Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2015-B-001 Ramucirumab

Stand: Februar 2015

Gemeinsamer Bundesausschuss

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA **Ramucirumab** **in Kombination mit FOLFIRI zur Zweitlinien-Behandlung des metastasierten Kolorektalkarzinoms**	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	chirurgische Resektion (neoadjuvante) Radio(-Chemo)therapie Radiofrequenz-Ablation/[Hochfrequenz-]Thermoablation
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschluss vom 15. August 2013 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Aflibercept Beschluss vom 20. März 2014 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Regorafenib • Abnahme des Abschlussberichts zum Qualitätssicherungsverfahren Kolorektales Karzinom der Institution nach §137a SGB V, Beschluss vom 15.12.2011 • Abschlussbericht Beratungsverfahren nach § 137c SGB V (Krankenhausbehandlung): Protonentherapie bei Lebermetastasen, 07.04.2011 • Richtlinie Methoden Krankenhausbehandlung (Protonentherapie bei Lebermetastasen), Beschluss vom 20.01.2011 • Aufhebung der Anlage XI der Arzneimittel-Richtlinie (Abschnitt N Verordnung besonderer Arzneimittel) wegen Aufhebung des § 73d SGB V mit Inkrafttreten des AMNOG, Beschluss 20.01.2011 • Einleitung eines Stellungnahmeverfahrens zur Änderung der Arzneimittel-Richtlinie: Anlage XI– Besondere Arzneimittel nach § 73d SGB V bei der Behandlung des vorbehandelten, metastasierten

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Ramucirumab **in Kombination mit FOLFIRI zur Zweitlinien-Behandlung des metastasierten Kolorektalkarzinoms**	
Kriterien gemäß 5. Kapitel § 6 VerfO	
	Kolorektalkarzinoms: Bevacizumab, Cetuximab, Panitumumab, Beschluss vom 17.09.2009 • Richtlinien Methoden Krankenhausbehandlung (Protonentherapie beim Rektumkarzinom), Beschluss vom 18.10.2007 • Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Anlage B „Nicht anerkannte Untersuchungs- und Behandlungsmethoden“ der Richtlinie zur Bewertung medizinischer Untersuchungs- und Behandlungsmethoden (BUB-Richtlinie) – 42. Hyperthermie
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 Beratungsanforderung/Fachinformation)
Zu prüfendes Arzneimittel:	
Ramucirumab	<u>Geplantes Anwendungsgebiet laut Beratungsanforderung:</u> Ramucirumab in Kombination mit FOLFIRI zur Zweitlinien-Behandlung des metastasierten Kolorektalkarzinoms
5-Fluorouracil L01BC02 (Benda 5-FU®)	Fortgeschrittenes kolorektales Karzinom […] Bezüglich der Anwendung 5-Fluorouracil enthaltender Protokolle in Kombination mit neueren Chemotherapeutika (z. B. Oxaliplatin, Irinotecan) wird auf die Fachliteratur verwiesen. […]
Tegafur,Uracil L01BC03 (UFT®)	UFT ist indiziert zur **primären** Chemotherapie bei metastasiertem kolorektalem Karzinom, in Kombination mit Calciumfolinat.
Capecitabin L01BC06 (Xeloda®)	Zur Behandlung des metastasierten Kolorektalkarzinoms.
Calciumfolinat V03AF03 (Bendafolin®)	in Kombination mit 5-Fluorouracil in der zytotoxischen Therapie: – bei fortgeschrittenem oder metastasiertem kolorektalem Karzinom – als adjuvante Chemotherapie des Kolonkarzinoms Stadium III (T1–4 N1–2) nach vorausgegangener kurativer Resektion des Primärtumors
Mitomycin L01DC03 (generisch, z.B.	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Bei intravenöser Gabe ist es in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei folgenden metastasierenden Tumoren

Mitomycin medac)	wirksam: fortgeschrittenes kolorektales Karzinom
Oxaliplatin L01XA03 (Oxaliplatin-bendalis®)	Oxaliplatin wird in Kombination mit 5-Fluorouracil und Folinsäure angewendet – zur adjuvanten Behandlung eines Kolonkarzinoms des Stadiums III (Dukes C) nach vollständiger Entfernung des primären Tumors, – zur Behandlung des metastasierenden kolorektalen Karzinoms
Irinotecan L01XX19 (z.B. Irinotecan aries)	Irinotecan aries ist angezeigt zur Behandlung von Patienten mit fortgeschrittenem kolorektalen 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. In Kombination mit Cetuximab ist Irinotecan aries zur Behandlung von Patienten mit EGFR (epidermaler Wachstumsfaktor-Rezeptor)-expremierendem kolorektalen Karzinom nach Versagen einer Irinotecan-haltigen zytotoxischen Therapie angezeigt. In Kombination mit 5-Fluorouracil, Folinsäure und Bevacizumab wird Irinotecan aries als Erstlinientherapie bei Patienten mit metastasiertem Karzinom des Kolons oder Rektums angezeigt.
Bevacizumab L01XC07 (Avastin®)	Bevacizumab wird in Kombination mit einer Chemotherapie auf Fluoropyrimidin-Basis zur Behandlung von erwachsenen Patienten mit metastasiertem Kolon- oder Rektumkarzinom angewendet.
Cetuximab L01XC06 (Erbitux®)	zur Behandlung des metastasierenden, EGFR (epidermalen Wachstumsfaktor-Rezeptor) exprimierenden Kolorektalkarzinoms mit Wildtyp-KRAS-Gen ▪ 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.

Panitumumab L01XC08 (Vectibix®)	zur Behandlung von Patienten mit metastasiertem kolorektalem Karzinom (mCRC) mit Wildtyp-KRAS ▪ in der Erstlinientherapie in Kombination mit FOLFOX. ▪ in der **Zweitlinientherapie in Kombination mit FOLFIRI** bei Patienten, die in der Erstlinientherapie eine Fluoropyrimidinhaltige Chemotherapie erhalten haben (ausgenommen Irinotecan). ▪ als Monotherapie nach Versagen von Fluoropyrimidin-, Oxaliplatin- und Irinotecan-haltigen Chemotherapieregimen.
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®	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).

Gemeinsamer Bundesausschuss

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Indikation für die Recherche bei Wirkstoff (evtl. Markenname):

Ramucirumab in Kombination mit FOLFIRI als Zweitlinientherapie des metastasierten Kolorektalkarzinoms (mCRC)

Berücksichtigte Wirkstoffe/Therapien:

Für das Anwendungsgebiet zugelassenen Arzneimittel, s.: „Übersicht zVT, Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet; Seite 4-6“

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation „X“ durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 20.01.2015 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of

Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP. Aufgrund der onkologischen Indikation wurde zusätzlich in folgenden Datenbanken bzw. Internetseiten folgende Organisationen gesucht: CCO, ESMO, NCI. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab **1015** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden **122** Quellen eingeschlossen. Die Evidenzsynopse enthält ergänzend eine Darstellung **5** pivotaler Studien von besonderer Bedeutung. Insgesamt ergab dies **30** Quellen, die in die synoptische Evidenzübersicht aufgenommen wurden.

Abkürzungen

aCRC	advanced colorectal cancer
ASCO	American Society of Clinical Oncology
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
CAPOX	CAP = Capecitabine OX = Oxaliplatin
CCO	Cancer Care Ontario
CTCAE	Common Terminology Criteria for Adverse Events
DAHTA	Deutsche Agentur für Health Technology Assessment
EORTC	European Organization for Research and Treatment of Cancer
EGFR-I	Epidermal Growth Factor Receptor
ESMO	European Society for Medical Oncology
FOLFIRI	FOL = Folinsäure (Leucovorin) F = 5-Fluorouracil (als Dauerinfusion) IRI = Irinotecan (Campto®)
FOLFOX	FOL = Folisäure (Leucovorin) F = 5-Fluorouracil (als Dauerinfusion) OX = Oxaliplatin
G-BA	Gemeinsamer Bundesausschuss
GI	Gastrointestinal
GIN	Guidelines International Network
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HFSR	Hand-Foot Skin Reaction
HRQoL	health-related quality of life
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IROX	irinotecan plus oxaliplatin
k.A.	Keine Angabe
LV	Leucovorin
mCRC	metastatic colorectal cancer
MDT	multidisciplinary team
MRC	Medical Research Council
NCCN	National Comprehensive Cancer Network
NCI	U.S. National Cancer Institute
NCRN	National Cancer Research Network
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination

NICE	National Institute for Health and Care Excellence
PBT	Panitumumabbased-therapy
Pmab	Panitumumab
SIGN	Scottish Intercollegiate Guidelines Network
SUE	schwerwiegende unerwünschte Ereignisse
TRIP	Turn Research into Practice Database
UE	Unerwünschte Ereignisse
WHO	World Health Organization
WT	wild type
XELOX	Capecitabine plus Oxaliplatin
5-FU	Flourouracil

IQWiG Berichte/ G-BA Beschlüsse

IQWiG, 2013 [1]: Nr. 165: Aflibercept (Zaltrap) – Nutzenbewertung gemäß § 35a SGB V	**Fragestellung/Ziele:** Bewertung des Zusatznutzens von Aflibercept in Kombination mit einer Chemotherapie, bestehend aus Irinotecan/5-Fluorouracil/Folinsäure (FOLFIRI), im Vergleich zu FOLFIRI als zweckmäßiger Vergleichstherapie (Vergleich von Aflibercept + FOLFIRI mit Placebo + FOLFIRI) **Population:** Erwachsene Patienten mit metastasiertem kolorektalem Karzinom (mCRC), das unter oder nach einem Oxaliplatin-haltigen Regime fortgeschritten ist Die Behandlung – sowohl in Kombination mit Aflibercept als auch für FOLFIRI allein – erfolgte in 14-tägigen Zyklen. **Endpunkte:** Primärer Endpunkt: Gesamtüberleben/Mortalität Sekundärer Endpunkt: Nebenwirkungen, Morbidität & HRQoL **Ergebnis /Fazit:** Mortalität: Für die Behandlung mit Aflibercept + FOLFIRI zeigte sich eine statistisch signifikante Verlängerung des Gesamtüberlebens gegenüber der Behandlung mit Placebo + FOLFIRI (HR = 0,82 [0,71; 0,93], p = 0,003) Nebenwirkungen: im Aflibercept-Arm jeweils statistisch signifikant höher als im Placebo-Arm. Der Effekt war unter den älteren Patienten (RR 1,88 [1,51; 2,35]) jedoch stärker ausgeprägt als unter den jüngeren (RR 1,27 [1,06; 1,52]). Zusammengefasst ergibt sich somit für mehrere Endpunkte des Komplexes „Nebenwirkungen“ *ein Hinweis auf einen größeren Schaden von Aflibercept + FOLFIRI im Vergleich zur zweckmäßigen Vergleichstherapie FOLFIRI*. Morbidität & HRQoL: keine verwertbaren Ergebnisse **Fazit:** für Patienten < 65 Jahre als auch für Patienten ≥ 65 Jahre ergeben sich positive und negative Effekte gleicher Ergebnissicherheit (Hinweis). Positiver Effekt: • Mortalität: Zusatznutzen mit dem Ausmaß „beträchtlich“ für beide Altersstrata Negativer Effekt: • schwerwiegende / schwere Nebenwirkungen (Endpunkt Abbruch wegen UEs) ein größerer Schaden mit dem Ausmaß „erheblich“ • Für mehrere Endpunkte des Komplexes „Nebenwirkungen“ zeigt sich *ein Hinweis auf einen größeren Schaden von Aflibercept + FOLFIRI im Vergleich zur zweckmäßigen Vergleichstherapie FOLFIRI.*

	Zusammenfassend ergibt sich ein Hinweis auf einen *geringen Zusatznutzen* von Aflibercept + FOLFIRI gegenüber der zweckmäßigen Vergleichstherapie FOLFIRI zur Behandlung erwachsener Patienten mit mCRC, das unter oder nach einem Oxaliplatin-haltigen Regime fortgeschritten ist.
IQWiG, 2013 [2]: **Nr. 200: Regorafenib – Nutzenbewertung gemäß § 35a SGB V**	**Fragestellung/Ziele:** Bewertung des Zusatznutzens von Regorafenib im Vergleich zu best supportive care (BSC) als zweckmäßiger Vergleichstherapie (Vergleich von Regorafenib + BSC mit Placebo + BSC) **Population:** Patienten mit metastasiertem Kolorektalkarzinom (mCRC), die zuvor mit verfügbaren Therapien behandelt wurden oder die für diese nicht geeignet sind (Fluoropyrimidin-basierte Chemotherapie, eine Anti-VEGF (vascular endothelial growth factor)-Therapie und eine Anti-EGFR (epidermal growth factor receptor)-Therapie) **Endpunkte:** • Primärer Endpunkt: Gesamtüberleben/Mortalität • Sekundärer Endpunkt: mediane Behandlungsdauer, Morbidität (Symptomatik), gesundheitsbezogene Lebensqualität und unerwünschte Ereignisse (UE). **Ergebnis /Fazit:** Mortalität: inkonsistente Datenlage, da zwei unterschiedliche Datenschnitte -→ daher keine weitere Betrachtung für die Nutzenbewertung Morbidität: verfügbaren Daten nicht ausreichend → daher *kein* Zusatznutzen von Regorafenib + BSC im Vergleich zur zweckmäßigen Vergleichstherapie BSC HRQoL: Instrument = EORTC QLQ-C30 & EQ-5D → verfügbaren Daten nicht ausreichend → daher *kein* Zusatznutzen von Regorafenib + BSC im Vergleich zur zweckmäßigen Vergleichstherapie BSC Nebenwirkungen: statistisch nicht signifikant für die Endpunkte: schwerwiegende unerwünschte Ereignisse (SUE) & Therapieabbrüche; für schwere UE des CTCAE-Grades 3 = Anhaltspunkt für einen größeren Schaden von Regorafenib + BSC im Vergleich zur zweckmäßigen Vergleichstherapie BSC. Insgesamt ergibt sich ein Anhaltspunkt für einen *geringen Zusatznutzen* von Regorafenib + BSC gegenüber der zweckmäßigen Vergleichstherapie. *(Siehe zusammenfassende Tabellen zur Therapie in Anlage 1!)*
IQWiG, 2014 [3]: **Nr. 207: Addendum zum Auftrag A13-37 (Regorafenib)**	Zusammenfassend ändern weder die nachgereichten Daten des pU zum Endpunkt gesundheitsbezogene Lebensqualität noch die Ausführungen des pU zu UE mit CTCAE-Grad 1 oder 2 das Ergebnis der Nutzenbewertung A13-37. Insgesamt ergibt sich daher weiterhin ein Anhaltspunkt für einen geringen Zusatznutzen von Regorafenib

	gegenüber BSC
G-BA, 2010 [4]: Bekanntmachung eines Beschlusses des Gemeinsamen Bundesausschusses über die Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage VI – Off-Label-Use 5-Fluorouracil-haltige Arzneimittel zur adjuvanten Chemotherapie des primären invasiven Mammakarzinoms und 5-Fluorouracil-haltige Arzneimittel bei kolorektalen Karzinomen – Monotherapie	**Fazit:** In Anlage VI der Arzneimittel-Richtlinie werden im Teil A folgende Nummern gestrichen: „I. 5-Fluorouracil-haltige Arzneimittel zur adjuvanten Chemotherapie des primären invasiven Mammakarzinoms“ Und „II. 5-Fluorouracil-haltige Arzneimittel bei kolorektalen Karzinomen – Monotherapie“
G-BA, 2014 [5]: Zusammenfassende Dokumentation über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Regorafenib [Vom 20. März 2014]	Die zweckmäßige Vergleichstherapie für Regorafenib ist Best-Supportive-Care. **Fazit:** **<u>Wahrscheinlichkeit und Ausmaß des Zusatznutzens</u>** Für Patienten mit metastasiertem kolorektalem Karzinom, die zuvor mit verfügbaren Therapien behandelt wurden oder die für diese nicht geeignet sind, liegt ein Anhaltspunkt für einen *<u>geringen Zusatznutzen</u>* vor. **<u>Begründung:</u>** Der G-BA stuft das Ausmaß des Zusatznutzens von Regorafenib auf Basis der Kriterien in § 5 Absatz 7 der AM-NutzenV unter Berücksichtigung des Schweregrades der Erkrankung und des therapeutischen Ziels bei der Behandlung der Erkrankung als gering ein. Gegenüber der zweckmäßigen Vergleichstherapie handelt es sich gemäß § 5 Abs. 7 i.V.m. § 2 Abs. 3 AM-NutzenV um eine moderate und nicht nur geringfügige Verbesserung des therapierele-vanten Nutzens, da eine relevante Verlängerung der Überlebensdauer bei gleichzeitig exis-tierenden Schadensaspekten erreicht wird. **<u>Grundlage der Bewertung:</u>** Für die Bewertung des Zusatznutzens liegen die Ergebnisse der CORRECT-Studie vor (siehe auch Tabellen „Systematische Reviews“ und „Primärstudien“ in dieser Synopse).

Cochrane Reviews

Zur Fragestellung wurden keine relevanten Cochrane Reviews identifiziert.

Systematische Reviews

Nach zwei Auswahlschritten waren sieben systematische Übersichtsarbeiten bzw. HTA-Berichte für die Fragestellung relevant. In allen waren überwiegend Studien eingeschlossen, die die Population im gesuchten Anwendungsgebiet nicht betrafen. Es wurden die Ergebnisse aus den Übersichtsarbeiten extrahiert, die für die gesuchte Population von Interesse sind. Die „Anmerkungen/Fazit der Autoren“ beziehen sich jeweils auf deren gesamte Arbeit. Zum Schadenpotential wurden vier Übersichtsarbeiten eingeschlossen. Diese sind im unteren Teil der Tabelle gelistet.

Segelov E, et al. 2014 [6] **The role of biological therapy in metastatic colorectal cancer after first-line treatment: a meta-analysis of randomised trials**	1. Fragestellung Systematic meta-analysis was undertaken to determine the efficacy of biological therapy.
	2. Methodik **Population:** histologically confirmed mCRC, received at least one prior line of chemotherapy for advanced disease **Intervention:** addition of biological agent to chemotherapy (Details siehe Ergebnisdarstellung) **Komparator:** chemotherapy alone (Group 1) or addition of a second biological agent to the same chemotherapy (Group 2) (Details siehe Ergebnisdarstellung) **Endpunkt:** OS, PFS, ORR and toxicity **Suchzeitraum:** bis Mai 2012 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 20/8 225 **Qualitätsbewertung der Studien:** k.A.
	3. Ergebnisdarstellung • overall quality of the studies good • Funnel plots: relative symmetry - no significant publication bias, for all parameters except ORR 2 der 20 Studien relevant (metanalytische Ergebnisse nicht extrahiert): Study 181 (Peeters et al. 2010): Panitumumab + FOLFIRI vs. FOLFIRI, n = 597, MERGE Quality A • subsequent EGFR-I use, allowed by protocol, was reported in 31% of patients in the FOLFIRI-only arm VELOUR (Van Cutsem et al, 2012): Aflibercept + FOLFIRI vs. FOLFIRI, n = 1 226, MERGE Quality A
	4. Anmerkungen/Fazit der Autoren This systematic review has provided evidence for a class effect with the addition of targeted therapies, when considered together, improving

	OS, PFS and ORR for patients with mCRC. When analysed separately by mechanism of action and by line of therapy, results demonstrate that progress has been made in the extension of life of patients with mCRC. *5. Hinweise durch FB Med* • *Sanofi-Aventis provided financial support to WriteSource Medical Pty Ltd to undertake the literature search and paper retrieval. Sanofi-Aventis had no role in data analysis/interpretation and were not involved in writing the manuscript.*
Gill S, et al. 2014 [7] **Navigating later lines of treatment for advanced colorectal cancer - Optimizing targeted biological therapies to improve outcomes**	1. Fragestellung The purpose of this paper is to provide a systematic overview of the available phase III trial data and offer practical, evidence-based recommendations for the post-progression treatment of patients with unresectable aCRC.
	2. Methodik **Population:** previously treated, surgically unresectable aCRC **Intervention:** targeted therapies **Komparator:** k.A. **Endpunkt:** k.A. **Suchzeitraum:** to September 18, 2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 14/k.A. **Qualitätsbewertung der Studien:** nicht erwähnt

	3. Ergebnisdarstellung
	
	<u>3 der 14 Studien</u> relevant (metanalytische Ergebnisse nicht extrahiert):
	
	<u>VELOUR (</u>Van Cutsem et al.):
	
	• Aflibercept 4 mg/kg d1 q2w + FOLFIRI until PD
	  ○ n = 612
	  ○ prior bevacizumab = 30,4 %
	  ○ Median age (years) [range] = 61.0 [21–82]
	  ○ ORR (%) [95% CI] = 19,8 [16.4–23.2]
	  ○ Median PFS (months) HR [95% CI] = 6,90 0.76h [0.66–0.87]
	  ○ Median OS (months) HR [95% CI] = 13,50* 0.82h [0.71–0.94])
	• vs. Placebo and FOLFIRI until PD
	  ○ n = 614
	  ○ prior bevacizumab = 30,5 %
	  ○ Median age (years) [range] = 61.0 [19–86]
	  ○ ORR (%) [95% CI] = 11,1 [8.5–13.8]
	  ○ Median PFS (months) HR [95% CI] = 4,67

	○ Median OS (months) HR [95% CI] = 12,06*) [h] Rounded to 2 decimal places using unbiased rounding (half to even) • subgroup analysis indicated that the efficacy benefits were independent of prior bevacizumab • higher rates of grade 3 AEs with aflibercept plus FOLFIRI compared to control (83.5% vs. 62.5%, respectively) • class-specific AEs with higher incidence in the aflibercept arm: ○ grade 3 hypertension (19.3% vs. 1.5%; aflibercept plus FOLFIRI vs placebo plus FOLFIRI), ○ proteinuria (7.8% vs. 1.2%), ○ hemorrhage (3.0% vs. 1.7%), ○ arterial thromboembolic events (1.85% vs. 0.5%) ○ venous thromboembolic events (7.8% vs. 6.3%) • CT-related AEs also increased in the aflibercept arm: ○ neutropenia, diarrhea, asthenia, stomatitis, ulceration, infections, hand–foot syndrome, thrombocytopenia, complicated neutropenia <u>EAGLE</u> (Tamagawa et al., dose comparison trial): • Bevacizumab 5 mg/kg q2w + FOLFIRI[i] ○ n = 181j ○ prior bevacizumab = 100 % ○ Median age (years) = 66 ○ ORR (%) = 11.1 (p = 1.00) ○ Median PFS (months) HR [95% CI] = 6.1* 0.95 [0.75–1.21] ○ Median OS = NR • Bevacizumab 10 mg/kg q2w and FOLFIRI[i] ○ n = 187 ○ Median age (years) = 65 ○ ORR (%) = 10.7 ○ Median PFS (months) = 6.4* [i] FOLFIRI as defined below with the following adjustments: irinotecan 150 mg/m2 with L-leucovorin 200 mg/m2 [j] n = 180 for analysis of overall response rate. <u>Study 181</u> (Peeters et al. KRAS WT subgroup): • Panitumumab 6.0 mg/kg + FOLFIRI q2w until PD ○ n = 303 ○ KRAS status assessed = 100 % ○ KRAS WT = 100 % ○ Median age (years) [range] = 60 [28–84]

	○ ORR (%) [95% CI] = 36.0 [30.6–41.8] ○ Median PFS (months) HR [95% CI] = 6.7* 0.82 [0.69–0.97] ○ Median OS (months) HR [95% CI] = 14.5* 0.92 [0.78–1.10] • FOLFIRI q2w until PD ○ n = 294 ○ Median age (years) [range] = 61 [29–86] ○ ORR (%) [95% CI] = 9.8 [6.6–13.8] ○ Median PFS (months) = 4.9* ○ Median OS (months) = 12.5* * Primary endpoint
	4. Anmerkungen/Fazit der Autoren … We have presented an evidence-based framework for post-progression treatment sequencing (Fig. 4, siehe Anhang dieser Synopse), however, it remains important to develop a personalized treatment strategy, considering prior therapy and the risk vs. benefit of available options beyond first-line. Continued research aims to further clarify optimal sequencing strategies, identify new biomarkers to improve the rationale for treatment selection, as well as spur the development of novel therapeutics and new targeted agent-CT combinations for aCRC. *5. Hinweise durch FB Med* • *Funding: work supported by Hoffman-La Roche, Inc; independent medical information management firm, Kaleidoscope Strategic, assisted in data collection and analysis, administrative support, and writing; lead medical writer is named as an author according to ICMJE criteria; opinions presented in the paper represent those of the authors and not of the sponsor; none of the clinical authors were paid for writing this review; sponsor did not contribute to design, data synthesis and interpretation, or writing of the article, and has not seen the drafts or final manuscript* • *Disclosures: Sharlene Gill has received consulting honoraria from Sanofi-Aventis, Hoffmann-La Roche, Amgen and Bristol-Myers Squibb, and has received research funding from Sanofi-Aventis.* • *Scot Dowden is a consultant for Amgen, Bayer, Bristol-Myers Squibb, Celgene, Pfizer, Hoffmann-La Roche and Sanofi-Aventis, and is on the speaker bureaus for Amgen, Bayer, Celgene, Pfizer, Hoffmann-La Roche and Sanofi-Aventis.* • *Bruce Colwell has received honoraria from Hoffmann-La Roche, Sanofi-Aventis, Bristol-Myers Squibb, Novartis and Celgene, and has received research funding from Novartis.*

	• *Loretta Collins has received research funding from Hoffmann-La Roche.* • *Scott Berry has received consultant honoraria from Amgen, Bayer, Hoffmann-La Roche and Sanofi-Aventis.*
Kirstein MM, et al. 2014 [8] **Targeted therapies in metastatic colorectal cancer: a systematic review and assessment of currently available data**	1. Fragestellung In this review, we summarize the efficacy of the currently approved targeted therapies bevacizumab, cetuximab, panitumumab, aflibercept, and regorafenib in mCRC. Based on the available phase II and phase III trials, as well as meta-analyses and systematic reviews, we will assess and elucidate their eligibility in clinical practice.
	2. Methodik **Population:** mCRC **Intervention:** with targeted therapy (bevacizumab, aflibercept, regorafenib, anti-EGFR-therapy) **Komparator:** without targeted therapy **Endpunkte:** k.A. **Suchzeitraum:** bis 2014 **Anzahl eingeschlossene Studien (Gesamt):** 24 RCTs, 2 long-term survival analyses, 7 reviews/meta-analyses, 7 pooled, updated, or subgroup analyses of the included randomized controlled trials **Qualitätsbewertung der Studien:** Checklists of the Scottish Intercollegiate Guidelines Network (SIGN) used
	3. Ergebnisdarstellung (nur aus Phase III Studien mit relevanten Arzneimitteln) **Bevacizumab** ML18147 trial (Bennouna, 2013): continuation of bevacizumab after progression in first-line therapy, choice between oxaliplatin-based or irinotecan-based second-line chemotherapy depended on first-line regimen (switch of chemotherapy (assessed as very well conducted) • FOLFOX, FOLFIRI, CAPOX, capecitabine with irinotecan evaluated with bevacizumab o n = 411 o OS (months) = 11,2 o PFS (month) = 5,7 • FOLFOX, FOLFIRI, CAPOX, capecitabine with irinotecan evaluated without bevacizumab o n = 409 o OS (months) = 9,8 o PFS (month) = 4,1 • OS (HR 0,81; p = 0,0062) and PFS (HR 0,68; p < 0,001) significantly improved **Aflibercept** VELOUR (Van Cutsem et al.): siehe Gill S, et al. 2014

	• assessed as very well conducted
	• no crossover allowed
	Regorafenib
	CORRECT trial (Grothey, 2013): last-line therapy in patients with chemorefractory mCRC (assessed as very well conducted)
	• regorafenib
	  ○ n = 505
	  ○ OS 6,4 month
	• Placebo
	  ○ n = 255
	  ○ OS 5,0 month
	• no crossover allowed
	• Regorafenib significantly improved primary endpoint OS (HR 0,77; p = 0,0052) and secondary endpoint PFS (HR 0,49; p < 0,0001)
	Panitumumab
	Study 181 (Peeters et al. 2010 und 2014): 1 186 patients prospectively analyzed for KRAS mutations in exon 2 → 597 (55 %) KRAS WT/486 (45 %) KRAS mut. (assessed as very well conducted)
	• Panitumumab significantly improved PFS and RR in patients with KRAS WT tumors
	• OS non significantly improved

	4. Anmerkungen/Fazit der Autoren Among various therapeutic options, the future challenge will be a better selection of the population that will benefit the most from specific anti-VEGF or anti- EGFR treatment and a careful consideration of therapy sequence. *5. Hinweise durch FB Med* • *DISCLOSURES: Stefan Kubicka: Roche, Amgen, Merck, Sanofi, Bayer (Honoraria received); Roche, Amgen, Merck, Bayer (Consulting/advisory relationship); Roche (other); Arndt Vogel: Roche, Bayer, Merck (H); Roche, Bayer, Amgen (Consulting/advisory relationship); Roche, Bayer (other). The other authors indicated no financial relationships.* • *No funding information*
Tang N-P, et al. 2014 [9] **Risk/benefit profile of panitumumab-based therapy in patients with metastatic colorectal cancer: evidence from five randomized trials**	1. 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.
	2. Methodik

	Population: patients with mCRC **Intervention:** panitumumab **Kompatrator:** k.A. **Endpunkte:** overall survival (OS), progression-free survival (PFS) and AEs **Suchzeitraum:** last search updated to March 2014 Anzahl eingeschlossene Studien (Gesamt): 5 RCTs/4 155 **Qualitätsbewertung der Studien:** using the quantitative 5-point Jadad scale
	3. Ergebnisdarstellung *(1 der 5 Studien relevant (metanalytische Ergebnisse nicht extrahiert):* Study 181 (Peeters et al. 2010): siehe auch Segelov, Gill, Kirstein • any events grade ≥3 in TA (Pmab+FOLFIRI) vs. CA (FOLFIRI): 219 (73 %) vs. 152 (52 %) • Jadad Score: 3
	4. Anmerkungen/Fazit der Autoren When used in the subsequent-line setting, PBT can improve the disease progression, especially in mCRC patients with wild-type KRAS. Regarding the adverse events associated with the PBT, close monitoring and necessary preparations are recommended during the therapy. *5. Hinweise durch FB Med* • *work supported by grants from Major Projects Foundation of the National Science and Technology of China (No. 2012ZX09302002 and No. 2012ZX09505001-003), the National Natural Science Foundation of China (no. 81273603), and the Shanghai Rising-Star Program (14QB1400400)* • *Conflicts of interest None*
Vale CL, et al. 2012 [10] **Does anti-EGFR therapy improve outcome in advanced colorectal cancer? A systematic review an meta-analysis**	1. Fragestellung We aimed to provide a comprehensive, unbiased synthesis of the effects of anti-EGFR MAbs for aCRC and to compare the effects of treatment in patients expressing WT KRAS with those expressing mutant KRAS oncogenes.
	2. Methodik **Population:** patients of any age with aCRC **Intervention:** anti-EGFR MAbs either alone, or combined with chemotherapy **Komperator:** the same standard treatment alone **Endpunkte:** k.A. **Suchzeitraum:** k.A. (“All methods were pre-specified in a protocol (available on request).”) **Anzahl eingeschlossene Studien:** 8/k.A. (“only one trial of second

	line treatment“) **Qualitätsbewertung:** The risk of bias of individual trials was assessed in terms of the randomisation sequence generation, allocation concealment, availability of complete outcome data or evidence of selective outcome reporting (Cochrane handbook for systematic reviews of Interventions)
	3. Ergebnisdarstellung (nur second line trials comparing chemotherapy ± anti-EGFR MAb) Study 181 (Peeters M, etal. 2010): siehe auch siehe auch Segelov, Gill, Kirstein, Tang • Patients randomized (n): 1 186 • Patients with known KRAS status (% KRAS WT): 1 083 (55%) • Sex (% male): 61% • Performance status 0–1 (%): 94% • Liver only metastases (%): 17% • Chemotherapy (dose per cycle): IRI 180 mg/m2, 5FU 400 mg/m2 bolus + 2400 mg/m2 infusion, LV 400 mg/m2 (or 200 mg/m2 l-leucovorin) • CT cycle length (weeks): 2 Discussion Our findings in the second line setting, are currently limited to the results of a single trial. Final results from one further study of anti-EGFR MAb combined with chemotherapy are as yet unreported.[14] However, it closed early due to poor recruitment and is underpowered to detect differences in survival or progression-free survival. Consequently, it is likely to have only minimal impact on the results of this analysis. 14. Venook A, Niedzwiecki D, Hollis D, et al. Phase III study of irinotecan/5FU/LV (FOLFIRI) or oxaliplatin/5FU/LV (FOLFOX) ± cetuximab for patients with untreated metastatic adenocarcinoma of the colon or rectum (MCRC): CALGB 80203 preliminary results. J Clin Oncol 2006;24(18S):3509.
	4. Anmerkungen/Fazit der Autoren For aCRC patients with WT KRAS, there are clear benefits of anti-EGFR MAbs in the third line and in the first and second line, when used alongside infusional 5FU-based regimens. However, there is no benefit for patients with KRAS mutations. *5. Hinweise durch FB Med* • *The UK Medical Research Council (MRC) funded this research. It had no input in writing this manuscript or in the decision to submit this work for publication.* • *None of the authors have reported financial conflicts of interest in relation to this submission. RAA received consultancy fees, speakers payments and travel expenses from both Roche and Merck Serono in relation to activities outside this submission. TM received grants for his institution from Cancer Research UK, Merck*

	Serono and Immatics, as well as personal payments for consultancy, travel and speakers payments from Merck Serono relating to the MRC COIN trial as well as in relation to activities outside this submission.
Petrelli F, et al. 2011 [11] **Cetuximab und panitumumab in KRAS wild-type colorectal cancer: a meta-analysis**	1. Fragestellung Evaluate the real effects of C and P in KRAS wild-type patients treated in randomized trials
	2. Methodik **Intervention:** combined chemotherapy (or best supportive care) **Komparator**: with or without cetuximab or panitumumab in advanced CRC **Endpunkt:** k.A. **Suchzeitraum:** Pubmed and ASCO articles published up to August 2010 • eligibility by the following criteria: (1) patients with advanced CRC; (2) combined chemotherapy (or best supportive care) with vs. without cetuximab or panitumumab and not confounded by additional biologic agents or interventions (i.e., in combination chemotherapy, control, and experimental arms had to differ only by monoclonal antibody component); (3) RCT; and (4) analysis of the outcome and the efficacy of the treatment restricted to the WT population only • Anzahl eingeschlossene Studien/Patienten (Gesamt): 7/k.A. (nur 2 Phase III) **Qualitätsbewertung der Studien:** keine Angaben
	3. Ergebnisdarstellung 2 der 7 Studien relevant (siehe Studie 181 (Peeters, 2010) & VELOUR (van Cutsem, 2012), metaanalytische Ergebnisse nicht extrahiert) Die Informationen zu diesen Studien gehen nicht über jene aus den oben zitierten hinaus (siehe auch siehe auch Segelov, Gill, Kirstein, Tang, Vale).
	4. Anmerkungen/Fazit der Autoren The addition of anti-EGFR monoclonal antibodies to standard anticancer therapy in KRAS wild-type colorectal cancer showed an overall significantly increased risk of objective response rate and increased progressionfree and overall survival. Only the results achieved in randomized trials are significant, and the strongest results have been achieved in pretreated patients.
Qi WX, et al. 2014 [12] **Risk of Hypertension in Cancer Patients Treated with**	1. Fragestellung Determine the overall incidence and risk of hypertension associated with aflibercept in cancer patients.

Aflibercept: A Systematic Review and Meta-Analysis	2. Methodik **Intervention:** k.A. **Komparator**: k.A. **Endpunkt:** Hypertension **Suchzeitraum:** We searched the PubMed (data from 2000 to August 2013), EMBASE (data from 2000 to August 2013), and the Cochrane Library electronic databases • eligibility by the following criteria: (1) prospective phase II and III clinical trials in cancer patients; (2) participants assigned to treatment with aflibercept at 4 or 6 mg/kg; and (3) data available regarding incidence of hypertension. If multiple publications of the same trial were retrieved or if there was a case mix among publications, only the most recent publication (and the most informative) was included. *Anzahl eingeschlossene Studien/Patienten (Gesamt): 15/4.451 (13 Artikel & 2 Abstracts)* **Qualitätsbewertung der Studien:** k.A.
	3. Ergebnisdarstellung 1 von 15 Studien für die Fragestellung relevant (VELOUR. 2012), metaanalytische Ergebnisse nicht extrahiert • Studienergebnisse zu Hypertonie als Nebenwirkung (siehe Tabelle “Primärstudien” in dieser Synopse)
	4. Anmerkungen/Fazit der Autoren The use of aflibercept is associated with a significantly increased risk of developing all-grade and high-grade hypertension compared with control. Close monitoring and adequate managements are highly recommended to decrease cardiovascular complication.
Qi WX, et al. 2014 [13] **Risk of gastrointestinal perforation in cancer patients treated with aflibercept: a systematic review and meta-analysis**	1. Fragestellung Investigate the incidence and risk of Gastrointestinal (GI) perforation in patients treated with aflibercept.
	2. Methodik **Intervention:** k.A. **Komparator**: k.A. **Endpunkt:** Gastrointestinal (GI) perforation **Suchzeitraum:** PubMed (data from 2000 to Jan 2014), Embase (data from 2000 to Jan 2014), and the Cochrane Library electronic database; searched abstracts containing the term “aflibercept” that were presented at the American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) annual meetings from 2004 to 2014 to identify relevant studies; searched the clinical trial registration website

	(http://www.ClinicalTrials.gov) to obtain information on the registered prospective trials • eligibility by the following criteria: (1) prospective phase 2 or 3 trials involving cancer patients; (2) participants assigned to treatment with aflibercept at 4 mg/kg or 6 mg/kg (alone or in combination); and (3) available data regarding events or incidence of GI perforation and sample size. *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 8/4.101 (4 Phase II & 4 Phase III) **Qualitätsbewertung der Studien:** k.A.
	3. Ergebnisdarstellung 1 von 15 Studien für die Fragestellung relevant (VELOUR. 2012), metaanalytische Ergebnisse nicht extrahiert • Studienergebnisse zu „GI perforation“ als Nebenwirkung (siehe Tabelle “Primärstudien” in dieser Synopse) The incidence of GI perforation ranged between 0.5 and 10.0 %, with the lowest in a prospective clinical trial in patients with metastatic CRC (Van Cutsem et al. (2012).
	4. Anmerkungen/Fazit der Autoren The use of aflibercept is associated with a significantly increased risk of GI perforation compared to controls.
Dai F, et al. 2013 [14] **Safety of Bevacizumab in Treating Metastatic Colorectal Cancer: A Systematic Review and Meta-analysis of All Randomized Clinical Trials**	1. Fragestellung Investigating use of bevacizumab in the treatment of mCRC to better understand the relative risks (RRs) of adverse drug effects.
	2. Methodik **Intervention:** k.A. **Komparator**: k.A. **Endpunkt:** *Primärer E.:* ‘any grade AE’ *Sekundärer E.:* endpoints—individual AEs—included 12 items and 5 grades, which were analyzed separately, such as any thrombotic event (venous or arterial), proteinuria, hypertension, any bleeding event, GI haemorrhage/perforation, diarrhoea, leucopoenia, epistaxis, neutropenia, asthenia and death related to an adverse event **Suchzeitraum:** Relevant studies were identified and selected by searching databases including PubMed (updated to Aug 2013), Ovid, MEDLINE, Cochrane Library databases (from 1990 to Aug 2013) and Chinese Biomedicine databases • eligibility by the following criteria: We selected all trials that evaluated bevacizumab alone or with chemotherapy, as compared with chemotherapy or placebo, for mCRC patients. reported the primary endpoint or at least one of the secondary

	endpoints were included, and all RCTs could be downloaded with full text. **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 15/k.A. (10 Phase III) **Qualitätsbewertung der Studien:** k.A.
	3. Ergebnisdarstellung 1 von 15 Studien für die Fragestellung relevant (ML18147 trial. 2013), metaanalytische Ergebnisse nicht extrahiert) • Studienergebnisse zu Nebenwirkungen (siehe Tabelle "Primärstudien" in dieser Synopse)
	4. Anmerkungen/Fazit der Autoren Bevacizumab has efficacy in all treatment regimens for advanced CRC. However, our meta-analysis raises safety concerns regarding an increased risk of serious adverse events associated with use of bevacizumab among patients with mCRC. Our findings warrant cautious use of bevacizumab in clinical oncology.
Belum VR, et al. 2013 [15] **Risk of hand-foot skin reaction with the novel multikinase inhibitor regorafenib: a meta-analysis**	1. Fragestellung Investigate the overall incidence and risk of developing HFSR (hand-foot skin reaction) in patients receiving regorafenib.
	2. Methodik **Intervention:** k.A. **Komparator**: k.A. **Endpunkt:** HFSR (hand-foot skin reaction) **Suchzeitraum:** Medical Literature Analysis and Retrieval System Online (U.S. National Library of Medicine's life science database; MEDLINE), SciVerse Scopus, Thomson-Reuters' Web of Science, American Society of Clinical Oncology (ASCO) meetings' abstracts (bis Januar 2013) **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 5/1 078 **Qualitätsbewertung der Studien:** k.A.
	3. Ergebnisdarstellung 1 von 5 Studien für die Fragestellung relevant (Grothey et al. 2013 = CORRECT-Studie) • Studienergebnisse zum HFSR (siehe Tabelle "Primärstudien" in dieser Synopse) The lowest incidence of HSFR was noted in a randomized, multicenter, placebo-controlled phase III trial of 500mCRC patients treated with regorafenib (Grothey et al. 2013)
	4. Anmerkungen/Fazit der Autoren The incidence and risk of development of HFSR with regorafenib is

	high, and may vary significantly with tumor type. Knowledge of this is important for patient counseling and clinical trial development, to ensure adherence and maximize clinical outcomes.

Leitlinien

Benson AB. et al, 2015 [16,17] **National Comprehensive Cancer Network (NCCN)** Rectal Cancer. Version 2.2015 and Colorectal Cancer. Version 2.2015	Fragestellunge(n) k.A.
	Methodik <u>Grundlage der Leitlinie:</u> Allgemeiner NCCN-Methodenreport beschreibt systematische Evidenzaufbereitung mit Konsensusprozessen - ob formalisierte Verfahren angewendet werden ist unklar – Update: jährlich – Suchzeitraum: Juli 2013 bis Juli 2014 – *Weitere Kriterien für die Qualität einer LL:* • *Repräsenativität des Gremiums unklar* • *industriefinanziert* • *Interessenkonflikte unklar (Link zu „NCCN Guideline Panel Disclosures“ nur über passwortgeschützten Zugang aktivierbar)* • *Empfehlungen nicht hervorgehoben* • *Empfehlungen, Algorithmen und Literatur nicht eindeutig miteinander verknüpft* LoE/GoR: eigenes Graduierungssystem (siehe Anlage dieser Synopse) Weitere methodische Hinweise: Für detaillierte Informationen zur systemischen Zweitlinientherapie wird in der Leitlinie „Rectal Cancer“ auf die Ausführungen in der Leitlinie „Colorectal Cancer“ verwiesen.
	Freitext/Empfehlungen/Hinweise All Recommendations are category 2A unless otherwise noted. <u>Rectal Cancer: Chemotherapy for advanced or metastatic disease</u> • current management involves various active drugs (combinations, or as single drugs): 5 FU/LV, capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab, panitumumab, ziv.aflibercept, regorafenib • choice of therapy based on considerations of goals of therapy, type and timing of prior therapy, efficacy and toxicity profiles of the constituent drugs • specific chemotherapy regimens designated according to whether they pertain to initial therapy or therapy after first, second or third progression • recommendations represent a continuum of care • lines of treatment are blurred rather than discrete <u>Colorectal Cancer: Chemotherapy for advanced or metastatic disease –</u>

	Therapy After Progression The recommended therapy options after first progression for patients who have received prior 5-FU/LV-based or capecitabine-based therapy are dependent on the initial treatment regimen. • FOLFOX, CapeOX → FOLFORI, irinotecan alone or +cetuximab or +panitumumab (WT KRAS/NRAS only), +bevacizumab, +ziv-aflibercept • FOLFORI → FOLFOX, CapeOX alone or +bevacizumab, +cetuximab or +panitumumab plus irinotecan, or single-agent cetuximab or panitumumab (for those not appropriate for the combination) • 5-FU/LV, capecitabine, irinotecan →FOLFOX, Cape OX, FOLFORI, single-agent irinotecan, or IROX, varyingly combined with bevacizumab or ziv-aflibercept • FOLFOXIRI → cetuximab or panitumumab plus irinotecan, cetuximab or panitumumab alone for those with WT KRAS/NRAS Use of single-agent bevacizumab is not recommended because it was shown to have inferior efficacy compared with the FOLFOX alone or FOLFOX + bevacizumab treatment arms. For patients with wild-type KRAS/NRAS progressing on therapies that did contain an EGFR-inhibitor, administration of an EGFR inhibitor is not recommended in subsequent lines of therapy. No data support switching to either cetuximab or panitumumab after failure of the other drug, and the panel recommends against this practice. If the patient does not experience response to oxaliplatin, irinotecan, and an EGFR inhibitor, the panel recommends best supportive care or enrolment in a clinical trial. The panel added regorafenib as an additional line of therapy for patients with metastatic colorectal cancer refractory to chemotherapy.
NICE, 2014 [18] Colorectal cancer: the diagnosis and management of colorectal cancer	Fragestellunge(n) In patients with colorectal cancer presenting with overt synchronous metastatic disease, what is the effectiveness of treating metastatic disease before, after or at the same time as treating the primary tumour? What is the effectiveness of oxaliplatin and irinotecan-based chemotherapy regimens for patients with advanced and metastatic colorectal cancer? What is the most effective additional treatment to systemic chemotherapy to achieve cure or long term survival in patients with apparently unresectable metastatic disease?
	Methodik

	Grundlage der Leitlinie: The basic steps in the process of developing a guideline are listed and discussed below: – using the remit, define the scope which sets the inclusion/exclusion criteria of the guideline – forming the GDG – developing clinical questions – developing the review protocol – systematically searching for the evidence – critically appraising the evidence – incorporating health economic evidence – distilling and synthesising the evidence and writing recommendations – agreeing the recommendations – structuring and writing the guideline – updating the guideline (siehe Addendum zur LL). Suchzeitraum: bis 2012 LoE/GoR: Anwendung von GRADE oder NICE methodology checklist for randomised trials/ “To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations.“ Sonstige methodische Hinweise Für die Indikation relevante Empfehlungen entsprechen der Version von 2011 und wurden im Jahr 2012 auf Aktualisierungsbedarf hin geprüft („NICE’s routine surveillance programme“). Im Ergebnis haben sie weiter Bestand. Für die Indikation relevante Empfehlungen zur Chemotherapie basieren auf einer „mixed or indirect treatment comparison“. Daher fand GRADE keine Anwendung. Empfehlungen sind direkt mit Literaturstellen verknüpft (siehe unten).
	Freitext/Empfehlungen/Hinweise **4.1 Management of patients presenting in stage IV** Recommendations Prioritise treatment to control symptoms if at any point the patient has symptoms from the primary tumour. If both primary and metastatic tumours are considered resectable, anatomical site-specific MDTs should consider initial systemic treatment followed by surgery, after full discussion with the patient. The decision on whether the operations are done at the same time or separately should be made by the anatomical site-specific MDTs in consultation with the patient. **4.4 Chemotherapy for advanced and metastatic colorectal cancer**

4.4.1 Oxaliplatin and irinotecan in combination with fluoropyrimidines

Recommendations

When offering multiple chemotherapy drugs to patients with advanced and metastatic colorectal cancer consider one of the following sequences of chemotherapy unless they are contraindicated:

- FOLFOX (folinic acid plus fluorouracil plus oxaliplatin) as first-line treatment then single agent irinotecan as second-line treatment or
- FOLFOX as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan15) as second-line treatment or
- XELOX (capecitabine plus oxaliplatin) as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan) as second-line treatment.

Decide which combination and sequence of chemotherapy to use after full discussion of the side effects and the patient's preferences.

Quellen:

The assessment showed that in almost all aspects the individual studies were of a high standard methodologically.

Rothenberg ML, et al (2008) Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/folinic acid plus oxaliplatin (FOLFOX-4) as second line therapy in metastatic colorectal cancer: a randomised phase III noninferiority study. Annals of Oncology 19(10):1720-6

Kim GP, et al (2009) Phase III noninferiority trial comparing irinotecan with oxaliplatin, fluorouracil and leucovorin in patients with advanced colorectal carcinoma previously treated with fluorouracil: N9841. Journal of Clinical Oncology 27(17):2848-2854

Rougier P, et al (1998) Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *Lancet* 352(9138):1407-1412

Haller DG, et al (2008) Oxaliplatin plus irinotecan compared with irinotecan alone as second line treatment after single agent fluoropyrimidine therapy for metastatic colorectal carcinoma. *Journal of Clinical Oncology* 26(28):4544-4550

Tournigand C, et al (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomised GERCOR study. *Journal of Clinical Oncology* 22(15):229-237

Koopman M, et al (2007) Sequential versus combination chemotherapy with Capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. *Lancet* 370(9582):135-142

Porschen R, et al; AIO Colorectal Study Group (2007) Phase III study of capecitabine plus oxaliplatin compared with fluorouracil and leucovorin plus oxaliplatin in metastatic colorectal cancer: A final report of the AIO colorectal study group. *Journal of Clinical Oncology* 25(27):4217-4223

Cunningham D, et al (2009) Two different first line 5 fluorouracil regimens with or without oxaliplatin in patients with metastatic colorectal cancer *Annals of Oncology* 20:244-250

4.5 Biological agents in metastatic colorectal cancer

Recommendations on „Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of monastic colorectal cancer" can be found in NICE technology appraisal guidance 212 (siehe "Ergänzende Dokumente" in dieser Synopse).

NICE"s advice on the use of „Cetuximab for the treatment of metastatic colorectal cancer following failure of oxaliplatin-containing chemotherapy

	(terminated appraisal)" can be found at http://guidance.nice.org.uk/TA150. - This appraisal has been updated and replaced by NICE technology appraisal guidance 242 (siehe "Ergänzende Dokumente" in dieser Synopse). Recommendations on the use of „Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer" can be found in NICE technology appraisal guidance 118 (siehe "Ergänzende Dokumente" in dieser Synopse). **4.6 Adjuncts to chemotherapy in unresectable metastatic disease** A systematic review of the literature identified no studies comparing any combination of the interventions of interest for this topic and although a small number of non-comparative studies, investigating individual interventions were identified, it was considered that the evidentiary benefits of including such studies was low and would not inform any recommendations regarding the best form of treatment for this patient group. <u>Research Recommendations</u> Prospective studies should investigate and compare the effectiveness of techniques for refining local ablation (radiofrequency ablation, radioembolisation, microwave, cryotherapy, laser and stereotactic radiotherapy) in patients with metastatic colorectal cancer. Outcomes of interest are technical feasibility, local control, disease-free survival, overall survival, toxicity and quality of life. Consider patients for entry into NCRN approved studies on local ablative therapies. Novel techniques for the treatment of metastatic disease, including peritoneal carcinomatosis, should be carefully audited so that case-mix adjusted outcome data may be collected and evaluated.
Leitlinienprogramm Onkologie, 2014 [19] **Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten (DGVS)** S3-Leitlinie Kolorektales Karzinom	Fragestellunge(n) Im Aktualisierungsprozess 2012/2013 legte die Leitliniengruppe fest, dass u.a. zu folgenden Fragen Stellung genommen werden sollte: • Welche Maßnahmen der Prävention können das KRK-Risiko reduzieren? • Welche Methoden sollten zur Vorsorge/Früherkennung einsetzt werden? • Welche Verfahren sollten in der präoperativen Diagnostik beim KRK eingesetzt werden? • Was ist bei der Stomaanlage zu beachten? • Wie ist der Stellenwert laparoskopischer Resektionsverfahren? • Zu welchem Zeitpunkt beginnt die Tumornachsorge? • Welchen Stellenwert haben Rehabilitation und Tertiärprävention nach kurativer Tumoroperation?

Methodik (S3-Leitlinie)

Grundlage der Leitlinie:

- Das methodische Vorgehen richtet sich nach dem AWMF Regelwerk (http://www.awmf-leitlinien.de) und ist im Leitlinienreport zu dieser Leitlinie (siehe z. B. http://leitlinienprogramm-onkologie.de/Leitlinien.7.0.html) dargelegt.
- Update: Entsprechend dieser Fragestellungen wurden alle Empfehlungen auf Aktualität überprüft und gegebenenfalls nach Literaturrecherchen überarbeitet.
- Suchzeitraum: bis 2010 (für relevante Fragestellungen)
- *Weitere Kriterien für die Qualität einer LL:*
  - *Die Gültigkeitsdauer der 2011/ 2012 überarbeiteten Themenkomplexe I, II, III, V, und VIII bzw. Kapitel 3, 4, 5, 7, 10 wird auf 5 Jahre geschätzt, sie werden spätestens 2017 einer erneuten Revision unterzogen.*
  - *Aktualisierung der Leitlinie erfolgte in redaktioneller Unabhängigkeit von der finanzierenden Organisation, der Deutschen Krebshilfe.*
  - *Alle Mitglieder der Leitliniengruppe legten eine schriftliche Erklärung zu eventuell bestehenden Interessenkonflikten vor*
  - *Die Gefahr der Beeinflussung durch Interessenkonflikte wurde reduziert, indem für die Recherche, Auswahl und Bewertung der Literatur politisch besonders brisanter Themen externe Institute beauftragt worden sind.*
  - *Die formale Konsensbildung und die interdisziplinäre Erstellung sind weitere Instrumente, die Einflussnahme der Industrie zu minimieren.*

LoE: Zur Klassifikation des Verzerrungsrisikos der identifizierten Studien wurde in dieser Leitlinie das System des Oxford Centre for Evidence-based Medicine in der Version von 2009 verwendet (siehe Anhang dieser Synopse)

GoR: In der Regel bestimmt der Evidenzklassifikation den Empfehlungsgrad. Abweichungen sind in begründeten Fällen möglich

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

Sonstige methodische Hinweise

- *Diese Leitlinie richtet sich vorrangig an:*
  - *Ärztinnen und Ärzte, die in der Prävention und Behandlung des KRK im ambulanten und stationären Sektor tätig sind,*
  - *Kooperationspartner der Ärzteschaft (Fachbereiche im Gesundheitswesen),*
  - *Kostenträger.*
- ***Empfehlungen erfolgen im Rahmen Konsensusverfahrens***
- ***Klassifikation der Konsensusstärke***

Konsensusstärke	Beschreibung
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

Freitext/Empfehlungen/Hinweise

Der folgende Teil der S3-Leitlinie enthält 2007/2008 aktualisierte Empfehlungen zur Tumortherapie beim metastasierten Kolorektalkarzinom, die vor allem Erkenntnisse aus Studien der Jahre 2003-2007 Jahre widerspiegeln.

9.2 Patienten mit einer Indikation für eine intensivierte systemische Therapie

9.19.	**Empfehlung**	**2008**
Empfehlungsgrad **B**	Patienten mit tumorbedingten Symptomen, Organkomplikationen oder raschem Progress sollten unter Berücksichtigung des Allgemeinzustandes des Patienten eine möglichst effektive Kombinationstherapie erhalten (intensivierte Therapie).	
Level of Evidence **5**	Starker Konsens	

9.4.3. Chemotherapieprotokolle in der Zweit- und Drittlinientherapie

Die Wahl der Zweit- und Drittlinientherapie hängt sowohl von vorangegangenen Therapien und der therapiefreien Zeit als auch von der individuellen Patientensituation und dem jeweiligen Therapieziel ab.

9.23.	**Empfehlung**	**2008**
Empfehlungsgrad **A**	Aufgrund unzureichender Evidenz soll mit Ausnahme der Fluoropyrimidine oder der Gabe von Irinotecan in Kombination mit Cetuximab nach Versagen einer irinotecanhaltigen Therapie keines der oben beschriebenen Therapeutika nach dokumentiertem Progress unter Therapie weiter appliziert werden. Dies gilt auch für Cetuximab und Bevacizumab.	
Level of Evidence **2**	Starker Konsens	

Hintergrund

Der Stellenwert einer effektiven Zweitlinientherapie für das Gesamtüberleben wurde in mehreren Phase III Studien untersucht.

915. 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 Irinotecan nach Versagen einer Fluorouracil Monotherapie im Vergleich mit BSC erbrachte deutlichen Vorteil im Gesamtüberleben

916. 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.

- Zweitlinientherapie mit Irinotecan nach Versagen einer Fluorouracil Monotherapie im Vergleich mit infusionalem 5-FU/FS erbrachte deutlichen Vorteil im Gesamtüberleben

917. 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. – Kombinationstherapie mit Oxaliplatin und Fluororuracil nach Versagen eines irinotecanhaltigen Protokolls war einer 5-FU/FS bzw. Oxaliplatin Monotherapie sowohl bezüglich der erzielten Ansprechraten als auch bezüglich der Zeit bis zur Progression überlegen 896. Tournigand, C., et al., FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol, 2004. 22(2): p. 229-37. – Vergleich von FOLFOX und FOLFIRI jeweils als Erst- respektive Zweitlinientherapie und vice versa – Kombinationstherapie von 5-FU/FS mit Oxaliplatin bzw. Irinotecan, die als Erstlinientherapie jeweils Ansprechraten (CR + PR) von 40-55% zeigen, erreichen in der Zweitlinientherapie Ansprechraten von 4% (FOLFIRI) bis 15% (FOLFOX) und ein progressionsfreies Überleben von ungefähr 2,5-4,2 Monaten – medianes Überleben der Patienten unterschied sich nicht signifikant zwischen den beiden Armen und beträgt für beide Therapiesequenzen (FOLFOX → FOLFIRI bzw. FOLFIRI → FOLFOX) jeweils etwa 20 Monate – auch Ansprechraten oder progressionsfreien Überleben ohne signifikante Unterschiede (siehe auch Tabelle 22 im Anhang dieser Synopse). Durch die Einführung monoklonaler Antikörper wie Cetuximab, Bevacizumab und Panitumumab, haben sich die Therapiemöglichkeiten auch in der Zweit- und Drittlinientherapie erweitert. 918. Cunningham, D., et al., Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med, 2004. 351(4): p. 337-45. – BOND 1-Studie belegte erstmals Effektivität von Cetuximab in Kombination mit Irinotecan in Zweitlinientherapie des fortgeschrittenen KRK nach Irinotecanversagen (RR 22,9%, Gesamtüberleben 8,6 Monate) – 329 Patienten die innerhalb von drei Monaten nach irinotecanhaltiger Therapie progredient waren – signifikant höhere Ansprechraten (22,9 vs 10,8%, p=0.007) – progressionsfreies Überleben signifikant verlängert. (4,1 vs 1,5 Monate, p<0.001) – Gesamtüberleben lag bei 8,6 resp. 6,9 Monaten (p=0.48) 919. Sobrero, A.F., et al., EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. J Clin Oncol, 2008. 26(14): p. 2311-9. 922. Eng C, M.J., Scheithauer W, et al. , Impact on quality of life of adding cetuximab to irinotecan in patients who have failed prior oxaliplatin-based therapy: the EPIC trial. Proc Am Soc Clin Oncol. 2007;25:164s. Abstract 4003., 2007. – EPIC-Studie konnte zeigen, dass Kombination Cetuximab plus Irinotecan (n=648) auch nach oxaliplatinhaltiger Vortherapie wirksam und im direkten Vergleich wirksamer ist als Irinotecan mono (n=650) – Patienten, die unter oxaliplatinbasierten Therapie progredient waren

	– Ansprechraten bei Kombinationstherapie signifikant verbessert (16.4% vs 4.2%; p<0.0001) – medianes PFS verlängerte sich mit Verfügbarkeit von Cetuximab von 2.6 Monate auf 4.0 Monate (HR: 0.692, p<0.0001) – medianes Gesamtüberleben (primärer Endpunkt) in beiden Armen vergleichbar, da nach Progression „crossover“ in anderen Studienarm gestattet war (10,7 vs 10 Monate, Hazard ratio für das Gesamtüberleben = 0.975, 95% CI: 0,854 -1,114, p=0,71) – begleitende Lebensqualitätsanalyse ergab Verbesserung für den allgemeinen Gesundheitsstatus (p=0.047) und für funktionelle und individuelle Symptome (Fatigue, Nausea/Vomitus (p<0.0001), Schmerz (p<0.0001)) im Kombinationsarm 921. Rothenberg M.L., e.a., Phase III trial of capecitabine + oxaliplatin (XELOX) vs. 5-fluorouracil (5-FU), leucovorin (LV), and oxaliplatin (FOLFOX4) as 2nd-line treatment for patients with metastatic colorectal cancer (MCRC). Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings (Post-Meeting Edition), 2007. 25(18S (June 20 Supplement)). – 627 Patienten mit Progress unter irinotecanhaltigen Therapie – in zweiter Linie entweder mit XELOX oder mit FOLFOX behandelt – mittlere Zeit bis zum Progress im XELOX Arm bei 4,8 Monaten gegenüber 4,7 Monaten im FOLFOX Arm – Grad 3/4 Toxizitäten: 60,1% der Fälle im XELOX Arm, 72,4 % im FOLFOX Arm – hauptsächlich Diarrhoen (20 vs 5%), Neutropenie (5 resp. 35%), Übelkeit und Erbrechen (5-6 %) 920. 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. – 829 (nicht mit Bevacizumab vorbehandelte) Patienten in Therapiearm FOLFOX-Bevacizumab, bzw. FOLFOX oder Bevacizumab jeweils mono randomisiert – Hinzunahme von Bevacizumab resultierte in signifikantem Überlebensvorteil von 2,1 Monaten im Vergleich mit FOLFOX alleine (12,9 vs 10,8 Monate, HR: 0,75; p=0.0011) – progressionsfreies Überleben signifikant länger als im alleinigen Chemotherapiearm (7,3 vs 4,7 Monate, HR: 0,61, p<0.0001) – Bevacizumab alleine ohne klinischen Stellenwert – Kombination mit VEGF-Antikörper erhöhte Rate an Grad 3 und 4 Toxizitäten um 14% – im experimentellen Arm signifikant häufiger Blutungen, Vomitus und Hypertonus – ebenfalls erhöhtes Neuropathierisiko ist am ehesten mit der längeren Behandlungsdauer im Kombinationsarm (10 Zyklen vs 7 Zyklen im FOLFOX Arm) assoziiert – Nachbeobachtungszeitraum betrug 28 Monate
SIGN, 2013 [20] Diagnosis and management	Fragestellunge(n) 14. Which chemotherapy regimen is optimal in the treatment of patients

of colorectal cancer (126)	with colon cancer and rectal cancer? Consider: a) Metastatic b) Adjuvant c) Dose, route, schedule, duration of treatment 15. What is the optimum treatment regimen for patients with advanced (metastatic) colon cancer? Key search terms: intensive regimen, palliative regimen, curative, non-curative, liver metastases, colon, metastatic metastectomy, KRAS and BRAF mutations.
	Methodik <u>Grundlage der Leitlinie:</u> Methodenreport beschreibt systematische Evidenzaufbereitung - eigene Checklisten - eigenes Graduierungssystem – repräsentatives Gremium - keine formalisierten Konsensusprozesse beschrieben – Suchzeitraum: bis März 2011 – *Weitere Kriterien für die Qualität einer LL:* • *CoI auf Anfrage einsehbar* • *core funding from Healthcare Improvement Scotland* LoE/GoR: eigenes Graduierungssystem (siehe Anlage dieser Synopse)
	Freitext/Empfehlungen/Hinweise 10.2 MANAGEMENT OF PATIENTS WITH METASTATIC COLORECTAL CANCER √ The optimal treatment strategy for patients with metastatic colorectal cancer should be determined following discussion at a multidisciplinary team meeting and is dependent on the site and extent of metastatic disease and the performance status, organ function and comorbidity of the patient. 10.2.4 SECOND LINE CHEMOTHERAPY Second line chemotherapy should be considered for patients with metastatic colorectal cancer with good performance status and adequate organ function. (GoR A) Irinotecan should be used as second line therapy following first line oxaliplatin (or vice versa). (GoR A) √ The choice of second line chemotherapy for patients with metastatic colorectal cancer will depend on patient fitness, comorbidity and previous chemotherapy exposure. 170. Hind D, Tappenden, P, Tumur, I, Eggington, S, Sutcliffe, P and Ryan, A. The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation 2008. (LoE 1+)

177. Roque IFM, Sola, I, Martin-Richard, M, Lopez, J J and Cosp, XB. Second-line chemotherapy in advanced and metastatic CRC. Cochrane Database of Systematic Reviews 2009, Issue 2. (LoE 1++)

10.2.5 BIOLOGICAL THERAPY

Cetuximab should be considered in combination with 5-FU/leucovorin/oxaliplatin or 5-FU/leucovorin/irinotecan chemotherapy for patients with unresectable liver metastases if patients fulfil the SMC criteria (siehe unten 14.4). The use of cetuximab in combination with oxaliplatin and capecitabine cannot currently be recommended. (GoR B)

183. Van Cutsem E, Kohne CH, Lang I, Folprecht G, Nowacki MP, Cascinu S, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: Updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol 2011;29(15):2011-9. (LoE 1+)

184. Maughan TS, Adams RA, Smith CG, Meade AM, Seymour MT, Wilson RH, 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):2103-14. (LoE 1++)

Although the use of cetuximab or panitumumab is associated with improved outcomes it is currently not recommended by the SMC in patients with chemo-refractory metastatic colorectal cancer (siehe unten 14.4).

180. Amado R, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008;26(10):1626-34. (LoE 1++)

181. Ibrahim E, Zekri JM, Bin Sadiq BM. Cetuximab-based therapy for metastatic colorectal cancer: a meta-analysis of the effect of K-ras mutations. Int J Colorectal Dis 2010;25(6):713-21. (LoE 1++)

182. Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy- refractory metastatic colorectal cancer. Clin Colorectal Cancer 2007;6(suppl2):S60-S5. (LoE 1++)

Although the use of bevacizumab is associated with improved outcomes in patients with metastatic colorectal cancer it is currently not recommended by the Scottish Medicines Consortium (siehe unten).

178. Tappenden P, Chilcott J, Brennan A, Pilgrim H. Systematic review of economic evidence for the detection, diagnosis, treatment, and follow-up of colorectal cancer in the United Kingdom. Int J Technol Assess Health Care 2009;25(4):470-8. (LoE 2++)

179. Welch S, Spithoff, K. Rumble, RB and Maroun, J. Bevacizumab combined with chemotherapy for patients with advanced colorectal cancer: A systematic review. Ann Oncol 2010;1152(21):1152-62. (LoE 2++)

14.4 ADVICE TO NHSSCOTLAND FROM THE SCOTTISH MEDICINES CONSORTIUM (SMC)

The Scottish Medicines Consortium concluded in 2005 that cetuximab is not recommended for use within NHSScotland in combination with irinotecan for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy.

Following a further submission in 2010 the SMC recommended that cetuximab is accepted for restricted use within NHSScotland for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, K-ras wild-type metastatic colorectal cancer in combination

	with chemotherapy. Cetuximab is restricted to use in patients who have not previously received chemotherapy for their metastatic disease, with liver metastases only that are considered non-resectable but in whom potentially curative liver metastasis resection would be undertaken if the lesions became resectable after treatment with chemotherapy and cetuximab. Panitumumab (Vectibix) is not recommended as monotherapy for the treatment of patients with EGFR-expressing metastatic colorectal carcinoma with non-mutated (wild-type) K-ras after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan- containing chemotherapy regimens. Bevacizumab (Avastin) is not recommended for use within NHSScotland in combination with fluoropyrimidine-based chemotherapy for treatment of patients with metastatic carcinoma of the colon or rectum due to insufficient evidence of cost effectiveness.

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

NICE, 2014 [21] Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy	Guidance 1.1 Aflibercept in combination with irinotecan and fluorouracil-based therapy is not recommended within its marketing authorisation for treating metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin containing regimen. 1.2 People currently receiving aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin-containing regimen should be able to continue treatment until they and their clinician consider it appropriate to stop.
NICE, 2012 [22] Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy (technology appraisal guidance 242) Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of technology appraisal 150 and part review of technology appraisal guidance 118)	Guidance 1.1 Cetuximab monotherapy or combination chemotherapy is not recommended for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy. 1.2 Bevacizumab in combination with non-oxaliplatin (fluoropyrimidine-based) chemotherapy is not recommended for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy. 1.3 Panitumumab monotherapy is not recommended for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy. 1.4 People currently receiving cetuximab monotherapy or combination chemotherapy, bevacizumab in combination with non-oxaliplatin chemotherapy, or panitumumab monotherapy for the treatment of metastatic colorectal cancer that has progressed after first-line chemotherapy should have the option to continue treatment until they and their clinician consider it appropriate to stop.
NICE, 2010 [23] Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer	Guidance 1.1 Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine is not recommended for the treatment of metastatic colorectal cancer. 1.2 People currently receiving bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer should have the option to continue treatment until they and their clinicians consider it appropriate to stop.
Nachtnebel, 2013 [24] Horizon Scanning in Oncology Regorafenib (Stivarga®) for heavily pretreated patients with metastatic colorectal cancer	2 Indication Regorafenib (Stivarga®) is indicated in patients with metastatic colorectal cancer (mCRC) who have been previously treated with: a fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy; an anti-VEGF therapy; an anti-EGFR therapy (if KRAS wild-type) 5 Current treatment In case of disease progression after these first-line therapies, treatment options will be selected according to the first-line regimen and include: • FOLFIRI ± bevacizumab • FOLFIRI ± ziv-aflibercept • Irinotecan ± bevacizumab • Irinotecan ± ziv-aflibercept

	• FOLFIRI ± cetuximab or panitumumab (KRAS wild-type gene only) • Cetuximab or panitumumab (KRAS wild-type gene only) + irinotecan • FOLFOX ± bevacizumab • CapeOX ± bevacizumab 6 Evidence Overall, 87 references were identified of which two have been included in this report: • a phase III study, assessing the effect of regorafenib on patients with mCRC that keeps progressing after administration of all approved standard therapies (CORRECT trial) and • a meta-analysis, evaluating the risk of hand-foot skin reactions in patients treated with regorafenib (Belum et al. 2013, siehe oben). 8 Ongoing research In July 2013 a search in databases www.clinicaltrials.gov and www.clinicaltrialsregister.eu was conducted; the following phase III trials were identified: • NCT01853319: an open-label phase III study of regorafenib in patients with mCRC who have progressed after standard therapy. The aim of this study is to provide additional information about the safety of regorafenib. The estimated study completion date is July 2014. • NCT01786538: a randomized phase III study of oxaliplatin, fluorouracil and leucovorin (FOLFOX) with or without regorafenib in patients with mCRC having progressed after first-line irinotecan plus fluoropyrimidines. The estimated study completion date is May 2017. • NCT01584830: a randomized, double-blind, placebo-controlled phase III study of regorafenib plus BSC versus placebo plus BSC in Asians with mCRC who have progressed after standard therapy. The estimated study completion date is May 2014. • NCT01538680 (EudraCT Number: 2011-005836-25): an open-label phase IIIb study of regorafenib in patients with mCRC who have progressed after standard therapy. The primary endpoint of this expanded-access study will be safety. There are four study locations in Austria. The study completion date has not been specified yet. Several phase I and phase II studies assessing the use of regorafenib for the first-line or second-line treatment (single-use or combination therapy) of mCRC were identified. For example, one of those studies (NCT01875380, EudraCT Number: 2013-000236-94) aims to evaluate the efficacy and safety of regorafenib in the first-line treatment of patients with mCRC who are frail and/or unfit for polychemotherapy. Moreover, a database search showed a number of studies investigating the effects of regorafenib on other types of cancer such as gastrointestinal stromal tumors (GIST) or hepatocellular carcinoma. 9 Commentary … In summary, regorafenib may represent a therapeutic option for patients who received all approved standard therapies while maintaining a good performance status. However, the modest gain in OS and PFS survival, the high-risk for adverse events, lack of improvements in QoL and potentially considerable costs of this therapy call into question whether this drug represents a viable treatment option in unselected patients.
Rothschedl, 2013 [25] Horizon Scanning in Oncology, Aflibercept (Zaltrap®) in addition to FOLFIRI for the 2nd line therapy of metastatic colorectal cancer	2 Indication Aflibercept (Zaltrap®) combined with FOLFIRI (5-fluorouracil/irinotecan/ leucovorin) treatment is indicated in adult patients with mCRC that is resistant to or has progressed after an oxaliplatin-containing regimen 5 Current treatment In case of disease progression after these first-line therapies, treatment options will be selected according to the first-line regimen received and include [10,11] • FOLFIRI ± bevacizumab • FOLFIRI ± aflibercept

	• Irinotecan ± bevacizumab • Irinotecan ± aflibercept • Cetuximab or panitumumab (KRAS WT gene only) +irinotecan • Regorafenib (not yet licenced in the European Union). [10] National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Colon Cancer. Version 2013. 2013 [cited 2013 20.May]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. [11] Schmoll, H.J., et al., Esmo consensus guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. Annals of Oncology, 2012. 23(10): p. 2479-2516. 6 Evidence Overall, 99 references were identified of which two were included in this report: • a phase III trial, evaluating the effect of adding aflibercept to FOLFIRI in patients with mCRC previously treated with an oxaliplatin – based regimen (VELOUR) and • a phase II study evaluating the safety and efficacy of aflibercept in pretreated patients with mCRC (Tang PA, et al. 2012) 8 Ongoing research A search in databases www.clinicaltrials.gov and www.clinicaltrialsregister.eu for trials concerning “metastatic colorectal cancer” and “aflibercept” was conducted in May 2013 with the following results: • NCT01661270: the aim of this multinational, randomized, double-blind phase III study is to evaluate the improvement in progression-free survival of aflibercept versus placebo in patients with mCRC (treated with FOLFIRI after failure of an oxaliplatin-based regimen. The estimated study completion date is January 2016. • NCT01571284 (EudraCT Number: 2011-005724-17): a multicenter, single-arm, open label phase III study to evaluate the safety and healthrelated quality of life of aflibercept in patients with mCRC (previously treated with an oxaliplatin-containing regimen). The estimated study completion date is June 2015. • NCT01670721: a multicenter, single arm, open label, phase III study to assess the safety of aflibercept in patients with (mCRC) treated with irinotecan/5FU combination (FOLFIRI) after failure of an oxaliplatin-based regimen. Furthermore, this study aims to evaluate the health-related quality of life (HRQL) of aflibercept within the patient population. The estimated study completion date is June 2014. • NCT01754272: a non-interventional Follow-up study to the VELOUR trial (NCT00561470). The archived colorectal cancer and metastasized tissue tumor blocks of patients who have participated in the VELOUR trial will be analyzed. The aim of the study is to identify proteins or markers which represent individual response to treatment. The estimated study completion date is December 2013. • NCT01646554: a randomized phase II/III study to evaluate the efficacy of FOLFOX alone versus FOLFOX and aflibercept in K-ras mutant in patients with resectable liver metastasis from CRC. The estimated study completion date is December 2016. Furthermore, several phase I and phase II studies were identified assessing single use of aflibercept or combined with capecitabine, OPTIMOX, FOLFIRI and modified FOLFOX6) in either pretreated or previously untreated patients. There are numerous partly ongoing, partly completed phase II and phase III studies evaluating the efficacy of aflibercept on further types of cancer including metastatic thyroid cancer, ovarian cancer, metastatic non-small-cell lung cancer, advanced esophageal/gastric, metastatic pancreatic cancer or metastatic androgen-independent prostate cancer to name but a few. 9 Commentary … In summary, it can be stated that the positive effects of aflibercept regarding increased overall survival and progression-free survival are to be balanced

	against the high incidence of adverse events. Currently there are no data available concerning aflibercept and quality-of-life, results of an ongoing study may give more information about this essential parameter.

Primärstudien

Per Handsuche wurden die Volltexte zu den Primärstudien identifiziert. Extrahiert sind die Angaben zur Vortherapie der eingeschlossenen Patientinnen und Patienten und zu relevanten Schadenaspekten.

Peeters et al. 2010 [26] 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	Aim: to evaluate the effect of the addition of panitumumab to FOLFIRI chemotherapy as second-line treatment form CRC Patients and Methods Eligible patients: Only one prior chemotherapy regimen for mCRC consisting of first-line fluoropyrimidine-based chemotherapy was allowed. Results – Patients Baseline demographics and disease characteristics were balanced between treatment arms within KRAS subpopulations, including patients with liver-only disease, prior oxaliplatin therapy, and prior bevacizumab therapy (Table 1, siehe Anhang dieser Synopse).
Van Cutsem et al. 2012 [27] 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	Aim: to evaluate the efficacy and safety of the combination of aflibercept plus FOLFIRI versus placebo plus FOLFIRI in patients with mCRC, following disease progression while on or *after completion of treatment with an oxaliplatin based regimen* Patients and Methods: Eligible patients: Although patients were to have documented progression while on or after completion of a single prior oxaliplatin-containing regimen, they were not selected for the timing of their progression. Results- Patients Patient characteristics and disease history (including prior anticancer treatments) were well balanced between the two treatment arms. Prior bevacizumab treatment was reported in 373 patients overall (30.4%) (Anmerkung FB Med: weitere Informationen zur Vortherapie liegen nicht vor) Results – Safety In particular, a higher incidence of grade 3 and 4 adverse events was reported in the aflibercept arm compared with the control arm for hypertension, hemorrhage (2.9% v 1.7%), arterial thromboembolic events (1.8% v 0.5%), and venous thromboembolic events (7.9% v 6.3%). With respect to the grade 3 and 4 hypertension, 19.1% of patients in the aflibercept arm and 1.5% of patients in the control arm developed grade 3 hypertension (ie, requiring adjustment in existing antihypertensive therapy or treatment with more than one drug); only one patient in the aflibercept arm (0.2%) experienced grade 4 hypertension. … The incidence of grade 3 or 4 GI fistula, other fistulae, and GI perforation was less than 2% in both treatment groups;

Kubicka S, et al. 2013 [28]
Bevacizumab plus chemotherapy continued beyond first progression in patients withmetastatic colorectal cancer previously treated with bevacizumab plus chemotherapy: ML18147 study KRAS subgroup findings

Aim:
ML18147 evaluated continued bevacizumab with second-line chemotherapy for patients with metastatic colorectal cancer (mCRC) progressing after the standard first-line bevacizumab-containing therapy.
Auszug aus "study design" im "supplementary material"
Patients were randomized 1:1 to infusional or bolus 5-fluorouracil or oral capecitabine at the investigator's discretion plus irinotecan or oxaliplatin, with or without bevacizumab (dose equivalent 2.5 mg/kg/wk, i.e. 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks). The choice of second-line chemotherapy depended on the first-line regimen used (switch of chemotherapy involved treating patients who received first-line oxaliplatin with second-line irinotecan and vice versa). All standard second-line treatments based on fluoropyrimidines plus oxaliplatin or irinotecan were permitted. Treatment was continued until progressive disease, unacceptable toxicity, or patient refusal.

Auszug aus Tabelle 1:

First-line chemotherapy in ITT population, n (%)	Chemotherapy group (n = 411)	Bevacizumab + Chemotherapy group (n = 409)
Irinotecan based	316 (77)	315 (77)
Oxaliplatin based	95 (23)	94 (23)

tolerability
The adverse-event profile of continued bevacizumab plus standard chemotherapy was generally comparable in patients with wild-type and mutant KRAS tumors (Table 3, siehe Anhang dieser Synopse).

Grothey A, et al. 2013 [29] Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): An international, multicentre, randomised, placebocontrolled, phase 3 trial

Aim:
No treatment options are available for patients with metastatic colorectal cancer that progresses after all approved standard therapies, but many patients maintain a good performance status and could be candidates for further therapy. An international phase 3 trial was done to assess the multikinase inhibitor regorafenib in these patients.

	Regorafenib (N=505)	Placebo (N=255)
(Continued from previous column)		
Number of previous systemic anticancer therapies (on or after diagnosis of metastatic disease)		
1–2§	135 (27%)	63 (25%)
3	125 (25%)	72 (28%)
≥4	245 (49%)	120 (47%)
Previous anti-VEGF treatment		
Bevacizumab	505 (100%)	255 (100%)
Patients stopping previous treatment because of progression		
Fluoropyrimidine	421 (83%)	221 (87%)
Bevacizumab	403 (80%)	214 (84%)
Irinotecan	405 (80%)	229 (90%)
Oxaliplatin	278 (55%)	160 (63%)
Panitumumab or cetuximab, or both	219 (43%)	107 (42%)
Time from diagnosis of metastases		
Median (months, [IQR])	31·0 (20·6–43·3)	29·9 (20·2–46·4)
<18 months	91 (18%)	49 (19%)
≥18 months	414 (82%)	206 (81%)

Data are n (%) unless otherwise specified. ECOG=Eastern Cooperative Oncology Group. VEGF=vascular endothelial growth factor. *Information missing from one patient in the regorafenib group. †*KRAS* mutation status was based on historical patient record. ‡*BRAF* mutation status was determined with plasma DNA samples collected from 502 patients (regorafenib 336, placebo 166) with BEAMing technology. §Five patients on placebo (2%) and 16 patients on regorafenib (3%) had received only one previous line of treatment for metastatic disease.

Table 1: **Baseline characteristics (efficacy population)**

Auszug aus Tabelle 2:

Clinical adverse event	Regorafenib (n = 500)			Placebo (n = 253)		
Hand-foot skin reaction	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
	233 (47%)	83 (17%)	0	19 (8%)	1 (<1%)	0

Tamagawa H, et al. 2013 [30] FOLFIRI plus bevacizumab (bev) as second-line therapy in patients (pts) with metastatic colorectal cancer (mCRC) who have failed first-line bev

Background: The phase III ML18147 study (NCT00700102) showed a survival benefit for the continuation of bev after 1st-line bev-containing therapy in pts with mCRC. Continuation of bev beyond disease progression in this setting was approved by the FDA in Jan 2013. In the randomized, phase II SPIRITT study (NCT00418938) assessing 2nd-line treatment for mCRC, progression-free survival (PFS) was longer in the bev arm compared with the panitumumab arm, but the difference was not statistically significant. We describe the results of EAGLE, a multicenter, randomized phase III study evaluating the optimal dose of 2nd-line bev in Japan (UMIN000002557). **Methods:** Pts were randomized 1:1 to receive bev 5 mg/kg (Arm A) or 10 mg/kg (Arm B) plus FOLFIRI Q2W. Key eligibility criteria: age ≥20 years, mCRC, ECOG PS ≤1, and treatment failure to prior 1st-line bev plus

plus oxaliplatin-based therapy: the randomized phase III EAGLE study **ASCO Meeting Abstract**	oxaliplatin-based therapy (≥4 cycles). The primary endpoint was PFS. Secondary endpoints included time to treatment failure (TTF), PFS from 1st-line therapy, response rate (RR) and safety. The planned sample size was 370 pts to detect 30% risk reduction with 90% power assuming a two-sided significance level of 0.05. **Results:** 387 pts were randomized between Sep 2009 and Jan 2012; 367 pts formed the full analysis set (Arm A 179 pts; Arm B 188 pts). Baseline characteristics were well balanced between the treatment arms. Respectively for Arm A and B, PFS was 6.2 and 6.3 months (HR 1.03, 95% CI: 0.82-1.30; p=0.815), TTF 5.3 and 5.3 months (HR 1.08, 95% CI: 0.87-1.33; p=0.485), PFS from 1st-line therapy 17.6 and 17.8 months (HR 0.99, 95% CI: 0.78-1.25; p=0.919) and RR 11.7% and 10.1%. Frequently reported AEs in Arm A and B, respectively, were: hypertension (13.0%, 18.1%), proteinurea (36.8%, 35.2%), GI perforation (4.7%, 3.1%), grade 3/4 neutropenia (46.1%, 39.9%), grade 3/4 fatigue (7.8%, 10.9%), and grade 3/4 anorexia (5.7%, 5.2%). Treatment-related deaths occurred in 2 pts in each arm. **Conclusions:** The study did not meet its primary endpoint. PFS in Arm A was comparable to that reported in the ML18147 study. Safety in both arms was consistent with previously reported studies. Clinical trial information: UMIN000002557.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) **am 20.01.2015**

#	Suchfrage
1	MeSH descriptor: [Colorectal Neoplasms] explode all trees and with qualifier(s): [Drug therapy - DT]
2	colorectal or bowel or colon or rectum:ti,ab,kw (Word variations have been searched)
3	cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or adenoma or neoplasm*:ti,ab,kw (Word variations have been searched)
4	#2 and #3
5	#1 or #4
6	drug or (drug therap*) or therapy or therapies or treat or treatment:ti,ab,kw (Word variations have been searched)
7	#5 and #6
6	#7 from 2010 to 2015

SR, HTAs in Medline (PubMed) am 20.01.2015

#	Suchfrage
1	"colorectal neoplasms/drug therapy"
2	colon*[Title/Abstract] OR colorectal[Title/Abstract] OR rectal[Title/Abstract]
3	(((((((cancer[Title/Abstract]) OR mass[Title/Abstract]) OR tumour*[Title/Abstract]) OR tumor*[Title/Abstract]) OR carcinom*[Title/Abstract]) OR neoplas*[Title/Abstract]) OR maligant*[Title/Abstract]) OR adenocarcinom*[Title/Abstract]
4	#2 AND #3
5	((((advanced[Title/Abstract]) OR metastat*[Title/Abstract]) OR metastas*[Title/Abstract]) OR recurren*[Title/Abstract]) OR progression*[Title/Abstract]
6	(((((drug[Title/Abstract]) OR (drug therap*)[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR treat[Title/Abstract]) OR treatment*[Title/Abstract]
7	#4 AND #5 AND #6
8	#1 OR #7
9	(#8) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
10	(#8) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
11	#9 OR #10
12	(#11) AND ("2010/01/01"[PDAT] : "2015/01/20"[PDAT])

Leitlinien in Medline (PubMed) am 13.01.2015

#	Suchfrage
1	Colorectal Neoplasms[MeSH]
2	Colon*[Title/Abstract] OR Colorectal[Title/Abstract] OR rectal[Title/Abstract]

3	(((((((cancer[Title/Abstract]) OR mass[Title/Abstract]) OR tumour*[Title/Abstract]) OR tumor*[Title/Abstract]) OR carcinom*[Title/Abstract]) OR neoplas*[Title/Abstract]) OR maligant*[Title/Abstract]) OR adenocarcinom*[Title/Abstract]) OR lesion*[Title/Abstract]
4	#2 OR #3
5	#1 OR #4
6	(((((drug[Title/Abstract]) OR (drug therap*)[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR treat[Title/Abstract]) OR treatment*[Title/Abstract]
7	#5 AND #6
8	(#7) AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title])
9	(#8) AND ("2010/01/01"[PDAT] : "2015/01/13"[PDAT])

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Anhang:

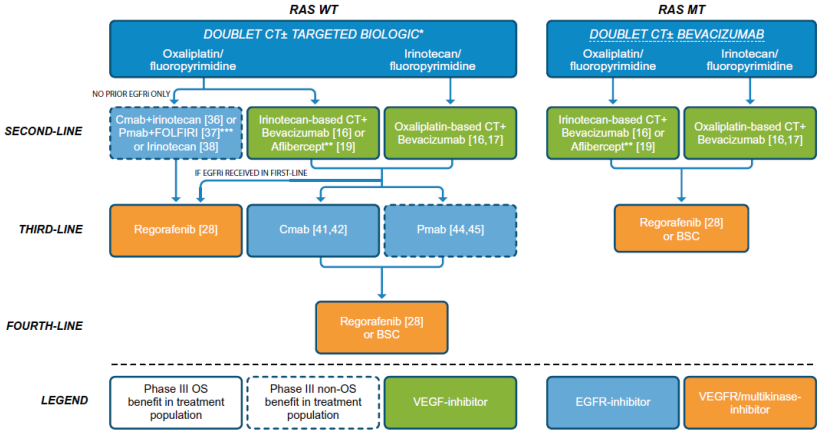

Fig. 4. Optimal sequencing of target-directed therapy for previously-treated, unresectable, advanced colorectal cancer. Solid (preferred option) and dashed borders indicate phase III OS and non-OS benefits, respectively. *Targeted biologic agents include bevacizumab, cetuximab and panitumumab. **Aflibercept was combined with FOLFIRI exclusively. ***Approximately two-thirds of patients in the 181 trial received prior oxaliplatin. *Abbreviations:* BSC, best supportive care; cmab, cetuximab; CT, chemotherapy; EGFR, epidermal growth factor receptor; EGFRi, epidermal growth factor receptor inhibitor; FOLFIRI, fluorouracil, leucovorin, and irinotecan; MT, mutant; OS, overall survival; Pmab, panitumumab; *RAS*, rat sarcoma viral oncogene homolog; VEGF, vascular endothelial growth factor; VEGFR, VEGF-receptor; WT, wild type.

Abbildung 1: aus Gill S, et al. 2014

Tabelle 1: NCCN Categories of Evidence and Consensus (aus Benson AB. et al, 2015)

Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

Tabelle 2: "Tabelle 3 Schema der Evidenzgraduierung nach Oxford (Version 2009)" (aus Leitlinienprogramm Onkologie, 2014)

Level	Therapy/Prevention, Aetiology/Harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval‡)	Individual inception cohort study with > 80% follow-up; CDR† validated in a single population	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts††	All or none case-series	Absolute better-value or worse-

Level	Therapy/Prevention, Aetiology/Harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
					value analyses ††††
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† or validated on split-sample§§§ only	Exploratory** cohort study with good†††reference standards; CDR† after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Tabelle 22: Oxaliplatinhaltige Protokolle in der Zweitlinientherapie

Referenz	N=	Therapieregime	Ansprechraten (%)	PFS (Mo)	Evidenzlevel
Giantonio 2007 [920]	829	FOLFOX 4 vs. FOLFOX + Bevacizumab vs. Bevacizumab mono	8,6 vs. 22,7 (p<0,0001) vs. 3,3	4,7 vs. 7,3 (p<0,0001) vs. 2,7	Ib
Rothenberg 2007 [921]	627	XELOX vs. FOLFOX	n.a.	TTP:4,8 vs. 4,7	Ib
Tournigand 2004	220	FOLFIRI → FOLFOX 6 vs. rev. Sequenz	4 vs. 15	2,5 vs. 4,2	Ib
Rothenberg 2003	463	FOLFOX 4 vs. FS-5 FU (vs. Oxaliplatin mono)	9,9 vs. 0 vs. 0	TTP: 4,6 vs. 2,7 (p<0,0001)	Ib

Abbildung 2: Tabelle 22 aus Leitlinienprogramm Onkologie, 2014

Tabelle 3: KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS (aus SIGN, 2012)

LoE	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 -	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies, high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 -	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion
GoR	
A	At least one meta-analysis, systematic review, or RCT rated as 1++,and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
GOOD PRACTICE	Recommended best practice based on the clinical experience of the guideline development group

POINTS	

Table 1. Demographics and Disease Characteristics

Characteristic	WT *KRAS*				MT *KRAS*			
	Panitumumab-FOLFIRI (n = 303)		FOLFIRI (n = 294)		Panitumumab-FOLFIRI (n = 238)		FOLFIRI (n = 248)	
	No.	%	No.	%	No.	%	No.	%
Sex, male	188	62	191	65	133	56	148	60
Age, years								
Median	60		61		61		64	
Minimum	28		29		29		29	
Maximum	84		86		83		86	
Race, white	294	97	278	95	226	95	238	96
ECOG performance status								
0-1	288	95	273	93	224	94	233	94
2	15	5	21*	7	14	6	15	6
Primary tumor type								
Colon	187	62	189	64	156	66	164	66
Rectal	116	38	105	36	82	34	84	34
Sites of metastatic disease								
Liver only	51	17	59	20	37	16	35	14
Liver + other	205	68	189	64	166	70	172	69
Other only	47	16	44	15	34	14	39	16
Missing or unknown	0	0	2	< 1	1	< 1	2	< 1
Prior therapy								
Oxaliplatin	204	67	191	65	164	69	169	68
Bevacizumab	55	18	60	20	45	19	43	17

Abbreviations: WT, wild-type; FOLFIRI, fluorouracil, leucovorin, and irinotecan; MT, mutant; ECOG, Eastern Cooperative Oncology Group.
*Includes one patient with ECOG performance status of 3.

Abbildung 3: aus Peeters et al. 2010

Table 3. Overview of adverse events in the KRAS population

Event, *n* (%)	KRAS wild type		KRAS mutant	
	Chemotherapy (*n* = 166)	Bevacizumab + chemotherapy (*n* = 148)	Chemotherapy (*n* = 135)	Bevacizumab + chemotherapy (*n* = 162)
Any adverse event	164 (99)	148 (100)	133 (99)	156 (96)
Serious adverse events	57 (34)	42 (28)	40 (30)	46 (28)
Grade 3–5 adverse events	101 (61)	89 (60)	69 (51)	103 (64)
Grade 5 adverse events	2 (1)	4 (3)	2 (1)	2 (1)
Discontinued any treatment due to adverse events	15 (9)	25 (17)	8 (6)	20 (12)
Discontinued any chemotherapy due to adverse events	15 (9)	22 (15)	8 (6)	16 (10)
All deaths	128 (77)	102 (69)	112 (83)	126 (78)
Death not due to progressive disease	8 (5)	6 (4)	3 (2)	7 (4)
Any adverse event of special interest with bevacizumab	39 (23)	64 (43)	31 (23)	64 (40)
Grade 3–5 adverse events of special interest with bevacizumab	11 (7)	17 (11)	7 (5)	20 (12)
Hypertension	2 (1)	2 (1)	1 (<1)	4 (2)
Proteinuria	0	2 (1)	0	1 (<1)
Bleeding/hemorrhage	1 (<1)	4 (3)	0	4 (2)
Abscesses/fistulas	0	0	0	2 (1)
Gastrointestinal perforation	1 (<1)	2 (1)	0	3 (2)
Congestive heart failure	1 (<1)	0	1 (<1)	0
Venous thromboembolic event	6 (4)	6 (4)	4 (3)	7 (4)
Arterial thromboembolic event	1 (<1)	2 (1)	1 (<1)	0
Wound-healing complications	0	0	0	1 (<1)

Abbildung 4: aus Kubicka S, et al. 2013