienten, die in der Zweitlinientherapie Bevacizumab plus Chemotherapie erhielten, zeigten im Vergleich zur alleinigen Chemotherapie ein längeres medianes Gesamtüberleben 11,2 Monate (95% CI, 10,4-12,2) für Bevacizumab plus Chemotherapie und 9,8 Monate (95% CI, 8,9-10,7) für Chemotherapie allein (HR 0·81, p=0.0062) [1164].

Die häufigsten, in der TML-Studie berichteten, Grad 3-5 Nebenwirkungen waren Neutropenie (16% vs 13%), Diarrhoe (10% vs 8%) und Asthenie (6% vs 4%). Unter der Behandlung mit Bevacizumab plus Chemotherapie traten im Vergleich zur alleinigen Behandlung mit Chemotherapie folgende Grad 3–5 Ereignisse häufiger auf: Blutungen/Hämorrhagie (2% vs <1%), gastrointestinale Perforationen (2% vs <1%) und venöse thromboembolische Ereignisse (5% vs 3%).

Fortführung der anti-EGFR Therapie in der Zweitlinienbehandlung

Die CAPRI-GOIM-Studie untersuchte KRAS-Wildtyp mKRK Patienten, die nach einer Erstlinientherapie mit FOLFIRI plus Cetuximab im randomisierten Vergleich entweder FOLFOX plus Cetuximab oder nur FOLFOX erhielten. Die Fortführung der Behandlung mit Cetuximab über die Progression hinaus (experimenteller Arm) führte in der Gesamtgruppe der untersuchten Patienten zu einer nicht signifikanten Verlängerung des PFS (6,4 vs 4,5 Monate, p=0,19). Dagegen wurde bei Patienten mit KRAS, NRAS, BRAF and PIK3CA Wildtyp Tumoren im experimentellen Arm eine signifikante Verlängerung des 2nd-line PFS (HR, 0,56, p=0,025) beschrieben, für das Gesamtüberleben wurde bei kleiner Fallzahl (n=66) das Signifikanzniveuau nicht erreicht (HR, 0,57, p=0,056) [1169].

Sequenzieller Einsatz von anti-EGFR und anti-VEGF-Therapie

Retrospektive klinische Untersuchungen weisen darauf hin, dass eine anti-EGFR Therapie dann weniger wirksam ist, wenn ihr eine anti-VEGF-Therapie voranging ([1170]). Präklinische Daten stützen diese Hypothese [1171] [1172]).

In der FIRE-3 Studie konnte nach initialer anti-EGFR Therapie eine deutlich längere anti-VEGF Therapie in der Zweitlinienbehandlung gezeigt werden als dies in der umgekehrten Sequenz der Fall war [1040]. Während die Kombination von Panitumumab mit einer Kombinationschemotherapie in der Erstlinientherapie (PEAK-Studie) deutlich effektiver war als die Bevacizumab-basierte Vergleichstherapie [1109], so konnte dieser Effekt in der Zweitlinientherapie (SPIRITT-Studie) nach Bevacizumab-Vorbehandlung nicht reproduziert

werden [1173]. Vergleichbare Daten wurden auch in der Prodige 18 UNICANCER GI Studie erhoben, die KRAS-wt mKRK Patienten nach Progression unter einer Bevacizumab-baiserten Chemotherapie untersuchte. Die Fortführung von Bevacizumab in Kombination mit einer „crossover“ Chemotherapie war mit einem (nicht statistisch signifikant) längeren medianen PFS und OS verbunden als die Behandlung mit Cetuximab plus Chemotherapie [1174]. Bisher sind die Ergebnisse dieser Studie allerdings nur in Abstractform verfügbar.

Während die verfügbaren Daten die Sequenz einer anti-VEGF- gefolgt von einer anti-EGFR-Therapie als eher ungünstig erscheinen lassen, so steht eine letztendliche Bewertung, die auch die Tumorlokalisation mit einbezieht, noch aus.

Die Daten der 181-Studie (FOLFIRI +/- Panitumumab) sprechen dafür, dass die anti-EGFR Therapie in der Zweitlinienbehandlung bei linksseitigen Primärtumoren effektiver ist als bei rechtsseitigen [1175]. Dies drückt sich bei linksseitigen RAS-Wildtyp Tumoren in günstigeren Effektivitätsparametern hinsichtlich ORR (50% vs 13%), PFS (8,0 vs 4,8 Monate) und OS (20,1 vs 10,3 Monate) aus.

Referenzen:
1040. Modest, D.P., et al., Impact of Subsequent Therapies on Outcome of the FIRE-3/AIO KRK0306 Trial: First-Line Therapy With FOLFIRI Plus Cetuximab or Bevacizumab in Patients With KRAS Wild-Type Tumors in Metastatic Colorectal Cancer. J Clin Oncol, 2015. 33(32): p. 3718-26.
1164. Bennouna, J., et al., Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol, 2013. **14**(1): p. 29-37.
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1171. Wainberg, Z.A. and A. Drakaki, The importance of optimal drug sequencing in metastatic colorectal cancer: biological rationales for the observed survival benefit conferred by first-line treatment with EGFR inhibitors. Expert Opin Biol Ther, 2015. 15(8): p. 1205-20.
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1173. Hecht JR, C.A., Dakhil SR, et al. , SPIRITT (study 20060141): A randomized phase II study of FOLFIRI with either panitumumab (pmab) or bevacizumab (bev) as second-line treatment (tx) in patients (pts) with wild-type (WT) KRAS metastatic colorectal cancer (mCRC). . Journal of Clinical Oncology, 2013. 31: p. 4_suppl, 454 - 454.
1174. Hiret S, B.C., Bertaut A, et al. , Bevacizumab or cetuximab plus chemotherapy after progression with bevacizumab plus chemotherapy in patients with wtKRAS metastatic colorectal cancer: A randomized phase II study (Prodige 18 – UNICANCER GI). . J Clin Oncol 2016. 34: p. suppl; abstr 3514.
1175. Peeters, M., et al., Analysis of KRAS/NRAS Mutations in a Phase III Study of Panitumumab with FOLFIRI Compared with FOLFIRI Alone as Second-line Treatment for Metastatic Colorectal Cancer. Clin Cancer Res, 2015. 21(24): p. 5469-79.

Empfehlungen zur Chemotherapie in späteren Therapielinien

Empfehlung 1 (GoR: B; LoE: 1b)

9.12.2. Effektivität von Trifluridin/Tipiracil

9.36.	Evidenzbasierte Empfehlung	2017
Empfehlungsgrad **B**	Trifluridin/Tipiracil sollte bei Patienten, welche alle verfügbaren Chemotherapien/ Antikörper durchlaufen haben oder für diese nicht geeignet sind, eingesetzt werden.	
Level of Evidence **1b**	Quellen: [1179, 1180]	
	Konsens	

Empfehlung 1 (GoR: B; LoE: 1b)

9.12.3. Regorafenib

9.37.	Evidenzbasierte Empfehlung	2017
Empfehlungsgrad **0**	Regorafenib kann bei mit allen verfügbaren Chemotherapien/Antikörpern vorbehandelten Patienten eingesetzt werden.	
Level of Evidence **1b**	Quellen: [1181, 1182]	
	Konsens	

Referenzen:
1179. Mayer, R.J., et al., *Randomized trial of TAS-102 for refractory metastatic colorectal cancer.* N Engl J Med, 2015. 372(20): p. 1909-19.
1180. Yoshino, T., et al., *TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial.* Lancet Oncol, 2012. 13(10): p. 993-1001.
1181. Li, J., et al., *Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial.* Lancet Oncol, 2015. 16(6): p. 619-29.
1182. Grothey, A., et al., Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet, 2013. 381(9863): p. 303-12.

Empfehlungen zur Re-Induktion / Re-„challenge“

Die Reinduktion von antineoplastischen Substanzen, deren Effektivität in frühen Therapielinien nachgewiesen wurde, ist zwar eine in der Onkologie bewährte Therapiestrategie, Nachweise für die klinische Effektivität dieses Vorgehens sind jedoch limitiert.

Santini und Mitarbeiter untersuchten im Rahmen einer kleinen Studie (n=39) die Effektivität einer „Re-challenge“ mit Cetuximab. Patienten, die auf eine Cetuximab-basierte Erstlinientherapie mit einer CR, PR oder SD >6 Monate angesprochen hatten und unter einer Cetuximab-freien „window therapy“ progredient waren konnte mit einer erneuten Cetuximab-basierten Therapie eine ORR von 54% und ein PFS von 6.6 Monaten erreicht werden [1183]. Aufgrund der sehr kleinen Fallzahl der Studie können diese Daten derzeit nur als hypothesengenerierend betrachtet werden.

Referenzen:
1183. Santini, D., et al., *Cetuximab rechallenge in metastatic colorectal cancer patients: how to come away from acquired resistance?* Ann Oncol, 2012. **23**(9): p. 2313-8.

Hinweis FBMed: Ergänzende Extraktion zur Thematik des Mikrosatelliten-instabilen (MSI) oder Mismatch-Reparaturmechanismus defizienten (dMMR) kolorektalen Karzinoms

Analysen zur Indikationsstellung gezielter Therapien nach Versagen der Erstlinientherapie

Der Nachweis eines Mikrosatelliten-instabilen Karzinoms (MSI) kann die Indikations-stellung für eine Behandlung mit Checkpoint-Inhibitoren unterstützen (siehe 9.4.1 Testung der Mikrosatelliteninstabilität (MSI)). Derzeit liegt hierfür keine Zulassung vor.

MSI

Immun-Checkpoint Inhibitoren haben in ersten klinischen Untersuchungen bei vorbehandelten mKRK Patienten mit Mikrosatelliteninstabilität (MSI) Aktivität gezeigt. Angesichts der derzeit

noch limitierten Datenlage wird bei Nachweis einer MSI zunächst eine Erstlinienbehandlung entsprechend dem RAS-Mutationsstatus empfohlen. In späteren Therapielinien sollte die Möglichkeit einer Behandlung mit Checkpoint-Inhibitoren evaluiert werden.

Hintergrund

Mutationen in den Mismatch Reparaturgenen (MLH1, MSH2, MSH6 und PMS2) führen zu einer fehlerhaften DNS-Replikation, die sich anhand variabler Längen der Mikro-satelliten-DNS als Mikrosatelliteninstabilität (MSI) manifestiert. Die defekte Mismatch Reparatur (MMRd) ist im Vergleich zur profizienten Mismatch Reparatur (MMRp) für eine um das 10-100-fache gesteigerte Mutationsrate ([1069]) verantwortlich. Diese bedingt eine gesteigerte Immunogenität und letztlich die deutlich vermehrten lymphozytäre Infiltrate der MSI-Tumoren ([1124]). Im Sinne eines „immune escape“ Mechanismus wird gerade bei MSI-Tumoren eine Hochregulation von Immun-Checkpoints, wie dem „programmed death“ (PD-1) Pathway nachgewiesen.

Beim kolorektalen Karzinom entsteht die MMRd sowohl im Rahmen von Keimbahn-mutationen in einem der vier Mismatch Reparaturgene (hereditäres nonpolyposis kolorektales Karzinom (HNPCC oder Lynch-Syndrom), als auch durch somatische Mutationen oder durch epigenetisches Silencing [1068].

Erste klinische Daten bestätigen die Hypothese, dass MSI-Tumoren – im Gegensatz zu MSS-Tumoren – gut auf eine PD-1 Blockade ansprechen. Im Rahmen einer Phase II Studie wurden 32 Patienten untersucht, die mindestens 2 vorangegangene Chemo-therapieregime erhalten hatten [1068]. Davon wurden 11 Patienten als MMRd und 21 als MMRp klassifiziert. Unter einer Behandlung mit dem PD-1 Inhibitor Pembrolizumab zeigten MMRd Patienten im Vergleich zu MMRp-Patienten eine deutlich höhere Rate an ORR (40% vs 0%) und SD (50% vs 11%) sowie eine hochsignifikante Verlängerung von PFS und OS (Mediane nicht erreicht).

Zum Zeitpunkt der Leitlinienerstellung sind immunologische Checkpointinhibitoren derzeit nicht für die Behandlung des mKRK zugelassen.

Cancer Council Australia Colorectal Cancer Guidelines Working Party, 2017 [3].

Clinical practice guidelines for the prevention, early detection and management of colorectal cancer.

Leitlinienorganisation/Fragestellung

These draft clinical practice guidelines are a revision and update of the 2005 Clinical practice guidelines for the prevention, early detection and management of colorectal cancer. The guideline was originally developed in 1999.

The guideline project commenced in December 2014, and in June 2015 the National Health and Medical Research Council (NHMRC) agreed to consider approving the guideline, provided it was developed according to NHMRC procedures and requirements.

MANAGEMENT OF NON-RESECTABLE LOCALLY RECURRENT DISEASE AND METASTATIC DISEASE

- What is the impact of different liver directed therapies in patients with incurable metastatic colorectal cancer?

THE ROLE OF SYSTEMIC THERAPIES IN NON-RESECTABLE METASTATIC DISEASE

- No clinical questions answered by systematic review for systemic therapies chapter.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;

- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- cut-off date of 31 August 2016

LoE/ GOR

NHMRC APPROVED RECOMMENDATION TYPES AND DEFINITIONS

TYPE OF RECOMMENDATION	DEFINITION
Evidence-based recommendation	A recommendation formulated after a systematic review of the evidence, indicating supporting references
Consensus-based recommendation	A recommendation formulated in the absence of quality evidence, after a systematic review of the evidence was conducted and failed to identify admissible evidence on the clinical question
Practice point	A recommendation on a subject that is outside the scope of the search strategy for the systematic review, based on expert opinion and formulated by a consensus process

SOURCE: National Health and Medical Research Council. Procedures and requirements for meeting the NHMRC standard for clinical practice guidelines. Melbourne: National Health and Medical Research Council, 2011

EVIDENCE-BASED RECOMMENDATION GRADES

GRADE OF RECOMMENDATION	DESCRIPTION
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

SOURCE: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: National Health and Medical Research Council; 2009. Available from: https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf.

Sonstige methodische Hinweise

- Last updated: January 2018

Molecular pathology and biomarkers – implications for systemic therapy

Practice point?

The BRAF mutation status should ideally be performed at the time of diagnosis of metastatic colorectal cancer, as this represents a distinct biologic subtype.

Practice point?

The presence of a BRAF mutation in metastatic colorectal cancer is considered a poor prognostic marker.

Practice point?

BRAF mutation status in combination with testing for DNA mismatch repair deficiency can assist in the identification of a germline versus somatic cause of DNA mismatch repair deficiency.

Practice point?

The preponderance of the available evidence is that response to EGFR-targeted agents is less likely in patients whose tumours harbour a BRAF mutation.

Practice point?

Metastatic colorectal cancer patients with a BRAF mutation should be considered for a clinical trial where available or triplet chemotherapy if suitable.

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Systemic options for second-line treatment

✓ Practice point?

Patients who did not receive bevacizumab as part of first-line therapy should be considered for bevacizumab in second-line therapy, in combination with a second-line cytotoxic regimen.

✓ Practice point?

Patients who received bevacizumab as part of the first-line regimen and have RAS wild-type (BRAF wild-type) metastatic colorectal cancer should be considered for combination EGFR monoclonal antibodies with FOLFIRI/irinotecan.

✓ Practice point?

Patients who received a first-line oxaliplatin-containing regimen should be switched to an irinotecan-containing regimen, and vice versa.

✓ Practice point?

Patients who experience disease progression during first-line 5FU monotherapy should be offered an irinotecan or oxaliplatin-containing regimen if they have adequate performance status.

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Systemic options for Third-line treatment

✓ Practice point?

Patients with mCRC considering treatment in the third-line setting have limited therapeutic options and typically have reduced quality of life; therefore physicians must carefully balance any efficacy benefit associated with therapy with its toxicity profile.

✓ Practice point?

Cetuximab or panitumumab treatment should be considered in patients with RAS wild-type and BRAF wild-type metastatic colorectal cancer not previously treated with these agents, taking into account the following:

- Cetuximab and Panitumumab are equally effective as single agents.
- Cetuximab in combination with irinotecan is more active than cetuximab alone in patients refractory to irinotecan with adequate performance status to receive combination therapy.

✓ Practice point?

If available, regorafenib or trifluridine/tipiracil can be considered for patients with metastatic colorectal cancer refractory to all standard available therapies.

✓ Practice point?

Patients receiving third-line therapy should be offered participation in clinical trials, wherever available.

✓ Practice point?

Symptom burden is often high in patients with mCRC especially as the disease progresses. Early palliative care intervention should be considered for all patients with mCRC as they can improve the quality of life of patients with cancer.

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Salvatore L et al., 2017 [29].

Italian Medical Oncology Association (AIOM)

Management of metastatic colorectal cancer patients: guidelines of the Italian Medical Oncology Association (AIOM)

Leitlinienorganisation/Fragestellung

The Italian Medical Oncology Association (AIOM) has developed evidence-based recommendations to help oncologists and all professionals involved in the management of patients with metastatic colorectal cancer in their daily clinical practice.

Methodik

Grundlage der Leitlinie

- The AIOM guidelines working group includes professionals from across the country with different professional skills, such as medical oncologists, surgeons, radiation oncologists and molecular biologists, which facilitated the analysis of scientific issues as well as different logistic and regulatory aspects in different regions.
- A systematic review of the literature was carried out and every 2 months conference calls between authors were held. During the final consensus meeting, a preliminary report was prepared and sent to reviewers for peer review.
- The guidelines were revised by several opinion leaders in CRC and by different scientific societies
- The final report, including the accepted recommendations of the reviewers, was eventually published online on the AIOM website.
- Each recommendation has been made based on the guidelines prescribed by the
- Scottish Intercollegiate Guidelines Network (SIGN).
- The quality of evidences according to SIGN reflects both the type of studies that have been considered, as outlined in table 2, and the clinical applicability of results.

LoE

Table 2 Evidence levels according to the Scottish Intercollegiate Guidelines Network

1	Meta-analyses and systematic reviews of randomised clinical trials
1++	Very low risk of bias
1+	Low risk of bias
1–	High risk of bias
2	Systematic reviews of cohort or case and control studies
2++	Very low risk of bias and high probability of a causal relationship
2+	Low risk of bias and moderate probability of a causal relationship
2–	High risk of bias and significant risk that the relationship is not causal
3	Non-analytical studies, such as case reports and case series
4	Expert opinion

Table 3 Quality of evidences according to the Scottish Intercollegiate Guidelines Network

A	At least one meta-analysis, systematic review or randomised clinical trial classified as 1++ and directly applicable to the target population
	Studies classified as 1+ and directly applicable to the target population
B	Studies classified as 2++ and directly applicable to the target population
	Evidences from studies classified as 1++ or 1+, but not directly applicable to the target population
C	Studies classified as 2+ and directly applicable to the target population
	Evidences from studies classified as 2++, but not directly applicable to the target population
D	Evidence level 3 or 4
	Evidences from studies classified as 2+, but not directly applicable to the target population

GoR

Table 4 Strength of recommendation

Strength of recommendation	Meaning
Strong for	The intervention should be considered as the first treatment option (benefits are higher than risks)
Conditional for	The intervention can be considered as a possible treatment option (not sure that benefits are higher than risks)
Conditional against	The intervention should not be considered as the first treatment option; it could be considered in selected cases after discussion with the patient (not sure that risks are higher than benefits)
Strong against	The intervention should not be considered as a possible treatment option (risks are higher than benefits)

Empfehlungen

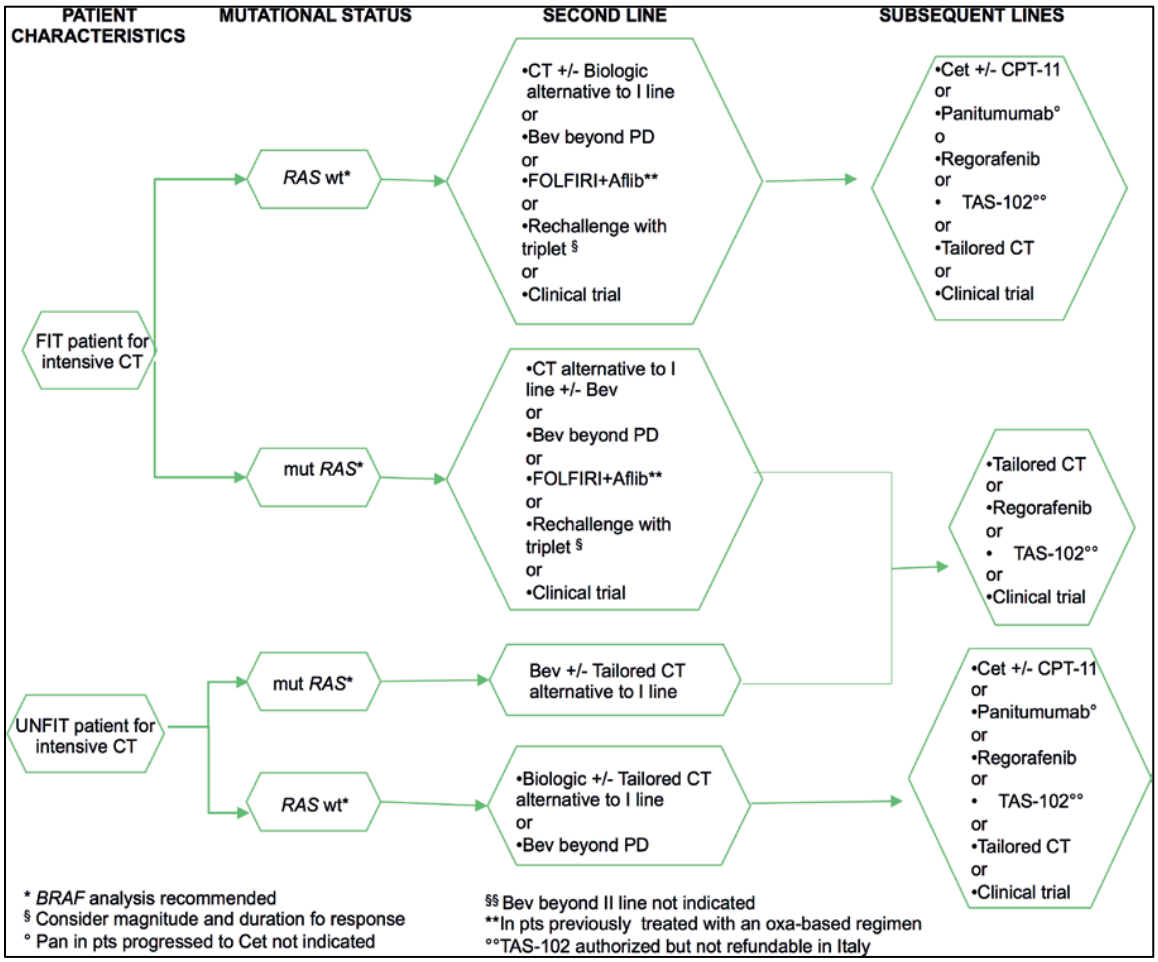

Figure 1 Algorithms for the management of metastatic colorectal cancer, subsequent lines. 5-FU, 5-fluorouracil; Aflib, aflibercept; Bev, bevacizumab; Cape, capecitabine; Cet, cetuximab; CT, chemotherapy; EGFR, epidermal growth factor receptor; FOLFIRI, 5-fluorouracil+lederfolin+irinotecan; FOLFIRI, folinic acid, 5-FU and irinotecan; FOLFOX, folinic acid, 5-FU and oxaliplatin; LV, lederfolin; mut, mutant; PD, progressive disease; PS, performace status; pts, patients; RT, radiotherapy; wt, wild type; XELOX, capecitabine+oxaliplatin.

Table 6 Metastatic colorectal cancer treatment: SIGN recommendations

Quality of evidences(SIGN)	Recommendation	Strength of recommendation
C	*RAS* status must be evaluated for the decision of treatment strategy for metastatic disease.[18]	Strong for
D*	*BRAF* status should be evaluated for the decision of treatment strategy for metastatic disease.	Conditional for
A	The combination of 5-fluorouracil (continuous infusion is preferable) and oxaliplatin and/or irinotecan must be used in patients deemed fit for a combination treatment (the combination with anti-VEGF or anti-EGFR monoclonal antibodies is preferable). For unfit patients the option is fluoropyrimidine±bevacizumab.[10–15 19–22 44–50]	Strong for
A	Capecitabine can substitute for monotherapy with 5-fluorouracil+folinic acid. When a monotherapy is indicated, capecitabine is the first option, preferably with bevacizumab.[10 50]	Strong for
A	Capecitabine can be used in combination with oxaliplatin.[51–53] Capecitabine plus irinotecan, due to increased toxicity, should be used only if there are contraindications to infusional 5-fluorouracil.[54 55]	Strong for
A	If no contraindications, bevacizumab can be used in combination with first-line chemotherapy.[10–15 49 50]	Strong for
A	If no contraindications, bevacizumab can be used in combination with second-line chemotherapy in patients not treated with bevacizumab as first-line treatment.[30]	Strong for
B	Bevacizumab beyond progression in combination with chemotherapy can be a treatment option.[28 29]	Conditional for
A	A second-line treatment must be always considered in fit patients. A third- and fourth-line treatment can be considered in several cases.[56 57]	Strong for
A	Cetuximab can be used in *RAS* wild-type patients in combination with irinotecan-based regimens (irrespective of treatment line) or as monotherapy in advanced lines.[19 36]	Strong for
B	Cetuximab can be associated with first-line oxaliplatin-based treatment. In this case, continuous infusion of 5-fluorouracil without bolus is preferable.[21 23 24]	Strong for
A	Panitumumab (anti-EGFR) can be used as monotherapy in advanced lines, in *RAS* wild-type patients not previously treated with cetuximab or after a severe infusion reaction to cetuximab.[37]	Strong for
A	In *RAS* wild-type patients, panitumumab can be used in combination with first-line FOLFOX or FOLFIRI,[20 22] and with second-line FOLFIRI.[33]	Strong for
A	The combination of aflibercept with second-line FOLFIRI in patients previously treated with an oxaliplatin-based treatment (with or without a biological drug) can be an option.[31]	Conditional for
B	A sequential and less toxic strategy can be considered in case of indolent disease.[44 45]	Conditional for
B	FOLFOXIRI plus bevacizumab should be considered as first-line treatment in *BRAF* mutated and fit patients.[58]	Strong for
B	To reduce treatment-related toxicity a 'stop-and-go' strategy or a less intensive treatment can be considered.[59–61]	Conditional for
B	In patients pretreated or not considered candidates for all the available drugs, regorafenib can be an option.[38] TAS-102 could be a further option in this setting.‡[39]	Conditional for

*Panel opinion.
‡At the moment authorised but not refundable in Italy.
EGFR, epidermal growth factor receptor; FOLFIRI, folinic acid, 5-fluorouracil and irinotecan; FOLFOX, folinic acid, 5-fluorouracil and oxaliplatin; SIGN, Scottish Intercollegiate Guidelines Network; VEGF, vascular endothelial growth factor.

Table 7 mCRC treatment: GRADE recommendations

Quality of evidences (GRADE)	Recommendation	Strength of clinical recommendation
Very low	Starting a treatment for metastatic disease at the time of diagnosis, also without disease-related symptoms, is recommended. A wait-and-see period might be considered in well-selected cases (elderly, comorbidities, minimal tumour load) after an adequate evaluation of risks/benefits.[62 63]	Strong for
Moderate	A maintenance treatment with bevacizumab±fluoropyrimidine can be considered in patients with mCRC after a first-line treatment with bevacizumab, after an adequate evaluation of risks/benefits and patient's motivation.[16 17]	Conditional for

GRADE, Grading of Recommendations, Assessment, Development and Evaluations; mCRC, metastatic colorectal cancer.

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Hinweis FBMed: Ergänzende Extraktion zur Thematik des Mikrosatelliten-instabilen (MSI) oder Mismatch-Reparaturmechanismus defizienten (dMMR) kolorektalen Karzinoms

(…) Analysis of mutations in mismatch repair genes is not currently recommended in clinical practice (at the moment it is recommended for genetic counselling), although it could help in selecting patients to be enrolled in specific clinical trials evaluating immunotherapy.9 (…)

Referenz:
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Dervenis C et al., 2016 [8].

Hellenic Society of Medical Oncology (HeSMO)

Clinical practice guidelines for the management of metastatic colorectal cancer: a consensus statement of the Hellenic Society of Medical Oncologists (HeSMO).

Leitlinienorganisation/Fragestellung

The Hellenic Society of Medical Oncology (HeSMO) selected an executive team on the grounds of their experience in colorectal cancer (CRC) and hepato-biliary and pancreatic malignancies which was assigned to develop a consensus statement and form guidelines on the main aspects of image staging, surgical treatment and follow up of metastatic CRC, based on the review of literature and the principles of the evidence-based medicine.

The present draft is part of a large consensus on the guidelines for the management of colorectal cancer. Guidelines on: 1) epidemiology, molecular biology, genetics, prognostic and predictive markers, hereditary forms, surveillance; 2) colon cancer care; 3) rectal cancer care; and 4) adjuvant treatment of CRC are presented elsewhere.

Methodik

Grundlage der Leitlinie

The methodology in setting our guidelines for the surgical management of rectal cancer has already been reported elsewhere [10]. The first round of the online Delphi voting process opened on September 29th 2013 and closed on December 6th 2013. The second round opened on January 6th 2014 and closed on January 24th 2014. In the final document, all statements are presented as recommendations of care. Even statements achieving a consensus of <80% were included. At the end of each recommendation the level of evidence (LOE) and the strength of recommendation (SOR) are mentioned, followed by the rate of voting consensus (ROVC)

Table 2 Rate of voting consensus of statements after the two voting processes

Rates of voting consensus	Statement numbers after 1st voting process	Resubmitted statement numbers	Statement numbers at the end of process
100%	24		24
90-99%	61		69
80-89%	13		15
70-79%	1	1	
60-69%	2	2	
New statements		7	
	Total: 101	Total: 10	Total: 108

LoE/GoR

Level of evidence	
I	Evidence from at least one large RCT of good methodological quality (low potential for bias) or meta-analyses of well-conducted RCTs without heterogeneity
II	Small RCTs or large RCTs 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, experts opinions
Strength of recommendation	
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) optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

RCT, randomized control trial

Empfehlungen

44. Patients with: 1) co-morbidities and unfit to undergo surgery; 2) multiple, rapidly progressing, metastatic deposits; and 3) severe symptomatic metastases, are amenable to palliative treatment (LOE IV, SOR B) (ROVC: 100%)

45. Aggressive chemotherapy should be personalized and aim to reduce metastatic tumor burden to alleviate symptoms (LOE III, SOR C) (ROVC: 95%)

subsequent treatment lines

The selection of the subsequent treatment lines should be based on the type of first-line treatment, response and/or PFS to first-line treatment, patient's performance status (PS) and preferences and taking into consideration the cost of treatment. New agents such as aflibercept (in second-line treatment) or regorafenib (≥ third-line treatment) could be considered in specific patient subpopulations.

46. Aggressive treatment regiments are FOLFOXIRI (LOE II; SOR C), FOLFIRI (LOE I; SOR B) and FOLFOX (LOE I; SOR B) and could be used alone or with the addition of anti-EGFR antibodies (RAS wt) or bevacizumab (LOE II, SOR B) (ROVC: 100%)

47. Duration of induction treatment may exceed 6 months, in case of favorable response (LOE II; SOR B) (ROVC: 84%)

48. RAS mutation precludes patients from treatment with anti-EGFR antibodies at the preoperative settings (LOE II, SOR B) (ROVC: 100%)

49. Alternative regimes, in patients with progressive metastatic disease are mXELIRI+/-bevacizumab or cetuximab (*RAS* wt) (LOE II; SOR C), or FOLFOX + panitumumab/ cetuximab (RAS wt) (LOE II; SOR B) (ROVC: 100%)

50. For *RAS* wt tumors, induction treatment with FOLFIRI + cetuximab or FOLFOX + anti-EGFR antibodies appears to be more effective in terms of major tumor shrinkage and secondary resectability, than bevacizumab based combinations, for which less data are available (LOE II; SOR B) (ROVC: 89%)

51. FOLFOXIRI should be considered as a treatment option especially for patients with *RAS* mutant tumors (LOE II; SOR C) (ROVC: 96%)

52. **For palliation**: i) fluoropyrimidine ±bevacizumab (sequential treatment) (LOE II; SOR B); or ii) doublets chemotherapy (LOE I; SOR A); or iii) doublets chemotherapy + anti-EGFR (*RAS* wt) (LOE II; SOR B) can be given (ROVC: 100%)

Alberta Health Service, 2020 [2].

Metastatic colorectal cancer.

Leitlinienorganisation/Fragestellung

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

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;

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

Recherche/Suchzeitraum:

- Update: PubMed and MEDLINE from 1990 forward (Year: 2020)

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

- Formulierungen im Text.

Recommendations

4. Standard palliative chemotherapy regimens to consider are described in Table 2.
5. Patients with metastatic colorectal cancer should receive testing for activating mutations of *Ras* (*Kras* and *Nras*) in tumour tissue at diagnosis of stage IV disease. *Douillard et al*. found that *Ras* mutations predict a lack of response in anti-Epidermal Growth Factor Receptor (EGFR) therapy in patients with metastatic colorectal cancer[28]. 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.
    b) When compared to best supportive care in patients with *Kras* wild-type colorectal cancer refractory or intolerant to a fluoropyrimidine (e.g.: 5-Fluorouracil, Capecitabine), Irinotecan, and Oxaliplatin, the use of monoclonal antibodies directed at the EGFR delays disease progression and deterioration in quality of life.

    Cetuximab administered as a 400 mg/m^2 IV loading dose followed by 250 mg/m^2 IV weekly maintenance prolongs median overall survival from 4.8 months to 9.5 months (p < 0.0001, HR 0.55, $CI_{95\%}$ 0.41-0.74)[32,33]. Panitumumab administered at 6 mg/kg IV over sixty minutes every two weeks prolongs progression-free survival[34,35]. Panitumumab is funded for patients with *Kras* wild-type disease on the Alberta Health Services Cancer Drug Benefit Program. Refer to the Panitumumab and Cetuximab: Toxicity Management Guidelines.

6. The Alberta Provincial Gastrointestinal Tumour Team supports the use of EGFR inhibitors in first-line treatment for patients with *Ras* wild-type metastatic colorectal cancer (i.e. non-mutated *Kras* or *Nras*) with left sided primary tumors.
7. Patients with BRAF mutated metastatic colorectal cancer represent a distinct group of patients who have a poor prognosis and are typically resistant to traditional doublet chemotherapy regimens. There is a paucity of research in this area to guide optimal upfront treatment. The TRIBE trial was a phase III open label randomized patients with metastatic colorectal cancer to either FOLFOXIRI + bevacizumab or FOLFIRI + bevacizumab[15]. Of the 508 patients in this study, 28 patients with BRAFV600E mutations were enrolled, of whom 12 patients were assigned to the FOLFIRI bevacizumab arm and 16 patients were assigned to the FOLFOXIRI bevacizumab arm. Across both arms, the median OS in the RAS-and BRAF-wild-type patients was 37.1 vs 13.4 months in the small subset of patients with tumors harboring BRAFV600E mutations (HR 2.79; 95% CI 1.75–4.46; P<0.0001). Although the number of patients with BRAFV600E mutations in this study was small, the median OS of patients treated with FOLFOXIRI plus bevacizumab in TRIBE was 19.0 months compared to 10.7 months in the FOLFIRI plus bevacizumab arm (HR 0.54; 95% CI 0.24–1.20). An overall response was reported in 56% of patients with a BRAFV600E mutation receiving FOLFOXIRI plus bevacizumab vs 42% of patients receiving FOLFIRI plus bevacizumab (odds ratio [OR] 1.82, 95% CI 0.91–2.62). A small single arm phase II trial also evaluating the triplet regimen plus bevacizumab as upfront treatment for BRAF mutant patients showed a mPFS of 11.8 months and mOS of 24.1 months[36]. Overall RR was 72%. Therefore for patients with good

performance status, a triplet regimen of FOLFOXIRI + bevacizumab can 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. Patients had progressed on 1 or 2 prior treatments[37]. 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 again the standard treatment arm. The median overall survival of the triplet regimen was 9 months vs. 5.2 months for the standard treatment (HR 0.52, 95% CI 0.39-0.70, p<0.001). The response rate was 26% (95% CI, 18 to 35) in the triplet-therapy group and 2% (95% CI, 0 to 7) in the control group (P<0.001). The overall survival in the doublet therapy group was 8.4 months (HR 0.60, 95% CI 0.45-0.79, p<0.001). In a descriptive analysis of survival comparing the triplet regimen with the doublet regimen, the estimated 6-month survival was 71% in the triplet-therapy group and 65% in the doublet-therapy group (hazard ratio for death, 0.79; 95% CI, 0.59 to 1.06). In the absence of access to cetuximab, and the specific BRAF and MEK inhibitors used in this trial, a similar option is a combination of panitumumab, dabrafenib and trametinib, which has proven to be a safe regimen[38].

8. Whether treatment is with combination chemotherapy or sequential monotherapy (with or without Bevacizumab) depends upon the patient's goals, their physical status, and other life circumstances, as assessed by their treating oncologist. Sequences of therapy may include:
    a. FOLFIRI followed by CAPOX/FOLFOX6
    b. CAPOX/FOLFOX6 followed by FOLFIRI or Irinotecan
    c. Capecitabine followed by Irinotecan followed by CAPOX/FOLFOX6
9. In the situation where a liver metastatectomy would be facilitated by a reduction in the size of the liver metastasis, patients should only be treated with chemotherapy until optimal resectability rather than to maximal response or progression. Only a limited number of cycles of chemotherapy should be delivered so as to minimize the consequences to the liver and their adverse effects. Oxaliplatin-based therapy is less likely to impact on post-metastatectomy mortality than Irinotecan-based therapy[39]. See Appendix: "Approach to Metastatic Colorectal Cancer."

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

Regimen	Details
FOLFIRI[12]	• Involves the administration of Irinotecan (180 mg/m^2 IV) and Leucovorin (400 mg/m^2 IV) concurrently over two hours followed by 5-Fluorouracil (400 mg/m^2 IV bolus and then an IV infusion of 2,400 mg/m^2 over forty-six hours) in every two-week cycle. This regimen requires placement of a port, central venous catheter (CVC), or peripherally inserted central catheter (PICC). • For patients who have complications with, or contraindications to, placement of a port, CVC, or PICC along with the capacity to tolerate the potential for

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

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

- Uncontrolled hypertension;
- Clinically significant cardio- or cerebro-vascular disease (e.g.: myocardial infarction or cerebrovascular accident within six months, unstable angina, congestive heart failure, use of a thrombolytic agent within six months, serious dysrhythmia);
- Inherited bleeding diathesis, coagulopathy, or esophageal varices;
- Significant proteinuria or renal dysfunction;
- Non-healing wound, ulcer, or bone fracture;
- Metastases within central nervous system or ophthalmologic abnormalities; and
- Pregnancy, lactation, or childbearing potential without effective contraception.

• If the medical oncologist feels the benefits outweigh the risks, it may be combined with chemotherapy in patients with a good performance status (ECOG ≤2). It can be administered over ten minutes at 5 mg/kg IV (Q2week chemotherapy schedule) or over fifteen minutes at 7.5 mg/kg IV (Q3week chemotherapy schedule).

Toxicities	Summary Incidence		Relative Risk	
	All-Grade Events	High-Grade Events	All-Grade Events	High-Grade Events
Arterial Thromboembolic Events[19] Cardiac Ischemia Cerebrovascular Ischemia	3.3%	2.0% 1.5% 1.2%	HR 2.08	HR 1.29 HR 2.14 HR 1.37
Proteinuria[22]	—	1.0%	HR 1.40	—
Hypertension[22]	—	8.7%	—	HR 3.00
Wound Healing Complications[20,21,24]	4.9%	3.7%	—	—
Gastrointestinal Perforation[25]	—	0.9%	—	HR 2.15

• Discrepant results exist as to the risk of venous thromboembolic events[23,26]
• It is not indicated for monotherapy and it is currently not funded by the Alberta Health Services Cancer Drug Benefit Program for treatment beyond progression.
  • Refer to the Bevacizumab Administration Guidelines.

EGFR inhibitor and chemotherapy [27-29]	• First-line anti-EGFR therapies may include: a. Cetuximab with FOLFIRI[27] b. Panitumumab with FOLFOX[28] c. Panitumumab with FOLFIRI (based on extrapolation from data in second-line treatment)[29]
	• EGFR inhibitors should not be given with bevacizumab as clinical trials with combinations of both EGFR inhibitor and bevacizumab give worse outcome[30,31]. • Refer to Panitumumab and Cetuximab: Toxicity Management Guidelines

10. Patients who have progressed on all standard therapy should be encouraged to participate in clinical trials.
    The following trials have been conducted in patients who have progressed on or were intolerant to a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and an EGFR inhibitor (if KRAS/NRAS wild type):
    The phase III CORRECT trial randomized 760 patients who progressed on standard therapy to best supportive care with placebo or regorafenib.38 OS for patients on regorafenib was 6.4 months versus 5.0 months for the placebo arm (HR 0.77, 95% CI 0.64–0.94, p=0.005). PFS improved modestly but significantly (1.9 months versus 1.7 months; HR 0.49, 95% CI 0.42 – 0.58, p<0.000001). The most common adverse events observed in the trial were hand-foot skin reactions (17%), fatigue (10%), hypertension (7%), diarrhea (7%) and rash/desquamation (6%). Regorafenib is currently not funded by the Alberta Health Services Outpatient Cancer Drug Benefit Program.
    The phase III RECOURSE trial randomized 800 patients to trifluridine-tipiracil or placebo. Median OS was significantly prolonged in patients treated with trifluridine-tipiracil compared to placebo (7.1 versus 5.3 months, HR 0.68, 95% CI 0.58- 0.81; P<0.001), and this benefit was irrespective of prior regorafenib use. Trifluridine-tipiracil is currently not funded by the Alberta Health Services Outpatient Cancer Drug Benefit Program[40].

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 1 of 12, Jan 2021) am 07.01.2021

#	Suchfrage
1	[mh "colorectal neoplasms"]
2	(colon OR colorectal OR rectal):ti,ab,kw
3	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma*):ti,ab,kw
4	#1 OR (#2 AND #3)
5	#4 with Cochrane Library publication date from Jan 2016 to present

Systematic Reviews in Medline (PubMed) am 07.01.2021

#	Suchfrage
1	colorectal neoplasms/therapy[majr]
2	colon[tiab] OR colorectal[tiab] OR rectal[tiab]
3	tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR sarcoma*[tiab] OR cancer*[tiab]
4	#2 AND #3
5	(#4) AND ((treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab]))
6	#1 OR #5
7	neoplasm metastasis[mh] OR advanced[tiab] OR metastat*[tiab] OR metastas*[tiab] OR recurren*[tiab] OR unresectab*[tiab]
8	#6 AND #7
9	(#8) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR

	meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
10	((#9) AND ("2016/01/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
11	(#10) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 07.01.2021

#	Suchfrage
1	colorectal neoplasms[majr]
2	colon[ti] OR colorectal[ti] OR rectal[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]
4	#1 OR (#2 AND #3)
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
6	(((#5) AND ("2016/01/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt])

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