Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-289 Nivolumab

Stand: Januar 2025

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

Nivolumab
[Hepatozelluläres Karzinom (HCC), Erstlinie]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	**Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V**: - Durvalumab (als Monotherapie): Beschluss vom 6. Juni 2024 - Tremelimumab: Beschluss vom 5. Oktober 2023 - Durvalumab (in Kombination): Beschluss vom 5. Oktober 2023 - Atezolizumab: Beschluss vom 20. Mai 2021 - Lenvatinib: Beschluss vom 22. März 2019 **Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie – Wirkstoffe, die in zulassungs-überschreitenden Anwendungen (Off-Label-Use) nicht verordnungsfähig sind:** - Octreotid beim hepatozellulären Karzinom
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Nivolumab L01FF01 Opdivo	Anwendungsgebiet laut Beratungsanforderung: Nivolumab ist in Kombination mit Ipilimumab für die Erstlinienbehandlung des nicht resezierbaren oder fortgeschrittenen Leberzellkarzinoms bei Erwachsenen indiziert.
Zytostatika	
Mitomycin L01DC03 generisch	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Bei intravenöser Gabe ist es in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei folgenden metastasierenden Tumoren wirksam: - fortgeschrittenes Leberzellkarzinom - […]
Proteinkinase-Inhibitoren	
Lenvatinib L01EX08 Lenvima	Lenvima ist indiziert als Monotherapie für die Behandlung von erwachsenen Patienten mit fortgeschrittenem oder inoperablem hepatozellulärem Karzinom (HCC), die zuvor noch keine systemische Therapie erhalten haben.
Sorafenib L01EX02 Nexavar	Leberzellkarzinom Nexavar ist angezeigt zur Behandlung des Leberzellkarzinoms.
Monoklonale Antikörper	
Atezolizumab L01FF05 Tecentriq	Tecentriq wird angewendet in Kombination mit Bevacizumab bei erwachsenen Patienten zur Behandlung des fortgeschrittenen oder nicht resezierbaren hepatozellulären Karzinoms (HCC – hepatocellular carcinoma), die keine vorherige systemische Behandlung erhalten haben.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Durvalumab L01FF03 Imfinzi	Imfinzi in Kombination mit Tremelimumab ist angezeigt bei Erwachsenen zur Erstlinienbehandlung des fortgeschrittenen oder nicht resezierbaren hepatozellulären Karzinoms (HCC). Imfinzi als Monotherapie ist angezeigt bei Erwachsenen zur Erstlinienbehandlung des fortgeschrittenen oder nicht resezierbaren hepatozellulären Karzinoms (HCC).
Tremelimumab L01FX20 Imjudo	Imjudo in Kombination mit Durvalumab ist angezeigt bei Erwachsenen zur Erstlinienbehandlung des fortgeschrittenen oder nicht resezierbaren hepatozellulären Karzinoms (hepatocellular carcinoma, HCC).

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2024-B-289 (Nivolumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	10. Dezember 2024

Inhaltsverzeichnis

Abkürzungsverzeichnis

A+B	Atezolizumab+Becacizumab
AE	Adverse Event
Atez	Atezolizumab
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BCLC	Barcelona Clinic Liver-Cancer
Bev	Bevacizumab
CR	complete response
D+T	Durvalumab+Tremelimumab
DCR	diesease control rate
ECRI	ECRI Guidelines Trust
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HCC	Hepatozelluläre Karzinom
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LEN	Lenvantinib
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
NOS	Newcastle-Ottawa Scale
OR	Odds Ratio
ORR	objective response rate
OS	Gesamtüberleben
PD	progressive disease
PFS	Progressionsfreies Überleben
PR	partial response
RCT	Randomisierte Kontrollierte Studie
RR	Relatives Risiko
SD	stable disease
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
u-HCC	unresectable HCC
WHO	World Health Organization

1 Indikation

Erstlinienbehandlung des fortgeschrittenen oder nicht resezierbaren hepatozellulären Karzinoms (HCC).

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Leberzellkarzinom durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (https://www.google.com/) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Die Erstrecherche wurde am 14.07.2023 durchgeführt, die folgende am 03.12.2024. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 2916 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 17 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es liegen keine relevanten Cochrane Reviews vor.

3.2 Systematische Reviews

Zhu, G. et al., 2024 [17].

Is atezolizumab plus bevacizumab as first-line therapy for unresectable hepatocellular carcinoma superior to lenvatinib? a systematic review and meta-analysis.

Fragestellung

to evaluating the effectiveness and safety of Atezolizumab plus Bevacizumab (Atez/Bev) and Lenvatinib (LEN) as first-line systematic therapy for unresectable hepatocellular carcinoma (u-HCC).

Methodik

Population:

- Patients with u-HCC of any age, gender, and race who have not received systemic treatment before

Intervention:

- Atez/Bev

Komparator:

- Lenvatinib

Endpunkte:

- OS, PFS, ORR, disease control rate (DCR), complete response (CR), partial response (PR), progressive disease (PD), stable disease (SD) and adverse events (AEs)

Recherche/Suchzeitraum:

- PubMed, EMBASE, Cochrane Library, and Web of Science

Qualitätsbewertung der Studien:

- Newcastle-Ottawa Scale (NOS)

Ergebnisse

Anzahl eingeschlossener Studien:

- 12 retrospective cohort studies (RCSs) involving a total of 4948 patients

Charakteristika der Population/Studien & Qualität der Studien:

Table 1 Characteristics of the included studies

Author (year)	Region	Intervention	Sample Size	Age (Years)	Gender (M/F)	BCLC stage: (A)B/C	Child-Pugh class: A/B	ECOG score: 0/1(2,3)	NOS
Casadei-Gardini et al. 2022 [21]	Multicenter	Atez/Bev	864	72 (64–78)	682/182	NA	778/86	679/185	8
		LEN	1343	72 (65–79)	1058/285	NA	1211/132	1057/286	
Hatanaka et al. 2023 [22]	Japan	Atez/Bev	92	83 (82–86)	64/28	38/54	83/9	NA	8
		LEN	170	83 (81–86)	119/51	84/86	155/15	NA	
Hiraoka et al. 2022 [16]	Japan	Atez/Bev	194	74 (68–79)	148/46	93/101	194/0	167/27	8
		LEN	57	73 (69–79)	41/16	34/23	57/0	47/10	
Kim et al. 2022 [15]	Korea	Atez/Bev	86	62 (56–71)	70/16	18/68	82/4	36/50	7
		LEN	146	62 (55–70)	124/22	14/132	127/19	105/41	
Maesaka et al. 2022 [23]	Japan	Atez/Bev	66	76 (49–93)	50/16	31/35	64/2	60/6	7
		LEN	66	73 (53–91)	48/18	40/26	62/4	56/10	
Niizeki et al. 2022 [24]	Japan	Atez/Bev	152	73 (51–93)	118/34	85/67	NA	NA	7
		LEN	152	75 (31–93)	127/25	84/68	NA	NA	
Ohama et al. 2023 [25]	Japan	Atez/Bev	29	72 (67–81)	23/6	26/3	NA	19/10	8
		LEN	99	71 (66–77)	74/25	94/5	NA	68/31	
Persano et al. 2023 [26]	Multicenter	Atez/Bev	231	NA	551/146	241/456	603/94	NA	8
		LEN	466						
Rimini et al. 2023 [27]	Multicenter	Atez/Bev	65	NA	58/7	19/46	0/65	38/27	7
		LEN	152	NA	115/37	55/97	0/152	94/58	
Su et al. 2022 [28]	China	Atez/Bev	46	61.2(38.4–83.9)	38/8	14/32	40/6	18/28	8
		LEN	46	69.6(39.8–86.9)	38/8	16/30	41/5	24/22	
Tada et al. 2023 [29]	Japan	Atez/Bev	177	74.0(70.0– 79.0)	134/43	178/0	163/14	NA	8
		LEN	181	73.0(68.0– 80.0)	145/36	181/0	158/23	NA	
Zhao et al. 2023 [30]	China	Atez/Bev	34	55.0(42.0–62.0)	29/5	5/29	34/0	23/11	8
		LEN	34	55.0(48.8–66.0)	30/4	9/25	34/0	26/8	

Studienergebnisse:

- Compared with LEN, Atez/Bev can improve the patient's PFS (HR = 0.80, 95% CI: 0.72 ~ 0.88; p < 0.0001) and reduce the rate of overall AEs (OR = 0.46 95% CI: 0.38 ~ 0.55, p < 0.00001) and grade ≥ 3 AEs (OR = 0.43; 95% CI: 0.36 ~ 0.51, p < 0.00001), while there is no difference between OS and treatment responses rate (objective response rate, disease control rate, complete response, partial response, progressive disease, and stable disease) between two groups.
- subgroup analysis shows that Atez/Bev can promote the OS of patients with viral hepatitis. (HR = 0.79, 95% CI: 0.67 ~ 0.95; p = 0.01), while LEN has an advantage in improving OS in patients with Child-Pugh grade B liver function (HR = 1.98, 95% CI: 1.50 ~ 2.63; p < 0.00001).

Fazit der Autoren

All in all, our research results show that the effectiveness and safety of Atez/Bev are better than that of LEN, mainly in terms of PFS and AEs. Moreover, the results of subgroup analysis show that Atez/Bev is more effective for patients with viral etiology. LEN treatment may benefit patients with Child-Pugh grade B liver function more. Of course, considering the limited number of patients included in this metaanalysis, higher quality, large samples, and multicenter RCTs are still needed to verify the reliability of our conclusions.

Kommentare zum Review

Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:

- Liu, J. et al., 2024 [11]

Lu, J.et al., 2024 [12].

Atezolizumab Plus Bevacizumab Versus Lenvatinib for Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis

Fragestellung

to determine the effect of ATE/BEV versus LENV on the prognosis of unresectable/advanced HCC.

Methodik

Population:

- adults with unresectable/advanced HCC

Intervention:

- ATE/BEV

Komparator:

- LENV

Endpunkte:

- PFS, OS, objective response rate (ORR), complete response (CR), partial response (PR), disease control rate (DCR), stable disease (SD), progressive disease (PD), or mortality

Recherche/Suchzeitraum:

- PubMed, Embase, and Web of Science from inception to February 2023

Qualitätsbewertung der Studien:

- Newcastle-Ottawa Scale (NOS)

Ergebnisse

Anzahl eingeschlossener Studien:

- Seven studies involving 4428 patients (1569 in the ATE/BEV group and 2859 in the LENV group)

Charakteristika der Population/Studien & Qualität der Studien:

Table 1. Baseline Characteristics of Include Studies and Methodological Assessment

Authors	Study period	Country	Study design	Patients (n) ATE-BEV/LENV	Median follow-up (months)	Quality score
Rimini et al.[18]	2016-2021	Italy	Prospective	190/569	13.7	7
Kim et al.[12]	2019-2021	Korea	Retrospective	86/146	15	8
Persano et al.[13]	2010-2022	Germany	Retrospective	823/1312	12.2	7
Maesaka et al.[14]	2018-2021	Japan	Prospective	69/161	9.4	7
Niizeki et al.[15]	2018-2021	Japan	Retrospective	161/568	54	7
Hiraoka et al.[16]	2020-2022	Japan	Retrospective	194/57	14.4	8
Su et al.[17]	2018-2022	Taiwan, China	Retrospective	46/46	9.4	7

Studienergebnisse:

- LENV group had longer OS and PFS than the ATE/BEV group.Moreover, patients on LENV were more likely to achieve SD, whereas those on ATE/BEV were more likely to achieve PR.

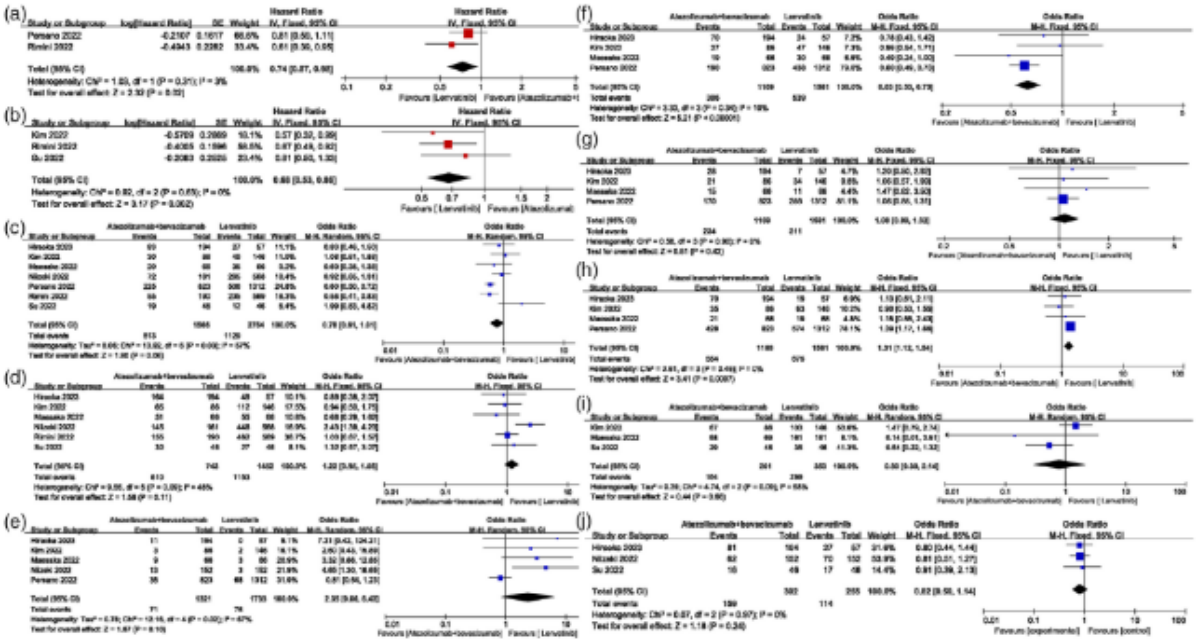

Figure 3. Forest plots of (a) OS, (b) PFS, (c) ORR, (d) DCR, (e) CR, (f) PR, (g) PD, (h) SD, (i) AE, and (j) mortality. AE, adverse event; CR, complete response; DCR, disease control rate; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Fazit der Autoren

Our meta-analysis showed that LENV is an effective and safe regimen superior to ATE/BEV in improving the OS, PFS, and SD, but not other outcome measures, of HCC patients. Due to the presence of variability and potential bias, medical practitioners ought to select their plan of action based on their expertise and the patient's conditions. We look forward to receiving further elaboration in the future regarding the optimal utilization of immunotherapy, anti-vascular endothelial growth factor, or tyrosine kinase inhibitors as first or second-line treatments, as well as the most appropriate stage of disease during which they are administered.

Luo J et al., 2022 [13].

Efficacy and safety of lenvatinib versus sorafenib in first-line treatment of advanced hepatocellular carcinoma: A meta-analysis

Fragestellung

This meta-analysis aimed to estimate the efficacy and safety of lenvatinib and sorafenib in patients with advanced HCC.

Methodik

Population:

- participants diagnosed advanced HCC

Intervention:

- Lenvatinib

Komparator:

- Sorafenib

Endpunkte:

- OS, PFS, ORR, disease control rate (DCR), complete response (CR), partial response (PR), and adverse events (AEs)

Recherche/Suchzeitraum:

- PubMed, Cochrane Library, Web of Science, and Embase databases were searched for relevant research published up to June 30, 2022.

Qualitätsbewertung der Studien:

- The Cochrane risk of bias assessment tool was used to evaluate the quality of the selected RCTs
- Quality of the included non-randomized comparative studies was assessed using the Newcastle-Ottawa scale (NOS)

Ergebnisse

Anzahl eingeschlossener Studien:

- Fifteen studies containing 3908 patients

Charakteristika der Population/Studien:

- participants with histologically or radiologically diagnosed advanced HCC, who were not previously treated with systemic therapies

Qualität der Studien:

- The bias risk of one RCT (13) was assessed using the Cochrane Collaboration tool and determined to be low (Figure 2).
- Besides, the 14 retrospective studies (18–31) had NOS scores ranging from 7 to 9, indicating a high quality of data in all included studies

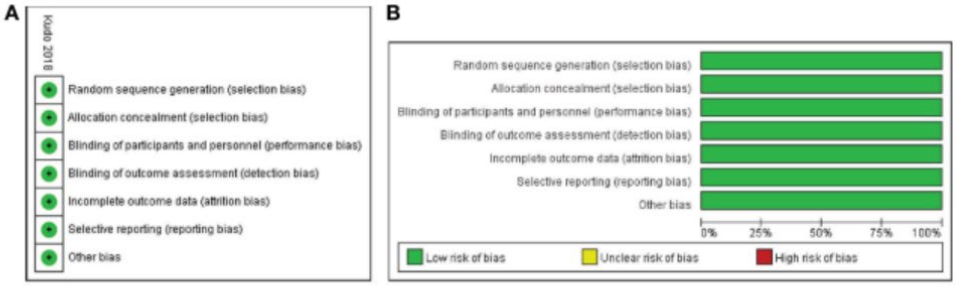

FIGURE 2
Assessment of risk of bias for RCT. Risk of bias summary **(A)**; risk of bias graph **(B)**.

Studienergebnisse:

- OS (Eleven studies involving 3347 patients)
  - no significant difference in the OS between the two groups (HR = 0.86; 95% CI: 0.72–1.02; p = 0.09).
  - A random-effects model was used, as statistical heterogeneity was identified among the included studies (p = 0.006, I2 =60%; Figure 3).
  - On the contrary, the pooled analysis showed that OS was significantly higher in the lenvatinib group as compared to the sorafenib group (HR= 0.90; 95% CI: 0.82–1.00; p = 0.04) when the heterogeneity was reduced (p =0.12, I2 =38%) by excluding two trials

- PFS (Thirteen studies enrolling 3760 patients)
  - pooled analysis showed that compared with sorafenib, lenvatinib was associated with significantly improved PFS (HR = 0.63; 95% CI: 0.53–0.74; p < 0.00001).
  - A random-effects model was used, due to statistical heterogeneity (p = 0.0002, I2 =68%).
  - To reduce the heterogeneity, two studies (20, 23) were removed (p =0.10, I2 = 38%). The recalculated results consistently showed that the treatment with lenvatinib was associated with greater improvement in PFS compared with sorafenib (HR = 0.60; 95% CI: 0.55–0.67; p < 0.00001)
- Treatment response
  - CR, PR, ORR, and DCR were used to evaluate tumor treatment response.
  - Eleven studies which included 2391 patients reported CR and PR, fourteen studies which enrolled 3803 patients investigated ORR, and thirteen studies which recruited 2863 patients documented DCR.
  - The pooled analysis showed that CR (3.22% vs. 0.60%; OR = 5.61; 95% CI: 2.71–11.64; p < 0.00001; Figure 5A), PR (23.94% vs. 6.97%; OR = 4.62; 95% CI: 3.06–6.98; p < 0.00001; Figure 5B), ORR (25.74% vs. 6.4%; OR = 5.61; 95% CI: 3.90–8.09; p < 0.00001; Figure 5C), and DCR (71.54% vs. 51.59%; OR = 2.42; 95% CI: 1.79–3.28; p < 0.00001; Figure 5D) of the lenvatinib group were better than those of the sorafenib group.
- Safety analysis (AEs was reported in 8 studies, which included a total of 3019 patients)
  - The pooled analysis showed no significant difference in the incidence of any grade AEs between the lenvatinib group (92.34%) and the sorafenib group (93.09%) (OR = 0.99; 95% CI: 0.47–2.09; p = 0.98).
  - The incidence of grade ≥ 3 AEs was reported in 11 studies, which involved a total of 3043 patients.
  - Similarly, the pooled data indicated no significant difference in the incidence of grade ≥ 3 AEs between the two groups, with lenvatinib and sorafenib groups exhibiting 38.89% and 33.25%, respectively (OR = 1.17; 95% CI: 1.00–1.37; p = 0.05;

Anmerkung/Fazit der Autoren

Given its potential survival benefit and good tolerability, lenvatinib is an appropriate and promising alternative to sorafenib as first-line systemic therapy in patients with advanced HCC.

Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:

- Hu, L. et al., 2023 [8]
- Wang, S. et al., 2022 [16]

Facciorusso A et al., 2021 [5].

Lenvatinib versus sorafenib as first-line therapy of advanced hepatocellular carcinoma: a systematic review and meta-analysis.

Fragestellung

to compare lenvatinib and sorafenib as first-line treatment.

Methodik

Population:

- Patients with advanced hepatocellular carcinoma

Intervention:

- Lenvatinib

Komparator:

- Sorafenib

Endpunkte:

- primary outcome was overall survival, computed from the start of the treatment and death or censoring.
- Secondary outcomes were survival rate at 1 and 2 years, progression-free survival (defined as time elapsed from treatment to radiological evidence of progression), PFS rate at 1 year, tumor response, both in terms of objective response (OR, defined as complete response + partial response) and disease control rate (DCR, defined as complete response + partial response + stable disease), and severe adverse event (SAE) rate.

Recherche/Suchzeitraum:

- MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Scopus, and Web of Science through November 2020;
- the search strategy used in Medline was based on the following search string: (((sorafenib [MeSH Terms]) OR (lenvatinib [MeSH Terms])) AND (hepatocellular carcinoma [MeSH Terms])) OR (hcc [MeSH Terms]).

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool for assessing the risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- Five studies enrolling 1481 patients were included.

Charakteristika der Population/Studien:

- Patients: adults HCC patients not previously treated with systemic therapies (first-line setting)

Qualität der Studien:

Supplementary Table 1. Risk of bias assessment and quality of included studies

Observational studies[a]	Selection	Comparability	Outcome	Overall quality
Kim 2020	*	**	*	L
Kuzuya 2020	**	***	**	M
Nakano 2020	***	***	**	H
Tomonari 2020	***	***	**	H

Randomized controlled trials[b]	1	2	3	4	5	6	7	
Kudo 2018	L	L	L	L	L	L	L	H

L, low; H, high; U, unclear; M, moderate. [a]Study quality assessment performed by means of Newcastle/Ottawa scale (each asterisk represents if the respective criterion within the subsection was satisfied). [b]Cochrane Collaboration's tool for assessing the risk of bias across 7 domains: 1 (Random sequence generation), 2 (Allocation concealment), 3 (Blinding of participants and personnel), 4 (Blinding of outcome assessment), 5 (Incomplete outcome data), 6 (Selective reporting) and 7 (Other bias).

Studienergebnisse:

- Overall survival
  - Comparison of overall survival, based on 4 studies [6, 8-10], was depicted in No difference was detected (HR 0.81, 0.581.11) with low evidence of heterogeneity (I2=18%) and median survival was 13.4 months (9.38-17.48) in lenvatinib and 11.4 months (8.46-14.47) in sorafenib patients, thus supporting the non-superiority of one treatment over the other in terms of overall survival.
  - This finding was confirmed in the comparative analysis of 1- and 2-year survival rate, with ORs 1.48 (0.84-2.6) and 0.99 (0.66-1.48), respectively (Table 2).
  - In particular, pooled survival rates at 1- and 2-year were 65.5% (53.8%77.2%) and 31.1% (27.2%-35.1%) with lenvatinib and 50.8% (34.3%-67.2%) and 34% (21.4%-46.7%) with sorafenib, respectively.
- Progression-free survival
  - As reported in Figure 3 and Table 2, lenvatinib led to a significant improvement of PFS (HR 0.67, 0.48-0.94), with low evidence of heterogeneity (I2 =17%).
  - Median PFS was 5.88 months (3.68-8) in lenvatinib and 4.17 months (3.08-5.25) in sora-fenib patients, hence with evidence of more favorable PFS outcomes in patients treated with lenvatinib.
  - Likewise, PFS rate at 1 year was significantly in favor of lenvatinib as compared to sorafenib (35.7%, 16.5%-54.8% versus 22.7%, 15.8%29.5%; OR 0.70, 0.68-0.95), with moderate evidence of heterogeneity (I2=36%).
- Other secondary outcomes
  - based on 4 studies [6, 8-10] lenvatinib determined a considerably higher rate of objective response (33.3%, 23.6%-43% versus 6.5%, 3.5%-9.5%; OR 7.70, 2.99-19.82), with moderate evidence of heterogeneity (I2=34%).
  - Disease control rate was also significantly higher in patients treated with lenvatinib in comparison to sorafenib (76.9%, 70.4%-83.5% versus 52.7%, 40.7%64.6%; OR 2.41, 1.55-3.77; I2=21%).

Anmerkung/Fazit der Autoren

No difference between lenvatinib and sorafenib in terms of severe adverse event rate was observed (OR 1.31, 0.82-2.09). Lenvatinib prolongs progression-free survival as compared to sorafenib in HCC patients, although this result does not translate to a significant survival benefit.

Kommentare zum Review

- Facciorusso A et al., 2021 wird in der deutschen S3 Leitlinie zitiert (Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften)

Du S et al., 2023 [4].

Atezolizumab plus bevacizumab versus lenvatinib as first-line therapy for advanced hepatocellular carcinoma: A systematic review and meta-analysis

Fragestellung

Assess the effectiveness and safety of treatment options atezolizumab plus bevacizumab (Atez/Bev) or lenvatinib for patients with advanced hepatocellular carcinoma (HCC) patients.

Methodik

Population:

- advanced HCC patients

Intervention:

- atezolizumab plus bevacizumab (Atez/Bev)

Komparator:

- lenvatinib

Endpunkte:

- OS, PFS, treatment response, adverse events

Recherche/Suchzeitraum:

- PubMed, Embase, and Web of Science. The scope of the search covered the time frame from the earliest available date until February 2023.

Qualitätsbewertung der Studien:

- The Newcastle Ottawa Scale were used to assess the quality of included studies because most of them were retrospective. Studies with 4–6 and 7–9 validity scores were regarded to be of low and high quality, respectively.

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 nonrandomized comparative studies

Charakteristika der Population/Studien:

- Over 7 years from 2015 to 2022, 6628 patients diagnosed with advanced liver cancer (HCC) received treatment with either the combination of Atez/Bev (n = 2492) or lenvatinib (n = 4136). Three of the studies were performed across multiple centers, while three were conducted in Japan, one in China, and one in Korea.

Table 1
Characteristics of included studies.

Study	Recruitment year	Country	Design	Group	Cases	Age (yr)	Sex (M/F)	Etiology (viral/non-viral)	ECOG PS (0/>0)	Child–Pugh (A/B)	BCLC stage (A&B/C)	Macrovascular invasion	Extrahepatic metastasis
Andrea Casadei-Gardini 2022	2015–2022	Multicenter	RCS	Atez/Bev	864	72 (IQR 64, 78)	682/182	484/380	679/185	778/86	NA	185 (21.5%)	285 (21.2%)
				Lenvatinib	1343	72 (IQR 65, 79)	1058/285	758/585	1057/286	1211/132	NA	316 (36.6%)	491 (36.6%)
Kazuki Maesaka 2022	2018–2021	Japan	PCS	Atez/Bev	66	76 (49–93)	50/16	36/30	60/6	64/2	31/35	12 (18.2%)	27 (40.9%)
				Lenvatinib	66	73 (53–91)	48/18	37/29	56/10	62/4	40/26	11 (16.7%)	18 (27.3%)
Beom Kyung Kim 2022	2019–2021	Korea	RCS	Atez/Bev	86	62 (56–71)	70/16	65/21	36/50	82/4	18/68	43 (50.0%)	37 (43.0%)
				Lenvatinib	146	62 (55–70)	124/22	109/37	105/41	127/19	14/132	76 (52.1%)	91 (62.3%)
Chung-Wei Su 2022	2018–2022	China	RCS	Atez/Bev	46	61.2 (38.4–83.9)	38/8	41/5	18/28	40/6	14/32	24 (52.2%)	15 (32.7%)
				Lenvatinib	46	69.6 (39.8–86.9)	38/8	38/8	24/22	41/5	16/30	24 (52.2%)	17 (37.0%)
Atsushi Hiraoka 2022	2020–2022	Japan	RCS	Atez/Bev	194	74 (68–79)	148/46	102/92	167/27	194/0	93/101	44 (22.7%)	71 (36.6%)
				Lenvatinib	57	73 (69–79)	41/16	27/30	47/10	57/0	34/23	5 (8.8%)	15 (26.3%)
Takashi Niizeki 2022	2018–2022	Japan	RCS	Atez/Bev	161	73 (38–93)	123/38	85/76	NA	NA	87/74	35 (21.7%)	47 (29.2)
				Lenvatinib	568	72 (31–93)	467/101	318/250	NA	NA	293/275	106 (18.7%)	204 (35.9%)
M. Rimini 2022	2017–2022	Multicenter	PCS	Atez/Bev	190	<75/≥75 (111/79)	149/41	NA	142/48	179/11	85/105	46 (24.2%)	NA
				Lenvatinib	569	<75/≥75 (319/250)	457/112	NA	466/103	488/81	235/334	462 (81.2)	NA
Mara Persano 2022	2010–2022	Multicenter	RCS	Atez/Bev	885	≤70/>70 (339/484)	657/228	442/381	615/208	769/54	335/488	175 (21.3%)	305 (37.1%)
				Lenvatinib	1341	≤70/>70 (598/714)	1032/309	763/549	1088/224	1166/146	554/758	260 (19.8%)	477 (36.4%)

Atez/Bev = atezolizumab plus bevacizumab, IQR = inter quartile range, NA = not available, PCS = prospective cohort study, RCS = retrospective control study.

Qualität der Studien:

Table 2

Risk of bias for inclusion studies.

Study, year	Selection	Comparability	Outcome	NOS score
Andrea Casadei-Gardini, 2022	4	1	3	8
Kazuki Maesaka, 2022	3	2	2	7
Beom Kyung Kim, 2022	3	1	3	7
Chung-Wei Su, 2022	3	2	3	8
Atsushi Hiraoka, 2022	4	1	3	8
Takashi Niizeki, 2022	4	1	2	7
M. Rimini, 2022	3	2	2	7
Mara Persano, 2022	4	1	3	8

NOS = Newcastle Ottawa Scale.

- All 8 studies that were … considered to be of high quality.

Studienergebnisse:

- no significant difference in 0.5-, 1-, 1.5-year OS rates (6 month: OR=1,25 [0,86; 1,83]; p=0,25; I^2 = 67%; 12 month: OR=0,41 [0,14; 1,17]; p=0,09; I^2 = 94%; 18 month: OR=0,77 [0,57; 1,06]; p=0,11; I^2 = 59%) and 0.5-, 1-year PFS rates between the 2 groups.
  - subgroup analysis indicated that patients with HCC caused by viral hepatitis would benefit more from the Atez/Bev therapy (HR=0,75 [0,63; 0,89]; p=0,001; I^2 = 0%) but patients with a Child–Pugh class B liver function would benefit more from Lenvatinib (HR=1,70 [1,07; 2,70]; p=0,03; I^2 = 0%)
- lenvatinib exhibited significantly greater ORR than Atez/Bev (OR: 0.76, 95% CI: 0.59–0.98, P = .004, I^2=57%)
- There was no significant difference in DCR between the 2 groups, with a combined OR of 1.07 (95% CI: 0.77–1.48, P = .069; I^2=56%)
- Among patients treated with Atez/Bev and lenvatinib, a combined prevalence of 71.9% and 83.9%, respectively, was observed. Meanwhile, no significant difference in the overall, grade 1–2 and grade 3–4 AEs (OR=0,62 [0,23; 1,66]; p=0,34; I^2 = 92%) rate between the 2 groups was found in the random-effect model.
- Patients receiving lenvatinib treatment face a greater risk of experiencing hypothyroidism and diarrhea, whereas those treated with Atez/Bev are more prone to developing a rash.

Anmerkung/Fazit der Autoren

This study has several potential limitations. Firstly, because there were no RCTs examining the effectiveness of Atez/Bev or Lenvatinib in the treatment of advanced HCC, a large number of NRCT studies were included in this meta-analysis, which may have resulted in selection bias. Secondly, significant heterogeneity was observed among some of the study outcomes, which could be due to a variety of factors such as the quality of the NRCT studies, the small number of studies included in subset analyses, and differences in patient characteristics. The limitations outlined above could have impacted the results of this meta-analysis.
To conclude, our study did not find any significant difference in effectiveness and safety between Atez/Bev and Lenvatinib. Nonetheless, there are indications that lenvatinib treatment may be more beneficial for patients with Child–Pugh class B liver function, and Atezolizumab plus Bevacizumab may be more effective for those with viral etiology. However, larger prospective studies are necessary to validate these findings.

Kommentar zum Review:
Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:

- Giri et al. 2023 [6]

Ahmed F et al., 2021 [1].
Atezolizumab plus bevacizumab versus sorafenib or atezolizumab alone for unresectable hepatocellular carcinoma: A systematic review

Fragestellung

To conduct a systematic literature review to evaluate the evidence supporting the efficacy and safety of atezolizumab/bevacizumab as preferred first-line drug therapy over the conventional sorafenib or atezolizumab monotherapies, which are used to improve survival outcomes and reduce disease progression in patients with unresectable HCC and non-decompensated liver disease.

Methodik

Population:

- adult patients (aged 18 and older) with unresectable HCC

Intervention:

- combination therapy of intravenous atezolizumab (1200 mg) plus bevacizumab (15 mg/kg) every 3 wk (or periodically)

Komparator:

- sorafenib monotherapy, atezolizumab monotherapy, or placebo.

Endpunkte:

- mortality
- PFS
- Tumor response, disease control rate
- Adverse events

Recherche/Suchzeitraum:

- The search was conducted using the Cochrane, Cochrane Central, PubMed Central, Scopus, Science-Direct, WHO trials, clinicaltrials.gov, Google Scholar, Embase, CINAHL, and MedLine databases. The data search was conducted until December 27, 2020.

Qualitätsbewertung der Studien:

- Cochrane RoB 2 tool for randomized trials

Ergebnisse

Anzahl eingeschlossener Studien:

- 4 RCTs, 2 ongoing, 2 completed
- The two completed trials were included in the final analyses.

Charakteristika der Population/Studien:

Completed studies	Finn *et al*[12], 2020	Lee *et al*[16], 2020
Country/ies of Enrollment	111 sites in 17 countries, which include the United States, China, Japan, Germany, France, South Korea, Russia, Canada, and Taiwan	26 sites in 7 countries, which include the United States, Japan, South Korea, Taiwan, Australia, and New Zealand
Study design	Open-label, randomized clinical trial	Multi-arm study with five cohorts However, only the two cohorts focusing on hepatocellular carcinoma, Groups A and F, are described here in this study
Phase	III	Ib
Study Quality	Low risk of bias	Low risk of bias
Intervention	Atezolizumab plus bevacizumab Dose: 1200 mg atezolizumab + 15 mg/kg of bevacizumab IV q3w	Atezolizumab plus bevacizumab Dose: 1200 mg atezolizumab + 15 mg/kg of bevacizumab IV q3w
Control	Sorafenib monotherapy Dose: 400 mg sorafenib PO BID	Atezolizumab monotherapy Dose: 1200 mg atezolizumab
Number of patients	501	403
Intervention/control	Intervention: 336	Group A[1]: 104
	Control: 165	Group F+: 60 **Control:** 59 included in efficacy analysis[1] 58 included in safety analysis 1 discontinued before receiving any treatment due to elevated alkaline phosphatase concentrations[1]
Median duration of follow-up (mo, [IQR])	Overall: 8.6 mo	Overall follow-up not given, see stratified data below
Intervention/control		Group A[1]: 12.4 (IQR 8.0-16.2)
	Intervention: 8.9	Group F+: 6.6 (IQR 5.5-8.5)
		Control: 6.7 (IQR 4.2-8.2)
	Control: 8.1	
Primary outcomes reported	Mortality rates	Mortality rates
	Hazard ratio for death	Hazard ratio for death
Secondary Outcomes reported	Overall survival	Overall survival
	Median progression free survival	Median progression free survival
	Grade 3-5 adverse events	Grade 3-4 adverse events
	Disease control	Disease control
	Objective response rate	Objective response rate
	Time to progression	Time to progression
	Duration of response	Duration of response
	Post-progression survival	Post-progression survival

Ongoing clinical trials	La Roche[14], 2020	Hack *et al*[15], 2020
Country of enrollment	Italy	170 sites in 25 countries (Asia)
Study design	Single-arm, multi-Center, randomized clinical control trial	Multi-center randomized open-label, clinical control trial
Study phase	IIIb	III
Study quality	NA (study is still ongoing)	NA (study is still ongoing)
Intervention	Atezolizumab plus bevacizumab	Atezolizumab plus bevacizumab
	Dose: atezolizumab 1200 mg IV infusion q3w + bevacizumab 15 mg/kg IV Q3W	Dose: atezolizumab 1200 mg every 3 wk + bevacizumab 15 mg/every 3 wk
Control	Standard of care	Active surveillance
	No specifications for control arm reported	
Number of patients	150	662
Intervention/control	Intervention not specified	Intervention 501
	Control: Not specified	Control: 119
Median age (range)	Not reported	Not reported
Intervention/control	Study included individuals > 18 yr	Study included individuals > 18 yr
-Duration of follow-up in mo	Not reported	Intervention: 8.6 mo
Intervention/control		Control: 6.5 mo
Types of outcomes reported	Overall survival	Overall survival
	Median progression-free survival	Median progression-free survival
	Grade 3-5 adverse events	Grade 3 or 4 adverse events
	Disease control	Disease control
	Objective response rate	
	Time to progression	
	Duration of response	
	Post-progression survival	
Data that could not be evaluated/data missing	NA (study is still ongoing)	NA (study is still ongoing)

Qualität der Studien:

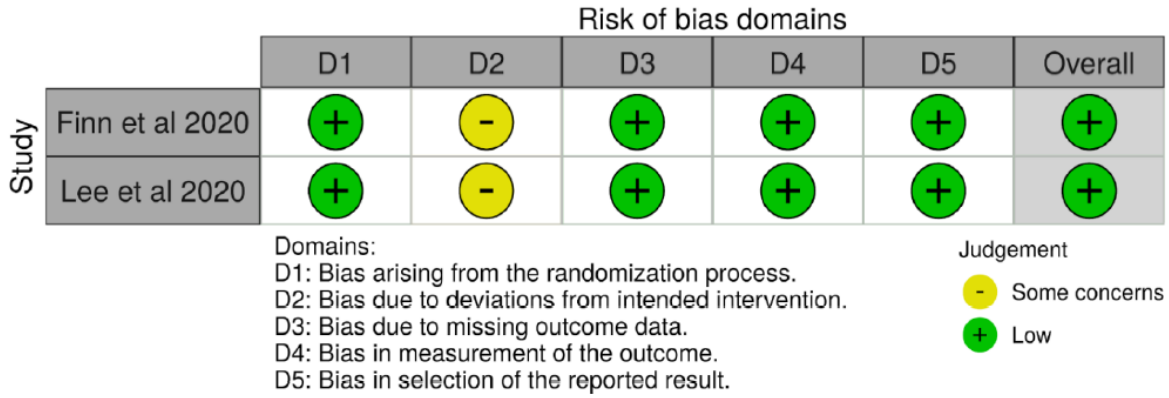

Figure 1 Traffic light plot showing the risk of bias of the two completed studies.

Studienergebnisse:

Es werden nur die Ergebnisse der Studie Finn et al dargestellt, da die Vergleichstherapie der Studie Lee et al (Atelzolizumab Mono) nicht zugelassen ist.

Table 3 Summary of the efficacy and safety findings

Ref.	Finn *et al*[12], 2020	
Schemes	Atezolizumab-bevacizumab combination therapy	Sorafenib monotherapy
Total patients		
	n = 336	*n* = 165
Primary efficacy outcomes		
Mortality		
n (%)	96 (28.6)	65 (39.4)
Two-tail *P* value	*P* = 0.0033	*P* = 0.0033
HR for disease progression, CI	0.59, 95% CI: 0.47-0.76	Not applicable
Two-tail *P* value	*P* < 0.001	
HR for death, CI	0.58, 95% CI: 0.42-0.79	NA
Two-tail *P* value	*P* < 0.001	
HR for progression-free survival, CI	NA	NA
Two-tail *P* value		
Secondary efficacy outcomes tumor survival and progression of disease		
Overall/survival rate, *n* (%)	*n* not explicitly reported	*n* not explicitly reported
n (%)	-67.2	-54.6
95% CI		
	61.3-73.1	45.2-64
Median overall survival in mo	Not estimable	13.2 mo
95% CI		
		(10.4 to not estimable)
6 mo overall survival rates		
95% CI	84.80%	72.20%
	80.9-88.7	80.9-88.7
12 mo overall survival rates	67.20%	54.60%
95% CI	61.3-73.1	45.2-64
Median progression-free survival (mo), (95% CI)	6.8 mo	4.3 mo
	(5.7-8.3)	(4.0-5.6)
Overall confirmed objective response		
n (%) as *per* RECIST 1.1		
95% CI	89 (27.3%)	19 (11.9%)
	(22.5-32.5)	(7.4-18)
Confirmed objective response-complete response as *per* RECIST 1.1, *n* (%)	18 (5.5)	0 (0)

Confirmed objective response-Partial response as *per* RECIST 1.1, *n* (%)	71 (21.8)	19 (11.9)
Stable disease *n* (%) as *per* RECIST 1.1	151 (46.3)	69 (43.4)
Progressive disease		
n (%) as *per* RECIST 1.1	64 (19.6)	39 (24.5)
Disease control rate, *n* (%)	240 (73.6)	88 (55.3)
Ongoing objective response at data cut off, *n* (%)	77/89 (86.5)	13/19 (68.4)
Safety outcomes (adverse events)		
Overall patients with an adverse event from any cause, *n* (%)	323 (98.2)	154 (98.7)
Treatment-related serious adverse events, *n* (%)	125 (38)	48 (30.8)
Treatment-related mortality	161 deaths (%)	
	It was not explicitly stated how many deaths there were in relation to treatment in either intervention or control arm[1]	
Adverse events leading to dose modifications, *n* (%)	163 (49.5)	95 (60.9)
Adverse events leading to withdrawal from any trial drug, *n* (%)	51 (15.5)	16 (10.3)
Number of participants with Grade 3 and above, *n* (%)	5-15 (4.6)	9 (5.8)

Anmerkung/Fazit der Autoren

In this review, findings confirm that atezolizumab/bevacizumab combination therapy can be an effective first-line treatment option to either sorafenib or atezolizumab monotherapy in patients with advanced HCC and non-decompensated liver disease. However, due to the small number of RCTs included, this systematic review may be considered insufficiently robust to provide strong recommendations. Consequently, further research and larger RCTs with cost-effectiveness analysis are necessary to validate our observations and identify the most efficacious and safe therapeutic regimen.

3.3 Leitlinien

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften), 2024 [9,10].

Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)

Diagnostik und Therapie des Hepatozellulären Karzinoms und biliärer Karzinome; S3-Leitlinie, Langversion 5.1

Zielsetzung/Fragestellung

Die interdisziplinäre S3-Leitlinie ist ein Instrument, um die Diagnostik und Therapie des Hepatozellulären Karzinoms (HCC), (…) zu verbessern.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert: gültig bis zur nächsten Aktualisierung bzw. bis max. August 2024

Recherche/Suchzeitraum:

- Update: Die Literatursuche, Evidenzbewertung und Erstellung der Evidenztabellen fand zwischen Juli 2023 und Januar 2024 statt.

LoE/GoR

- Evidenzgraduierung nach Oxford (Version 2011)

Tabelle 3: Schema der Evidenzgraduierung nach Oxford (Version 2011)[1]

Frage	Level 1*	Level 2*	Level 3*	Level 4*	Level 5
Wie verbreitet ist das Problem?	Lokale und aktuelle Zufallsstichprobe oder Zählung (Vollerhebung)	Systematische Übersichtsarbeit von Erhebungen, die auf die lokalen Umstände übertragen werden können**	Lokale Erhebung, die nicht auf einer Zufallsstichprobe basiert**	Fallserie**	Nicht anwendbar
Ist dieser diagnostische oder kontrollierende Test genau? (Diagnose)	Systematische Übersichtsarbeit von Querschnitt-studien mit durchgehend angewandtem Referenzstandard und Verblindung	Einzelne Querschnittsstudie mit durchgehend angewandtem Referenzstandard und Verblindung	Nicht konsekutive*** Studie oder Studie ohne angewandten Referenz-standard**	Fall-Kontroll-Studie oder Studie mit ungeeignetem oder nicht unabhängigem Referenz-standard**	Experten-meinung basierend auf pathophysiologischen Überlegungen
Was würde passieren, wenn wir keine Therapie anwenden würden? (Prognose)	Systematische Übersichtsarbeit von Kohorten-studien, die Patienten im Anfangsstadium der Erkrankung beobachten (Inception cohort study)	Einzelne Kohortenstudie von Patienten im Anfangsstadium der Erkrankung (Inception cohort study)	Kohortenstudie oder Kontrollarm einer randomisierten Studie*	Fallserie oder Fall-Kontroll-Studie oder eine prognostische Kohortenstudie mit niedriger methodischer Qualität†**	Nicht anwendbar
Hilft dieses Vorgehen? (Nutzen der Intervention)	Systematische Übersichtsarbeit von randomisierten Studien oder N-von-1-Studien‡	Randomisierte Studie oder Beobachtungs-studie mit dramatischen Effekten	Kontrollierte Kohortenstudie/ Follow-up-Studie†**	Fallserien oder Fall-Kontroll-Studien oder Studien mit historischen Kontrollen**	Experten-meinung basierend auf pathophysiologischen Überlegungen
Was sind häufige Neben-wirkungen?	Systematische Übersichtarbeit von entweder randomisierten	Randomisierte Studie oder (ausnahmsweise) Beobachtungsstudie	Kontrollierte Kohortenstudie/ Follow-up-Studie (Post-Marketing-		

Frage	Level 1*	Level 2*	Level 3*	Level 4*	Level 5
(Schaden der Intervention)	Studien oder eingebetteten Fall-Kontroll-Studien* oder N-von-1-Studie mit zur Fragestellung passenden Patienten oder beobachtende Studie mit dramatischen Effekten	mit dramatischen Effekten	Überwachung), mit ausreichender Fallzahl, um eine häufige Nebenwirkung zu identifizieren. Sollen Langzeitneben-wirkungen erfasst werden, muss das Follow-up ausreichend sein**		
Was sind seltene Neben-wirkungen? (Schaden der Intervention)	Systematischer Überblick über randomisierte Studien oder N-von-1-Studien	Randomisierte Studie oder (ausnahmsweise) Beobachtungsstudie mit dramatischen Effekten			
Ist dieser Früher-kennungs-Test sinnvoll? (Screening)	Systematische Übersichtsarbeit von randomisierten Studien	Randomisierte Studie	Kontrollierte Kohortenstudie/ Follow-up-Studie**		

* Level kann ggf. wegen der Studienqualität, wegen ausgedehnter Konfidenzintervalle (unpräzise Effektschätzer), Inkonsistenzen zwischen Studien, oder weil der absolute Effektwert sehr klein ist, sowie wegen mangelnder Übertragbarkeit (Fragestellung der Studie entspricht nicht der klinischen relevanten Frage) abgewertet werden. Eine Aufwertung des Evidenzlevels ist möglich bei großen oder sehr großen Effekten.
** Grundsätzlich gilt: Ein systematischer Überblick ist immer besser als eine Einzelstudie.
***Konsekutiver Einschluss = Patienten werden fortlaufend rekrutiert.
1 Zur Qualitätsbeurteilung kann u.a. das STROBE-Statement verwendet werden: http://www.strobe-statement.org/index.php?id=strobe-aims.
2 Einzelpatientenstudien, bei denen die Patienten abwechselnd Intervention und Kontrollintervention erhalten.
3 Nachbeobachtungsstudie einer Population aus einem abgeschlossenen RCT.
4 Studie, bei der aus einer laufenden Kohortenstudie Fälle und Kontrollen gezogen werden.
Übersetzung des englischen Originaltextes von Dr. M. Nothacker, MPH (AWMF); Dr. M. Follmann, MPH, MSc (OL) und Dipl.-Soz.Wiss. T. Langer (OL)

- Schema der Empfehlungsgraduierung

Tabelle 4: Schema der Empfehlungsgraduierung

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

Tabelle 5: Konsensstärke

Konsensstärke	Prozentuale Zustimmung
Starker Konsens	> 95% der Stimmberechtigten
Konsens	> 75 – 95% der Stimmberechtigten
Mehrheitliche Zustimmung	50 – 75% der Stimmberechtigten
Dissens	< 50% der Stimmberechtigten

Empfehlungen

Substanzen mit einem Wirksamkeitsnachweis in Phase III Studien für die Systemtherapie des HCC

3.66	Evidenzbasiertes Statement	modifiziert 2024
Level of Evidence 1 ⊕⊕⊖⊖	Für HCC-Patienten mit erhaltener Leberfunktion (im Child-Pugh-Stadium A), mit Fernmetastasen und/oder einer Tumorlokalisation, die lokoregionär nicht kontrolliert oder reseziert werden kann, liegen Zulassungen aus Phase-III-Studien mit Wirksamkeitsnachweis vor, für • die Kombinationstherapie mit den Antikörpern Atezolizumab gegen PD-L1 und Bevacizumab gegen VEGF; • die Kombinationstherapie mit den Antikörpern Durvalumab gegen PD-L1 und Tremelimumab gegen CTLA-4; • den PD-L1 Antikörper Durvalumab • Tyrosinkinase-Inhibitoren mit Sorafenib und Lenvatinib, und für Regorafenib und Cabozantinib nach einer Vortherapie mit Sorafenib; • den VEGF-R2 Antikörper Ramucirumab für Patienten nach Sorafenib und einem Alpha-Fetoprotein-Wert von ≥ 400 ng/ml.	
	[379], [380], [381], [382], [383], [384], [385] 1: - 2 (Oxford 2011) Erneute Recherche 2021, neue Literatur Facciorusso 2021, neue Literatur Abou-Alfa 2022	
	Starker Konsens	

Medikamentöse Erstlinien-Therapie des HCC

3.67	Evidenzbasierte Empfehlung	modifiziert 2024
Empfehlungsgrad A	Eine Erstlinientherapie mit der Kombination Atezolizumab und Bevacizumab (A+B) oder mit Durvalumab und Tremelimumab (D+T) soll angeboten werden bei HCC-Patienten im Child-Pugh-Stadium A und BCLC B oder C, mit Fernmetastasen oder einer Tumorlokalisation, die lokoregionär nicht kontrolliert oder reseziert werden kann. Patienten mit Kontraindikationen für A+B und D+T soll eine Erstlinientherapie entweder mit Durvalumab als Monotherapie oder mit einem der beiden Tyrosinkinase-Inhibitoren Lenvatinib oder Sorafenib angeboten werden.	
Level of Evidence 2 ⊕⊕⊖⊖	[379], [387], [381], [385] 2: Erneute Recherche 2021, neue Literatur Facciorusso 2021, neue Literatur Abou-Alfa 2022	
	Starker Konsens	

Medikamentöse Therapie bei Leberzirrhose CHILD-Pugh B/C

3.68	Evidenzbasierte Empfehlung	modifiziert 2024
Empfehlungsgrad **0**	Einzelnen HCC-Patienten im Child-Pugh-Stadium B (bis 8 Punkte), mit Fernmetastasen oder einer Tumorlokalisation, die lokoregionär nicht kontrolliert oder reseziert werden kann und mit einem ECOG-Status von 0 – 1, kann eine Systemtherapie mit Sorafenib oder Lenvatinib angeboten werden.	
Level of Evidence **2**	[398], [399], [400], [401], [402], [403] 2: LoE 3 für Lenvatinib	
	Konsens	

3.69	Evidenzbasierte Empfehlung	geprüft 2024
Empfehlungsgrad **0**	Für einzelne HCC-Patienten im Child-Pugh-Stadium B (bis 8 Punkte), mit Fernmetastasen oder einer Tumorlokalisation, die lokoregionär nicht kontrolliert oder reseziert werden kann und einem ECOG-Status von 0 - 1, kann eine Immuntherapie mit einem anti-PD-1-Antikörper angeboten werden.	
Level of Evidence **2, 3**	[399], [400], [398], [402], [401], [404], [391] 2: Yau 2022 3: Kudo 2021	
	Starker Konsens	

3.70	Evidenzbasierte Empfehlung	modifiziert 2024
Empfehlungsgrad **B**	Bei HCC-Patienten im Stadium Child-Pugh C sollte keine Systemtherapie durchgeführt werden.	
Level of Evidence **5**	5: Nach ausführlicher Recherche, konnte keine ausreichende Datenlage zur Erstellung einer positiven Empfehlung gefunden werden.	
	Starker Konsens	

Kombination von Systemtherapie mit lokoregionärer Therapie

3.71	Evidenzbasiertes Statement	modifiziert 2024
Level of Evidence **2, 3**	Bei HCC-Patienten im Stadium Child-Pugh A und BCLC B, die eine lokoregionäre Therapie erhalten, kann keine generelle Empfehlung für eine zusätzliche Systemtherapie aufgrund der aktuellen Datenlage erfolgen.	
	[411], [337], [412], [413], [414], [415], [416], [417], [418], [419] 3: neue Recherche Update 2024	
	Konsens	

Medikamentöse Therapie nach Versagen, Unverträglichkeit oder bei Kontraindikationen der Erstlinientherapie des HCC

3.72	Konsensbasierte Empfehlung	modifiziert 2024
EK	Eine Systemtherapie mit einem zugelassenen Tyrosinkinaseinhibitor soll nach Progress oder bei Unverträglichkeit von Atezolizumab und Bevacizumab bzw. Durvalumab +/- Tremelimumab angeboten werden bei HCC-Patienten im Child-Pugh-Stadium A und BCLC B oder C, mit Fernmetastasen oder einer Tumorlokalisation, die lokoregionär nicht kontrolliert oder reseziert werden kann.	
	Starker Konsens	

3.73	Evidenzbasierte Empfehlung	geprüft 2024
Empfehlungsgrad A	Bei HCC-Patienten mit Tumorprogress unter einer Therapie mit Sorafenib, Child-Pugh-Stadium A und ECOG 0 - 1, soll eine weitere Systemtherapie angeboten werden. Hierfür stehen die beiden Tyrosinkinase-Inhibitoren Regorafenib und Cabozantinib oder bei einem Alpha-Fetoprotein-Wert von ≥ 400 ng/ml der VEGFR2-Antikörper Ramucirumab zur Verfügung.	
Level of Evidence 2	[383], [384], [429]	
	Starker Konsens	

3.74	Konsensbasierte Empfehlung	geprüft 2024
EK	Bei HCC-Patienten im Child-Pugh-Stadium A und ECOG 0 - 1 mit Tumorprogress unter einer Therapie mit Lenvatinib soll eine weitere tumorspezifische Therapie angeboten werden.	
	Konsens	

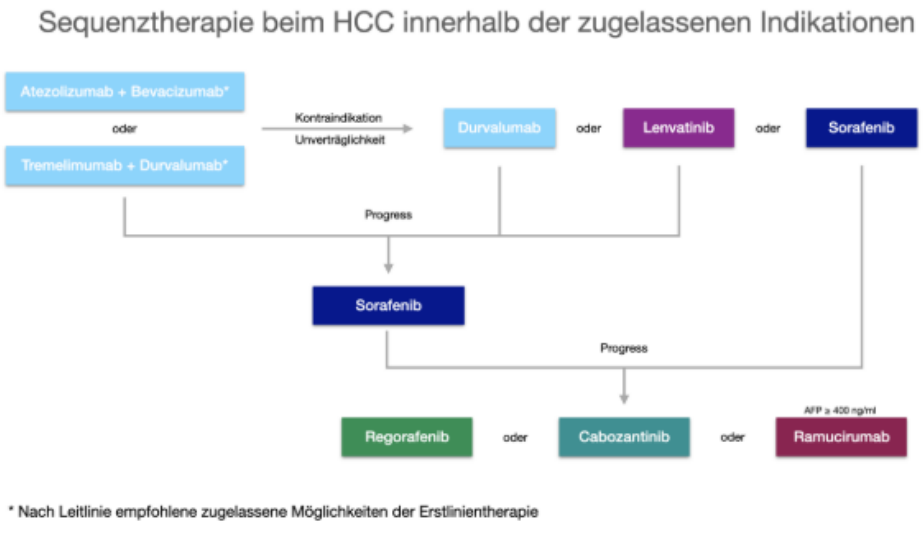

Abbildung 4: Sequenztherapie beim HCC innerhalb der zugelassenen Indikationen

3.75	Konsensbasierte Empfehlung	geprüft 2024
EK	Die laufende Systemtherapie sollte nicht über einen radiologischen Progress hinaus fortgesetzt werden. Die Toxizität der Therapie sollte engmaschig überwacht und berücksichtigt werden.	
	Konsens	

3.76	Evidenzbasierte Empfehlung	geprüft 2024
Empfehlungsgrad 0	Einzelnen Immuntherapienaiven HCC-Patienten mit erhaltener Leberfunktion (im Stadium Child-Pugh A), mit Fernmetastasen oder einer Tumorlokalisation, die lokoregionär nicht kontrolliert oder reseziert werden kann und für die keine zugelassene Therapie mehr zur Verfügung steht, kann eine Immuntherapie mit einem anti-PD-1-Antikörper angeboten werden.	
Level of Evidence 2, 3	[430], [431], [432], [433], [434], [435] 2: Yau 2022, Parikh 2021, Rao 2020, Finn 2020 3: Kudo 2022, He 2021	
	Konsens	

Cabibbo, G. et al., 2024 [3].

Multidisciplinary treatment of hepatocellular carcinoma in 2023: Italian practice Treatment Guidelines of the Italian Association for the Study of the Liver (AISF), Italian Association of Medical Oncology (AIOM), Italian Association of Hepato-Bilio-Pancreatic Surgery (AICEP), Italian Association of Hospital Gastroenterologists (AIGO), Italian Association of Radiology and Clinical Oncology (AIRO), Italian Society of Pathological Anatomy and Diagnostic Cytology (SIAPeC-IAP), Italian Society of Surgery (SIC), Italian Society of Gastroenterology (SIGE), Italian Society of Medical and Interventional Radiology (SIRM), Italian Organ Transplant Society (SITO), and Association of Patients with Hepatitis and Liver Disease (EpaC) - **Part II - Non-surgical treatments**.

Zielsetzung/Fragestellung

This report summarizes the recommendations of Clinical Practice Guidelines regarding non-surgical treatments of Hepatocellular Carcinoma (HCC).

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- MEDLINE/Pubmed, Embase and Cochrane Library databases

LoE/GoR

- GRADE / RoB

Table 1
Graduation of certainty of Evidence [1].

Certainty of Evidence	Significance	Consequence
High	High degree of confidence in the results	It is very likely that the true treatment effect is similar to the estimated one
Moderate	Fair degree of confidence in the results	The true treatment effect is likely to be similar to the estimated one but there is the possibility that the effect is different
Low	Results not very credible	Confidence in the estimate of the effect is limited: the true effect could be substantially different from the estimated one
Very Low	Data examined totally unreliable	Confidence in the estimate of the effect is very limited: it is likely that the true effect is substantially different from the estimated one

Empfehlungen

Table 2
PICO questions, Recommendations, Certainty of evidence, and Strength of recommendation about non-Surgical treatment, of Clinical Practice Guidelines for the management of Hepatocellular Carcinoma (HCC).

PICO		Recommendation	Certainty of evidence	Strength of recommendation
1	In patients with compensated cirrhosis and single intermediate-sized (3.1–5 cm) unresectable HCC, is the combined treatment of percutaneous ablation + intra-arterial therapy versus ablation alone indicated?	In patients with compensated cirrhosis and single unresectable intermediate-sized (3.1–5 cm) HCC, the panel suggests not using the combined treatment of intra-arterial therapy and percutaneous ablation versus ablation alone.	Very low	Conditional against combined treatment
2	In patients with liver cirrhosis (maximum Child-Pugh score B7) with not transplantable, unresectable, multifocal HCC and without intrahepatic vascular invasion or extrahepatic tumor spread, is transarterial chemoembolization (TACE) with DC-beads indicated compared to conventional TACE?	In patients with liver cirrhosis (maximum Child-Pugh score B7) with not transplantable, unresectable multifocal HCC and without intrahepatic vascular invasion or extrahepatic tumor spread, the panel suggests using DC-bead TACE or conventional TACE, according to the local availability of treatment.	Very low	Conditional for equivalence
3	In patients with HCC not eligible for surgical and/or ablative treatment, is treatment with TACE followed by radiotherapy rather than TACE alone indicated?	In patients with HCC not eligible for surgical and/or ablative treatment, the panel suggests TACE followed by radiotherapy instead of TACE alone	Low	Conditional in favor of TACE followed by radiotherapy
4	In patients with Child-Pugh class A cirrhosis and unresectable single ≤8 cm or multifocal HCC, without ascites, portal invasion and extrahepatic tumor spread, transarterial radioembolization (TARE) is indicated compared to conventional transarterial chemoembolization (cTACE) or transarterial chemoembolization with microspheres (DEB-TACE)?	In patients with Child-Pugh class A cirrhosis and unresectable single ≤8 cm or multifocal HCC, without ascites, portal invasion and extrahepatic tumor spread, the panel suggests not performing TARE compared to cTACE or DEB-TACE	Very low	Conditional against TARE
5	In patients with compensated cirrhosis and HCC technically eligible (by size and number of lesions) for surgical treatment, but excluded from it due to contraindications, is the treatment with external (stereotactic) radiotherapy indicated compared to alternative therapies (thermal ablation, TACE, TARE or systemic therapy)?	In patients with compensated cirrhosis and HCC technically eligible (by size and number of lesions) for surgical treatment, but excluded from them due to other contraindications, the panel suggests using external (stereotactic) radiotherapy compared to alternative therapies.	Very low	Conditional in favor of radiotherapy
6	In Child-Pugh class A patients with intermediate or advanced BCLC stage HCC who are not eligible for surgical or loco-regional treatments (or in whom these approaches have failed), is systemic therapy with sorafenib/lenvatinib indicated instead of best supportive care (BSC)?	For Child-Pugh class A patients with intermediate or advanced or BCLC stage HCC who are not eligible for surgery or loco-regional treatment (or in whom these approaches have failed), the panel recommends the use of sorafenib/lenvatinib instead of BSC.	Sorafenib: high Lenvatinib: moderate	Strong in favor of systemic therapy
7	In Child-Pugh class A patients with intermediate or advanced BCLC stage HCC not eligible for surgical or loco-regional treatments (or in whom these approaches have failed), is treatment with lenvatinib indicated compared to sorafenib?	In Child-Pugh class A patients with intermediate or advanced BCLC stage HCC not eligible for surgical or loco-regional treatments (or in whom these approaches have failed), the panel suggests using sorafenib or lenvatinib according to the local drug availability.	Moderate	Conditional for equivalence

8	In Child-Pugh B patients with intermediate or advanced BCLC stage HCC not eligible for surgical or loco-regional treatments, is the use of sorafenib or lenvatinib indicated instead of best supportive care?	In Child-Pugh B patients with intermediate or advanced stage HCC not eligible for surgical or loco-regional treatments, the panel suggests not using sorafenib or lenvatinib instead of BSC alone.	Low	Conditional against sorafenib/lenvatinib
9	In Child-Pugh class A patients with HCC progressing to sorafenib therapy, is a second-line treatment with regorafenib indicated instead of best supportive care?	For Child-Pugh class A patients with HCC progressing on sorafenib therapy, provided that they tolerated this treatment, the panel suggests using regorafenib instead of BSC.	Moderate	Conditional in favor of regorafenib
10	In Child-Pugh A patients with intermediate or advanced BCLC stage HCC not eligible for loco-regional treatments (or in whom these approaches have failed), progressing on or intolerant to sorafenib, and even in progression on post-sorafenib treatment, is cabozantinib indicated instead of best supportive care?	In Child-Pugh A patients with intermediate or advanced BCLC stage HCC not eligible for loco-regional treatment (or in whom this approach has failed), progressing on or intolerant to sorafenib, and even after failure of a post-sorafenib systemic therapy, the panel suggests using cabozantinib.	Moderate	Conditional in favor of cabozantinib
11	In Child-Pugh A patients with intermediate or advanced BCLC stage HCC not eligible for loco-regional treatments (or in whom these approaches have failed), progressing on or intolerant to sorafenib, and with alpha-fetoprotein ≥400 ng/ml, is ramucirumab indicated instead of best supportive care?	In Child-Pugh A patients with intermediate or advanced BCLC stage HCC not eligible for loco-regional treatments (or in whom these approaches have failed), progressing on or intolerant to sorafenib, and with alpha-fetoprotein ≥400 ng/ml, the panel suggests considering ramucirumab instead of best supportive care.	Low	Conditional in favor of ramucirumab
12	In Child-Pugh A patients with intermediate or advanced BCLC stage HCC not eligible for surgical or loco-regional treatments, is the atezolizumab + bevacizumab combination indicated as first-line systemic therapy compared to sorafenib?	In Child-Pugh A patients with intermediate or advanced BCLC stage HCC not eligible for surgical or loco-regional treatments, the panel suggests using the combination atezolizumab + bevacizumab as first-line systemic therapy.	High	Conditional in favor of atezolizumab + bevacizumab

GRADE Working Group grades of evidence:.
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

AHS, 2024 [2].

Alberta Health Services (AHS)

Hepatocellular Carcinoma; version 9

Zielsetzung/Fragestellung

Management of HCC.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert: A formal review of the guideline will be conducted in 2025. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Recherche/Suchzeitraum:

- PubMed and MEDLINE from 1990 forward.

- The 2023 update did not necessitate a full literature review; recommendations were modified based on a consensus discussion at the 2023 Annual Gastrointestinal Tumour Team Meeting.

LoE/GoR

Table 4. Strength of Recommendations

Grade	Description of Recommendation Strength
A	Strongly recommended; strong evidence for efficacy with a substantial clinical benefit.
B	Generally recommended; strong or moderate evidence for efficacy but with a limited clinical benefit.
C	Optional; insufficient evidence for efficacy or benefit does not outweigh the risks/disadvantages.
D	Generally not recommended; moderate evidence against efficacy or for adverse outcomes.
E	Never recommended; strong evidence against efficacy or for adverse outcomes.

Empfehlungen

Advanced Stage HCC	*Patient Requirements:*	· Good performance status (ECOG 0 or 1). · Well-compensated liver function (Child-Pugh class A).
	Tumour Requirements:	· Disease ineligible for, or that progressed after, surgical or locoregional therapy.
	Goals:	· To maintain or to improve the patient's quality of life (to control or to delay the onset of tumour-related symptoms). · To prolong survival, if possible.
	Recommendations:	· First-line treatment: Atezolizumab-Bevacizumab[50], Tremelimumab-Durvalumab[51] (STRIDE) or participation in a clinical trial, if available. Lenvatinib or sorafenib should be considered in patients ineligible for or who decline atezolizumab-bevacizumab or STRIDE [note Tremelimumab-Durvalumab (STRIDE) is not currently funded in Alberta]. · Second-line treatment: For patients who received atezolizumab-bevacizumab or tremelimumab-durvalumab (STRIDE) first-line, second-line treatment should be lenvatinib or sorafenib, For patients who received lenvatinib or sorafenib first-line, second-line treatment should be regorafenib or cabozantinib. · Third-line: Regorafenib (if previously tolerated Sorafenib), Cabozantinib, or participation in a clinical trial[51], if available. [Third line therapy is currently not funded in Alberta] Consider early referral to palliative care. Consider referral to dietician and for psychosocial support.

First-line systemic therapy Child Pugh A

- Imaging modality: CT chest, abdomen, and pelvis (triphasic liver) or MRI liver and CT chest. Bone scan if clinically indicated.
- Frequency: Every 3 months in the absence of clinical progression.
- If not already completed, patients should be screened for hepatitis B/C. Consider a referral to Hepatology for patients with cirrhosis and HBV or HCV. There is evidence suggesting improved outcomes for patients with HCC in the setting of treatment of NAFLD/HBV/HCV cirrhosis.[53]

First-Line Systemic Therapy:

Atezolizumab-Bevacizumab (Type of recommendation: evidence based, benefits outweigh harms; Evidence quality: moderate to high; Strength of recommendation: strong)[50, 52]

- Atezolizumab-bevacizumab was compared to sorafenib in the open-label phase 3 IMbrave150 trial.[50] Hazard ratio for death was 0.58 (95%CI: 0.42-0.79; p<0.001) in favor of atezolizumab-bevacizumab. Additionally, hazard ratio for disease progression or death was superior in the atezolizumab-bevacizumab arm (HR: 0.59; 95%CI: 0.47-0.76; p<0.001). Overall survival at 12 months was 67% (95%CI: 61.3 to 73.1%) in the atezolizumab-bevacizumab arm compared to 54.6% (95%CI: 45.2-64.0%) in the sorafenib arm. An updated survival analysis showed median overall survival was 19.2 mo with atezolizumab-bevacizumab vs 13.4 months with sorafenib (HR, 0.66 [95% CI, 0.52, 0.85]; *P*=0.0009)[53]
- Grade 3 or 4 adverse events occurred in 56.5% of atezolizumab-bevacizumab patients (n=329) and 55.1% of the sorafenib patients (n=156). Grade 3 or 4 hypertension occurred in 15.2% of atezolizumab-bevacizumab group; however, other high-grade toxic effects were infrequent.
- Treatment with Atezolizumab-Bevacizumab reduced the risk of deterioration in quality of life compared to sorafenib.[54]
- Patients had an ECOG of 0-1, no contraindications to immunotherapy and were not at risk for bleeding. An EGD is strongly recommended within 6 months prior to starting therapy and varices should be treated according to the standard practice[55] (especially if the transient elastography (FibroScan®) >20 kPa or if the platelet count is <150).[56] Patients with incompletely treated varices should not be treated with this combination.

Tremelimumab-Durvalumab (STRIDE) Type of recommendation: evidence based, benefits outweigh harms; Evidence quality: moderate to high; Strength of recommendation: strong)[57]

- Tremelimumab plus durvalumab in an infusion regimen termed STRIDE (Single Tremelimumab Regular Interval Durvalumab) were compared to durvalumab or sorafenib alone in the open-label, phase 3, HIMALAYA trial. Median OS was 16.4m (95%CI: 14.2-19.6) with STRIDE, and 13.8m (95%CI: 12.3-16.1) with sorafenib. Risk of death was lower with STRIDE compared to sorafenib; HR: 0.78(95%CI: 0.65-0.93; p=0.0035). Median PFS was not significantly different between treatment arms.
- Grade 3/4 treatment-emergent adverse events occurred for 50.5% of patients with STRIDE, and 52.4% with sorafenib.

In those patients where Atezolizumab-Bevacizumab or STRIDE is not appropriate/contraindicated:

Lenvatinib (Type of recommendation: evidence based, benefits outweigh harms; Evidence quality: moderate to high; Strength of recommendation: strong)

- Lenvatinib was shown to be non-inferior to sorafenib for overall survival in an open-label, phase 3, multicenter, non-inferiority trial in patients with unresectable hepatocellular carcinoma, who had not received treatment for advanced disease (median OS 13.6m lenvatinib vs 12.3m sorafenib, respectively, HR: 0.92, 95%CI: 0.79-1.06). Patients had Child Pugh A liver function, and ECOG 0-1.[58]
- It is worth noting that lenvatinib was superior to sorafenib in terms of progression-free survival (7.4m vs 3.7m, respectively, HR: 0.66, 95%CI: 0.57-0.77, p<0.001). Objective response rates were also higher in the lenvatinib group (24.1% vs. 9.2%, respectively, p<0.001).
- Treatment-related adverse events of grade 3 or higher occurred in 57% of patients treated with lenvatinib and 49% with sorafenib. Rates of hand-foot syndrome are lower in the lenvatinib arm compared to sorafenib arm. In the lenvatinib arm, the most common any-grade adverse events included hypertension (42%), diarrhea (39%), decreased appetite (34%), and decreased weight (31%).

or

ECOG 0-2 *Sorafenib* (Type of recommendation: evidence based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong)

- Represents an orally active inhibitor of multiple cell surface tyrosine kinases (e.g.: VEGFR, PDGFR-ß, *c-kit*, *FLT3*, *RET*) as well as downstream intracellular kinases (e.g.: *Raf*) involved in angiogenesis and tumour progression.
- Delays progression and improves overall survival when compared to placebo in two randomized, double blind, placebo-controlled, phase III trials.[59, 60]
- Hypothyroidism develops in 18% of patients within two to four months of starting Sorafenib. Obtain a baseline TSH and then monitor levels every six weeks.[44, 61]
- Increases the incidence of arterial thromboembolic events (1.4%, RR 3.03, $p = 0.015$).[45]

Goals and Recommendations

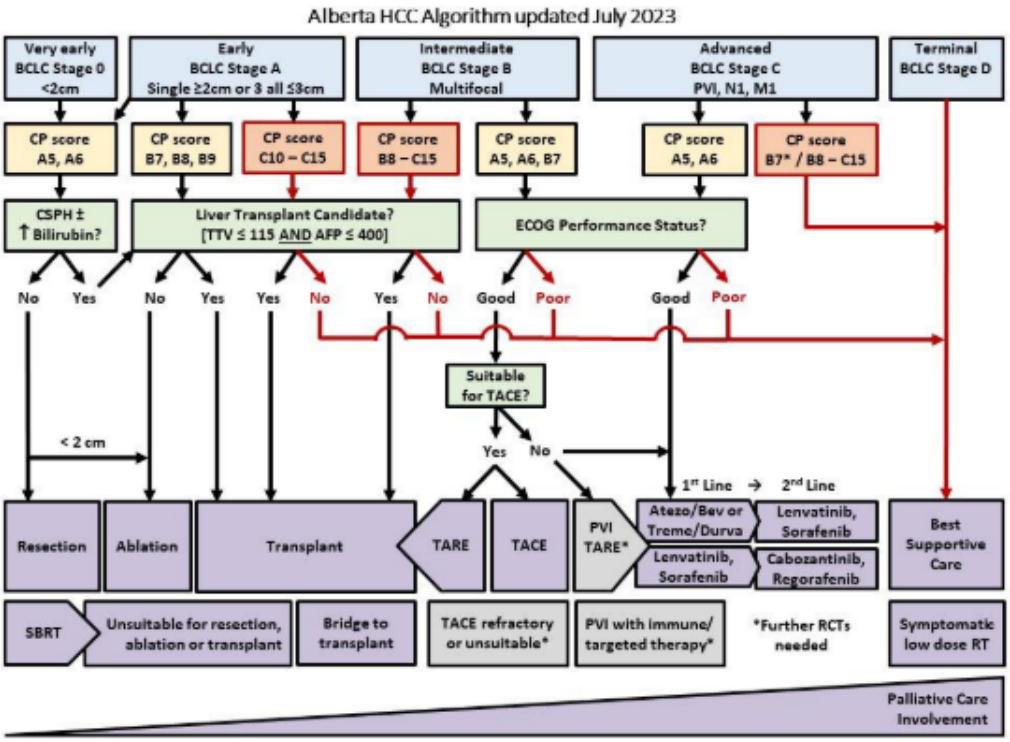

Figure 1. Alberta HCC Algorithm. Reproduced with permission from Dr. K. Burak.

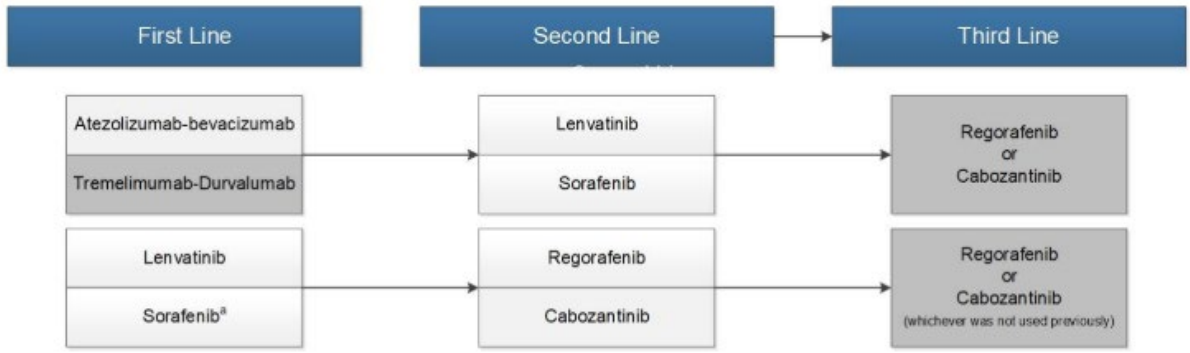

Figure 2. Systemic Therapy for Advanced HCC.

Su GL et al., 2022 [15].

AGA clinical practice guideline on systemic therapy for hepatocellular carcinoma.

Leitlinienorganisation/Fragestellung

Leitlinie der American Gastroenterological Association

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Überprüfung der Aktualität 3 Jahre nach Veröffentlichung

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) until December 4, 2020

LoE/GoR

- GRADE Methodik

Table 1. Interpretation of the Certainty in Evidence of Effects Using the Grading of Recommendations, Assessment, Development and Evaluation Framework

Certainty	Description
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

Empfehlungen

Recommendations	Strength of recommendation	Certainty of evidence
1. First-line treatment for HCC in patients with preserved liver function		
In patients with HCC with preserved liver function not eligible for LRT or resection or with metastatic disease, the AGA suggests atezolizumab+bevacizumab over sorafenib.	Conditional	Low
Comment: Gastrointestinal bleeding is a known adverse effect of bevacizumab and individuals should undergo endoscopic evaluation and treatment for esophageal varices before treatment.		
In patients with HCC with preserved liver function not eligible for LRT or resection or with metastatic disease who are not candidates for treatment with atezolizumab+bevacizumab, the AGA suggests either lenvatinib or sorafenib over no systemic therapy.	Conditional	Low
Comments: Patients who place a higher value on delayed radiologic disease progression and lower value on the increase in adverse events (both serious and leading to discontinuation of the drug) may reasonably choose lenvatinib over sorafenib. Patients who place a higher value on blood pressure control and a lower value on the adverse skin reactions would reasonably select sorafenib over lenvatinib. It should be noted that lenvatinib has not been studied in patients with invasion of the main portal vein and thus may not be appropriate for this population. Patients who place a higher value on the adverse events associated with sorafenib or lenvatinib and lower value on the reduction in mortality (2.8 mo for sorafenib, unknown for lenvatinib) may reasonably select no systemic therapy.		
3. Systemic therapy for HCC in patients with poor liver function		
In patients with HCC with poor liver function not eligible for LRT or resection or with metastatic disease, the AGA suggests against routine use of sorafenib.	Conditional	Very low
Comment: Patients, particularly those who are not CTP C, who place a higher value on the uncertain reduction in mortality and lower value on the harms, may reasonably select to use sorafenib.		

Gordan JD et al., 2024 [7,14].

American Society of Clinical Oncology (ASCO)

Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline Update.

Zielsetzung/Fragestellung

To update an evidence-based guideline to assist in clinical decision-making for patients with advanced hepatocellular carcinoma (HCC).

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- ASCO convened an Expert Panel to update the 2020 guideline on systemic therapy for HCC. The panel updated the systematic review to include randomized controlled trials (RCTs) published through October 2023 and updated recommendations.
- Ten new RCTs were included.

LoE

- Certainty of the evidence (ie, evidence quality) for each outcome was assessed using the Cochrane Risk of Bias tool and elements of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) quality assessment and recommendations development process.[21] To facilitate the quality assessment ratings, MAGICApp guideline development software was used; within this framework, outcomes from RCTs are rated high quality and can subsequently be downgraded as factors that affect quality (ie, certainty) are identified.[22]

21. Higgins JPT, Thomas J, Chandler J, et al (eds): Cochrane Handbook for Systematic Reviews of Interventions (ed 2). Chichester, UK, Wiley, 2019.

22. Bro˙zek JL, Akl EA, Compalati E, et al: Grading quality of evidence and strength of recommendations in clinical practice guidelines part 3 of 3. The GRADE approach to developing recommendations. Allergy 66:588-595, 2011.

GoR

- The Expert Panel provides a rating of the strength of each recommendation. This assessment reflects the extent to which a guideline panel is confident that desirable effects of an intervention outweigh undesirable effects, or vice versa, across the range of patients for whom the recommendation is intended. Recommendations may fall into two categories; strong and weak. Factors determining the strength of a recommendation include balance between benefits and harms, certainty of evidence, confidence in values & preferences, and resource use. Recommendations may be made for or against the use of an intervention.

Empfehlungen

First-Line Therapy

Recommendation 1.1.

- Atezolizumab 1 bevacizumab (atezo 1 bev) or durvalumab 1 tremelimumab (durva 1 treme) may be offered as first-line treatment for patients with Child-Pugh classA, andEasternCooperativeOncologyGroupperformance status (ECOG PS) 0-1 advanced HCC (Evidence quality: Moderate to High, Strength of recommendation: Strong).

Qualifying statements

- For patients receiving atezo 1 bev, screening for and management of esophageal varices when present are recommended prior to initiation of therapy and according to institutional guidelines.
- The choice between treatment options in Recommendation 1.1 should be made through a discussion involving the physician and patient (and caregiver, where applicable), and should include factors such as medical history, toxicities associated with treatment, cost, goals of treatment, patient preference, and expected treatment benefit.
- When choosing between the two combination therapy options, consider risk of bleeding and thrombosis with the vascular endothelial growth factor (VEGF) inhibitor bevacizumab.
- Patients with active or previously documented autoimmune disease should consider the risk of immunerelated adverse effects associated with atezo and durva 1 treme.

Recommendation 1.2.

Where there are contraindications to atezo 1 bev or durva 1 treme, sorafenib, lenvatinib, or durvalumab may be offered as first-line treatment for patients with Child-Pugh class A, and ECOG PS 0-1 advanced HCC (Evidence quality: Moderate; Strength of recommendation: Strong).

Qualifying statements:

- The choice between treatment options should take into account the factors listed in the second qualifying statement to Recommendation 1.1.

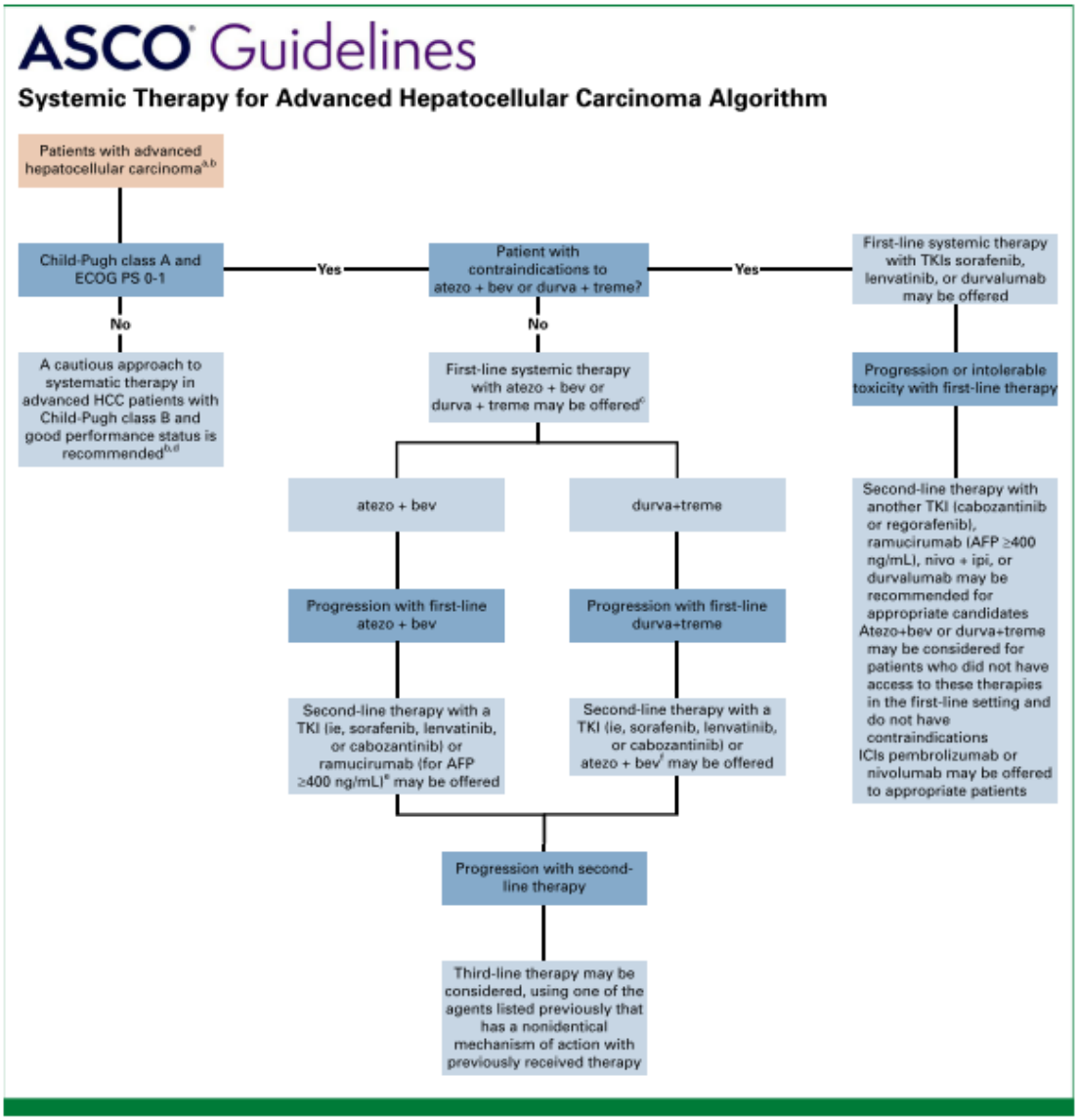

FIG 2. Systemic therapy for advanced hepatocellular carcinoma algorithm. [a]The target population includes patients who are no longer candidates for surgical or liver-directed therapies, ie, patients with characteristics such as multifocal and/or infiltrative disease within the liver, vascular invasion, or extrahepatic spread. [b]Treatment options should be discussed within a multidisciplinary team. [c]Patients in the IMbrave150 trial of atezo + bev were required to have undergone esophagogastroduodenoscopy within 6 months of trial initiation and to have received treatment for esophageal varices when necessary. [d]Considerations include underlying liver function, bleeding risk, presence of portal hypertension, extent of extrahepatic spread, tumor burden, and major vascular invasion. [e]While there is currently no published evidence to support a recommendation for durva + treme, the ASCO Advanced HCC Expert Panel agreed that this option may be considered following first-line treatment with atezo + bev. [f]There are no data available to select patients for atezo + bev vs. second-line therapy with a TKI. AFP, alpha fetoprotein; atezo + bev, atezolizumab + bevacizumab; durva + treme, durvalumab + tremelimumab; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; nivo + ipi, nivolumab + ipilimumab; TKI, tyrosine kinase inhibitor.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 11 of 12, November 2024) am 28.11.2024

#	Suchschritt
1	[mh "Liver Neoplasms"]
2	(hepatocarcinoma* OR (hepato NEXT carcinoma*) OR hepatoma* OR HCC):ti
3	(liver OR hepatic OR hepatocellular OR (hepato NEXT cellular) OR hepatobiliary OR (heapato NEXT biliary)):ti
4	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesion* OR malignan*):ti
5	#3 AND #4
6	#1 OR #2 OR #5
7	#6 with Cochrane Library publication date from Nov 2019 to present, in Cochrane Reviews

Systematic Reviews und Leitlinien in PubMed am 28.11.2024

verwendeter Suchfilter für Systematic Reviews ohne Änderung:

Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

verwendeter Suchfilter für Leitlinien ohne Änderung:

Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchschritt
	Leitlinien
1	liver neoplasms[mh:noexp] OR carcinoma, hepatocellular[majr]
2	hepatocarcinoma*[ti] OR hepato-carcinoma*[ti] OR hepatoma*[ti] OR HCC[ti]
3	liver[ti] OR hepatic[ti] OR hepatocellular[ti] OR hepato-cellular[ti] OR hepatobiliary[ti] OR hepato-biliary[ti]
4	tumor[ti] OR tumors[ti] OR tumour*[ti] OR carcinoma*[ti] OR adenocarcinoma*[ti] OR neoplas*[ti] OR sarcoma*[ti] OR cancer*[ti] OR lesion*[ti] OR malignan*[ti]
5	#3 AND #4
6	#1 OR #2 OR #5
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
8	(#7) AND ("2019/11/01"[PDAT] : "3000"[PDAT])

#	Suchschritt
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])
	Systematische Reviews
10	"carcinoma, hepatocellular/therapy"[majr]
11	liver neoplasms/therapy[mh:noexp] OR liver neoplasms/surgery[mh:noexp] OR liver neoplasms/drug therapy[mh:noexp] OR liver neoplasms/radiotherapy[mh:noexp]
12	(#2 OR #5) AND ((treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab]))
13	(#10 OR #11 OR #12) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
14	(#13) AND ("2019/11/01"[PDAT] : "3000"[PDAT])
15	(#14) NOT "The Cochrane database of systematic reviews"[Journal]
16	(#15) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
17	(#16) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])
	Systematische Reviews ohne Leitlinien
18	(#17) NOT (#9)

Iterative Handsuche nach grauer Literatur, abgeschlossen am 03.12.2024

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- National Cancer Institute (NCI)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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Gemeinsamer Bundesausschuss

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO