Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2019-B-219 Encorafenib/Cetuximab

Stand: April 2020

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

Encorafenib/ Cetuximab
[zur Behandlung des metastasierten Kolorektalkarzinoms nach systemtischer Vortherapie]

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 2. Februar 2017 - Ramucirumab (neues Anwendungsgebiet): Beschluss vom 1. September 2016 - Regorafenib (Neubewertung nach Fristablauf): Beschluss vom 17. März 2016 - Aflibercept: Beschluss vom 15. August 2013
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Encorafenib L01XE46 Braftovi®	<u>Geplantes Anwendungsgebiet laut Beratungsanforderung</u>: Encorafenib in Kombination mit Cetuximab ist angezeigt zur Behandlung von erwachsenen Patienten mit metastasiertem Kolorektalkarzinom mit einer BRAF-V600E-Mutation, die eine systematische Vortherapie erhalten haben.
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.
Capecitabin L01BC06 Xeloda®	Xeloda wird angewendet: - zur Behandlung des metastasierten Kolorektalkarzinoms (siehe Abschnitt 5.1).
5-Fluorouracil L01BC02 Benda-5 FU	- Fortgeschrittenes oder metastasiertes 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
Calciumfolinat V03AF03 Calciumfolinat-	Calciumfolinat ist indiziert: - in Kombination mit 5-Fluorouracil in der zytotoxischen Therapie

II. Zugelassene Arzneimittel im Anwendungsgebiet	
GRY®	- bei fortgeschrittenem oder metastasiertem kolorektalem Karzinom
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
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.
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.
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.
Regorafenib L01XE21 Stivarga®[1]	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).
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.
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.
Panitumumab L01XC08	Vectibix ist indiziert zur Behandlung von erwachsenen Patienten mit metastasiertem kolorektalem Karzinom (mCRC, metastatic colorectal

[1] Marktrücknahme in Deutschland

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Vectibix®	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.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2019-B-219 (Encorafenib/ Cetuximab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	10. September 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

5-FU	5-Fluorouracil
AE	Adverse Events
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BSC	Best supportive Care
CTC	Chemotherpie
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
IRI	Irinotecan
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
KRAS	Kirsten rat sarcoma viral oncogene homolog
LoE	Level of Evidence
LV	Leucovorin
mCRC/KRK	Metastasiertes Kolorektales-Karzinom
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 systemischer Vortherapie.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Kolorektalkarzinom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 12.03.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1618 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 29 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA-Beschlüsse/IQWiG-Berichte

G-BA, 2013 [9].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – **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 [10].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – **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 [11].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – **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 [12].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – **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. (these, as well as subsequent chemotherapy regimens, are briefly explained in Appendix 6).

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.

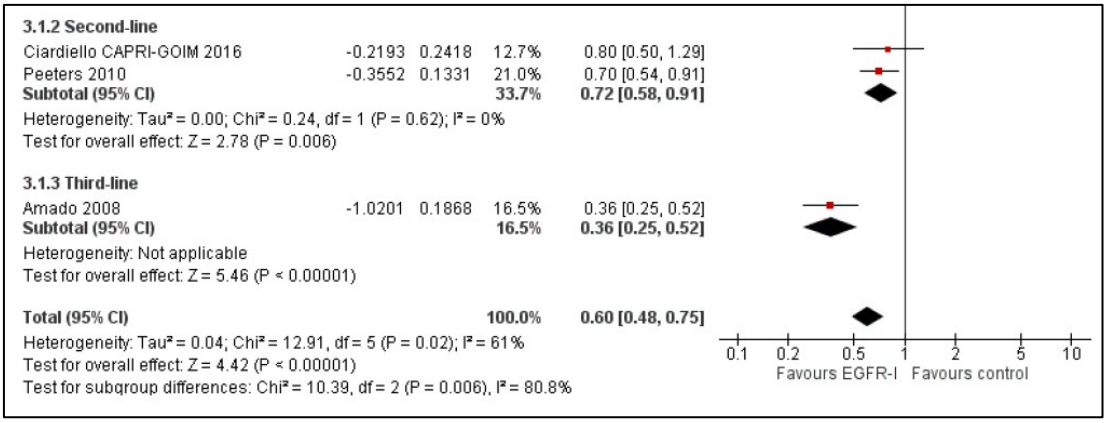
- **Tumour response rate**
  - Pooled analysis of second-line trials (4 RCTs, 1243 participants) in KRAS exon 2WT populations showed that adding EGFRMAb to second-line chemotherapy increased the rate of response by 21.8% from 11.3% (70/618) to 33.1% (206/625) (OR 3.60, 95% CI 2.45 to 5.30; P < 0.001), 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

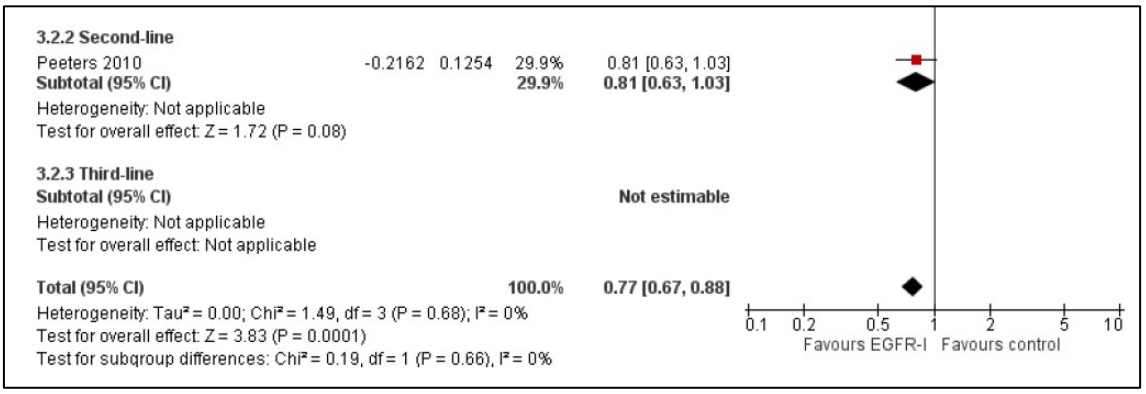
- **PFS**
  - The only second-line trial reporting PFS outcomes in KRAS exon 2 MT populations was Peeters 2010 (1 RCT, 486 participants). The risk of progression did not significantly decrease (HR 0.85, 95% CI 0.68 to 1.06; P = 0.15)
  - Pooled analysis of third-line trials (2 RCTs, 348 participants) 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 [17].

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:

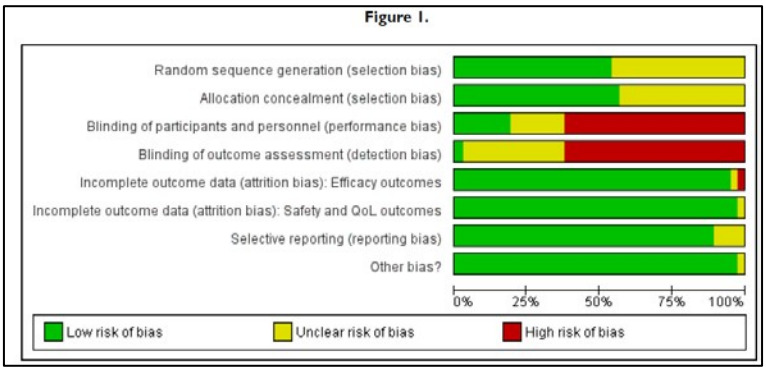
The main features of each of the 34 included trials (overall enrolling 13,787 participants; range: 55 to 1298; median: 247) are reported in the Characteristics of included studies table.

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 5FU	Corresponding risk 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 [27].

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

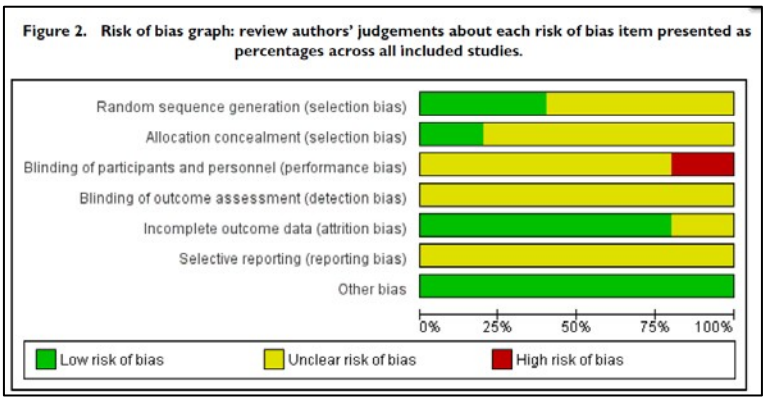
Ergebnisse

Anzahl eingeschlossener Studien:

Charakteristika der Population:

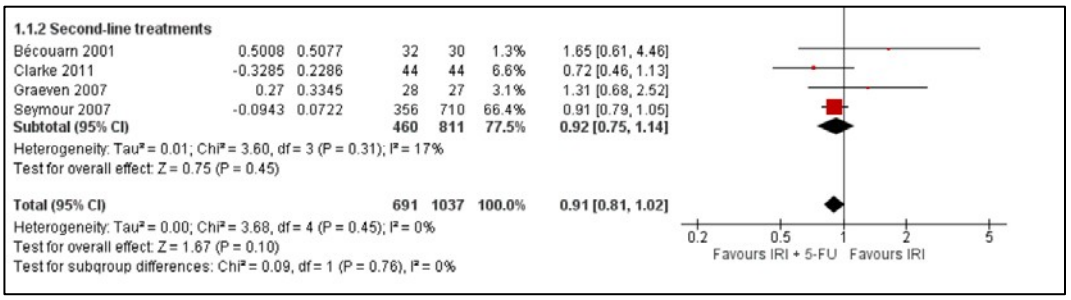
A total of 1,726 patients were randomised: 686 in the IRI-fluoropyrimidine combination group and 1,040 in the control group. Four of the studies administered IRI and the combination of IRI with fluoropyrimidine as a second-line treatment (Bécouarn 2001; Clarke 2011; Graeven 2007; Seymour 2007) and one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

Qualität der Studien:

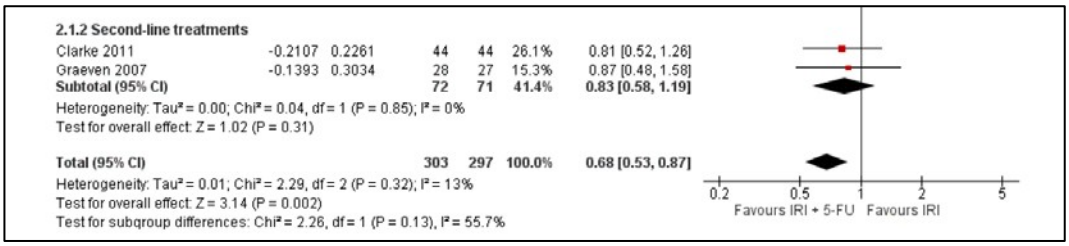


Studienergebnisse:

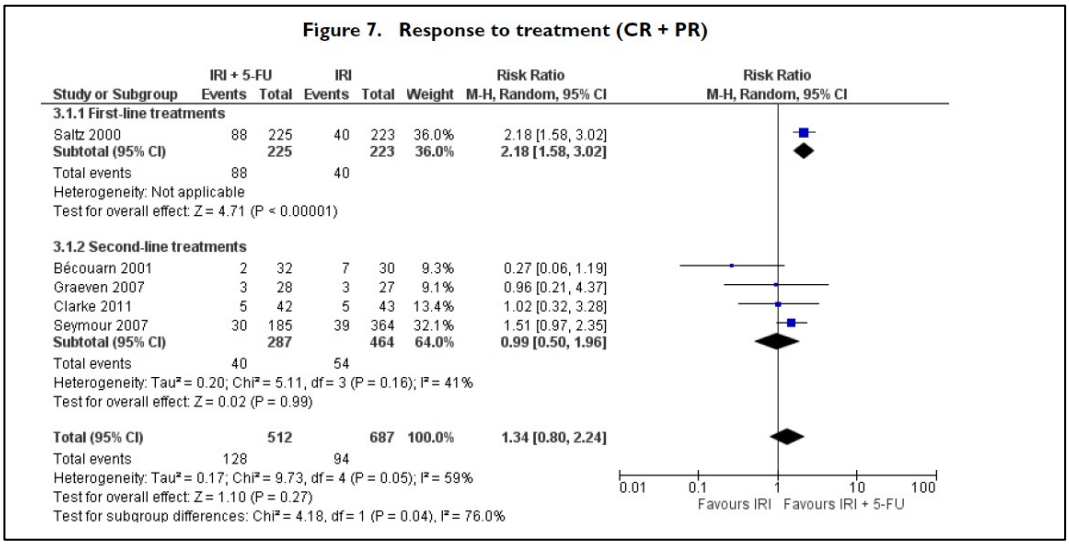
- **OS**



- **PFS**



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



- **Adverse events**

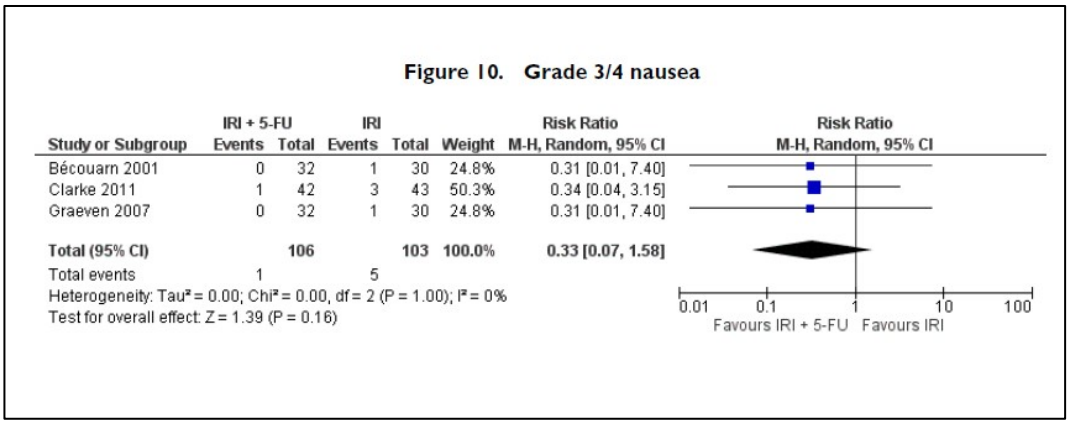


Figure 14. Grade 1/2 alopecia

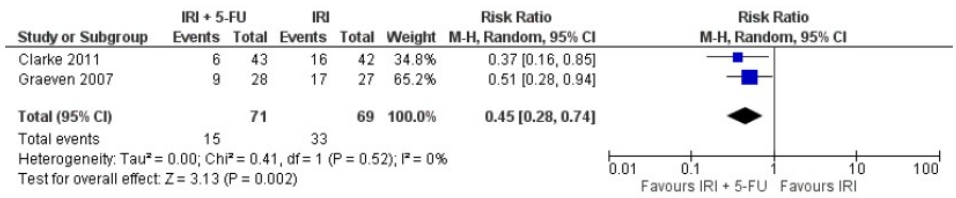
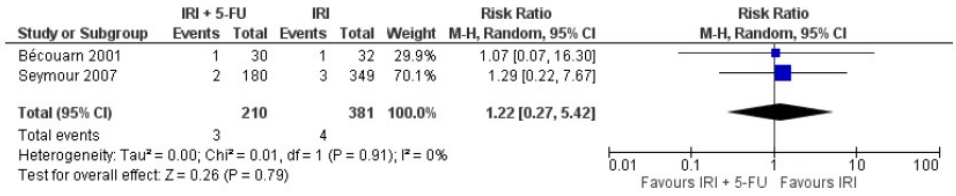


Figure 15. Neuropathy



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

Ruan WC et al., 2018 [20].

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**

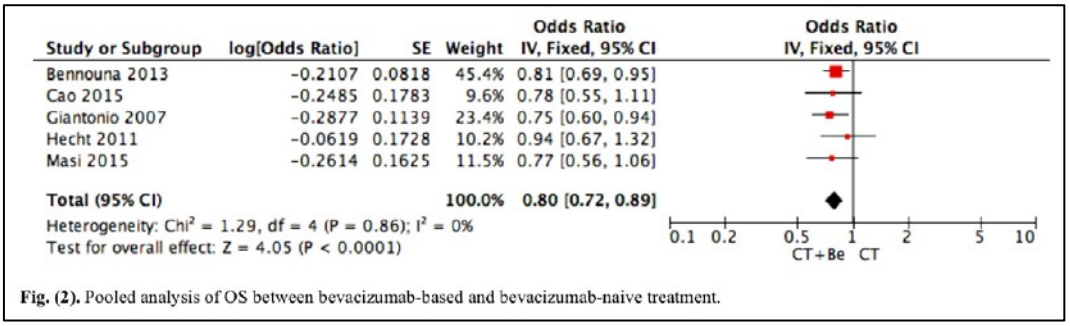


Fig. (2). Pooled analysis of OS between bevacizumab-based and bevacizumab-naive treatment.

- **PFS und ORR**

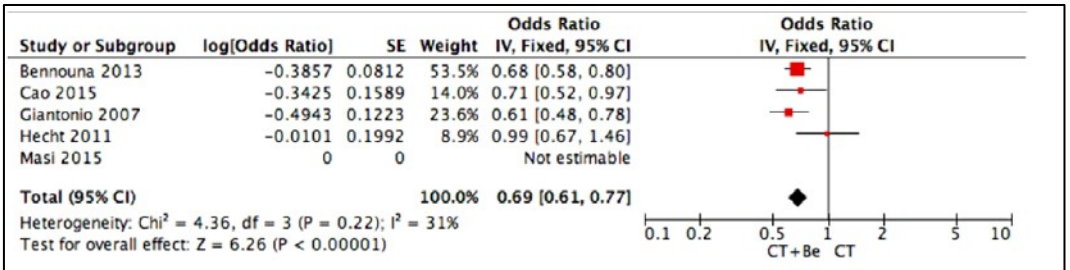


Fig. (3). Pooled analysis of PFS between bevacizumab-based and bevacizumab-naive treatment.

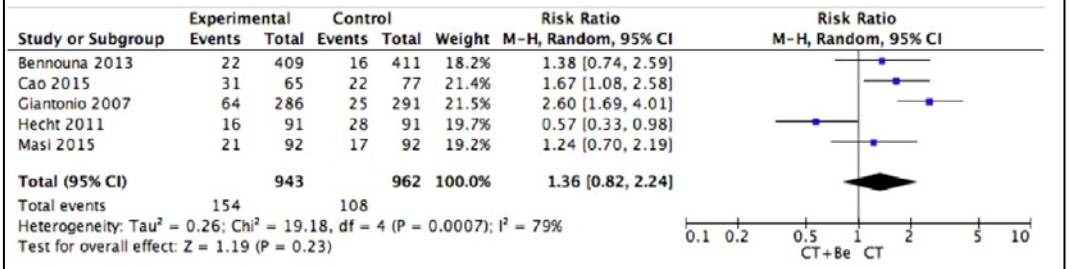


Fig. (4). Pooled analysis of ORR between bevacizumab-based and bevacizumab-naive treatment.

- **SAE**

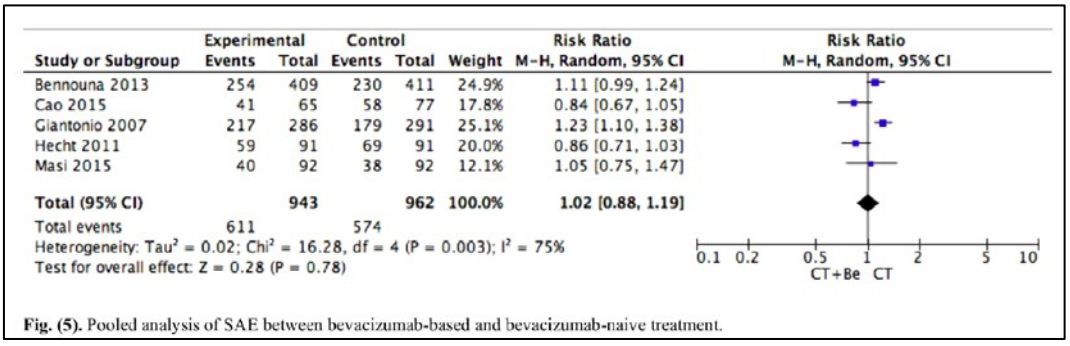


Fig. (5). Pooled analysis of SAE between bevacizumab-based and bevacizumab-naive treatment.

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 [29].

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**

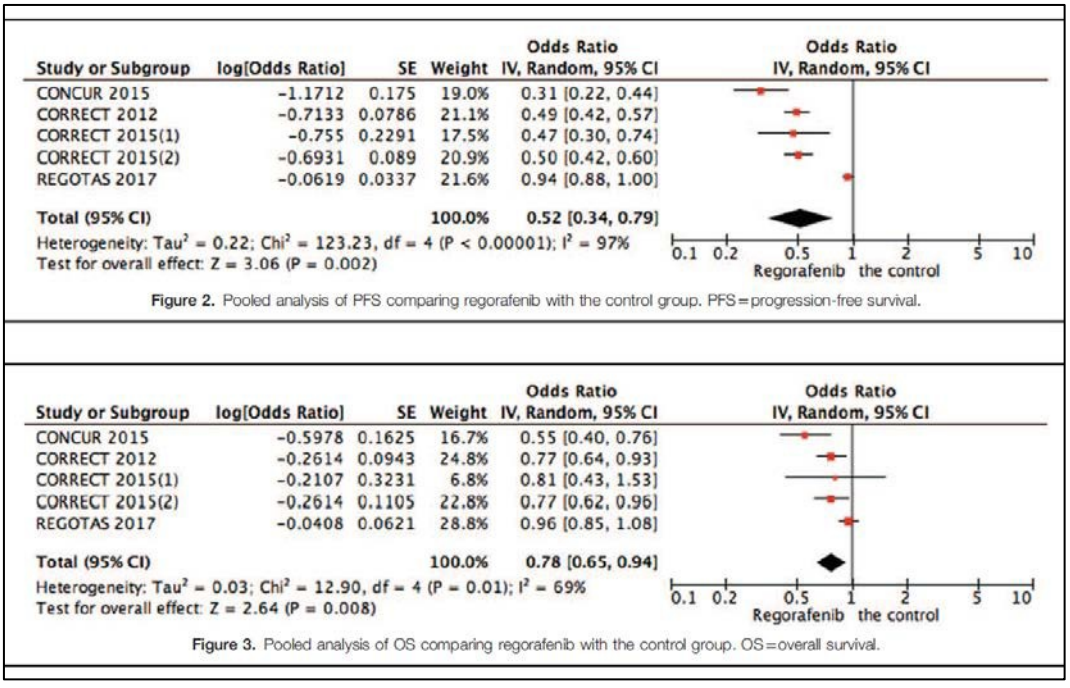


Figure 2. Pooled analysis of PFS comparing regorafenib with the control group. PFS = progression-free survival.

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 [14].

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 [19].

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

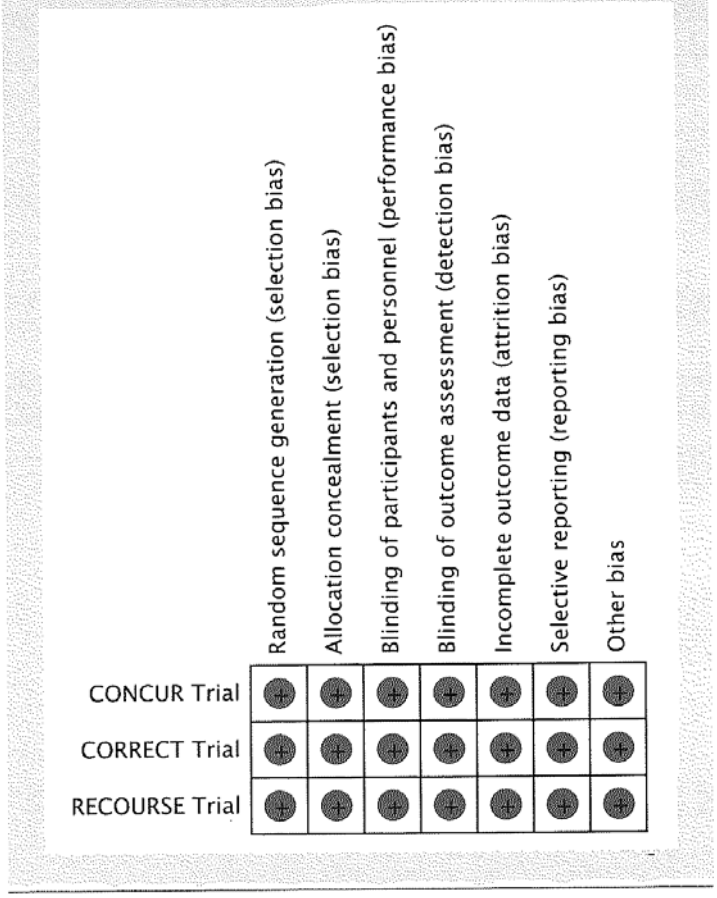
Abbreviations: CONCUR = regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer: a randomised, double-blind, placebo-controlled, phase 3 trial; CORRECT = regorafenib monotherapy for previously treated metastatic 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 [28].

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 [25].

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:

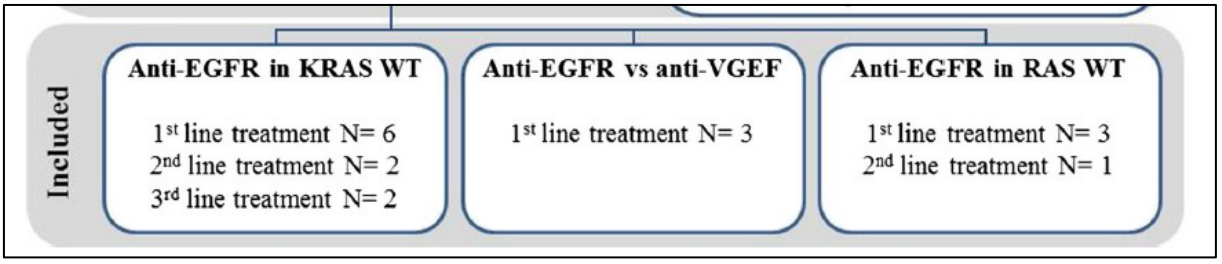
- Februar 2016 (PubMed, Embase.com, and Wiley/Cochrane Library)

Qualitätsbewertung der Studien:

- Cochrane collaboration's tool

Ergebnisse

Anzahl eingeschlossener Studien:



Charakteristika der Population:

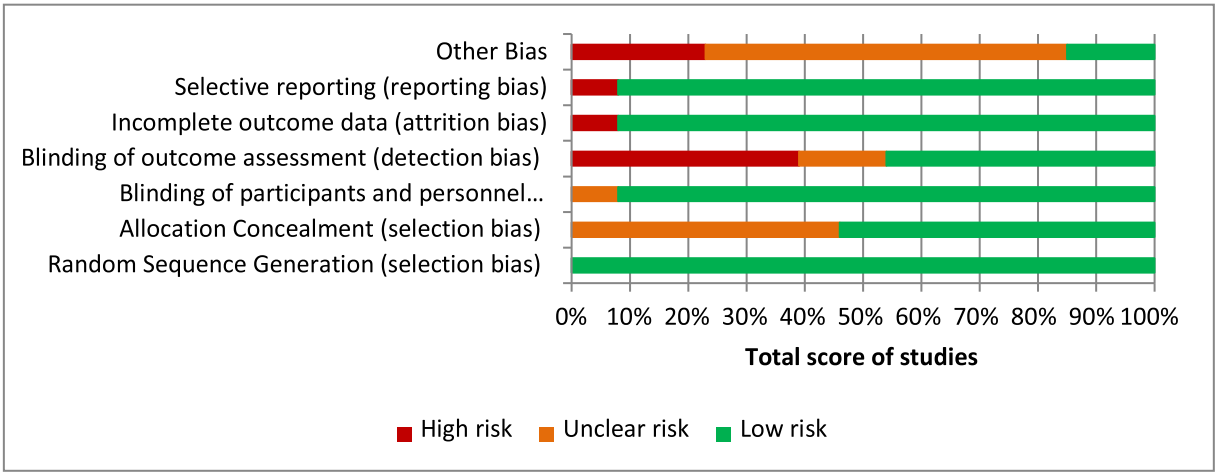
C. The addition of an anti-EGFR mAb to the second-line treatment of mCRC					
20,050,181 (Peeters)	Pani + FOLFIRI (303)	FOLFIRI (294)	36 *versus* 10 (5.5, 3.3–8.9, <0.001)	6.7 *versus* 4.9 (0.82, 0.7–1.0, 0.02)	14.5 *versus* 12.5 (0.92, 0.8–1.1, 0.37)
PICCOLO (Seymour)	Pani + irinotecan (230)	Irinotecan (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 [15].

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 [26].

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)

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.

Tang NP et al., 2014 [22].

Risk/benefit profile of panitumumab-based therapy in patients with metastatic colorectal cancer: evidence from five randomized controlled trials

Fragestellung

Therefore, we conducted a meta-analysis on relevant randomized controlled trials (RCTs) to determine the risk profile of PBT in patients with mCRC and analyze the results in terms of risk–benefit of the treatment

Methodik

Population:

- CRC patients

Intervention:

- PBT

Komparator:

- non-PBT

Endpunkte:

- overall survival (OS), progression-free survival (PFS) and AEs

Recherche/Suchzeitraum:

- updated to March 2014 (PubMed, Medline, EMBASE and Cochrane Library)

Qualitätsbewertung der Studien:

- 5-point Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- N=5 RCTs

Charakteristika der Population:

- A total of 4,155 patients with mCRC (PBT group, n=2,076; non-PBT group, n=2,079) from five RCTs were included for analysis.
- In two of the included RCTs [12, 13]
- PBT was used in the first-line setting, **and in the other three RCTs [10, 14, 15], PBT was used in the subsequent-line setting.**

Table 1 Characteristics of randomized controlled clinical trials included in the meta-analysis

Source	TA vs. CA	*KRAS* status	Patients in TA vs. CA	HR (95 % CI) for PFS	HR (95 % CI) for OS	Any events grade ≥3 in TA vs. CA	Any events any grade in TA vs. CA	Jadad score
van Cutsem et al. 2007	Pmab+BSC vs. BSC	NA	231 vs. 232	0.54 (0.44–0.66)	1.00 (0.82–1.22)	79 (34 %) vs. 45 (19 %)	229 (100 %) vs. 202 (86 %)	3
Amado et al. 2008 [a]	Pmab+BSC vs. BSC	WT	124 vs. 119	0.45 (0.34–0.59)	0.99 (0.75–1.29)	NA	124 (100 %) vs. 107 (90 %)	3
		MT	84 vs. 100	0.99 (0.73–1.36)	1.02 (0.75–1.39)	NA	84 (100 %) vs. 84 (84 %)	
Hecht et al. 2009a	Pmab+Bev/ Ox-CT vs. Bev/Ox-CT	Total	413 vs. 410	1.27 (1.06–1.52)	1.43 (1.11–1.83)	367 (90 %) vs. 305 (77 %)	NA	3
		WT	201 vs. 203	1.36 (1.04–1.77)	1.89 (1.30–2.75)	NA	NA	
		MT	47 vs. 44	1.25 (0.91–1.71)	1.02 (0.67–1.54)	NA	NA	
Hecht et al. 2009b	Pmab+Bev/Iri-CT vs. Bev/ Iri-CT	Total	115 vs. 115	1.19 (0.79–1.79)	1.42 (0.77–2.62)	100 (90 %) vs. 71 (63 %)	NA	3
		WT	54 vs. 48	1.50 (0.82–2.76)	1.28 (0.50–3.25)	NA	NA	
		MT	47 vs. 39	1.19 (0.65–2.21)	2.14 (0.82–5.59)	NA	NA	
Douillard et al. 2010	Pmab+ FOLFOX4 vs. FOLFOX4	WT	325 vs. 331	0.80 (0.66–0.97)	0.83 (0.67–1.02)	270 (84 %) vs. 227 (69 %)	NA	3
		MT	221 vs. 219	1.29 (1.04–1.62)	1.24 (0.98–1.57)	173 (80 %) vs. 159 (73 %)	NA	
Peeters et al. 2010	Pmab+FOLFIRI vs. FOLFIRI	WT	303 vs. 294	0.73 (0.59–0.90)	0.85 (0.70–1.04)	219 (73 %) vs. 152 (52 %)	NA	3
		MT	238 vs. 248	0.85 (0.68–1.06)	0.94 (0.76–1.15)	151 (64 %) vs. 123 (50 %)	NA	
Seymour et al. 2013	Pmab+Irinotecan vs. Irinotecan	WT	230 vs. 230	0.78 (0.64–0.95)	1.01 (0.83–1.23)	NA	NA	3

The number of patients of studies by van Cutsem et al., Hecht et al. (a and b, total number), Douillard et al. (sum of WT and MT), Peeters et al. (sum of WT and MT) and Seymour et al. was used for the calculation of the total number of patients

Bev bevacizumab, *BSC* best supportive care without antineoplastic agents, *CA* control arm, *CI* confidence interval, *FOLFIRI* fluorouracil, leucovorin, and irinotecan, *FOLFOX4* fluorouracil, leucovorin, and oxaliplatin, *HR* hazard ratio, *Iri-CT* fluorouracil, leucovorin and irinotecan-based chemotherapy, *mCRC* metastatic colorectal cancer, *MT* mutant type, *NA* not available, *Ox-CT* fluorouracil, leucovorin and oxalipatin-based chemotherapy, *Pmab* panitumumab, *TA* treatment arm, *WT* wild type

[a] The study by Amado et al. was used only in genotype stratified analysis

Qualität der Studien:

- The quality of each included studies was evaluated according to Jadad scale, and all the studies had scores of 3, indicating their high quality.

Studienergebnisse:

- PFS
  - The pooled analysis showed that PBT was associated with 34 % reduction in the risk of disease progression when used in the subsequent-line setting (HR random=0.66, 95 % CI=0.45–0.95).
  - Because the significant effect was only observed in PFS in patients with wild-type KRAS in the subsequent-line setting, the NNT was calculated only for PFS in wild-type KRAS groups in studies with subsequent-line setting. NNT is expressed for PFS at 1 year based on the available data. As presented in Table 2, the NNT for PFS is 11 to 23 (minimum to maximum).
- OS
  - The pooled analysis showed that PBT did not benefit patients for OS in either the subsequent-line setting (HRfixed=0.93, 95 % CI=0.83–1.04) or the first-line setting (HRrandom=1.21, 95 % CI=0.90–1.63).
  - When used in the subsequent-line setting, PBT significantly improved PFS in patients with wild-type KRAS (HRrandom=0.64, 95 % CI=0.47–0.87; Fig. 4a), but not in patients with mutant-type KRAS (HRfixed=0.89, 95 % CI= 0.75–1.07; Fig. 4a). No significant effect of KRAS status on OS was observed in the subsequent-line or first-line setting (Fig. 4b and d). Interestingly, when used in the first-line setting, PBT was associated with an increase in the risk of disease progression (HRfixed=1.27, 95 % CI=1.07–1.51; Fig. 4c).

10. van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol. 2007;25:1658–64.
14. Peeters M, Price TJ, Cervantes A, 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: 4706–13.
15. Seymour MT, Brown SR, Middleton G, et al. Panitumumab and irinotecan versus irinotecan alone for patients with KRAS wildtype, fluorouracil-resistant advanced colorectal cancer (PICCOLO): a prospectively stratified randomised trial. Lancet Oncol. 2013;14: 749–59.

Anmerkung/Fazit der Autoren

In conclusion, the results of this meta-analysis showed that PBT significantly improved the disease progression in mCRC patients with wild-type KRAS when used in subsequent-line settings. The effects of PBT on OS in mCRC patients need to be further confirmed in large, well-designed RCTs. In addition, PBT was associated with significantly increased risk of skin toxicity, infections, diarrhea, dehydration, mucositis, hypokalemia, fatigue, hypomagnesemia, pulmonary embolism and paronychia. Physicians and investigators should strengthen the AEs monitoring and make necessary preparations during the treatment.

Pei X et al., 2016 [18].

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

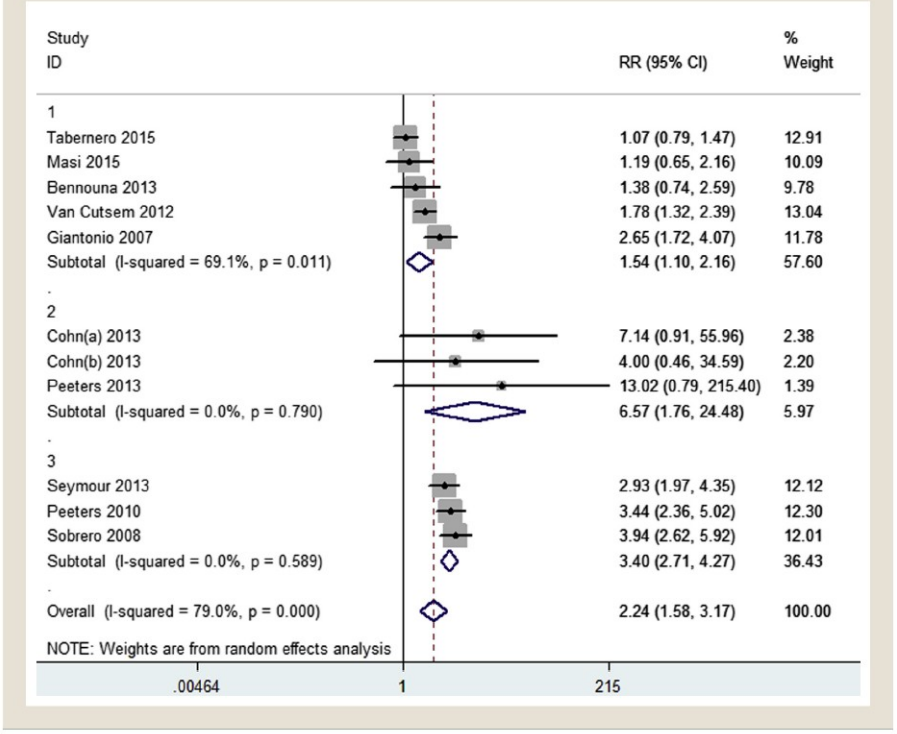
Studienergebnisse:

- 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).

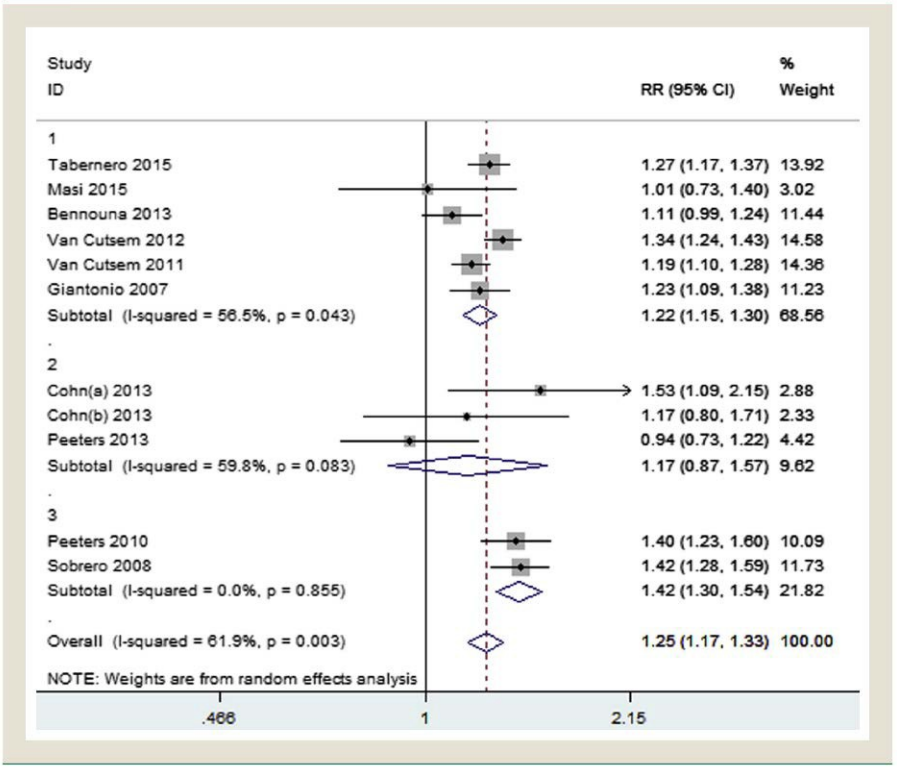
Figure 4 The Forest Plot of ORR Comparing Chemotherapy Plus Molecular Targeted Agent With Chemotherapy Alone. Subgroup 1: Anti-VEGF Agents; 2: Other Pathway Inhibitors; 3: EGFR Inhibitors



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

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)), 2019 [16].

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 zur Wahl der systemischen 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 aus Leitlinien:
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 aus Leitlinien:
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 Chemo-therapie 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 aus Leitlinien:
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.
1169. Ciardiello, F., et al., Cetuximab continuation after first progression in metastatic colorectal cancer (CAPRI-GOIM): a randomized phase II trial of FOLFOX plus cetuximab versus FOLFOX. Ann Oncol, 2016. **27**(6): p. 1055-61.
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.
1172. Zaniboni, A. and V. Formica, The Best. First. Anti-EGFR before anti-VEGF, in the first-line treatment of RAS wild-type metastatic colorectal cancer: from bench to bedside. Cancer Chemother Pharmacol, 2016. 78(2): p. 233-44.
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 aus Leitlinien:
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 aus Leitlinien:

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.

Cancer Council Australia Colorectal Cancer Guidelines Working Party, 2017 [5].

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.

Referenzen aus Leitlinien

Loupakis F, Ruzzo A, Cremolini C, Vincenzi B, Salvatore L, Santini D, et al. KRAS codon 61, 146 and BRAF mutations predict resistance to cetuximab plus irinotecan in KRAS codon 12 and 13 wild-type metastatic colorectal cancer. Br J Cancer 2009 Aug 18;101(4):715-21 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/19603018

Lochhead P, Kuchiba A, Imamura Y, Liao X, Yamauchi M, Nishihara R, et al. Microsatellite instability and BRAF mutation testing in colorectal cancer prognostication. J Natl Cancer Inst 2013 Aug 7;105(15):1151-6 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/23878352.

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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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Cancer Care Ontario (CCO)

Strategies of Sequential Therapies in Unresectable, Metastatic Colorectal Cancer Treated with Palliative Intent.

Leitlinienorganisation/Fragestellung

QUESTION

What is the impact of different strategies of sequential and combination chemotherapy on efficacy (including overall survival), toxicity and quality of life in unresectable metastatic colorectal cancer treated with palliative intent?

TARGET POPULATION

These recommendations apply to adult patients (≥18 years old) with unresectable metastatic colorectal cancer. The cytotoxic agents covered in this guideline include initial fluoropyrimidine (5-FU or capecitabine) either alone or in combination, irinotecan and oxaliplatin.

Methodik

Grundlage der Leitlinie

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

- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

The MEDLINE (2000 through July [week5] 2013) and EMBASE (2000 through week 32 2013) databases were searched for relevant evidence. The year 2000 was chosen as the starting point as it predates the approval of irinotecan and oxaliplatin for use in metastatic colorectal cancer. The full MEDLINE and EMBASE literature search strategies can be found in Appendix 3). The reference lists from retained articles were also searched for additional relevant trials. In addition, the proceedings of the 2004-2013 American Society of Clinical Oncology (ASCO) and the 2002-2012 European Society of Medical Oncology (ESMO) annual meetings were searched for abstract reports of relevant studies.

LoE/ GoR

- Evidenzklassifizierung und Empfehlungsgraduierung mit verschiedenen Systemen (in Evidenztabellen dargestellt)

RECOMMENDATIONS AND KEY EVIDENCE

Planned sequential chemotherapy and upfront combination chemotherapy are both acceptable standards of care. While there is a statistically significant difference in overall survival in favour of combination chemotherapy, the magnitude of the difference between the two strategies may not be clinically significant. Furthermore, sequential therapies may reduce upfront toxicities. Therefore, choice of treatment should be made on a case-by-case basis based on considerations that include patient and tumour characteristics, toxicity of each strategy and patient preference.

Sequential chemotherapy consists of a fluoropyrimidine monotherapy followed by either:

- another monotherapy with irinotecan OR
- combination chemotherapy consists of a doublet of a fluoropyrimidine with irinotecan or oxaliplatin

Combination chemotherapy consists of an upfront doublet of a fluoropyrimidine with irinotecan or oxaliplatin.

QUALIFYING STATEMENTS

- The FOCUS (2) trial is the largest trial of the five included trials. The individual hazard ratio for the FOCUS (2) trial only includes two arms of this trial. Therefore, one third of the data from this trial is missing from the overall meta-analysis of the five trials.
- Based on the results of this systematic review, patients should have access to all effective cytotoxic drugs using a sequential strategy.
- Combination chemotherapy may be more appropriate for patients with rapidly progressing, very symptomatic or bulky life-threatening visceral disease given their higher overall response rates.
- The studies included in this systematic review were done in an era prior to the use of biologics in the treatment of mCRC. Definitive statements about the integration of biologics into a sequential strategy cannot be made at this time.

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Cancer Care Ontario (CCO)

Continuous versus Intermittent Chemotherapy Strategies in Inoperable, Advanced Colorectal Cancer.

Leitlinienorganisation/Fragestellung

QUESTION

What is the impact of intermittent strategies of administering systemic therapy on length and quality of survival in patients with untreated, unresectable metastatic colorectal cancer?

TARGET POPULATION

These recommendations apply to adult patients (≥18 years old) with inoperable, advanced (Stage IV) 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;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

The MEDLINE (2000 through July [week4] 2013) and EMBASE (2000 through week 30 2013) databases were searched for relevant evidence. The full MEDLINE and EMBASE literature search strategies can be found in Appendix 3. The reference lists from retained articles were also searched for additional relevant trials. In addition, the proceedings of the 2000-2013 American Society of Clinical Oncology (ASCO) and the 2000-2012 European Society of Medical Oncology (ESMO) annual meetings were searched for abstract reports of relevant studies.

LoE/ GoR

- Evidenzklassifizierung und Empfehlungsgraduierung mit verschiedenen Systemen (in Evidenztabellen dargestellt).

RECOMMENDATIONS AND KEY EVIDENCE

Intermittent strategies of administering first-line systemic therapies to patients with unresectable metastatic colorectal cancer (mCRC) do not result in a statistically significant reduction in overall survival and either improve or maintain quality of life compared to continuous administration of therapy. Patients who want a break from treatment can be reassured that intermittent strategies of administering first-line therapy are a reasonable alternative to continuous administration. Intermittent systemic treatment strategies should be part of an informed discussion of treatment options for this group of patients.

QUALIFYING STATEMENTS

- Given that the trials included in this systematic review included a variety of maintenance strategies, a definitive recommendation regarding an optimal maintenance strategy is not possible. However, our analyses of strategies that did not use any maintenance systemic therapy did not demonstrate any statistically significant detriment in overall survival. Therefore, this approach may be preferred by patients, as it offers them a complete break from treatment.
- All but one of the intermittent strategies offered 12 to 18 weeks of induction treatment and were monitored with imaging at least every 8 to 12 weeks during the intermittent phase of treatment, with reintroduction of the induction chemotherapy at disease progression. These represent reasonable guidelines to consider when using an intermittent strategy, but adaptation of a strategy to individual circumstances should always be considered. A longer induction period or closer clinical monitoring of patients on maintenance therapy or chemotherapy-free interval might be appropriate for patients with very bulky or symptomatic disease. For some patients like this, an intermittent strategy may not be appropriate.
- Five of the seven trials that contributed to the meta-analyses were based on treatments with FOLFOX chemotherapy, one of the commonly used first-line chemotherapy regimens for mCRC in Ontario. The other two trials included in the meta-analyses used fluoropyrimidine monotherapy or FOLFIRI as induction chemotherapy regimens. Given the acceptability of fluoropyrimidine monotherapy as one of the options for first-line therapy (see EBS #2-5) and the accepted equivalence of FOLFIRI and FOLFOX as first-line therapies (11,12), extrapolation of our conclusions to all commonly used induction chemotherapy regimens is reasonable.
- During maintenance therapy or a chemotherapy-free interval, best supportive care should be continued for patients.

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European Society for Medical Oncology (ESMO)

ESMO Rectal cancer: ESMO Clinical Practice Guidelines.

Leitlinienorganisation/Fragestellung

Treatment recommendations for rectal cancer.

Methodik

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. A summary of key recommendations is given in Table 8. Levels of evidence and grades of recommendation have been applied using the system shown in Table 9. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty. This manuscript has been subjected to an anonymous peer review process.

LoE/ GoR

Table 9. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

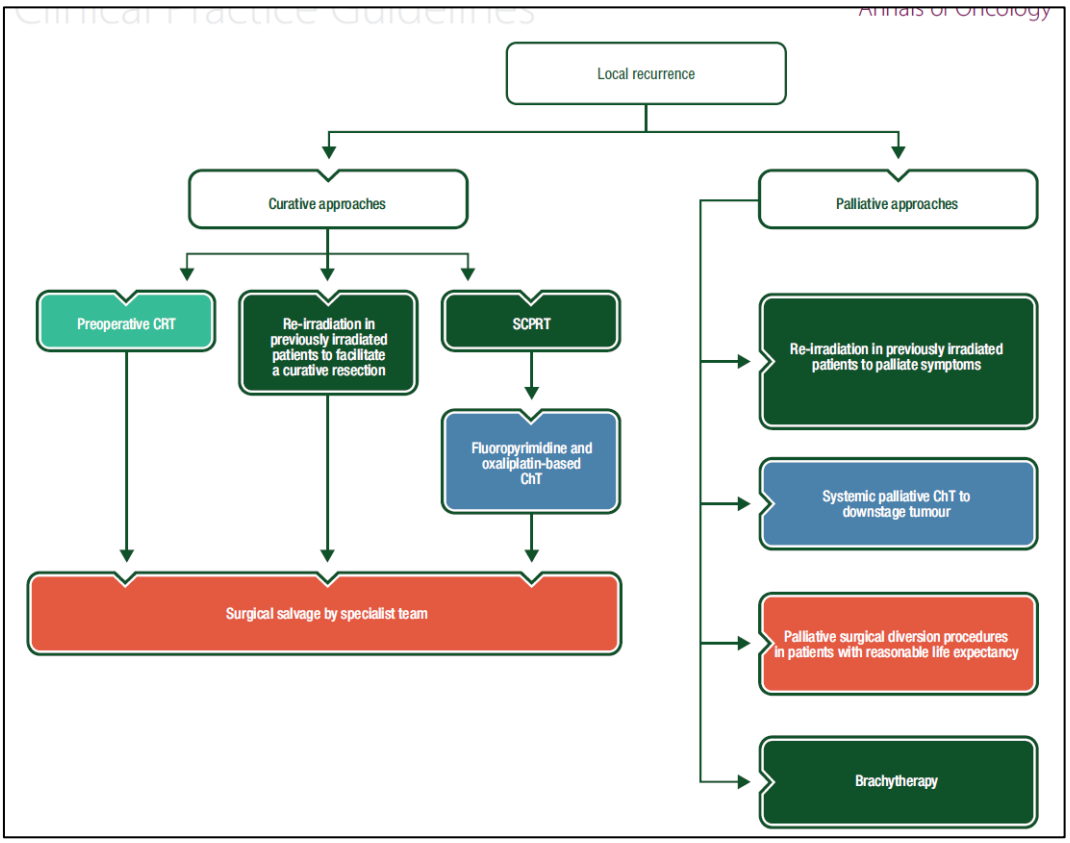
Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower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

[a]By permission of the Infectious Diseases Society of America [108].

Sonstige methodische Hinweise

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Da die Leitlinie ein Teil des Anwendungsgebietes umfasst und Bezug nimmt auf die ESMO LL zum metastasierten Kolorektalkarzinom (siehe Ausführungen unten), wird diese ergänzend dargestellt.

Empfehlungen



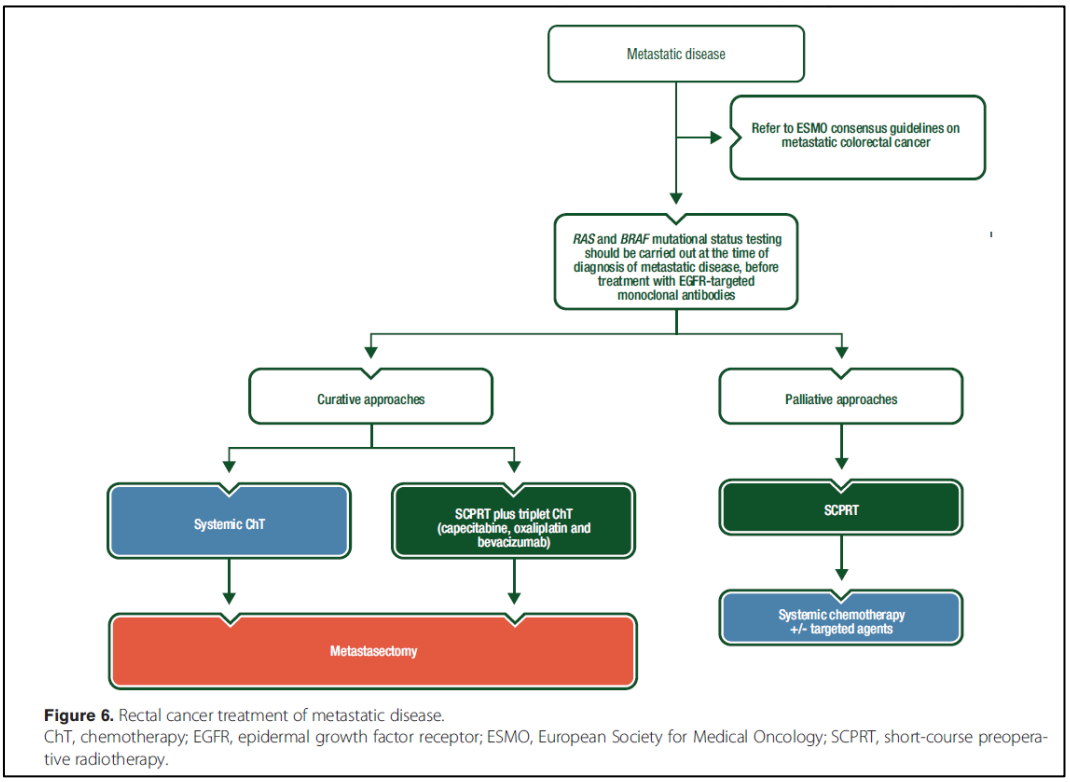


Figure 6. Rectal cancer treatment of metastatic disease.
ChT, chemotherapy; EGFR, epidermal growth factor receptor; ESMO, European Society for Medical Oncology; SCPRT, short-course preoperative radiotherapy.

Van Cutsem E et al., 2016 [23].

European Society for Medical Oncology (ESMO)

ESMO consensus guidelines for the management of patients with metastatic colorectal cancer

Siehe auch: Van Cutsem E et al., 2014 [24].

Leitlinienorganisation/Fragestellung

These ESMO Consensus Guidelines therefore aim to reflect the diagnostic, therapeutic and strategic improvements which have contributed to the current 'state-of-the-art' treatment approaches and to provide guidance for the comprehensive management of patients with mCRC going forward.

Methodik

Grundlage der Leitlinie

- In 2014, the ESMO Guidelines Committee decided to update the clinical recommendations for mCRC using a consensus conference approach. An international panel of experts in the management of patients with CRC, from a range of diagnostic and therapeutic disciplines, was convened in Zurich in December 2014 to update the existing ESMO Consensus Guidelines for the management of patients with colon and rectal cancer [3]. A set of pre-formulated topics was prepared and three working groups convened in the areas of:
  - (i) molecular pathology and biomarkers;
  - (ii) local and ablative treatment (LAT) [including surgery and the management of patients with oligometastatic disease (OMD)];
  - (iii) the treatment of metastatic disease.

- Each panel member was assigned to one of the above working groups. Three consensus conference chairs (EVC, AC and DA) were also appointed. Before the consensus conference, clinically relevant questions were identified for each working group. Each working group was responsible for reviewing relevant literature in order to draft preliminary recommendations relating to each of their assigned questions. No systematic literature search was undertaken. The experts in each group were invited to submit their recommendations in advance to structure the on-site discussions.
- During the conference, in parallel sessions, the three working groups discussed and reached agreement on recommendations relating to each of their assigned questions. Recommendations fromeach group were then presented to the entire panel of experts, where they were discussed and modified as required until consensus was reached.

LoE/ GoR

Table 1. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America—United States Public Health Coding System[a] [4])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (low methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
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Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
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C	Insufficient evidence for efficacy or benefit does not outweigh the risk of 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

[a]By permission of the Infectious Diseases Society of America.

Sonstige methodische Hinweise

- Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, hinsichtlich der Fragestellung zur Therapie für Patienten mit BRAF-V600E-mutierten KRK, wird die LL ergänzend dargestellt.

Empfehlungen

Empfehlung 1 (second-line)

- Patients who are bevacizumab naïve should be considered for treatment with an antiangiogenic (bevacizumab or aflibercept) second line [I, A]. The use of aflibercept should be restricted to combination with FOLFIRI for patients progressing on an oxaliplatin-containing regimen [I, A].
- Patients who received bevacizumab first line should be considered for treatment with:
  - Bevacizumab post-continuation strategy [I, A].
  - Aflibercept or ramucirumab (in combination with FOLFIRI) when treated in first line with oxaliplatin [I, A].
  - EGFR antibodies in combination with FOLFIRI/irinotecan for patients with RAS wild-type (BRAF wild-type) disease

  - Relative benefit of EGFR antibodies is similar in later lines compared with second line [II, A].
- Patients who are fast progressors on first-line bevacizumab containing regimens should be considered for treatment with aflibercept or ramucirumab (only in combination with FOLFIRI) [II, B], and—in the case of patients with RAS wildtype disease and no pre-treatment with anti-EGFR therapy—EGFR antibody therapy, preferably in combination with chemotherapy [II, B].

Empfehlung 2 (third line)

- In RAS wild-type and BRAF wild-type patients not previously treated with EGFR antibodies, cetuximab or panitumumab therapy should be considered
  - Cetuximab and panitumumab are equally active as single agents [I, A].
  - The combination of cetuximab with irinotecan is more active than cetuximab alone, in irinotecan refractory patients [II, B]
  - There is no unequivocal evidence to administer the alternative EGFR antibody, if a patient is refractory to one of the EGFR antibodies [I, C].
- Regorafenib is recommended in patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in RAS wild-type patients with EGFR antibodies [I, B].
  - Regorafenib is superior to placebo in terms of OS, although there are toxicity concerns in frail patients.
- Trifluridine/tipiracil is recommended for patients pretreated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in RAS wild-type patients with EGFR antibodies [I, B].

Empfehlung 3 (consensus recommendations on the use of cytotoxics and biologicals in the first- and subsequent-line treatment of patients with mCRCthird line)

Systemic therapy choices according to the Zurich treatment algorithm for patients with unresectable metastatic disease (excluding those with oligometastatic disease) **Siehe Anhang 1**

Salvatore L et al., 2017 [21].

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 randomis 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 causa relationship
2+	Low risk of bias and moderate probability of a caus relationship
2–	High risk of bias and significant risk that the relationship is not causal
3	Non-analytical studies, such as case reports and ca 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 directl 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

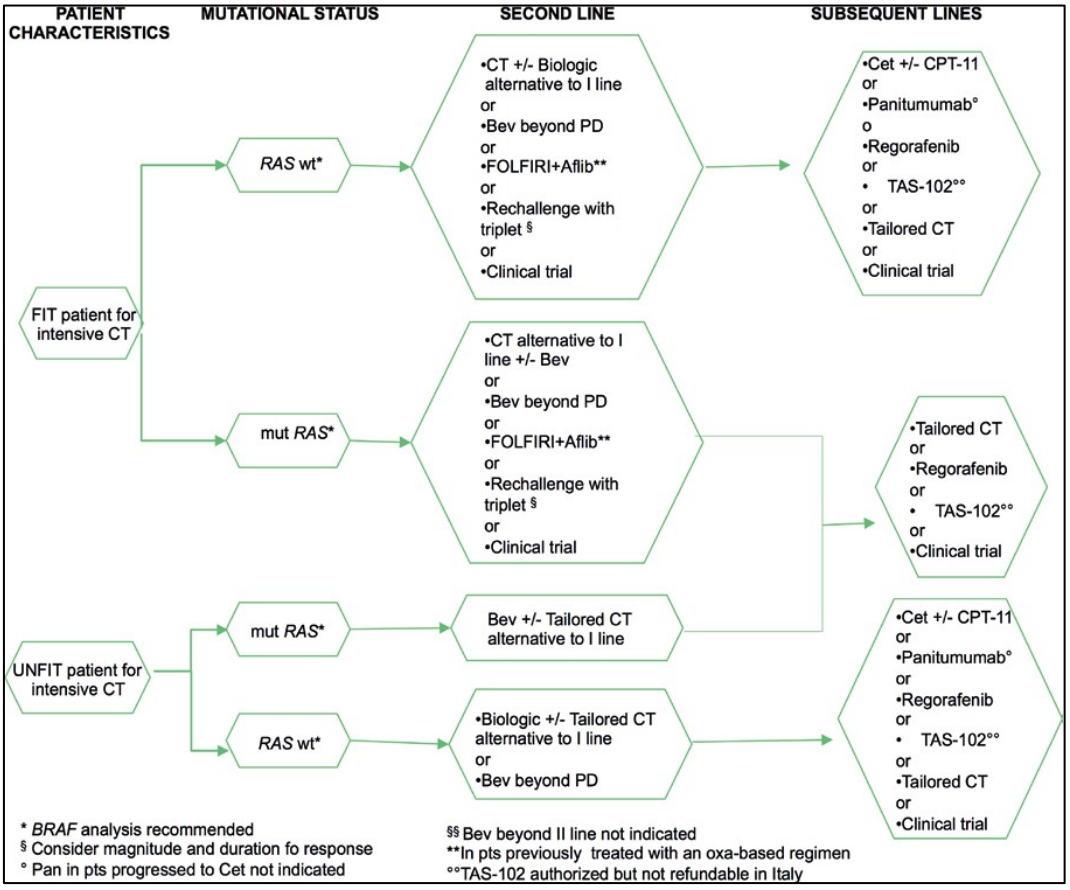

Figure 1 Algorithms for the management of metastatic colorectal cancer, subsequent lines. 5-FU, 5-fluorouracil; Aflib, aflibercept; Bev, bevacizumab; Cape, capecitabine; Cet, cetuximab; CT, chemotherapy; EGFR, epidermal growth factor receptor; FOLFIRI, 5-fluorouracil+lederfolin+irinotecan; FOLFIRI, folinic 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.

Referenzen aus Leitlinien

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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
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	Strength of recommendation
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
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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, 2018 [2].

METASTATIC COLORECTAL CANCER.

Leitlinienorganisation/Fragestellung

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

Methodik

Grundlage der Leitlinie

This guideline was reviewed and endorsed by the Alberta Provincial Gastrointestinal Tumour Team. Members of the Alberta Provincial Gastrointestinal Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, hepatologists,

gastroenterologists, interventional radiologists, nurses, nurse practitioners, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Gastrointestinal Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit. A detailed description of the methodology

followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in January 2008. This guideline was revised in March 2009, August 2009, March 2010, June 2011, October 2013, March, 2014, July 2015, and February, 2018.

SEARCH STRATEGY

This guideline was developed to outline the management recommendations for patients with metastatic colorectal cancer. It was compiled from the results of randomized controlled trials and systematic reviews, derived from an English language and relevant term search of PubMed and MEDLINE from 1990 forward. It takes into consideration related information presented at local, national, and international meetings as well as the Alberta Provincial Gastrointestinal Tumour Team's interpretation of the data. The 2017 update did not necessitate a full literature review; recommendations were modified based on a consensus discussion at the 2017 Annual Gastrointestinal Tumour Team Meeting.

TARGET POPULATION

The recommendations outlined in this guideline apply to adults over the age of 18 years with metastatic colorectal cancer. Different principles may apply to pediatric patients.

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)

Recherche/Suchzeitraum:

- 1990-2017 (Update)

LoE/GoR

- eigenes Graduierungssystem **/** Formulierungen im Text**.**

Empfehlungen

Goals of Therapy

1. To maintain or to improve the patient's quality of life (to control or to delay the onset of tumour-related symptoms).

2. To prolong life, if possible.

Recommendations

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

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

3. The location of the tumour within the colon (proximal/distal) appears to be important. A multivariate analysis of 1,437,846 patients in sixty-six trials published between 1995 and 2016 demonstrated that the location of the primary tumor site in the distal (versus proximal) colon is associated with a better survival (HR 0.82, CI95% 0.79-0.84, p < 0.001).7 Beyond outcome, differences in epidemiology, pathogenesis, genetic and epigenetic alterations, and molecular pathways are now recognized between proximal and distal primary tumor site

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

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

Regimen	Details
FOLFIRI[12]	• Involves the administration of Irinotecan (180 mg/m^2 IV) and Leucovorin (400 mg/m^2 IV) concurrently over two hours followed by 5-Fluorouracil (400 mg/m^2 IV bolus and then an IV infusion of 2,400 mg/m^2 over forty-six hours) in every two-week cycle. This regimen requires placement of a port, central venous catheter (CVC), or peripherally inserted central catheter (PICC). • For patients who have complications with, or contraindications to, placement of a port, CVC, or PICC along with the capacity to tolerate the potential for greater toxicity, consider CAPIRI (administers Irinotecan 250 mg/m^2 IV over ninety minutes followed by Capecitabine 1,000 mg/m^2 PO Q12h for fourteen days in every twenty-one day cycle). • 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. • **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. If this diagnosis is suspected, Irinotecan should be considered relatively contraindicated (or consider a dose reduction).
CAPOX[13] 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,

<table>
<tr><th>Regimen</th><th>Details</th></tr>
<tr><td></td><td>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.
• After a hypersensitivity reaction, pre-medicate patients with hydrocortisone, ranitidine, and dimenhydrinate and prolong the next Oxaliplatin infusions to four to six hours.</td></tr>
<tr><td>FOLFOXIRI[15]</td><td>• 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]</td></tr>
<tr><td>Capecitabine[16]</td><td>• Involves the administration of Capecitabine 1,250 mg/m^2 PO Q12h for fourteen days in every twenty-one day cycle. Refer to “Capecitabine: A Guide for Patient Care.”
• Supplement with Bevacizumab, where appropriate (see below).</td></tr>
<tr><td>Irinotecan[17]</td><td>• Involves the administration of Irinotecan (350 mg/m^2 IV over ninety minutes) in every three-week cycle.
• Decrease the dose by 20% for patients over seventy years of age or for patients who have received prior radiotherapy to the pelvis.
• 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. If this diagnosis is suspected, Irinotecan should be considered relatively contraindicated (or consider a dose reduction).</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[19-21]</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;
· 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;</td></tr>
</table>

<table>
<tr><th>Regimen</th><th>Details</th></tr>
<tr><td></td><td>· Non-healing wound, ulcer, or bone fracture;
· Metastases within central nervous system or ophthalmologic abnormalities; and
· Pregnancy, lactation, or childbearing potential without effective contraception.
• If the medical oncologist feels the benefits outweigh the risks, it may be combined with chemotherapy in patients with a good performance status (ECOG ≤2). It can be administered over ten minutes at 5 mg/kg IV (Q2week chemotherapy schedule) or over fifteen minutes at 7.5 mg/kg IV (Q3week chemotherapy schedule).
<table>
<tr><th rowspan="2">Toxicities</th><th colspan="2">Summary Incidence</th><th colspan="2">Relative Risk</th></tr>
<tr><th>All-Grade Events</th><th>High-Grade Events</th><th>All-Grade Events</th><th>High-Grade Events</th></tr>
<tr><td>Arterial Thromboembolic Events[19]
Cardiac Ischemia
Cerebrovascular Ischemia</td><td>3.3%</td><td>2.0%
1.5%
1.2%</td><td>HR 2.08</td><td>HR 1.29
HR 2.14
HR 1.37</td></tr>
<tr><td>Proteinuria[22]</td><td>—</td><td>1.0%</td><td>HR 1.40</td><td>—</td></tr>
<tr><td>Hypertension[22]</td><td>—</td><td>8.7%</td><td>—</td><td>HR 3.00</td></tr>
<tr><td>Wound Healing Complications[20,21,23]</td><td>4.9%</td><td>3.7%</td><td>—</td><td>—</td></tr>
<tr><td>Gastrointestinal Perforation[24]</td><td>—</td><td>0.9%</td><td>—</td><td>HR 2.15</td></tr>
</table>
• Discrepant results exist as to the risk of venous thromboembolic events.[25,26]
• It is not indicated for monotherapy and it is currently not funded by the Alberta Health Services Cancer Drug Benefit Program for treatment beyond progression.
• Refer to the Bevacizumab Administration Guidelines.</td></tr>
<tr><td>EGFR inhibitor and chemotherapy[27,28,29]</td><td>• First-line anti-EGFR therapies may include:
a. Cetuximab with FOLFIRI[27]
b. Panitumumab with FOLFOX[28]
c. Panitumumab with FOLFIRI (based on extrapolation from data in second-line treatment)[29]
• EGFR inhibitors should not be given with bevacizumab as clinical trials with combinations of both EGFR inhibitor and bevacizumab give worse outcome. [30,31]
• Refer to Panitumumab and Cetuximab: Toxicity Management Guidelines</td></tr>
</table>

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/m2 IV loading dose followed by 250 mg/m2 IV weekly maintenance prolongs median overall survival from 4.8 months to 9.5 months (p < 0.0001, HR 0.55, CI95% 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*).

7. The presence of a BRAF mutation is associated with a poor prognosis and the use of an EGFR inhibitor in the first line setting, in combination with chemotherapy is unlikely to be beneficial. After progression on an irinotecan and an oxaliplatin based regimen, there is insufficient evidence to suggest that a BRAF mutation is a predictive marker and participation in clinical trials is encouraged.[36]

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.[37] See Appendix: "Approach to Metastatic Colorectal Cancer."

10. Patients who have progressed on all standard therapy can receive regorafenib as a fourth-line therapy. 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%).

- **a.** Note: Regorafenib is currently not funded by the Alberta Health Services Outpatient Cancer Drug Benefit Program; however, an application for funding to the Alberta Health Services Cancer Drug Evaluation Committee is forthcoming.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 3 of 12) am 05.03.2019

#	Suchfrage
1	[mh colorectal neoplasms/therapy]
2	(colon:ti,ab,kw OR colorectal:ti,ab,kw OR rectal:ti,ab,kw)
3	(cancer*:ti,ab,kw OR tum*r*:ti,ab,kw OR carcinoma*:ti,ab,kw OR neoplas*:ti,ab,kw OR adenocarcinoma*:ti,ab,kw OR sarcoma*:ti,ab,kw OR lesion*:ti,ab,kw)
4	#2 AND #3
5	#1 OR #4
6	#5 AND with Cochrane Library publication date from Mar 2014 to Mar 2019

Systematic Reviews in Medline (PubMed) am 05.03.2019

#	Suchfrage
1	colorectal neoplasms/therapy[mh]
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] OR lesion*[tiab])
4	#2 AND #3
5	#1 OR #4
6	(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])
7	#5 AND #6
8	neoplasm metastasis[mh]
9	(advanced[tiab] OR metastat*[tiab] OR metastas*[tiab] OR recurren*[tiab] OR unresectab*[tiab])
10	#8 OR #9
11	#7 AND #10
12	(#11) AND ((Meta-Analysis[ptyp] 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 systematic 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 (systematic review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation studies[pt] OR validation studies[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]))))
13	((#12) AND ("2014/03/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
14	(#13) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 07.03.2019

#	Suchfrage
1	colorectal neoplasms/therapy[mh]
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] OR lesion*[tiab])
4	#2 AND #3
5	#1 OR #4
6	(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])
7	#5 AND #6
8	(#7) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
9	(((#8) AND ("2014/03/01"[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]))
10	(#9) NOT retracted publication[ptyp]

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Anhang 1

Table 7. Systemic therapy choices according to the Zurich treatment algorithm for patients with unresectable metastatic disease (excluding those with oligometastatic disease)[a]

Category	Fit patients[b]					Unfit[b]	
						May be unfit	Unfit
Treatment goal	Cytoreduction (tumour shrinkage)		Disease control (control of progression)			Palliation	
Molecular profile	*RAS* wt	*RAS* mt	*BRAF* mt	*RAS* wt	*RAS* mt	*BRAF* mt	Any	Any
First-line								
Preferred choice (s)	CT doublet + EGFR antibody[c,d]	CT doublet + bevacizumab	FOLFOXIRI + bevacizumab	CT doublet + bevacizumab or CT doublet + EGFR antibody[c]	CT doublet + bevacizumab	FOLFOXIRI ± bevacizumab	FP + bevacizumab	BSC
Second choice	FOLFOXIRI ± bevacizumab	FOLFOXIRI + bevacizumab	CT doublet + bevacizumab	FP + bevacizumab		CT doublet + bevacizumab	Reduced-dose CT doublet	—
Third choice	CT doublet + bevacizumab	FOLFOXIRI	FOLFOXIRI				If *RAS* wt may consider EGFR antibody therapy	—
Maintenance								
Preferred choice	FP + bevacizumab[e]	FP + bevacizumab	FP + bevacizumab	FP + bevacizumab[e]	FP + bevacizumab	FP + bevacizumab	FP + bevacizumab	—
Second choice	Pause	Pause	Pause	Pause	Pause	Pause	FP	—
Second line								
Preferred choice(s)	CT doublet + bevacizumab	CT doublet + bevacizumab	CT doublet + bevacizumab	CT doublet + bevacizumab or CT doublet + EGFR antibody	CT doublet + bevacizumab	CT doublet + bevacizumab	CT doublet + bevacizumab	—
Second choice	CT doublet + EGFR antibody[c,f] or FOLFIRI + aflibercept/ ramucirumab	FOLFIRI + aflibercept/ ramucirumab	FOLFIRI + aflibercept/ ramucirumab	FOLFIRI + aflibercept/ ramucirumab	FOLFIRI + aflibercept/ ramucirumab	FOLFIRI + aflibercept/ ramucirumab	FOLFIRI + aflibercept/ ramucirumab	.
Third line								
Preferred choice (s)	CT doublet + EGFR antibody[c,f] or irinotecan + cetuximab[f]	Regorafenib or trifluridine/ tipiracil	Regorafenib or trifluridine/ tipiracil	CT doublet + EGFR antibody[c] or irinotecan + cetuximab	Regorafenib or trifluridine/tipiracil	Regorafenib or trifluridine/tipiracil	Regorafenib or trifluridine/tipiracil	—
Second choice	EGFR antibody monotherapy[f]			EGFR antibody monotherapy[f]				—
Third choice	Regorafenib or trifluridine/ tipiracil			Regorafenib or trifluridine/ tipiracil				—

BSC, best supportive care; CT, chemotherapy; EGFR, epidermal growth factor receptor; FP, fluoropyrimidine; FOLFOXIRI, infusional 5-fluorouracil, leucovorin, irinotecan and oxaliplatin; mt, mutant; wt, wild-type.

[a]Cross references to Figure 4.

[b]Patients assessed as fit or unfit according to medical condition not due to malignant disease.

[c]EGFR antibodies: cetuximab and panitumumab.

[d]In patients in need of a rapid reduction in tumour burden because of impending clinical threat, impending organ dysfunction and severe disease-related symptoms, a similar strategy can be proposed, although the consensus on the preferred treatment of choice was less strong. For those patients who have *RAS* wild-type disease, a cytotoxic doublet plus an EGFR antibody is a preferred option, although a cytotoxic doublet plus bevacizumab is an equally valid alternative. A cytotoxic triplet plus or minus bevacizumab may be an alternative for selected, very fit and motivated patients.

[e]In patients where a bevacizumab-containing regimen was started. In patients where a cetuximab-containing combination was started: pause or less intensive regimen.

[f]If not yet pretreated with an EGFR antibody.

Abbildung 1: Systemic therapy choices according to the Zurich treatment algorithm for patients with unresectable metastatic disease (excluding those with oligometastatic disease)