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: 2018-B-102 Atezolizumab

Stand: Juni 2020

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

Atezolizumab
[zur Erstlinienbehandlung des fortgeschrittenen Leberzellkarzinoms]

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	D-379 Lenvatinib (Beschluss vom 21.03.2019)
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:	
Atezolizumab Tecentriq®	Geplantes Anwendungsgebiet laut Beratungsanforderung: Tecentriq (Atezolizumab) in Kombination mit Avastin wird angewendet zur Erstlinienbehandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem hepatozellulärem Karzinom.
Sorafenib L01XE05 Nexavar®	Leberzellkarzinom Nexavar ist angezeigt zur Behandlung des Leberzellkarzinoms (siehe Abschnitt 5.1).
Mitomycin L01DC03 (Mitomycin medac)	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
Lenvatinib L01XE29 Lenvima®	zur Behandlung des fortgeschrittenen oder inoperablen hepatozellulären Karzinoms (HCC), die zuvor noch keine systemische Therapie erhalten haben.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BSC	best supportive care
ECRI	ECRI Guidelines Trust
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HCC	Hepatozelluläres Karzinom
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Erstlinienbehandlung des fortgeschrittenen Leberzellkarzinoms bei Erwachsenen.

Hinweis: Nicht-medikamentöse Behandlungen wurden für die Synopse nicht berücksichtigt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Leberzellkarzinom durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 29.05.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NCCN, NCI, 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.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 1522 Quellen. 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 Quellen 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 7 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2019 [5].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 22. März 2019 - Lenvatinib (neues Anwendungsgebiet: hepatozelluläres Karzinom).

Anwendungsgebiet

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

a) Erwachsene Patienten mit fortgeschrittenem oder inoperablem HCC mit Child-Pugh A oder keiner Leberzirrhose ohne systemische Vortherapie

Zweckmäßige Vergleichstherapie

Sorafenib

Fazit / Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) Erwachsene Patienten mit fortgeschrittenem oder inoperablem HCC mit Child-Pugh B ohne systemische Vortherapie

Zweckmäßige Vergleichstherapie

Best-Supportive-Care

Fazit / Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

3.2 Cochrane Reviews

keine

3.3 Systematische Reviews

Canadian Agency for Drugs and Technologies in Health (CADTH), 2019 [3].

Lenvatinib (Lenvima) for Hepatocellular Carcinoma.

Fragestellung

to evaluate the safety and efficacy of lenvatinib on patient outcomes in the first line treatment of adult patients with unresectable HCC.

Methodik

Population:

- Adults (≥18 years) with advanced, unresectable, HCC with no prior syst. therapy for disease

Intervention:

- Lenvatinib

Komparator:

- Sorafenib

Endpunkte:

- Primary: OS, PFS, HRQoL
- Secondary: TTP, ORR, CBR
- Safety: AEs. TEAEs, SAEs, withdrawals due to adverse events (WDAEs)

Recherche/Suchzeitraum:

- EBM Reviews - Cochrane Central Register of Controlled Trials January 2019, Embase 1974 to 2019 February 21, Ovid MEDLINE(R) ALL 1946 to February 21, 2019

Qualitätsbewertung der Studien:

- Qualitätsbewertung unter Berücksichtigung von Randomisierung, Allocation Concealment, Verblindung, ITT

Ergebnisse

Anzahl eingeschlossener Studien:

- 1 RCT: REFLECT trial (n=954), non-inferiority (NI) trial

Charakteristika der Population:

- The majority of study participants were <65 years of age (58%), male (84%), Asian (69%), and had a body weight ≥60 kg (69%). Participants almost exclusively had a liver function of Child-Pugh class A (99%), and the majority had Barcelona Clinic Liver Cancer (BCLC) stage C disease (79%).
- Baseline characteristics generally well balanced between study arms, with the exception of a higher proportion of patients in the lenvatinib arm with baseline α-fetoprotein (AFP) concentration ≥200ng/mL (46%) compared to the sorafenib arm (39%). Aetiology of chronic liver disease differed between the 2 treatment arms, with more (HBV aetiology participants in the lenvatinib arm (53% vs. 48% in sorafenib), and more participants with HCV aetiology in the sorafenib arm (26% vs. 19% in lenvatinib).

Qualität der Studie:

The trial was overall, well conducted. Since REFLECT was open-label (and the sorafenib vs. placebo trials were not), the possibility of investigator and participant biases remain a concern.

Study	Treatment vs. Comparator	Primary outcome	Required s=Sample Size	Sample Size	Randomization Method	Allocation Concealment	Blinding	ITT Analysis	Final Analysis	Early Termination	Ethics Approval
REFLECT	Lenvatinib vs sorafenib	OS	940	954	1:1 based on a computer-generated randomization scheme with a block size of 2; reviewed and approved by independent statistician	Yes, via interactive voice-web response system	No	Yes	Yes	No	Yes

Studienergebnisse:

	REFLECT	
Primary Outcome	**Lenvatinib (n=478)**	**Sorafenib (n=476)**
Overall survival		
Median, months (95% CI)	13.6 (12.1, 14.9)	**12.3 (10.4, 13.9)**
HR (95%CI)	0.92 (0.79, 1.06)	
p-value†	NR	
Secondary Outcomes‡ (Investigator Assessed)		
Progression-free survival		
Median, months (95% CI)	7.4 (6.9, 8.8)	3.7 (3.6, 4.6)
HR (95% CI)	0.66 (0.57, 0.77)	
p-value††	<0.0001	
Time to progression		
Median, months (95% CI)	**8.9 (7.4, 9.2)**	**3.7 (3.6, 5.4)**
HR (95%CI)	0.63 (0.53, 0.73)	
p-value††	<0.0001	
Objective response rate		
Best response (CR + PR), % (95% CI)	24.1 (20.2, 27.9)	9.2 (6.6, 11.8)
OR (95%CI)	3.13 (2.15, 4.56)	
p-value††	<0.0001	
DOR, median, months (95% CI)	7.3 (5.6, 7.7)	11.2 (5.6, 16.6)
HrQoL		
TCW (based on EORTC QLQ-C30)		
Median, months (95% CI)	1.7 (1.05, 1.84)	1.8 (1.05, 1.84)
HR (95% CI)	0.87 (0.75, 1.01)	
p-value‡‡	0.0742	

Harms Outcome, n (%)	Lenvatinib (n=476)	Sorafenib (n=475)
TEAEs (any grade)	470 (99%)	472 (99%)
Grade ≥3 TEAEs	357 (75%)	316 (67%)
Serious TEAEs	205 (43%)	144 (30%)
Treatment-related TEAEs (any grade)	447 (94%)	452 (95%)
Treatment-related TEAEs (grade ≥3)	270 (57%)	231 (49%)
Treatment-related serious TEAEs	84 (18%)	48 (10%)
WDAEs	94 (20%)	69 (15%)
Fatal TEAEs	11 (2%)	4 (1%)
Exploratory Endpoints	**Lenvatinib (n=478)**	**Sorafenib (n=476)**
Disease control rate		
Best response (CR + PR + SD), % (95% CI)	75.5 (71.7, 79.4)	60.5 (56.1, 64.9)
Clinical benefit rate		
Best response (CR + PR + durable SD), % (95% CI)	NR	NR

	REFLECT	
IIR-assessed progression-free survival‡		
Median, months (95% CI)	7.3 (5.6, 7.5)	3.6 (3.6, 3.7)
HR (95%CI)	0.64 (0.55, 0.75)	
p-value††	<0.0001	
IIR-assessed time to progression‡		
Median, months (95% CI)	7.4 (7.2, 9.1)	3.7 (3.6, 3.9)
HR (95%CI)	0.60 (0.51, 0.71)	
p-value††	<0.0001	
IIR-assessed objective response rate‡		
Best response (CR + PR), % (95% CI)	40.6 (36.2, 45.0)	12.4 (9.4, 15.4)
OR (95%CI)	5.01 (3.59, 7.01)	
p-value††	<0.0001	
DOR, median, months (95% CI)	7.4 (5.6, 9.2)	15.8 (5.8, NE)

Data cut-off date: November 16th, 2016
†Non-inferiority margin for the HR or lenvatinib vs sorafenib is 1.08.
‡Assessed using mRECIST criteria.
††p-value is for the stratified log-rank test for the superiority of lenvatinib vs. sorafenib.
‡‡Nominal p-value.
Abbreviations:
CI = confidence interval; **CR** = complete response; **DOR** = duration of response; **HR** = hazard ratio; **HRQoL** = health-related quality of life; **IIR** = independent imaging review; **NE** = not estimable; **NR** = not reported; **OR** = odds ratio; **ORR** = objective response rate; **PR** = partial response; **SAE** = serious adverse event; **SD** = standard deviation; **TCW**= time to clinically meaningful worsening; **TEAE** = treatment-emergent adverse event; **WDAE** = withdrawal due to adverse event
Sources:
EMA Assessment report[8]
Kudo 2018[5]
Clinicaltrials.gov[12]

Anmerkung/Fazit der Autoren

The Clinical Guidance Panel concluded that there may be a net overall clinical benefit to lenvatinib in the treatment of advanced HCC, with Child Pugh A liver function, ECOG 0-1, based on one well-conducted randomized controlled trial that demonstrated non-inferiority in overall survival for lenvatinib compared with sorafenib and similar adverse event profiles between the two drugs. Lenvatinib significantly improved clinically relevant secondary endpoints such as progression free survival, time to progression, and response rate compared to sorafenib. Progression free survival and time to progression are important endpoints due to imbalances in second line therapy which may have favoured the sorafenib treated patients. According to the ESMO magnitude of clinical benefit scale, for the overall population, lenvatinib demonstrated a

clinically relevant improvement in progression free survival over sorafenib (score 4/5).73 However, there were uncertainties with regard to the magnitude of the progression free survival benefit in Western patients. Additionally, the proportional hazards assumption was not met for progression free survival. The side effect profile of lenvatinib may be preferable for some patients, as hypertension is asymptomatic, whereas hand-foot syndrome can affect daily activities; this did not translate into any significant differences in quality of life summary scores.

Huang Y et al., 2019 [7].

Supplementary Sorafenib Therapies for Hepatocellular Carcinoma-A Systematic Review and Meta-Analysis: Supplementary Sorafenib for Liver Cancer.

Fragestellung

To evaluate the efficacy and safety of sorafenib as a supplementary therapy used in combination with common treatments compared with common treatments alone for HCC

Methodik

SR nach a priori spezifiziertem Protokoll

Population:

- Patients with HCC regardless of the stage of disease, metastasis or recurrence were included.
- Patients with secondary liver cancers or those who had undergone liver transplantation were excluded

Intervention/ Komparator:

- sorafenib alone versus placebo or best supportive care (BSC) or
- Sorafenib in combination with a common treatment versus the same common treatment alone

Endpunkte:

- OS, TTP, disease control rate, objective response rate, AE

Recherche/Suchzeitraum:

- CENTRAL; EMBASE; MEDLINE; Institute for Scientific Information (ISI) Web of Science
- April 12, 2018

Qualitätsbewertung der Studien:

- Cochrane Collaboration’s tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 RCT

Charakteristika der Studien

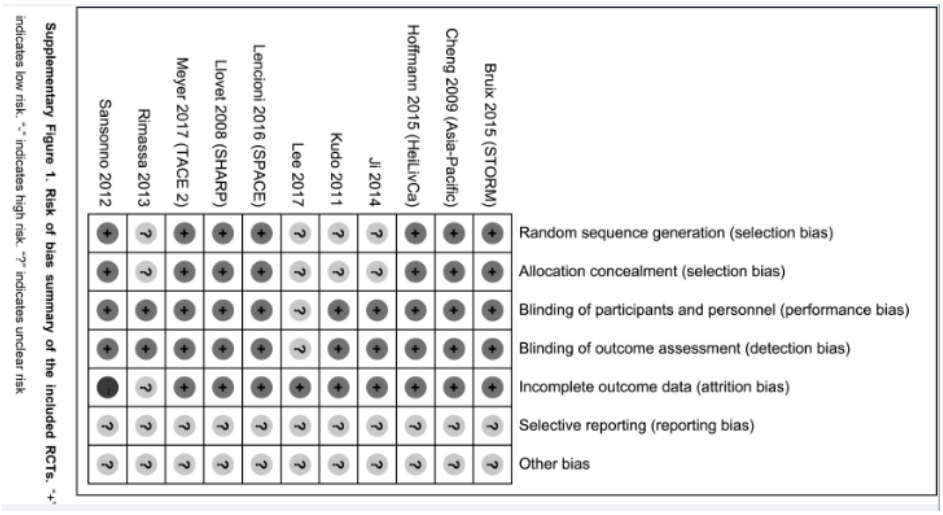
- 3 studies on Sorafenib Versus Placebo or BSC as first-line therapy for unresectable HCC
- 1 study on Sorafenib versus Placebo as second-line therapy

- 1 study on Sorafenib as an adjuvant therapy for BCLC stage A HCC after curative treatment in patients with an intermediate or high recurrence risk
- 6 studies on Sorafenib Plus TACE Versus Placebo Plus TACE

Trials	Design	Countries or Regions	Patient Status	Intervention vs. Control	Evaluation Criteria	Remarks
Cheng et al[30] (Asia-Pacific)	Phase III, randomized, controlled, double-blind, intention-to-treat	China, South Korea	BCLC stage B, C HCC Child-Pugh A ECOG PS = 0-2 No previous systemic therapy	Sorafenib (n = 150) vs. placebo (n = 76)	RECIST 1.0	Patients with PD after surgical or locoregional therapies were also eligible
Ji et al[32]	Randomized, controlled, open label, intention-to-treat	China	BCLC stage B, C HCC Child-Pugh B, C ECOG PS = 0-2 No previous systemic therapy	Sorafenib (n = 95) vs. Best supportive care (n = 94)	RECIST 1.1	Patients with PD after surgical or locoregional therapies were also eligible
Llovet et al[7] (SHARP)	Phase III, randomized, controlled, double-blind, intention-to-treat	Americas, Australasia, Europe	BCLC stage B, C HCC Child-Pugh A ECOG PS = 0-2 No previous systemic therapy	Sorafenib (n = 299) vs. placebo (n = 303)	RECIST 1.0	Patients with PD after surgical or locoregional therapies were also eligible
Rimassa et al[37]	Phase II, randomized, controlled, open label	Italy	BCLC stage C HCC with PD after sorafenib 400 mg po bid as a first-line therapy Child-Pugh A, B	Sorafenib (600 mg po bid) +best supportive care (n = 49) vs. best supportive care (n = 52)	RECIST 1.0	More patients with BCLC stage C and Child-Pugh class B were included in the control arm
Bruix et al[29] (STORM)	Phase III, randomized, controlled, double-blind, intention-to-treat	Americas, Asia-Pacific, Europe	BCLC stage A HCC with CR 6-12 wk after curative resection/ PEI/RFA with an intermediate or high recurrence risk Child-Pugh A, B ECOG PS = 0 No previous systemic therapy	Sorafenib (n = 556) vs. placebo (n = 558)	RECIST	Sorafenib was initiated 6-12 wk after curative treatments
Kudo et al[33]	Phase III, randomized, controlled, double-blind, intention-to-treat	Japan, South Korea	BCLC stage B HCC with PR or CR 1-3 mo after curative TACE Child-Pugh A ECOG PS = 0-1 No previous systemic or locoregional therapy	Sorafenib+TACE (n = 229) vs. placebo+TACE (n = 229)	Kanzo criteria	Sorafenib was initiated 1-3 mo after curative TACE PR was defined by the Kanzo criteria from Japan as ≥ 25% tumor necrosis and/or shrinkage
Sansonno et al[38]	Randomized, controlled, double-blind	Italy	BCLC stage B HCC with a CR 30 d after curative TACE Child-Pugh A ECOG PS = 0-1 No previous systemic therapy	Sorafenib+TACE (n = 31) vs. placebo+TACE (n = 31)	Not reported	Sorafenib was initiated 30 d after curative TACE
Hoffmann et al[31] (HeiLivCa)	Phase III, randomized, controlled, double-blind	Germany	HCC meeting the Milan Criteria before liver transplantation No previous systemic or locoregional therapy	Sorafenib+TACE (n = 24) vs. placebo+TACE (n = 26)	mRECIST	Sorafenib was discontinued 3 d before and continued 3 d after each TACE treatment TACE was performed every 4 wk
Lee et al[34]	Post hoc analysis, randomized, controlled	Taiwan	BCLC stage A, B HCC Child-Pugh A, B ECOG PS = 0-1 No previous locoregional therapy	Sorafenib+TACE (n = 36) vs. TACE (n = 36)	mRECIST	Sorafenib was initiated on day 4 and the first TACE was performed on day 1 TACE was repeated when HCC was viable every 4-8 wk
Lencioni et al[35] (SPACE)	Phase II, randomized, controlled, double-blind, intention-to-treat	Asia-Pacific, Europe, North America	BCLC stage B HCC Child-Pugh A ECOG PS = 0 No previous systemic, surgical or locoregional therapy	Sorafenib+DEB-TACE (n = 154) vs. placebo +DEB-TACE (n = 153)	mRECIST	Sorafenib was initiated on day 1 and the first TACE treatment was performed 3-7 d later Subsequent TACE treatments were performed on day 1 of cycles 3, 7, and 13 and every 6 cycles thereafter
Meyer et al[36] (TACE 2)	Phase III, randomized, controlled, double-blind, intention-to-treat	UK	BCLC stage B, C HCC Child-Pugh A ECOG PS = 0-1 No previous systemic or locoregional therapy	Sorafenib+DEB-TACE (n = 157) vs. placebo +DEB-TACE (n = 156)	RECIST 1.1, mRECIST	Sorafenib was initiated within 24 h of randomization and TACE was performed 2-5 wk after randomization TACE was repeated when HCC was viable at week 10, 22 and every 3 mo thereafter

BCLC indicates The Barcelona Clinic Liver Cancer; bid, twice daily; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HCC, Hepatocellular carcinoma; mRECIST, modified RECIST; PD, progressive disease; PEI, percutaneous ethanol injection; po, taken orally; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; RFA, radiofrequency ablation; TACE, transarterial chemoemboliztion.

Qualität der Studien:

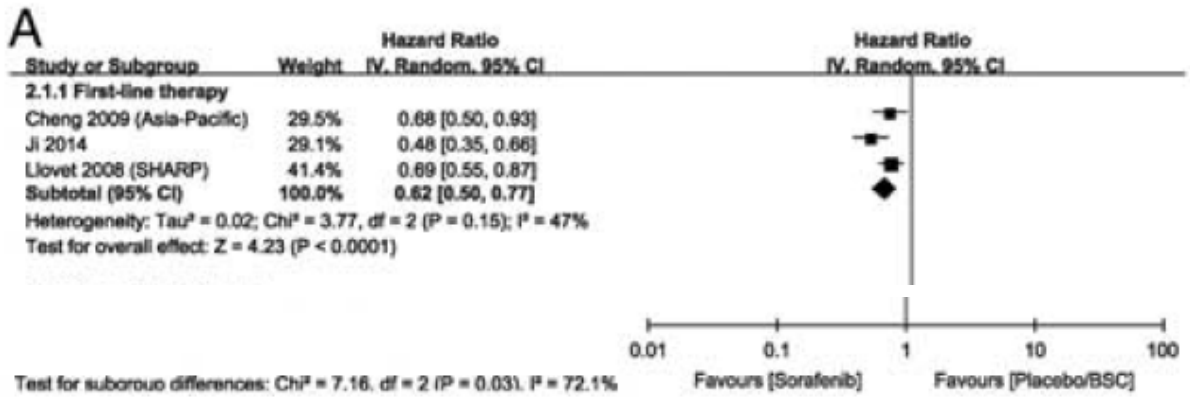


Studienergebnisse:

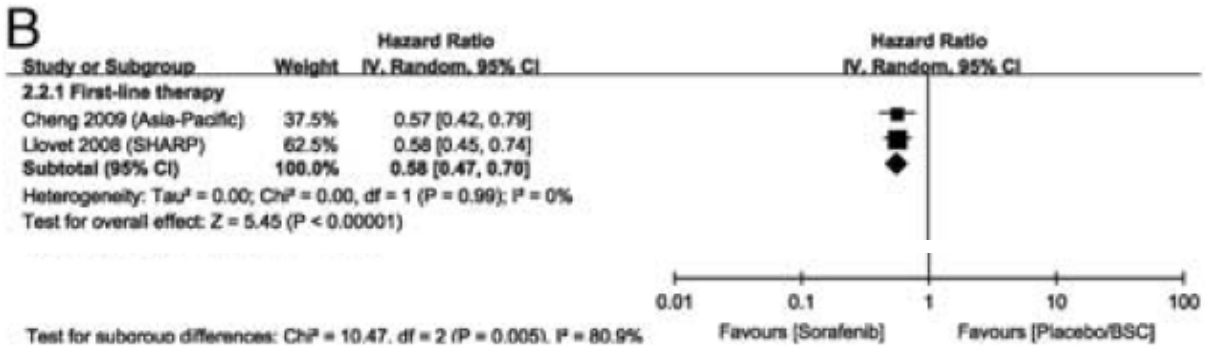
Darstellung beschränkt auf:

„Sorafenib Versus Placebo or BSC as first-line therapy for unresectable HCC“ (3 studies)

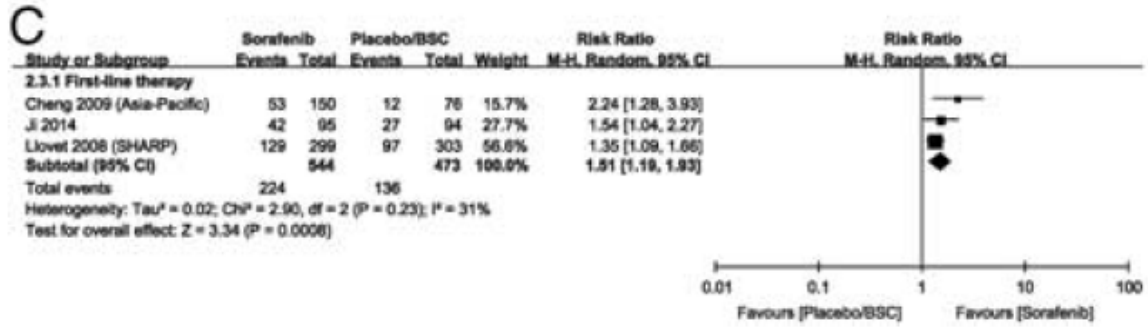
OS



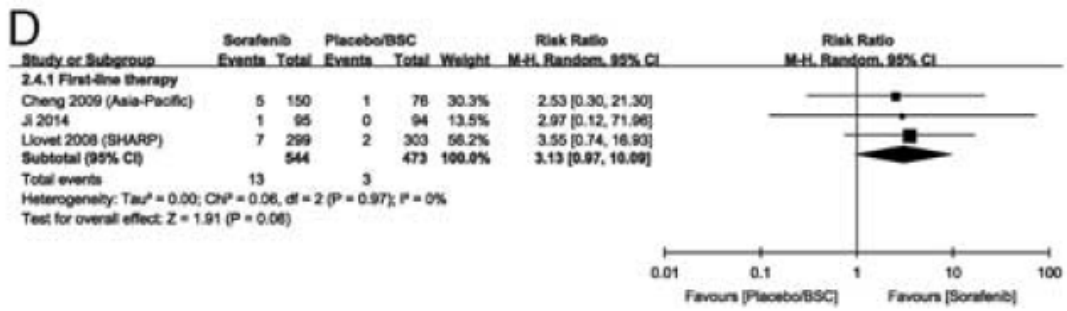
Time to progression



Disease control rate



Objective response rate



AE

(nur deskriptive Ergebnispräsentation)

TABLE 2. Overall Incidence of Adverse Events

	Sorafenib Supplementary to			
	Placebo/BSC (n = 1143, %)		TACE (n = 603, %)	
Adverse Events	All	Grades 3-5	All	Grades 3-5
Hand-foot skin reaction	50.4	17.6	54.4	18.7
Diarrhea	39.3	7.3	26.9	5.1
Alopecia	23.4	0.0	19.4	0.2
Rash/Desquamation	20.6	2.4	34.2	6.8
Fatigue	18.7	3.1	35.5	7.6
Hypertension	17.0	3.8	18.2	6.3
Nausea/vomiting	12.5	0.8	21.6	4.0
Weight loss	10.8	1.7	18.1	1.0
Abdominal pain	8.7	1.4	15.4	3.3
Anorexia	6.7	0.3	0.5	0.2
Pruritus	6.1	0.3	1.8	0.0
Voice change	5.2	0.1	7.8	0.5
Constipation	4.6	0.2	18.6	0.3
Thrombocytopaenia	4.6	1.4	14.8	5.0
Bleeding	2.4	0.3	15.6	11.4

BSC indicates best supportive care; TACE, transarterial chemoemboliztion.

Anmerkung/Fazit der Autoren

Sorafenib was effective as a first-line therapy for unresectable HCC, but it was ineffective as a second-line or adjuvant therapy. Sorafenib did not increase the efficacy of TACE.

3.4 Leitlinien

Alberta Health Service, 2020 [2].

Hepatocellular Carcinoma.

Zielsetzung/Fragestellung

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

- 2020-Update der LL von 2017 (GL was originally developed in August 2009 and revised in March 2010, June 2011, October 2013, March 2014, June 2015 and Dec 2017.)
- Repräsentatives Gremium: surgical oncologists, radiation oncologists, medical oncologists, dermatologists, nurses, pathologists and pharmacists; Patientenbeteiligung unklar
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Gemäß allg. Methodenhandbuch Formulierung von PICO-Fragestellungen, systematische Suche, Auswahl und Klassifikation der Evidenz und Erstellung von Evidenztabellen; syst. Bewertung der Studien: unklar; Evidenztabellen nicht verfügbar
- Gemäß allg. Methodenhandbuch sind je nach Evidenzlage und erwartetem Grad an Kontroversen formale oder informale Konsensusprozesse möglich; tatsächlich angewendete Verfahren nicht berichtet
- externes Begutachtungsverfahren: gemäß allg. Methodenhandbuch Feedback von Stakeholdern im Rahmen eines „provincial review“ eingeholt
- Empfehlungen der Leitlinie sind eindeutig
- Verbindung zw. Empfehlung und der zugrundeliegenden Evidenz sind dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

Guideline development 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 2020update did not necessitate a full literature review; recommendations were modified based on a consensus discussion at the 2019 Annual Gastrointestinal Tumour Team Meeting.

LoE

Level	Description of Evidence
I	• evidence from at least one large randomized controlled trial (RCT) of good methodological quality with low potential for bias • meta-analyses of RCTs without heterogeneity
II	• small RCTs • phase II RCTs • large RCTs with potential bias or meta-analyses including such trials RCTs with heterogeneity
III	• prospective cohort studies • post-hoc and ad-hoc analyses of RCTs
IV	• retrospective cohort studies • case-control studies • instrument validation studies (*note:* could be level III, based on size of population, methods)
V	• studies without a control group • case reports • expert opinions • review articles or narrative reviews • Delphi studies • cross-sectional studies (interviews, focus groups, surveys)

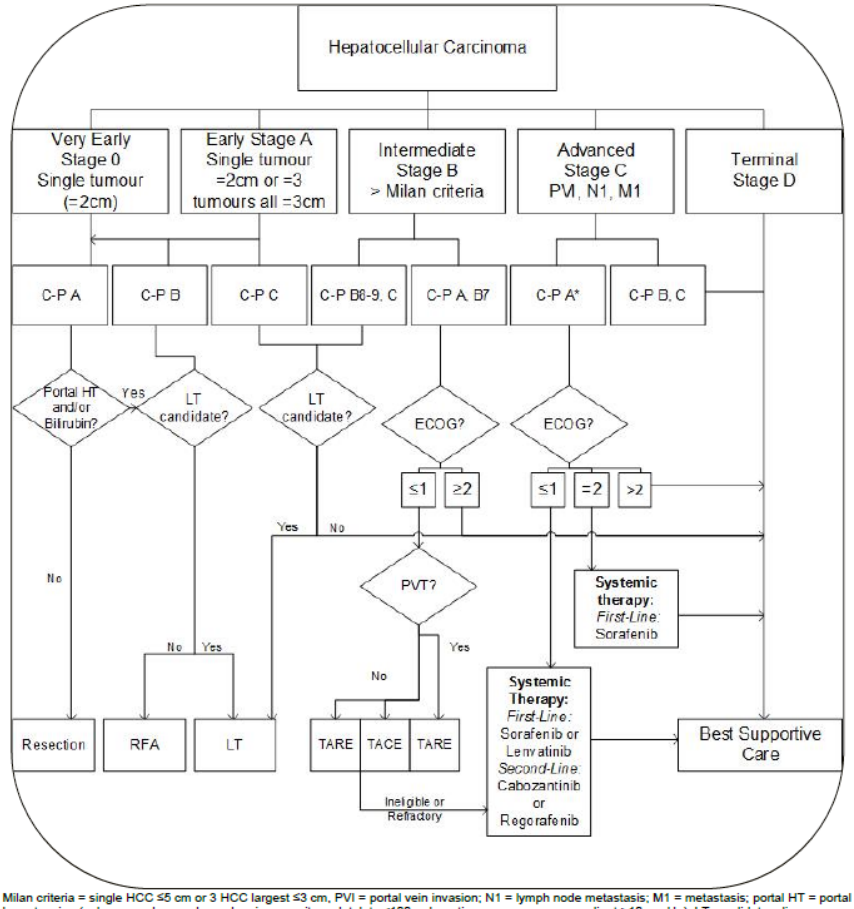
GoR: keine

Methodische Hinweise

Es wird auf methodische Limitationen der Leitlinie bzw. Mängel in der LL-Berichterstattung hingewiesen. Aufgrund fehlender hochwertiger Evidenz wird die Leitlinie ergänzend dargestellt.

Empfehlungen

Figure 1. Algorithm for the Management of HCC According to the Updated AHS Clinical Practice Guidelines (adapted from the Alberta[8] and Canadian[7] HCC algorithms).



Milan criteria = single HCC ≤5 cm or 3 HCC largest ≤3 cm, 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 >10 mmHg); LT candidate = liver transplant candidate = total tumour volume <115 mm^3 and alphafetoprotein <400 ng/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; TACE = transarterial chemoembolization; TARE = transarterial radioembolization with yttrium90 microspheres; SBRT =stereotactic body radiotherapy.

Informationen zur Erstlinientherapie:

Stage	Definitions, Goals, and Recommendations:
Advanced Stage HCC	*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, Lenvatinib, or participation in a clinical trial[36], if available. · Second-line treatment: Regorafenib (if previously tolerated Sorafenib), Cabozantinib, or participation in a clinical trial[36], if available.

First-Line Systemic Therapy:

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:

End-Point	SHARP Trial[37]		Asia-Pacific Trial[38]	
	Sorafenib	Placebo	Sorafenib	Placebo
Median Survival	10.7 months	7.9 months	6.5 months	4.2 months
	HR 0.69 ($CI_{95\%}$ 0.55-0.87) $p < 0.001$		HR 0.68 ($CI_{95\%}$ 0.50-0.93) $p < 0.014$	
Time to Progression (Radiologic)	5.5 months	2.8 months	2.8 months	1.4 months
	HR 0.58 ($CI_{95\%}$ 0.45-0.74) $p < 0.001$		HR 0.57 ($CI_{95\%}$ 0.42-0.79) $p = 0.0005$	

- 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[33,39].
- Increases the incidence of arterial thromboembolic events (1.4%, RR 3.03, $p = 0.015$)[34].

Lenvatinib 12 mg po daily (for bodyweight ≥60 kg) or 8 mg po daily (for bodyweight <60 kg):

- 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[40].
- 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%).
- Lenvatinib is not yet publicly funded for this use.

:

EASL, 2018 [1].

European Association for the Study of the Liver

EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma.

Zielsetzung/Fragestellung

These EASL CPGs define the use of surveillance, diagnosis and therapeutic strategies recommended for patients with HCC.

Methodik

Grundlage der Leitlinie

- LL-Gremiumzusammensetzung: experts in the field hepatology, surgery, radiology, oncology and pathology; Patientenbeteiligung unklar
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Definition von Schlüsselfragen; systematische Suche und Auswahl der Evidenz; Klassifizierung der Studien basierend auf Studiendesign ("The studies were assessed and assigned to categories related to study design and strength of evidence according to endpoints"); systematische Bewertung der Validität der Studien unklar
- Formaler Konsensusprozess: Nominaler Gruppenprozess
- externes Begutachtungsverfahren: "final version of these CPGs was subject to peer review"
- Empfehlungen der Leitlinie sind eindeutig
- Verbindung zwischen Empfehlung und der zugrundeliegenden Evidenz ist im Hintergrundtext dargestellt; LoE der einzelnen Studien nicht berichtet
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Keine Angaben

LoE

Table 1. Level of Evidence and Grade of Recommendations (adapted from GRADE system).

Level of evidence*		Confidence in the evidence
High	Data derived from meta-analyses or systematic reviews or from (multiple) randomized trials with high quality.	Further research is unlikely to change our confidence in the estimate of benefit and risk.
Moderate	Data derived from a single RCT or multiple non-randomized studies.	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate.
Low	Small studies, retrospective observational studies, registries.	Any estimate of effect is uncertain.

GoR

Recommendations[†]

Grade	Wording associated with the grade of recommendation
strong	"must", "should", or "EASL recommends"
weak	"can", "may", or "EASL suggests"

[*]Level was graded down if there is a poor quality, strong bias or inconsistency between studies; Level was graded up if there is a large effect size.
[†]Recommendations were reached by consensus of the panel and included the quality of evidence, presumed patient important outcomes and costs.

Sonstige methodische Hinweise

- Es wird auf methodische Limitationen der Leitlinie bzw. Mängel in der LL-Berichterstattung hingewiesen: keine konkreten Angaben zur Literaturrecherche, keine Angaben zur syst. Bewertung der Literatur; keine Angaben zur LoE der identifizierten Literatur. Aufgrund fehlender hochwertiger Evidenz wird die Leitlinie ergänzend dargestellt

Empfehlungen zur systemischen Therapie

Empfehlung 1

Sorafenib is the standard first-line systemic therapy for HCC. It is indicated for patients with well-preserved liver function (Child-Pugh A) and with advanced tumours (BCLC–C) or earlier stage tumours progressing upon or unsuitable for loco-regional therapies (evidence high; recommendation strong).

Empfehlung 2

Lenvatinib has been shown to be non-inferior to sorafenib and is also recommended in first-line therapy for HCC given its approval. It is indicated for patients with well-preserved liver function (Child-Pugh A class), good performance status and with advanced tumours – BCLC-C without main portal vein invasion – or those tumours progressing upon or unsuitable for loco-regional therapies (evidence high; recommendation

strong).

Empfehlung 3

There are no clinical or molecular biomarkers established to predict response to first or second-line systemic treatments (evidence moderate).

Empfehlung 4

Regorafenib is recommended as second-line treatment for patients tolerating and progressing on sorafenib and with well-preserved liver function (Child-Pugh A class) and good performance status (evidence high; recommendation strong). Recently, Cabozantinib has shown survival benefits vs. placebo in this setting.

Empfehlung 5

Based on uncontrolled but promising data, immune therapy with nivolumab has received FDA approval in second-line treatment, pending phase III data for conventional approval. At present, the data are not mature enough to give a clear recommendation (evidence moderate; recommendation weak).

Empfehlung 6

Treatments that failed to meet their endpoints in randomised trials are not recommended. Further clinical trials are needed to confirm claims of non-inferiority, or any trends of better outcome identified in subgroup analysis (evidence high). TARE in combination with systemic therapy is under investigation.

Empfehlung 7

Patients at BCLC D stage, who are not candidates for liver transplantation should receive palliative support, including management of pain, nutrition and psychological support. In general, they should not be considered for clinical trials (evidence low; recommendation strong).

Hintergrund zu Erstlinientherapie

First-line therapies

Sorafenib

Sorafenib, an oral multi-TKI, was the first drug to demonstrate a survival benefit in patients with advanced HCC. Following an initial phase II study showing a signal of efficacy,[576] a large double-blinded placebo-controlled phase III investigation was conducted, leading to positive survival results.[320] In this trial, the median overall survival (OS) of patients in the sorafenib group was 10.7 months compared to 7.9 months in the placebo group (HR, 0.69; 95% CI 0.55–0.87; $p = 0.00058$), representing a 31% decrease in the relative risk of death. The magnitude of survival benefit was similar to that demonstrated in a parallel phase III trial conducted in the Asian-Pacific population, in which hepatitis B was the main cause of HCC.[321] Sorafenib is well tolerated, the most common grade 3 drug-related adverse events observed are diarrhoea and hand-foot skin reaction, which occurred in 8–9%, and 8–16% of patients, respectively. Discontinuation due to adverse events was 15% in the sorafenib arm and 7% in the placebo. As a result, sorafenib received approval by regulatory agencies in 2007. Following the approval of sorafenib, several phase III trials compared sorafenib with investigational agents, resulting in a median OS of around 10 months (range between 6.5 and 11.8 months [Table 5]). In addition, several post-marketing studies produced real-life data and reported OS for Barcelona Clinic Liver Cancer (BCLC) B patients of 15.6–20.1 months and for BCLC-C of 8.4–13.6 months.[577–580]

The panel of experts recommends using sorafenib as the standard systemic therapy for HCC. It is indicated for patients with well-preserved liver function (Child-Pugh A class) and with advanced tumours, BCLC-C, or tumours progressing on loco-regional therapies (concept of treatment stage migration). No clear recommendation can be made in Child-Pugh B patients, although cohort studies have reported a similar safety profile in patients of this class with no decompensation,[581,582] however, the reported outcome for Child-Pugh B patients from the non-interventional GIDEON trial was poor.[583] Sorafenib treatment should be maintained at least until radiographic progression, and beyond that point second-line treatment with regorafenib is recommended.

Sorafenib has been tested in the adjuvant setting after resection or complete local ablation for early HCC stages and in combination with chemoembolisation for intermediate stages.[394,538,540] These trials did not support the use of sorafenib as an adjuvant agent nor in combination with TACE.

Lenvatinib

Lenvatinib is an oral multi-kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR1-3); fibroblast growth factor receptor (FGFR1-4); platelet-derived growth factor receptor α (PDFGRα), RET, and KIT.[584] Lenvatinib was investigated in an open-label, phase III, multicentre, non-inferiority trial involving patients (two-thirds from the Asia-Pacific region) with advanced HCC (excluding main portal vein invasion and >50% tumour to total liver volume occupancy), Child-Pugh A, performance status 0/1, randomised to lenvatinib (body weight ≥60 kg: 12 mg/day; <60 kg: 8 mg/day) *vs.* sorafenib (Table 5). The study met its primary endpoint of non-inferiority in OS (median OS: lenvatinib, 13.6 months *vs.* sorafenib, 12.3 months; hazard ratio [HR]: 0.92; 95% CI 0.79–1.06). Lenvatinib also improved progression-free survival (7.4 months *vs.* 3.7 months on sorafenib) and TTP (8.9 months *vs.* 3.7 months on sorafenib). In terms of response, the objective response rate defined by modified Response Evaluation Criteria In Solid Tumours (mRECIST) was significantly better for lenvatinib (24.1% *vs.* 9.2% sorafenib; p <0.001). Grade ≥3 TEAEs were more common with lenvatinib *vs.* sorafenib (57% *vs.* 49%, respectively). The most common grade 3/4 treatment-related AEs with lenvatinib and sorafenib, respectively, were hypertension (23% *vs.* 14%), decreased weight (8% *vs.* 3%), decreased platelet count (6% *vs.* 3%), elevated aspartate aminotransferase (5% *vs.* 8%), decreased appetite (5% *vs.* 1%), diarrhoea (4% *vs.* 4%), and palmar-plantar erythrodysesthesia (3% *vs.* 11%). Median time on lenvatinib and sorafenib was 5.7 months and 3.7 months, respectively. These results indicate that lenvatinib is an active drug that provides clinically significant benefits to patients with advanced HCC or those progressing to chemoembolisation.[323] The open-label design makes it difficult to interpret other differences related to patient reported outcomes. No cost-effectiveness studies comparing both drugs are available. In summary, the panel recommend its use in the indicated populations once the drug is approved by regulatory agencies.

Treatments with no benefit in first-line

Sunitinib is an oral multi-TKI approved for the treatment of renal cell carcinoma, gastrointestinal stromal tumours and pancreatic neuroendocrine tumours. A multicentre, open-label sorafenib-controlled randomised phase III trial was prematurely discontinued for safety issues and futility reasons.[568] This drug is presently not recommended for treatment of HCC.

Brivanib alaninate, an oral VEGFR and FGFR TKI, was evaluated in two phase II studies in first and second-line patients with advanced stage HCC. The median OS was 10 months in the first-line treated group and 9.8 months in the second-line treated group, with manageable adverse events.[585] Three phase III trials testing brivanib in first-line blinded to sorafenib,[566] in second-line blinded to placebo[572] and in combination with chemoembolisation[541] resulted in negative results for primary endpoints.

Linifanib, an oral TKI targeting VEGF and PDGF, and ramucirumab, a monoclonal antibody against VEGFR2[586] failed in phase III studies in first-line and second-line indications, respectively.[295,567] Other new anti-angiogenic agents, such as vatalanib, axitinib and cediranib are at very early stages of investigation. Other molecules such as c-MET inhibitors, MEK (MAP2K1) inhibitors, transforming growth factor-beta (TGFβ) and Janus kinase 2 (JAK2) inhibitors are being tested in early clinical investigations.[587]

Chemotherapy

The problem of using chemotherapy in HCC stems from the coexistence of two diseases. Cirrhosis can perturb the metabolism of chemotherapeutic drugs and enhance their toxicity. In addition, some chemotherapy-related complications, such as systemic infections, are particularly severe in immunocompromised patients, like cirrhotics. HCC has also been shown to be chemo-resistant to the most common chemotherapies, which as single agents have caused modest anti-tumoural responses.[310,588–590] Systemic doxorubicin has been evaluated in more than 1,000 patients in clinical trials with an objective response rate of around 10% and negative or inconclusive survival benefits. Furthermore, a recent phase III trial combining doxorubicin and sorafenib *vs.* sorafenib alone did not meet its primary endpoint. The addition of doxorubicin to sorafenib resulted in higher toxicity but did not improve OS[570] (Table 5).

Three other regimens have also shown negative results: PIAF regimen (Cisplatin/Interferon α2b/Doxorubicin/Fluorouracil-PIAF regimen), FOLFOX and hepatic intra-arterial chemotherapy (HIAC) with cisplatin and 5-FU. The phase III trial comparing PIAF *vs.* doxorubicin showed median survival of 8.67 months and 6.83 months, respectively, without differences between groups. PIAF was associated with a significantly higher rate of myelotoxicity compared with doxorubicin and treatment-related mortality of 9%.[590] A second randomised controlled trial (RCT) conducted in Asia compared the efficacy of the FOLFOX regimen combining 5-fluorouracil, folinic acid and oxaliplatin against doxorubicin alone. This study included 371 patients with Child-Pugh A/B advanced non-operable or metastatic HCC (BCLC-B/C). There was a non-significant trend favouring the FOLFOX group (median survival 6.4 months *vs.* 4.9 months; $p = 0.07$) associated with a better time to progression (2.9 months *vs.* 1.7 months).[571] Finally, HIAC with cisplatin and 5-FU combined with sorafenib did not meet the primary endpoint of better survival compared to sorafenib alone (Table 5) Chemotherapy for HCC in non-cirrhotic patients is an underexplored area.[591] Thus, considering the available evidence, systemic chemotherapy is not recommended for the treatment of HCC, nor as a control regimen for any trial because of its well-known toxic effects, although the panel acknowledges that inappropriate patient selection and trial design have contributed to the failure of appropriate drug development for chemotherapy. Chemotherapy for HCC in non-cirrhotic patients needs to be further investigated.[591]

Hormonal compounds

Hormonal compounds have not shown survival benefits in HCC. A meta-analysis of seven RCTs comparing tamoxifen *vs.* conservative management, comprising 898 patients, showed neither anti-tumoural effects nor survival benefits for tamoxifen.[310] Two large RCTs were reported afterwards assessing tamoxifen[592,593] with negative results in terms of survival. Thus, this treatment is discouraged in advanced HCC. Anti-androgen therapy is not recommended.[594]

Other treatments

A large RCT compared seocalcitol – a vitamin-D like anti-proliferative molecule – with placebo in 746 patients and showed no differences in OS (9.6 months seocalcitol *vs.* 9.2 months placebo).[311] Finally, negative results were also reported with a tubulin inhibitor (T-67) in a large multicentre RCT.[595]

Table 5. Phase III clinical trials testing molecular targeted therapies and devices in advanced HCC.

Trial	Drugs	n	Median OS (months)	Hazard Ratio (95% CI)	p-value
First-line					
SHARP[a]					
	Sorafenib	299	10.7	0.69	<0.001
	Placebo	303	7.9	(0.55–0.87)	
Asian-Pacific[a]					
	Sorafenib	150	6.5	0.68	0.01
	Placebo	76	4.2	(0.5–0.93)	
SUN1170[b]					
	Sunitinib	530	7.9	1.3	0.001
	Sorafenib	544	10.2	(1.13–1.5)	
BRISK-FL[b]					
	Brivanib	577	9.5	1.07	0.31
	Sorafenib	578	9.9	(0.94–1.23)	
LIGHT[b]					
	Linifanib	514	9.1	1.046	
	Sorafenib	521	9.8	(0.896–1.221)	
SEARCH[b]					
	Sorafenib + Erlotinib	362	9.5	0.92	0.2
	Sorafenib	358	8.5	(0.781–1.106)	
REFLECT/Study304[a]					
	Lenvatinib	478	13.6	0.92	
	Sorafenib	476	12.3	(0.79–1.06)	<0.05
ALLIANCE[b]					
	Sorafenib+ doxo	173	9.3	1.06	n.s.
	Sorafenib	173	10.5	(0.8–1.4)	
SILIUS[b]					
	Sorafenib+ HIAC	88	11.8	1	n.s.
	Sorafenib	102	11,8	(0.7–1.4)	
SARAH[b]					
	SIRT (Y-90)	Total 459	8	1.15	n.s.
	Sorafenib		9.9	(0.94–1.41)	
SIRveNIB[b]					
	SIRT (Y-90)	182	8.8	1.12	n.s.
	Sorafenib	178	10	(0.88–1.42)	

Heimbach JK et al., 2018 [6].

American Association for the Study of Liver Diseases

AASLD guidelines for the treatment of hepatocellular carcinoma

Zielsetzung

This document presents official recommendations of the American Association for the Study of Liver Diseases (AASLD) on the surveillance, diagnosis, and treatment of hepatocellular carcinoma (HCC) occurring in the setting of adults with cirrhosis.

Methodik

Grundlage der Leitlinie

The current guideline was developed in compliance with the Institute of Medicine standards for trustworthy practice guidelines and uses the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach

- Zusammensetzung der LL-Entwicklungsgruppe: Experts in the field of hepatology, surgery, oncology and diagnostics, Beteiligung von Patienten unklar
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;

- Systematische Reviews zu 10 Schlüsselfragen, Evidenzprofile für jede Schlüsselfrage einschließlich der Bewertung der quality of evidence mit dem GRADE approach dargelegt,
- Formale Konsensusprozesse: keine Angaben
- Begutachtungsverfahren: AASLD Practice Guidelines Committee provided the peer review.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt
- Regelmäßige Überprüfung der Aktualität: keine Angaben

Recherche/Suchzeitraum:

Für Key Question 10: Februar 2016 [4]

LoE/GoR

- GRADE approach zur Bewertung der quality of evidence (high, moderate, low oder very low)
- GoR : strong oder conditional

TABLE 1. The GRADE Approach

1. Rating the quality of evidence			
Study design	*Initial rating of quality of evidence*	*Rate down when:*	*Rate up when:*
RCT	High	Risk of bias	Large effect (e.g., RR = 0.5)
	Moderate	Inconsistency	Very large effect (e.g., RR = 0.2)
		Imprecision	Dose response gradient
Observational	Low	Indirectness	All plausible confounding would increase the association
	Very low	Publication bias	

2. Determinants of the strength of a recommendation
Quality of evidence
Balance of benefit and harms
Patient values and preferences
Resources and costs

3. Implication of the strength of a recommendation
Strong
Population: Most people in this situation would want the recommended course of action and only a small proportion would not.
Health care workers: Most people should receive the recommended course of action.
Policy makers: The recommendation can be adapted as policy in most situations.
Conditional
Population: The majority of people in this situation would want the recommended course of action, but many would not.
Health care workers: Be prepared to help patients make a decision that is consistent with their values using decision aids and shared decision making.
Policy makers: There is a need for substantial debate and involvement of stakeholders.

For patients, a strong recommendation implies that most patients in this situation would want the recommended course of action and only a small proportion would not. For clinicians, this would imply that patients should receive the recommended course of action, with consistent benefits and few side effects. For policy makers, the recommendation could be adopted as a policy in most situations and potentially could be used as a quality measure. For strong recommendations, the recommendation is prefaced by "The AASLD recommends..." In contrast, a conditional recommendation (also sometimes termed a "weak" recommendation) for patients would imply that the majority of patients in this situation would want the recommended course of action, but many would not. For clinicians making a conditional recommendation, the balance of benefits, harms, and burdens is uncertain; and they should be prepared to help patients make a decision that is consistent with their own values using a shared decision-making approach. For policy makers, this recommendation type could imply a need for substantial debate and involvement of all stakeholders and is likely insufficient to be used as a quality measure. For conditional recommendations, the recommendation is prefaced by "The AASLD suggests..."

Sonstige methodische Hinweise

Systematischer Review zur Key Question 10 separat publiziert: Finn et al. 2018 [4]

Empfehlungen

10. SHOULD ADULTS WITH CHILD-PUGH CLASS A/B CIRRHOSIS AND ADVANCED HCC WITH MACROVASCULAR INVASION AND/OR METASTATIC DISEASE BE TREATED WITH SYSTEMIC THERAPY OR LRT OR NO THERAPY?

The AASLD recommends the use of systemic therapy over no therapy for patients with Child-Pugh class A cirrhosis or well-selected patients with Child-Pugh class B cirrhosis plus advanced HCC with macrovascular invasion and/or metastatic disease.

Quality/Certainty of Evidence: Moderate; Strength of Recommendation: Strong

Technical Remarks

1. It was not possible to make a recommendation for systemic therapy over LRT, because there was inadequate evidence to inform the balance of benefit versus harm.
2. Advanced HCC is a heterogeneous group. The selection of treatment type may vary depending on the extent of macrovascular invasion and/or metastatic disease, the degree of underlying cirrhosis, and patient's performance status, and when patients have very poor performance status and/or advanced cirrhosis, no therapy may be the best option.
3. It is not possible to identify a preferred type of LRT based on the available evidence.
4. Most patients involved in the studies had Child-Pugh class A cirrhosis, although studies were mixed and included some patients with Child-Pugh class B cirrhosis.

BACKGROUND

Patients with advanced HCC (macrovascular invasion and/or metastatic disease) represent a unique clinical challenge. The prognosis and treatment decision is generally dependent on the extent of the vascular invasion and/or metastatic disease, the severity of underlying cirrhosis, and the performance status of the patient. Even for patients with metastatic disease, particularly those with limited extrahepatic tumor burden, the presence of concurrent macrovascular invasion often leads to rapid tumor progression with disease-related symptoms. Therefore, many patients with limited extrahepatic metastatic disease burden and concurrent macrovascular vascular invasion have been treated with LRT. While various LRTs are provided in this setting, the evidence supporting the routine use of many of these approaches has not been established, and thus far, regardless of the treatment strategy used, the prognosis remains poor.

The intent of this question was to review the existing evidence to determine the optimal treatment recommendation for those patients with advanced HCC (macrovascular invasion and/or metastatic disease) in the setting of underlying Child-Pugh class A/B cirrhosis.

EVIDENCE AND RATIONALE

The evidence of a *de novo* systematic review including all studies that enrolled adults with advanced HCC is summarized in Supporting Table 7. Of the 15 studies identified, four were RCTs, and the other 11 were observational studies. The four RCTs were not designed to compare the outcome of sorafenib with LRT in advanced HCC. There were no comparative trials and only a few noncomparative studies that addressed the question of whether patients should be treated with either sorafenib or LRT. The only level-one evidence that exists in patients with advanced HCC (macrovascular invasion and/or metastatic disease) is a randomized phase 3 trial with sorafenib in comparison with placebo. In the pivotal SHARP trial, of the total 602 patients enrolled, 231 patients had macrovascular invasion and 309 patients had extrahepatic metastasis. In the sorafenib arm, there were 108 patients (35%) with macrovascular invasion versus the placebo arm, which had 123 patients (41%) with macrovascular invasion. Additionally, in the sorafenib arm, 159 patients (53%) had extrahepatic disease versus the placebo arm, which had 150 patients (50%) with extrahepatic disease. Of note, the extent of macrovascular invasion was not detailed, and the extent of metastatic disease was only provided for lungs and lymph nodes. Sorafenib significantly improved the median OS in the entire population included in the study (sorafenib, 10.7 months versus placebo, 7.9 months; HR, 0.69; 95% CI, 0.55-0.87) and demonstrated a trend for improvement both for patients with macrovascular invasion (sorafenib, 8.1 months versus placebo, 4.9 months; HR, 0.68; 95% CI, 0.49-0.93) and for patients with metastatic disease (sorafenib, 8.9 months versus placebo, 8.3 months; HR, 0.85; 95% CI, 0.64-1.15).[52,91]

Similarly, in the Asia-Pacific phase 3 trial, of the 226 patients randomized, 80 (35%) patients had macrovascular invasion and 155 (69%) patients had extrahepatic disease. Sorafenib significantly improved the median OS in comparison with placebo in the whole study population (sorafenib, 6.5 months versus placebo, 4.2 months; HR, 0.68; 95% CI, 0.50-0.93) and demonstrated a positive trend in both patients with macrovascular invasion (HR, 0.63; 95% CI, 0.39-1.03) and with metastatic disease to either lungs or lymph nodes (HR, 0.82; 95% CI, 0.57-1.18).[92,93]

The definitive benefits of sorafenib in advanced HCC with underlying Child-Pugh class B cirrhosis has not been clearly established, though an ongoing randomized phase 3 trial conducted in Italy is evaluating sorafenib versus placebo in patients with advanced HCC and underlying Child-Pugh B cirrhosis (NCT01405573). There have been four published phase 3 randomized trials comparing sorafenib versus either other targeted agents (sunitinib, brivanib, linifanib) or the combination of sorafenib with erlotinib.[92,94,95] Collectively, there were an additional 2001 patients enrolled in the sorafenib arm, with 688 patients with macrovascular invasion and 1220 patients with metastatic disease, reinforcing the benefits of sorafenib in advanced HCC. No RCTs have been published to critically assess the relative benefits of sorafenib versus LRT in advanced HCC with either macrovascular invasion or metastatic disease.

Specific to patients with macrovascular disease, one single-center retrospective observational study (N = 557) has attempted to compare the relative benefits of TACE alone (n = 295) or TACE with radiation (n = 196) with sorafenib (n = 66) in patients with advanced HCC with portal vein thrombosis (PVT).[96] The TACE/radiation group had longer median time to progression and OS than the chemoembolization alone and sorafenib groups ($P < 0.001$). In an observational retrospective study, Nakazawa et al.[97] compared the survival benefits of sorafenib versus radiation in patients with advanced HCC with PVT in the main trunk or its first branch. Of the 97 patients included, 40 received sorafenib and 57 received radiation. Median survival did not differ significantly between the sorafenib group (4.3 months) and the radiation group (5.9 months; $P = 0.115$). In another retrospective observational study, Song et al.[98] compared the efficacy of hepatic arterial infusion chemotherapy (HAIC)—which involves an actual infusion catheter directly in the hepatic artery as opposed to embolized particles mixed with chemotherapy released in the artery—with sorafenib in advanced HCC with PVT. The median OS was significantly longer in the HAIC group than in the sorafenib group (7.1 versus 5.5 months; $P = 0.011$).

Evidence profile for Q10: Should adults with Child–Pugh A/B cirrhosis and advanced HCC with macrovascular invasion and/or metastatic disease be treated with systemic or locoregional therapy (LRT) or no therapy?

Intervention vs comparison	Design	Studies (n)	Child–Pugh	Outcome	Patients (n)	ES (95% CI)	GRADE
Macrovascular invasion:							
Sorafenib vs placebo	RCTs	2	Class A (96.6%) Class B (0.4%)	Overall Survival	311	HR 0.66 (0.51-0.87), $I^2 = 0\%$	⊕⊕⊕◯ MODERATE†
**Sorafenib-cryoRx vs sorafenib	RCT	1	Class A (80.9%)	1-year survival rate	104	RR 1.7 (0.99-2.78)	⊕⊕⊕◯ MODERATE†

			Class B (0.19%)				
**Percutaneous RFA vs control	Observational study	1	Class A (78.9%) Class B (21.1%)	Mortality	57	RR 0.81 (0.67-0.97)	⊕◯◯◯ VERY LOW *†
**TACE vs Y 90	Observational study	1	NR	Median Survival	323	OR 2.1 (1.04-4.2)	⊕◯◯◯ VERY LOW *†
**131 I-lipiodol vs TACE/TAE	Observational study	1	Class A (59.7%) Class B (33.9%) Class C (6.4%)	1-year survival rate	20	RR 2.6 (0.39-16.9)	⊕◯◯◯ VERY LOW *†
Cytotoxic chemotherapy vs sorafenib	Observational study	1	Class A (76.1%) Class B (23.9%)	Overall Survival	49	HR 0.5 (0.1-1.7)	⊕◯◯◯ VERY LOW *†
**Transhepatic arterial chemotherapy vs control	Observational study	1	Intervention (7.0 ± 2.10) Control (8.5 ± 2.20)	6-month survival rate	23	RR 11.5 (0.69 – 190.8)	⊕◯◯◯ VERY LOW *†
**Chemoembolization with or without RT vs sorafenib	Observational study	1	Class A (64.4%) Class B (35.6%)	Overall survival	262	HR 0.28 (0.20-0.40)	⊕◯◯◯ VERY LOW *†
**Chemoembolization with or without RT vs sorafenib	Observational study	1	Class A (100%)	Overall survival	413	HR 0.34 (0.24-0.48)	⊕◯◯◯ VERY LOW *†
**Chemoembolization with or without RT vs sorafenib	Observational study	1	Class B (100%)	Overall survival	144	HR 0.26 (0.16-0.43)	⊕◯◯◯ VERY LOW *†
**Chemoembolization vs sorafenib	Observational study	1	Class A (79.8%) Class B (20.2%)	Overall survival	361	HR 0.67(0.47–0.95)	⊕◯◯◯ VERY LOW *†
**Chemoembolization and RT vs chemoembolization	Observational study	1	Class A (75.4%) Class B (24.6%)	Overall survival	491	HR 0.56 (0.45–0.71)	⊕◯◯◯ VERY LOW *†
**TACE + portal vein embolization vs TACE	Observational study	1	Class A (50%) Class B (50%)	1-year survival	116	RR 1.3 (1.05-1.7)	⊕◯◯◯ VERY LOW *†
				3-year survival rate	116	RR 1.5 (0.84-2.54)	⊕◯◯◯ VERY LOW *†
				5-year survival rate	116	RR 15.9 (0.92-276.6)	⊕◯◯◯ VERY LOW *†
**HAIC + sorafenib vs HAIC	Observational study	1	Class A (43.6%) Class B (56.4%)	1-year survival	38	RR 1.33 (0.5-3.6)	⊕◯◯◯ VERY LOW *†
				3-year survival rate	38	RR 3.3 (0.38-29.25)	⊕◯◯◯ VERY LOW *†
**HAIC + sorafenib vs HAIC	Observational study	1	Class A (100%)	1-year survival	17	RR 1.1 (0.28-4.32)	⊕◯◯◯ VERY LOW *†
				3-year survival rate	17	RR 2.92 (0.16-52.47)	⊕◯◯◯ VERY LOW *†
**HAIC + sorafenib vs HAIC	Observational study	1	Class B (100%)	1-year survival	21	RR 1.33 (0.29-6.23)	⊕◯◯◯ VERY LOW *†

				3-year survival rate	21	RR 2 (0.15-27.45)	⊕◯◯◯ VERY LOW *†
**Sorafenib vs sorafenib-TACE	Observational study	1	Class 5(49.4%), 6 (26.9%)and 7 (23.6%)	Overall survival	89	HR 1.17 (0.52 - 1.8)	⊕◯◯◯ VERY LOW *†
**RT vs sorafenib	Observational study	1	Class A (100%)	1-year survival	56	RR 1.3 (0.67-2.7)	⊕◯◯◯ VERY LOW *†
**HAIC vs sorafenib	Observational study	1	Class A (83.6%) Class B (16.4%)	Mortality	110	RR 0.94 (0.79-1.21)	⊕◯◯◯ VERY LOW *†
Metastatic disease:							
Sorafenib vs placebo	RCTs	2	Class A (96.6%) Class B (0.4%)	Overall Survival	311	HR 0.84 (0.67-1.1), I^2 = 0%	⊕⊕⊕◯ MODERATE†
Cytotoxic chemotherapy vs sorafenib	Observational study	1	Class A (76.1%) Class B (23.9%)	Overall Survival	66	HR 0.7 (0.2-1.9)	⊕◯◯◯ VERY LOW *†
Chemoembolization with or without RT vs sorafenib	Observational study	1	Class A (64.4%) Class B (35.6%)	Overall Survival	101	HR 0.66 (0.43-1.02)	⊕◯◯◯ VERY LOW *†

*Serious risk of bias. †Imprecision

** Studies included only portal vein tumor thrombosis

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 5 of 12, May 2020) am 29.05.2020

#	Suchfrage
1	[mh "Liver Neoplasms"]
2	(hepatocarcinoma* OR hepatoma* OR HCC):ti
3	(Liver OR hepatic OR hepatocellular OR hepatobiliary):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 Between May 2015 and May 2020

Systematic Reviews in Medline (PubMed) am 29.05.2020

#	Suchfrage
1	"carcinoma, hepatocellular/therapy"[MeSH Major Topic]
2	liver neoplasms/therapy[mh:noexp] OR liver neoplasms/surgery[mh:noexp] OR liver neoplasms/drug therapy[mh:noexp] OR liver neoplasms/radiotherapy[mh:noexp]
3	hepatocarcinoma*[Title] OR hepatoma*[Title] OR HCC[Title]
4	liver[Title] OR hepatic[Title] OR hepatocellular[Title] OR hepatobiliary[Title]
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 lesion*[ti]) OR malignan*[ti]
6	#4 AND #5
7	#3 OR #6
8	(#7) 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]))
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 study[pt] OR validation study[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

#	Suchfrage
	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 ("2015/05/01"[PDAT] : "3000"[PDAT])
12	(#11) NOT ("The Cochrane database of systematic reviews"[Journal])
13	(#12) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 29.05.2020

#	Suchfrage
1	liver neoplasms[mh:noexp] OR carcinoma, hepatocellular[Mesh Major Topic]
2	hepatocarcinoma*[Title] OR hepatoma*[Title] OR HCC[Title]
3	liver[Title] OR hepatic[Title] OR hepatocellular[Title] OR hepatobiliary[Title]
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 ("2015/05/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])

Referenzen

1. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69(1):182-236.

2. **Alberta Health Services (AHS).** Hepatocellular carcinoma [online]. Edmonton (CAN): AHS; 2020. [Zugriff: 11.06.2020]. (Clinical Practice guideline; Band GI-007 - Version 8). URL: https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-gi007-hepatocellular-carcinoma.pdf.

3. **Canadian Agency for Drugs and Technologies in Health (CADTH).** Lenvatinib (Lenvima) for hepatocellular carcinoma [online]. Ottawa (CAN): CADTH; 2019. [Zugriff: 29.05.2020]. (Pan-Canadian Oncology Drug Review). URL: https://www.cadth.ca/sites/default/files/pcodr/Reviews2019/10175LenvatinibHCC_inCGR_NOREDACT_Post_05Jul2019_final.pdf.

4. **Finn RS, Zhu AX, Farah W, Almasri J, Zaiem F, Prokop LJ, et al.** Therapies for advanced stage hepatocellular carcinoma with macrovascular invasion or metastatic disease: a systematic review and meta-analysis. Hepatology 2018;67(1):422-435.

5. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 22. März 2019 - Lenvatinib (neues Anwendungsgebiet: hepatozelluläres Karzinom) [online]. Berlin (GER): G-BA; 2019. [Zugriff: 29.05.2020]. URL: https://www.g-ba.de/downloads/91-1385-395/2019-03-22_Geltende-Fassung_Lenvatinib-nAWG.pdf.

6. **Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al.** AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67(1):358-380.

7. **Huang Y, Cheng X, Sun P, Li T, Song Z, Zheng Q.** Supplementary Sorafenib therapies for hepatocellular carcinoma - a systematic review and meta-analysis: supplementary Sorafenib for liver cancer. J Clin Gastroenterol 2019;53(7):486-494.

Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Kontaktdaten

Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)

Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS)

Indikation gemäß Beratungsantrag

„zur Erstlinienbehandlung des fortgeschrittenen Leberzellkarzinoms bei Erwachsenen“

Was ist der Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz in der “ Erstlinienbehandlung des fortgeschrittenen Leberzellkarzinoms bei Erwachsenen**“? Wie sieht die Versorgungspraxis in Deutschland aus?**

Zusammenfassung

Das fortgeschrittene, nicht resektable Leberzellkarzinom gehört zu den malignen Erkrankungen mit der schlechtesten Prognose. Hier besteht ein großer, ungedeckter medizinischer Bedarf an neuen, wirksamen Therapiestrategien.

Entscheidend für die Therapie ist das Stadium der Erkrankung. Bei Patienten mit fortgeschrittenem, nicht resektablem Karzinom und fehlender Option einer Lebertransplantation ist die systemische Therapie mit einem Multikinase-Inhibitor indiziert. Die Therapie ist palliativ. Standard in der Erstlinientherapie sind Lenvatinib oder Sorafenib.

Behandlungsstandard als Basis der vergleichenden Bewertung eines neuen Arzneimittels in der Erstlinientherapie von Patienten mit fortgeschrittenem Leberzellkarzinom sind die Multikinase-Inhibitoren Lenvatinib oder Sorafenib.

Fragestellung

Gefragt wird nach dem Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz in der Erstlinienbehandlung des fortgeschrittenen Leberzellkarzinoms bei Erwachsenen.

Eine weitere Präzisierung der Fragestellung durch den pharmazeutischen Unternehmer liegt nicht vor. Insbesondere fehlt eine Differenzierung nach dem Stadium der Erkrankung und der Leberfunktion.

Kontaktdaten

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Stand des Wissens

Das Leberzellkarzinom gehört in Deutschland zu den selteneren, malignen Erkrankungen. Für das Jahr 2016 wurden 9.500 neue Patienten mit primärem Leberkrebs erwartet. Hepatozelluläre Karzinome (HCC) machen etwa zwei Drittel der Fälle mit „Leberkrebs“ aus [1]. Das mittlere Erkrankungsalter für Leberkrebs liegt für Frauen bei 74, für Männer bei 71 Jahren. Die Prognose des HCC ist schlecht, die 5-Jahres-Überlebensraten liegen unter 20% [1, 2]

Größter Risikofaktor ist die Leberzirrhose, entweder auf dem Boden einer chronischen Hepatitis C oder einer Alkoholkrankheit. Weitere Risikofaktoren sind eine chronische Hepatitis-B-Virusinfektion oder eine nicht-alkoholische Fettleberhepatitis [3]. Aufgrund der hohen Relevanz dieser Vorerkrankung ist neben dem Tumorstaging vor allem auch die Leberfunktion von großer Bedeutung für die Prognose des HCC. Die S3 Leitlinie formuliert: „Die pTNM-Klassifikation soll als morphologisches Staging eingesetzt werden. Um die Prognose eines HCCs beurteilen zu können, sollte das Staging-System zusätzlich das Tumorstadium, die Leberfunktion und den körperlichen Leistungszustand des Patienten sowie den Effekt der Therapie auf die Lebenserwartung berücksichtigen. Die Barcelona-Clinic Liver Cancer (BCLC)-Klassifikation sollte daher als integriertes Staging in der Therapiestratifikation des HCCs eingesetzt werden“ [3].

a-Fetoprotein (AFP) ist ein Tumormarker bei Patienten mit hepatozellulärem Karzinom und als Verlaufsparameter geeignet. Ein hoher Wert ist mit vermehrter Angiogenese und ungünstiger Prognose assoziiert. Die Höhe des AFP-Wertes ist prädiktiv für den Einsatz von Ramucirumab in der Zweitlinientherapie.

Die systemische Therapie des fortgeschrittenen HCC hat sich 2007 durch die Einführung von Sorafenib grundlegend gewandelt. Bisher eingesetzte Formen der zytostatischen Therapie waren wenig wirksam. Sorafenib führte im Vergleich zu Placebo zu einer Verlängerung der Überlebenszeit und zu einer höheren Rate von Langzeitüberlebenden, war aber auch mit einer hohen Nebenwirkungsrate belastet [4]. 2018 wurde für Lenvatinib eine Nicht-Unterlegenheit gegenüber Sorafenib bezüglich der Überlebenszeit bei höherer Remissionsrate, längerem progressionsfreiem Überleben und unterschiedlichem Nebenwirkungsspektrum gezeigt [6].

Tabelle 1: Systemische Erstlinientherapie beim fortgeschrittenen HCC

	Patienten-	**Kontrolle**	**Neue**	**N[1]**	**RR[2]**	**PFÜ[3]**	**ÜLZ[5]**

Kontaktdaten

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Erstautor / Jahr	gruppe		Therapie			(HR[4])	(HR[4])
Llovet, 2008 [4]	**Erstlinie Child-Pugh A**	**Placebo**	**Sorafenib**	**602**	**1 vs 2**	**2,8 vs 5,5** **0,58** **p < 0,001**	**7,9 vs 10,7** **0,69** **p < 0,001**
Cheng, 2013 [5]	**Child-Pugh A**	**Sorafenib**	**Sunitinib**	**1074**		**3,0 vs 3,6** **1,13** **n. s.**	**10,2 vs 7,9** **1,30** **p = 0,0014**
Kudo, 2018 [6]	**Erstlinie Child-Pugh A und B**	**Sorafenib**	**Lenvatinib**	**954**	**6,5 vs 18,8** **p < 0,001**	**3,6 vs 7,3** **0,64** **p < 0,0001**	**12,3 vs 13,6** **0,92** **n. s.**

[1] N - Anzahl Patienten; [2] RR - Remissionsrate in % nach mRECIST-Kriterien; [3] PFÜ - progressionsfreie Überlebenszeit, in Monaten; [4] HR - Hazard Ratio; [5] ÜLZ - Gesamtüberlebenszeit, in Monaten; [6] ÜLR – Überlebensrate nach 12 Monaten, in %; [7] **Ergebnis für Kontrolle, Ergebnis für Neue Therapie**;

Zahlreiche weitere Ansätze zeigten keine Verbesserung der Prognose gegenüber Sorafenib.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung des „fortgeschrittenen Leberzellkarzinoms in der Erstlinie bei Erwachsenen**“ die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

Ja, entscheidend sind das Stadium der Erkrankung und die Funktion der Leber.

In begrenzten Stadien sind Operation oder Lebertransplantation die Therapie der Wahl mit kurativem Anspruch. Bei nicht resektablen Karzinomen wird die Leberzirrhose nach Child-Pugh klassifiziert. In den Zulassungsstudien zu Sorafenib und zu Lenvatinib wurde fast ausschließlich bei Patienten im Stadium Child-Pugh A eingeschlossen. Die Zulassungen der beiden Multikinase-Inhibitoren enthalten keine Beschränkungen.

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Indikation gemäß Beratungsantrag

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Literatur

1. Gesellschaft der epidemiologischen Krebsregister in Deutschland / Robert - Koch Institut: Krebs in Deutschland 2015/2016. http://www.gekid.de/Atlas/CurrentVersion/atlas.html
2. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2018. CA Cancer J Clin 68:7-30, 2018. DOI: 10.3322/caac.21442
3. AWMF S3 Leitlinie H Diagnostik und Therapie des hepatozellulären Karzinoms, Mai 2013. https://www.awmf.org/uploads/tx_szleitlinien/032-053OLl
4. Llovet JM, Ricci S, Mazzaferro V et al.: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359:378–390, 2008. DOI: 10.1056/NEJMoa0708857
5. Cheng AL, Kang YK, Lin DY et al.: Sunitinib versus sorafenib in advanced hepatocellular cancer: Results of a randomized phase III trial. J Clin Oncol 31:4067–4075, 2013. DOI: 10.1200/JCO.2012.45.8372
6. Kudo M, Finn RS, Qin S et al.: A Randomised Phase 3 trial of lenvatinib vs. sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma. Lancet. 2018;391:1163–1173. DOI: 10.1016/S0140-6736(18)30207-1
7. Kudo M: Systemic therapy for hepatocellular carcinoma: Latest advances. Cancers 10:412, 2018. DOI: 10.3390/cancers10110412

Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Kontaktdaten

Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de); Stand: 22.06.2020

Indikation gemäß Beratungsantrag:

„zur Erstlinienbehandlung des fortgeschrittenen Leberzellkarzinoms bei Erwachsenen“

Was ist der Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz in der “ Erstlinienbehandlung des fortgeschrittenen Leberzellkarzinoms bei Erwachsenen**“? Wie sieht die Versorgungspraxis in Deutschland aus?**

Gemäß aktuellen Leitlinien wird die Barcelona Clinic Liver Cancer (BCLC)-Klassifikation für die Stadienbestimmung und Therapiestratifizierung des hepatozellulären Karzinoms (HCC) benutzt (1;2). Ergänzend ist bei Therapieentscheidungen der funktionelle Status des Patienten zu berücksichtigen, der nach ECOG eingeteilt wird (3).

In den frühen Stadien BCLC 0, A und B wird in kurativer Absicht eine Resektion oder Lebertransplantation durchgeführt, oder es kommen lokoregionale Therapieverfahren wie transarterielle Chemoembolisation zur Anwendung, die nur bei einem kleinen Teil der Patienten kurativ sind. Gemäß Leitlinien ist im fortgeschrittenen Stadium BCLC C eine systemische Therapie mit palliativer Zielsetzung indiziert. Diese kann auch bei Patienten mit früheren Tumorstadien erfolgen, wenn für das Stadium indizierte Verfahren nicht zur Anwendung kommen können (1). Eine tumorspezifische Therapie, ist bei weit fortgeschrittener Erkrankung und erheblich eingeschränkter Leberfunktion im Stadium BCLC D nicht mehr indiziert. Bei diesen Patienten beträgt die durchschnittliche Lebenserwartung drei Monate (4).

In der Erstlinientherapie des fortgeschrittenen HCC bei Patienten mit erhaltener Leberfunktion (Child-Pugh Stadium A) und gutem Performance Status (ECOG 0–2) sollten Sorafenib oder Lenvatinib eingesetzt werden.

Aktuell publizierte Daten einer offenen Phase-III-Studie zur Behandlung des fortgeschrittenen HCC mit Atezolizumab plus Bevacizumab 2:1 randomisiert zu Sorafenib, zeigen ein signifikant besseres progressionsfreies Überleben (PFS) und besseres Gesamtüberleben (OS) für Atezolizumab plus Bevacizumab (HR 0,58; 95 % Konfidenzintervall (CI) 0,42–0,79; $p < 0,001$), so dass bei Zulassung dieser Therapie zur Behandlung des fortgeschrittenen HCC diese zu bewerten und zu berücksichtigen wären (5).

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung des „fortgeschrittenen Leberzellkarzinoms in der Erstlinie bei Erwachsenen**“ die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

Kriterien, die bei Behandlungsentscheidungen bei fortgeschrittenem Leberzellkarzinom in der Erstlinie regelhaft berücksichtigt werden, sind:

1. **Die Leberfunktion:**

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Für Patienten mit eingeschränkter Leberfunktion (Leberzirrhose im Child-Pugh Stadium B und C) ist ein Zusatznutzen für systemische Therapie im Vergleich zu Best Supportive Care (BSC) nicht belegt. Diese Patienten sollten keine tumorspezifische medikamentöse Behandlung erhalten.

2. Performance Status von Patient*in:

Für Patienten mit eingeschränktem Performance Status ECOG > 2 ist ein Zusatznutzen durch systemische Therapie im Vergleich zu BSC nicht belegt, so dass diese Patienten keine tumorspezifische medikamentöse Behandlung erhalten sollten. Für Sorafenib liegen Daten zum Einsatz bei Patienten mit ECOG 0–2 vor, für Lenvatinib liegen Daten für Patienten mit ECOC 0–1, nicht aber für ECOG 2 vor.

Bei Patienten mit Performance Status ECOG 2 sollte Sorafenib, nicht aber Lenvatinib in Erwägung gezogen werden.

3. Tumorinvasion großer Gefäße:

Patienten mit Tumorinvasion großer Gefäße (in der Regel Pfortaderhauptstamm betroffen) machten mindestens 30 % der in der SHARP-Studie mit Sorafenib behandelten Patienten mit fortgeschrittenem HCC aus (6). Patienten mit Gefäß- oder Gallengangsinvasion wurden in der Studie zu Lenvatinib vs. Sorafenib bei fortgeschrittenem HCC ausgeschlossen (7).

Bei Patienten mit Tumorinvasion großer Gefäße oder Gallengänge sollte Sorafenib, nicht aber Lenvatinib in Erwägung gezogen werden.

4. Tumormasse > 50 % des Lebervolumens:

Patienten mit Tumormasse > 50 % des Lebervolumens wurden in der Studie zu Lenvatinib ausgeschlossen, nicht aber in der SHARP Studie zu Sorafenib bei fortgeschrittenem HCC (6;7).

Bei Patienten mit Tumormasse > 50 % des Lebervolumens sollte Sorafenib, nicht aber Lenvatinib in Erwägung gezogen werden.

Bitte begründen Sie Ihre Ausführungen.

Sorafenib, ist ein Multityrosinkinasehemmer, der u. a. VEGFR2 und BRAF hemmt. Sorafenib war der erste Wirkstoff, für den in der SHARP-Studie eine signifikante Verbesserung des Überlebens im Vergleich zu Placebo bei fortgeschrittenem HCC demonstriert werden konnte (10,7 Monate vs. 7,9 Monate unter Placebo; HR 0,69; 95 % CI 0,55–0,87; p = 0,00058) (6). 50 % der Patienten im SHARP-Trial wiesen bei Einschluss extrahepatische Tumormanifestation auf, 35 % zeigten makrovaskuläre Tumorbeteiligung. Die Ergebnisse des SHARP-Trial wurden durch den Asia-Pacific-Trial (Phase III) und durch 10 weitere Studien bestätigt (8;9). Bei etwa 15 % der Patienten muss die Therapie wegen Nebenwirkungen abgebrochen werden, bei etwa 35 % ist eine Dosisreduktion erforderlich. Symptomatische koronare Herzerkrankung oder periphere arterielle Verschlusskrankheit sind Kontraindikationen der Behandlung mit Sorafenib. Eine Metaanalyse zeigt, dass HCV-assoziiertes HCC und auf die Leber beschränkte Erkrankung günstige Prognosefaktoren sind (10).

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Lenvatinib ist ein oral applizierbarer Multikinaseinhibitor, der u. a. VEGFR1–3 und FGFR1–4 hemmt. Für Lenvatinib wurde in einer Phase-III-Multicenterstudie Nichtunterlegenheit im Vergleich mit Sorafenib in der Behandlung des fortgeschrittenen HCC demonstriert. Patienten mit tumorbedingter Pfortaderinvasion, Gallengangsinvasion oder Tumormasse > 50 % des Lebervolumens wurden nicht in die Studie eingeschlossen (7). Bezüglich des primären Endpunktes OS wurde Nichtunterlegenheit demonstriert (HR 0,92; 95 % CI 0,79–1,06; 13,6 Monate OS Lenvatinib vs. 12,3 Monate OS Sorafenib). Bezüglich des sekundären Endpunktes PFS wurde Überlegenheit von Lenvatinib im Vergleich zu Sorafenib gezeigt. In der Zeitspanne bis zur Verschlechterung der Lebensqualität konnte kein Unterschied gezeigt werden (HR 1,01) (7).

Der pU plant folgende spezielle Patientenpopulation zu untersuchen: BCLC stage C oder B, nicht kurativ, Child-Pugh class A, ECOG PS 0-1

Ergibt sich bei Berücksichtigung dieser Patientencharakteristika bzw. der beschriebenen Behandlungssituation eine andere Vergleichstherapie?

Nein.

Bitte begründen Sie Ihre Ausführungen:

Die Definition der vom pU gewählten Patientengruppe entspricht der Patientengruppe, bei der gemäß Leitlinie eine systemische Behandlung mit Sorafenib oder Lenvatinib zu erwägen ist. Bezüglich des Performance Status ist das Patientenkollektiv entsprechend den Studien zu Lenvatinib gewählt, während Untersuchungen zu Sorafenib auch Patienten mit ECOG 2 eingeschlossen haben.

Die vom pU gemachten Angaben lassen nicht erkennen, wie mit anderen prognoserelevanten Faktoren wie Tumorausdehnung (z. B. > 50 % des Lebervolumens betroffen), Tumorinfiltration von großen Blutgefäßen und Gallengängen und extrahepatischem Tumorbefall umgegangen wird.

Literatur

1. Vogel A, Cervantes A, Chau I et al.: Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018; 29: iv238-iv255.

2. Llovet JM, Bru C, Bruix J: Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999; 19: 329-338.

3. Azam F, Latif MF, Farooq A et al.: Performance Status Assessment by Using ECOG (Eastern Cooperative Oncology Group) Score for Cancer Patients by Oncology Healthcare Professionals. Case Rep Oncol 2019; 12: 728-736.

4. Forner A, Reig M, Bruix J: Hepatocellular carcinoma. Lancet 2018; 391: 1301-1314.

5. Finn RS, Qin S, Ikeda M et al.: Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020; 382: 1894-1905.

Kontaktdaten

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„zur Erstlinienbehandlung des fortgeschrittenen Leberzellkarzinoms bei Erwachsenen“

6. Llovet JM, Ricci S, Mazzaferro V et al.: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359: 378-390.

7. Kudo M, Finn RS, Qin S et al.: Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018; 391: 1163-1173.

8. Lencioni R, Llovet JM: Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010; 30: 52-60.

9. Cheng AL, Kang YK, Chen Z et al.: Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009; 10: 25-34.

10. Bruix J, Cheng AL, Meinhardt G et al.: Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: Analysis of two phase III studies. J Hepatol 2017; 67: 999-1008.