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1. Leitlinienrecherche

In der aktuellen Version wurde keine Leitlinienrecherche durchgeführt.

2. Methodisches Vorgehen

2.1 Systematische Literaturrecherche

2.1.1 Formulierung von Schlüsselfragen

Es handelt sich um Amendement-Recherchen ergänzend zu der S3- Leitlinie „Kolorektales Karzinom V3.0“ vom 30.08.2023 (AWMF-Registernummer 032 - 053OL).

Es wurden 3 Recherchen neu erstellt, um auf die Veröffentlichung neuer und relevanter klinischer Studien zu reagieren und diese in die Leitlinie aufzunehmen, unabhängig vom regulären Aktualisierungszyklus der Leitlinie.

Die Auflistung der neuen Schlüsselfragen mit genauer Beschreibung des PICO-Schemas findet sich in Abbildung 1.

PICO	Population	Intervention	Comparison	Outcome
	Neoadjuvante / adjuvante Therapie:			
Amendment 1	Verbessert körperliche Aktivität nach kurativer Therapie des KRK im Stadium II/III das Überleben?			
	KRK Stadium II/III, nach adjuvanter Therapie	Standardisiertes Trainingsprogramm	Standard of Care	OS, rezidivfreies Überleben, LQ, Nebenwirkungen
	Systemtherapie im Stadium IV			
Amendment 2	Wertigkeit der Therapie mit Encorafenib, Cetuximab, und mFOLOFX6 in BRAFV600E-mutierten KRK			
	BRAFV600E mut KRK, Erstlinie	Encorafenib, Cetuximab, und mFOLOFX6	Standard of Care	OS, PFS, RR, Tox, Lebensqualität
Amendment 3	Wertigkeit der Checkpointblockade bei MSI/dMMR KRK im Stadium IV			
	MSI/dMMR KRK, Stadium IV Erstlinie	IO	Chemo	OS, PFS, RR, Tox, Lebensqualität

Abb. 1 PICO-Fragen für Amendement Recherchen

2.1.2 Durchführung der Recherche

Die systematische Literaturrecherche wurde in der Medline Datenbank über die PubMed Suchoberfläche <https://pubmed.ncbi.nlm.nih.gov/> durchgeführt. Zusätzlich erfolgten Recherchen in der Cochrane Central Datenbanken über die Cochrane Suchoberfläche <https://www.cochranelibrary.com/>.

Die Suchen wurden am 18.09.2025 ohne zeitliche Einschränkung durchgeführt und beschränkte sich auf randomisiert kontrollierte Studien (RCTs).

Es wurden 52 Suchtreffer in Medline und 24 Suchtreffer in Cochrane Central erzielt. Die Suchtreffer wurden kombiniert und die Duplikate wurden entfernt.

In Summe verblieben 57 Literaturstellen, die über die Recherchen identifiziert wurden. Die Ergebnisse der Suchen zu den einzelnen Datenbanken sind in Tabelle 1 aufgelistet. Die detaillierten Darstellungen der Recherchen sind im Appendix zur jeweiligen Schlüsselfrage dargestellt.

Tabelle 1 Ergebnisse der Literaturrecherche nach Kapitel und Datenbank

	PubMed	Cochrane Central	Kombiniert ohne Duplikate
PICO Amendment 1	9	11	13
PICO Amendment 2	4	4	4
PICO Amendment 3	39	9	40
			57

2.2 Auswahl der Evidenz

Die Literaturarbeit wurde über das Leitlinienportal der Clinical Guideline Services GmbH (CGS) durchgeführt. Die in den Suchen identifizierten Literaturstellen wurden nach dem Deduplizieren als Literatursammlungen für jede PICO Frage im Leitlinienportal (<https://www.guideline-service.de>) hinterlegt.

Die Literatursammlungen waren der Leitliniengruppe zu jedem Zeitpunkt zur Einsicht verfügbar.

2.2.1 Ein- und Ausschlussgründe

Folgende Ein- und Ausschlussgründe wurden für die Recherche und Auswahl der Evidenz festgelegt:

- Deutsche und englische Veröffentlichungen
- Probandenstudien (keine Tierversuche)
- Veröffentlichungszeitraum: keine Einschränkungen
- Studientyp: RCTs

Generelle Ausschlussgründe wurden ebenfalls zur Auswahl herangezogen:

- Doppelpublikation bzw. aktuellere Version vorhanden
- Primärstudie ist bereits in einer Übersichtsarbeit enthalten
- Kein Volltext verfügbar (bzw. Studien-Protokoll, Abstract)
- Nicht die gesuchte Population für die Fragestellung
- Nicht die gesuchte Intervention für die Fragestellung
- Nicht die gesuchten Outcomes für die Fragestellung
- Anderer Publikationstyp (Editorial, Fallbericht, Brief etc.)

2.2.2 Screening

Die Auswahl der Evidenz erfolgte durch ein mehrstufiges Screening im Leitlinienportal (<https://www.guideline-service.de>). Im ersten Schritt, dem Titel-Abstract Screening wurden die Suchtreffer anhand der Ein- und Ausschlussgründe auf potentielle Relevanz gesichtet. Die Auswahl wurde von den Mitarbeitenden der CGS GmbH getroffen und ggf.

Rücksprache mit den fachlichen Experten der Leitlinienrguppe gehalten.

Von den von Duplikaten bereinigten 57 Suchtreffern wurden 7 als potenziell relevant eingeordnet. Alle im Titel-Abstract als relevant für die jeweilige Fragestellung identifizierten Artikel wurden daraufhin als Volltext akquiriert.

Im zweiten Schritt des Screenings wurden die Volltexte der ausgewählten Publikationen auf die Erfüllung der o.g. Ausschlussgründe überprüft. Es wurden sechs relevante Literaturstellen identifiziert. Die Auswahl wurde von den Mitarbeitenden der CGS getroffen und im Leitlinienportal durchgeführt, welche im Anschluss der Evidenzbewertung zugeführt wurden.

Die Teilschritte des Screenings sind im Appendix zur jeweiligen Recherche grafisch als PRISMA Flussdiagramm dargestellt.

2.2.3 Experten beigesteuerte Literatur

Zusätzlich zur Recherche wurden keine Studien durch die Experten nachnominiert.

2.3 Leitlinienadaptation

Es wurde keine Leitlinienadaptation vorgenommen.

2.4 Bewertung der Evidenz

Die Literaturbewertung wurde nach der Evidenzklassifizierung des Oxford Centre for Evidence-Based Medicine 2011¹ (Tabelle 2) für Interventions- und diagnostische Studien durchgeführt. Die methodische Qualität der Literaturstelle wurde mit Hilfe von Checklisten überprüft und die gefundenen Mängel im „Notes“ Bereich der Evidenztabelle festgehalten. Studien mit bedeutenden methodischen Schwächen und/ oder bedeutsamer Heterogenität wurden um eine Note abgewertet. Eine entsprechende detaillierte Begründung findet sich in der Evidenztabelle im Feld „Notes“.

2.4.1 Risk-of-Bias Bewertung der Einzelstudien

Für randomisierte kontrollierte Studien fand das Risk-of-Bias (RoB) Tool der Cochrane Collaboration² Anwendung. Das RoB-Tool stellt ein Instrument zur Bewertung des Verzerrungspotentials in RCTs dar und setzt sich aus sieben Domänen zusammen:

- Generierung der Randomisierungssequenz
- Verdeckte Gruppenzuteilung
- Verblindung von Teilnehmer*innen und Studienpersonal
- Verblindung der Endpunkterhebung
- Unvollständige Daten zu Endpunkten
- Selektives Berichten
- Andere Ursachen für Bias.

Für jede der Domänen erfolgt eine Beurteilung mit „Geringes Risiko für Bias“, „Hohes Risiko für Bias“ oder „Unklares Risiko für Bias“.

¹ CEBM (Centre for Evidence-Based Medicine) Critical Appraisal tools (2017). <http://www.cebm.net/critical-appraisal/> (abgerufen am 05.03.2020)

² Higgins J P T, Altman D G, Gotzsche P C, Jüni P, Moher D, Oxman A D et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials BMJ 2011; 343 :d5928 doi:10.1136/bmj.d5928

Abschließend erfolgte eine Gesamtbewertung. Hierbei wurde eine Studie mit einem unklaren Bias Risiko bewertet, wenn mindestens drei der sieben Domänen ein unklares Bias-Risiko aufwiesen. Eine Studie wurde mit einem hohen Bias-Risiko bewertet, wenn mindestens eine Domänen ein hohes Bias- Risiko aufwiesen.

Die Ergebnisse der RoB-Bewertungen sind in den Evidenztabelle zusammengefasst.

Tabelle 2: Evidenzklassifizierung nach Oxford 2011

Fragestellung	Schritt 1 (Level 1*)	Schritt 2 (Level 2*)	Schritt 3 (Level 3*)	Schritt 4 (Level 4*)	Schritt 5 (Level 5*)
Wie häufig ist das Problem	Lokale und aktuelle randomisierte Proben aus Umfragen (oder Volkszählungen)	Systematische Reviews von Umfragen die eine Anpassung an die örtlichen Gegebenheiten ermöglichen**	Lokale Nicht-Zufalls Probe	Fall-Serie**	Nicht verfügbar
Ist der diagnostische oder Monitoring Test akkurat? (Diagnose)	Systematische Reviews von Querschnittsstudien mit konsistent applizierten Referenzstandard und Verblindung	Einzelne Querschnitts-Studien mit konsistent applizierten Referenzstandard und Verblindung	Nicht konsekutive Studien oder Studien ohne konsistent applizierten Referenzstandard**	Fall-Kontroll Studien, oder minderwertiger, nicht unabhängiger Referenz Standard**	Mechanismus-basierte Argumentation
Was wird ohne Therapie passieren? (Prognose)	Systematische Reviews von Inzeptions Kohorten Studien	Inzeptions Kohorten Studien	Kohorten Studien oder Kontrollarme von randomisierten Studien*	Fall Serien oder Fall-Kontroll Studien, oder minderwertiger prognostische Kohorten Studien	Nicht verfügbar
Hilft die Intervention? Behandlungsvorteil	Systematische Reviews von randomisierten Studien oder n=1 Studien	Randomisierte Studien oder Observationsstudien mit dramatischem Effekt	Nicht-randomisierte kontrollierte Kohorten/Follow-up Studien**	Fall Serien oder Fall-Kontroll Studien, oder historische kontrollierte Studien	Mechanismus-basierte Argumentation
Was sind die häufigen Nachteile/ Schäden durch die Intervention? Behandlungsnachteil	Systematische Reviews von randomisierten Studien oder Nested Fall Kontroll Studien, n=1 Studien, oder	Randomisierte Studien oder (herausragende) Observationsstudien mit dramatischen Effekt	Nicht-randomisierte kontrollierte Kohorten / Follow-up Studien (Beobachtung nach Marktzulassung), ausreichende Fallzahl	Fall Serien oder Fall-Kontroll Studien, oder historische kontrollierte Studien	Mechanismus-basierte Argumentation

	Observationsstudien mit dramatischem Effekt		vorausgesetzt um häufige Schäden auszuschließen (Für Langzeit Schäden muss die Nachfolgezeit ausreichend sein)		
Was sind die seltenen Nachteile/ Schäden durch die Intervention? Behandlungsnachteil	Systematische Reviews von randomisierten Studien oder n=1 Studien	Randomisierte Studien oder herausragende Observationsstudien mit dramatischen Effekt		Fall Serien oder Fall-Kontroll Studien, oder historische kontrollierte Studien	Mechanismus-basierte Argumentation
Ist der (frühe Detektion) Test lohnenswert? (Screening)	Systematische Reviews von randomisierten Studien	Randomisierte Studien	Nicht-randomisierte kontrollierte Kohorten / Follow-up Studien**	Fall Serien oder Fall-Kontroll Studien, oder historische kontrollierte Studien	Mechanismus-basierte Argumentation

* Das Evidenzlevel kann herabgestuft werden auf Grund der Studienqualität, Ungenauigkeit, Indirektheit (Studien PICO passt nicht genau zur Frage PICO), Inkonsistenz zwischen Studien, oder weil die absolute Effektgröße sehr klein ist. Das Evidenzlevel kann hochgestuft werden, wenn der beobachtete Effekt groß oder sehr groß ist.

** Wie immer ist ein Systematisches Review generell besser als eine einzelne Studie

¹ Entwickelt von OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson 2011. *Übersetzt und angepasst von CGS Usergroup 2020.*

2.5 Erstellung von Evidenztabelle

Aus allen eingeschlossenen Literaturstellen wurden nach der positiven Bewertung die wichtigsten Daten extrahiert. Diese sind je nach Studientyp unterschiedlich (Diagnostik, Intervention, Beobachtung, Übersichtsarbeit) beinhalten aber in jedem Falle eine Beschreibung der Population, Intervention/ Exposure, Endpunkte, Resultate inklusive Zahlenwerte, Konklusion der Autor*innen und einer Auflistung der bei der Durchsicht offenkundigen methodischen Mängel. Diese Daten sind in Form von Evidenztabelle geordnet und nach Studientyp im Leitlinienportal zusammengefasst.

Die Evidenztabelle sind in Appendix zu den jeweiligen PICO-Schlüsselfragen dargestellt. Ebenfalls wurden Inhaltsverzeichnisse zu den Evidenztabelle erstellt. Diese beinhalten eine Auflistung der Literaturstellen der zugeordneten Literatur, das Evidenzlevel und die Angabe des Studientypes.

Appendix:

Amendement Recherche 1:

Alle Recherchen wurden am 18.9.2025 durchgeführt.

PubMed/Medline:

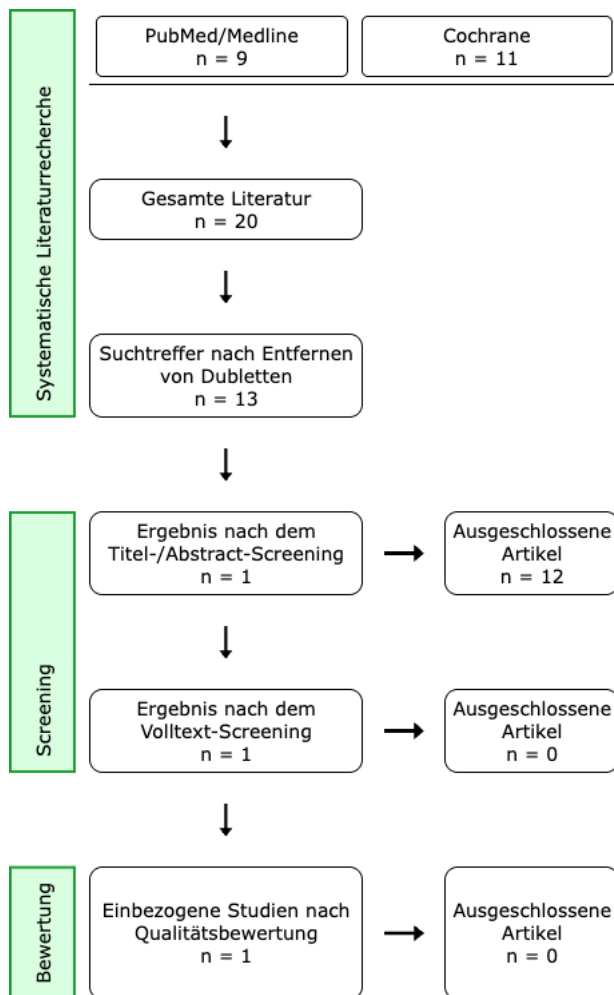
Verbessert körperliche Aktivität nach kurativer Therapie des KRK im Stadium II/III das Überleben?		
Population		
#1	Colonic Neoplasms[Mesh]	86.311
#2	colon*[tiab]	615.481
#3	neoplasm*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR cancer*[tiab] OR malignan*[tiab]	4.462.903
#4	#2 AND #3	226.491
#5	#1 OR #4	254.797
#6	Chemotherapy, Adjuvant[Mesh] OR Chemotherap*, Adjuvant[Title/Abstract] OR Adjuvant Chemotherap*[Title/Abstract] OR Adjuvant Drug Therap*[Title/Abstract] OR Drug Therap*, Adjuvant[Title/Abstract]	71.939
#7	#5 AND #6	5.180
Intervention		
#8	Exercise Therapy/methods[Mesh] OR Exercise Therap*[Title/Abstract] OR Rehabilitation* Exercise[Title/Abstract] OR Remedial Exercise[Title/Abstract] OR exercise group[Title/Abstract] OR exercise program[Title/Abstract]	50.953
#9	#7 AND #8	9
Filter		
#10	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[tj]	1.730.470
#11	#9 AND #10	9

Cochrane:

ID	Search	Hits
#1	MeSH descriptor: [Colonic Neoplasms] explode all trees	2612
#2	(colon*):ti,ab,kw	41105
#3	(neoplasm*):ti,ab,kw OR (tumor*):ti,ab,kw OR (carcinoma*):ti,ab,kw OR (cancer*):ti,ab,kw OR (malignan*):ti,ab,kw	294083
#4	#2 AND #3	15521

#5	#1 OR #4	15554
#6	MeSH descriptor: [Chemotherapy, Adjuvant] explode all trees	6068
#7	(Chemotherap*, Adjuvant OR Adjuvant Chemotherap* OR Adjuvant Drug Therap* OR Drug Therap*, Adjuvant):ti,ab,kw	29847
#8	#6 OR #7	29929
#9	#5 AND #8	1872
#10	MeSH descriptor: [Exercise Therapy] explode all trees	23260
#11	(Exercise Therap* OR Rehabilitation* Exercise OR Remedial Exercise OR exercise group* OR exercise program*):ti,ab,kw	119341
#12	#10 AND #11	20456
#13	#9 AND #12	11
#14	#13 in Trials	11

Prisma-Schemata:



Amendement Recherche 2:

PubMed/Medline:

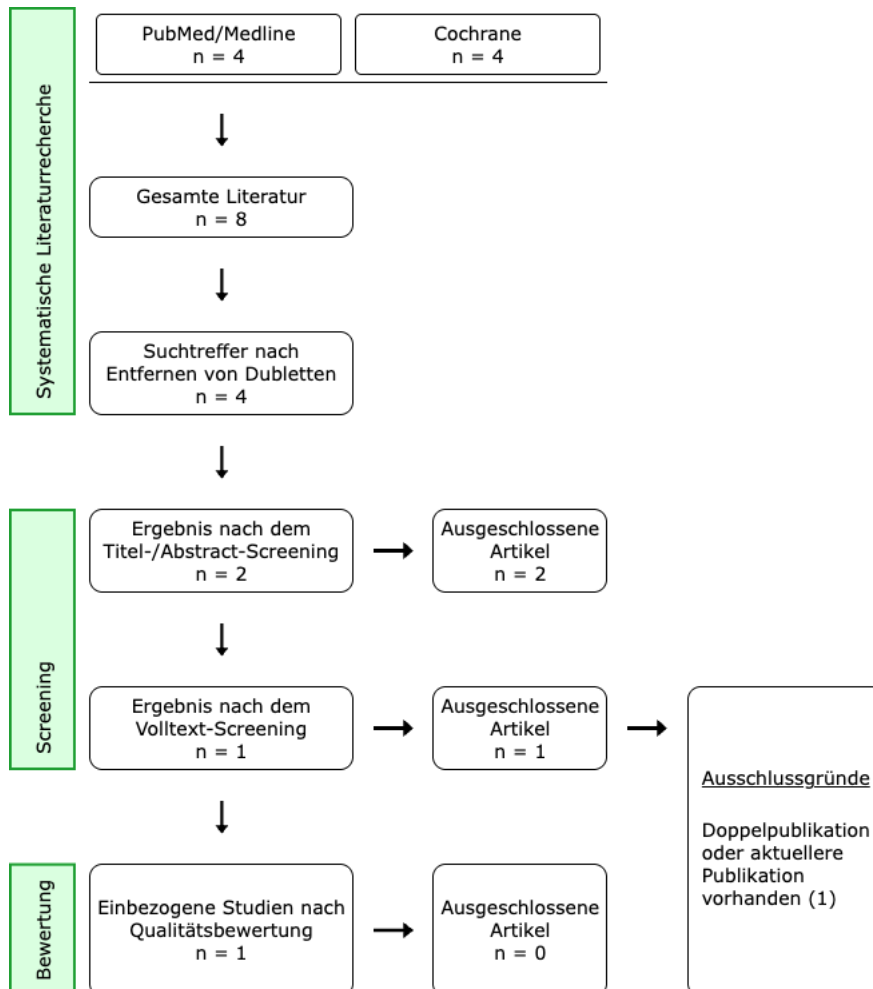
Wertigkeit der Therapie mit Encorafenib, Cetuximab, und mFOLOFX6 in BRAFV600E-mutierten KRK		
Population		
#1	Colorectal Neoplasms[Mesh]	259.115
#2	colorectal[tiab] OR colonic[tiab] OR sigmoid[tiab] OR rectal[tiab]	405.726
#3	neoplasm*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR cancer*[tiab] OR malignan*[tiab]	4.463.965
#4	#2 AND #3	270.613
#5	#1 OR #4	359.662
Intervention		
#6	((("encorafenib" [Supplementary Concept])) OR ("Carbamates/administration and dosage"[Mesh] OR "Carbamates/adverse effects"[Mesh])) OR ("Sulfonamides/administration and dosage"[Mesh] OR "Sulfonamides/adverse effects"[Mesh])) OR (encorafenib [tiab])	46.285
#7	(("Cetuximab"[Mesh]) OR ("Antibodies, Monoclonal, Humanized/administration and dosage"[Mesh] OR "Antibodies, Monoclonal, Humanized/adverse effects"[Mesh])) OR (cetuximab[Title/Abstract])	39.152
#8	FOLFOX[Title/Abstract] OR Folfox regimen[Title/Abstract] OR mFOLFOX6[Title/Abstract] OR (oxaliplatin[Title/Abstract] AND leucovorin[Title/Abstract] AND fluorouracil[Title/Abstract])	5.209
#9	#6 AND #7 AND #8	14
#10	#5 AND #9	14
Filter		
#11	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]	1.730.860
#12	#10 AND #11	4

Cochrane:

ID	Search	Hits
#1	MeSH descriptor: [Colorectal Neoplasms] explode all trees	
#2	(colorectal OR colonic OR sigmoid OR rectal):ti,ab,kw	44972
#3	(neoplasm* OR tumor* OR tumour* OR carcinoma* OR cancer* OR malignan*):ti,ab,kw	296239
#4	#2 AND #3	30122

#5	#1 AND #4	13011
#6	(encorafenib):ti,ab,kw	180
#7	("cetuximab"):ti,ab,kw	2817
#8	MeSH descriptor: [Antibodies, Monoclonal, Humanized] explode all trees	16817
#9	(FOLFOX OR Folfox regimen OR mFOLFOX6):ti,ab,kw	2309
#10	(oxaliplatin AND leucovorin AND fluorouracil):ti,ab,kw	1600
#11	#7 OR #8	18656
#12	#9 OR #10	3298
#13	#6 AND #11 AND #12	11
#14	#5 AND #13	4

Prisma-Schemata:



Amendement Recherche 3:

PubMed/Medline:

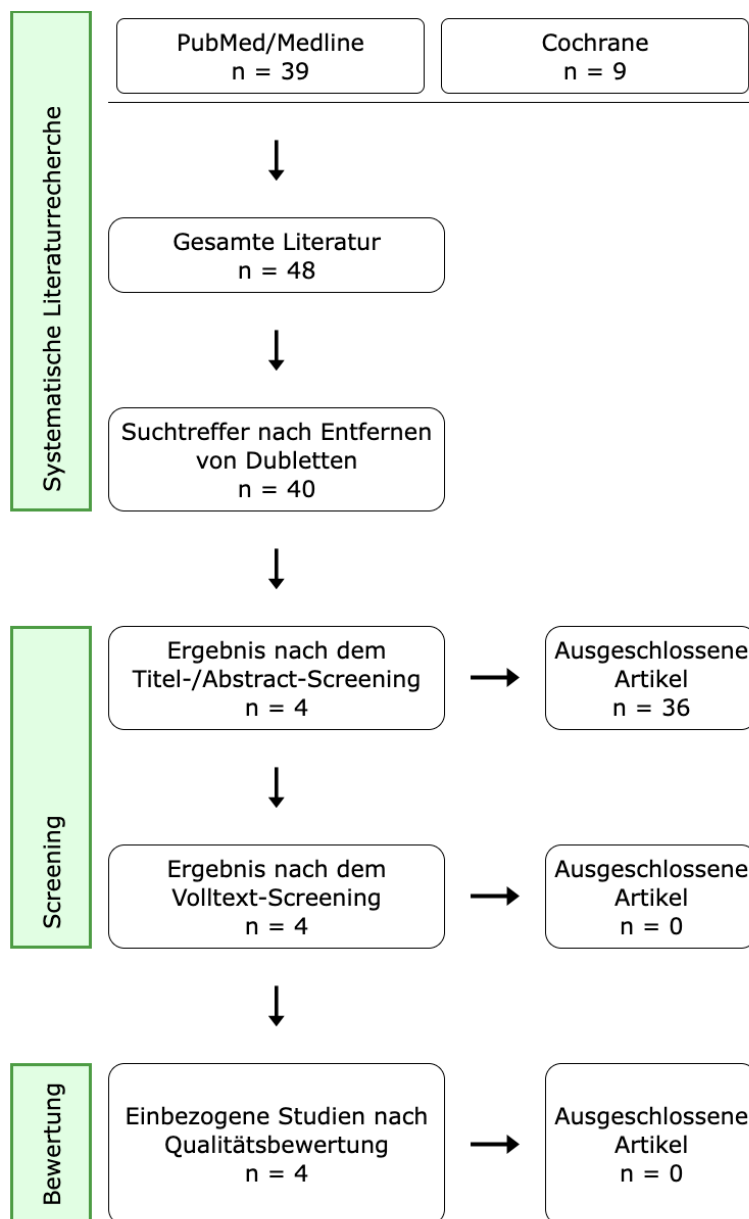
Wertigkeit der Checkpointblockade bei MSI/dMMR KRK im Stadium IV		
Population		
#1	Colorectal Neoplasms[Mesh]	259.115
#2	colorectal[tiab] OR colonic[tiab] OR sigmoid[tiab] OR rectal[tiab]	405.726
#3	neoplasm*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR cancer*[tiab] OR malignan*[tiab]	4.463.965
#4	#2 AND #3	270.613
#5	#1 OR #4	359.662
#6	("Microsatellite Instability"[Mesh]) OR "DNA Mismatch Repair"[Mesh] OR (Microsatellite Instabilit*[tiab]) OR DNA Mismatch Repair*[tiab]	19.381
#7	#5 AND #6	10.273
Intervention		
#8	("Immune Checkpoint Inhibitors" [Pharmacological Action]) OR ("Ipilimumab"[Mesh] OR "Nivolumab"[Mesh] OR "Antibodies, Monoclonal, Humanized"[Mesh]) OR (Ipilimumab[tiab] OR Nivolumab[tiab]))	123.744
#9	first line[tiab] OR firstline[tiab] OR first-line[tiab] OR 1st line[tiab] OR naive[tiab]	249.183
#10	#7 AND #8 AND #9	105
Filter		
#11	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]	1.730.470
#12	#10 AND #11	39

Cochrane:

ID	Search	Hits
#1	MeSH descriptor: [Colorectal Neoplasms] explode all trees	13239
#2	(colorectal OR colonic OR sigmoid OR rectal):ti,ab,kw	44972
#3	(neoplasm* OR tumor* OR tumour* OR carcinoma* OR cancer* OR malignan*):ti,ab,kw	296239
#4	#2 AND #3	30122
#5	#1 AND #4	13011
#6	MeSH descriptor: [Microsatellite Instability] explode all trees	122
#7	MeSH descriptor: [DNA Mismatch Repair] explode all trees	86
#8	(Microsatellite Instabilit* OR DNA Mismatch Repair*):ti,ab,kw	687
#9	#6 OR #7 OR #8	687

#10	#5 AND #9	218
#11	MeSH descriptor: [Immune Checkpoint Inhibitors] explode all trees	400
#12	("Ipilimumab"):ti,ab,kw OR (nivolumab):ti,ab,kw	4195
#13	MeSH descriptor: [Nivolumab] explode all trees	1069
#14	MeSH descriptor: [Ipilimumab] explode all trees	624
#15	#11 OR #12 OR #13 OR #14	4491
#16	(first line OR firstline OR first-line OR 1st line OR naive):ti,ab,kw	62275
#17	#10 AND #15 AND #16	9

Prisma-Schemata:



Amendment Evidenztabelle Recherche 1

Schlüsselfrage:

--2025 Amendment 1 Verbessert körperliche Aktivität nach kurativer Therapie des KRK im Stadium II/III das Überleben?

P: KRK Stadium II/III, nach adjuvanter Therapie

I: Standardisiertes Trainingsprogramm

C: Standard of Care

O: OS, rezidivfreies Überleben, LQ, Nebenwirkungen

Inhalt: 1 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Courneya, K. S. 2025	2	Phase 3 randomized trial (open-label) - CHALLENGE

Cochrane Risk of Bias Tool 1 (RCT): 1 Bewertung(en)

Courneya, K. S. et al. Structured Exercise after Adjuvant Chemotherapy for Colon Cancer. N Engl J Med. 393. 13-25. 2025			
Population	Intervention / Comparison	Outcomes/Results	Methodical Notes
Evidence level: 2	Intervention: Exercise group: n= 445	Primary: Disease-free survival	Funding Sources: Canadian Cancer Society, the

<p>Study type: Phase 3 randomized trial (open-label) - CHALLENGE</p> <p>Number of Patients: 889 patients with complete resection of stage III or high-risk stage II adenocarcinoma of the colon and had completed adjuvant chemotherapy within the past 2 to 6 months.</p> <p>Recruiting Phase: 2009 until 2024 (at 55 sites (mostly in Canada and Australia))</p> <p>Inclusion Criteria:</p> <ul style="list-style-type: none"> - complete resection of stage III or high-risk stage II adenocarcinoma of the colon - completed adjuvant chemotherapy within the past 2 to 6 months - ECOG performance-status score of 0 or 1 - reported that they were currently exercising less than the equivalent of 150 minutes per week of moderate-to-vigorous intensity - able to complete at least two stages of a submaximal 	<p>patients</p> <p>Structured exercise program and health-education materials including support from a certified physical activity consultant for 3 years.</p> <p>Comparison: Health-education group: n= 444 patients Receive health-education materials only.</p>	<p>defined as the time from randomization to the first event that was either recurrent (local or distant) colon cancer, a new primary colorectal cancer, a second primary cancer, or death from any cause.</p> <p>Secondary: Overall survival - time from randomization to death from any cause. The prespecified quality-of-life outcome of interest — physical functioning- was assessed according to the physical-functioning subscale on the 36-Item Short Form (SF-36) survey every 6 months during the intervention and at years 4 and 5.</p> <p>Adverse events were monitored for 36 months after randomization.</p> <p>Results: Physical activity: At baseline, the patients reported participating in 11.5 metabolic equivalent task (MET)-hours per week of moderate-to-vigorous physical activity. Attendance at mandatory behavioral-support sessions was:</p> <ul style="list-style-type: none"> - 1-6 months(mo): 83 ± 28% - 7-12 mo: 68 ± 37% - 13-18 mo: 71 ± 41% - 19-36 mo: between 59 and 64% (±43-45%) 	<p>Australian National Health and Medical Research Council, and Cancer Research UK.</p> <p>COI: see publication</p> <p>Randomization: stratified according to trial center, disease stage, body-mass index (≤ 27.5 or >27.5), and ECOG performance-status score (0 or 1) before being randomly assigned in a 1:1 ratio with the use of a dynamic minimization procedure.</p> <p>Blinding: open label</p> <p>Dropout Rate/ITT-Analysis: see text</p> <p>Notes: Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial)</p> <p>Cochrane risk of bias tool (Rob)-1: 3 questions(s) were considered to be unclear risk of bias; 0 question(s) were considered to be high risk of bias Overall risk of bias: Unclear</p> <p>Notes:</p>
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treadmill test or the 6-minute walk test

Exclusion Criteria:

-

Completion rates for the measures of physical activity and fitness were similar in the exercise group and the health-education group: 94 to 99% at baseline and 54 to 63% at 36 months.

Moderate-to-vigorous physical activity was higher in exercise group than in health education group (over 3-years period) (between group differences ranging from 5.2 to 7.4 MET.

Efficacy (median follow-up of 7.9 years):

Disease-free survival: HR 0.72 (95% CI 0.55 to 0.94), p= 0.02.

5-year disease-free survival: exercise group: 80.3%, Health-education: 73.9%.

Overall survival: HR 0.63 (95% CI 0.43 to 0.94)

Safety:

- adverse event of any grade: exercise group n= 351 (82.0%), health-education group: n= 352 (76.4%) .

- musculoskeletal adverse events: exercise group n= 79 (18.5%), health-education group n= 53 (11.5%)

- of the 79 musculoskeletal adverse events in the exercise group, 8 (10%)

- open label
- no details for outcome assessment
- as primary outcome (as well as majority of further outcomes) is objective (Recurrence-free survival), no downgrades were performed.

		<p>were considered to be related to the exercise intervention.</p> <p>- Grade 3 or higher adverse event: exercise group: n= 66 (15.4%), health-education group: n= 42 patients (9.1%).</p> <p>Author's Conclusion: A 3-year structured exercise program initiated soon after adjuvant chemotherapy for colon cancer resulted in significantly longer disease-free survival and findings consistent with longer overall survival.</p>	
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Amendment Evidenztabelle Recherche 2

Schlüsselfrage:

--2025 Amendment 2 Wertigkeit der Therapie mit Encorafenib, Cetuximab, und mFOLOFX6 in BRAFV600E-mutierten KRK

P: BRAFV600E mut KRK, Erstlinie

I: Encorafenib, Cetuximab, und mFOLOFX6

C: Standard of Care

O: OS, PFS, RR, Tox, Lebensqualität

Inhalt: 1 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Elez, E. 2025	2	Phase 3 RCT (BREAKWATER, ongoing, open-label)

Cochrane Risk of Bias Tool 1 (RCT): 1 Bewertung(en)

Elez, E. et al. Encorafenib, Cetuximab, and mFOLFOX6 in BRAF-Mutated Colorectal Cancer. New England journal of medicine. 392. 2425?2437. 2025			
Population	Intervention / Comparison	Outcomes/Results	Methodical Notes

<p>Evidence level: 2</p> <p>Study type: Phase 3 RCT (BREAKWATER, ongoing, open-label)</p> <p>Number of Patients: Patients enrolled in 28 countries: - 158 patients were assigned to the EC group, - 236 to the EC+mFOLFOX6 group, and - 243 to the standard- care group (197 patients (81.1%) received bevacizumab with chemotherapy)</p> <p>Recruiting Phase: November 16, 2021, until December 22, 2023.</p> <p>Inclusion Criteria: - 16 years of age (where permitted locally; otherwise, ≥ 18 years of age) - histologically or</p>	<p>Intervention: EC group received encorafenib (300 mg, orally once daily) and cetuximab (500 mg per square meter of body-surface area, intravenously once every 2 weeks).</p> <p>EC+mFOLFOX6 group received encorafenib (300 mg, orally once daily) and cetuximab (500 mg per square meter, i.v. once every 2 weeks) plus all the components of mFOLFOX6 once every 2 weeks in a 28-day cycle: oxaliplatin (85 mg/m² i.v.), leucovorin (400 mg/m² i.v.), and fluorouracil (400 mg /m² as i.v. bolus and then 2400 mg/m² as a continuous intravenous infusion over a period of 46 to 48 hours)</p> <p>Comparison: Standard-care group received the investigator's choice of chemotherapy: - mFOLFOX6 with or without bevacizumab, - FOLFOXIRI with or without bevacizumab, - CAPOX with or without bevacizumab.</p>	<p>Primary: - objective response (assessed in the objective response analysis set, defined as the first 110 patients who were randomly assigned to each of the EC+mFOLFOX6 and standard- care groups) and - progression-free survival (defined as the time from randomization to the earliest documented disease progression as assessed according to RECIST, version 1.1,17 or death from any cause)</p> <p>Secondary: overall survival, which was defined as the time from randomization to death from any cause and was compared between the EC+mFOLFOX6 group and the standard-care group. - time to response, - duration of response, - disease progression after the next line of therapy, - patient-reported outcomes, - pharmacokinetics, safety, and - biomarker end points.</p>	<p>Funding Sources: Designed and overseen by the sponsor (Pfizer) and a steering committee.</p> <p>COI: see text</p> <p>Randomization: Originally, randomly assigned in a 1:1:1 ratio to receive EC, EC+mFOLFOX6; or standard care. After a protocol amendment, enrollment in the EC group was stopped, and subsequently enrolled patients were randomly assigned in a 1:1 ratio to receive either EC+mFOLFOX6 or standard care. Randomization was implemented by means of interactive response technology.</p> <p>Blinding: Open-label- An independent data and safety monitoring committee oversaw the trial for unblinded safety monitoring. Data collection and analyses were performed by the sponsor in collaboration with the authors.</p> <p>Dropout Rate/ITT-Analysis:</p>
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<p>cytologically confirmed colorectal adenocarcinoma with evidence of stage IV metastatic disease</p> <ul style="list-style-type: none"> - measurable disease - BRAF V600E mutation <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> - previous receipt of systemic treatment for metastatic disease; - previous receipt of a BRAF or EGFR inhibitor; - symptomatic brain metastases; - MSI-H–dMMR tumors (unless the patient was ineligible to receive immune checkpoint inhibitors); - RAS mutation 		<p>Results:</p> <p><u>Data-cutoff date for the analyses was January 6, 2025</u></p> <p>Disease progression or death, HR 0.53; 95% CI, 0.41 to 0.68; P<0.001</p> <p>Median progression-free survival:</p> <ul style="list-style-type: none"> - EC+mFOLFOX6 group: 12.8 months (95% CI, 11.2 to 15.9) - Standard-care group: 7.1 months (95% CI, 6.8 to 8.5) - EC group: 6.8 months (95% CI, 5.7 to 8.3) - median follow-up between 10 and 17 months. <p>Overall survival:</p> <ul style="list-style-type: none"> - HR for death, 0.49; 95% CI, 0.38 to 0.63; P<0.001) <p>Median overall survival:</p> <ul style="list-style-type: none"> - EC+mFOLFOX6 group: 30.3 months (95% CI, 21.7 to could not be estimated) - Standard-care group: 15.1 months (95% CI, 13.7 to 17.7) - EC group: 19.5 months (95% CI, 17.6 to 22.5) 	<p>see text</p> <p>Notes:</p> <p>Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial)</p> <p>Cochrane risk of bias tool (Rob)-1:</p> <p>1 question(s) were considered to be unclear risk of bias; 0 question(s) were considered to be high risk of bias</p> <p>Overall risk of bias: Low</p> <p>Notes:</p> <ul style="list-style-type: none"> - Open-label, however majority of outcomes are objective - Enrollment in the EC group was closed on the basis of the low likelihood of this combination therapy showing superiority over standard care after the results of the phase 2 ANCHOR study of EC plus binimetinib were published (Van Cutsem E. et al. 2023).
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		<p>- median follow-up 21.7/22.2-26.3 months</p> <p><u>Subsequent study treatments:</u></p> <ul style="list-style-type: none">- 12 of 158 patients (7.6%) in the EC+group,- 67 of 236 (28.4%) in the EC+mFOLFOX6 group, and- 16 of 243 (6.6%) in the standard care group were still receiving trial treatment as of the data-cutoff date. <p><u>Median time to second progression or death was</u></p> <ul style="list-style-type: none">- 20.7 months (95% CI, 19.0 to 23.9) in the EC+mFOLFOX6 group,- 12.7 months (95% CI, 11.2 to 13.7) in the standard-care group, and- 14.3 months (95% CI, 12.7 to 16.6) in the EC group <p>Safety: Adverse events during treatment occurred in</p> <ul style="list-style-type: none">- 97.4% of the patients who received EC,- 100% of those who received EC+mFOLFOX6, and	
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		<p>- 99.1% of those who received standard care.</p> <p>The most frequent adverse events during treatment (occurring in $\geq 30\%$ of the patients in any group) were</p> <ul style="list-style-type: none"> - arthralgia (in 34.6% of the patients) in the EC group; - nausea (in 53.9%), anemia (in 46.1%), diarrhea (in 41.8%), decreased appetite (in 37.5%), vomiting (in 36.2%), decreased neutrophil count (in 34.1%), arthralgia (in 31.5%), and rash (in 30.2%) in the EC+mFOLFOX6 group; and - diarrhea (in 50.2%) and nausea (in 49.8%) in the standard-care group. <p><u>Adverse events of grade 3 or 4</u> occurred in</p> <ul style="list-style-type: none"> - 42.5% of the patients who received EC, - 81.5% of those who received EC+mFOLFOX6, and - 66.8% of those who received standard care. <p><u>Grade 5 (fatal) adverse events</u> occurred in</p> <ul style="list-style-type: none"> - 2.6% of the patients who 	
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		<p>received EC, - 4.3% of those who received EC+mFOLFOX6, and - 4.4% of those who received standard care. Adverse events leading to permanent discontinuation of any trial intervention occurred in - 13.1% of the patients in the EC group, - 26.7% of those in the EC+mFOLFOX6 group, and - 17.5% of those in the standard-care group.</p> <p>Author's Conclusion: This trial showed significantly longer progression-free survival and overall survival with first-line treatment with EC+mFOLFOX6 than with standard care among patients with BRAF V600E–mutated metastatic colorectal cancer.</p>	
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Amendment Evidenztabelle Recherche 3

Schlüsselfrage:

--2025 Amendment 3 Wertigkeit der Checkpointblockade bei MSI/dMMR KRK im Stadium IV

P: MSI/dMMR KRK, Stadium IV Erstlinie

I: IO

C: Chemo

O: OS, PFS, RR, Tox, Lebensqualität

Inhalt: 4 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
André, T. 2025	2	Randomised, open-label, international, phase 3 trial (ongoing, CheckMate 8HW)
Andre, T. 2024	2	Randomised, open-label, international, phase 3 trial (ongoing, CheckMate 8HW, interim analysis nivolumab plus ipilimumab vs. chemotherapy)
André, T. 2025		Follow-up analyse (>5 years) of KEYNOTE-177
Diaz, L. A., Jr. 2022	2	Randomised, open-label, phase 3 study (final analysis, KEYNOTE-177)

Cochrane Risk of Bias Tool 1 (RCT): 4 Bewertung(en)

André, T. et al. Nivolumab plus ipilimumab versus nivolumab in microsatellite instability-high metastatic colorectal cancer (CheckMate 8HW): a randomised, open-label, phase 3 trial. Lancet. 405. 383-395. 2025

Population	Intervention / Comparison	Outcomes/Results	Methodical Notes
<p>Evidence level: 2</p> <p>Study type: Randomised, open-label, international, phase 3 trial (ongoing, CheckMate 8HW)</p> <p>Number of Patients: 839 Patients underwent randomization</p> <p>First line-therapy patients: - 202 (57%) of 354 patients in the nivolumab plus ipilimumab group, - 201 (57%) of 353 patients in the nivolumab group, and - 101 (77%) of 132 patients</p>	<p>Intervention: <u>Patients with zero or one previous treatment</u> for metastatic disease were randomly assigned (2:2:1) to one of three treatment groups: 1 - nivolumab plus ipilimumab (nivolumab 240 mg in combination with ipilimumab 1 mg/kg of bodyweight was administered intravenously every 3 weeks for the first 12 weeks (up to four total doses of ipilimumab), followed by nivolumab 480 mg monotherapy every 4 weeks.</p> <p><u>Patients in the nivolumab or nivolumab plus ipilimumab groups received study treatment for a maximum of 2 years.</u></p>	<p>Primary: Progression-free survival (PFS, by blinded independent central review) for nivolumab plus ipilimumab versus chemotherapy in the first-line setting.</p> <p>PFS for nivolumab plus ipilimumab versus nivolumab across all lines of therapy.</p> <p>Secondary: - overall survival, - PFS as determined by investigator assessment, - PFS as determined by blinded independent central review in all patients who underwent random assignment - objective response (as</p>	<p>Funding Sources: Bristol Myers Squibb and Ono Pharmaceutical.</p> <p>COI: See text</p> <p>Randomization: The treatment allocation list was developed by the study sponsor (Bristol Myers Squibb). Patients were centrally randomly assigned by use of an interactive response technology system with a permuted blocks method (block size of 5).</p> <p>Blinding: CheckMate 8HW was an open-label trial, and the treatments administered to the patients remained unmasked.</p>

in the chemotherapy group.

Recruiting Phase:
Between Aug 16, 2019, and April 10, 2023, 839 patients in 128 hospitals and cancer centres in 23 countries were randomly assigned in two parts:

- part 1 was open to patients across all treatment lines and
- part 2 was open to patients with no previous treatment for metastatic disease after completion of part 1

Inclusion Criteria:

- aged at least 18 years
- diagnosis of unresectable or metastatic colorectal cancer and high microsatellite instability or mismatch repair deficiency (or both) status per local testing
- presence of measurable disease per RECIST version 1.1 and an ECOG performance status of 0 or 1 were required for eligibility

Exclusion Criteria:

Comparison:

2 - nivolumab alone (nivolumab 240 mg intravenously every 2 weeks for the first 12 weeks, followed by nivolumab 480 mg monotherapy every 4 weeks)

3- investigator's choice of chemotherapy with or without targeted therapies.

Optional crossover to nivolumab (240 mg every 2 weeks for the first 12 weeks, followed by 480 mg every 4 weeks) plus ipilimumab (1 mg/kg of bodyweight every 6 weeks) was permitted for patients with disease progression in the chemotherapy group (as determined by blinded independent central review).

determined by investigator and blinded independent central review)

- safety
- health-related quality of life (HRQoL)

Results:

- data cutoff on Aug 28, 2024, median follow-up was 47.0 months (IQR 38.4–53.2)

Nivolumab + ipilimumab vs nivolumab

Treatment discontinuation:

- 173 (49%) of 352 patients in the nivolumab plus ipilimumab group and 201 (57%) of 351 patients in the nivolumab group discontinued treatment.
- reason disease progression 82 (23%) of 352 patients (nivolumab plus ipilimumab); 137 (39%) of 351 patients (nivolumab group)

PFS: HR 0.62, 95% CI 0.48 to 0.81; p=0.0003
In patients with centrally confirmed MSI/dMMR metastatic

Dropout Rate/ITT-Analysis:
see text

Notes:
Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial)

Cochrane risk of bias tool (Rob)-1:
2 question(s) were considered to be unclear risk of bias; 0 question(s) were considered to be high risk of bias
Overall risk of bias: Low

Notes:
- open label
- as primary outcome (as well as majority of further outcomes) is objective (PFS), no downgrades were performed
- data to chemotherapy comparison group preliminary due to differences in recruiting

Notes by study authors:
- The trial is ongoing to assess secondary endpoints according to the hierarchical testing plan including progression-free

Patients who had received previous immunotherapies (anti-PD-1, anti-PD-L1 or antiPD-L2, anti-cytotoxic T-lymphocyte antigen-4, or any other antibody or drug targeting T-cell co-stimulation or checkpoint pathways) were excluded

colorectal cancer
Median PSF was not reached with nivolumab plus ipilimumab (95% CI 53.8 to not estimable) and was 39.3 months with nivolumab (22.1 to not estimable).

Adverse events (grade 3 or 4):
- Nivolumab + ipilimumab n= 168 (48%), nivolumab n= 151 (43%)
- Most common diarrhoea or colitis, hypophysitis and adrenal insufficiency

Nivolumab + ipilimumab vs chemotherapy

At this updated analysis (Aug 28, 2024 data cutoff and minimum follow-up of 16.7 months):

Median PFS (MSI/dMMR confirmed, first line setting): HR 0.21, 95% CI 0.14 to 0.31

- nivolumab plus ipilimumab group: 54.1 months (95% CI 54.1 to not estimable)
- chemotherapy group: 5.9 months (4.4 to 7.8)

The 24-month PFS rate with longer follow-up was 74% (95% CI 67 to 80) with nivolumab plus ipilimumab and 11% (4 to 21)

survival for nivolumab plus ipilimumab versus nivolumab in the first-line setting, which did not meet the prespecified statistical criteria for significance at this interim analysis, as determined by the data monitoring committee, and therefore remains masked until its final analysis.

		<p>with chemotherapy; 36-month progression-free survival rates were 69% (61 to 76) and 11% (4 to 21), respectively.</p> <p>Author's Conclusion: Nivolumab plus ipilimumab showed superior progression-free survival versus nivolumab across all treatment lines, with a manageable safety profile, in patients with microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer. These results, together with the first-line results of superior progression-free survival with nivolumab plus ipilimumab versus chemotherapy, suggest nivolumab plus ipilimumab as a potential new standard of care for patients with microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer.</p>	
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Andre, T. et al. Nivolumab plus Ipilimumab in Microsatellite-Instability-High Metastatic Colorectal Cancer. N Engl J Med. 391. 2014-2026. 2024

Population	Intervention / Comparison	Outcomes/Results	Methodical Notes
<p>Evidence level: 2</p> <p>Study type: Randomised, open-label, international, phase 3 trial (ongoing, CheckMate 8HW, interim analysis nivolumab plus ipilimumab vs. chemotherapy)</p> <p>Number of Patients: 303 First-line therapy Patients underwent randomization</p> <p>Recruiting Phase: Between Aug 16, 2019, and April 10, 2023, 839 patients in 128 hospitals and cancer centres in 23 countries were randomly assigned in two parts: - part 1 was open to patients across all treatment lines and - part 2 was open to patients with no previous treatment for metastatic disease after</p>	<p>Intervention: Patients with zero or one previous treatment for metastatic disease were randomly assigned (2:2:1) to one of three treatment groups:</p> <p>1 - nivolumab plus ipilimumab (nivolumab 240 mg in combination with ipilimumab 1 mg/kg of bodyweight was administered intravenously every 3 weeks for the first 12 weeks (up to four total doses of ipilimumab), followed by nivolumab 480 mg monotherapy every 4 weeks.</p> <p>Comparison: 2 - nivolumab alone (nivolumab 240 mg intravenously every 2 weeks for the first 12 weeks, followed by nivolumab 480 mg monotherapy every 4 weeks)</p> <p>3- investigator's choice of chemotherapy with or without targeted therapies.</p> <p>Optional crossover to nivolumab (240 mg every 2 weeks for the first 12</p>	<p>Primary: progression-free survival with nivolumab plus ipilimumab as compared with chemotherapy in patients who had not previously received systemic treatment for metastatic disease</p> <p>Secondary:</p> <p>Results: Data-cutoff date, October 12, 2023, with a median follow-up (the time from randomization to the data-cutoff date) of 31.5 months (range, 6.1 to 48.4)</p> <p>Progression-free survival 12 months: 79% (95% confidence interval [CI], 72 to 84) with nivolumab plus ipilimumab and 21% (95% CI, 11 to 32) with chemotherapy 24 months: 72% (95% CI, 64</p>	<p>Funding Sources: Bristol Myers Squibb and Ono Pharmaceutical.</p> <p>COI: See text</p> <p>Randomization: The treatment allocation list was developed by the study sponsor (Bristol Myers Squibb). Patients were centrally randomly assigned by use of an interactive response technology system with a permuted blocks method (block size of 5).</p> <p>Blinding: CheckMate 8HW was an open-label trial, and the treatments administered to the patients remained unmasked.</p> <p>Dropout Rate/ITT-Analysis: see text</p> <p>Notes: Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial)</p>

<p>completion of part 1 Inclusion Criteria: - aged at least 18 years - diagnosis of unresectable or metastatic colorectal cancer and high microsatellite instability or mismatch repair deficiency (or both) status per local testing - presence of measurable disease per RECIST version 1.1 and an ECOG performance status of 0 or 1 were required for eligibility Exclusion Criteria: Patients who had received previous immunotherapies (anti-PD-1, anti-PD-L1 or antiPD-L2, anti-cytotoxic T-lymphocyte antigen-4, or any other antibody or drug targeting T-cell co-stimulation or checkpoint pathways) were excluded</p>	<p>weeks, followed by 480 mg every 4 weeks) plus ipilimumab (1 mg/kg of bodyweight every 6 weeks) was permitted for patients with disease progression in the chemotherapy group (as determined by blinded independent central review).</p>	<p>to 79) and 14% (95% CI, 6 to 25) At 24 months, the restricted mean survival time was 10.6 months (95% CI, 8.4 to 12.9) longer with nivolumab plus ipilimumab than with chemotherapy Safety Adverse events of any grade and from any cause occurred in 99% of the patients in the nivolumab-plus-ipilimumab group and in 98% of the patients in the chemotherapy group; grade 3 or 4 adverse events occurred in 48% and in 67%, respectively Quality of life The differences between the groups exceeded the prespecified threshold for meaningful change from week 13 onward, which indicated a health-related quality-of-life benefit with nivolumab plus ipilimumab as compared with chemotherap</p>	<p>Cochrane risk of bias tool (Rob)-1: 2 questions(s) were considered to be unclear risk of bias; 0 question(s) were considered to be high risk of bias Overall risk of bias: Low Notes: - open label - as primary outcome (as well as majority of further outcomes) is objective (PFS), no downgrades were performed - data to chemotherapy comparison group preliminary due to differences in recruiting Notes by study authors: - The trial is ongoing to assess secondary endpoints according to the hierarchical testing plan including progression-free survival for nivolumab plus ipilimumab versus nivolumab in the first-line setting, which did not meet the prespecified statistical criteria for significance at this interim analysis, as determined by the data monitoring committee, and therefore remains masked until its final analysis.</p>
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		<p>Author's Conclusion: Progression-free survival was longer with nivolumab plus ipilimumab than with chemotherapy among patients who had not previously received systemic treatment for MSI-H or dMMR metastatic colorectal cancer</p>	
<p>André, T. et al. Pembrolizumab versus chemotherapy in microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer: 5-year follow-up from the randomized phase III KEYNOTE-177 study. Ann Oncol. 36. 277-284. 2025</p>			
Population	Intervention / Comparison	Outcomes/Results	Methodical Notes
<p>Evidence level:</p> <p>Study type: Follow-up analyse (>5 years) of KEYNOTE-177</p> <p>Number of Patients:</p> <p>Recruiting Phase:</p>	<p>Intervention:</p> <p>Comparison:</p>	<p>Primary:</p> <p>Secondary:</p> <p>Results: - data cut-off of 17 July 2023 - the median follow-up (time from randomization to data cut-off) was 73.3 months (range, 64.9-89.2 months)</p> <p>OS: HR, 0.73; 95% CI 0.53- 0.99</p>	<p>Funding Sources:</p> <p>COI:</p> <p>Randomization:</p> <p>Blinding:</p> <p>Dropout Rate/ITT-Analysis:</p> <p>Notes:</p>

<p>Inclusion Criteria:</p> <p>Exclusion Criteria:</p>		<p>- pembrolizumab arm median OS was 77.5 months (95% CI 49.2 months-NR) - chemotherapy arm 36.7 months (95% CI 27.6-65.3 months)</p> <p>The percentages of patients alive and without disease progression at - 36 months pembrolizumab arm: 42.7% vs. chemotherapy: 13.4% - 60 months pembrolizumab arm: 34.0% vs. chemotherapy: 7.6%</p> <p>The 36- and 60-month survival rates were 94.9% and 86.4%, respectively. The ORR was 69.5% (95% CI 56.1% to 80.8%); 18 patients (30.5%) had a CR, and 23 (39.0%) had a PR.</p> <p>Author's Conclusion:</p>	<p>Hier werden nur die ergänzenden Daten des 5-Jahre Follow-up dargestellt; die anderen Ergebnisse und allgemeinen Angaben zu Ein- und Ausschluss, Recruiting etc. sind in der finalen Analyse Diaz et al 2022 zu finden.</p>
<p>Diaz, L. A., Jr. et al. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. Lancet Oncol. 23. 659-670. 2022</p>			
<p>Population</p>	<p>Intervention / Comparison</p>	<p>Outcomes/Results</p>	<p>Methodical Notes</p>

Evidence level:

2

Study type:

Randomised, open-label, phase 3 study (final analysis, KEYNOTE-177)

Number of Patients:

307 patients with previously untreated MSI-H and or dMMR mCRC were randomized;
- pembrolizumab n= 153
- Chemotherapy n= 154

Recruiting Phase:

February 11, 2016 until February 19, 2018

Inclusion Criteria:

- aged ≥ 18 years
- with locally confirmed MSI-H or dMMR stage IV CRC
- with measurable disease per RECIST v1.1 by local investigator/radiology assessment,
- ECOG performance status of 0 or 1,
- adequate organ function
- adequate hematological function, renal function, hepatic function

Exclusion Criteria:

Intervention:

Pembrolizumab (intravenous 200 mg every three weeks)
- max. of 35 treatments

Comparison:

Investigator choice chemotherapy (chosen at least 3 days before randomization) with mFOLFOX every 2 weeks or FOLFIRI every 2 weeks with or without intravenous bevacizumab (5 mg/kg on day 1) every 2 weeks or intravenous cetuximab (400 mg/m² in week 1 followed by 250 mg/m² weekly thereafter).

Patients randomized to chemotherapy had the option to cross over and receive 35 treatments with pembrolizumab after disease progression confirmed by blinded independent central review.

Primary:

Progression-free survival (PFS, per RECIST v1.1 by central review (randomization to first disease progression or death of any cause) and

Overall survival (OS, randomization to death of any cause) in the intent-to-treat population (ITT).

Secondary:

- objective response per RECIST v1.1 by central review in the ITT,
- safety and tolerability in all patients as treated.

Results:

- data cut-off date of February 19, 2021,
- the median time from randomization to data cut-off was 44.5 months (IQR, 39.7–49.8). - At final analysis, 59 patients in the pembrolizumab group had completed 35 treatments according to protocol; no patients in the pembrolizumab group and 2 in the chemotherapy group were still receiving first-line treatment.

OS: HR 0.74, 95% CI, 0.53–1.03; p = 0.0359

- pembrolizumab: median not reached

Funding Sources:

This study and assistance with medical writing were funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD).

COI:

See text

Randomization:

- Treatment allocation and randomization occurred centrally
- patients randomly allocated 1:1
- interactive voice response system (IVRS)/integrated web response system in a block size of four per stratum.
- no stratification.

Blinding:

Patients, investigators, and site staff were not masked to study treatment.

Dropout Rate/ITT-

Analysis:

see text

Notes:

- patients who received prior systemic therapy for stage IV CRC, although patients may have received adjuvant therapy for CRC if completed at least 6 months before randomization,
- patients with an active autoimmune disease that required systemic treatment within the previous 2 years,
- and those with a diagnosis of immunodeficiency or receiving systemic steroid therapy or other immunosuppressive therapy at least 7 days before randomization.

(NR), 95% CI, 49.2 to NR
- chemotherapy: median 36.7 months, 95% CI, 27.6 to NR
- a total of 140/307 (45.6%) died,
-- pembrolizumab group: 62/153 (40.5%)
-- chemotherapy group: 78/154 (50.6%)

At data cut-off, 56 (36%) of 154 patients had crossed over on study to pembrolizumab from the chemotherapy group following progression.

PFS: HR 0.59, 95% CI 0.45–0.79
- pembrolizumab: median 16.5 months, 95% CI 5.4–38.1
- chemotherapy: median 8.2 months, 95% CI 6.1–10.2

Adverse events:

- Grade ≥ 3 events 86 (56%) of 153 versus 112 (78%) of 143 patients in the pembrolizumab and chemotherapy groups.
- any cause grade 5 adverse events observed in 6 (3.9%) of 153 patients in the pembrolizumab group and 7 (4.9%) of 143 patients in the

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 2 (Randomized trial)

Cochrane risk of bias tool (Rob)-1:
2 question(s) were considered to be unclear risk of bias; 0 question(s) were considered to be high risk of bias
Overall risk of bias: Low

Notes:
- open label
- as primary outcome (as well as majority of further outcomes) is objective (OS), no downgrades were performed

		<p>chemotherapy group.</p> <ul style="list-style-type: none">- discontinuation of pembrolizumab due to a treatment-related adverse event occurred in 15 (10%) of 153 patients.- discontinuation of chemotherapy due to a treatment-related adverse event occurred in 10 (7%) of 143 patients. <p>Author's Conclusion: Pembrolizumab versus chemotherapy continued to provide durable antitumor activity, with no significant difference in OS, and fewer treatment-related events. These findings support pembrolizumab as effective first-line therapy in patients with MSI-H/dMMR mCRC.</p>	
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