Literaturrecherchen und Evidenztabellen für die Version 5 der S3-Leitlinie Diagnostik und Therapie des Hepatozellulären Karzinoms und biliärer Karzinome

Inhaltsverzeichnis

1 Methodisches Vorgehen

1.1 Leitlinienrecherche

In der aktuellen Version wurde keine Leitlinienrecherche durchgeführt.

1.2 Systematische Literaturrecherche

1.2.1 Formulierung von Schlüsselfragen

Es handelt sich um die Aktualisierung der S3- Leitlinie „Hepatozelluläres Karzinom, Diagnostik und Therapie“ vom 30.08.2023 (AWMF Registernummer 032 - 053OL).

Es wurden drei Recherchen durchgeführt, davon zwei aktualisierte Fragestellungen und eine neue Fragestellungen.

Die Auflistung der Schlüsselfragen mit genauer Beschreibung des PICO Schemas für die de-novo Fragestellungen finden sich im Anhang Appendix.

1.2.2 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 library und Cochrane Central Datenbanken über die Cochrane Suchoberfläche https://www.cochranelibrary.com/.

Die Suchen wurden am dem 20.06.2023 durchgeführt, jedoch wurde nur Literatur berücksichtigt, die bis ab dem 31.10.2022 publiziert wurde für die beiden Aktualisierungsrecherchen, bzw. ab dem 01.10.2017 für die neue Recherche.
Es wurden 664 Suchtreffer in Medline und 438 Suchtreffer in der Cochrane-Library und Cochrane Central erzielt. Die Suchtreffer wurden kombiniert und die Duplikate wurden entfernt.

In Summe verblieben 1071 Literaturstellen, die über die Recherche 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 Library	Cochrane Central	**Kombiniert ohne Duplikate**
HCC Kombination TACE + System-therapie	227	3	98	**311**
HCC 20 System-therapie	318	1	280	**587**
CCA 15	119	0	56	**173**
				1071

1.3 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.

1.3.1 Ein- und Ausschlussgründe

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

- Deutsche und englische Veröffentlichungen
- Probandenstudien (keine Tierversuche)
- Veröffentlichungszeitraum
    - zwischen 31/10/2022 und 20.06.2023 für die Aktualisierungs-recherchen zum hepatozellulären Karzinom und Cholangiokarzinom (HCC 20, CCA 15)
    - zwischen 01/10/2017 und 20.06.2023 für die neuen Fragestellungen zur Kombinationstherapie des hepatozellulären Karzinoms (HCC TACE + Systemtherapie)

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)
- Überlappende Übersichtsarbeiten
- 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.)

1.3.2 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 Mitgliedern der Leitlinienkoordination getroffen und selbst im Leitlinienportal durchgeführt.

Von den von Duplikaten bereinigten 1071 Suchtreffern wurden 52 als potentiell 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. Ausschlüssgründe überprüft. Es wurden 14 relevante Literaturstellen identifiziert. Die Auswahl wurde von den Mitgliedern der Leitlinienkoordination getroffen und selbst im Leitlinienportal durchgeführt, welche im Anschluss der Evidenzbewertung zugeführt wurden.

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

1.3.3 Experten beigesteuerte Literatur

Zusätzlich zur Recherche wurden drei Literaturstellen durch die ExpertInnen nachnominiert.
Diese sind in der Bewertung eindeutig als solche gekennzeichnet und werden im folgenden Absatz aufgelistet:

- Goyal L, et al. Futibatinib for FGFR2-Rearranged Intrahepatic Cholangiocarcinoma. N Engl J Med 2023 Jan 19;388(3):228-239.
- Qin S, et al. Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050): a randomised, open-label, multicentre, phase 3 trial. Lancet 2023 Nov 18;402(10415):1835-1847.
- Rimini M, et al. Survival outcomes from atezolizumab plus bevacizumab versus Lenvatinib in Child Pugh B unresectable hepatocellular carcinoma patients. J Cancer Res Clin Oncol. 2023 Aug;149(10):7565-7577. Bewertung

1.4 Leitlinienadaptation

Es wurde keine Leitlnienadaptation vorgenommen

1.5 Bewertung der Evidenz

Nach Abschluss des Screeningprozesses wurden die eingeschlossenen Studien den jeweiligen Schlüsselfragen bzw. bestehenden evidenzbasierten Empfehlungen im Leitlinienportal zugeordnet.

Die Literaturbewertung wurde nach der Evidenzklassifizierung des Oxford Centre for Evidence-Based Medicine 2011[1] (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 Evidenztabellen 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“.

Für randomisierte kontrollierte Studien fand das Risk-of-Bias (RoB) Tool der Cochrane Collaboration[2] Anwendung. Das RoB-Tool stellt ein Instrument zur Bewertung des Verzerrungspotentials in randomisierten kontrollierten Studien (RCTs) dar und setzt sich aus sieben Domänen zusammen:

- Generierung der Randomisierungssequenz
- Verdeckte Gruppenzuteilung
- Verblindung von Teilnehmer*innen und Studienpersonal

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[1] Levels of Evidence Working Group*. “The Oxford Levels of Evidence 2”. Oxford Centre for Evidence-Based Medicine. https://www.cebm.net/index.aspx?o=5653
** OCEBM Levels 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* (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

- 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“.

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 zwei Domänen ein hohes Bias- Risiko aufwiesen.
Die Ergebnisse der RoB-Bewertungen sind in den Evidenztabellen zusammengefasst.

Zur Erfassung des Bias-Risikos fand in Kohortenstudien und Fall-Kontroll Studien die New-Castle Ottawa Scale (NOS)[3] Anwendung.

NOS ist ein Instrument zur Erfassung der Qualität von nicht-randomisierten Studien. Es umfasst ein „Sternesystem“, bei dem die vorliegende Studie anhand von drei Domänen beurteilt wird: Auswahl der Studiengruppen (Selection Domain), Vergleichbarkeit der Gruppen (Comparability Domain) sowie Erfassung der Exposition von Interesse (bei Kohortenstudien) oder bei Fall Kontrollstudien Erfassung des Outcomes von Interesse (Outcome/Exposure Domain).

Sowohl für Kohortenstudien als auch für Fall-Kontroll-Studien ist eine maximale Anzahl von neun Sternen möglich. Für diese Leitlinie wurde ein hohes Bias-Risiko festgestellt, wenn eines der nachfolgenden Szenarien festgestellt wurde:

- 0 oder 1 Stern in der Selection Domain
- 0 Sterne in der Comparability Domain
- 0 oder 1 Stern in der Outcome/Exposure Domain

Dieses Vorgehen orientiert sich an dem Vorschlag der Agency for Healthcare Research and Quality (AHRQ)[4] zur Konvertierung der NOS in die AHRQ-Standards (good, fair and poor).

[3] The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (abgerufen am 06.03.2023).

[4] Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor). https://www.ncbi.nlm.nih.gov/books/NBK115843/bin/appe-fm3.pdf (Abgerufen am 06.02.2023).

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	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

	Studien				
Was sind die häufigen Nachteile/ Schäden durch die Intervention? Behandlungsnachteil	Systematische Reviews von randomisierten Studien oder Nested Fall Kontroll Studien, n=1 Studien, oder Observationsstudien mit dramatischem Effekt	Randomisierte Studien oder (herausragende) Observationsstudien mit dramatischen Effekt	Nicht-randomisierte kontrollierte Kohorten / Follow-up Studien (Beobachtung nach Marktzulassung), ausreichende Fallzahl vorausgesetzt um häufige Schäden auszuschließen (Für Langzeit Schäden muss die Nachfolgezeit ausreichend sein)	Fall Serien oder Fall-Kontroll Studien, oder historische kontrollierte Studien	Mechanismus-basierte Argumentation
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.

1.6 Erstellung von Evidenztabellen

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 Evidenztabellen geordnet und nach Studientyp im Leitlinienportal zusammengefasst.

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

Nicht bei allen Studien lag zum Zeitpunkt der Bewertung und dem Abschluss der Artikel im Volltext vor, weswegen abschließend zwei Artikel nicht bewertet werden konnten, da diese generell nur als Abstract verfügbar waren.

Diese sind:

- Bai X, et al. 712P CAPT: A multicenter randomized controlled trial of perioperative versus postoperative camrelizumab plus apatinib for resectable hepatocellular carcinoma. Annals of oncology VOLUME 33, SUPPLEMENT 7, S868, SEPTEMBER 2022
- Finn R,S, et al. LBA34 Primary results from the phase III LEAP-002 study: Lenvatinib plus pembrolizumab versus lenvatinib as first-line (1L) therapy for advanced hepatocellular carcinoma (aHCC). Annals of oncology VOLUME 33, SUPPLEMENT 7, S1401, SEPTEMBER 2022

Insgesamt wurden daher 12 Literaturstellen bewertet.

2 Ergebnisse der Literaturrecherchen

2.1 HCC 20 Updaterecherche

Frage	Population	Intervention	Alternativ maßnahme	Outcome	Prio-risierung
HCC 20 Systemtherapie Von welchen Systemtherapien profitieren Patienten mit fortgeschrittenem HCC?	Patienten mit fortgeschrittenem HCC Child A und Child B	Atezolizumab, Bevacizumab Durvalumab, Tremelimumab Sorafenib Lenvatinib Regorafenib Cabozantinib Ramucirumab PD1-Inhibitoren CTLA4-Inhibitoren	Keine Therapie oder gegen Sorafenib/ andere Therapien	Overall survival	9
				Time to Progression oder Progression free survival	8
				Adverse Events	7
				Quality of life	7

Einschlusskriterien	**Allgemeine Einschlusskritieren**
Zielgruppe	Patienten mit hepatozellulärem Karzinom, nicht resektabel, keine lokoregionäre Therapie
Publikationstyp	Randomisierte kontrollierte Studien (RCTs) oder systematische Übersicht mit/ohne Metaanalyse von RCTs, Phase II-Studien
Sprachen	Deutsch oder Englisch
Suchzeitraum	31.10.2022-01.06.2023

Recherche in PubMed (20.06.2023)

	HCC 20 Systemtherapie Von welchen Systemtherapien profitieren Patienten mit fortgeschrittenem HCC?	
Nr	**Query**	**Hits**
#1	Carcinoma, Hepatocellular[Mesh] OR HCC[tiab] OR Hepatom*[tiab] OR ((Carcinoma*[tiab] OR Cancer[tiab] OR cancers[tiab]) AND (hepatocellular[tiab] OR liver cell[tiab] OR adult liver[tiab]))	178.308
#2	(Neoplasms[Mesh] OR Neoplas*[tiab] OR Tumor[tiab] OR Tumors[tiab] OR Cancer*[tiab] OR Malignanc*[tiab]) AND (hepatocellular[tiab] OR hepatic*[tiab] OR liver*[tiab] OR "Liver"[Mesh])	336.791
#3	Liver Cirrhosis[Mesh] OR ((liver[Mesh]) AND ("Fibrosis"[Mesh] OR cirr*[tiab] OR fibrosis[tiab]))	115.937
#4	#1 OR #2 OR #3	479.879
#5	atezolizumab [Supplementary Concept] OR atezolizumab[tiab] OR anti-PDL1[tiab] OR MPDL3280A[tiab] OR MPDL-3280A[tiab] OR Tecentriq[tiab] OR RG7446[tiab] OR RG-7446[tiab]	3.173
#6	Bevacizumab[Mesh] OR Bevacizumab[tiab] OR Mvasi[tiab] OR Avastin[tiab]	229.808
#7	durvalumab [Supplementary Concept] OR durvalumab[tiab] OR MEDI4736[tiab] OR MEDI-4736[tiab] OR Imfinzi[tiab]	1.473
#8	tremelimumab [Supplementary Concept] OR tremelimumab[tiab] OR ticilimumab[tiab] OR CP 675[tiab] OR CP675 cpd[tiab] OR CP-675[tiab] OR CP-675,206[tiab] OR CP-675206[tiab] OR CP675206[tiab] OR CP 675206[tiab]	505
#9	Sorafenib[Mesh] OR Sorafenib[tiab] OR Nexavar[tiab] OR BAY 43-9006[tiab] OR BAY 43 9006[tiab] OR BAY 439006[tiab] OR Sorafenib N-Oxide[tiab] OR Sorafenib N Oxide[tiab] OR BAY-673472[tiab] OR BAY 673472[tiab] OR BAY 545-9085[tiab] OR BAY 545 9085[tiab] OR BAY 5459085[tiab] OR BAY-545-9085[tiab] OR BAY5459085[tiab]	11.712
#10	"lenvatinib" [Supplementary Concept] OR Lenvatinib[tiab] OR E 7080[tiab] OR E-7080[tiab] OR Lenvima[tiab]	2.089
#11	regorafenib [Supplementary Concept] OR Regorafenib[tiab] OR Stivarga[tiab] OR BAY 73-4506[tiab] OR BAY73-4506[tiab] OR BAY-73-4506[tiab]	1.873
#12	cabozantinib [Supplementary Concept] OR Cabozantinib[tiab] OR Cometriq[tiab] OR XL 184[tiab] OR XL184 cpd[tiab] OR XL-184[tiab] OR BMS 907351[tiab] OR BMS907351[tiab] OR BMS-907351[tiab]	1.569
#13	ramucirumab [Supplementary Concept] OR Ramucirumab[tiab] OR Cyramza[tiab] OR IMC 1121B[tiab] OR IMC1121B[tiab] OR IMC-	1.245

	1121B[tiab]	
#14	("Programmed Cell Death 1 Receptor"[Mesh] OR PD-1[tiab] OR PD 1[tiab] OR programmed cell death protein 1[tiab] OR CD279 Antigen[tiab] OR Antigen, CD279[tiab]) AND (inhibitor*[tiab] OR antibod*[tiab] OR antagonist[tiab]) OR PD-L1[tiab] OR PD L1[tiab]	35.276
#15	Nivolumab[Mesh] OR Opdivo[tiab] OR ONO-4538[tiab] OR ONO 4538[tiab] OR ONO4538[tiab] OR MDX-1106[tiab] OR MDX 1106[tiab] OR MDX1106[tiab] OR BMS-936558[tiab] OR BMS 936558[tiab] OR BMS936558[tiab]	5.156
#16	pembrolizumab [Supplementary Concept] OR Pembrolizumab[tiab] OR lambrolizumab[tiab] OR Keytruda[tiab] OR MK-3475[tiab]	8.810
#17	avelumab [Supplementary Concept] OR avelumab[tiab] OR MSB-0010682[tiab] OR MSB0010682[tiab] OR bavencio[tiab] OR MSB0010718C[tiab] OR MSB-0010718C[tiab]	924
#18	cemiplimab [Supplementary Concept] OR cemiplimab[tiab] OR REGN2810[tiab]	346
#19	dostarlimab [Supplementary Concept] OR dostarlimab[tiab] OR Jemperli[tiab] OR dostarlimab-gxly[tiab] OR TSR-042[tiab] OR GSK4057190[tiab]	94
#20	Retifanlimab[tiab]	10
#21	(CTLA-4 Antigen[Mesh] OR CTLA-4[tiab] OR CD152[tiab] OR Cytotoxic T-Lymphocyte-Associated Antigen 4[tiab] OR Cytotoxic T Lymphocyte Associated Antigen 4[tiab] OR Cytotoxic T-Lymphocyte Antigen 4[tiab] OR Cytotoxic T Lymphocyte Antigen 4[tiab]) AND (inhibitor*[tiab] OR antibod*[tiab] OR antagonist[tiab])	7.576
#22	Ipilimumab[Mesh] OR Ipilimumab*[tiab] OR Yervoy[tiab] OR MDX 010[tiab] OR MDX010[tiab] OR MDX-010[tiab] OR MDX-CTLA-4[tiab] OR MDX CTLA 4[tiab]	5.478
#23	Immunotherapy, Active[Mesh] OR Immunotherap*[tiab] OR (immun*[tiab] AND therap*[tiab])	731.375
#24	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	782.116
#25	#4 AND #24	35.224
#26	(systematic*[tiab] AND (bibliographic*[tiab] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[tiab] AND (bibliographic*[tiab] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR	850.954

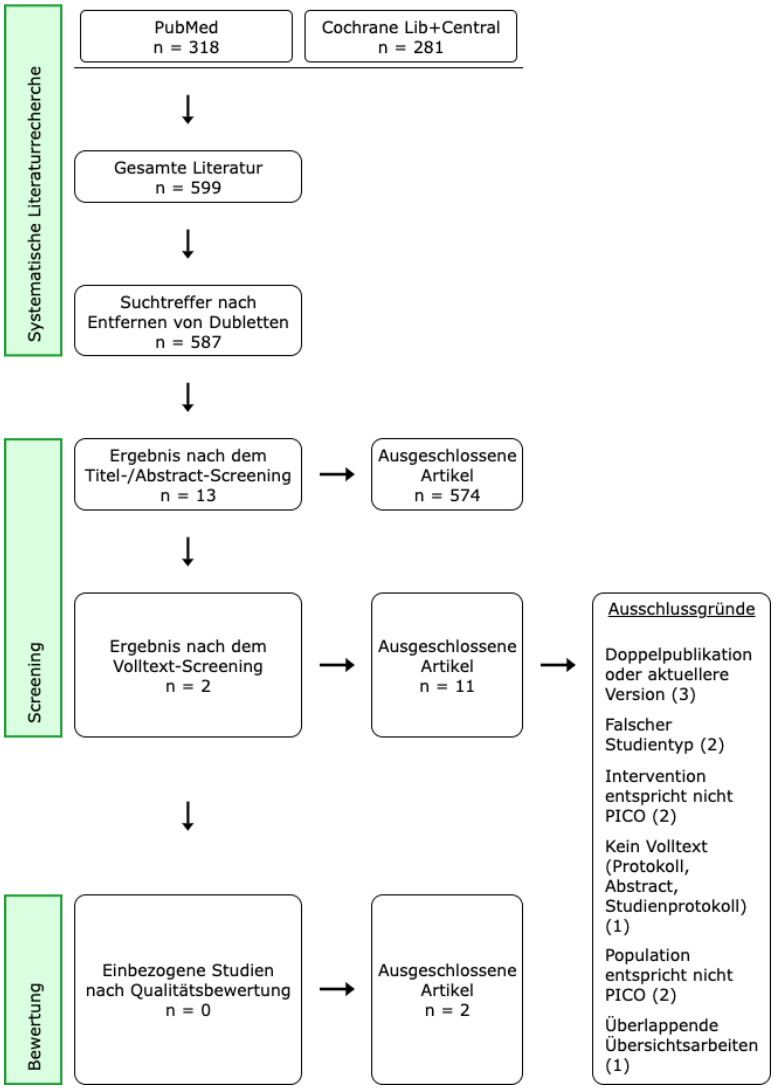
	cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT "psycinfo database"[tiab]) OR pubmed[tiab] OR scopus[tiab] OR "web of science"[tiab] OR "data synthesis"[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR "meta-analysis as topic"[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])	
#27	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]	1.625.049
#28	#26 OR #27	2.305.780
#29	animals[mh] NOT humans[mh]	5.129.019
#30	#28 NOT #29	2.167.565
#31	#25 AND #30	3.923
#32	Publication date from 31/10/2022 to date of search, English and German articles, Abstract available	318

Recherche in der Cochrane Library (20.06.2023)

Search Name:	HCC 2023 - HCC 20	
Date Run:	20.06.23 20:12	
Comment:		
ID	Search	Hits
#1	MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees	2384
#2	(Carcinoma, Hepatocellular OR hepatocellular carcinoma OR HCC OR Hepatom* OR ((Carcinoma* OR Cancer OR cancers) AND (hepatocellular OR liver cell OR adult liver))):ti,ab,kw	13151
#3	MeSH descriptor: [Neoplasms] explode all trees	111266
#4	(Neoplas* OR Tumor OR Tumors OR Cancer* OR Malignanc* OR carcinom):ti,ab,kw	250630
#5	#3 OR #4	263723
#6	MeSH descriptor: [Liver] explode all trees	5486
#7	(hepatocellular OR hepatic* OR liver*):ti,ab,kw	71301

#8	#6 OR #7	71346
#9	#5 AND #8	21140
#10	MeSH descriptor: [Liver Cirrhosis] explode all trees	4344
#11	MeSH descriptor: [Liver] explode all trees	5486
#12	(liver OR hepat*):ti,ab,kw	87457
#13	#11 OR #12	87497
#14	MeSH descriptor: [Fibrosis] explode all trees	8467
#15	(cirrh* OR fibros* OR fibrot*):ti,ab,kw	27622
#16	#14 OR #15	29633
#17	#13 AND #16	13610
#18	#1 OR #2 OR #9 OR #10 OR #17	34130
#19	(atezolizumab OR anti-PDL1 OR MPDL3280A OR MPDL-3280A OR Tecentriq OR RG7446 OR RG-7446):ti,ab,kw	1352
#20	MeSH descriptor: [Bevacizumab] explode all trees	2637
#21	(Bevacizumab OR Mvasi OR Avastin):ti,ab,kw	7458
#22	(durvalumab OR MEDI4736 OR MEDI-4736 OR Imfinzi):ti,ab,kw	1053
#23	(tremelimumab OR ticilimumab OR CP 675 OR CP675 cpd OR CP-675 OR CP-675,206 OR CP-675206 OR CP675206 OR CP 675206):ti,ab,kw	423
#24	MeSH descriptor: [Sorafenib] explode all trees	628
#25	(Sorafenib OR Nexavar):ti,ab,kw	2124
#26	(Lenvatinib OR E 7080 OR E-7080 OR Lenvima):ti,ab,kw	696
#27	(Regorafenib OR Stivarga):ti,ab,kw	641
#28	(Cabozantinib OR Cometriq OR XL 184 OR XL184 cpd OR XL-184 OR BMS 907351 OR BMS907351 OR BMS-907351):ti,ab,kw	513
#29	(Ramucirumab OR Cyramza OR IMC 1121B OR IMC1121B OR IMC-1121B):ti,ab,kw	631
#30	MeSH descriptor: [Programmed Cell Death 1 Receptor] explode all trees	170
#31	(("Programmed Cell Death 1 Receptor" OR PD-1 OR PD 1 OR programmed cell death protein 1 OR CD279 Antigen OR Antigen, CD279) AND (inhibitor* OR antibod* OR antagonist) OR PD-L1 OR	11557

	PD L1):ti,ab,kw	
#32	(Nivolumab OR Opdivo OR ONO-4538 OR ONO 4538 OR ONO4538 OR MDX-1106 OR MDX 1106 OR MDX1106 OR BMS-936558 OR BMS 936558 OR BMS936558):ti,ab,kw	2800
#33	MeSH descriptor: [Nivolumab] explode all trees	760
#34	(Pembrolizumab OR lambrolizumab OR Keytruda OR MK-3475):ti,ab,kw	2802
#35	(avelumab OR MSB-0010682 OR MSB0010682 OR bavencio OR MSB0010718C OR MSB-0010718C):ti,ab,kw	360
#36	(cemiplimab OR REGN2810):ti,ab,kw	120
#37	(dostarlimab OR Jemperli OR dostarlimab-gxly OR TSR-042 OR GSK4057190):ti,ab,kw	57
#38	(Retifanlimab):ti,ab,kw	14
#39	MeSH descriptor: [CTLA-4 Antigen] explode all trees	78
#40	((CTLA-4 Antigen OR CTLA-4 OR CD152 OR Cytotoxic T-Lymphocyte-Associated Antigen 4 OR Cytotoxic T Lymphocyte Associated Antigen 4 OR Cytotoxic T-Lymphocyte Antigen 4 OR Cytotoxic T Lymphocyte Antigen 4) AND (inhibitor* OR antibod* OR antagonist)):ti,ab,kw	603
#41	MeSH descriptor: [Ipilimumab] explode all trees	381
#42	(Ipilimumab* OR Yervoy OR MDX 010 OR MDX010 OR MDX-010 OR MDX-CTLA-4 OR MDX CTLA 4):ti,ab,kw	1771
#43	MeSH descriptor: [Immunotherapy, Active] explode all trees	4083
#44	(Immunotherap* OR (immun* AND therap*)):ti,ab,kw	93480
#45	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44	114680
#46	#18 AND #45	6434
#47	#46 with Cochrane Library publication date Between Oct 2022 and Oct 2023, in Cochrane Reviews	1
#48	#46 with Publication Year from 2022 to 2023, in Trials	564
#49	#48 NOT (clinicaltrials.gov OR CT.gov OR ICTRP OR pubmed)	280



**Bei den beiden ausgeschlossenen Studien handelt es sich um die Studien, die zum Zeitpunkt der Bewertung nur als Abstract vorlagen und daher nicht bewertet wurden (siehe 2.5 Methodenreport). Letztendlich bewertet wurden zwei Studien, die von den Experten übermittelt wurden.*

2.2 CCA 15 Updaterecherche

Frage	Population	Intervention	Alternativmaßnahme	Outcome	Priorisierung
CCA 15 Systemtherapie Von welchen Systemtherapien profitieren Patienten mit fortgeschrittenem biliären Karzinom?	Intrahepatisches CCA Perihiläres CCA Distales CCA Gallenblasenkarzinom	Durvalumab FGFR-Inhibitoren Pemigatinib Gemcitabin Cisplatin Capecitabine, 5-FU Irinotecan Oxaliplatin Ivosidenib Futibatinib Infigratinib PD1/PDL1-Inhibtion Pembrolizumab	Keine Therapie, andere Systemtherapie	Overall survival	9
				Time to Progression oder Progression free survival	8
				Adverse Events	7
				Quality of life	7

Einschlusskriterien	
Zielgruppe	Patienten mit biliärem Karzinom, nicht resektabel
Publikationstyp	Randomisierte kontrollierte Studien (RCTs) oder systematische Übersicht mit/ohne Metaanalyse von RCTs, Phase II-Studien
Sprachen	Deutsch oder Englisch
Suchzeitraum	31.10.2022-01.06.2023

Suche in PubMed (20.06.2023)

	CCA 15 Systemtherapie Von welchen Systemtherapien profitieren Patienten mit fortgeschrittenem biliären Karzinom?	
Nr	**Query**	**Hits**
#1	**Cholangiocarcinoma[Mesh]** OR Cholangiocarcinoma*[tiab] OR Cholangiocellular Carcinoma[tiab] OR Carcinoma, Cholangiocellular[tiab] OR Carcinomas, Cholangiocellular[tiab] OR Cholangiocellular Carcinoma*[tiab]	20.476
#2	(**Neoplasms[Mesh]** OR Neoplas*[tiab] OR Tumor[tiab] OR Tumors[tiab] OR Cancer*[tiab] OR Malignanc*[tiab] OR carcinom*[tiab]) AND (bile duct*[tiab] OR biliary tract[tiab] OR bile canaliculi[tiab] OR cholangio*[tiab])	40.241
#3	#1 OR #2	42.706
#4	((gallbladder[tiab] OR gall bladder[tiab] OR biliary tract[tiab]) AND (Tumor[tiab] OR Tumors[tiab] OR Cancer*[tiab] OR Malignanc*[tiab] OR carcinom*[tiab])) OR "**Gallbladder Neoplasms"[Mesh]**	20.549
#5	#3 OR #4	54.437
#6	**durvalumab [Supplementary Concept]** OR durvalumab[tiab] OR MEDI4736[tiab] OR MEDI-4736[tiab] OR Imfinzi[tiab]	1.473
#7	(**Receptors, Fibroblast Growth Factor[Mesh]** OR FGFR[tiab] OR Receptors, FGF[tiab] OR Fibroblast Growth Factor Receptor[tiab] OR Fibroblast Growth Factor Receptors[tiab] OR FGF Receptor[tiab] OR Receptor, FGF[tiab] OR FGF Receptors[tiab] OR Heparin-Binding Growth Factor Receptor[tiab] OR Heparin Binding Growth Factor Receptor[tiab]) AND (inhibitor*[tiab] OR antagonist*[tiab])	4.061
#8	**"pemigatinib" [Supplementary Concept]** OR Pemigatinib[tiab] OR Pemazyre[tiab] OR INCB054828[tiab] OR INCB-054828[tiab]	124
#9	**gemcitabine [Supplementary Concept]** OR gemcitabin*[tiab] OR dFdCyd[tiab] OR LY 188011[tiab] OR LY-188011[tiab] OR Gemzar[tiab]	30.735
#10	**Cisplatin[Mesh]** OR cis-plat*[tiab] OR cis plat*[tiab] OR Platinum Diamminodichloride[tiab] OR Diamminodichloride, Platinum[tiab] OR Dichlorodiammineplatinum[tiab] OR cis-Diamminedichloroplatinum[tiab] OR cis Diamminedichloroplatinum[tiab] OR NSC-119875[tiab] OR Platino[tiab] OR Platinol[tiab] OR Biocisplatinum[tiab] OR Platidiam[tiab]	59.746
#11	**Capecitabine[Mesh]** OR capecitabin*[tiab]	8.770
#12	**"Fluorouracil"[Mesh]** OR Fluorouracil[tiab] OR 5FU[tiab] OR 5-FU[tiab] OR 5-Fluorouracil[tiab] OR 5 Fluorouracil[tiab] OR Fluoruracil[tiab] OR Adrucil[tiab] OR Carac[tiab] OR Efudix[tiab] OR Fluoro-Uracile[tiab] OR Fluoro Uracile[tiab] OR Efudex[tiab] OR Fluoroplex[tiab] OR Flurodex[tiab] OR Fluorouracilo[tiab] OR Fluracedyl[tiab] OR Haemato-FU[tiab] OR Haemato FU[tiab] OR Neofluor[tiab] OR Onkofluor[tiab] OR Ribofluor[tiab]	68.300

	OR 5-Fluorouracil-Biosyn[tiab] OR 5 Fluorouracil Biosyn[tiab]	
#13	**Irinotecan[Mesh]** OR Irinotecan[tiab] OR Camptothecin-11[tiab] OR Camptothecin 11[tiab] OR SN 38 11[tiab] OR SN-38-11[tiab] OR SN3811[tiab] OR SN 38[tiab] OR SN-38[tiab] OR NK012 Compound[tiab] OR CPT-11[tiab] OR CPT11[tiab] OR CPT 11[tiab] OR Camptosar[tiab]	13.567
#14	**Oxaliplatin[Mesh]** OR Oxaliplatin[tiab] OR Oxaliplatine[tiab] OR Eloxatine[tiab] OR Eloxatin[tiab] OR ACT 078[tiab] OR ACT-078[tiab] OR ACT078[tiab]	15.141
#15	ivosidenib [Supplementary Concept] OR ivosidenib[tiab] OR AG-120[tiab] OR Tibsovo[tiab]	245
#16	futibatinib [Supplementary Concept] OR futibatinib[tiab]	45
#17	infigratinib [Supplementary Concept] OR infigratinib[tiab] OR BGJ398[tiab] OR truseltiq[tiab]	231
#18	**("Programmed Cell Death 1 Receptor"[Mesh]** OR PD-1[tiab] OR PD 1[tiab] OR programmed cell death protein 1[tiab] OR CD279 Antigen[tiab] OR Antigen, CD279[tiab]) AND (inhibitor*[tiab] OR antibod*[tiab] OR antagonist[tiab]) OR PD-L1[tiab] OR PD L1[tiab]	35.276
#19	**Nivolumab[Mesh]** OR Opdivo[tiab] OR ONO-4538[tiab] OR ONO 4538[tiab] OR ONO4538[tiab] OR MDX-1106[tiab] OR MDX 1106[tiab] OR MDX1106[tiab] OR BMS-936558[tiab] OR BMS 936558[tiab] OR BMS936558[tiab]	5.166
#20	**pembrolizumab [Supplementary Concept]** OR Pembrolizumab[tiab] OR lambrolizumab[tiab] OR Keytruda[tiab] OR MK-3475[tiab]	8.810
#21	**atezolizumab [Supplementary Concept]** OR atezolizumab[tiab] OR anti-PDL1[tiab] OR MPDL3280A[tiab] OR MPDL-3280A[tiab] OR Tecentriq[tiab] OR RG7446[tiab] OR RG-7446[tiab]	3.173
#22	**avelumab** [Supplementary Concept] OR avelumab[tiab] OR MSB-0010682[tiab] OR MSB0010682[tiab] OR bavencio[tiab] OR MSB0010718C[tiab] OR MSB-0010718C[tiab]	924
#23	**cemiplimab** [Supplementary Concept] OR cemiplimab[tiab] OR REGN2810[tiab]	346
#24	**dostarlimab** [Supplementary Concept] OR dostarlimab[tiab] OR Jemperli[tiab] OR dostarlimab-gxly[tiab] OR TSR-042[tiab] OR GSK4057190[tiab]	94
#25	**Retifanlimab[tiab]** OR "futibatinib" [Supplementary Concept] OR **futibatinib[tiab]** OR TAS-120[tiab]	60

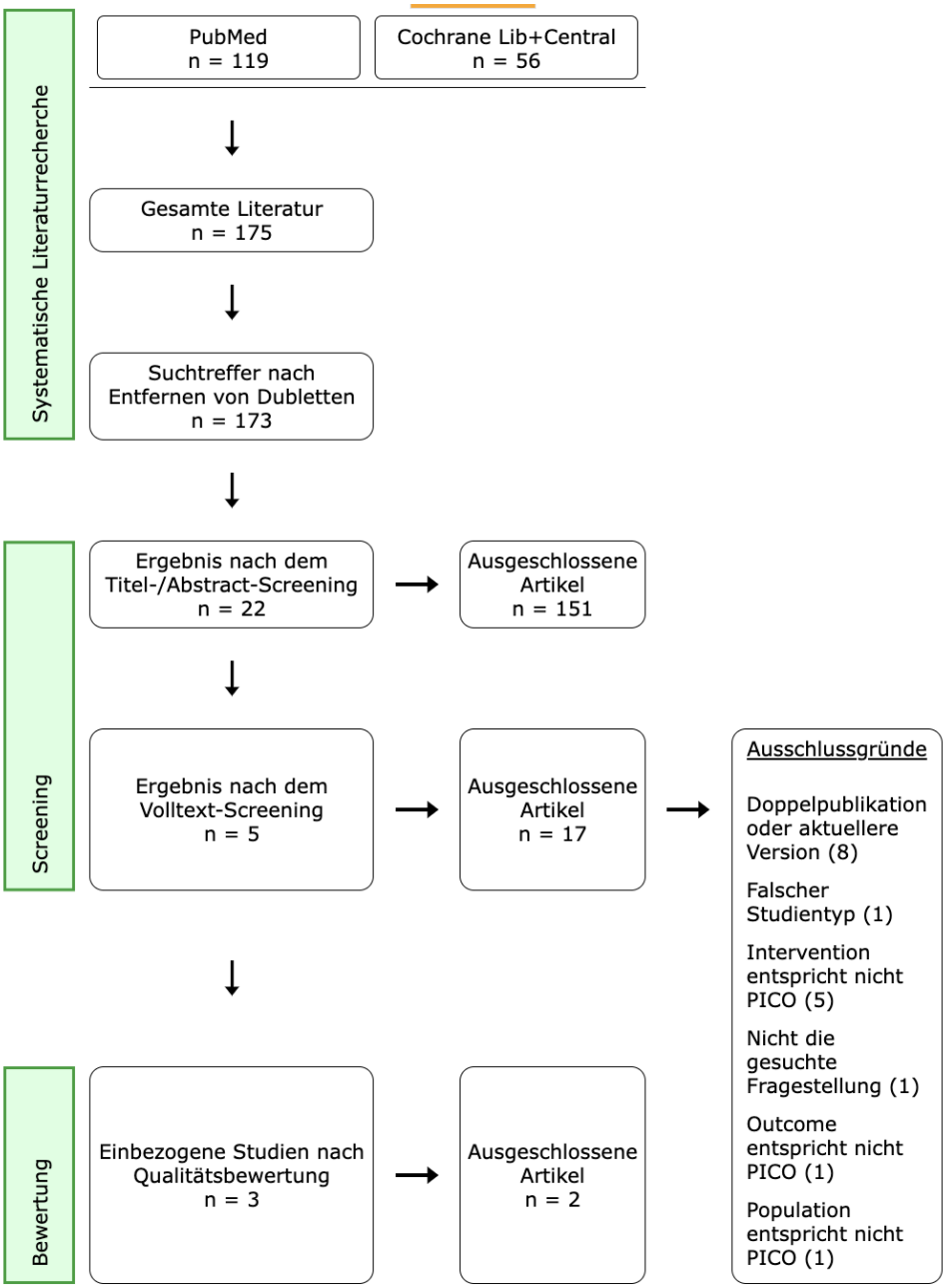
#26	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	194.721
#27	#5 AND #26	3.193
#28	(systematic*[tiab] AND (bibliographic*[tiab] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[tiab] AND (bibliographic*[tiab] OR literature[tiab])) OR "cochrane database syst rev"[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR "research synthesis"[tiab] OR "research integration"[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT "psycinfo database"[tiab]) OR pubmed[tiab] OR scopus[tiab] OR "web of science"[tiab] OR "data synthesis"[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR "meta-analysis as topic"[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])	850.954
#29	randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]	5.763.578
#30	#28 OR #29	6.338.282
#31	animals[mh] NOT humans[mh]	5.129.019
#32	#30 NOT #31	5.596.112
#33	#27 AND #32	2.075
#34	**Publication date from 31/10/2022 to date of search, English and German articles, Abstract available**	**119**

Recherche in der Cochrane Library (20.06.2023)

ID	Search	Hits
#1	MeSH descriptor: [Cholangiocarcinoma] explode all trees	315
#2	(Cholangiocarcinoma* OR Cholangiocellular Carcinoma OR Carcinoma, Cholangiocellular OR Carcinomas, Cholangiocellular OR Cholangiocellular Carcinoma* OR CCA):ti,ab,kw	1359
#3	MeSH descriptor: [Neoplasms] explode all trees	111266
#4	(Neoplasms OR Neoplas* OR Tumor OR Tumors OR Cancer* OR Malignanc* OR carcinom*):ti,ab,kw	258025

#5	#3 OR #4	270207
#6	(bile duct* OR biliary tract OR bile canaliculi OR cholangio* OR gallbladder OR gall bladder OR biliary tract):ti,ab,kw	9253
#7	#5 AND #6	2963
#8	MeSH descriptor: [Gallbladder Neoplasms] explode all trees	121
#9	#1 OR #2 OR #7 OR #8	3436
#10	(durvalumab OR MEDI4736 OR MEDI-4736 OR):ti,ab,kw	0
#11	MeSH descriptor: [Receptors, Fibroblast Growth Factor] explode all trees	86
#12	((Receptors, Fibroblast Growth Factor OR FGFR OR Receptors, FGF OR Fibroblast Growth Factor Receptor OR Fibroblast Growth Factor Receptors OR FGF Receptor OR Receptor, FGF OR FGF Receptors OR Heparin-Binding Growth Factor Receptor OR Heparin Binding Growth Factor Receptor) AND (inhibitor* OR antagonist*)):ti,ab,kw	370
#13	(Pemigatinib OR Pemazyre OR INCB054828 OR INCB-054828):ti,ab,kw	16
#14	(gemcitabin* OR dFdCyd OR LY 188011 OR LY-188011 OR Gemzar):ti,ab,kw	6924
#15	(Cisplatin OR cis-plat* OR cis plat* OR Platinum Diamminodichloride OR Diamminodichloride, Platinum OR Dichlorodiammineplatinum OR cis-Diamminedichloroplatinum OR cis Diamminedichloroplatinum OR NSC-119875 OR Platino OR Platinol OR Biocisplatinum OR Platidiam):ti,ab,kw	16711
#16	MeSH descriptor: [Cisplatin] explode all trees	5936
#17	(capecitabin*):ti,ab,kw	4659
#18	MeSH descriptor: [Capecitabine] explode all trees	1598
#19	MeSH descriptor: [Fluorouracil] explode all trees	7298
#20	("Fluorouracil" OR Fluorouracil OR Fluoruracil OR Adrucil OR Carac OR Efudix OR Fluoro-Uracile OR Fluoro Uracile OR Efudex OR Fluoroplex OR Flurodex OR Fluorouracilo OR Fluracedyl OR Haemato-FU OR Haemato FU OR Neofluor OR Onkofluor OR Ribofluor):ti,ab,kw	11515
#21	MeSH descriptor: [Irinotecan] explode all trees	1173

#22	(Irinotecan OR Camptothecin):ti,ab,kw	3893
#23	MeSH descriptor: [Oxaliplatin] explode all trees	1606
#24	(ivosidenib OR AG-120 OR Tibsovo):ti,ab,kw	67
#25	(futibatinib):ti,ab,kw	9
#26	(infigratinib OR BGJ398 OR truseltiq):ti,ab,kw	26
#27	MeSH descriptor: [Programmed Cell Death 1 Receptor] explode all trees	170
#28	((Programmed Cell Death) AND (inhibitor* OR antibod* OR antagonist)):ti,ab,kw	1214
#29	MeSH descriptor: [Nivolumab] explode all trees	760
#30	(Nivolumab OR Opdivo OR ONO-4538 OR ONO 4538 OR ONO4538 OR MDX-1106 OR MDX 1106 OR MDX1106 OR BMS-936558 OR BMS 936558 OR BMS936558):ti,ab,kw	2800
#31	(Pembrolizumab OR lambrolizumab OR Keytruda OR MK-3475):ti,ab,kw	2802
#32	(atezolizumab OR anti-PDL1 OR MPDL3280A OR MPDL-3280A OR Tecentriq OR RG7446 OR RG-7446):ti,ab,kw	1352
#33	(avelumab OR MSB-0010682 OR MSB0010682 OR bavencio OR MSB0010718C OR MSB-0010718C):ti,ab,kw	360
#34	(cemiplimab OR REGN2810):ti,ab,kw	120
#35	(dostarlimab OR Jemperli OR dostarlimab-gxly OR TSR-042 OR GSK4057190):ti,ab,kw	57
#36	(Retifanlimab OR futibatinib OR TAS-120):ti,ab,kw	26
#37	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36	40806
#38	#9 AND #37	853
#39	#38 with Cochrane Library publication date Between Oct 2022 and Dec 2023, in Cochrane Reviews	0
#40	#38 with Publication Year from 2021 to 2022, in Trials	146
#41	#40 NOT (ct.gov OR ICTRP) with Publication Year from 2022 to 2023, in Trials	56



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**Neben den Studien, die durch die systematische Suche identifiziert wurden, wurde hier noch eine Studie bewertet, die von den Experten übermittelt wurden.*

2.3 HCC TACE und Systemtherapie

Neue Recherche

Frage	Population	Intervention	Alternativ-maßnahme	Outcome	Prio-risierung
HCC Kombination TACE + Systemtherapie Profitieren Patienten mit einem HCC im Stadium BCLC B von einer Kombination aus TACE und Systemtherapie?	Patienten mit HCC im Stadium BCLC B	TACE + Checkpoint-Inhibition TACE + Atezolizumab/ Bevacizumab, Pembrolizumab, Nivolumab TACE + Durvalumab/ Tremelimumab TACE + Tyrosinkinaseinhibitor TACE + Sorafenib TACE + Lenvatinib TACE + CPI + TKI	TACE alleine	Overall survival	9
				Time to Progression oder Progression free survival	8
				Adverse Events	7
				Quality of life	7

Einschlusskriterien	
Zielgruppe	Patienten mit hepatozellulärem Karzinom im Stadium BCLC B
Publikationstyp	Randomisierte kontrollierte Studien (RCTs) oder systematische Übersicht mit/ohne Metaanalyse von prospektiven Studien, Phase II-Studien
Sprachen	Deutsch oder Englisch
Suchzeitraum	01.01.2017-01.06.2023

Suche in PubMed (20.06.2023)

	HCC Kombination TACE + Systemtherapie	
Nr	**Query**	**Hits**
#1	**Carcinoma, Hepatocellular[Mesh]** OR HCC[tiab] OR Hepatom*[tiab] OR ((Carcinoma*[tiab] OR Cancer[tiab] OR cancers[tiab]) AND (hepatocellular[tiab] OR liver cell[tiab] OR adult liver[tiab]))	178.308
#2	(**Neoplasms[Mesh]** OR Neoplas*[tiab] OR Tumor[tiab] OR Tumors[tiab] OR Cancer*[tiab] OR Malignanc*[tiab]) AND (hepatocellular[tiab] OR hepatic*[tiab] OR liver*[tiab] OR "**Liver"[Mesh**])	336.791
#3	**Liver Cirrhosis[Mesh]** OR ((liver[Mesh]) AND ("Fibrosis"[Mesh] OR cirr*[tiab] OR fibrosis[tiab]))	115.937
#4	#1 OR #2 OR #3	479.879
#5	arterial chemoembolization[tiab] OR transarterial chemoembolization[tiab] OR **TACE**[tiab] OR "Chemoembolization, Therapeutic"[Mesh]	12.215
#6	**("Programmed Cell Death 1 Receptor"[Mesh]** OR PD-1[tiab] OR PD 1[tiab] OR programmed cell death protein 1[tiab] OR CD279 Antigen[tiab] OR Antigen, CD279[tiab]) AND (inhibitor*[tiab] OR antibod*[tiab] OR antagonist[tiab]) OR PD-L1[tiab] OR PD L1[tiab]	35.276
#7	**Nivolumab[Mesh]** OR Opdivo[tiab] OR ONO-4538[tiab] OR ONO 4538[tiab] OR ONO4538[tiab] OR MDX-1106[tiab] OR MDX 1106[tiab] OR MDX1106[tiab] OR BMS-936558[tiab] OR BMS 936558[tiab] OR BMS936558[tiab]	5.166
#8	**pembrolizumab [Supplementary Concept]** OR Pembrolizumab[tiab] OR lambrolizumab[tiab] OR Keytruda[tiab] OR MK-3475[tiab]	8.810
#9	**atezolizumab [Supplementary Concept]** OR atezolizumab[tiab] OR anti-PDL1[tiab] OR MPDL3280A[tiab] OR MPDL-3280A[tiab] OR Tecentriq[tiab] OR RG7446[tiab] OR RG-7446[tiab]	3.173
#10	**avelumab** [Supplementary Concept] OR avelumab[tiab] OR MSB-0010682[tiab] OR MSB0010682[tiab] OR bavencio[tiab] OR MSB0010718C[tiab] OR MSB-0010718C[tiab]	924
#11	**durvalumab** [Supplementary Concept] OR durvalumab[tiab] OR MEDI4736[tiab] OR MEDI-4736[tiab] OR Imfinzi[tiab]	1.473
#12	**cemiplimab** [Supplementary Concept] OR cemiplimab[tiab] OR REGN2810[tiab]	346
#13	**dostarlimab** [Supplementary Concept] OR dostarlimab[tiab] OR Jemperli[tiab] OR dostarlimab-gxly[tiab] OR TSR-042[tiab] OR GSK4057190[tiab]	94

#14	**Retifanlimab[tiab]**	10
#15	(**CTLA-4 Antigen[Mesh]** OR CTLA-4[tiab] OR CD152[tiab] OR Cytotoxic T-Lymphocyte-Associated Antigen 4[tiab] OR Cytotoxic T Lymphocyte Associated Antigen 4[tiab] OR Cytotoxic T-Lymphocyte Antigen 4[tiab] OR Cytotoxic T Lymphocyte Antigen 4[tiab]) AND (inhibitor*[tiab] OR antibod*[tiab] OR antagonist[tiab])	7.576
#16	**Ipilimumab[Mesh]** OR Ipilimumab*[tiab] OR Yervoy[tiab] OR MDX 010[tiab] OR MDX010[tiab] OR MDX-010[tiab] OR MDX-CTLA-4[tiab] OR MDX CTLA 4[tiab]	5.478
#17	**Bevacizumab[Mesh]** OR Bevacizumab[tiab] OR Mvasi[tiab] OR Avastin[tiab]	22.808
#18	**tremelimumab [Supplementary Concept]** OR tremelimumab[tiab] OR ticilimumab[tiab] OR CP 675[tiab] OR CP675 cpd[tiab] OR CP-675[tiab] OR CP-675,206[tiab] OR CP-675206[tiab] OR CP675206[tiab] OR CP 675206[tiab]	505
#19	**Tyrosine Protein Kinase Inhibitors[Mesh]** OR Tyrosine Kinase Inhibitors[tiab] OR Inhibitors, Tyrosine Kinase[tiab] OR Kinase Inhibitors, Tyrosine[tiab] OR TKI Tyrosine Kinase Inhibitors[tiab] OR Tyrosine Kinase Inhibitor[tiab]	37.114
#20	**cabozantinib [Supplementary Concept]** OR cabozantinib[tiab] OR Cometriq[tiab] OR XL 184[tiab] OR XL184 cpd[tiab] OR XL-184[tiab] OR BMS 907351[tiab] OR BMS907351[tiab] OR BMS-907351[tiab]	1.569
#21	**lenvatinib [Supplementary Concept]** OR lenvatinib[tiab] OR Lenvima[tiab] OR E 7080[tiab] OR E-7080[tiab] OR ER-203492-00[tiab] OR E7080[tiab] OR E-7080 mesylate[tiab] OR E7080 mesylate[tiab]	2.094
#22	**regorafenib [Supplementary Concept]** OR regorafenib[tiab] OR Stivarga[tiab] OR BAY 73-4506[tiab] OR BAY73-4506[tiab] OR BAY-73-4506[tiab]	1.873
#23	**Sorafenib[Mesh]** OR Sorafenib[tiab] OR Nexavar[tiab] OR BAY 43-9006[tiab] OR BAY 43 9006[tiab] OR BAY 439006[tiab] OR BAY-673472[tiab] OR BAY 673472[tiab] OR BAY 545-9085[tiab] OR BAY 545 9085[tiab] OR BAY 5459085[tiab] OR BAY-545-9085[tiab] OR BAY5459085[tiab]	11.712
#24	**apatinib [Supplementary Concept]** OR apatinib[tiab] OR rivoceranib[tiab] OR YN968D1[tiab] OR YN-968D1[tiab]	1.143
#25	**Immunotherapy, Active[Mesh]** OR Immunotherap*[tiab] OR (immun*[tiab] AND therap*[tiab])	731.375
#26	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	811.684
#27	#4 AND #5 AND #26	1.646

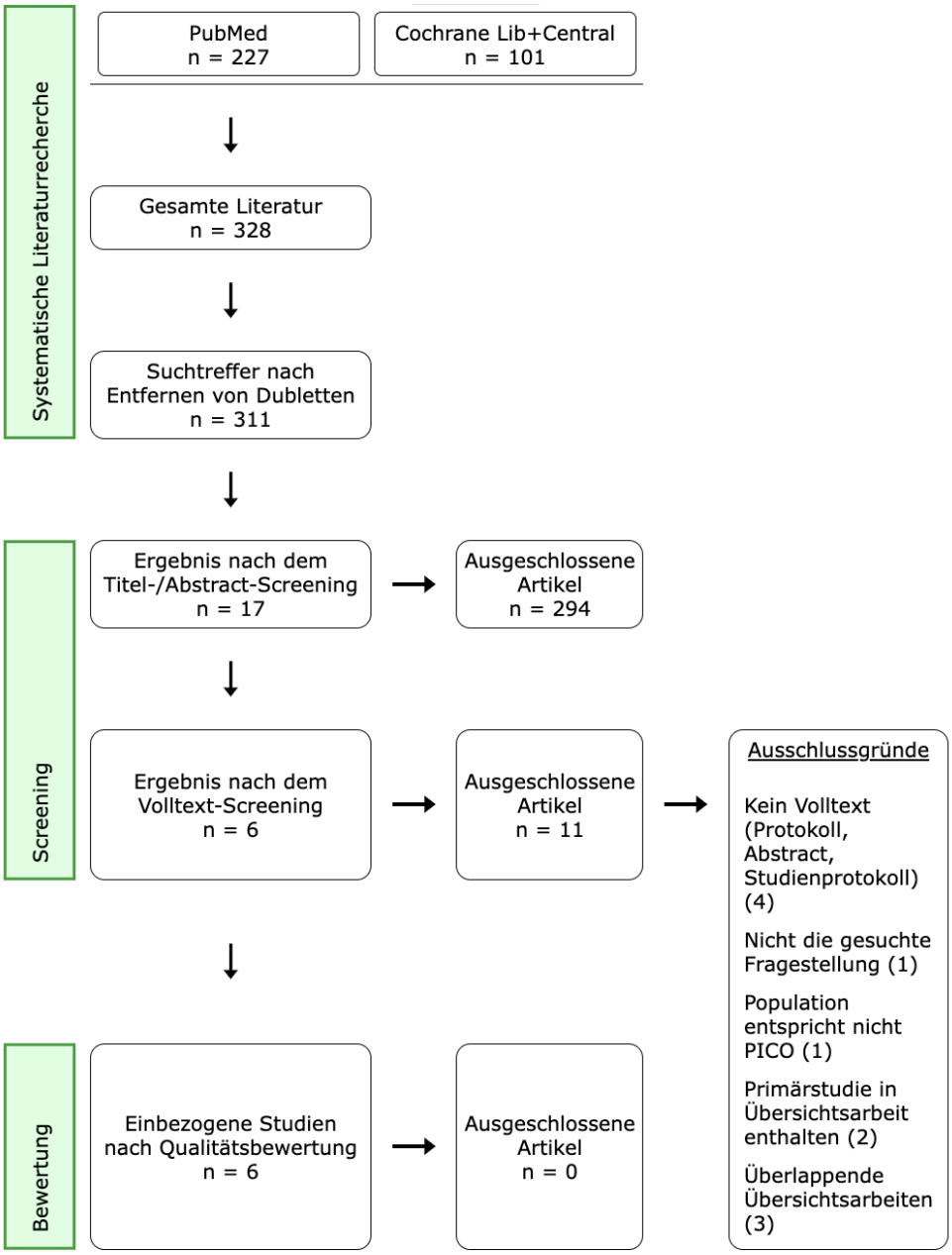
#28	(systematic*[tiab] AND (bibliographic*[tiab] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[tiab] AND (bibliographic*[tiab] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])	850.954
#29	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]	1.625.049
#30	#28 OR #29	2.305.780
#31	animals[mh] NOT humans[mh]	5.129.019
#32	#30 NOT #31	2.167.565
#33	#27 AND #32	403
#34	**Publication date from 01/10/2017 to date of search, English and German articles, Abstract available**	**227**

Recherche in der Cochrane Library (20.06.2023)

ID	Search	Hits
#1	MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees	2384
#2	(Carcinoma, Hepatocellular OR hepatocellular carcinoma OR HCC OR Hepatom* OR ((Carcinoma* OR Cancer OR cancers) AND (hepatocellular OR liver cell OR adult liver))):ti,ab,kw	13151
#3	MeSH descriptor: [Neoplasms] explode all trees	111266
#4	(Neoplas* OR Tumor OR Tumors OR Cancer* OR Malignanc* OR carcinom):ti,ab,kw	250630
#5	#3 OR #4	263723
#6	MeSH descriptor: [Liver] explode all trees	5486
#7	(hepatocellular OR hepatic* OR liver*):ti,ab,kw	71301
#8	#6 OR #7	71346
#9	#5 AND #8	21140
#10	MeSH descriptor: [Liver Cirrhosis] explode all trees	4344
#11	MeSH descriptor: [Liver] explode all trees	5486
#12	(liver OR hepat*):ti,ab,kw	87457
#13	#11 OR #12	87497
#14	MeSH descriptor: [Fibrosis] explode all trees	8467
#15	(cirrh* OR fibros* OR fibrot*):ti,ab,kw	27622
#16	#14 OR #15	29633
#17	#13 AND #16	13610
#18	#1 OR #2 OR #9 OR #10 OR #17	34130
#19	(arterial chemoembolization OR transarterial chemoembolization OR TACE OR "Chemoembolization, Therapeutic"):ti,ab,kw	1744
#20	MeSH descriptor: [Chemoembolization, Therapeutic] explode all trees	394
#21	#19 OR #20	1744
#22	MeSH descriptor: [Programmed Cell Death 1 Receptor] explode all trees	170
#23	(Nivolumab OR Opdivo OR ONO-4538 OR ONO 4538 OR ONO4538 OR MDX-1106 OR MDX 1106 OR MDX1106 OR BMS-936558 OR BMS 936558	2800

	OR BMS936558):ti,ab,kw	
#24	(Pembrolizumab OR lambrolizumab OR Keytruda OR MK-3475):ti,ab,kw	2802
#25	(atezolizumab OR anti-PDL1 OR MPDL3280A OR MPDL-3280A OR Tecentriq OR RG7446 OR RG-7446):ti,ab,kw	1352
#26	(avelumab OR MSB-0010682 OR MSB0010682 OR bavencio OR MSB0010718C OR MSB-0010718C):ti,ab,kw	360
#27	(durvalumab OR MEDI4736 OR MEDI-4736 OR Imfinzi):ti,ab,kw	1053
#28	(cemiplimab OR REGN2810):ti,ab,kw	120
#29	(dostarlimab OR Jemperli OR dostarlimab-gxly OR TSR-042 OR GSK4057190):ti,ab,kw	57
#30	(Retifanlimab):ti,ab,kw	14
#31	MeSH descriptor: [CTLA-4 Antigen] explode all trees	78
#32	((CTLA-4 Antigen OR CTLA-4 OR CD152 OR Cytotoxic T-Lymphocyte-Associated Antigen 4 OR Cytotoxic T Lymphocyte Associated Antigen 4 OR Cytotoxic T-Lymphocyte Antigen 4 OR Cytotoxic T Lymphocyte Antigen 4) AND (inhibitor* OR antibod* OR antagonist)):ti,ab,kw	603
#33	MeSH descriptor: [Ipilimumab] explode all trees	381
#34	(Ipilimumab* OR Yervoy OR MDX 010 OR MDX010 OR MDX-010 OR MDX-CTLA-4 OR MDX CTLA 4):ti,ab,kw	1771
#35	MeSH descriptor: [Bevacizumab] explode all trees	2637
#36	(Bevacizumab OR Mvasi OR Avastin):ti,ab,kw	7458
#37	(tremelimumab OR ticilimumab OR CP 675 OR CP675 cpd OR CP-675 OR CP-675,206 OR CP-675206 OR CP675206 OR CP 675206):ti,ab,kw	423
#38	MeSH descriptor: [Tyrosine Protein Kinase Inhibitors] explode all trees	4
#39	(Tyrosine Kinase Inhibitors OR Inhibitors, Tyrosine Kinase OR Kinase Inhibitors, Tyrosine OR TKI Tyrosine Kinase Inhibitors OR Tyrosine Kinase Inhibitor):ti,ab,kw	3783
#40	(cabozantinib OR Cometriq OR XL 184 OR XL184 cpd OR XL-184 OR BMS 907351 OR BMS907351 OR BMS-907351):ti,ab,kw	513
#41	(lenvatinib OR Lenvima OR E 7080 OR E-7080 OR E7080 OR E-7080 mesylate OR E7080 mesylate):ti,ab,kw	699
#42	(regorafenib OR Stivarga):ti,ab,kw	641
#43	MeSH descriptor: [Sorafenib] explode all trees	628
#44	(Sorafenib OR Nexavar):ti,ab,kw	2124

#45	(apatinib OR rivoceranib OR YN968D1 OR YN-968D1):ti,ab,kw	481
#46	MeSH descriptor: [Immunotherapy, Active] explode all trees	4083
#47	(Immunotherap* OR (immun* AND therap*)):ti,ab,kw	93480
#48	#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47	111787
#49	#18 AND #21 AND #48	467
#50	#49 with Cochrane Library publication date Between Jan 2017 and Dec 2023, in Cochrane Reviews	3
#51	#49 with Publication Year from 2017 to 2023, in Trials	257
#52	#51 NOT (clinicaltrials.gov OR CT.gov OR ICTRP OR pubmed)	98


Systematische Literaturrecherche
PubMed
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Cochrane Lib+Central
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Gesamte Literatur
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Suchtreffer nach Entfernen von Dubletten
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Ergebnis nach dem Volltext-Screening
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Ausgeschlossene Artikel
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Ausschlussgründe
Kein Volltext (Protokoll, Abstract, Studienprotokoll) (4)
Nicht die gesuchte Fragestellung (1)
Population entspricht nicht PICO (1)
Primärstudie in Übersichtsarbeit enthalten (2)
Überlappende Übersichtsarbeiten (3)
Bewertung
Einbezogene Studien nach Qualitätsbewertung
n = 6
Ausgeschlossene Artikel
n = 0

3 Evidenztabellen

3.1 HCC 20 Updaterecherche

Schlüsselfrage:

2023 Update - HCC 20 Systemtherapie
Von welchen Systemtherapien profitieren Patienten mit fortgeschrittenem HCC?
P: Patienten mit fortgeschrittenem HCC
Child A und Child B
I: Atezolizumab, Bevacizumab
Durvalumab, Tremelimumab
Sorafenib
Lenvatinib
Regorafenib
Cabozantinib
Ramucirumab
PD1-Inhibitoren
CTLA4-Inhibitoren
C: Keine Therapie oder gegen Sorafenib/ andere Therapien
O: Overall survival
Time to Progression oder Progression free survival
Adverse Events
Quality of life

Inhalt: *2 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Qin, Shukui 2023	2	Randomised controlled trial.
Rimini, Margherita 2023	3	Retrospective cohort study

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

Qin, Shukui. Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050): a randomised, open-label, multicentre, phase 3 trial. Lancet (London, England). . . 2023			
Population	**Intervention / Comparison**	**Outcomes/Results**	**Methodical Notes**
Evidence level: 2 **Study type:** randomised controlled trial. **Number of Patients:** 668 randomized 1:1 **Recruiting Phase:** Dec 31, 2019 - Nov 25, 2021. **Inclusion Criteria:** 18 years or older at the time of recruitment, had a first diagnosis of hepatocellular carcinoma, and had undergone either complete surgical resection (R0, grossly and microscopically negative margins) or ablation (microwave or radiofrequency ablation with complete response on imaging) within 4–12 weeks of random allocation. Patients had Child-Pugh class	**Intervention:** I V 1200 mg atezolizumab plus 15 mg/kg bevacizumab every 3 weeks for 17 cycles (12 months). **Comparison:** active surveillance.	**Primary:** RFS (time from randomisation to disease recurrence per independent review facility, or death from any cause, whichever occurred first). **Secondary:** Investigator-assessed RFS, investigator-assessed and independent review facility- assessed time to recurrence, and OS. **Results: Only outcomes related to the PICO reported in this section.** Disease recurrence: The risk of disease recurrence or death was 28% lower with adjuvant atezolizumab plus bevacizumab than with active surveillance (HR 0·72, adjusted 95% CI 0·53–0·98; p=0·012). Overall survival: At the time of the RFS interim analysis, OS was very immature, with a 7% event-to-patient ratio. There were 47 deaths across the study, 27 (8%) with atezolizumab plus bevacizumab and 20 (6%) with active surveillance. Median OS was not reached in either group . The HR for death was 1·42 (95% CI 0·80–2·54).	**Funding Sources:** Study funded by Hoffmann-La Roche/Genentech. **COI:** Declared, see article for list. **Randomization:** Rando m allocation was performed via an interactive voice–web response system using permuted blocks, using a block size of 4, stratified by geographical region and a composite stratification factor including number of high-risk features, curative procedure (ablation vs resection), and use of adjuvant transarterial

A liver function (a three-category scale of A, B, or C, in which C is the most severe compromise of liver function) with adequate haematological and organ function, and an Eastern Cooperative Oncology Group performance status score of 0 or 1 (on a five-point scale, with higher scores indicating greater disability). **Exclusion Criteria:** Any previous treatment for hepatocellular carcinoma, infection with both hepatitis B and hepatitis C virus, and untreated or incompletely treated oesophageal or gastric varices (assessed per oesophagogastroduodenoscopy and treated per local clinical practice) with bleeding or at high risk for bleeding.		Adverse events: AEs of any cause occurred in 326 patients (98%) of 332 who received atezolizumab plus bevacizumab and 205 (62%) of 330 in the active surveillance group before crossover. The most common AEs events of any grade regardless of causality in the atezolizumab plus bevacizumab group were proteinuria, hypertension, and decreased platelet count. Most of these common adverse events were grade 1 or 2. Grade 3 or 4 adverse events occurred in 136 (41%) of 332 patients in the atezolizumab plus bevacizumab group and 44 (13%) of 330 patients in the active surveillance group. **Author's Conclusion:** "Among patients at high risk of hepatocellular carcinoma recurrence following curative-intent resection or ablation, recurrence-free survival was improved in those who received atezolizumab plus bevacizumab versus active surveillance. To our knowledge, IMbrave050 is the first phase 3 study of adjuvant treatment for hepatocellular carcinoma to report positive results. However, longer follow-up for both recurrence-free and overall survival is needed to assess the benefit–risk profile more fully".	chemoembolisation. **Blinding:** open-label. **Dropout Rate/ITT-Analysis:** Comparable number of dropouts, ITT analysis performed. **Notes: Article submitted by hand search.** Cochrane risk of bias tool (Rob)-1: 1 question were considered to be high risk of bias, 0 questions were considered to be unclear risk of bias. Overall risk of bias: Low Oxford CEBM Levels of Evidence (2011): 2 Randomized trial

NEWCASTLE - OTTAWA Checklist: Cohort: *1 Bewertung(en)*

Rimini, Margherita. Survival outcomes from atezolizumab plus bevacizumab versus Lenvatinib in Child Pugh B unresectable hepatocellular carcinoma patients. Journal of cancer research and clinical oncology. 149. . 2023			
Evidence level	**Methodical Notes**	**Patient characteristics**	**Interventions**
Evidence level: 4 **Study type:** Retrospective cohort study	**Funding sources:** The present work received no fnancial support. **Conflict of Interests:** Stated, see article. **Randomization:** / **Blinding:** /	**Total no. patients:** 217 **Recruiting Phase:** Patients underwent treatment with atezolizumab plus bevacizumab between December 2018 and May 2022, or Lenvatinib between June 2018 and August 2021 or sorafenib between September 2009 and December 2019 **Inclusion criteria:** Eligible patients had Child–Pugh B (B7–B8) histologically confirmed or clinically confirmed diagnosis of	**Interventions:** All patients received Lenvatinib until Atezolizumab plus bevacizumab approval. Then, the choice between the two treatments was left to the treating physician. Lenvatinib was administered according to the REFLECT trial, thus patients received 12 mg if baseline bodyweight was≥60 kg or 8 mg if baseline bodyweight was<60 kg, once daily orally. Atezolizumab plus bevacizumab was administered as reported in the IMbrave150 trial, thus all patients received 1200 mg of atezolizumab plus 15mg/ kg of body weight of bevacizumab intravenously every 3 weeks. 65 (30%) received atezolizumab plus bevacizumab, and 152 (70%) received lenvatinib. **Comparison:**

	Dropout rates:	HCC according to international guidelines, and no previous systemic therapy. **Exclusion criteria:**	
Notes:	**Article submitted by hand search.** Newcastle-Ottawa Scale (NOS) for Cohort studies 8 /9 stars. Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Treatment benefits): 4 **Author's conclusion:** The present study suggests for the first time a major benefit from Lenvatinib compared to atezolizumab plus bevacizumab in a large cohort of patients with CP B class HCC.		
Outcome Measures/results	**Primary** o verall survival (OS) of CP B patients treated with Lenvatinib	**Results:** The median follow-up for the entire population was 11.3 months (95% CI 7.2–20.7). The median follow-up for patients receiving Lenvatinib was 12.2 months (95% CI 10.1–33.2); the median follow-up for patients receiving atezolizumab plus bevacizumab was 10.9 (95% CI 6.2–20.7). **Overall survival** The mOS for patients receiving Lenvatinib was 13.8 months (95% CI: 11.6–16.0), compared to 8.2 months (95% CI 6.3–10.2) for patients receiving atezolizumab plus bevacizumab as first-line treatment	

	compared to atezolizumab plus bevacizumab **Secondary** progression-free survival (PFS), the objective response rate (ORR) and the safety profle experienced in Child B patients receiving Lenvatinib versus atezolizumab plus bevacizumab.	(atezolizumab plus bevacizumab Vs Lenvatinib: HR 1.9, 95% CI 1.2–3.0, p=0.0050). The multivariate analysis confirmed that patients receiving Lenvatinib as first-line treatment have a significantly longer OS compared to patients receiving atezolizumab plus bevacizumab (HR 2.01; 95% CI 1.29–3.25, p=0.0023). By evaluating the cohort of patients who received atezolizumab plus bevacizumab, we found that Child B patients with ECOG PS 0, or BCLC B stage or ALBI grade 1 were those who had benefited from the treatment thus showing survival outcomes no significantly different compared to those receiving Lenvatinib. **Progression-free survival** No statistically significant differences were found since patients receiving Lenvatinib experienced an mPFS of 8.2 months (95% CI 6.5–9.9) compared to 6.9 months (95% CI:4.8–9.0) in patients receiving atezolizumab plus bevacizumab (atezolizumab plus bevacizumab Vs Lenvatinib: HR 1.0, 95% CI 0.7–1.5; p = 0.8443) **ORR and DCR** Statistically differences were reported in patients treated with lenvatinib compared to atezolizumab plus bevacizumab in terms of ORR (35 Vs 18%, p = 0.0185), but not in terms of DCR (65 Vs 55%, p=0.2213 **Safety outcomes** The overall incidence of drug-related AEs was 44%. No statistically diferences were reported in patients treated with atezolizumab plus bevacizumab and Lenvatinib (40 Vs 45%, respectively). Most frequent AEs were diarrhea (13%) and hypertension (14%).

3.2 CCA 15 Updaterecherche

2023 Update - CCA 15 Systemtherapie
Von welchen Systemtherapien profitieren Patienten mit fortgeschrittenem biliären Karzinom?
P: Intrahepatisches CCA
Perihiläres CCA
Distales CCA
Gallenblasenkarzinom
I: Durvalumab
FGFR-Inhibitoren
Pemigatinib
Gemcitabin
Cisplatin
Capecitabine, 5-FU
Irinotecan
Oxaliplatin
Ivosidenib
Futibatinib
Infigratinib
PD1/PDL1-Inhibtion
Pembrolizumab
I: Keine Therapie, andere Systemtherapie
O: Overall survival
Time to Progression oder Progression free survival
Adverse Events
Quality of life

Inhalt: 4 Literaturstellen

Literaturstelle	**Evidenzlevel**	**Studientyp**
Goyal, Lipika 2023	3	Phase 2 single group study.
Hyung, J. 2023	3	Randomized, multicenter, open-label, phase 2b clinical trial
Jeong, H. 2023	3	Randomized controlled trial
Kelley, R. K. 2023	2	Randomized controlled trial

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

Goyal, Lipika. Futibatinib for FGFR2-Rearranged Intrahepatic Cholangiocarcinoma. The New England journal of medicine. 388. . 2023			
Population	Intervention / Comparison	Outcomes/Results	Methodical Notes
Evidence level: 4 Study type: Phase 2 single group study. Number of Patients: 109 patients Recruiting Phase: Between April 16, 2018, and November 29, 2019 Inclusion Criteria: 18 years of age and had unresectable or metastatic intrahepatic chol- angiocarcinoma harboring an FGFR2 fusion or rearrangement that had been prospectively iden- tified by local testing of tumor tissue or ctDNA or by testing of tumor tissue at a central or local laboratory with the use of a 324-gene-panel	Intervention: Oral futibatinib at a dose of 20 mg once daily in a continuous regimen. Comparison: No comparison.	Primary: Objective response (partial or complete response), as assessed by independent central review. Secondary: Response duration, disease control, progression-free survival, overall survival, safe- ty, and patient-reported outcomes Results: Response: 43 of 103 patients (42%; 95% confidence interval, 32 to 52) had a response, and the median duration of response was 9.7 months. Responses were consistent across patient subgroups, including patients with heavily pretreated disease, older adults, and patients who had co-occurring TP53 mutations. PFS: Median progression- free survival was 9.0 months. OS: Median overall survival was 21.7 months. Adverse events: Common treatment-related grade 3 adverse events were hyperphosphatemia (in 30% of the patients), an increased aspartate aminotransferase level (in 7%), stomatitis (in 6%), and fatigue (in 6%). Treatment-related adverse events led to permanent discontinuation of futibatinib in 2% of the patients. No treatment-related deaths oc- curred. QoL: Quality of life was maintained throughout treatment. Author's Conclusion: In previously treated patients with FGFR2 fusion or rearrangement–positive intra- hepatic	Funding Sources: Taiho Oncology and Taiho Pharmaceutical study sponsor. COI: Declared. Randomization: not randomized. Blinding: Not blinded. Dropout Rate/ITT-Analysis: Not applicable. Notes: Article submitted by hand search. Cochrane risk of bias tool (Rob)-1: One questions were considered to be high risk of bias, two questions were considered as unclear risk of bias. Overall risk of bias: Low NIH-Tool (Before/after studies): https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools: Fair quality ROB Oxford CEBM Levels of Evidence (2011):4

assay. Exclusion Criteria: Patients with a history of or current clinically significant retinal disorder or altered non–tumor-related calcium–phospho- rus homeostasis.		cholangiocarcinoma, the use of futibatinib, a covalent FGFR inhibitor, led to measurable clinical benefit. (Funded by Taiho Oncology and Taiho Pharmaceu- tical; FOENIX-CCA2.	

Hyung, J. et al. Treatment With Liposomal Irinotecan Plus Fluorouracil and Leucovorin for Patients With Previously Treated Metastatic Biliary Tract Cancer: The Phase 2b NIFTY Randomized Clinical Trial. JAMA Oncol. 9. 692-699. 2023			
Population	Intervention / Comparison	Outcomes/Results	Methodical Notes
Evidence level: 3 Study type: Randomized, multicenter, open-label, phase 2b clinical trial Number of Patients: 178 Recruiting Phase: September 5, 2018, and December 31, 2021 Inclusion Criteria: Histologically or cytologically confirmed diagnosis of advanced BTC, including age of 19 years or older; disease progression as assessed by Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,	Intervention: Patients assigned to the liposomal irinotecan (nal-IRI) plus s fluorouracil (FU) /leucovorin (LV) group received 70 mg/m2 of nal-IRI for 90 minutes intravenously before the administration of LV and FU. Comparison: 400 mg/m2 of LV for 30 minutes and 2400 mg/m2 of FU for 46 hours intravenously every 2 weeks.	Primary: Progression-free survival (PFS) as assessed by MICR Secondary: PFS as assessed by the investigator, overall survival, and objective response rate. Results: The median follow-up duration of the patients in the full analysis set was 33.2months (IQR, 27.6-35.7), with 12 patients (6.9%; 8 in the nal-IRI plus FU/LV group and 4 in the FU/LV group) continuing follow-up for survival as of the data cut-off date (December 31, 2021).	Funding Sources: This study was funded in part by Servier and HK inno.N. Servier supported this study by providing liposomal irinotecan and financing the study operation costs. HK inno.N provided palonosetron and financed its pharmacy cost COI: Stated, see article. Randomization: Patients were randomly assigned at a 1:1 ratio to receive either nal-IRI plus FU/LV or FU/LV and were stratified by the primary tumor location (intrahepatic vs extrahepatic vs gallbladder),

while receiving first-line gemcitabine plus cisplatin; at least 1 measurable lesion as defined by RECIST, version 1.1; an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1; and adequate organ function. Exclusion Criteria:		Progression-free survival The MICR-assessed median PFS of the nal-IRI plus FU/LV group (4.2 months [IQR, 2.0-7.2]; 95% CI, 2.8-5.3) was significantly longer than the FU/LV group (1.7 months [IQR, 1.2-4.1]; 95% CI, 1.4-2.6) with a stratified HR of 0.61 (95% CI, 0.44-0.86; stratified log-rank P = .004). The MICR-assessed 6-month PFS rate was 31.8% (95% CI, 21.7%-41.8%) for the nal-IRI plus FU/LV group and 15.1% (95% CI, 7.5%-22.7%) for the FU/LV group. The investigator-assessed median PFS of the nal-IRI plus FU/LV group (3.9 months [IQR, 2.0-7.0]; 95% CI, 2.7-5.2) was also significantly longer than that of the FU/LV group (1.6 months [IQR, 1.2-3.8]; 95% CI, 1.3-2.2)with stratified HR of 0.51 (95% CI, 0.36-0.71; stratified log-rank P < .001). Investigator assessed 6-month PFS was 30.0% (95% CI, 20.2%-39.8%) for the nal-IRI plus FU/LV group and 11.6% (95% CI, 4.9%-18.4%) for the FU/LV group. The discordance rate for tumor progression date between the	previous surgery with curative intent (yes vs no), and participating centers. Method of randomization not specified. Blinding: No masking was performed (open-label study) Dropout Rate/ITT-Analysis: ITT-analysis was performed Notes: Cochrane risk of bias tool (Rob)-1: 1 question were considered to be unclear risk of bias, 3 questions(s) were considered to be high risk of bias Overall risk of bias: High Oxford CEBM Levels of Evidence (2011): Randomized trial Downgraded one level due to high risk of bias.

		MICR and investigators was 17.8% (vs 30% in the previous study). Overall survival Median OS was significantly longer for the nal-IRI plus FU/LV group (8.6 months [IQR, 3.8-15.7]; 95% CI, 5.4-10.5) compared with the FU/LV group (5.3 months [IQR, 3.4-9.4]; 95% CI, 4.7-7.2), with a stratified HR of 0.68 (95% CI, 0.48-0.95; stratified log-rank P = .02). The 6-month OS rate was 60.7% (95% CI, 50.3%-71.2%) for the nal-IRI plus FU/LV group and 44.7% (95% CI, 34.2%-55.3%) for the FU/LV group (Table 2). The ORRs were significantly higher for the nal-IRI plus FU/LV group compared with the FU/LV group according to MICR (12.5% vs 3.5%; P = .04) and investigators (19.3% vs 2.3%; P < .001) Author's Conclusion: The NIFTY randomized clinical trial demonstrated significant improvement in PFS with treatment with nal-IRI plus FU/LV compared with FU/LV alone for patients with advanced BTC after progression to gemcitabine plus cisplatin. The combination of nal-IRI plus FU/LV	

		could be considered as a second-line treatment option for patients with previously treated advanced BTC.	

Jeong, H. et al. Adjuvant gemcitabine plus cisplatin versus capecitabine in node-positive extrahepatic cholangiocarcinoma: the STAMP randomized trial. Hepatology. 77. 1540-1549. 2023

Population	Intervention / Comparison	Outcomes/Results	Methodical Notes
Evidence level: 3 Study type: Randomized controlled trial Number of Patients: 101 Recruiting Phase: July 2017 to November 2020 Inclusion Criteria: patients aged ≥ 19 years who had histologically confirmed adenocarcinoma of extrahepatic (perihilar or distal) bile duct with at least 1 regional lymph node metastasis and had undergone complete (R0 or R1) surgical resection within 12 weeks before randomization. Patients had to have no evidence of distant metastases or residual (R2) disease, no previous chemotherapy or radiotherapy	Intervention: Capecitabine (CAP) 1250 mg/m2 orally twice daily on days 1 through 14, every 3 weeks (n = 101) Comparison: Intravenously cisplatin 25 mg/m2 over 1 hour, followed by gemcitabine 1000 mg/m2 over 30 minutes on days 1 and 8, every 3 weeks (GemCis) (n = 101)	Primary: disease-free survival (DFS) Secondary: Overall survival, adverse events, health-related QoL, and exploratory biomarker analysis using tumor tissues and serially collected blood samples. Results: Median follow-up duration from randomization in the intention-totreat population was 33.4 months. Disease free survival (DFS) The 2-year DFS rate was 38.5% (1-sided 90% CI, 29.5–47.4%) in the GemCis group and 25.1% (1-sided 90% CI, 17.4%–33.5%) in the CAP group. The median DFS was 14.3 months (1-sided 90% CI, 10.7–16.5) in the GemCis group and 11.1 months (1-sided 90% CI, 8.4–12.7) in the CAP group [HR, 0.96 (1-sided 90% CI, 0.71–1.30), 1-sided p =0.430]	Funding Sources: Stated, see article. COI: Changhoon Yoo has received honoraria from Servier, Bayer, AstraZeneca, Merck Sharp & Dohme, Eisai, Celgene, Bristol-Myers Squibb, Debiopharm, Ipsen, Kyowa Kirin, Novartis, Boryung Pharmaceuticals, Merck Randomization: Randomization was performed Blinding: No masking was performed (open-label study) Dropout Rate/ITT-Analysis: ITT analysis was performed Notes: Cochrane risk of bias tool (Rob)-1: 3 questions(s) were considered to be high risk of bias Overall risk of bias: High

for BTC, Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and adequate major organ functions. Exclusion Criteria: Patients with tumor histology other than adenocarcinoma, a serum CA 19-9 level of ≥ 100 U/mL, or gastrointestinal obstruction were ineligible.		Overall survival The 2-year OS rate was 77.8% (1-sided 90% CI, 68.4–84.7%) in the GemCis group and 71.0% (1-sided 90% CI, 61.1–78.8) in the CAP group. The median OS was 35.7 months (1-sided 90% CI, 29.5 to not estimated) in the GemCis group and 35.7 months (1-sided 90% CI, 30.9 to not estimated) in the CAP group [HR, 1.08 (1-sided 90% CI, 0.71–1.64), 1-sided p =0.404] Safety Grade 3–4 adverse events occurred in 42 patients (84%) in the GemCis group and 8 patients (16%) in the CAP group. The most common grade 3 or higher adverse event was neutropenia (n =36, 72%) in the GemCis group, with 1 patient experiencing febrile neutropenia. Palmar-plantar erythrodysesthesia (n =4, 8%) was the most common grade 3 or higher adverse event in the CAP group. No treatment-related deaths were reported in both groups. Quality of life During study treatment, no significant deterioration in the global health status/quality of life (GHS/QoL) scores was observed during treatment in both groups. No significant differences in the GHS/QoL scores were observed between groups during treatment. Overall, the baseline functional scales were similar between the 2 groups,	Oxford CEBM Levels of Evidence (2011): Randomized trial Downgraded one level due to high risk of bias.

		without significant deterioration during treatment. Among the symptom scales, the constipation score was higher in the GemCis group from cycles 2 to 8, whereas the diarrhea score was higher in the CAP group from cycles 2 to 5 Author's Conclusion: In resected lymph node–positive extrahepatic cholangiocarcinoma, adjuvant GemCis did not improve survival outcomes compared with capecitabine.	

Kelley, R. K. et al. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 401. 1853-1865. 2023			
Population	Intervention / Comparison	Outcomes/Results	Methodical Notes
Evidence level: 2 Study type: Randomized controlled trial Number of Patients: 1069 Recruiting Phase: Between Oct 4, 2019, and June 8, 2021 Inclusion Criteria: aged 18 years or older; had histologically confirmed unresectable locally advanced or metastatic extrahepatic cholangiocarcinoma	Intervention: pembrolizumab 200 mg intravenously every 3 weeks (maximum 35 cycles), in combination with gemcitabine (1000 mg/m² intravenously on days 1 and 8 every 3 weeks; no maximum duration) and cisplatin (25 mg/m² intravenously on days 1 and 8 every 3 weeks; maximum 8 cycles)(n = 533). Pembrolizumab and placebo were limited to 35 cycles, and cisplatin was limited	Primary: overall survival Secondary: progression-free survival, objective response rate, and duration of response Results: Median study follow-up at final analysis was 25.6 months (IQR 21.7–30.4). Overall survival Median overall survival was 12.7 months (95% CI 11.5–13.6) in the pembrolizumab group versus 10·9	Funding Sources: Merck Sharp & Dohme, a subsidiary of Merck & Co, Rahway, NJ, USA. COI: Stated, see full text Randomization: Randomisation was done using a central interactive voice-response system and stratified by geographical region, disease stage, and site of origin in block sizes of four. Blinding: Double-blind trial Dropout Rate/ITT-Analysis: The primary endpoint of overall survival was

(including mixed hepatocellular carcinoma and cholangiocarcinoma), gallbladder cancer, or intrahepatic cholangiocarcinoma; had disease measurable per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 determined by the investigator; had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; provided tumour tissue for biomarker assessment; had adequate organ function; and had life expectancy of more than 3 months. Exclusion Criteria: Individuals were excluded from enrolment if they had ampullary cancer or had active autoimmune disease that required systemic treatment in the previous 2 years.	to eight cycles; there was no limit to the number of cycles of gemcitabine. Comparison: placebo administered intravenously every 3 weeks (maximum 35 cycles), in combination with gemcitabine (1000 mg/m² intravenously on days 1 and 8 every 3 weeks; no maximum duration) and cisplatin (25 mg/m² intravenously on days 1 and 8 every 3 weeks; maximum 8 cycles)(n = 536)	months (9.9–11.6) in the placebo group. Estimated 12-month overall survival rates were 52% (95% CI 47–56) in the pembrolizumab group and 44% (40–48) in the placebo group; estimated 24-month overall survival rates were 25% (95% CI 21–29) in the pembrolizumab group and 18% (15–22) in the placebo group. The efficacy boundary for a statistically significant overall survival benefit for the pembrolizumab group was met (HR 0·83 [95% CI 0·72–0·95]; p=0·0034). Progression-free survival Median progression-free survival was 6·5 months (95% CI 5·7–6·9) in the pembrolizumab group and 5·6 months (5·1–6·6) in the placebo group. Estimated 6-month progression-free survival was 52% (95% CI 48–57) in the pembrolizumab group and 46% (42–50) in the placebo group; estimated 12-month progression-free survival was 25% (21–30) in the pembrolizumab group and 20% (16–24) in the placebo group. The efficacy boundary for a statistically significant	evaluated in the intention-to-treat population. The secondary endpoint of safety was evaluated in the as-treated population Notes: Cochrane risk of bias tool (Rob)-1: 0 question were considered to be unclear risk of bias, 0 questions were considered to be high risk of bias. Overall risk of bias: Low Oxford CEBM Levels of Evidence (2011): 2 Randomized trial

		progression-free survival benefit for the pembrolizumab group was not met (HR 0·86 [95% CI 0·75–1·00]; p=0·023) Response At the first interim analysis, 153 (29% [95% CI 25 to 33]) of 533 participants in the pembrolizumab group and 153 (29% [25 to 33]) of 536 participants in the placebo group had a complete or partial response. The efficacy boundary for a statistically significant objective response rate benefit for the pembrolizumab group was not met (treatment difference 0.2 percentage points [95% CI −5.2 to 5·6]; p=0·47). Median duration of response was 9.7 months (95% CI 6.9 to 12.2) in the pembrolizumab group and 6.9 months (5.7 to 8.2) in the placebo group. Estimates of ongoing response at 24 months were 18% (95% CI 11–26) in the pembrolizumab group and 6% (2–13) in the placebo group. Adverse events In the as-treated population, the maximum adverse event grade was 3 to 4 in 420 (79%) of 529 participants in the pembrolizumab	

		group and 400 (75%) of 534 in the placebo group; 369 (70%) participants in the pembrolizumab group and 367 (69%) in the placebo group had treatment-related adverse events with a maximum grade of 3 to 4. 31 (6%) participants in the pembrolizumab group and 49 (9%) in the placebo group died due to adverse events, including eight (2%) in the pembrolizumab group and three (1%) in the placebo group who died due to treatment-related adverse events. Potentially immune-mediated adverse events and infusion reactions occurred in 117 (22%) of 529 participants in the pembrolizumab group and 69 (13%) of 534 participants in the placebo group, including 37 (7%) in the pembrolizumab group and 21 (4%) in the placebo group who had a grade 3 or 4 adverse event. Author's Conclusion: Based on a statistically significant, clinically meaningful improvement in overall survival compared with gemcitabine and cisplatin without any new safety signals, pembrolizumab plus gemcitabine and cisplatin could be a new	

		treatment option for patients with previously untreated metastatic or unresectable biliary tract cancer	

3.3 HCC TACE und Systemtherapie

2023 Update - HCC Kombination TACE + Systemtherapie

Profitieren Patienten mit einem HCC im Stadium BCLC B von einer Kombination aus TACE und Systemtherapie

P: Patienten mit HCC im Stadium BCLC B

I: TACE + Checkpoint-Inhibition

TACE + Atezolizumab/Bevacizumab, Pembrolizumab, Nivolumab

TACE + Durvalumab/Tremelimumab

TACE + Tyrosinkinaseinhibitor

TACE + Sorafenib

TACE + Lenvatinib

TACE + CPI + TKI

C: TACE alleine

O: Overall survival

Time to Progression oder Progression free survival

Adverse Events

Quality of life

Inhalt: 6 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Cai, R. 2017	2	Systematic review and meta-analysis of nine randomized controlled trials and five non-randomized controlled trials.
Dai, Y. 2021	2	Systematic review and meta-analysis (7 randomized controlled trials)
Duan, R. 2023	3	Systematic review and meta-analysis (9 RCTs, 21 observational studies)
Gu, H. 2020	3	Randomized controlled trial.
Kudo, M.	3	Randomised controlled trial
Zhao, S. 2020	2	Systematic review and meta-analysis of 23 studies (18 RCTs, 5 case-control)

OXFORD (2011) - AMSTAR 2: Systematic Reviews: 4 Bewertung(en)

Cai, R. et al. Transcatheter arterial chemoembolization plus sorafenib versus transcatheter arterial chemoembolization alone to treat advanced hepatocellular carcinoma: a meta-analysis. BMC Cancer. 17. 714. 2017				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 2 Overall confidence in the results of the review: AMSTAR II critical appraisal tool for systematic reviews: 3 critical flaws (items 4, 2, 7), 2 non-critical flaws (items 5,10) Overall quality of evidence: CRITICALLY LOW Oxford CEBM Levels of Evidence (2011): Systematic review of randomized trials Downgraded one level due to "Critically low" quality of the AMSTAR appraisal Study type: Systematic review and meta-analysis of nine randomized controlled trials and five non-randomized controlled trials. Databases: PubMed, Web of Science, the Cochrane Li- brary, CNKI, Wan Fang and China Science and Tech- nology Journal Database (CSTJ) Search period: from January 2009 to June 2016.	Population: patients with advanced hepatocellular carcinoma (HCC) Intervention: sorafenib with transcatheter arterial chemoembolization (TACE) Comparison: TACE alone	Primary: Efficacy outcomes (ORR, DCR), OS, AE. Secondary: - Results: Only PICO outcomes reported here Overall survival (8 studies): 0.5-year OS higher in combination therapy group (OR = 2.60, 95% CI = 1.57–4.29, p = 0.0002) 1-year OS higher in combination therapy group (OR =1.88, 95% CI = 1.39–2.53, p < 0.0001). Median OS and median time to progression (5 studies): significantly increased in the combination group compared to the control group (no meta-analysis) Adverse reactions (7 studies) The incidence of hand-foot skin, hypertension, diarrhoea, fatigue, hepatotoxicity and rash were significantly increased for combination treatment compared with that for TACE alone (RR = 9.83, 95% CI = 6.12–15.81, p < 0.00001;	14 studies (9 RCTs, 5 RCTs): Hu 2013, Wu 2010, Jiang 2010, Chen 2012, Wei 2009, Wei 2012, Yu 2011, Yang 2013, Ye 2013, Sun 2014, Zhou 2014, Wang 2015, Lencioni 2016, Kudo 2011	

Inclusion Criteria: (1) Research subjects were diagnosed with advanced HCC by clinical and pathological assessment. Moreover, these patients were not eligible for surgical treatment. (2) Research subjects were recruited to a clinical case- control study and were assigned to the TACE plus soraf- enib group or the TACE group randomly or based on their wishes. In the TACE group, patients received TACE combination chemotherapeutics, and the chemothera- peutic agents that were concurrently used were epirubi- cin, cisplatin, gemcitabine, doxorubicin, irinotecan and mitomycin. In the combination group, 400 mg of sorafe- nib was administered twice daily from 3 to 7 days after TACE until the disease progressed or the patient died. (3) Studies must be published, and the primary data from case-control or cohort studies must have been pro- vided in the publication. (4) Studies providing original data concerning the ORR, DCR, survival rate and adverse reactions. The data were either reported in these studies or calculated Exclusion Criteria: 1) The original data were not suitable for analysis. (2) Meeting abstracts, case reports, editorials, reviews and other meta-analyses were not included. (3) Multiple publications, duplicate records and similar studies were excluded.		RR = 2.76, 95% CI =1.89–4.02, p < 0.00001; RR = 3.35, 95% CI =2.48–4.52, p < 0.00001; RR = 1.25, 95% CI = 1.05–1.48, p = 0.01; RR = 1.27, 95% CI = 1.03–1.56, p = 0.03; and RR = 3.92, 95% CI = 2.58–5.94, p < 0.00001, respectively). The incidence of myelosuppression and alopecia did not significantly increase in the combination treatment group compared with the TACE alone group (RR = 1.38, 95% CI =0.89–2.12, p = 0.15; and RR = 2.87, 95% CI =0.71–11.67, p = 0.14, respectively). Author's Conclusion: The meta-analysis indicated that combination therapy is safe and efficient for clinical application.		

Dai, Y. et al. Optimal timing of combining sorafenib with trans-arterial chemoembolization in patients with hepatocellular carcinoma: A meta-analysis. Transl Oncol. 14. 101238. 2021				
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 2 Overall confidence in the results of the review: AMSTAR II critical appraisal tool for systematic reviews: 2 critical flaws (items 2, 7), 3 non-critical flaws (items 5,10,14) Overall quality of evidence: CRITICALLY LOW Downgraded one level due to "Critically low" quality of the AMSTAR appraisal Study type: Systematic review and meta-analysis (7 randomized controlled trials) Databases: PubMed, EMBASE, the Cochrane Library, MEDLINE, and Web of Science Search period: Inception - May 15, 2021 Inclusion Criteria: (a) patients diagnosed with HCC according to the diagnostic criteria; (b) the studies were RCTs; (c) treatments included TACE and sorafenib; (d) English articles and adult patients; (e) study endpoints involved the hazard ratio (HR) and its corresponding 95% confidence interval (CI) for overall survival (OS), time to progression (TTP), time to untreatable progression (TTUP), progression-free survival (PFS) which were avail-	Population: Patients with unresectable HCC Intervention: TACE + sorafenib Comparison: TACE + placebo / alone	Primary: overall survival (OS), time to progression (TTP), time to untreatable progression (TTUP), progression-free survival (PFS), tumor response, objective response rate (ORR), disease control rate (DCR), and adverse events (AEs). Secondary: - Results: OS (3 RCTs): Median OS time ranged from 9.0 to 29.7 months (TACE + sorafenib) and 9.1 to 22.5 months (TACE + placebo / alone). No improvement by combination therapy (not significant): HR 0.93 (95% CI 0.59–1.46, P = 0.75) fixed effects model. TTP (6 RCTs): The median TTP time ranged from 2.4 to 26.7 months and 2.8 to 16.4 months for patients with TACE + sorafenib and those with TACE + placebo / alone. Combination therapy prolonged TTP: HR 0.73 (95% CI 0.55–0.96, P = 0.003), random effects model. TTUP (2 RCTs): Median TTUP time was 3.2 to 26.7 months (TACE + sorafenib) and 7.5 to 20.6 (TACE + placebo / alone).	7 RCTs included: Hoffmann, Kudo, Kudo, Lencioni, Liu, Meyer, Sansonno.	

able or could be calculated, and tumor response, objective response rate (ORR), disease control rate (DCR), and adverse events (AEs). Exclusion Criteria: (a) reviews, meta-analysis, abstracts, letters, consensus, editorials, papers, as well as case reports; (b) animal experiments; (c) none-English articles; (d) incomplete information.		Likely no improvement by combination therapy (not significant). HR for TTUP was 0.76 (95% CI 0.31–1.89, P = 0.56),random effects model. PFS (3 RCTs): Higher PFS in combination group: HR 0.62 (95% CI 0.52–0.73, P < 0.00001), fixed effects model. Adverse effects (AEs) (7 RCTs): Incidence of AEs higher in combination group, hetero- geneities were discovered in alopecia, amylase, constipation, diarrhea, elevated ALT, elevated AST, elevated lipase, fatigue, hypertension, thrombocytopenia. Author's Conclusion: The combination of TACE and sorafenib significantly can improve TTP and PFS, and reduce the level of risk of adverse reactions of unresectable HCC, especially in the combination before TACE.		

Duan, R. et al. Transarterial chemoembolization (TACE) plus tyrosine kinase inhibitors versus TACE in patients with hepatocellular carcinoma: a systematic review and meta-analysis. World J Surg Oncol. 21. 120. 2023

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 3 Overall confidence in the results of the review: AMSTAR II critical appraisal tool for systematic reviews: 3 critical flaws (items 4,7,11), 3 non-	Population: Unresectable hepatocellular carcinoma patients. Intervention: TACE plus TKIs	Primary: Time to progression (TTP). Secondary: Overall survival (OS), tumor response rates, and adverse events (AEs). Results: Time to progression TTP (14	30 studies included: 9 RCTs: Hidaka 2019, Hoffmann 2015, Kudo 2014, Kudi 2011, Kudo 2017, Kudo 2019, Lencioni 2016, Meyer 2017, Inaba	

critical flaws (items 3,5,10) Overall quality of evidence: CRITICALLY LOW Oxford CEBM Levels of Evidence (2011): Systematic review of randomized trials and observational studies. Downgraded because of the majority of observational evidence and joint analysis. Downgraded one level due to "Critically low" quality of the AMSTAR appraisal Study type: Systematic review and meta-analysis (9 RCTs, 21 observational studies) Databases: PubMed, Embase, Cochrane Library, and Web of Science Search period: Inception to March 15, 2022. Inclusion Criteria: (1) study design: RCTs, retrospective or prospective cohort studies, and case control studies; (2) study population: patients with uHCC; (3) intervention: TACE plus sorafenib/lenvatinib/ apatinib/brivanib/orantinib versus TACE plus placebo or TACE alone (including conventional TACE and TACE with drug-eluting beads); and (4) the study was limited to English language articles and required adult	Comparison: TACE monotherapy.	studies) TACE plus TKIs vs. TACE plus placebo or TACE alone: HR of 0.72 (95% CI, 0.65–0.80), random-effects model Overall survival OS (28 studies) TACE plus TKIs vs. TACE plus placebo or TACE alone: combined HR, 0.57; 95% CI, 0.49–0.67). Adverse effects AEs Most common AE in TACE plus TKIs treatment were hand and foot skin reactions (OR, 87.17; 95% CI, 42.88–177.23), diarrhea (OR, 18.13; 95% CI, 9.32–35.27), and hypertension (OR, 12.24; 95% CI, 5.89–25.42), random-effects model. Common AE in TACE plus sorafenib were hand-foot skin reactions, diarrhea, hypertension, hair loss, and bleeding. TACE plus brivanib included hand-foot skin reactions, hypertension, rash/desquamation, nausea, and fever. TACE plus orantinib included diarrhea, gastrointestinal disease, abdominal pain, elevated alanine transaminase (ALT) levels, and fever. TACE plus lenvatinib included diarrhea, nausea, hypertension, gastric ulcers, and bleeding. TACE plus apatinib included diarrhea, gastric ulcers, hemorrhage, erythema multiforme, and hypoalbuminemia. Author's Conclusion: Our meta-analysis found that TACE plus TKIs may be	2013. 21 observational studies: Fan 2019, Shen 20202, Li 2021, Kan 2020, Liu 2019, Sun 2020, Yao 2016, Zhu 2014, Zhao 2016, Wu 2017, Ren 2019, Zou 2021, Ohki 2015, Wan 2016, Wang 2020, Bi 2013, Lei 2018, Hu 2014, Peng 2019, Peng 2019, Fu 2021.	

patient information including overall survival (OS) and time to progression (TTP) (HR and corresponding 95% confidence interval [CI]), tumor response rates, and adverse events (AEs). Exclusion Criteria: (1) comments, editorials, systematic reviews, meta-analyses, and studies unrelated to our topics were excluded from the final analysis, as were those unrelated to our topic or lacking useful information; (2) the same study was published by the same authors or based on the same database; (3) cases treated with TACE combined with other anti-tumor drugs were excluded; and (4) cases treated with TACE combined with TKIs and immuno- therapy were excluded		beneficial for patients with uHCC in terms of TTP, OS, and tumor response rates. However, combination therapy is also associated with a significantly increased risk of adverse reactions. Therefore, we must evaluate the clinical benefits and risks of combination therapy. Further well- designed RCTs are needed to confirm our findings.		

Zhao, S. et al. A comparison of transcatheter arterial chemoembolization used with and without apatinib for intermediate- to advanced-stage hepatocellular carcinoma: a systematic review and meta-analysis. Ann Transl Med. 8. 542. 2020

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 2 Overall confidence in the results of the review: AMSTAR II critical appraisal tool for systematic reviews: 3 critical flaws (items 2, 7, 13), 3 non-	Population: patients with intermediate- to advanced-stage HCC Intervention: TACE plus apatinib	Primary: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) according to the mRECIST to evaluate tumor response.	23 studies (18 RCTs and 5 case-control): Yang et al. 2019, Xiu et al. 2019, Wu et al. 2018, Wu et al. 2019, Wu et al. 2019, Wang et al. 2017, Song et al. 2018, Shen	

critical flaws (items 5,6,10) Overall quality of evidence: CRITICALLY LOW Oxford CEBM Levels of Evidence (2011): Systematic review of randomized trials Downgraded one level due to "Critically low" quality of the AMSTAR appraisal Study type: Systematic review and meta-analysis of 23 studies (18 RCTs, 5 case-control) Databases: PubMed, Embase, Web of Science, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Database, Chinese Biomedical Literature Database (CBM), Chinese Science and Technology Periodical Database (VI Search period: Inception - July 31, 2019 Inclusion Criteria: (I) patients should be clearly diagnosed with intermediate- to advanced-stage HCC by computed tomography (CT), magnetic resonance imaging (MRI) or pathology; (II) studies should include an experimental group and a control group, with the experimental group having received apatinib combined with TACE and the control group having received TACE monotherapy; (III) evaluation indicators should include	combination therapy Comparison: TACE alone	Secondary: Adverse events (AEs), half-year survival rate and one-year survival rate. Results: Only outcomes listed in the PICO reported here: Half-year survival rate (6 studies). Higher in combined therapy group (TACE + apatinib) than in monotherapy group (OR, 2.741, 95% CI, 1.745–4.306, P<0.001). One-year survival rate (6 studies). Higher in combined therapy group (TACE + apatinib) than in monotherapy group (OR, 2.284, 95% CI, 1.442–3.620, P<0.001). Adverse events: Fever (12 studies): Not significant (OR, 1.057, 95% CI, 0.749–1.492). Abdominal pain (9 studies): Not significant (OR, 1.080, 95% CI, 0.748–1.558). Nausea/vomit (12 studies): Not significant (OR, 1.099, 95% CI, 0.778–1.554). Myelosuppression (9 studies): Not significant (OR, 1.119, 95% CI, 0.682–1.835) OR, 20.681, 95% CI, 9.399–45.503). Proteinuria (11 studies): Higher incidence in TACE plus apatinib in comparison to TACE alone incidence of proteinuria (OR, 9.830, 95% CI, 4.685–	et al. 2019, Lu et al. 2019, Li et al. 2017, Li et al. 2018, Jin et al. 2017, Huang et al. 2018, Huang et al. 2017, He et al. 2018, Cui et al. 2019, Zeng et al. 2018, Zeng et al. 2018, Bai et al. 2018, Yang et al. 2018, Zhu et al. 2019, Lu et al. 2017, Chen et al. 2018,	

complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) according to the mRECIST to evaluate tumor response. Other evaluation indicators such as adverse events (AEs), half-year survival rate and one-year survival rate were also assessed if the number of included studies was more than three. Exclusion Criteria: (I) repetitive studies, narrative reviews, systematic reviews, letters, comments, case reports or studies unrelated to our topic; (II) studies in which patients had other malignancies or had received other interventions; (III) studies where no available data was extracted or no control group was established		20.625). Diarrhea (12 studies): Higher incidence in TACE plus apatinib in comparison to TACE alone (OR, 3.375, 95% CI, 1.932–5.897). Oral ulcer (4 studies): Higher incidence in TACE plus apatinib in comparison to TACE alone (OR, 3.843, 95% CI, 0.834–17.720) Author's Conclusion: The combination treatment of apatinib and TACE provides better survival benefits for intermediate- to advanced-stage HCC patients when compared to TACE monotherapy and should be recommended for suitable patients with unresectable HCC. However, further investigation into future prospective clinical studies is warranted.		

Cochrane Risk of Bias Tool 1 (RCT): 2 Bewertung(en)

Gu, H. et al. Efficacy and safety of apatinib combined with transarterial chemoembolization (TACE) in treating patients with recurrent hepatocellular carcinoma. Ann Transl Med. 8. 1677. 2020			
Population	Intervention / Comparison	Outcomes/Results	Methodical Notes
Evidence level: 3 Study type: Randomized controlled trial. Number of Patients: 80 patients with postoperative recurrent HCC. Recruiting Phase: Between January 2018 and January 2020 at the Xinqiao Hospital of Army Medical University. Inclusion Criteria: (I) aged 18 years or older; (II) diagnosed with HCC by two imaging modalities or biopsy; (III) intrahepatic recurrence after hepatic resection; (IV) Barcelona Clinic Liver Cancer (BCLC) stage B/C; (V) Child-Pugh class A/ B; (VI) could not tolerate or refuse performing re-resection or salvage transplantation; (VII) adequate organ function; (VIII) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0–2; and (IX) no vascular invasion or extra-hepatic metastasis. Exclusion Criteria: (I) combined use of other anticancer therapy after the surgery; (II) accompanied by other malignancies; (III) severe coagulation disorders; (IV) serious medical	Intervention: TACE plus apatinib. Comparison: TACE-alone.	Primary: PFS, OS, Tumor response, AEs Secondary: - Results: Only PICO outcomes reported here. PFS and OS The median PFS was significantly improved in the TACE plus apatinib vs. TACE-alone [17.2 months, 95% confidence interval (CI): 13.6–20.8 vs. 12.5 months, 95% CI: 11.3–13.7, hazard ratio (HR) =0.563, 95% CI: 0.336–0.943, P=0.041]. At the end of the follow-up, more patients survived in the TACE plus apatinib group than in the TACE-alone group [90.0% (36/40) vs. 75.0% (30/40)], but the median OS has not yet been reached in either group, and the differences were not statistically significant (HR =0.360, 95% CI: 0.113–1.150, P=0.072). The 1- and 2-year OS rates in the two groups were 95.0% vs. 85.0% (P=0.136) and 90.0% vs. 75.0% (P=0.077). AEs Two categories of AEs were considered	Funding Sources: Declared. COI: Declared. Randomization: randomized (1:1) into TACE plus apatinib group or TACE-alone group by using the block randomization method. No patient was allowed to switch groups once randomized. Blinding: Open-label study. Dropout Rate/ITT-Analysis: no intention-to-treat analysis, no description of dropouts. Notes: Cochrane risk of bias tool (Rob)-1: 4 questions(s) were considered to be high risk of bias Overall risk of bias: High Oxford CEBM Levels of Evidence (2011): Randomized trial Downgraded one level due to high risk of bias.

comorbidity; and (V) a large amount of ascites or refractory ascites.		in this study: postembolization syndrome (PES) and apatinib-related AEs. Features of PES typically include fever, abdominal pain, nausea and vomiting, and myelosuppression. No significant difference was found in the incidence of PES between the two groups (all P>0.05). The incidence of apatinib-related AEs was 80.0% (32/40) in the TACE plus apatinib group. Treatment- related AEs in the TACE plus apatinib group included the following: hand-foot syndrome (16/40, 40.0%), hypertension (11/40, 27.5%), fatigue (10/40, 25.0%), diarrhea (9/40, 22.5%), oral ulcer (9/40, 22.5%), and proteinuria (6/40, 15.0%). The majority of toxicities were grade 1–2, which is consistent with the known toxicities associated with apatinib. Once the patients developed grade 3 AE, the dose of apatinib was reduced from 500 mg qd to 250 mg qd until remission of symptoms, and the patients could then resume apatinib at 500 mg per day Thus,no patient developed grade 4 toxicity. The addition of apatinib to TACE significantly increased the incidence of apatinib-related complications compared to treatment with TACE alone (all P<0.05,). No unexpected toxicity or procedure-related mortality was observed in either group, and all AEs were effectively	

		alleviated after symptomatic treatment. Author's Conclusion: The combination treatment of apatinib and TACE might be safe and of potential benefit on patients with intrahepatic recurrent HCC.	

Kudo, M. et al. Final Results of TACTICS: a Randomized, Prospective Trial Comparing Transarterial Chemoembolization Plus Sorafenib to Transarterial Chemoembolization Alone in Patients with Unresectable Hepatocellular Carcinoma. . . .

Population	Intervention / Comparison	Outcomes/Results	Methodical Notes
Evidence level: 3 Study type: Randomised controlled trial Number of Patients: 156 patients with unresectable HCC, randomized 1:1 Recruiting Phase: between February 2011 and March 2016 Inclusion Criteria: All patients included in the study were older than 20 years and had a life expectancy of 12 weeks or longer, with tumors local- ized in the liver without vascular invasion or extrahepatic metastasis. The patients had a maximum of 10 tumors, each with a maximum size of 10 cm. Patients who had received 1–2 prior TACE procedures were allowed to enroll in the study provided that the previous TACE was performed more than 6 months before the enrolment. The	Intervention: TACE plus sorafenib Comparison: TACE alone	Primary: TACE-specific PFS and OS. Secondary: objective response rate after the first session of TACE and safety. Results: TACE-specific PFS: TACE-specific PFS significantly longer in the TACE plus sorafenib group than in the TACE alone group (25.2 vs. 13.5 months; HR = 0.59; 95% CI, 0.41–0.87; p = 0.006) TACE-specific OS: Median OS in the TACE plus sorafenib group 36.2 months (95% CI, 30.5–44.1) vs. TACE monotherapy group 30.8 months (95% CI, 23.5–40.8). TACE plus sorafenib did not provide a significantly greater survival benefit TACE Plus Sorafenib in Unresectable HCC than TACE monotherapy (HR = 0.861; 95% CI, 0.607– 1.223; p = 0.40). Subgroup analysis not reported here. AEs:	Funding Sources: This work was supported by the Japan Liver Oncology Group with funding from Bayer Yakuhin Ltd., Japan under a research contract. COI: Declared. Randomization: Patients were randomized 1:1 to treatment with either TACE plus sorafenib or TACE alone. Randomization was performed by a centralized data center using an interactive web response system involving a computer-generated sequence and electric data cap- ture system software (Viedeoc, Uppsala, Sweden). Patient alloca- tion factors were: (1) site, (2) meeting or not meeting Milan crite- ria (one lesion ≤5 cm or ≤3 lesions of ≤3 cm each), and (3) number of prior TACE sessions (0 vs. 1–2 times). Blinding: open-label study. parti Dropout Rate/ITT-Analysis: Efficacy data were analyzed on an intention-to-treat basis.

participants had an Eastern Cooperative Oncology Group performance status of zero or one, Child-Pugh score ≤7, and well-preserved organ function. Exclusion Criteria: Patients with a history of sys- temic chemotherapy were excluded.		treatment-related AEs affecting more than 10% of either treatment group and Grades three and four AEs occurring within 8 weeks after the first TACE. Patients in the TACE plus sorafenib group expe- rienced more AEs of all grades than patients in the TACE alone group, including hand-foot skin reaction (66.2% vs. 0.0%), hypertension (58.4% vs. 39.4%), elevated lipase (49.4% vs. 25.4%), fatigue (26.0% vs. 9.9%), diarrhea (16.9% vs. 0.0%), erythema multiforme (11.7% vs. 0.0%), weight loss (13.0% vs. 2.8%), and hoarseness (13.0% vs. 0.0%). Author's Conclusion: In TAC- TICS trial, TACE plus sorafenib did not show significant OS benefit over TACE alone; however, clinical meaningful OS prolongation and significantly improved PFS was observed. Thus, the TACE plus sorafenib can be considered a choice of treatment in intermediate-stage HCC, especially in patients with high tumor burden.	Notes: Cochrane risk of bias tool (Rob)-1: 3 questions(s) were considered to be high risk of bias Overall risk of bias: High Oxford CEBM Levels of Evidence (2011): Randomized trial Downgraded one level due to high risk of bias. <u>Other considerations:</u> Final analysis of the TACTICS trial; other publications of the same study are included in the included meta-analyses such as the one by Duan et al. 2023.