Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2018-B-106 Cabozantinib

Stand: Mai 2018

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

Cabozantinib
[zur Behandlung des fortgeschrittenen Leberzellkarzinoms 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. Hierbei wird davon ausgegangen, dass 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 kommt.
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	• Qualitätssicherungsmaßnahmen bei Protonentherapie des inoperablen hepatozellulären Karzinoms; Beschluss vom 16. Juli 2009, 27. November 2015 und 27. 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:	
Cabozantinib L01XE26 Cabometyx®	Vorläufig geplantes Anwendungsgebiet: Cabozantinib ist indiziert für die Behandlung des fortgeschrittenen Leberzellkarzinoms (HCC) bei erwachsenen Patienten die vorher Sorafenib erhalten haben.
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
Sorafenib L01XE05 Nexavar®	Leberzellkarzinom Nexavar ist angezeigt zur Behandlung des Leberzellkarzinoms (siehe Abschnitt 5.1).
Regorafenib[1] L01XE21 Stivarga®	Stivarga ist angezeigt als Monotherapie zur Behandlung von erwachsenen Patienten mit: […] - hepatozellulärem Karzinom (HCC), die zuvor mit Sorafenib behandelt wurden.

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: 2018-B-106 (Cabozantinib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	29. Mai 2018

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
DAHTA	DAHTA Datenbank
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
NCCN	National Comprehensive Cancer Network
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
OS	overall survival
PFS	progression free survival
RR	relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
TAE	transarterial embolization
TACE	transarterial chemoembolization
WHO	World Health Organization

1 Indikation

Cabozantinib ist indiziert für die Behandlung des fortgeschrittenen Leberzellkarzinoms (HCC) bei erwachsenen Patienten die vorher Sorafenib erhalten haben

Gemäß Beratungsanfrage kommen eine kurative Therapie (z.B. Ablation, Transplantation, Resektion) oder eine lokoregionäre Therapie (z.B. TACE, TAE) nicht in Frage. Diese Therapieoptionen wurden also in dieser Synopse nicht berücksichtigt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *Leberzellkarzinom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 27.04.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, 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 1775 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 4 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 IQWiG Berichte/G-BA Beschlüsse

Es liegen keine IQWiG-Berichte und G-BA vor.

3.2 Cochrane Reviews

Es liegen keine IQWiG-Berichte und G-BA vor.

3.3 Systematische Reviews

Kim JH et al., 2017 [2].

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

Komparator:

-

Endpunkt:

- Any (nicht präspezifiziert)

Recherche/Suchzeitraum:

- Bis Mai 2017

Qualitätsbewertung der Studien:

- K.A.

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 (2388)

Charakteristika der Population:

- Siehe Tabelle 1

Qualität der Studien:

- K.A.

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.

10. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, Pracht M, Yokosuka O, Rosmorduc O, Breder V, Gerolami R, Masi G, Ross PJ, et al, and RESORCE Investigators. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017; 389:56–66

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.

Das SR weist einige methodische Mängel auf. So z.B. sind der Recherchezeitraum und die methodische Qualität der eingeschlossenen Studien nicht angegeben. Weiterhin fehlen Angaben zur Dauer, Menge/ Dosierung der Vorbehandlung mit Sorafenib. Aufgrund der insgesamt geringen Evidenz wurde dieses Review dennoch in die Evidenzsynopse aufgenommen.

3.4 Leitlinien

Alberta Health Services, 2015 [1].

HEPATOCELLULAR CARCINOMA

Leitlinienorganisation/Fragestellung

GUIDELINE QUESTIONS

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

- intermediate stage hepatocellular carcinoma?
- advanced stage hepatocellular carcinoma?
- terminal stage hepatocellular carcinoma?

Methodik

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.

Grundlage der Leitlinie

This guideline was developed to promote evidence-based practice in Alberta. 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.

Suchzeitraum: This guideline was developed to promote evidence-based practice in Alberta. 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.

Recherche/Suchzeitraum:

- From 1990; Update 2015

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”

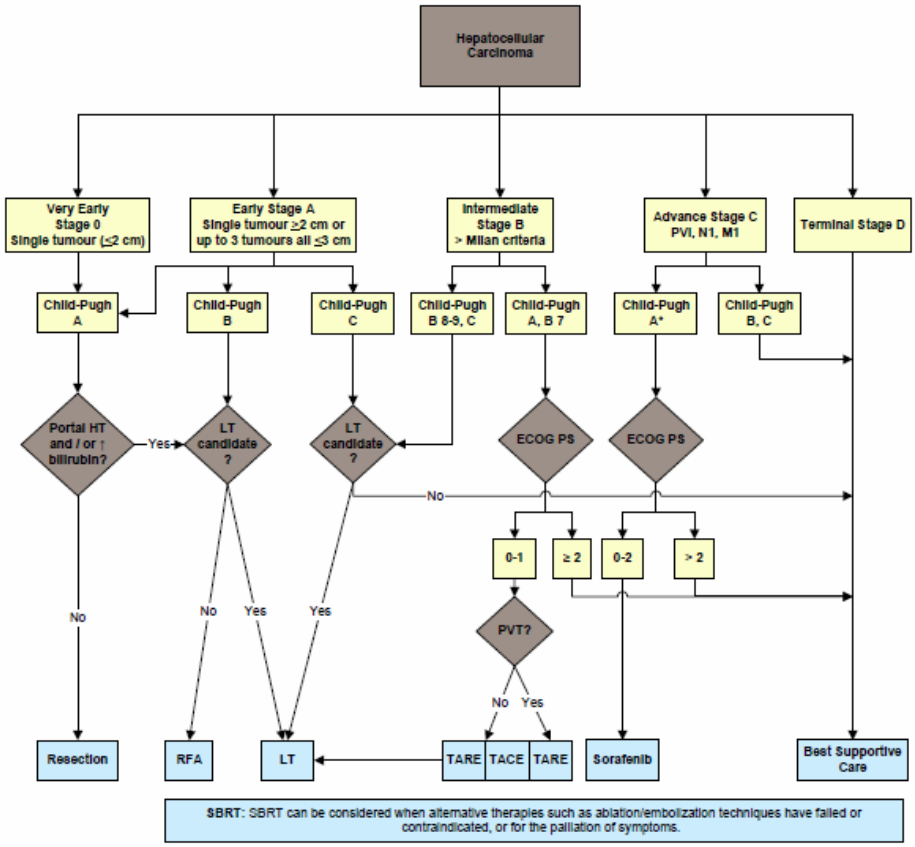
Empfehlungen

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

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

Advanced Stage Hepatocellular Carcinoma

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.

[36] Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, 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 Jan;10(1):25-34.

NCCN, 2017 [3].

National Comprehensive Cancer Network; Version 1.2018 – Februrary 14,2018

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

Methodik

Grundlage der Leitlinie

Vorher bestehende NCCN-Leitlinie

Recherche/Suchzeitraum:

- Update der vorher bestehenden NCCN-Leitlinie; Suchzeitraum 26.08.2015-25.08.2016

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.

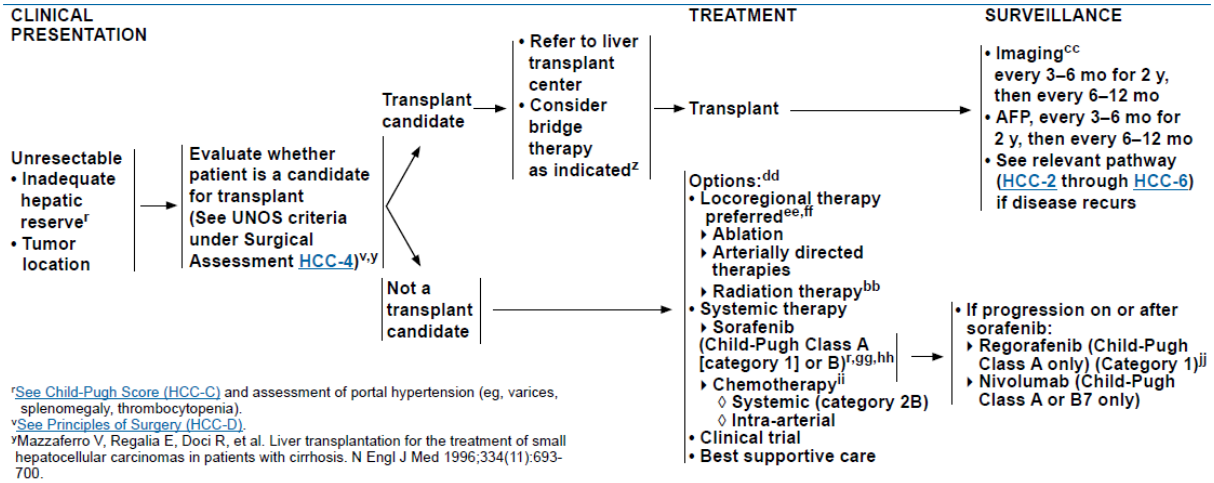
Treatment Options

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.[31]

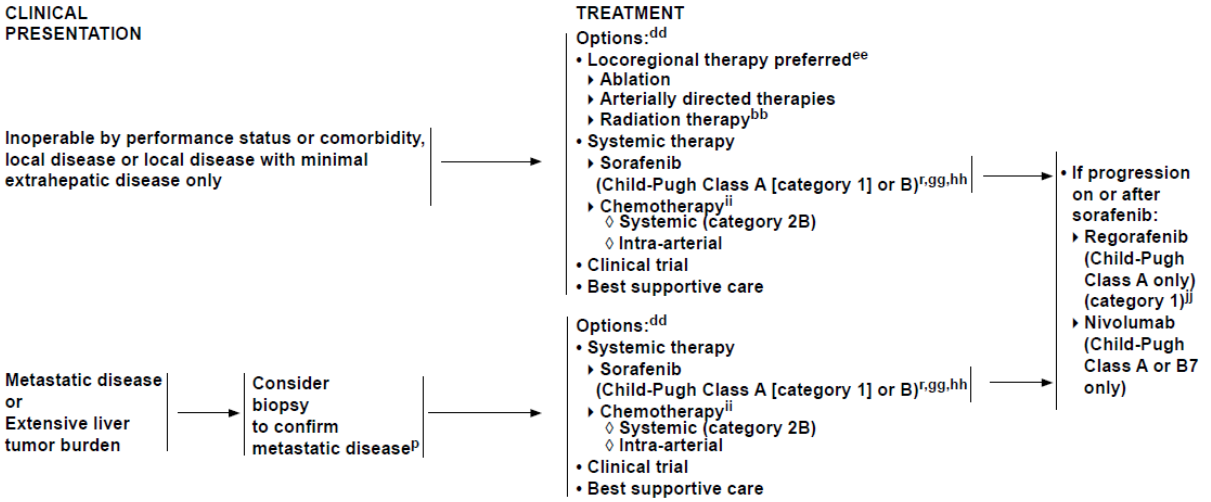
Sonstige methodische Hinweise

Diese Leitlinie erfüllt nicht die methdoischen 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.

Empfehlungen



[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(11):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]For selected patients, two randomized phase 3 clinical trials have demonstrated survival benefits. (Llovet J, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma New Engl J Med 2008;359(4):378-390) and (Cheng A, Kang Y, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia Pacific region with advanced hepatocellular carcinoma: a phase III randomized,double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34).
[hh]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.
[ii]There are limited data supporting the use of chemotherapy, and its use in the context of a clinical trial is preferred.
[jj]Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomized, double-blind, placebo-controlled, phase 3 trial. Bruix J, Qin S, Merle P, et al. Lancet 2017;389:56-66.



[p] See Principles of Biopsy (HCC-B).
[r] See Child-Pugh Score (HCC-C) and assessment of portal hypertension (eg, varices, splenomegaly, thrombocytopenia).
[bb] Case series and single-arm studies demonstrate safety and efficacy of radiation therapy in selected cases. See Principles of Locoregional Therapy (HCC-E).
[dd] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease, hepatic reserve, and institutional capabilities.
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[gg] For selected patients, two randomized phase 3 clinical trials have demonstrated survival benefits. (Llovet J, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. New Engl J Med 2008;359(4):378-390) and (Cheng A, Kang Y, 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).
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3.5 Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

NICE, 2017 [4].

Sorafenib for treating advanced hepatocellular carcinomaRecommendations

1.1 Sorafenib is recommended as an option for treating advanced hepatocellular carcinoma only for people with Child-Pugh grade A liver impairment, only if the company provides sorafenib within the agreed commercial access arrangement.

1.2 This recommendation is not intended to affect treatment with sorafenib thatwas started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Evidence:

3.1 The appraisal committee (section 6) considered evidence submitted by Bayer and a review of this submission by the evidence review group. This appraisal was a Cancer Drugs Fund reconsideration of the published NICE technology appraisal guidance on sorafenib for treating advanced hepatocellular carcinoma.

3.2 The company's original submission presented clinical effectiveness data from the SHARP study. SHARP was a multicentre, double-blind, placebo-controlled, randomised trial in patients with advanced hepatocellular carcinoma who had not received previous systemic treatment. The study

included 602 patients and assessed the effect of sorafenib plus best supportive care (n=299) compared with placebo plus best supportive care (n=303). The primary outcomes in

SHARP were overall survival and time to symptomatic progression

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 27.04.2018

#	Suchfrage
1	[mh “Carcinoma, Hepatocellular”] or [mh “Liver Neoplasms”]
2	(hepatoma or HCC or hepatocarcinoma* or (hepatocellular next carcinom*) or (liver cell carcinoma*)):ti,ab,kw
3	(liver or hepatic or hepatocellular or hepatobiliary):ti
4	(cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*):ti
5	#3 and #4
6	#1 or #2 or #5
7	#6 Publication Year from 2013 to 2018

SR, HTAs in Medline (PubMed) am 27.04.2018

#	Suchfrage
1	(Carcinoma, Hepatocellular/TH) OR Liver Neoplasms/TH[mh:noexp]
2	((hepatocarcinoma*[ti]) OR hepatoma*[ti]) OR HCC[ti]
3	((liver[ti]) OR hepatic[ti] OR hepatocellular[ti]) OR hepatobiliary[ti]
4	((((((((tumor[tiab]) OR tumors[tiab]) OR tumour[tiab]) OR tumors*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplasm*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]
5	((((((((((((treatment*[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 treating[tiab]) OR treated[tiab]) OR management[tiab]) OR drug*[tiab]) or chemotherap*[tiab]
6	(#2 OR (#3 AND #4))
7	#1 OR (#5 AND #6)
8	(#7) AND ((Meta-Analysis[ptyp] OR systematic[sb] 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]))))
9	((#8) AND ("2013/04/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 27.04.2018

#	**Suchfrage**
1	(Carcinoma, Hepatocellular[mh]) OR Liver Neoplasms[mh:noexp]
2	((hepatocarcinoma*[ti]) OR hepatoma*[ti]) OR HCC[ti]
3	((liver[ti]) OR hepatic[ti] OR hepatocellular[ti]) OR hepatobiliary[ti]

4	(((((((tumor[tiab]) OR tumors[tiab]) OR tumour[tiab]) OR tumors*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplasm*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]
5	#1 OR #2 OR (#3 AND #4)
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
7	(((#6) AND ("2013/04/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]))
8	(#7) NOT retracted publication[ptyp]
9	(((#6) AND ("2017/10/01"[CRDT] : "3000"[CRDT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]))

Referenzen

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2. **Kim JH, Kim BJ, Jang HJ, Lee J.** Molecular targeted agents as second-line treatment for hepatocellular carcinoma: a meta-analysis and review. Oncotarget 2017;8(60):102321-102327.

3. **National Comprehensive Cancer Network (NCCN).** Hepatobiliary Cancers: Version 3.2017 [online]. Fort Washington (USA): NCCN; 2017. [Zugriff: 04.05.2018]. (NCCN Clinical Practice Guidelines in Oncology). URL: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

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