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Hepatocellular carcinoma (HCC)

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

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- Conflict of interests

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1 Summary

The treatment of hepatocellular carcinoma (HCC) has developed very dynamically in recent years due to newly approved drugs and drug combinations. This raises new questions about the best first-line treatment, sequential therapy and the rational use of local treatment options.

In order to reliably evaluate curative treatment options and determine the best possible treatment sequence, every patient with suspected HCC must therefore initially be presented at a center with liver transplant experience.

2 Basics

2.1 Epidemiology

Hepatocellular carcinoma (HCC) is the most common malignant tumor of the liver in Germany, with around 6,000 new cases recorded in cancer registries each year. Around three quarters of patients are men. According to causes-of-death statistics, around 4,300 deaths annually in recent years are attributable to HCC. The age-standardized rates of new cases and deaths have recently declined slightly in men but have remained unchanged in women (Figure 1).

The mean age at onset (median) is 71 years for men and 74 years for women. Figure 2 shows the current incidence rates in Germany by age and gender.

More recently (2016-2020), the median survival was 13 months for those under 60 years of age, 12 months for those aged 60 to 74 and 8 months for those over 75 years of age. The relative survival rates, which put observed survival in relation to survival in the general population of the same age and gender, are 20% after 5 years and 13% after 10 years. Relative 5-year survival has thus increased by around 5 percentage points in the last 10 years.

Figure 1: Age-standardized rates of new cases and deaths from HCC in Germany, by gender (2010-2020/22, per 100,000 persons, old European standard)

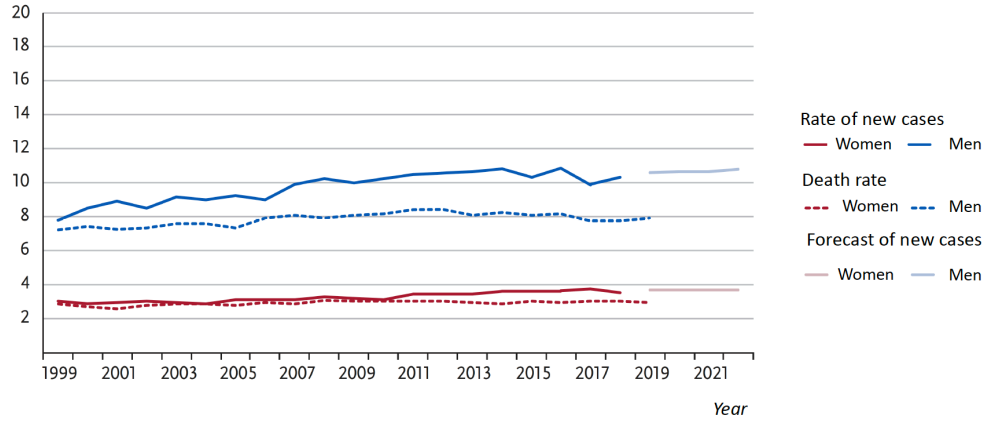


Figure 2: HCC incidence rates by age and gender (Germany 2018-2020, per 100,000 persons)

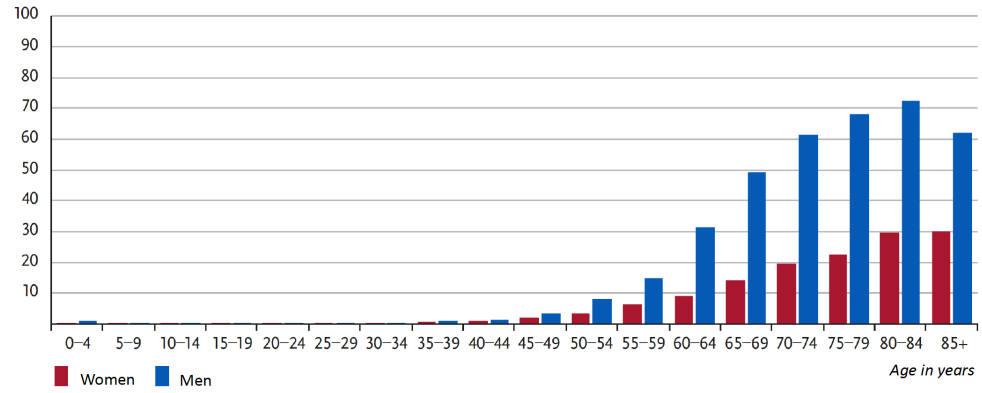
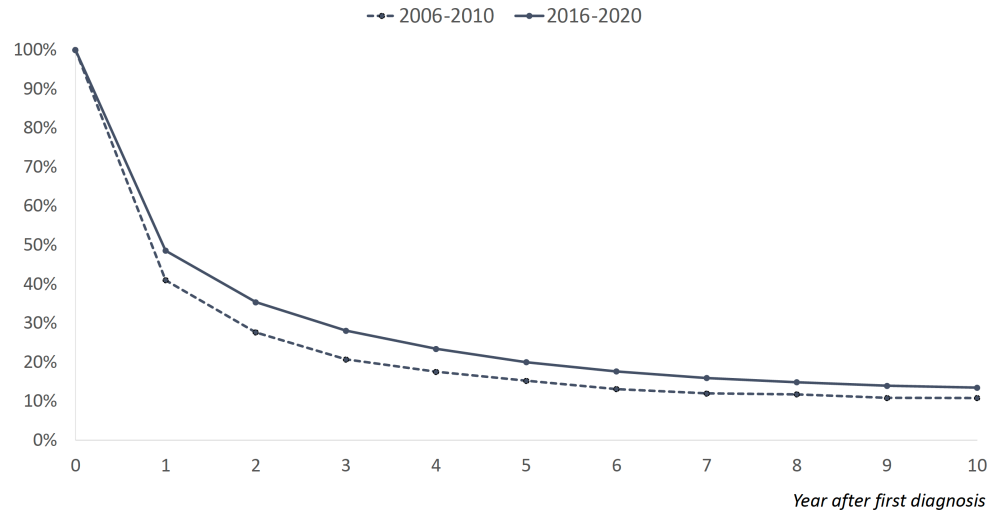


Figure 3: Relative survival rates in Germany up to 10 years after initial diagnosis of HCC, by time period (period analysis, selected registries)



According to epidemiological data from GLOBOCAN, 905,700 new diagnoses of primary liver cancer and 830,200 deaths per year were registered worldwide in 2020 [70], including cholangiocarcinomas. The incidence has been rising globally in recent years. Up to 80% of global cases affect South-East Asian countries and countries on the sub-Saharan African continent. The high incidence of chronic hepatitis B virus infection plays a decisive role here.

2.2 Risk factors

Liver cirrhosis is considered the most important risk factor for the development of HCC, in Germany mainly due to excessive alcohol consumption and/or chronic hepatitis C. The annual risk of developing HCC associated with liver cirrhosis is 2.5% per year [12]. However, this rate varies with the cause and is 2% for hepatitis B-related cirrhosis and 3-8% for hepatitis C-related cirrhosis. Rates of 0.004% to 7.6% are reported for non-alcoholic fatty liver disease (MASLD, previously known as NAFLD) and non-alcoholic fatty liver hepatitis (MASH, previously known as NASH) [94].

In the case of chronic hepatitis B or C and MASLD, the risk of developing HCC also exists without cirrhosis and is 0.12% and 1.3%, respectively.

The underlying risk factors for primary HCC vary greatly around the world [31]. For example, alcohol consumption is the cause of 32% of cases in Western Europe and 53% in Eastern Europe, but only 13% of cases in North Africa and the Middle East. In Latin America and West Africa, chronic hepatitis B dominates with 45% each, while in Western Europe, North Africa and the Middle East, chronic hepatitis C is the main cause of HCC with 44% each and 55% in the Asia-Pacific region. MASH and MASLD are clearly on the rise as triggers of liver cirrhosis and HCC in Europe, but also in the USA and China [61, 94].

Patients with hemochromatosis have an increased risk of HCC by a factor of 1.8 compared to patients with other forms of chronic liver disease [28].

In addition to nutritional and infection-related causes, germline genetic polymorphisms play a role in the risk of developing HCC. For example, the phospholipase *PNPLA3* variant rs738409 and the *TM6SF2* variant rs58542926 are associated with an increased risk of HCC in patients with alcohol-related liver cirrhosis. In contrast, a polymorphism in the rs2242652(A) locus of the telomerase reverse transcriptase TERT is associated with relative protection against HCC development [87, 12]. To estimate the risk of developing HCC associated with MASH/MASLD, various polygenic risk scores have been developed [8, 52], which can describe the probability of developing HCC from cirrhosis depending on the genesis of the liver damage and the population studied (Asian vs. non-Asian).

The molecular pathogenetic drivers of HCC development are *TP53*, *TERT* and activation of the hepatic *WNT* signaling pathway [74, 87].

3 Prevention and early detection

3.1 Prevention

Key measures to reduce the risk of HCC in Western European countries are listed in Table 1.

Table 1: Effective measures for HCC prevention

A. Prevention of the development of cirrhosis (assured preventive)
• Vaccination against hepatitis B
• Treatment of the causes of chronic liver disease, in particular alcohol cessation, weight correction in obesity [67]
• Treatment of hyperlipidemia with statins, especially in the presence of a phospholipase *PNPLA3* variant rs738409 [79, 75, 84]
• Metformin therapy for non-insulin-dependent diabetes mellitus [17, 77]
• Antiviral treatment for chronic hepatitis B / C infection with and without HCC, for hepatitis B preferably with tenofovir [55]
B. Prevention of HCC (not confirmed - retrospective data)
• Low-dose ASA in addition to metformin [76, 77] ◦ Intake of ≥ 3 cups of caffeinated coffee per day [7, 37]. Not proven for decaffeinated coffee [7] ◦ Also not proven for green tea [25]

3.2 Early detection

For early detection of HCC, regular check-ups are recommended in patients with advanced liver fibrosis, such as chronic HCV infection or MASLD, as well as in patients with rare predisposing hereditary diseases such as acute intermittent porphyria, hereditary hemochromatosis, glycogen storage disease, Gaucher's disease or tyrosinemia type I [3].

In patients with liver cirrhosis, an HCC screening program with quality-assured ultrasound ± serum alpha-fetoprotein (AFP) every 6 months is recommended. Regular determination of the AFP value appears to make sense, as values ≥ 20 ng/mL indicate HCC < 5 cm with a sensitivity of 49-71% and a specificity of 49-86% [80]. At the same time, a retrospective Korean analysis of more than 185,000 HCC patients showed that regular AFP testing improved survival [56]. This effect was particularly pronounced in hepatitis B patients.

A randomized study showed an improvement in the early detection of HCC, surgical resectability and overall survival through screening [95], these results were confirmed in a meta-analysis of 59 studies including 145,396 patients [78]. Structured screening in patients with liver cirrhosis enabled almost twice as many patients to be diagnosed at an early HCC stage (HR 1.83) and treated with curative intent (HR 1.83). This also had a significant impact on overall survival (OS; HR 0.67) [78].

In patients with hemochromatosis, HCC can also develop without cirrhosis, so that screening is recommended as soon as the extent of liver fibrosis has reached a certain degree of severity (METAVIR F3, Ishak stage 4-5) [24].

Patients with chronic hepatitis B and non-cirrhotic liver represent a special cohort. Here, a prognosticator was validated with the PAGE-B score for Caucasian patients [57] (Table 2). A PAGE-B score of <10 had a negative predictive value of 99% for the occurrence of HCC in the next 5 years. For patients with HBsAg positive hepatitis B with cirrhosis, the AASLD guidelines recommend an ultrasound and AFP monitoring every 6 months.

Table 2: PAGE-B score calculation (after [57])

Age in years (points)		Gender (points)		Platelet count (points)	
16-29	0	Female	0	>200/nl	0
30-39	2	Male	6	100-199/nl	6
40-49	4			<100/nl	9
50-59	6				
60-69	8				
>70	10				

4 Clinical characteristics

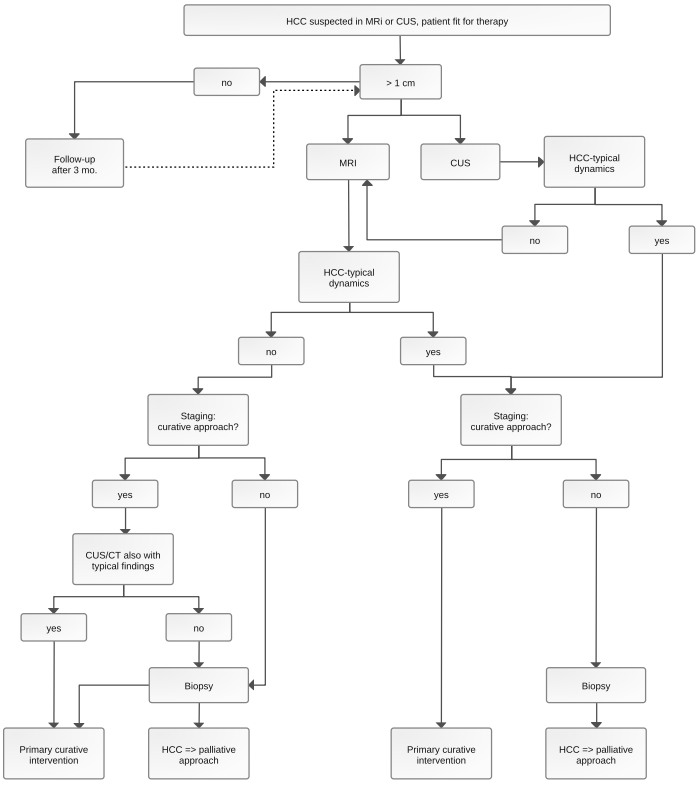
In the early stages of HCC, when there is a curative treatment option, patients usually show no specific symptoms. In developed healthcare systems, the diagnosis is therefore typically made as part of the recommended surveillance for cirrhosis or other severe chronic liver disease. Clinical signs of advanced disease are summarized in Table 3.

Table 3: Possible clinical signs of advanced HCC

• Tenderness on palpation in the upper abdomen
• Palpable swelling under the right costal arch
• Loss of appetite, nausea or increased body temperature of unexplained cause
• Weakness, reduced performance
• Unintentional weight loss
• Increasing jaundice and itching
• Increase in abdominal circumference due to ascites (already advanced cirrhosis, portal vein infiltration)

5 Diagnosis

Figure 4: Diagnostic algorithm for suspected HCC (in accordance with [3])



Legend:
MRI = magnetic resonance imaging; CUS = contrast-enhanced ultrasound; CT = computed tomography

To confirm the diagnosis of hepatocellular carcinoma, imaging with pathognomonic findings and histopathological examination are suitable (Figure 4). Histological confirmation is always necessary before initiation of palliative therapy and also in the potentially curative setting if the contrast medium dynamics remains unclear in two independent imaging studies [87]. If a primary surgical treatment approach is decided with curative intent, histopathological confirmation can be performed on the resected tumor tissue. For patients who are suitable for liver transplantation, the LI-RADS criteria (see 5.1) are preferably applied, and a biopsy to exclude a mixed tumor (HCC/cholangiocarcinoma) should only be performed if the findings are unclear (LR3 or LR4) [73]. In patients with suspected HCC who do not have liver cirrhosis, histopathologic confirmation is required [31].

5.1 HCC criteria in diagnostic imaging

Diagnostic categories of diagnostic confirmation by imaging using dynamic MRI according to the Liver Imaging and Reporting System (LI-RADS) include tumor size, contrast medium dynamics (arterial and washout phase), capsular enhancement and growth dynamics (≥ 50% increase in ≤ 6 months, ≥ 100% increase in > 6 months, new mass ≥ 10 mm). These criteria result in the LI-RADS categories [38], which are currently used in the revised version (revised LI-RADS or rLI-RADS [34].

Despite the high diagnostic accuracy, however, approximately 9% false-negative assessments result from imaging alone [18], so that histologic confirmation is recommended, especially in the palliative setting.

5.2 Histopathological assessment

The histopathological typing of HCC should be based on the current WHO classification (most recently from 2019) [51], for which a biopsy is required. Diagnosis is based on defined histomorphological criteria of hepatocellular differentiation (trabecular growth, bile production, medium-sized to large cells with round nuclei and prominent nucleoli) and signs of malignancy (architectural disorder with reduction of the reticulin fiber scaffold, nuclear atypia, vascular invasion). Specific subtypes (steatohepatitic, clear cell, macrotrabecular, cirrhotic, neutrophil-rich, lymphocyte-rich, chromophobe, fibrolamellar) can be identified by the characteristic morphology, and in part by molecular changes (e.g., *DNAJB1-PRKACA* fusion in fibrolamellar HCC) and the aspect of the non-malignant liver parenchyma. The immunohistochemical expression of arginase-1 and HepPar1 is helpful in the differentiation of non-hepatocellular tumors, for example metastases, and in the determination of lineage differentiation in combined HCC-CCC. Particularly challenging on biopsies is the distinction of highly differentiated HCC from benign, preinvasive and early hepatocellular lesions. These include focal nodular hyperplasia (FNH), hepatocellular adenoma, dysplastic nodules, early HCC (<2 cm in diameter, highly differentiated, not encapsulated) and small, progressive HCC, in which intra- and extrahepatic metastases can occur [35]. An immunohistochemical panel with the antibodies glypican-3, HSP70 and glutamine synthetase can be helpful here [87]. If ≥ 2 of these markers are positive, there is a specificity of 100% for the diagnosis of HCC [22, 82]. The detection of mutations in the *hTERT* promoter also supports the diagnosis of HCC.

The histopathological findings on resected tissue or explanted liver should include the extent of the tumor (staging) according to the current TNM classification, its type and degree of differentiation (grading) and the question of tumor cells at the resection margins (R classification). The template of the International Collaboration on Cancer Reporting (ICCR) is recommended for standardized reporting [58]. Grading has prognostic relevance after resection and liver transplantation; a three-stage system is currently recommended.

5.3 Molecular pathological testing

Molecular testing is not (yet) necessary for the treatment of HCC. However, molecular pathological techniques can be used to specify the tumor entity and/or malignant features. Molecular testing to identify optional therapeutic target structures is not a standard in curatively treatable HCC, but may be useful as an individualized treatment approach or for inclusion in clinical studies. Potential targets for molecularly targeted systemic therapies are summarized in Table 4.

Molecular pathological techniques may be used to support tumor typing and determine malignant features of hepatocellular tumors.

- In studies on cell-free DNA from circulating blood, molecular alterations were detected in 92.2% and possible therapeutic target structures (TSC1/2 18%, *BRCA1/BRCA2* 8% and *PIK3CA* 8%) in 37% [19].
- A specific fusion transcript (*DNAJB1- PRKACA*) is pathognomonic for fibrolamellar HCC and is also being evaluated as a target for molecularly targeted therapy [4].

In general, molecular sequencing in HCC typically reveals a low to moderately increased tumor mutation burden (TMB) with an average of 2.9 mut/megabase, corresponding to about 40-60 coding somatic mutations. Recurrent genetic alterations include *TERT* promoter mutations (50-60%), *TP53* alterations (20-40%), *CTNNB1* mutations (15-40%) and *ARID1A* mutations (10-20%) [87].

Activation of oncogenic signaling pathways (*Wnt-TGFβ, PI3K-AKT-mTOR, RAS-MAPK, MET* overexpression, *IGF*) is frequently detectable, as is *FGF19/FGFR4* overexpression [43], potentially allowing the targeted use of *FGFR4* inhibitors.

The determination of MSI/MMR status, tumor mutation burden (TMB) or PD-L1 expression have not yet been established as routine parameters for the primary diagnosis of HCC. By now, the use of immunotherapeutic treatment modalities has not been stratified according to these findings (see chapter 6 Therapy). Routine testing for neurotrophic receptor kinase (*NTRK*) fusions is also not indicated for primary diagnosis. However, testing for these molecular alterations may be helpful for an individual decision on systemic treatment after standard options have failed. If an *NTRK* fusion (very rare) or a TMB > 10 mutations/megabase is detected, reference can be made to tumor-agnostic approvals of entrectinib or larotrectinib, or of pembrolizumab, respectively.

Testing for germline mutations is not yet regularly recommended [53].

Table 4: Possible targets for molecularly targeted therapies (modified after [54])

Extracellular domain	VEGF	PDGF	FGF	EGF	IGF	SCF	HGF	Angiopoietin	FL	GDNF
Receptor/signaling pathway	VEGFR	PDGFR	FGFR	EGFR	IR	c-KIT	c-MET	Tie-2	FLT3	RET
Agents	Sorafenib Lenvatinib Regorafenib Cabozantinib Ramucirumab Sunitinib Brivanib Vandetanib Nintedanib Donafenib Dovitinib Linifanib	Sorafenib Lenvatinib Regorafenib Sunitinib Linifanib Nintedanib Dovitinib Donafenib	Lenvatinib Regorafenib Brivanib Nintedanib Dovitinib Fisogatinib	Erlotinib Vandetanib	Cixutumumab	Sorafenib Lenvatinib Regorafenib Cabozantinib Sunitinib Donafenib	Cabozantinib Tivantinib Tepotinib Capmatinib Foretinib Emibetuzumab	Regorafenib Trebananib	Sorafenib Sunitinib Cabozantinib	Sorafenib Lenvatinib Regorafenib Cabozantinib Sunitinib Vandetanib Donafenib

5.4 Staging

The staging of an HCC should include a contrast-enhanced CT of thorax and abdomen. If the preceding contrast-enhanced MRI has covered the entire abdomen diagnostically, only a native CT thorax should be added. With regard to the morphological aspects of the tumor, imaging analysis methods that take vascularity into account should be used [3]. A contrast-enhanced MRI performed with gadobutrol (Gadovist®) is recommended to specify possible vascular invasion, which is an important prognostic factor. For subsequent imaging procedures, a liver-specific contrast medium is also preferred.

Staging is useful to determine the TNM formula, the resulting staging (currently according to AJCC 8th edition 2017), the grading and degree of fibrosis and the determination of the BCLC stage according to the Barcelona criteria [68] (Table 5). To assess treatment options, it is necessary to determine the hepatic functional reserve in liver cirrhosis according to the Child-Pugh score [62] (Table 6). Focusing solely on the BCLC stage does not represent current clinical practice when making treatment decisions. Several studies have shown that the decision of the multidisciplinary tumor board of the respective center regarding the appropriate therapy for the patient will result in better success rates than the sole BCLC-guided decision [33, 47].

Liver transplant (LTx) is indicated if macrovascular invasion as well as extrahepatic tumor spread has been ruled out and the patient is suitable for LTx. The allocation of a match-MELD by standard exception [88, 48] is based on the Milan criteria [49], whereby tumors smaller than 20 mm should be surgically resected and thus Milan criteria are replaced by UNOS T2. The static classification is only used for prioritization on the waiting list.

It is becoming increasingly apparent that dynamic selection criteria such as biological response, AFP slope, G3 or vessel invasion are more suitable than static ones.

Table 5: Barcelona stages of HCC (after [53])

Stage	Definition
Very early stage (0)	Single liver lesion ≤ 2 cm Preserved liver function, general condition ECOG 0
Early stage (A)	Single lesion or up to 3 liver lesions, each ≤ 3 cm Preserved liver function, general condition ECOG 0
Intermediate stage (B)	Multiple liver lesions Preserved liver function, general condition ECOG 0
Advanced stage (C)	Portal invasion and/or extrahepatic spread Preserved liver function, general condition ECOG 1-2
Terminal stage (D)	Any tumor spread End-stage liver failure, general condition ECOG 3-4

Legend:
ECOG = Eastern Cooperative Oncology Group Performance Score

Table 6: Child-Pugh score to determine the degree of liver function reserve in liver cirrhosis (after [62]).

Clinical/biochemical parameters	Score points for increasing abnormality		
	1	2	3
Degree of encephalopathy	None	1-2	3-4
Ascites	Not available	Light	Moderate
Albumin (g/dL)	Over 3.5	2,8-3,5	Under 2.8
PTT seconds above standard INR	Less than 4 Under 1.7	4-6 1,7-2,3	More than 6 over 2.3
Bilirubin (mg/dL) - for primary biliary cirrhosis	Under 2 Under 4	2-3 4-10	Over 3 Over 10

Legend:
PTT = partial thromboplastin time; INR = international normalized ratio
Class A = 5-6 points; Class B = 7-9 points; Class C = 10-15 points
Class A: Favorable surgical risk; Class B: Moderately increased surgical risk; Class C: High surgical risk

6 Therapy

6.1 Basic principles

All patients with HCC should be presented at a multidisciplinary tumor conference at a center associated with a liver transplant center in order to decide on the appropriate treatment procedure. This requires the participation of competent representatives from the disciplines of radiology (diagnostic and interventional), radiotherapy, nuclear medicine, pathology, gastroenterology/hepatology, visceral surgery and hematology/oncology. For a correct decision, histopathological findings (if biopsy has been done), radiological findings, infection status (hepatitis), tumor burden (stage and TNM formula according to UICC), BCLC stage, current liver function para-

meters, AFP value, platelet count, Child-Pugh/ALBI stage in the case of liver cirrhosis and general condition (Karnofsky or ECOG) should be available.

Guideline-based antiviral therapy is indicated for patients with chronic HBV infection and HCC. Tenofovir and entecavir are established as the standard here. The indication for antiviral therapy also applies to patients with chronic HCV infection and HCC, here adapted to the HCV genotype and the corresponding approval status, although the benefit in patients with advanced and non-curatively treatable HCC has not yet been proven [59]. In curative treatment, antiviral therapy of HCV infection has been shown to improve overall survival [13].

6.2 Liver transplantation (LTx)

The involvement of a center for LTx is recommended for primary decision-making in the case of curatively treatable HCC. This also applies to patients with resectable HCC; in particular, however, to patients with non-resectable HCC in cirrhosis within the Milan criteria (BCLC A), but can also be performed for resectable or borderline resectable HCC in cirrhosis if the Milan criteria [49] are met [3] (see Table 7). The indication and urgency for an LTx must therefore be made as quickly as possible in an LTx center. LTx may also be indicated outside the UNOS T2 criteria (see Table 7). In Germany, listing using SE (standard exceptions) criteria is not possible for these tumors, so that other listing options must be evaluated with the respective LTx center (living liver donation, listing without "Standard Exceptions" (SE) criteria, center options). This applies in particular to tumors that have responded very well to local and systemic therapy. The level of AFP correlates with the outcome of LTx [6], and an AFP > 1,000 ng/ml is considered a contraindication to LTx in many countries. A decrease to < 500 ng/ml through local or systemic therapy leads to an improvement of the prognosis after LTx [50].

Comparing patients who received an LTx within the Milan criteria with those who only reached the Milan criteria after downstaging, the 10-year survival and the rate of relapses are comparable (61.5 vs 52.1% and 13.3 vs 20.6% respectively) [81].

If there is a recurrence-free interval of more than 2 years, a de novo HCC may be assumed according to the guidelines of the German Medical Association, which may result in an indication for LTx.

LTx is not indicated for extrahepatic HCC manifestations and/or macrovascular invasion of the liver vessels.

If LTx is indicated, bridging should be attempted by means of local ablation (see below), surgical resection or transarterial embolization (see below). The indication for bridging therapy should always be discussed with the LTx center.

Outside of studies, patients with HCC after LTx should not receive adjuvant systemic treatment. The multidisciplinary decision to continue antiviral therapy for HBV/HCV-related HCC (see above) remains unaffected by this.

Table 7: Criteria for liver transplantation (LTx) in HCC patients (after German S2k guideline AWMF/DGAV/DGVS, [5])

• Suitable patients with liver cirrhosis and non-resectable HCC within the Milan criteria (BCLC-A/UNOS T2) should be evaluated for LTx.
• Even in the case of formally resectable or borderline resectable HCC findings in cirrhosis, there may be an indication for LTx within the Milan criteria, particularly if portal hypertension is present.
• In patients with HCC without liver cirrhosis, LTxshould only be performed in exceptional cases.
• LTx should not be performed in the case of extrahepatic tumor manifestations and/or macrovascular invasion of the liver vessels.
• If the AFP value is > 1,000 ng/ml, there should be no indication for LTx without neoadjuvant therapy.
• If AFP increases to > 1,000 ng/ml during downstaging/bridging therapy, LTx should not be performed.
• Patients with HCC (BCLC A) within the Milan criteria should receive bridging therapy if liver function is sufficient.
• Local ablation, resection or transarterial procedures (TACE, TARE) should be used for bridging.
• A transplant center should be contacted before starting bridging therapy.

6.3 Primary surgical procedure with or without neoadjuvant/adjuvant therapy

A prerequisite for primary surgical resection is the possibility of R0 resection. Portal hypertension (splenomegaly, esophageal varices, ascites, thrombocytopenia) should be excluded beforehand, if necessary, by determining the wedge pressure.

If not all intrahepatic HCC manifestations can be R0 resected, a decision should be made pre-operatively on the combination with local ablative or embolization procedures (see below) with curative intent.

Liver resection should be performed for a single HCC nodule <2 cm in liver cirrhosis with functional resectability. In this constellation, however, LTx may also be indicated [5]. For tumors >2 cm, an individual discussion should take place in which the location of the tumor, the tumor biology, the risk of recurrence and a possible living liver donation option should be included in the decision. Liver resection can be performed as an open or minimally invasive procedure. If the resection is performed as a bridge to a planned LTx, it should be minimally invasive.

If neoadjuvant or adjuvant systemic therapy is planned before/after R0 resection, inclusion in clinical trials is recommended. Currently available study results can be summarized as follows:

- **For adjuvant therapy, a significant improvement in PFS (primary endpoint) was shown for the first time for treatment with atezolizumab plus bevacizumab in a randomized comparison with follow-up alone (IMbrave 050 phase III study) [64]. Even though the study was not powered for OS, the mature OS data [93] showed no advantage of the therapy over the follow-up control, so that treatment with atezolizumab plus bevacizumab should possibly only be discussed as an early palliative therapy. This should be discussed with the patient.**
- **Neoadjuvant and postoperative immunotherapy with cemiplimab in patients with resectable HCC has so far been experimental [46].**
- **Perioperative systemic therapy with nivolumab or nivolumab plus ipilimumab has been shown to be safe, and a major histopathological response has been documented in individual patients after neoadjuvant administration [36].**

- **With histopathological evidence of vascular infiltration (V1), a reduction in the recurrence rate (from 55.7% to 40.1%) has been demonstrated with intra-arterial chemotherapy using the FOLFOX protocol [41].**

6.4 Local ablative treatment alternatives to surgery

6.4.1 Potentially curative setting

Patients with a primarily local ablative therapy concept have an overall curative potential of 20-30%, and up to 40% for small HCC single foci (n = 1,571) [20], whereby percutaneous ablation of HCC should be performed using radiofrequency ablation (RFA) or microwave ablation (MWA).

In patients with HCC of up to 3 cm, surgical resection and ablation are equivalent procedures in terms of clinical outcomes. Primary thermal ablation is particularly indicated for HCC ≤ 3 cm in locations unfavorable for resection and in the case of significantly impaired liver function.

The advantages of percutaneous MWA are the low associated morbidity, particularly with regard to subsequent pain symptoms, a short hospitalization and the option of performing the procedure under sedation instead of general anesthesia.

Patients with an HCC focus > 3 cm and ≤ 5 cm with good liver function (Child Pugh A) and mild or moderate portal hypertension should undergo TACE prior to thermal ablation [3].

Transarterial chemoembolization (TACE) may be indicated as downstaging prior to planned surgical treatment [9].

6.5 Local therapeutic procedures in intermediate stage HCC

In the intermediate stage, primarily the indication for intra-arterial treatment procedures should be explored in non-resectable patients. TACE and TARE/SIRT are available as local therapy procedures. If a good response has been achieved, the procedures can be repeated in patients with good liver function [11, 86]. The decision to do so should be made in the multidisciplinary tumor board and should be re-evaluated after two treatments. The two procedures were found to be equivalent in meta-analyses [10, 45, 16].

In the results of the EMERALD-1 study, first presented in 2024, the combination of TACE with durvalumab and bevacizumab showed a significant advantage over TACE alone in terms of progression-free survival in 616 HCC patients (HR 0.77, 95% CI 0.61-0.98, p=0.032), but no advantage in overall survival to date [40]. The randomized comparison of lenvatinib + pembrolizumab + TACE vs placebo + TACE (LEAP-012) also showed a significant PFS benefit for the combination therapy in 480 HCC patients with Child Pugh A in first-line therapy (HR 0.66, 95% CI 0.51-0.84; p=0.0002), while no mature data on overall survival are available here either [44].

6.6 Systemic treatment

Systemic tumor therapy using tyrosine kinase inhibitors (TKI) such as sorafenib, lenvatinib, regorafenib or cabozantinib or immunotherapeutics such as atezolizumab, durvalumab, pembrolizumab, tislelizumab, nivolumab, ipilimumab, tremelimumab or anti-angiogenic antibodies (bevacizumab, ramucirumab), partly in

combination, has been established as the current treatment standard since the SHARP study publication in 2008 [42]. While sorafenib was compared with placebo in the SHARP study, subsequent studies compared new treatment modalities with sorafenib and/or lenvatinib as a control arm. A randomized comparison with placebo was no longer used for ethical reasons, but neither was a randomized comparison of newer treatment methods against each other, which does not allow a differential assessment of the benefits of the numerous newer treatment options.

In general, treatment with atezolizumab plus bevacizumab, durvalumab with and without tremelimumab as well as sorafenib, lenvatinib, regorafenib, cabozantinib and ramucirumab is suitable for patients with cirrhosis in stage Child-Pugh A for whom the liver transplant center sees no curative treatment option. In the Child-Pugh B stage, data is available for sorafenib from observational studies and for immune checkpoint inhibitors from smaller phase 2 studies. In a meta-analysis of previously published reports with PD1 antibodies in patients in this Child-Pugh stage, an overall acceptable safety profile for the substances was confirmed, albeit with higher associated morbidity than in patients with Child Pugh A liver cirrhosis [89]. Accordingly, systemic therapy can also be considered in selected patients with Child Pugh B in a good general condition (ECOG PS ≤ 1) [3]. In patients with cirrhosis stage Child-Pugh C, systemic tumor treatment for HCC is not indicated.

Systemic tumor treatment should not be continued beyond the point of proven treatment failure, but rather be switched to another systemic therapy, if recommended by a multidisciplinary tumor board.

If patients with primarily non-curative HCC without distant metastases show a very good response to systemic tumor therapy, it is recommended that they be presented again to the tumor board with the question of secondary, potentially curative, surgical approach [3].

6.7 Systemic first-line therapy

The currently available study results on the above-mentioned substances for first-line systemic therapy of HCC can be summarized as follows:

- **Compared to placebo, sorafenib showed a response rate of 2.3%, a progression-free survival (PFS) of 4.9 vs. 4.1 months (mo.) and a significantly improved overall survival (OS) of 10.7 vs. 7.9 mo. (HR 0.69; p<0.001) [42]. In recent phase III studies in which sorafenib acted as the control arm, a survival of 13 to 15 months was achieved, which is probably primarily due to the use of evidence-based second-line therapies.**
- **Lenvatinib showed a PFS of 7.4 vs. 3.7 mo. and an OS of 13.6 vs. 12.3 mo. (HR 0.92) compared to sorafenib [39]. Similar to sorafenib, an OS of up to 20 months was achieved with lenvatinib in recent phase 3 studies.**
- **With the combination of atezolizumab plus bevacizumab vs. sorafenib, an overall response of 27.3 vs. 11.9%, a PFS of 6.8 vs. 4.3 mo. (HR 0.66; p<0.001) and a 1-year OS of 67.2 vs. 54.6% were observed [26]. The longer follow-up resulted in a median OS of 19.2 vs. 13.4 mo. (HR 0.65; p<0.001) [69]. The results could also be reproduced under "real world" conditions [29]. Due to potential bleeding events, esophageal varices requiring treatment should endoscopically be excluded or treated by ligation before bevacizumab is given.**
- **In the HIMALAYA study, the combination of tremelimumab and durvalumab ("STRIDE" regimen) vs. sorafenib resulted in a response rate of 20.1 vs. 5.1%**

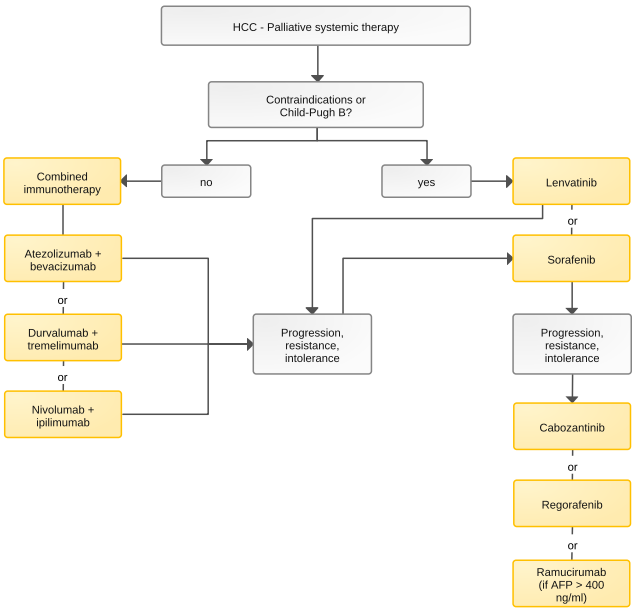
(for the STRIDE regimen), a PFS of 3.8 vs. 4.1 mo. (for sorafenib) (HR 0.90 for STRIDE) and an OS of 16.4 vs. 13.8 mo. (HR 0.76; p=0.0008) [1].

- **The combination of nivolumab plus ipilimumab (CheckMate-9DW study) versus lenvatinib or sorafenib showed a response rate of 36 vs. 13%, a PFS of 7.5 vs. 7.5 mo. (HR 0.72) and an OS of 23.7 vs. 20.6 mo. (HR 0.79; p=0.018) [21, 32].**
- **In the comparison of the immunotherapy/TKI combination of atezolizumab plus cabozantinib vs. sorafenib in the COSMIC study, a significantly prolonged PFS of 6.9 vs. 4.3 mo. (HR 0.63; p=0.0012), but a comparable OS of 16.5 vs. 15.5 mo. (HR 0.90; p=0.44) was observed [91].**
- **Despite the differences between the study results, which are likely to be primarily due to study-specific selection characteristics, meta-analyses show no significant difference between the various combination therapies tested [15, 30].**
- **In the CARES-310 study, camrelizumab plus rivoceranib (formerly apatinib) vs. sorafenib achieved an improved PFS of 5.6 vs. 3.7 mo. (HR 0.52; p<0.0001) and a significantly longer OS of 22.1 vs. 15.2 mo. (HR 0.62; p<0.0001). Overall, treatment toxicity was increased with this combination, but without a negative impact on the patients' quality of life [63].**
- **According to current data, first-line treatment with an immune checkpoint inhibitor as monotherapy is not superior to sorafenib:**
  - **Durvalumab vs. sorafenib ([1]) - however, there is an EMA approval for durvalumab as monotherapy for first-line HCC treatment**
  - **Tislelizumab vs. sorafenib [63]**
  - **Nivolumab vs. sorafenib [91]**
    - **The previously accelerated FDA approval of nivolumab for this indication was withdrawn in July 2021.**
- **In a randomized phase III trial from China, the combination of lenvatinib with TACE showed a significant improvement in OS (17.8 vs. 11.5 mo.) and PFS (10.6 vs. 6.4 mo.) as well as a better response rate according to modified RECIST criteria (54.1 vs. 25.0%) in advanced-stage patients, as compared to lenvatinib alone [60]. However, the use of local therapies for BCLC C is not an accepted standard option [3] and should only be used after multidisciplinary discussion in the tumor board.**
- **According to the results of the CATCH-IT study, treatment with immune checkpoint inhibitors can be used in patients with HIV infection with comparable efficacy and safety as in HIV-negative patients [23].**

This results in the recommendation for systemic first-line therapy in non-curatively treatable patients in cirrhosis stage Child-Pugh A without contraindications to use the combination of atezolizumab plus bevacizumab or durvalumab plus tremelimumab or nivolumab plus ipilimumab, in each case until radiologically detectable tumor progression.

In patients with contraindications or intolerance to these substances, lenvatinib or sorafenib should primarily be used as monotherapy (see Figure 5).

Figure 5: Recommended first-line and follow-up therapies for patients with HCC without curative treatment options



Legend:
palliative intention; AFP, alpha fetoprotein

6.8 Systemic treatment options for second-line and beyond

After failure of first-line systemic therapy, second-line therapy should be administered. Phase 3 studies have shown the efficacy of regorafenib, cabozantinib and ramucirumab after failure of sorafenib therapy. For patients who have not been treated with sorafenib, no formal phase 3 data are yet available, but treatment with the approved substances is recommended, particularly for patients with well-preserved liver function. To date, there are no randomized comparisons between the TKIs in this indication.

None of the above-mentioned immunotherapeutic agents (atezolizumab, pembrolizumab, durvalumab, nivolumab, ipilimumab, tremelimumab) have by now been approved for second-line therapy after TKI failure. If patients have not received immunotherapy-based first line treatment (e.g., due to relative contraindications), this can be considered in the subsequent therapy. The studies conducted to date have yielded the following results:

- **In the Checkmate-040 study, the combination of nivolumab plus ipilimumab after sorafenib pre-treatment showed a response rate of around 30% [90].**
- **Pembrolizumab as monotherapy in a randomized comparison with placebo led to a PFS of 3.0 vs. 2.8 mo. and an OS of 13.9 vs. 10.6 mo. [27].**
- **In Asian patients after prior treatment with sorafenib or oxaliplatin-based chemotherapy, pembrolizumab monotherapy compared to placebo resulted in a response rate of 12.7 vs. 1.3%, a PFS of 2.6 vs. 2.3 mo. and an OS of 14.6 vs. 13.0 mo. [65].**

However, the *VEGFR2* inhibitor ramucirumab is approved as monotherapy after sorafenib pre-treatment for patients with an AFP value of ≥ 400 ng/ml. While no significant benefit was observed in this indication in unselected patients compared to placebo [97], a significant OS benefit (8.5 vs. 7.3 mo.) was shown in a follow-up study in patients with an initial AFP value ≥ 400 ng/ml. The PFS was also significantly prolonged at 2.8 vs. 1.6 mo. [96].

The TKIs available after failure of sorafenib are lenvatinib and cabozantinib, regorafenib and ramucirumab (for AFP ≥ 400ng/mL) and (after failure of lenvatinib) sorafenib and cabozantinib (see Figure 5 for subsequent therapy). Lenvatinib is not approved for second-line therapy after sorafenib failure.

Second-line therapies are also generally restricted to patients with a sufficient general condition (ECOG ≤ 1) and a cirrhosis stage of Child-Pugh A; only in selected individual cases is such therapy to be discussed in the case of Child-Pugh B.

Experimental treatment options may be derived from molecular pathology findings. These include dostarlimab if high microsatellite instability/defective mismatch repair (MSI-H/dMMR) has been demonstrated, selpercatinib if a RET fusion is detected, larotrectinib or entrectinib if an *NTRK* fusion has been shown (extremely rare), and pembrolizumab or nivolumab plus ipilimumab in case of increased tumor mutational burden (TMB) [53], provided that no immune checkpoint inhibitors have been given before. These are individual case decisions outside of established treatment standards that can be proposed by a molecular tumor board.

7 Drugs for systemic tumor therapy (alphabetical)

7.1 Atezolizumab

Atezolizumab is a humanized IgG1 antibody directed against PD-L1 and belongs to the class of immune checkpoint inhibitors (ICIs). It is approved for the treatment of hepatocellular carcinoma [27] in combination with bevacizumab and a broad spectrum of other malignant neoplasms. No evidence of PD-L1 expression is required for use in HCC. As with other immune checkpoint inhibitors directed against PD1 or PD-L1, immune-mediated side effects such as hepatitis, pneumonitis, colitis, endocrinopathies or skin reactions have been documented in clinical studies, as well as pronounced fatigue in some cases. There is a risk of exacerbation of a pre-existing autoimmune disease. Clinically significant pharmacological interactions with other active substances have not been described, although the efficacy of atezolizumab is expected to be impaired if immunosuppressive drugs are administered in advance.

7.2 Apatinib (see Rivoceranib)

See chapter 7.13 Rivoceranib.

7.3 Bevacizumab

Bevacizumab is a monoclonal anti-angiogenic antibody against the vascular endothelial growth factor VEGF. The prescribing information for atezolizumab indicates approval in combination with bevacizumab for the first-line treatment of HCC, whereas this indication is missing in the prescribing information for the various bevacizumab preparations. Side effects (grade 3 or 4) that occurred in more than 5% of patients in the pivotal trials were hypertension and proteinuria. Rarer critical complications are arterial thromboembolic events and perforations in the gastrointestinal tract. The note in the guideline text on the risk of bleeding in the presence of esophageal varices must be observed.

Bevacizumab is proteolytically degraded in the body. Elimination does not occur via the kidneys or liver. A relevant pharmacokinetic influence on the effect of bevacizumab by other drugs is therefore unlikely. Cases of microangiopathic hemolytic

anemia have been reported in patients undergoing combination therapy with bevacizumab and sunitinib, which are also referred to in the prescribing information for bevacizumab.

7.4 Cabozantinib

Cabozantinib is a multikinase inhibitor. In addition to the *VEGFR1*, *VEGFR2* and *VEGFR3* kinases, it also inhibits *AXL* and *MET*. Cabozantinib is approved for second-line treatment after failure of sorafenib in hepatocellular carcinoma (prolonged OS compared to placebo), besides renal cell carcinoma and differentiated thyroid carcinoma. In first-line HCC therapy, no improvement in overall survival was found in combination with atezolizumab compared to sorafenib [92]. The most frequently documented adverse events in larger clinical trials with cabozantinib monotherapy were palmoplantar erythrodysesthesia (17%), hypertension (16%), diarrhea (10%) and fatigue (10%).

Cabozantinib has a very high plasma protein binding. As a result, it can displace other drugs that are strongly bound to plasma proteins from plasma protein binding. This can lead to an increase in the desired and undesired effects of drugs with a narrow therapeutic range if their degradation and excretion pathways are restricted at the same time. If cabozantinib is taken with a very high-fat meal, its oral bioavailability is increased by 57% compared to taking cabozantinib on an empty stomach. Cabozantinib is mainly metabolized via CYP3A4. Concomitant treatment with cabozantinib and strong inducers of CYP3A4 may reduce the systemic availability of cabozantinib and thus its clinical efficacy. Concomitant treatment with cabozantinib and strong inhibitors of CYP3A4 may result in increased adverse effects. Concomitant treatment with cabozantinib and drugs that are strong CYP3A4 inducers or CYP3A4 inhibitors should be avoided. The consumption of grapefruit, grapefruit-like fruits (e.g., pomelo, bitter orange) and their preparations should be avoided for the entire duration of treatment with cabozantinib. Myelosuppression caused by cabozantinib, which occurs very frequently, can be enhanced by the simultaneous use of other myelosuppressive drugs. During treatment with cabozantinib, attention should be paid to a possible decrease of blood cell counts. If necessary, appropriate measures should be taken. Since electrolyte disturbances have been observed very frequently during treatment with cabozantinib, concomitant treatment with cabozantinib and QTc-prolonging drugs may increase the risk of polymorphic ventricular arrhythmias, so-called "torsade de pointes". Concomitant treatment with cabozantinib and QTc time-prolonging drugs should be avoided. If this is not possible, attention should be paid to electrolyte balance and the QTc time should be checked regularly. Taking cabozantinib can sometimes lead to severe bleeding. This risk is increased by the simultaneous administration of cabozantinib with anticoagulant drugs. In the case of concomitant treatment with cabozantinib and anticoagulants, coagulation-related laboratory parameters should be checked regularly. Cases of gastrointestinal perforation have been reported in clinical studies. This risk may be increased by concomitant use of cabozantinib with substances with a known risk of gastrointestinal perforation, so that concomitant treatment of these drugs with cabozantinib should be avoided.

7.5 Camrelizumab

Camrelizumab is a humanized monoclonal IgG4 antibody directed against PD1, which belongs to the substance class of ICIs. It has not yet been approved in the EU. Camrelizumab was tested in combination with rivoceranib (formerly: apatinib) for the first-line treatment of HCC in comparison to sorafenib in the CARES-310 study [63]

and showed an advantage in overall survival. In early August 2024, the EMA granted "orphan medicinal product designation“ for this combination for the first-line treatment of HCC (https://elevartherapeutics.com/2024/08/01/elevar-therapeutics-granted-orphan-designation/). Under monotherapy for HCC, the main treatment-associated side effects reported were vascular skin reactions (up to 70%), proteinuria (23%), liver transaminase and bilirubin elevations (15-20%) as well as thrombocytopenia (15%). Serious pharmacological interactions are not expected due to the properties of camrelizumab, but no reliable data are yet available.

7.6 Durvalumab

Durvalumab is a humanized monoclonal IgG1 antibody against PD-L1 and belongs to the substance class of ICIs. Besides for the treatment of small cell and non-small cell lung cancer, it is approved for hepatocellular and biliary carcinomas. In HCC, approval exists as monotherapy and in combination with tremelimumab (an ICI targeting CTLA4) for first-line therapy. When used as monotherapy for HCC, severe treatment-related side effects were reported in 8.2% of patients [1]. As with other ICIs, immune-mediated side effects such as pneumonitis, colitis, endocrinopathies, skin reactions, hepatitis, pancreatitis and others have been documented with the use of durvalumab. There is a risk of exacerbation of pre-existing autoimmune diseases. In addition, fatigue and gastrointestinal side effects are frequently described. Clinically relevant pharmacological interactions with other active substances have not been identified, although an impairment of the efficacy of durvalumab is to be expected with prior administration of immunosuppressive drugs.

7.7 Entrectinib

Entrectinib is a strong inhibitor of neurotrophic tropomyosin receptor kinases (*NTRK*) A, B, and C and is approved for the treatment of *NTRK* fusion-positive tumors and *ROS1*-mutated non-small cell lung cancer. Adverse side effects reported in three tumor-agnostic studies included taste disturbances, constipation, diarrhea, fatigue, confusion, increased serum creatinine, paresthesia, nausea, vomiting, arthralgia, myalgia and weight gain as well as individual cases of severe neurotoxicity. QT prolongation may also occur.

The concomitant use of strong or moderate CYP3A inhibitors (e.g. ritonavir, saquinavir, ketoconazole, itraconazole, voriconazole, posaconazole, grapefruit or bitter orange) should be avoided or, if unavoidable, the dose of entrectinib should be reduced in accordance with the prescribing information. The simultaneous intake of strong CYP3A4/PGP inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort, apalutamide, ritonavir) should be avoided. Entrectinib can inhibit P-glycoprotein, but clinically relevant effects, e.g., on digitoxin, have not been observed.

7.8 Ipilimumab

Ipilimumab is a monoclonal antibody from the group of ICIs. It blocks the inhibitory T-cell regulator CTLA-4 and thereby boosts the autologous immune response. It is approved for first-line therapy of HCC and for the treatment of melanoma, renal cell carcinoma, non-small cell lung cancer, malignant pleural mesothelioma, squamous cell carcinoma of the oesophagus and colorectal cancer. With the exception of melanoma, this approval is linked to the combination with nivolumab. In the CheckMate 040 phase I/II study on HCC treatment in combination with nivolumab [90], treatment-related side effects were recorded in 70-94% of patients with 3 different

dosage variants. The focus was on skin reactions, gastrointestinal complaints such as diarrhea and immune-mediated inflammatory reactions or organ dysfunction. Interstitial pneumonitis occurred in 10% of patients. Clinically relevant pharmacological interactions with other active substances have not been identified; if immunosuppressive drugs are administered before the start of ipilimumab therapy, an impairment of the efficacy of ipilimumab is to be expected.

7.9 Larotrectinib

Larotrectinib is a selective *NTRK* inhibitor approved for the treatment of *NTRK* fusion-positive tumors. Side effects reported in clinical trials include fatigue, liver enzyme elevation, confusion/dizziness, constipation, nausea/vomiting and constipation, but also, in less frequent cases, muscle and joint pain, edema, headache, weight gain, hyperglycemia and peripheral neuropathy.

Pharmacological interactions are to be expected with inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole or grapefruit) and inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin or St. John's wort) of CYP3A and P-glycoprotein. The prescribing information states that if concomitant administration with a strong CYP3A4 inhibitor is necessary, the dose of larotrectinib should be reduced by 50%.

7.10 Lenvatinib

Lenvatinib is a multi-tyrosine kinase inhibitor that inhibits *VEGFR1-3, FGFR1-4, PDGFR alpha, PDGF, KIT* and *RET*. It has been approved for the treatment of renal cell carcinoma. In the phase III study comparing sorafenib with sorafenib in the first-line treatment of HCC [39], palmoplantar erythrodysesthesia, hypertension, gastrointestinal complaints (e.g., diarrhea, constipation, nausea/vomiting, loss of appetite and weight loss), hypothyroidism and liver enzyme elevations were reported. According to the prescribing information, proteinuria, aneurysms, aortic dissections, renal failure, central nervous system toxicity, fistulas/perforations, bleeding, arterial thromboembolism, impaired wound healing, osteonecrosis of the jaw and cardiac dysfunction such as QT prolongation may also occur.

Myelosuppression caused by lenvatinib can be exacerbated by the concomitant use of other myelosuppressive drugs. Since prolongation of ventricular repolarization has been observed during therapy with lenvatinib, concomitant administration of lenvatinib with QTc time-prolonging drugs may increase the risk of polymorphic ventricular arrhythmias, so-called "torsade de pointes". Concomitant treatment with lenvatinib and QTc-prolonging drugs should be avoided. If this is not possible, care should be taken to maintain a balanced electrolyte balance and the QTc time should be checked regularly. Bleeding also occurs very frequently with the use of lenvatinib. Concomitant treatment with lenvatinib and anticoagulant drugs can further increase the risk of bleeding. Co-treatment with lenvatinib and anticoagulants should be combined with regular monitoring of coagulation-related laboratory parameters. Renal dysfunction, especially acute renal insufficiency, frequently occurs during treatment with lenvatinib. Concomitant administration of lenvatinib and drugs that interfere with the renin-angiotensin-aldosterone system (RAAS) may result in an increased risk of acute renal failure. If lenvatinib and drugs that interfere with the RAAS are administered at the same time, renal function should be monitored regularly. The administration of corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs) during therapy with lenvatinib should be avoided.

Gastrointestinal perforations have been observed during therapy with lenvatinib. The risk of this may be increased by the simultaneous administration of lenvatinib and drugs that interfere with prostaglandin metabolism (e.g., NSAIDs, corticosteroids).

Lenvatinib is mainly degraded via oxidation by aldehyde oxidase. N-demethylation via CYP3A4 and glutathione conjugation are secondary pathways of degradation. Therefore, both CYP3A4 inhibitors and CYP3A4 inducers have no significant influence on the systemic availability of lenvatinib.

7.11 Nivolumab

Nivolumab is a monoclonal anti-PD1 antibody and belongs to the class of ICIs. It has been approved in combination with ipilimumab for the first-line treatment of HCC and as a monotherapy or combination therapy for the treatment of a broad spectrum of malignant neoplasms. In the phase III study on first-line treatment of HCC in comparison with sorafenib [91], the main treatment-related side effects of nivolumab reported were fatigue, skin reactions, gastrointestinal complaints (diarrhea, nausea, inappetence) and transaminase elevations. Other possible side effects include anemia, hypoalbuminemia, hyperkalemia, liver enzyme elevations, heart failure, serum amylase elevation, hyponatremia, creatine phosphokinase elevation and renal dysfunction as well as sometimes severe pyrexia and interstitial pneumonia (immune-mediated pneumonitis) as well as immune-mediated liver or kidney inflammation and endocrinopathies.

As with other humanized monoclonal antibodies, there is no pharmacological interaction with the cytochrome P450 isoenzyme system or other enzymes of drug metabolism. The efficacy of nivolumab is expected to be impaired by prior administration of immunosuppressive drugs.

7.12 Ramucirumab

Ramucirumab is a human IgG1 antibody that binds specifically to the vascular endothelial growth factor receptor-2 (*VEGFR2*). It has been approved for second-line therapy after failure of sorafenib in patients with HCC and a serum AFP of ≥ 400 ng/ml as well as for adenocarcinomas of the stomach or gastroesophageal junction, colorectal cancer and non-small cell lung cancer. In the placebo-controlled phase III REACH-2 trial for second-line treatment of HCC [96], the main treatment-related adverse events reported in the ramucirumab arm were fatigue, nausea/vomiting, inappetence, proteinuria, hypertension, bleeding tendency, peripheral edema and diarrhea or constipation. To avoid infusion-associated intolerance reactions, premedication with an H1 antagonist is recommended.

Clinically relevant pharmacological interactions with other active substances are not described in the prescribing information and, as with other humanized monoclonal antibodies, are not to be expected.

7.13 Rivoceranib (formerly: Apatinib)

Rivoceranib is a TKI directed against *VEGFR2* that has not yet been approved in the USA or the EU. It was investigated in combination with camrelizumab for the first-line treatment of HCC in comparison with sorafenib in the CARES-310 study [63] and showed an advantage in overall survival. In early August 2024, the EMA granted "orphan medicinal product designation" for this combination for first-line treatment

of HCC (https://elevartherapeutics.com/2024/08/01/elevar-therapeutics-granted-orphan-designation/). Side effects reported from monotherapy studies mainly include hypertension, gastrointestinal symptoms such as nausea and vomiting, fatigue, hand-foot syndrome and skin reactions.

The main metabolic pathway is CYP3A4, so that relevant pharmacological interactions with CYP3A4 inhibitors such as itraconazole or voriconazole and CYP3A4 inducers such as rifampicin or St. John's wort are to be expected. A prescribing information is not yet available.

7.14 Selpercatinib

Selpercatinib is a highly selective *RET* kinase inhibitor. It has a tumor-agnostic approval for the treatment of *RET* fusion-positive tumors and *RET*-mutated thyroid carcinomas. The main side effects in a tumor-agnostic phase I/II study were hypertension and liver enzyme elevation, as well as fatigue, proteinuria and abdominal discomfort. Severe treatment-related adverse events were reported in 40% of patients. The prescribing information also points at pneumonia, hypersensitivity reactions, headache, QT prolongation, bleeding, interstitial pneumonitis, gastrointestinal complaints such as nausea, vomiting, diarrhea or constipation, edema and myelosuppression as frequent side effects. In patients with known QT prolongation, special cardiological examinations are recommended prior to the use of selpercatinib (see prescribing information). Due to its metabolization via CYP3A4 and P-glycoprotein and its influence on CYP2C8, selpercatinib has numerous interactions with other drugs and substances (St. John's wort, azole antifungals, grapefruit juice, phenytoin, rifampicin, rifabutin, carbamazepine, HIV virustatics, and others for CYP3A4, as well as cerivastatin, enzalutamide, paclitaxel, repaglinide, torasemide, sorafenib, rosiglitazone, buprenorphine, selexipag, dasabuvir or montelukast for CYP2C8) and is influenced in its absorption after oral intake by concomitant use of proton pump inhibitors (PPI). For details, see prescribing information.

7.15 Sorafenib

Sorafenib is a tyrosine kinase inhibitor directed against *PDGFR-beta, VEGFR2* and *VEGFR3, BRAF, CRAF, FLT3* and *c-KIT*, which is approved for the treatment of HCC as well as for renal cell carcinoma and differentiated thyroid carcinoma. In the pivotal trial for the treatment of HCC, the main treatment-related adverse events reported with sorafenib compared to placebo were diarrhea, weight loss, palmoplantar erythrodysesthesia (hand-foot syndrome) and hypophosphatemia. The prescribing information lists numerous other possible sorafenib-associated side effects that should be taken into account.

Sorafenib is primarily metabolized in the liver by oxidative degradation via CYP3A4 as well as by UGT1A9-mediated glucuronidation. According to the prescribing information, the group of CYP3A4 inducers (rifampicin, St. John's wort, phenytoin, carbamazepine, phenobarbital and dexamethasone) is of particular clinical relevance, as their simultaneous administration can lead to a reduction in sorafenib levels.

7.16 Tislelizumab

Tislelizumab is a humanized IgG4 monoclonal antibody with high affinity and binding specificity for PD-1, specifically designed to minimize binding to FcγR on macrophages. The binding surface of tislelizumab to PD-1 largely overlaps with that of PD-L1, resulting in complete blockade of the PD-1/PD-L1 interaction. Tislelizumab

is an ICI. It has been approved for the treatment of non-small cell lung cancer and esophageal carcinoma. In the first-line treatment of HCC, tislelizumab has not shown superiority in a randomized comparison with sorafenib (RATIONALE-301) [66]. The main tislelizumab-associated side effects reported were increases in liver transaminases and bilirubin, skin reactions, thrombocytopenia and gastrointestinal complaints (diarrhea, loss of appetite, weight loss). Immune-mediated side effects (pneumonitis, hepatitis, colitis, endocrinopathy, etc.) occurred in 18.3% of patients.

Tislelizumab is eliminated by catabolic degradation. No formal pharmacokinetic interaction studies have been conducted. Since monoclonal antibodies are not metabolized by cytochrome P450 enzymes or other drug-degrading enzymes, inhibition or induction of these enzymes by concomitantly administered drugs is not expected to affect the pharmacokinetics of tislelizumab (prescribing information). The use of systemic corticosteroids and other immunosuppressants before starting treatment with tislelizumab should be avoided, with the exception of physiological doses of systemic corticosteroids (10 mg/day prednisone or equivalent), due to their potential influence on pharmacodynamic activity and efficacy (prescribing information).

7.17 Tremelimumab

Tremelimumab is a human monoclonal IgG2a antibody directed against the cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), and is an ICI. It has been approved for the first-line treatment of HCC in combination with durvalumab and for non-small cell lung cancer.

When tremelimumab is used in combination with durvalumab for the treatment of HCC, immune-mediated side effects such as pneumonitis, colitis, endocrinopathies, skin reactions, hepatitis, pancreatitis and others have been documented. There is a risk of exacerbation of pre-existing autoimmune diseases. In addition, fatigue and gastrointestinal side effects are frequently described. Early monotherapy studies on melanoma treatment with tremelimumab have reported fatigue, nausea/vomiting, diarrhea/colitis, skin reactions and endocrinopathies in particular, but also numerous other therapy-associated side effects.

Clinically relevant pharmacological interactions with other active substances have not been identified, but if immunosuppressive drugs are administered before the start of ipilimumab therapy, an impairment of the efficacy of tremelimumab is to be expected.

8 Rehabilitation

Please refer to: https://www.krebsgesellschaft.de/onko-internetportal/basis-informationen-krebs/krebsarten/andere-krebsarten/leberkrebs/reha-und-nachsorge.html

9 Monitoring and follow-up

***In accordance* with [3]:**

- **After resection of HCC without liver cirrhosis, regular follow-up should be carried out for 5 years.**
- **After liver resection for HCC in cirrhosis, regular follow-up should be carried out.**

- **Monitoring after local therapy should be performed using biphasic contrast-enhanced CT or dynamic MRI at intervals of 4-12 weeks after ablation/resection or after each TACE cycle.**
- **The follow-up after successful local therapy should be carried out every 3 months in the first year and every 3-6 months in the second year using biphasic contrast-enhanced CT or dynamic MRI.**
- **In HCC undergoing systemic therapy, appropriate cross-sectional imaging (CT or MRI) should be ordered every 6-12 weeks, optionally also checking the serum AFP.**
- **In clinical practice, assessment should be based on the criteria of RECIST 1.1 and mRECIST, as well as iRECIST for patients undergoing immunotherapy.**
- **Under systemic therapy, the tolerability of the therapy should be closely monitored and taken into consideration for the continuation or modification of treatment.**
- **After completion of follow-up, patients should be included in the screening program again with ultrasound ± AFP determination every 6 months.**

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17 Disclosure of Potential Conflicts of Interest

in accordance with the rules of the relevant professional associations.