Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2019-B-157-z Ramucirumab

Stand: August 2019

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

Ramucirumab
[zur Behandlung des hepatozellulären Karzinoms nach vorheriger Sorafenib-Therapie]

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.	Eine nicht-medikamentöse Behandlung kommt als zweckmäßige Vergleichstherapie nicht in Betracht. Es wird davon ausgegangen, dass im vorliegenden Anwendungsgebiet sowohl eine kurative Behandlung (entsprechend BCLC-Stadium 0 und A) als auch eine lokoregionäre Therapie im BCLC-Stadium B, insbesondere eine transarterielle (Chemo)-Embolisation (TACE oder TAE), nicht (mehr) infrage kommen.
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	− Cabozantinib: Beschluss über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V vom 6. Juni 2019 − Qualitätssicherungsmaßnahmen bei Protonentherapie des inoperablen hepatozellulären Karzinoms; Beschluss vom 16. Juli 2009, Stand: 20. Juli 2017 − Bewertung nach § 137h SGB V: Ultraschallgesteuerter hoch-intensiver fokussierter Ultraschall zur Behandlung des hepatozellulären Karzinoms; Beschluss vom 16. März 2017
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Beratungsanforderung/Fachinformation)
Zu bewertendes Arzneimittel:	
Ramucirumab L01XC21 Cyramza®	<u>Zugelassenes Anwendungsgebiet:</u> Cyramza ist als Monotherapie indiziert zur Behandlung von erwachsenen Patienten mit fortgeschrittenem oder inoperablem hepatozellulärem Karzinom, die ein Serum-Alpha-Fetoprotein (AFP) von ≥ 400 ng/ml aufweisen und die zuvor mit Sorafenib behandelt wurden.
Cabozantinib L01XE26 CABOMETYX™	<u>Leberzellkarzinom (hepatocellular carcinoma, HCC)</u> CABOMETYX ist indiziert als Monotherapie für die Behandlung des Leberzellkarzinoms (HCC) bei Erwachsenen, die zuvor mit Sorafenib behandelt wurden.
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
Regorafenib[1] L01XE21 Stivarga®	Stivarga ist angezeigt als Monotherapie zur Behandlung von erwachsenen Patienten mit: […] − hepatozellulärem Karzinom (HCC), die zuvor mit Sorafenib behandelt wurden.
Sorafenib L01XE05 Nexavar®	<u>Leberzellkarzinom</u> Nexavar ist angezeigt zur Behandlung des Leberzellkarzinoms (siehe Abschnitt 5.1).

Quellen: AMIS-Datenbank, Fachinformationen

[1] Regorafenib ist derzeit in Deutschland nicht im Handel.

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2019-B-157-z (Ramucirumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	6. August 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

ADI-PEG 20	Polyethylene Glycol-Arginine Deiminase
AE/s	Adverse Event/s
AFP	Alpha Fetoprotein
AGREE II	Appraisal of Guidelines for Research and Evaluation II
ASCO	American Society of Clinical Oncology
AWG	Anwednungsgebiet
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BRAF	potentiell vorliegende Mutation
BSC	Best Supportive Care
c-KIT	potentiell vorliegende Mutation
CI	Confidence Interval
cTACE	Conventional Transarterial Chemo-Embolization
DCR	Disease Control Rate
DNA	Desoxyribonukleinsäure
DR	Discontinuation Rate
ECOG	Eastern Co-operative Oncology Group
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FGF	Fibroblast Growth Factor
FGFR	Fibroblast Growth Factor Receptor
FLT-3	Fms Like Tyrosine Kinase 3
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HAIC	Hepatic Artery Infusion Chemotherapy
HBV	Hepatitis B Virus
HCC	Hepato Cellular Carcinom

HFSR	Hand-Foot Skin Reaction
HR	Hazard Ratio
ICI	Immune Checkpoint Inhibitors
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
KLCA	Korean Liver Cancer Association
KPGRC	Korea Practice Guideline Revision Committee
LL	Leitlinie/n
LoE	Level of Evidence
mTOR	mechanistic Target of Rapamycin
NA	Not Available
NCC	National Cancer Center
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NMA	Network Meta Analyses
OR	Odds Ratio
ORR	Overall Response Rate
OS	Overall Survival
OSS	Objective Response Rate
PDGFR/-β	Platelet-Derived Growth Factor Receptors
PFS	Progression-Free Survival
RCT	Randomised Controlled Trial
RET	Rezeptor-Tyrosinkinase
RFA	Radiofrequency Ablation
RR	Relatives Risiko
SAE/s	Serious Adverse Event/s
SBRT	Stereotactic Body Radiotherapy
SGB	Sozialgesetzbuch
SIGN	Scottish Intercollegiate Guidelines Network

SR	Systematischer Review
TACE	Transarterial Chemo-Embolization
TRIP	Turn Research Into Practice Database
TTP	Time-To-Progression
VEGF-2	Vascular Endothelial Growth Factor-2
VEGFR/VEGF receptor	Vascular Endothelial Growth Factor Receptor
WHO	World Health Organization
yr	Year

1 Indikation

Zur Behandlung des hepatozellulären Karzinoms nach vorheriger Sorafenib-Therapie bei Erwachsenen.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation hepatozelluläres Karzinom durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 12.07.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1469 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 13 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2019 [5].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Cabozantinib (neues Anwendungsgebiet: hepatozelluläres Karzinom)

Anwendungsgebiet

CABOMETYX ist indiziert als Monotherapie für die Behandlung des Leberzellkarzinoms (hepato cellular carcinoma, HCC) bei Erwachsenen, die zuvor mit Sorafenib behandelt wurden

Erwachsene Patienten mit Leberzellkarzinom ohne kurative Therapieintention und für die eine lokoregionäre Therapie nicht in Frage kommt, die vorher Sorafenib erhalten haben

Zweckmäßige Vergleichstherapie

Best-Supportive-Care

Ausmaß des Zusatznutzens

Anhaltspunkt für einen geringen Zusatznutzen

G-BA, 2017 [8].

Beschluss des Gemeinsamen Bundesausschusses über eine Bewertung nach § 137h des Fünften Buches Sozialgesetzbuch (SGB V): Ultraschallgesteuerter hoch-intensiver fokussierter Ultraschall zur Behandlung des nicht chirurgisch behandelbaren hepatozellulären Karzinoms

Fazit

- I. Der Nutzen der Methode „Ultraschallgesteuerter hoch-intensiver fokussierter bei Patientinnen und Patienten mit nicht chirurgisch behandelbaren hepatozellulärem Karzinom“ ist noch nicht als hinreichend belegt anzusehen, sie bietet aber das Potenzial einer erforderlichen Behandlungsalternative.
- II. Es werden Beratungen über eine Richtlinie zur Erprobung der in Abschnitt I genannten Methode gemäß § 137e Absatz 1 SGB V eingeleitet.
- III. Der Unterausschuss Methodenbewertung wird mit der Durchführung der Beratungen gemäß Abschnitt II und mit der Ankündigung des Beratungsverfahrens beauftragt.

G-BA, 2009 [9].

Beschluss des Gemeinsamen Bundesausschusses über Maßnahmen zur Qualitätssicherung bei Protonentherapie bei Patientinnen und Patienten mit inoperablem hepatozellulärem Karzinom (HCC) – in der Fassung vom 16. Juli 2009 zuletzt geändert am 20. Juli 2017

Siehe auch:

- Bekanntmachung eines Beschlusses des Gemeinsamen Bundesausschusses über Maßnahmen zur Qualitätssicherung bei Protonentherapie des inoperablen hepatozellulären Karzinoms – 16.07.2009 [4]
- Beschluss des Gemeinsamen Bundesausschusses über eine Änderung des Beschlusses über Maßnahmen zur Qualitätssicherung bei Protonentherapie bei Patientinnen und Patienten mit inoperablem hepatozellulärem Karzinom (HCC): Verlängerung der Gültigkeitsdauer – 27.11.2015 [6]
- Beschluss des Gemeinsamen Bundesausschusses über eine Änderung des Beschlusses über Maßnahmen zur Qualitätssicherung bei Protonentherapie bei Patientinnen und Patienten mit inoperablem hepatozellulärem Karzinom (HCC) – 20.07.2017 [7]

§ 1 Grundlage und Zweck des Beschlusses

(3) [1]Der Beschluss beinhaltet verbindliche Anforderungen (Anlage I), die von allen Krankenhäusern, die die Protonentherapie bei der Behandlung von Patientinnen und Patienten mit inoperablem hepatozellulärem Karzinom zu Lasten der gesetzlichen Krankenkassen erbringen, zu erfüllen sind. [2]Die Vorgaben beruhen auf Expertenaussagen und fachlichen Empfehlungen. [3]Die Bewertung von Nutzen und Notwendigkeit hat ergeben, dass die Protonentherapie eine mögliche therapeutische Option für Patientinnen und Patienten mit HCC ist, die für ein operatives Vorgehen nach einer Gesamtbetrachtung der therapeutischen Perspektiven nicht geeignet sind. [4]Als inoperable Patientinnen und Patienten gelten dabei auch die Patientinnen und Patienten, für die die Indikation zu einer Transplantation gestellt wurde und für die kein Transplantationsorgan in medizinisch vertretbarer Zeit zu erwarten ist. [5]Die Patientin bzw. der Patient ist über die verschiedenen interventionellen Methoden sowie die verschiedenen strahlentherapeutischen Modalitäten aufzuklären und unter Berücksichtigung der individuellen Befundkonstellation nebst Komorbiditäten und Risikofaktoren in angemessener Weise in die Auswahl des Behandlungsverfahrens einzubeziehen.

(4) Ziel des Beschlusses ist, eine qualitätsgesicherte Versorgung in diesem Leistungsbereich zu gewährleisten.

§ 2 Gegenstand der Regelung

Der Beschluss regelt in Ergänzung der bestehenden gesetzlichen Regelungen zur Strahlentherapie die Anforderungen an die Qualität und die Dokumentation für die Erbringung der Strahlentherapie mit Protonen alleine oder in Kombination bei der Behandlung bei Patientinnen und Patienten mit inoperablem hepatozellulärem Karzinom.

3.2 Cochrane Reviews

Es konnten keine für das vorliegende Anwendungsgebiet relevanten Cochrane Reviews identifiziert werden.

3.3 Systematische Reviews

Bakouny Z et al., 2019 [3].

Second-line Treatments of Advanced Hepatocellular Carcinoma: Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

Fragestellung

The aim of this NMA of RCTs was to synthesize and compare the efficacy and safety of the secondline treatments of advanced HCC.

Methodik

Population:

patients: adults aged 18 years or above, diagnosed with advanced HCC (not amenable to surgical management with curative intent), and who had been previously treated with sorafenib

Intervention:

systemic therapies, which could include chemotherapy, targeted therapy, immune therapy, or any combination of these agents.

Komparator:

systemic therapy, supportive care, placebo, any combination of these agents, or no intervention

Endpunkte:

OS, progression-free survival (PFS), the rate of grade 3 to 5 adverse events, and the rate of discontinuation of therapy due to adverse events

Recherche/Suchzeitraum:

An independent review of the published articles in PubMed/Medline, Cochrane Central Register of Controlled Trials, European Society for Medical Oncology (ESMO) meeting abstracts, American Society of Clinical Oncology (ASCO) meeting abstracts, and clinical trial registries (Clinicaltrials.gov and International Clinical Trials Registry Platform of WHO) was conducted from inception until May 1, 2018.

Qualitätsbewertung der Studien:

Cochrane Handbook for Systematic Reviews of Interventions

Ergebnisse

Anzahl eingeschlossener Studien:

13 included studies with 5076 patients from 26 arms

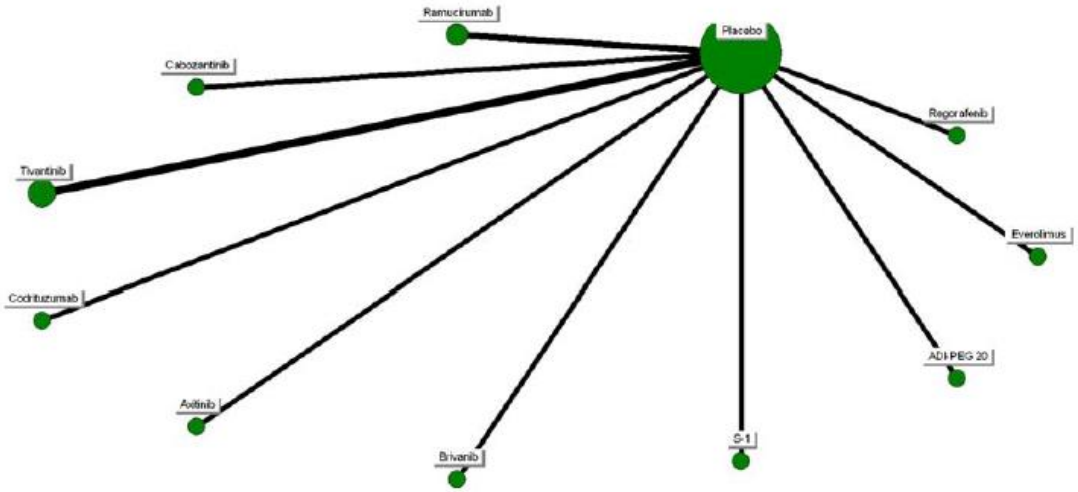

FIGURE 2. Network plot for the analysis of the overall survival and progression-free survival outcomes. full color online

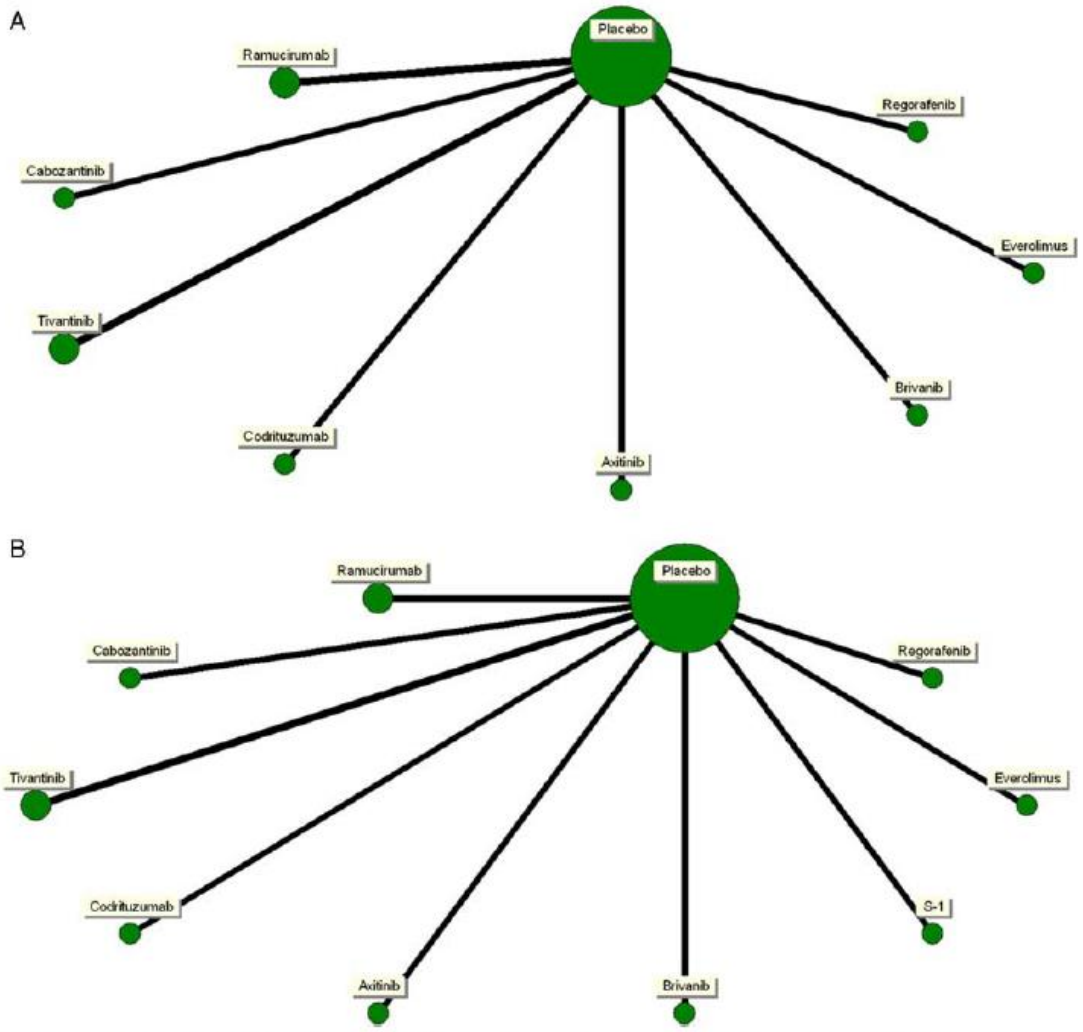

FIGURE 3. Network plot for the analysis of the rate of grade 3 to 5 adverse events (A) and rate of discontinuation of treatment due to adverse events (B). full color online

Charakteristika der Population:

TABLE 1. Characteristics of the Included Randomized Controlled Trials of Second-line Treatment of Advanced Hepatocellular Carcinoma

References	Study Name	Ph	N	Experimental Arm (A)	N (A)	Control Arm (B)	N (B)
Zhu et al[10]	REACH 2	3	292	Ramucirumab	197	Placebo	95
Rimassa et al[17]	Metiv-HCC	3	340	Tivantinib	226	Placebo	114
Abou-Alfa et al[22]	NCT01287585	3	635	ADI-PEG 20	424	Placebo	211
Abou-Alfa et al[8]	CELESTIAL	3	707	Cabozantinib	470	Placebo	237
Bruix et al[7]	RESORCE	3	591	Regorafenib	397	Placebo	194
Kudo et al[21]	S-CUBE	3	334	S-1	223	Placebo	111
Kobayashi et al[19]	JET-HCC	3	195	Tivantinib	134	Placebo	61
Abou-Alfa et al[20]	NCT01507168	2	185	Codrituzumab	125	Placebo	60
Kang et al[18]	NCT01210495	2	202	Axitinib	134	Placebo	68
Zhu et al[9]	REACH	3	568	Ramucirumab	283	Placebo	285
Zhu et al[15]	EVOLVE-1	3	546	Everolimus	362	Placebo	184
Santoro et al[14]	NCT00988741	2	107	Tivantinib 240 mg	33	Placebo	36
				Tivantinib 360 mg	38	Placebo	36
Llovet et al[16]	BRISK-PS	3	395	Brivanib	263	Placebo	132

A indicates experimental arm; ADI-PEG 20, pegylated arginine deiminase 20; B, control arm; N, number of patients; Ph, phase.

TABLE 2. Efficacy and Safety Endpoints of the Included Randomized Controlled Trials of Second-line Treatment of Advanced Hepatocellular Carcinoma

References	Experimental Arm (A)	PFS (A) (mo)	PFS (B) (mo)	HR (95% CI)	ORR (A) (%)	ORR (B) (%)	OS (A) (mo)	OS (B) (mo)	HR (95% CI)	Grade 3-5 AE (A) (%)	Grade 3-5 AE (B) (%)	DR (A) (%)	DR (B) (%)
Zhu et al[10]	Ramucirumab	2.8	1.6	0.45 (0.34-0.60)	4.6	1.1	8.5	7.3	0.71 (0.53-0.95)	58.9	44.2	10.7	3.2
Rimassa et al[17]	Tivantinib	2.1	2	0.96 (0.75-1.22)	0	0	8.4	9.1	0.97 (0.75-1.25)	55.6	55.3	12	10
Abou-Alfa et al[22]	ADI-PEG 20	2.6	2.6	1.18 (0.96-1.34)	0.2	2.8	7.8	7.4	1.02 (0.85-1.23)	NA	NA	NA	NA
Abou-Alfa et al[8]	Cabozantinib	5.2	1.9	0.44 (0.36-0.52)	4	0.4	10.2	8	0.76 (0.63-0.92)	68	36	1.2	0.4
Bruix et al[7]	Regorafenib	3.4	1.5	0.43 (0.35-0.52)	7	3	10.7	7.9	0.61 (0.50-0.75)	67	39	10	4
Kudo et al[21]	S-1	2.63	1.38	0.60 (0.46-0.77)	5.4	0.9	11.1	11.2	0.86 (0.67-1.10)	NA	NA	19.2	5.4
Kobayashi et al[19]	Tivantinib	2.8	2.3	0.72 (0.51-1.02)	NA	NA	9.9	8.5	0.85 (0.59-1.22)	NA	NA	NA	NA
Abou-Alfa et al[20]	Codrituzumab	2.6	1.5	0.97 (0.67-1.39)	0.8	0	8.7	10	0.96 (0.65-1.41)	25.6	31.7	3.2	5
Kang et al[18]	Axitinib	3.6	1.9	0.62 (0.44-0.87)	9.7	2.9	12.7	9.7	0.91 (0.65-1.27)	82	38	29	12
Zhu et al[9]	Ramucirumab	2.8	2.1	0.63 (0.52-0.75)	7	<1	9.2	7.6	0.87 (0.72-1.05)	36	29	10	3
Zhu et al[15]	Everolimus	3	2.6	0.93 (0.75-1.15)	2.2	1.6	7.6	7.3	1.05 (0.86-1.27)	70.9	52.2	16.6	7.6
Santoro et al[14]	Tivantinib 240 mg	1.5	1.4	0.67 (0.44-1.04)	3	0	6.6	6.2	0.90 (0.57-1.40)	34	39	18	22
	Tivantinib 360 mg	—	—		0	0	—	—	—	—	—	—	—
Llovet et al[16]	Brivanib	4.2	2.7	0.56 (0.42-0.76)	10	2	9.4	8.2	0.89 (0.69-1.15)	68	24	23	7

A indicates experimental arm; ADI-PEG 20, pegylated arginine deiminase 20; AE, adverse events; B, control arm; CI, confidence interval; DR, discontinuation rate; HR, hazard ratio; NA, not available; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Qualität der Studien:

One of the 13 studies had incomplete outcome data and, for 3 studies (the 3 abstracts), the assessment for incomplete outcome data was not possible, 2 studies selectively reported their results but all 13 studies were randomized, had adequate allocation concealment, had adequate blinding of participants and personnel, and had adequate blinding of outcome assessment.

Studienergebnisse:

- OS

  […] global treatment effects on OS […] are represented in Figure 4A. On global estimates of treatment effect, regorafenib (HR =0.60, 95% CI= 0.44-0.81) and cabozantinib (HR =0.72, 95% CI= 0.55-0.95) were found to significantly prolong OS compared with everolimus. All other treatments tended to prolong OS compared with everolimus, although none of these treatments reached the threshold for statistical significance.

- PFS

  […] global treatment effects on PFS […] are represented in Figure 4B. On global estimates of treatment effect, regorafenib (HR =0.46, 95% CI= 0.35-0.62), cabozantinib (HR =0.47, 95% CI= 0.36-0.63), brivanib (HR= 0.60, 95% CI= 0.42-0.87), ramucirumab (HR= 0.62, 95% CI= 0.41-0.92), and S-1 (HR=0.65, 95% CI=0.46-0.90) were found to significantly prolong PFS compared with everolimus. Axitinib and tivantinib tended to prolong PFS compared with everolimus, whereas codrituzumab, placebo, and pegylated arginine deiminase 20 tended to

decrease PFS, although none of these treatments reached the threshold for statistical significance.

- Grade 3 to 5 Adverse Events

  […] global treatment effects on the rate of grade 3 to 5 adverse events […] are represented in Figure 4C. On global estimates of treatment effect, axitinib (OR= 7.43, 95% CI =3.85-14.36), brivanib (OR=6.73, 95% CI =4.18-10.83), cabozantinib (OR= 3.78, 95% CI= 2.72-5.25), regorafenib (OR =3.18, 95% CI =2.22-4.54), everolimus (OR=2.23, 95% CI=1.54-3.22), and ramucirumab (OR= 1.51, 95% CI= 1.13-2.01) were found to be associated with a significantly increased rate of grade 3 to 5 adverse events compared with placebo. Tivantinib and codrituzumab tended to be associated with a decreased rate of grade 3 to 5 adverse events, although both treatments did not reach the threshold for statistical significance.

- Discontinuation of Treatment due to Adverse Events

  […] global treatment effects on the rate of discontinuation of treatment due to adverse events […] are represented in Figure 4D. On global estimates of treatment effect, S-1 (OR =4.16, 95% CI= 1.71-10.12), brivanib (OR=3.97, 95% CI= 1.92-8.22), ramucirumab (OR= 3.60, 95% CI= 1.86-6.97), axitinib (OR =3.00, 95% CI= 1.32-6.81), regorafenib (OR=2.67, 95% CI= 1.21-5.87), and everolimus (OR=2.42, 95% CI =1.31-4.46) were found to be associated with a significantly increased rate of discontinuation of treatment due to adverse events compared with placebo. Cabozantinib and tivantinib tended to be associated with an increased rate of discontinuation of treatment due to adverse events, whereas codrituzumab tended to be associated with a decreased rate of treatment discontinuation due to adverse events compared with placebo, although none of these treatments reached the threshold for statistical significance.

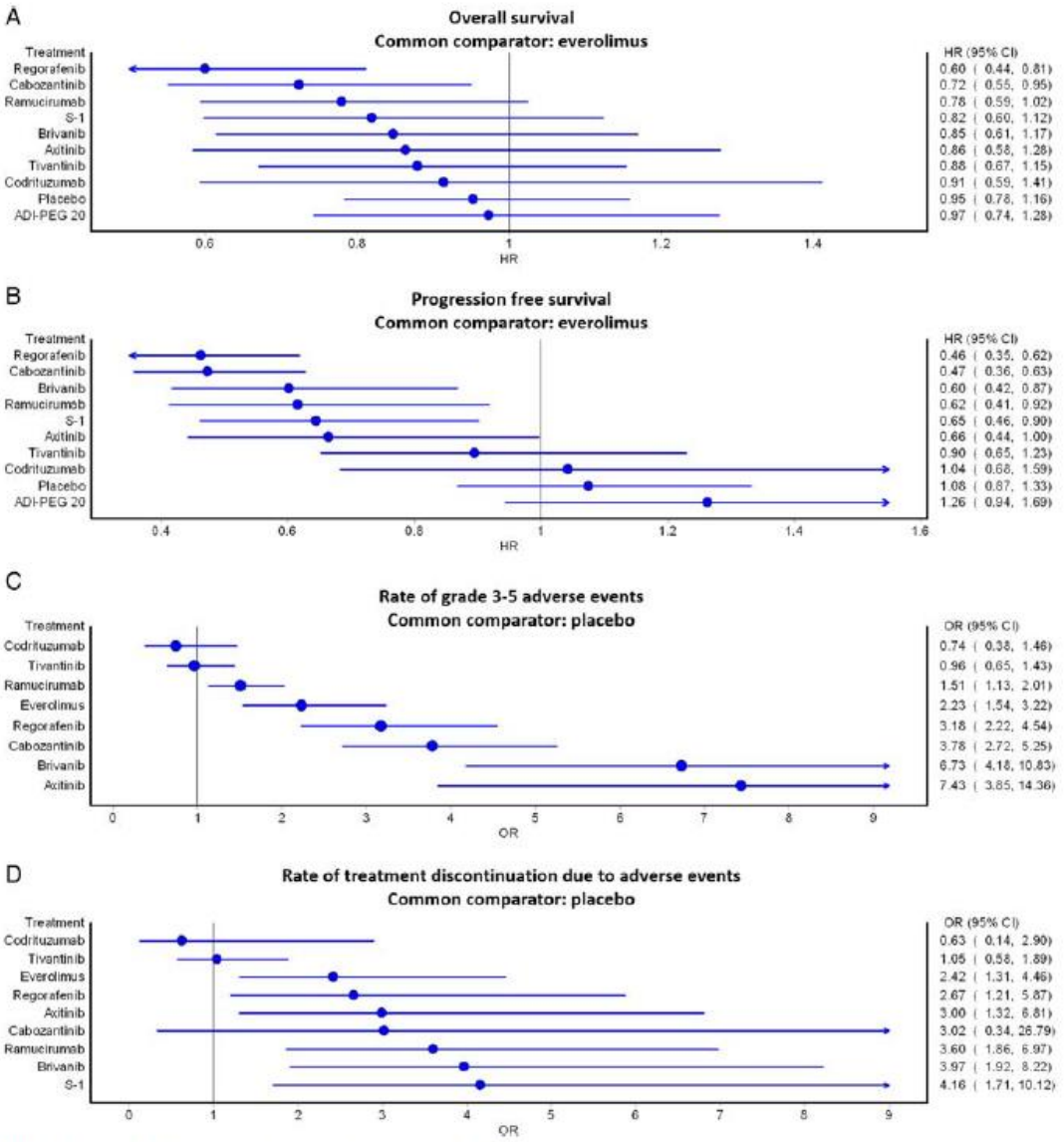

FIGURE 4. Forest plot for the analysis of OS (A), PFS (B), the rate of grade 3 to 5 adverse events (C), and the rate of treatment discontinuation due to adverse events (D). For OS (A) and PFS (B), everolimus is the common comparator with a treatment effect of 1. For the rate of grade 3 to 5 adverse events (C) and the rate of treatment discontinuation due to adverse events (D), placebo is the common comparator with a treatment effect of 1. CI indicates confidence interval; HR, hazard ratio; OR, odds ratio; OS, overall survival; PFS, progression-free survival. full color online

Anmerkung/Fazit der Autoren

The emergence of these novel treatment options has revolutionized the management of advanced HCC after the failure of frontline treatment. However, the phase III trials of the experimental regimens had only been compared with placebo and not head-to-head. In this systematic review and NMA, regorafenib was shown to confer the greatest OS benefit, which was maintained across patient subgroups, and had a relatively well-tolerated safety profile compared with other agents in this setting. Cabozantinib may be the best alternative for patients who had been previously intolerant to sorafenib. It remains essential to compare these results with that of ICI, in particular, nivolumab and pembrolizumab, which have shown promising results in early-phase trials.

Kommentare zum Review

Es liegen keine Informationen zu den AFP-Werten der einzelnen Studien vor. Folgende im hier diskutierten SR aufgeführte Arzneimittel sind für das relevante AWG **nicht** zugelassen:

- ADI-PEG 20
- Axitinib
- Brivanib
- Codrituzumab
- Everolimus
- S-1
- Tivantinib

Nicht aufgeführt, da Auftragsgegenstand:

- Ramucirumab

Folgende, in der vorliegenden LL diskutierten Studien zu zugelassenen AM werden ebenso in anderen innerhalb der Evidenzsynopse aufgeführten SRs und LL behandelt:

- CELESTIAL trial in NCCN, 2019 [13] und Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC), 2019 [11].
- RESORCE trial in Kim JH et al., 2017 [10], NCCN, 2019 [13] und Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC), 2019 [11]

Referenzen innerhalb des SR

siehe Table 1 (S. 11)

Kim JH et al., 2017 [10].

Molecular targeted agents as second-line treatment for hepatocellular carcinoma: a meta-analysis and review

Ähnliche Reviews zu dem Thema:

- Abdel-Rahman O et al., 2015 [1]. Second line systemic therapy options for advanced hepatocellular carcinoma; a systematic review
- Li X et al., 2017 [12]. Efficacy of anti-VEGF agents in the treatment of elderly hepatocellular carcinoma: a systematic review

Fragestellung

With more understanding of molecular mechanisms of pathogenesis, several novel targeted agents have been investigated in advanced HCC. Recently, a phase III placebo-controlled RESORCE trial reported that regorafenib significantly improved OS of patients with sorafenib refractory HCC. However, there has been a debate as to whether targeted agents can produce survival advantage in patients with advanced HCC previously treated with sorafenib. We performed this meta-analysis of randomized trials and reviewed clinical outcomes of molecular targeted agents as a second-line treatment for advanced HCC.

Methodik

Population:

patients with advanced HCC, pretreated with sorafenib

Intervention:

Molecular targeted agents:

- Brivanib
- Tivantinib
- Everolismus
- Axitinib
- Ramucirumab
- Regorafenib

Komparator:

Placebo

Endpunkt:

- OS
- TTP

(siehe „Kommentare zum Review“)

Recherche/Suchzeitraum:

PubMed, Embase, Google Scholar and Cochrane Library up to 2017

Qualitätsbewertung der Studien:

k. A.

(siehe „Kommentare zum Review“)

Ergebnisse

Anzahl eingeschlossener Studien:

6 (2388 patients)

Charakteristika der Population:

siehe „Table 1“

Qualität der Studien:

k. A.

(siehe „Kommentare zum Review“)

Studienergebnisse:

Die Auswertung (Metaanalyse) erfolgte für alle Wirkstoffe gemeinsam, so dass das Ergebnis der Metaanalyse hier nicht dargestellt wird. Im zitierten/übernommenen Text wird nur auf die in Deutschland zugelassenen Substanzen eingegangen (hier: Regofarinib).

Table 1: Summary of the six randomized studies comparing a targeted agent and placebo in second-line treatment setting for advanced hepatocellular carcinoma

First author (yr) Study	Phase	First-line Treatment	Treatment	Primary endpoint	No. of patients	ORR	Incidence of ≥ Gr 3 AEs	Median TTP (mo)	HR for TTP (95% CI)	Median OS (mo)	HR for OS (95% CI)
Llovet (2013) BRISK-PS	III	Sorafenib	Brivanib Placebo	OS	263 132	10% 2%	68% 38%	4.2 2.7	0.56 (0.42–0.76) *P* < 0.001	9.4 8.2	0.89 (0.69–1.15) *P* = 0.3307
Santoro (2013) APR 197-215	II	Sorafenib (103) Sunitibib (4)	Tivantinib Placebo	TTP	71 36	1% 0%	59% 9%	1.6 1.4	0.64 (0.43–0.94) *P* = 0.04	6.6 6.2	0.90 (0.57–1.40) *P* = 0.63
Zhu (2014) EVOLVE-1	III	Sorafenib	Everolimus Placebo	OS	362 184	2.2% 1.6%	71% 52%	3.0 2.6	0.93 (0.75–1.15) *P* = 0.01	7.6 7.3	1.05 (0.86–1.27) *P* = 0.68
Kang (2015)	II	Sorafenib (182)	Axitinib Placebo	OS	134 68	NA	82% 38%	3.6 1.9	0.62 (0.44–0.87) *P* = 0.004	12.7 9.7	0.91 (0.65–1.27) *P* = 0.287
Zhu (2015) REACH	III	Sorafenib	Ramucirumab Placebo	OS	283 282	6.7% 0.7%	41% 32%	2.8 2.1	0.63 (0.52–0.75) *P* < 0.0001	9.2 7.6	0.87 (0.72–1.05) *P* = 0.14
Bruix (2017) RESORCE	III	Sorafenib	Regorafenib Placebo	OS	379 194	10% 4%	67% 39%	3.2 1.5	0.44 (0.36–0.55) *P* < 0.0001	10.6 7.8	0.63 (0.50–0.79) *P* < 0.0001

TTP, time-to-progression; OS, overall survival; ORR, overall response rate; Gr, grade; AEs, adverse events; HR, hazard ratio; CI, confidence interval; NA, not available.

- On April 27, 2017 the FDA approved the use of regorafenib for patients with advanced HCC who have been previously treated with sorafenib. Regorafenib is an oral multi-kinase inhibitor that blocks VEGFR, PDGFR, RET, c-KIT, BRAF, and fibroblast growth factor receptor (FGFR). The approval was based on the RESORCE study of 573 patients with documented disease progression following sorafenib [10]. Patients were randomly allocated to receive regorafenib 160 mg orally once daily plus best supportive care (BSC) or matching placebo with BSC for the first 21 days of each 28-day cycle. The drug significantly increased OS (median 10.6 vs. 7.8 months, HR = 0.63, 95% CI: 0.50–0.79, P < 0.0001) and progression-free survival (PFS) (median 3.1 vs. 1.5 months, HR = 0.46, 95% CI: 0.37–0.56, P < 0.0001) compared with placebo. The common adverse events observed in 20% or more of patients included pain, handfoot skin reaction, fatigue, diarrhea, decreased appetite, hypertension, infection, dysphonia, elevated bilirubin, fever, mucositis, weight loss, rash, and nausea.
- In the subgroup analysis of the phase III REACH trial, patients with elevated baseline levels of serum alpha-fetoprotein (AFP ≥ 400 ng/mL), an adverse prognostic maker, benefited from ramucirumab (median OS 7.8 vs. 4.2 months, HR = 0.67, 95% CI: 0.51–0.90, P = 0.0059) [15].

Anmerkung/Fazit der Autoren

In conclusion, this meta-analysis indicates that molecular targeted agents have a potential to improve prognosis after failure of first-line treatment with sorafenib in patients with advanced HCC.

Kommentare zum Review

Das SR weist einige methodische Mängel auf. So sind z. B. der Recherchezeitraum unvollständig und die methodische Qualität der eingeschlossenen Studien nicht angegeben. Endpunkte sind nicht präspezifiziert. Drei, der sechs in das hier diskutierte SR eingeschlossene Studien, sind innerhalb eines anderen SR mit Hilfe der Jadad five-item scale bewertet worden (siehe „Ähnliche Reviews zu dem Thema“, [12]). Die Studien wurden mit folgenden Jadad Scores bewertet:

- Kang YK, et al. 2015 Jadad Score: 3

- Zhu AX, et al. 2015. (REACH) Jadad Score: 5
- Bruix J, et al. 2017 Jadad Score: 5

Weiterhin fehlen Angaben zur Dauer, Menge/ Dosierung der Vorbehandlung mit Sorafenib. Angaben zu AFP-Werten sind unvollständig und nur für eine Subgruppenanalyse einer Studie diskutiert (siehe „Studienergebnisse“). Aufgrund der insgesamt geringen Evidenz wurde dieses Review dennoch in die Evidenzsynopse aufgenommen.

Folgende im hier diskutierten SR aufgeführte Arzneimittel sind für das relevante AWG **nicht** zugelassen:

- Axitinib
- Brivanib
- Everolimus
- Tivantinib

Nicht aufgeführt, da Auftragsgegenstand:

- Ramucirumab

Bis auf die Studie von Santoro (2013) APR 197-215 werden alle hier diskutierten Studien auch im SR von Bakouny Z et al., 2019 [3] behandelt.

Folgende, in der vorliegenden LL diskutierten Studien zu zugelassenen AM werden ebenso in anderen innerhalb der Evidenzsynopse aufgeführten SRs und LL behandelt:

- RESORCE trial in Bakouny Z et al., 2019 [3], NCCN, 2019 [13] und Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC), 2019 [11].

Referenzen innerhalb des SR

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3.4 Leitlinien

NCCN, 2019 [13].

National Comprehensive Cancer Network; Version 2.2019 – March 6, 2019

Hepatobiliary Cancers

Leitlinienorganisation/Fragestellung

> The NCCN Guidelines for Hepatobiliary Cancers are the work of the members of the NCCN Hepatobiliary Cancers Guidelines Panel. The types of hepatobiliary cancers covered in these guidelines include: HCC, gallbladder cancer, and intrahepatic and extrahepatic cholangiocarcinoma. Guidelines for HCC are consistent with those offered by the European Association for the Study of the Liver/European Organization for Research and Treatment of Cancer and the consensus statement from the 2009 Asian Oncology Summit.[2] However, some discrepancies exist regarding treatment and surveillance, largely due to geographical differences such as available resources. By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Although not explicitly stated at every decision point of the guidelines, participation in prospective clinical trials is the preferred option for treatment of patients with hepatobiliary cancers.

Methodik

Grundlage der Leitlinie

vorher bestehende NCCN-Leitlinie;

- Repräsentativtät des Gremiums unklar;
- Interessenkonflikte und finanzielle Unabhängigkeit nicht dargelegt (NCCN ist industriefinanziert);
- Systematische Suche dargelegt; Auswahl der Evidenz unklar; Bewertung teilweise dargelegt;
- Formale Konsensusprozesse und externes Begutachtungsverfahren nicht dargelegt;
- Empfehlungen der Leitlinie und die Verbindung zu der zugrundeliegenden Evidenz sind teilweise dargestellt;
- Regelmäßige Überprüfung der Aktualität unklar; aktuelle Überprüfung in Arbeit.

Recherche/Suchzeitraum:

> Prior to the update of this version of the NCCN Guidelines for Hepatobiliary Cancers, an electronic search of the PubMed database was performed to obtain key literature in the field of hepatobiliary cancers published between August 26, 2016 and July 27, 2017, using the following search terms: (hepatocellular carcinoma) OR (liver cancer) OR (biliary tract cancer) OR (gallbladder cancer) OR (cholangiocarcinoma). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[3]

LoE/ GoR

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

Sonstige methodische Hinweise

Diese Leitlinie erfüllt nicht die methodischen Anforderungen einer S3-Leitlinie. Hier fehlen unter anderem die Darstellung der Recherche, der Bewertungs- und Konsensbildungsprozess sowie die Regeln für die die Überleitung der Evidenzbewertung in die Festlegung der Empfehlungsgrade. Aufgrund fehlender höherwertiger Evidenz wurde diese Leitlinie jedoch ergänzend dargestellt.

Folgende in der hier diskutierten LL aufgeführte Arzneimittel sind für das relevante AWG nicht zugelassen:

- Levantinib
- Nivolumab
- Prembrolizumab

Nicht aufgeführt, da Auftragsgegenstand:

- Ramucirumab

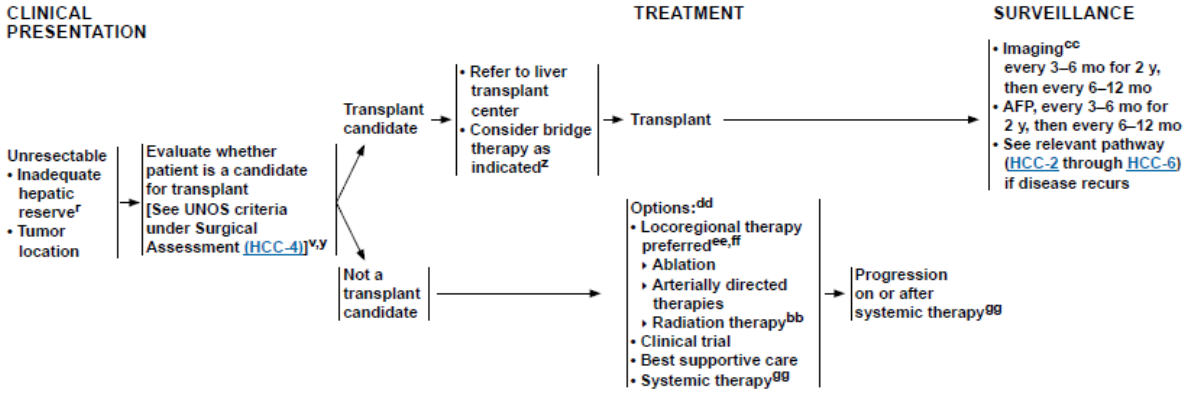
Folgende, in der vorliegenden LL diskutierten Studien zu zugelassenen AM werden ebenso in anderen innerhalb der Evidenzsynopse aufgeführten SRs behandelt:

- CELESTIAL trial in Bakouny Z et al., 2019 [3], NCCN, 2019 [13] und Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC), 2019 [11].
- RESORCE trial in Bakouny Z et al., 2019 [3], Kim JH et al., 2017 [10] und NCCN, 2019 [13] und Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC), 2019 [11]

Empfehlungen

Treatment Options

All patients with HCC should be carefully evaluated for the many available treatment options. It is important to reiterate that the management of patients with HCC is complicated by the presence of underlying liver disease. Furthermore, it is possible that the different etiologies of HCC and their effects on the host liver may impact treatment response and outcome. The treatment of patients with HCC often necessitates multidisciplinary care with the involvement of hepatologists, cross-sectional radiologists, interventional radiologists, transplant surgeons, pathologists, medical oncologists, and surgical oncologists, thereby requiring careful coordination of care.[35]



[r] See Child-Pugh Score (HCC-C) and assessment of portal hypertension (eg, varices, splenomegaly, thrombocytopenia).
[v] See Principles of Surgery (HCC-D).
[y] Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-700.
[z] Many transplant centers consider bridge therapy for transplant candidates. (See Discussion).
[bb] Case series and single-arm studies demonstrate safety and efficacy of radiation therapy in selected cases. See Principles of Locoregional Therapy (HCC-E).
[cc] Multiphasic abdominal/pelvic MRI or multi-phase CT scans for liver assessment are recommended. Consider chest CT. See Principles of Imaging (HCC-A).
[dd] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease, hepatic reserve, and institutional capabilities.
[ee] See Principles of Locoregional Therapy (HCC-E).
[ff] Use of chemoembolization has also been supported by randomized controlled trials in selected populations over best supportive care. (Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164-1171) and (Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomized controlled trial. Lancet 2002;359:1734-1739).
[gg] See Principles of Systemic Therapy (HCC-F).

PRINCIPLES OF SYSTEMIC THERAPY

- **First-line systemic therapy**
  - **Preferred**
    - **Sorafenib (Child-Pugh Class A [category 1] or B7)[a,b,1,2]**
    - **Lenvatinib (Child-Pugh Class A only)[3]**
  - **Other Recommended**
    - **Systemic Chemotherapy (category 2B)[c]**

- **Subsequent-line therapy if disease progression:**
  - **Regorafenib (Child-Pugh Class A only) (category 1)[d,4]**
  - **Cabozantinib (Child- Pugh Class A only) (category 1)[d,5]**
  - **Ramucirumab (AFP ≥ 400 ng/mL only) (category 1)[d,6]**
  - **Nivolumab (Child-Pugh Class A or B7)[7]**
  - **Sorafenib (Child-Pugh Class A or B7)[a,b] (after first-line lenvatinib[e])**
  - **Pembrolizumab (Child-Pugh Class A only)[8] (category 2B)**

[a]See Child-Pugh Score (HCC-C) and assessment of portal hypertension (eg, varices, splenomegaly, thrombocytopenia).
[b]Caution: There are limited safety data available for Child-Pugh Class B or C patients and dosing is uncertain. Use with extreme caution in patients with elevated bilirubin levels. (Miller AA, Murry K, Owzar DR, et al. Phase I and pharmacokinetic study of sorafenib in patients with hepatic or renal dysfunction:CALGB 60301. J Clin Oncol 2009;27:1800-1805).The impact of sorafenib on patients potentially eligible for transplant is unknown.
[c]There are limited data supporting the use of FOLFOX, and use of chemotherapy in the context of a clinical trial is preferred. (Qin S, Bai Y, Lim HY, et al. Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. J Clin Oncol. 2013;31:3501-3508.)
[d]The data reflect use on or after sorafenib.
[e]There are no data to define optimal treatment for those who progress after lenvatinib, nor for the use of lenvatinib after sorafenib.

Second-line Therapy Following Sorafenib

Therapeutic agents are being assessed in patients with advanced HCC, particularly in those who had disease progression following treatment with sorafenib. The randomized, double-blind, placebo-controlled, international phase III RESORCE trial assessed the efficacy and safety of regorafenib in 573 patients with HCC and Child-Pugh A liver function who progressed on sorafenib.[388] Compared to the placebo (median survival of 7.8 months), regorafenib (median survival of 10.6 months) improved OS (HR, 0.63; 95% CI, 0.50–0.79; $P < .001$), PFS (HR, 0.46; 95% CI, 0.37–0.56; $P < .001$), TTP (HR, 0.44; 95% CI, 0.36–0.55; $P < .001$), objective response (11% vs. 4%; $P = .005$), and disease control (65% vs. 36%; $P < .001$). Adverse events were universal among patients randomized to receive regorafenib ($n = 374$), with the most frequent grade 3 or 4 treatment-related events being hypertension (15%), hand-foot skin reaction (13%), fatigue (9%), and diarrhea (3%). Seven deaths that occurred were considered by the investigators to have been related to treatment with regorafenib. Based on the results of this trial, the FDA approved use of regorafenib in 2017 for patients with HCC who progressed on or after

sorafenib, and the panel recommends regorafenib as a category 1 option for this setting in patients with Child-Pugh A liver function.

Nivolumab, an anti-PD-1 antibody, was assessed in the phase I/II nonrandomized multi-institution CheckMate 040 trial including 48 patients with advanced HCC in a dose-escalation phase and 214 patients in a dose-expansion phase.[389] In patients treated with nivolumab 3 mg/kg, the objective response rate was 20% for patients in the dose-expansion phase and 15% for patients in the dose-escalation phase. The disease control rates were 64% and 58% for patients in these phases, respectively. Nine-month OS for patients in the dose-expansion phase was 74%. In the dose-escalation phase, 25% of patients had grade 3 or 4 treatment-related adverse events. In the dose-expansion phase, analyses of 57 patients without viral hepatitis who progressed following sorafenib showed a disease control rate of 61%. Median OS and 6-month OS rates for these patients were 13.2 months and 75%, respectively. Additional analyses from this trial showed a median duration of response of 17 months in sorafenib-naïve patients (n = 80) and 19 months in patients who had been previously treated with sorafenib (n = 182). Eighteen-month OS rates for these patients were 57% and 44%, respectively.[390] Based on the results from the CheckMate 040 trial, the FDA approved use of nivolumab in 2017 for patients with HCC who progressed on or after sorafenib, and the panel recommends nivolumab for this setting in patients with Child-Pugh A or B7 liver function. CheckMate 459, a phase III RCT in which nivolumab is being compared to sorafenib as definitive treatment in patients with advanced HCC, is currently in process (NCT02576509).

Cabozantinib, a tyrosine kinase inhibitor, was assessed in the phase III randomized CELESTIAL trial including 707 patients with incurable HCC who have progressed on or after sorafenib, with 7.6% of the sample having received more than one line of previous treatment.[391] Median OS and PFS rates were significantly greater in patients randomized to receive

cabozantinib (10.2 months and 5.2 months, respectively), compared to patients randomized to receive a placebo (8.0 and 1.9 months, respectively), HR, 0.76; 95% CI, 0.63—0.92; *P* = .005 for OS; HR, 0.44; 95% CI, 0.36—0.52; *P* < .001 for PFS. Though the objective response rate was better in the cabozantinib arm than in the placebo arm (*P* = .009), this value was low, with a partial response having been reported in only 4% of patients who received cabozantinib (vs. 0.4% in patients who received a placebo).

In a phase III RCT, the effects of the VEGF receptor inhibitor ramucirumab were assessed as second-line therapy following sorafenib in patients with advanced HCC (*N* = 565).[392,393] Though this regimen did not improve OS, median PFS (HR, 0.63; 95% CI, 0.52–0.75; *P* < .001) and time to tumor progression (HR, 0.59; 95% CI, 0.49–0.72; *P* < .001) were improved, relative to the placebo group. Analyses of patient-focused outcomes showed that deterioration of symptoms was not significantly different in patients randomized to receive ramucirumab, compared to the placebo group.[393]

Data from a phase II trial has demonstrated potential activity of axitinib and tolerability for patients with intermediate/advanced Child Pugh class A disease as a second-line therapy.[394]

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Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC), 2019 [11].
2018 Korean Liver Cancer Association – National Cancer Center Korea Practice Guidelines for the Management of Hepatocellular Carcinoma

Leitlinienorganisation/Fragestellung

These guidelines are intended to provide useful clinical information and direction for all clinicians in charge of the diagnosis and treatment of HCC in Korea. It also provides specific and practical information for medical residents in training, specialists, and their instructors.

Internal Medicine

13. What is effective secondary targeted agent for patients who failed treatment with sorafenib?
    - P: Patients who received sorafenib treatment for HCC but failed treatment
    - I: Regorafenib, nivolumab, cabozantinib
    - C: Conservative treatment
    - O: Survival rate

Methodik

<u>Grundlage der Leitlinie</u>

- Eingeschränkt repräsentatives Gremium: keine Patientenbeteiligung;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche dargelegt; Systematische Auswahl und Bewertung der Evidenz nur eingeschränkt ersichtlich;
- Formale Konsensusprozesse und externes Begutachtungsverfahren nur teilweise dargelegt;
- Empfehlungen der Leitlinie und die Verbindung zu der zugrundeliegenden Evidenz sind dargestellt;
- Überprüfung der Aktualität gesichert: Regelmäßigkeit unklar.

The KPGRC selected sub-topics and clinical questions from four departments regarding the revision of the guidelines, reviewed the evidence of each item, and suggested recommendations through discussion with each subcommittee and the KPGRC.

Recommendation drafts were made through several intradepartmental meetings after the initial meeting of the KPGRC and three interdepartmental meetings attended by all members of the committee. The drafts were then thoroughly reviewed through several online discussions and three department head meetings. In addition to the integrity of the contents, methodological validity of the manuscript was also evaluated on the basis of the Appraisal of Guidelines for Research and Evaluation II (AGREE II).The complete draft was then reviewed by the advisory board and through a public meeting and was modified further at the KPGRC department head meeting. The advisory board consists of nine clinical specialists in liver cancer. The guidelines made through this process were endorsed by the open meeting, board of directors of the KLCA, and the NCC.

The KLCA and NCC Korea will update part or all of these guidelines when new test methods, drugs, or treatments regarding HCC are developed and new significant research findings are

made, and thus revision of the guidelines is deemed necessary for promoting the national health of Korea. The schedule for this plan will be posted when necessary.

Recherche/Suchzeitraum:

The 2018 KPGRC collected and analyzed the Korean and international literature published on HCC since the announcement of the 2014 guidelines through a PubMed search for revisions of the guidelines based on latest updated evidence. Only English and Korean literature was searched, and the keywords included HCC and other keywords specific to related subtopics. The subtopics encompassed a wide range of clinically important items such as epidemiology, prevention, diagnosis, staging, treatment, and response assessment of HCC.

LoE/ GoR

Table 1. Grading of Recommendations, Assessment, Development and Evaluation

Grade	Criteria
Quality of evidence	
High (A)	Further research is unlikely to change confidence in estimate of clinical effect
Moderate (B)	Further research may change confidence in estimate of clinical effect
Low (C)	Further research is very likely to impact confidence on estimate of clinical effect
Strength of recommendation	
Strong (1)	Factors influencing strength of recommendation included the quality of evidence, presumed patient-important outcomes, and cost
Weak (2)	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption

Regarding quality of evidence, we excluded "very low quality (D)" in our guidelines for convenience, which was originally included in Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system and indicates that any estimate of effect is very uncertain. Evidence levels were downgraded if there was only abstract or there was poor quality or inconsistency between studies; levels were upgraded if there was large effect size.

Sonstige methodische Hinweise

Der spezifische AFP-Wert ≥ 400 ng/mL erfährt in dieser LL nur eingeschränkt Beachtung. Die Leitlinie erfüllt nicht die methodischen Anforderungen einer S3-Leitlinie. Aufgrund fehlender hochwertiger Evidenz wurde diese Leitlinie jedoch ergänzend dargestellt.
Übertragbarkeit des Versorgungskontextes bzw. der Versorgungspopulation ist fraglich, da:

> „These guidelines are intended to provide useful clinical information and direction for all clinicians in charge of the diagnosis and treatment of HCC in Korea."
>
> und
>
> „Many studies have been conducted and a substantial body of knowledge has been accumulated on diagnosis, staging, and treatment specific to Asia that shows different clinical behaviors of HCC from the West, especially in Korea; this has provided action plans and measures based on the new research findings."

Folgende in der hier diskutierten LL aufgeführte Arzneimittel sind für das relevante AWG **nicht** zugelassen:

- Cytotoxic chemotherapy
- Hepatic arterial infusion chemotherapy
- Nivolumab

Nicht aufgeführt, da Auftragsgegenstand:

- Ramucirumab

Folgende, in der vorliegenden LL diskutierten Studien zu zugelassenen AM werden ebenso in anderen innerhalb der Evidenzsynopse aufgeführten SRs und LL behandelt:

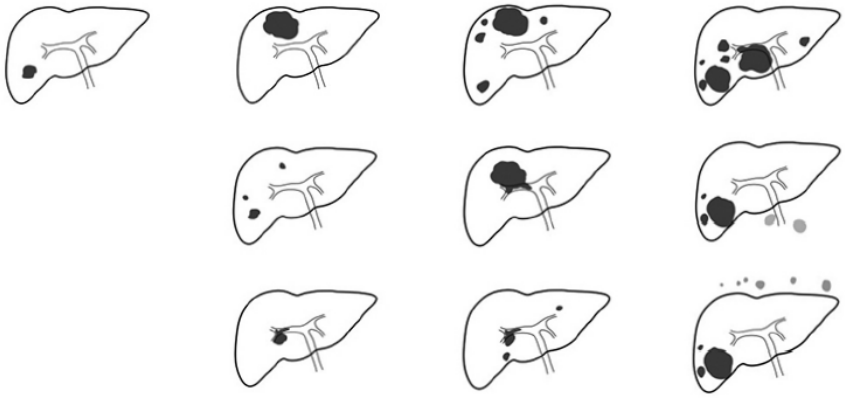
- CELESTIAL trial in Bakouny Z et al., 2019 [3] und NCCN, 2019 [13].
- RESORCE trial in Bakouny Z et al., 2019 [3], Kim JH et al., 2017 [10] und NCCN, 2019 [13].

Empfehlungen

Table 4. Modified Union for International Cancer Control Stage*

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
IV A	T4	N0	M0
	T1, T2, T3, T4	N1	M0
IV B	T1, T2, T3, T4	N0, N1	M1

Criteria	T1	T2	T3	T4
(1) Number of tumors: solitary (2) Diameter of largest tumor ≤ 2 cm (3) No vascular or bile duct invasion: Vp0, Vv0, B0	All three criteria are fulfilled	Two of three criteria are fulfilled	One of three criteria is fulfilled	None of three criteria are fulfilled



*Adapted from Liver Cancer Study Group of Japan (134, 135). B = bile duct invasion, M = metastasis, N = node, T = tumor, Vp = portal vein invasion, Vv = hepatic vein invasion

Table 5. Child-Pugh Classification

	1	2	3
Albumin, g/dL	> 3.5	2.8–3.5	< 2.8
Bilirubin, mg/dL	< 2.0	2.0–3.0	> 3.0
Prothrombin time prolonged, sec	0–4	4–6	> 6
Ascites	None	Slight	Moderate
Encephalopathy, grade	None	1–2	3–4

Class A ≤ 6 points, Class B = 7–9 points, Class C ≥ 10 points.

Table 6. Eastern Cooperative Oncology Group Performance Status*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

*Adapted from Oken, et al. *Am J Clin Oncol* 1982;5:649-655, with permission of Wolters Kluwer Health, Inc. (164). ECOG = Eastern Cooperative Oncology Group

Recommendations

1. Regorafenib is recommended for patients with progressive HCC after at least 3 weeks of sorafenib (≥ 400 mg/day) treatment and with Child-Pugh class A and good performance status (ECOG score 0–1) (A1).
2. Nivolumab could be used for patients with progressive HCC after sorafenib or for those intolerant of sorafenib and with Child-Pugh class A and good performance status (ECOG score 0–1) (B2).
3. Cabozantinib is recommended for patients with progressive HCC after one or two systemic therapies including sorafenib and with Child-Pugh class A and good performance status (ECOG score 0–1) (A1).
4. Ramucirumab has shown survival benefit in patients with progressive HCC and serum AFP level ≥ 400 ng/mL after sorafenib treatment or sorafenib-intolerance and with Child-Pugh class A, ECOG score 0–1 (A2).
5. Cytotoxic chemotherapy can be considered for patients with HCC for whom primary or secondary systemic treatments, such as sorafenib, lenvatinib, regorafenib, nivolumab, cabozantinib, or ramucirumab have failed, or cannot be used, and who still have both good liver function and good performance status (C1).
6. HAIC might be considered for patients with progressive HCC and portal vein invasion for whom systemic therapies, such as sorafenib, lenvatinib, regorafenib, nivolumab, cabozantinib, or ramucirumab, have failed or cannot be used, and who still have both good liver function and good performance status (C2).

Second-Line Treatment after Failure of First Treatment

The second-line treatment to improve survival in HCC that has recurred after liver resection, liver transplantation, and RFA is very important; however, a prospective comparative study comparing the guidelines and each treatment has not been conducted except for second-line systemic treatment. Nevertheless, in actual clinical practice, the secondline treatment after the first treatment failure of HCC is very common due to the nature of the HCC. Therefore, the current evidence for second-line treatment after first treatment failure is described in this guideline.

Second-Line Therapy after Sorafenib Failure

Sorafenib failure is usually defined as pre-existing disease progression or appearance of a new intrahepatic or extrahepatic lesion during sorafenib treatment, and various patterns of disease progression after sorafenib failure are associated with prognosis (608). In clinical practice, the median duration of sorafenib administration is 12 weeks (523, 609). Long-term administration of sorafenib is often prohibited by disease progression, adverse events, and deterioration of liver function. To develop second-line systemic therapy for HCC patients who stopped sorafenib due to disease progression or adverse events, several phase III clinical trials have been conducted using targeted agents such as brivanib, which inhibits FGF and VEGF (610), everolimus, which is an mTOR inhibitor (611), ramucirumab, which blocks VEGF-2 (612), and tivantinib, which is a nonselective c-Met inhibitor (613). However, all these new agents failed to show improved survival compared with placebo.

Regorafenib

Regorafenib is an oral multikinase inhibitor that blocks the activity of protein kinases involved in angiogenesis, oncogenesis, metastasis, and tumor immunity. Although regorafenib has a similar molecular structure to sorafenib, it has a distinct molecular target profile and had more potent pharmacological activity than sorafenib in preclinical studies (614-616). A international phase III RCT was conducted to validate the efficacy and safety of regorafenib as a secondline therapy for HCC patients with Child-Pugh A function and an ECOG score 0–1 who progressed after sorafenib treatment. Participants tolerated sorafenib (≥ 400 mg/day for ≥ 20 days of last 28 days of treatment), progressed on sorafenib, and had Child-Pugh A liver function. They were randomly assigned to receive regorafenib or placebo in a 2:1 ratio fashion. Regorafenib improved OS with an HR of 0.63 (95% CI, 0.50 to 0.79; $p < 0.0001$); median survival was 10.6 months (95% CI, 9.1 to 12.1 months) for regorafenib versus 7.8 months (95% CI, 6.3 to 8.8 months) for placebo. Based on this result, regorafenib was the first drug to show an improvement in survival as second-line systemic therapy (617). Median PFS by mRECIST was 3.1 months (95% CI, 2.8 to 4.2) with regorafenib and 1.5 months (95% CI, 1.4 to 1.6 months) with placebo ($p < 0.001$). Median TTP by mRECIST was 3.2 months (95% CI, 2.9 to 4.2 months) with regorafenib and 1.5 months (95% CI, 1.4 to 1.6 months) with placebo ($p < 0.001$). The mean duration of regorafenib administration was 5.9 months and that with sorafenib was 3.3 months. Grade 3 or 4 adverse events associated with regorafenib were hypertension (15%), HFSR (13%), fatigue (9%), and diarrhea (3%) (617).

Nivolumab

Nivolumab, a checkpoint inhibitor, is a fully human IgG4- type, monoclonal inhibitory antibody against PD- 1. As an anti-PD-1 inhibitor, it binds to the PD-1 receptor on the T-cell to restore the suppressed tumor-killing effect. In a phase I/II, open-label, non-comparative, dose escalation and expansion trial of nivolumab, patients with histologically confirmed HCC with or without hepatitis C or B infection were recruited. The patients had compensated liver function (Child-Pugh score ≤ 6 in the dose expansion group, ≤ 7 in the dose escalation group), ECOG score 0–1, and HBV DNA < 100 IU/mL if the etiology was HBV (529). Patients received intravenous nivolumab 0.1 to 10 mg/kg every 2 weeks in the dose-escalation phase and nivolumab 3 mg/kg was administered every 2 weeks in the doseexpansion phase in four cohorts: sorafenib untreated or intolerant patients without viral hepatitis, sorafenib progression patients without viral hepatitis, HCV infected patients, and HBV infected patients. The primary endpoints were safety and tolerability for the escalation phase and OSS for the expansion phase. In a total of 262 treated patients (48 in the dose-escalation phase and 214 in the dose-expansion phase),

the response rate was 20% (95% CI, 15% to 26%) in the dose-expansion phase and 15% (95% CI, 6% to 28%) in the dose-escalation phase. Three patients (6%) had treatment-related SAEs (pemphigoid, adrenal insufficiency, and liver disorder) (529, 530). The U.S. Food and Drug Administration conditionally approved nivolumab as a second-line therapy after sorafenib failure based on the results of a randomized phase I/II trial, and it is also prescribed in Korea. However, the final approval of nivolumab as first-line therapy for HCC needs data from CheckMate-459 (ClinicalTrials.gov ID: NCT02576509), which is a phase III, multi-institutional, RCT to compare the efficacy and safety of nivolumab.

Cabozantinib

Cabozantinib is an oral, molecular targeted agent which blocks MET, VEGFR-2, and RET. An international phase III RCT was conducted to validate the efficacy and safety of cabozantinib as second- or third-line therapy in patients with advanced HCC who failed sorafenib treatment and had Child-Pugh A liver function and ECOG score 0–1. Enrolled patients had showed progressive diseases in spite of one or two systemic therapies, including sorafenib, prior to participating in the study. The primary endpoint was OS, and the secondary endpoint was PFS and ORR according to RECIST 1.1. Among all the participants, 27% received two systemic therapies, including sorafenib. The median OS in the cabozantinib group was 10.2 months, which was significantly longer than 8.0 months in control group (HR, 0.76; 95% CI, 0.63 to 0.92; p = 0.0049). Thus, the clinical trial met the primary endpoint. In subgroup analysis, among patients who experienced sorafenib alone, the median OS in the cabozantinib group was 11.3 months, which was also significantly longer than 7.2 months in the control group (stratified HR, 0.70; 95% CI, 0.55 to 0.88). The median PFS was longer in the cabozantinib group (5.2 months) than in the control group (1.9 months) (HR, 0.44; 95% CI, 0.36 to 0.52; p < 0.001), and ORR was also higher in the cabozantinib group than in the control group (4% vs. 0.4%, p = 0.0086). The median duration of cabozantinib therapy was 3.8 months. The grade 3 or 4 adverse events were reported in 68% of the patients in the cabozantinib group and in 36% in the placebo group. The most common grade 3 or 4 AEs were HFSR (17%), hypertension (16%), elevation of transaminase levels (12%), fatigue (10%), and diarrhea (10%) (618).

Ramucirumab

Ramucirumab is an intravenous monoclonal antibody targeting VEGFR-2. A phase III RCT (REACH, ClinicalTrials. gov ID: NCT01140347) of ramucirumab as a second-line therapy for patients with advanced HCC who failed sorafenib was conducted. The trial failed to meet the primary endpoint of improvement of OS compared with control (612). However, in a post-hoc subgroup analysis, the OS in patients with a serum AFP level ≥ 400 ng/mL was 7.8 months, which was significantly higher than 4.2 months in the placebo group (HR, 0.67; 95% CI, 0.51 to 0.90). Based on this result, a subsequent phase III RCT of 2:1 assignment to ramucirumab or placebo for patients with high AFP levels (REACH-2, ClinicalTrials.gov ID: NCT02435433) was conducted. Enrolled patients had progressive HCC even after sorafenib or stopped sorafenib due to adverse events. The Child-Pugh class in the patients was A, the ECOG score was 0 to 1, and the serum AFP level was ≥ 400 ng/mL. The primary endpoint of the study was OS. The OS in patients who received 8 mg/kg of ramucirumab every 2 weeks was 8.5 months, which was significantly longer than 7.3 months in the placebo group (HR, 0.71; 95% CI, 0.531 to 0.949; p = 0.0199). Thus, the trial met the primary endpoint. The median PFS in the ramucirumab group was 2.8 months, which was also significantly longer than 1.6 months in the control group (HR, 0.452; 95% CI, 0.339 to 0.603; p < 0.0001). The DCR in the ramucirumab and control group was 59.9% and 38.9%, respectively (p = 0.0006); however, there was no difference in ORR

between the two groups. The median duration of ramucirumab administration was 12 weeks. SAE of any grade and cause were recorded in 35% of participants in the ramucirumab group and 29% in the placebo group. The most common grade 3 or 4 adverse event that were noted in 5% or more of patients was hypertension and hyponatremia (619).

Cytotoxic Chemotherapy and Hepatic Arterial Infusion Chemotherapy

Cytotoxic chemotherapy can be considered for patients with HCC for whom primary or secondary systemic treatments—such as sorafenib, lenvatinib, regorafenib, nivolumab, cabozantinib, and ramucirumab— have failed, or for patients with progressive HCC for whom systemic treatments cannot be used, but who have good remnant liver function (620-622). Doxorubicin is the most commonly used systemic drug for HCC treatment; however, in most cases, the response rate of patients taking doxorubicin is less than 20% (623-625). Other systemic treatments, including 5-fluorouracil (626), gemcitabine (627, 628), oxaliplatin (629), capecitabine (630), irinotecan (631), octreotide (632, 633), interferon (634), and tamoxifen (635), also failed in demonstrating effectiveness and improving survival rates. Combination chemotherapy has been tested, since single-drug therapy had minimal effects on HCC. FOLFOX (oxaliplatin/ fluorouracil/leucovorin) combination therapy has been studied the most. A multicenter RCT (EACH study) including 317 Asian patients (China [70%], Korea [14%], Thailand [11%], and Taiwan [5%]) compared FOLFOX combination chemotherapy with doxorubicin single-drug therapy. The combination chemotherapy did not significantly extend median survival time, which was the primary outcome measure (6.4 months vs. 2.9 months; $p = 0.07$) or the PFS time (2.9 months vs. 1.77 months; $p < 0.01$). Moreover, the stable disease rate (52.2% vs. 31.6%; $p < 0.001$) was higher compared with doxorubicin single-drug therapy (636). Interestingly, sub-analysis of the results of Chinese patients alone in the EACH study suggested that FOLFOX combination chemotherapy significantly extended survival time compared with doxorubicin single-drug therapy (637). A multicenter retrospective study of 204 patients with progressive HCC evaluated the effectiveness of GEMOX (oxaliplatin/ gemcitabine) combination therapy. The PFS time and OS time were 4.5 months and 11.0 months, respectively (638). Another retrospective study of 40 patients with progressive HCC not responding to sorafenib therapy also evaluated the effectiveness of GEMOX combination chemotherapy as a secondary anticancer therapy. The partial response and stable disease rates in this study were 20% and 46%, respectively. The PFS time was 3.1 months and the median survival time was 8.3 months (639). A meta-analysis of 17 oxaliplatin clinical studies comprising 800 patients revealed that the partial reaction rate was 16%, while the median PFS and median OS were 4.2 months and 9.3 months, respectively (640). Another metaanalysis, which included studies written in Chinese (641), suggested that the partial reaction rate of combination chemotherapy, including oxaliplatin, was 14%, while the median PFS time and median OS time were 4.7 months and 9.5 months, respectively. In most cases, HCC is accompanied by cirrhosis, which affects the absorption and metabolism of anticancer drugs. Therefore, drug-induced toxicity may increase, and often administration of the therapeutic dose becomes impossible (642). Therefore, cytotoxic chemotherapy needs to be used in a limited manner in HCC patients with good systemic condition and liver function. To prevent a decline in the quality of life, less toxic drugs need to be used as per the requirements for each case or dose reduction needs to be considered if the drug has strong toxicity. HAIC is a type of cytotoxic chemotherapy that involves direct injection of the cytotoxic anticancer drugs into the hepatic artery, thus causing fewer adverse systemic reactions, while exposing HCC to high concentrations of anticancer drugs. The most commonly used HAIC drug is 5-fluorouracil, which is used alone or in combination with cisplatin. Studies have shown that the overall response rate in patients with progressive HCC was 3.8%

to 38.5% with a partial response rate of 7% to 81% and a median survival time of 5 to 19.5 months (643-647). A long term (median follow-up period: 28 years) retrospective study conducted in Japan evaluated the outcomes of HAIC treatment in 14246 cases. The 5-year survival rate was 32% and the median survival time was 31 months. Moreover, the results were similar to that of cTACE (647). Factors affecting the poor outcomes of HAIC treatment were the remaining liver function and an increased Child-Pugh score assessed 4 weeks after HAIC treatment (648). There are no reports of a prospective study that directly compared the efficacy of sorafenib with that of HAIC. However, a retrospective study suggested that HAIC resulted in a longer survival time and higher tumor response than sorafenib (648-651), but there was no difference in survival time between the two groups. A sub-analysis of progressive HCC patients with hepatic portal vein invasion also suggested that HAIC produced better results than sorafenib (652). A domestic multicenter retrospective study of progressive HCC patients with main hepatic portal vein invasion compared HAIC and TACE. This study showed that HAIC resulted in higher tumor response and survival rates than TACE (118). A phase II RCT conducted in Japan in a small group of patients with progressive HCC revealed that the sorafenib- HAIC combination chemotherapy group had higher survival rates than the sorafenib single-drug therapy group (653). In contrast, a phase III RCT in 210 patients showed no difference in survival rates between the sorafenib- HAIC combination chemotherapy group and the sorafenib monotherapy group (654).

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Alberta Health Services, 2017 [2].

HEPATOCELLULAR CARCINOMA

Leitlinienorganisation/Fragestellung

GUIDELINE QUESTIONS

What are the goals of therapy and recommendations for the treatment of adult patients with…

…very early stage hepatocellular carcinoma?

…early stage hepatocellular carcinoma?

…intermediate stage hepatocellular carcinoma?

…advanced stage hepatocellular carcinoma?

…terminal stage hepatocellular carcinoma?

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

From 1990; Update 2017

It was compiled from the results of randomized controlled trials and systematic reviews, derived from an English language and relevant term search of PubMed and MEDLINE from 1990 forward. It takes into consideration related information presented at local, national, and international meetings as well as the Alberta Provincial Gastrointestinal Tumour Team's

interpretation of the data. The 2015 update did not necessitate a full literature review; recommendations were modified based on a consensus discussion at the 2014 Annual Gastrointestinal Tumour Team Meeting.

Update: This guideline was originally developed in August 2009. This guideline was revised in March 2010, June 2011, October 2013, March 2014, June 2015 and Dec 2017. The 2015 update did not necessitate a full literature review; recommendations were modified based on a consensus discussion at the 2014 Annual Gastrointestinal Tumour Team Meeting.

LoE/ GoR

Level	Description of Evidence
1a	Systematic reviews of randomized controlled trials
1b	Individual randomized controlled trials
1c	All or none randomized controlled trials
2a	Systematic reviews of cohort studies
2b	Individual cohort study or low quality randomized controlled trial
2c	Outcomes research
3a	Systematic review of case-control studies
3b	Individual case-control study
4	Case series
5	Expert opinion without explicit critical appraisal or based on physiology, bench research, or “first principles”

Sonstige methodische Hinweise

Der spezifische AFP-Wert ≥ 400 ng/mL erfährt in dieser LL nur eingeschränkt Beachtung. Diese Leitlinie erfüllt nicht die methodischen Anforderungen einer S3-Leitlinie (siehe „Grundlagen der Leitlinie“). Aufgrund fehlender hochwertiger Evidenz wurde diese Leitlinie jedoch ergänzend dargestellt.

„A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook. (http://www.albertahealthservices.ca/hp/if-hp-cancer-guide-utilization-handbook.pdf“

Das Guideline Resource Unit Handbook ist bei Zugriffsversuch am 02.08.2019 nicht unter dem angegebenen Link verfügbar.

Empfehlungen

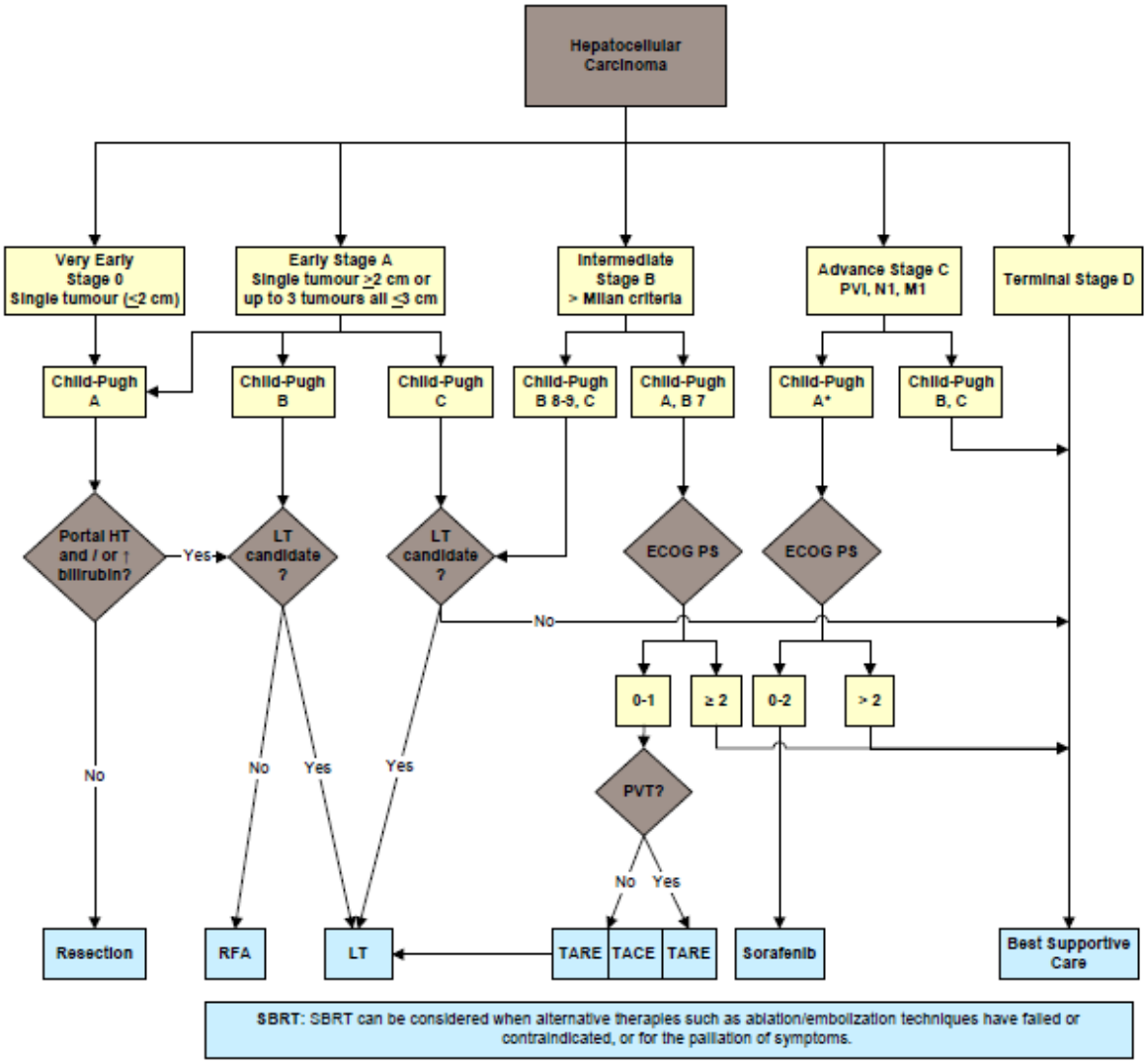
The recommendations outlined in this guideline apply to adults over the age of 18 years with hepatocellular carcinoma (HCC). Different principles may apply to pediatric patients.

Table 1. Barcelona Clinic Liver Cancer Staging System.[7]*

BCLC Stage	Tumour Stage	Child-Pugh Class	ECOG PS	Therapy options recommended by Sherman et al. 2011[7]
Very early (0)	Single ≤ 2cm	A	0	Resection or Transplantation or RFA
Early (A)	Single ≤ 5cm Or up to three all ≤ 3cm	A or B	0	
Intermediate (B)	Multinodular	A or B	0	TACE
Advanced (C)	PVI, N1, M1	A or B	1-2	Sorafenib
End-stage (D)**	Any	C	>2	Symptomatic treatment

*This table is adapted from Sherman et al. 2011[7] Please see Figure 2 for Alberta specific recommendations for the management of HCC
**Patients who are PVI, N1, M1 and Child-Pugh B or C may be treated as end-stage.
BCLC = Barcelona Clinic Liver Cancer; PS = performance status; PVI = portal vein invasion; N1 = lymph node metastasis; M1 = distant metastasis; PS = Performance Status; RFA = radiofrequency ablation; TACE = transarterial chemoembolization

Figure 2. Algorithm for the Management of HCC According to the Updated AHS Clinical Practice Guidelines (adapted from the Alberta[8] and Canadian[7] HCC algorithms).



Abbreviations / Notes: Milan criteria = single HCC ≤5cm or 3 HCC largest ≤3cm; PVI = portal vein invasion; N1 = lymph node metastasis; M1 = metastasis; portal HT = portal hypertension (splenomegaly, esophageal varices, ascites, platelets < 100 or hepatic venous pressure gradient >10mmHg); LT candidate = liver transplant candidate = total tumour volume <115mm³ AND alphafetoprotein <400ng/mL, age <70 (if age 65-69 no major comorbidities), good social support and appropriate abstinence and rehabilitation if addiction issues; ECOG PS= Eastern Cooperative Oncology Group performance status; PVT = portal vein thrombosis (bland); RFA = radiofrequency ablation; LT = liver transplantation; TACE = transarterial chemoembolization; TARE = transarterial radioembolization with yttrium90 microspheres; SBRT = stereotactic body radiotherapy.

* Consider enrollment of patients with Child-Pugh A, B 7 in a clinical trial

Tab. 2 Definitions, Goals, and Recommendations for Management of Hepatocellular Carcinoma

<table>
<tr><td>Advanced Stage Hepatocellular Carcinoma</td><td>
Patient Requirements: · Good performance status (ECOG 0, 1, or 2).
· 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 life, if possible.
Recommendations: · First-line treatment: Sorafenib or participation in a clinical trial,[36] if available.
· Second-line treatment: participation in a clinical trial,[36] if available.

Sorafenib 400 mg po BID:
• 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:
<table>
<tr><th rowspan="2">End-Point</th><th colspan="2">SHARP Trial[37]</th><th colspan="2">Asia-Pacific Trial[38]</th></tr>
<tr><th>Sorafenib</th><th>Placebo</th><th>Sorafenib</th><th>Placebo</th></tr>
<tr><td>Median Survival</td><td>10.7 months</td><td>7.9 months</td><td>6.5 months</td><td>4.2 months</td></tr>
<tr><td></td><td colspan="2">HR 0.69 (CI95% 0.55-0.87)
p < 0.001</td><td colspan="2">HR 0.68 (CI95% 0.50-0.93)
p < 0.014</td></tr>
<tr><td>Time to Progression (Radiologic</td><td>5.5 months</td><td>2.8 months</td><td>2.8 months</td><td>1.4 months</td></tr>
<tr><td></td><td colspan="2">HR 0.58 (CI95% 0.45-0.74)
p < 0.001</td><td colspan="2">HR 0.57 (CI95% 0.42-0.79)
p = 0.0005</td></tr>
</table>
</td></tr>
<tr><td></td><td>
• 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.[33]
• Increases the incidence of arterial thromboembolic events (1.4%, RR 3.03, p = 0.015).[34]

Stereotactic Body Radiotherapy (SBRT)
• There is growing experience with providing ionizing radiotherapy to HCC using very conformal dose distribution, with image guidance and motion management to provide high doses of radiation to the HCC while minimizing exposure to the adjacent liver or other tissues.[39]
• SBRT can provide good local control of HCC range (ranging from 43% to 100% at 1 year) which can depend on factors such as lesion size and number, and the delivered radiation dose. It has been used in patients with portal vein invasion [40] and to bridge patients to liver transplantation.[41]
• Patients should be discussed at multidisciplinary rounds. SBRT can be considered when alternative therapies such as ablation/embolization techniques have failed or are contraindicated.
• Patients can experience worsening of liver function with SBRT[40] and tolerance to normal liver is the main dose limiting constraint. Most safety evidence is for patients with Child-Pugh class A disease. Evidence is more limited for Child-Pugh class B disease and in practice treatment dose is lowered to reduce the chance of treatment toxicities. Treatment of patients with Child-Pugh class C disease is not recommended as the safety of liver SBRT in this population has not been determined.
• Continued clinical trials in the use of liver SBRT are recommended. Studies evaluating SBRT in combination with sorafenib are currently underway. Enrollment of patients into clinical trials or investigational protocols should be encouraged.
</td></tr>
<tr><td>Terminal Stage Hepatocellular Carcinoma</td><td>
Patient Requirements: · Poor performance status (ECOG > 2).
· Decompensated liver function (Child-Pugh class C).
Goals: · To maintain or to improve the patient's quality of life (to control tumour-related symptoms).
Recommendations: · Best supportive care.
· Palliative chemotherapy may adversely affect outcome.[42]
</td></tr>
</table>

Referenzen innerhalb der LL

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Level of Evidence: 1a
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Level of Evidence: 4
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Level of Evidence: 1a

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 7 of 12, July 2019) am 11.07.2019

#	Suchfrage
1	MeSH descriptor: [Liver Neoplasms] this term only
2	MeSH descriptor: [Carcinoma, Hepatocellular]
3	(hepatoma* OR HCC OR hepatocarcinoma* OR (hepatocellular NEXT carcinom*) OR (liver cell carcinoma*)):ti,ab,kw
4	(liver OR hepatic OR hepatocellular OR hepatobiliary):ti
5	(cancer* OR tumor* OR tumour* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesions* OR malignan*):ti
6	#4 AND #5
7	#1 OR #2 OR #3 OR #6
8	#7 with Cochrane Library publication date from Jul 2014 to present, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 11.07.2019

#	Suchfrage
1	liver neoplasms/therapy[mh:noexp] OR liver neoplasms/surgery[mh:noexp] OR liver neoplasms/drug therapy[mh:noexp] OR liver neoplasms/radiotherapy[mh:noexp]
2	carcinoma, hepatocellular/therapy[mh]
3	((hepatocarcinoma*[ti]) OR hepatoma*[ti]) OR HCC[ti]
4	((liver[ti]) OR hepatic[ti] OR hepatocellular[ti]) OR hepatobiliary[ti]
5	(((((((((tumor[ti]) OR tumors[ti]) OR tumour*[ti]) OR carcinoma*[ti]) OR adenocarcinoma*[ti]) OR neoplas*[ti]) OR sarcoma*[ti]) OR cancer*[ti]) OR lesions*[ti]) OR malignan*[ti]
6	#4 AND #5
7	(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])
8	(#3 OR #6) AND #7
9	#1 OR #2 OR #8
10	(#9) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR

	(predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
11	((#10) AND ("2014/07/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
12	(#11) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 11.07.2019

#	**Suchfrage**
1	liver neoplasms[mh:noexp]
2	carcinoma, hepatocellular[mh]
3	((hepatocarcinoma*[ti]) OR hepatoma*[ti]) OR HCC[ti]
4	((liver[ti]) OR hepatic[ti] OR hepatocellular[ti]) OR hepatobiliary[ti]
5	(((((((((tumor[ti]) OR tumors[ti]) OR tumour*[ti]) OR carcinoma*[ti]) OR adenocarcinoma*[ti]) OR neoplas*[ti]) OR sarcoma*[ti]) OR cancer*[ti]) OR lesions*[ti]) OR malignan*[ti]
6	#4 AND #5
7	#1 OR #2 OR #3 OR #6
8	(#7) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
9	(#8) AND ("2014/07/01"[PDAT] : "3000"[PDAT])
10	(#9) NOT retracted publication[ptyp]

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