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Hepatocellular carcinoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up<sup>†</sup>

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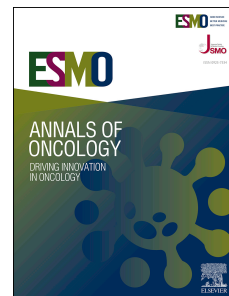
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## Hepatocellular carcinoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up†

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**Highlights (online only):**

- This ESMO Clinical Practice Guideline provides key recommendations for managing hepatocellular carcinoma.
- The guideline covers imaging and diagnosis, staging and risk assessment, treatment and follow-up.
- Algorithms for the management of early-, intermediate- and advanced-stage disease are provided.
- The authors comprise a multidisciplinary group of experts from different institutions and countries.
- Recommendations are based on available scientific data and the authors' collective expert opinion.

## INCIDENCE AND EPIDEMIOLOGY

Liver cancer is the sixth most common cancer and the third leading cause of cancer deaths globally.<sup>1,2</sup> Hepatocellular cancer (HCC) accounts for 80% of the global liver cancer burden, with >900 000 new cases and an age-standardised rate of 7.3 per 100 000 in 2020.<sup>2</sup> Over the past two decades, there has been a reduction in the incidence of HCC in Asian countries including Japan, China and Korea,<sup>3</sup> but incidence is rising in Europe and North America.<sup>4,5</sup> HCC shows a strong male preponderance and incidence increases progressively with advancing age.<sup>2</sup> Information on the aetiology of HCC is available in **Supplementary Material Section 1**.

### *Recommendations*

- Due to the association of HCC with chronic liver disease, universal vaccination at birth against hepatitis B virus (HBV) [II, A] and early antiviral treatment for HBV and hepatitis C virus (HCV) [III, A] are recommended.
- Antiviral therapy is recommended in all patients with active HBV who are diagnosed with HCC [II, A].
- Direct-acting antiviral therapy is generally recommended for patients with active HCV who are diagnosed with HCC, but the timing should be individualised [IV, B].

## SURVEILLANCE

Surveillance of HCC involves the repeated application of screening tools in patients at risk for HCC and aims to reduce mortality. The success of surveillance is influenced by the incidence of HCC in the target population, availability and acceptance of efficient diagnostic tests and availability of effective treatment. Surveillance for HCC can be considered when the annual risk of HCC is >1% per year in patients with cirrhosis and >0.2% per year in those without cirrhosis.<sup>6</sup> In Asian patients, serum HBV DNA >10 000 copies/ml has been associated with a

higher annual risk of HCC compared with patients with a lower viral load.<sup>7</sup> The PAGE-B score estimates the risk of HCC in patients with chronic HBV receiving entecavir or tenofovir, based on age, gender and platelet count.<sup>8</sup> Patients with HCV and advanced fibrosis remain at increased risk for HCC even after achieving sustained virological response following antiviral treatment and should, therefore, remain in a surveillance programme.<sup>9</sup>

Liver ultrasound (US) is a standard tool for HCC surveillance but has limited sensitivity and specificity, particularly in livers with significant steatosis.<sup>10</sup> In Western countries and less experienced centres, the sensitivity of US for identifying early-stage HCC is considerably lower than in more experienced centres.<sup>11</sup> Adding measurement of serum  $\alpha$ -foetoprotein (AFP) to US can provide an improvement in the early HCC detection rate, but at the price of false-positive results.<sup>12</sup> Cell-free DNA-based liquid biopsies have shown encouraging preliminary results for the early detection of HCC but remain to be prospectively validated.<sup>13</sup> A randomised controlled trial (RCT) compared surveillance (US and serum AFP measurements every 6 months) with no surveillance in Chinese patients with chronic HBV infection.<sup>14</sup> Despite low compliance with the surveillance programme (55%), HCC-related mortality was reduced by 37% in the surveillance arm. Regarding the most appropriate surveillance interval, a randomised study comparing 3- and 6-month schedules did not report any differences in detection of early HCC.<sup>15</sup>

### **Recommendations**

- Surveillance for HCC is recommended in all patients with cirrhosis, irrespective of its aetiology, if liver function and comorbidities allow tumour treatment [II, A].
- HCC surveillance is recommended for patients with chronic HBV infection and a moderate or high HCC risk score (e.g. PAGE-B) at the onset of nucleoside analogue therapy [II, A].
- HCC surveillance should include abdominal US (or multiphase cross-sectional imaging if available) every 6 months, with or without AFP evaluation [II, A].

- Liquid biopsy and analysis of circulating tumour DNA (ctDNA) cannot be recommended for HCC surveillance [IV, D].

## DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

### *Diagnosis*

Diagnosis methods vary according to clinical context and whether the patient is at risk for HCC (**Supplementary Table S1**). High-risk patients include those with cirrhosis and chronic HBV infection. In such settings, non-invasive imaging-based criteria on computed tomography (CT), magnetic resonance imaging (MRI) or contrast-enhanced US (CEUS) can provide a diagnosis without formal pathological proof; therefore, technique optimisation is critical.

For diagnosis of HCC, multiphase CT and MRI follow the technical recommendations of the CT and MRI Liver Imaging Reporting and Data System (LI-RADS)<sup>®</sup> v2018. Any magnetic resonance (MR) contrast agent may be used. Multiphase MRI offers several advantages over CT, including depiction of more ancillary features favouring the diagnosis of HCC or other malignancies, such as fat in mass, moderate T2 hyperintensity and restricted diffusion. It also allows hepatocyte function measurement using hepatobiliary contrast agents; internalisation of hepatobiliary MR contrast agents is mediated by organic anionic transporting polypeptides expressed on the sinusoidal membrane of functional hepatocytes and loss of hepatocellular function occurs early during hepatocarcinogenesis, before tumour neoangiogenesis.<sup>16</sup> If imaging criteria are not met on the first imaging examination (e.g. CT), repeat imaging can be considered after 3 months for lesions  $\leq 1$  cm. For larger lesions, imaging should be repeated using a different modality (e.g. MRI) or a biopsy should be carried out. Further details on diagnostic imaging for HCC are available in **Supplementary Material Section 2** and **Supplementary Table S2**.

### *Pathology*

The increasing number of HCCs related to metabolic dysfunction-associated steatotic liver disease in the absence of cirrhosis can make diagnosis challenging, as it can be difficult to discriminate between HCC and other liver tumours, particularly less common primary malignant liver tumours such as cholangiocarcinoma, combined hepato-cholangiocarcinoma and fibrolamellar HCC.<sup>17</sup> Furthermore, differential diagnosis between HCC and benign nodules may be difficult and pathological examination is required to rule out high- or low-grade cirrhotic dysplastic nodules and hepatocellular adenoma, particularly for lesions that are difficult to resect.<sup>18</sup> A precise differential diagnosis is, therefore, important since non-HCC patients require specific management and therapeutic strategies.

In the case of specific risk factors for HCC, a biopsy of the non-tumour liver tissue and/or specialised molecular and genetic tests can optimise surveillance of the patient and their relatives. Patients with undiagnosed genetic disease and a mild phenotype (particularly those with a familial context of liver disease or tumour) could benefit from genetic counselling and tests for metabolic diseases (e.g. haemochromatosis, alpha-1 antitrypsin deficiency, porphyria, maturity-onset diabetes of the young). Paired tumour and non-tumour liver biopsy should be carried out in an expert centre by an experienced radiologist or hepatologist using an 18 gauge needle to minimise side-effects such as bleeding and tumour seeding, which are rare.<sup>19</sup> Panels of immunohistochemistry markers can help assess diagnosis, prognosis and specific subtypes of tumours.

### ***Molecular biology***

HCC is a heterogeneous disease that includes various pathological and molecular subtypes. Molecular classifications have shown that the varied natural history at the origin of each subtype can be identified by mutations in cancer driver genes, including *TERT*, *TP53*, *CTNNB1*, *ARID1A*, *RB1*, *FGF19* and *CCND1*.<sup>20</sup> These oncogenic defects are translated in molecular classification, enabling categorisation of HCC in more homogeneous subgroups according to their specific proliferative rate, level of differentiation and signalling pathway activation. Recent proof-of-concept studies have shown that molecular-guided therapy using next-generation sequencing (NGS) is feasible; some patients progressing after first-line treatment

may benefit from this approach to define a second-line targeted therapy based on molecular subtyping.<sup>21</sup>

## **Recommendations**

### **Diagnosis**

- Diagnostic work-up for HCC should include history, clinical examination, laboratory analysis, imaging and tumour biopsy [III, A].
- An HCC diagnosis should be based on histological analysis and/or contrast-enhanced imaging findings [III, A].
- For diagnosis by CT or MRI in patients at high risk for HCC, imaging features including tumour size, non-rim arterial phase hyperenhancement (APHE), peripheral washout, enhancing capsule and tumour growth can be combined [IV, B].
- For diagnosis by CEUS in patients at high risk for HCC, imaging features including non-rim APHE with late-onset (>60 seconds) and mild washout can be combined [IV, B].

### **Pathology**

- In patients without cirrhosis at low risk or without known risk factors for HCC, histopathological confirmation (obtained via tumour biopsy from the liver or metastatic site, if present) is recommended for diagnosis [IV, A].
- In patients with advanced HCC, histopathological diagnosis of HCC is recommended before initiating systemic therapy [III, A].
- NGS should be carried out for tumours with mixed histology features [IV, A].

### **Molecular biology**

- To facilitate biomarker development, tumour biopsy is recommended for all patients included in clinical trials [IV, A].



- Systematic germline genetic tests cannot be routinely recommended at diagnosis [IV, D], except in rare cases of familial HCC or suspicion of genetic liver diseases after genetic counselling [IV, B].
- Liquid biopsy and analysis ctDNA cannot be recommended in routine clinical practice for the diagnosis of HCC [IV, D].

## STAGING AND RISK ASSESSMENT

Staging is important to determine the optimal treatment strategy; it includes assessment of tumour extent, liver function, portal hypertension, AFP and clinical performance status (PS).

Contrast-enhanced MRI (CEMRI) or contrast-enhanced CT (CECT) can assess tumour extent, including the number and size of nodules, vascular invasion and extrahepatic spread. CT scans of the chest, abdomen and pelvis can exclude extrahepatic spread. Routine preoperative bone scintigraphy for detecting asymptomatic skeletal metastases in patients with resectable HCC lacks justification, and its utility in advanced HCC remains undetermined.<sup>22</sup> Despite evidence linking higher [<sup>18</sup>F]2-fluoro-2-deoxy-D-glucose (FDG) uptake in FDG-positron emission tomography (PET) scans with poor differentiation, tumour size, serum AFP levels and microvascular invasion, FDG-PET is not a routine staging modality; however, it may be useful in selected cases to further characterise CT or MRI findings.<sup>23,24</sup>

Liver function is assessed using the Child-Pugh (serum bilirubin, serum albumin, ascites, prothrombin time and hepatic encephalopathy) and/or albumin-bilirubin (ALBI) scoring system.<sup>25</sup> In the context of orthotopic liver transplantation (OLT), the Model of End Stage Liver Disease with sodium (MELD-Na) score (incorporating serum creatinine, serum bilirubin, international normalised ratio and serum sodium) is used to prioritise patients on waiting lists. Over 90% of ALBI grade 1 HCCs are Child-Pugh A5, while ALBI grade 2 comprise a high proportion of Child-Pugh A6.<sup>26</sup> The Baveno VII criteria classify portal hypertension using indirect (oesophageal varices and/or splenomegaly, blood platelet count  $<100 \times 10^9$  cells/l) or invasive

measures (transjugular hepatic-venous pressure gradient >10 mmHg).<sup>27</sup> Patients with portal hypertension and advanced liver fibrosis or cirrhosis should undergo regular oesophagogastroduodenoscopy according to national and international guidelines.

Staging systems that incorporate the above-mentioned items include TNM (tumour–node–metastasis), Okuda, Cancer of the Liver Italian Program, Japanese Integrated Staging score and the Barcelona Clinic Liver Cancer (BCLC) system. The eighth edition of the Union for International Cancer Control TNM classification (**Supplementary Table S3**) provides a means of standardising histopathological reports in patients treated with resection or transplantation.<sup>28,29</sup> The BCLC algorithm is the most prevalent staging system, categorising HCC into five clinical stages: very early stage (BCLC 0), early stage (BCLC A), intermediate stage (BCLC B), advanced stage (BCLC C) and terminal stage (BCLC D).<sup>30</sup> Median overall survival (OS) with therapeutic interventions is >5 years for stages 0 and A, 2.5 years for stage B, 2 years for stage C and 3 months for stage D.<sup>30</sup> Although the aetiology of concurrent liver disease has not been established as an independent predictive or prognostic factor, identifying and addressing treatable underlying liver conditions is relevant. For example, initiating antiviral therapy for HBV and HCV, administering corticosteroids for autoimmune hepatitis or cessation of alcohol consumption may lead to substantial improvements in liver function and prognosis.

### **Recommendations**

- HCC staging is recommended for optimal therapy planning and should include assessment of tumour extent, liver function, portal hypertension, AFP and PS [III, A].
- FDG–PET cannot be recommended as a routine staging modality [III, D], but may be appropriate in selected cases to further characterise findings on CT or MRI [IV, C].
- Liver function should be assessed by the Child–Pugh and/or ALBI scoring systems [III, A]. MELD-Na should be used to assign priority to liver transplant candidates [IV, A].

- Portal hypertension should be assessed according to the Baveno VII criteria by indirect measures or invasively via the transjugular route [III, A].
- BCLC is the recommended staging system for prognostic prediction and treatment allocation [IV, A].

## **MANAGEMENT OF EARLY (BCLC 0-A)- OR INTERMEDIATE (BCLC B)-STAGE HCC**

Multidisciplinary decision making (taking into account anatomical complexity, comorbidities, underlying liver dysfunction and heterogeneous tumour biology) is associated with improved HCC outcomes. Liver resection, OLT and local thermal and radiation ablative therapies comprise potentially curative treatment modalities. The predominant arterial vascularisation of HCC is well suited for intra-arterial administration of chemotherapy (ChT), embolising material or radioactive particles to shrink tumours; these therapies are considered palliative but may lead to complete tumour destruction. An algorithm for the management of early- or intermediate-stage HCC is shown in **Figure 1**.

### ***Liver resection***

Solitary tumours (irrespective of tumour size) should be resected in patients with well-preserved liver function, provided resection with no tumour at the margin (R0) can be achieved. Patients with Child–Pugh C liver function are not suitable for resection. A recent meta-analysis demonstrated that the presence of portal hypertension is not an absolute contraindication for resection.<sup>31</sup> Compared with open surgery, minimally invasive surgery via robotic or laparoscopic resection results in reduced intraoperative blood loss, faster post-operative recovery and similar oncological outcomes.<sup>32</sup> Well-selected patients with unilobar multifocal disease or peripheral macrovascular invasion (Vp1-Vp2) may benefit from resection; however, there is no high-level evidence to recommend this.<sup>33,34</sup>

After resection, tumours recur in 50%-70% of patients within 5 years. Recurrence risk depends on a combination of clinical and pathological features, including

multifocality, tumour size, histological differentiation, presence of vascular invasion and elevation of pre- and post-operative serum AFP.<sup>35,36</sup> Removal of the hepatic segment via anatomic resection (AR) is considered more effective than non-anatomical wedge resection (NAR) in terms of tumour clearance and eradication of micrometastases. In patients with HCC and cirrhosis, AR may not be possible and a tissue-sparing NAR favoured to reduce the risk of post-operative liver failure.<sup>37</sup> No clear recommendation for AR or NAR can be given in the absence of high-level evidence.

### ***Thermal tumour ablation***

In tumours <2 cm, radiofrequency ablation (RFA) has demonstrated similar outcomes to resection and is less invasive.<sup>38</sup> In early-stage HCC, ablation has been adopted as an alternative first-line option to resection.<sup>39,40</sup> Microwave ablation (MWA) has evolved as a popular choice over RFA based on the shorter intervention time, lower susceptibility to cooling effects and potentially superior results for tumours ≤5 cm.<sup>41</sup> Thermal ablation has limitations, including heat sink for tumours adjacent to vessels, which reduces local control, and toxicity risk in tumours adjacent to the gallbladder, intestines, liver hilum or bile ducts, which may be mitigated with laparoscopic approaches.<sup>42</sup> There is no role for chemical tumour ablation (e.g. ethanol injection) since thermal ablation has better outcomes.

### ***Adjuvant treatment after liver resection or ablation in high-risk patients***

The phase III STORM trial evaluated adjuvant sorafenib versus placebo after resection or ablation of HCC in patients at intermediate or high risk of recurrence.<sup>43</sup> There was no difference in recurrence-free survival (RFS) between the treatment arms. The role of adjuvant immune checkpoint inhibitor (ICI)-based therapies has also been studied in selected high-risk patients. The phase III IMbrave050 trial compared adjuvant atezolizumab–bevacizumab for 12 months versus active surveillance after resection or ablation in patients with high-risk features [single tumour >5 cm, multinodular disease, high serum AFP levels, poor differentiation, presence of microvascular invasion or segmental macrovascular invasion (Vp1-Vp2)].<sup>44</sup> Although the primary endpoint (RFS) was met at the first interim analysis,

the second interim analysis revealed that the benefit was not sustained over time.<sup>45</sup> OS was immature at the time of interim analyses.

### ***Liver transplantation***

OLT can cure both HCC and the underlying liver disease; this approach is associated with the best OS (median 10 years) and RFS outcomes. The Milan criteria (one lesion <5 cm or ≤3 lesions, each <3 cm; no extrahepatic manifestations; no evidence of macrovascular invasion) are currently the standard for selecting patients with HCC for OLT.<sup>46</sup> Among more liberal proposals [e.g. University of California San Francisco (UCSF) criteria, extended Toronto criteria], only the UCSF criteria (one tumour ≤6.5 cm or ≤3 nodules with the largest ≤4.5 cm and total tumour diameter ≤8 cm) have been prospectively validated and show similar outcomes.<sup>46</sup> The XXL RCT compared OLT with locoregional therapy in patients with an expected 5-year OS rate of >50% according to the Metroticket 2.0 criteria.<sup>47</sup> The study closed early due to improved outcomes in the OLT arm [hazard ratio (HR) 0.32, 95% confidence interval 0.11-0.92,  $P = 0.035$ ]. With improved therapies to downstage or downsize HCC, several groups are developing less stringent criteria while reporting excellent outcomes.

The low availability of liver allografts is a major limitation for OLT, resulting in long waiting times and the associated risk of progression. Transarterial chemoembolisation (TACE), transarterial radioembolisation (TARE), radiotherapy (RT) and thermal ablation have been shown to minimise the risk of tumour progression during the waiting period.<sup>48</sup>

Small, single-institution case series suggest that patients with localised HCC who achieve a prolonged response with ICI-based systemic therapy may be candidates for OLT, although prospective data are limited.<sup>49,50</sup> Receipt of an ICI within a shorter timeframe before transplantation may be associated with a higher risk of acute allograft rejection. A United Network for Organ Sharing policy update in 2022 clarified that “the use of immunotherapy does not preclude consideration for an HCC exception”.<sup>51</sup>

There is no established role for adjuvant therapy after OLT. A randomised phase III trial of patients who had undergone OLT for HCC reported no significant improvement in RFS following adjuvant mammalian target of rapamycin (mTOR)-based immunosuppression versus non-mTOR-based immunosuppression,<sup>52</sup> although subgroup analyses suggested a benefit in patients with elevated AFP and HCV-associated HCC.<sup>53</sup>

For HCC recurrence or a new diagnosis after OLT, treatment depends on the location and extent of disease. They include resection, stereotactic body RT (SBRT), proton therapy, image-guided high-dose-rate (HDR) brachytherapy, thermal ablation or other locoregional therapies for solitary recurrence or metastases and tyrosine kinase inhibitors (TKIs) for multifocal recurrence or metastases. ICIs are relatively contraindicated due to the risk of acute rejection and fatal allograft loss.<sup>54-58</sup>

### **RT**

For HCC that is not suitable for (or is recurrent following) thermal ablation, SBRT,<sup>59</sup> proton therapy<sup>60</sup> and image-guided HDR brachytherapy<sup>61</sup> are alternative options. RT may be delivered in one or few treatment fractions for HDR brachytherapy, one to five fractions for SBRT and 5-15 fractions for proton therapy, with favourable safety profiles and tumour control rates >80% at 2-5 years for tumours ≤12 cm in diameter.<sup>59,60,62</sup> Unlike thermal ablation, RT is not limited by adjacency to large vessels, exophytic growth or central location, and it is less size-dependent. RT is less appropriate for tumours adjacent to luminal gastrointestinal organs. In a phase III randomised trial, proton therapy was non-inferior to thermal ablation regarding local progression-free survival (PFS) for tumours <3 cm.<sup>60</sup> In a propensity-matched study, the risks of death and progression were higher following TACE versus HDR brachytherapy.<sup>62</sup>

### **Transarterial therapies**

Near-exclusive arterial vascularisation of HCC has led to use of intra-arterial ChT either alone or mixed with lipiodol (which is selectively retained by HCC nodules), embolising material (gelatine sponge pieces or polyvinyl alcohol-calibrated particles) or radioactive beads containing yttrium-90 (<sup>90</sup>Y). Absolute contraindications for

transarterial therapies are decompensated cirrhosis or extensive tumour burden. Relative contraindications include bile duct occlusion or incompetent papilla, reduced PS, impaired liver function (Child–Pugh  $\geq$ B) and high-risk oesophageal varices, as well as portal vein thrombosis for TACE.<sup>63</sup>

**TACE.** The benefit of TACE in prolonging OS has been demonstrated in selected asymptomatic patients with maintained liver function, BCLC A or early BCLC B disease and a low tumour burden not amenable to surgery or ablation.<sup>64</sup> A median OS of 30-45 months can be expected in this population.<sup>65</sup> Staged approaches and meticulous liver-sparing techniques have proven decisive for good patient outcomes.<sup>66</sup> Poor outcomes have been reported following TACE in patients with Child–Pugh B disease, portal vein invasion, high tumour burden or deteriorating liver function.<sup>67-69</sup> Several scores have been developed to identify patients that can benefit from TACE. The hepatoma arterial embolisation prognostic score defines four distinct prognostic groups with respect to OS.<sup>67</sup> The TACE Predict model similarly identifies four risk groups, including those undergoing TACE repetition, where response is an additional variable.<sup>70</sup>

Compared with conventional TACE, doxorubicin-eluting beads (DEB)-TACE is associated with fewer side-effects related to systemic doxorubicin exposure.<sup>71</sup> Three randomised phase II trials have compared conventional TACE with bland embolisation;<sup>72-74</sup> none reported clinical benefit with the addition of ChT and non-inferiority was not formally proven. The optimal duration and frequency of TACE is not defined.

No clinically meaningful benefit has been shown for systemic therapy with TKIs (sorafenib, brivanib or orantinib) in combination with or following TACE compared with TACE alone.<sup>75-78</sup> A small, prospective, randomised study and a meta-analysis of RCTs evaluating TACE–lenvatinib demonstrated improved rates of radiographic response but higher rates of toxicity.<sup>79,80</sup> EMERALD-1 reported improved PFS by adding durvalumab–bevacizumab to TACE in patients with early- and intermediate-stage HCC.<sup>81</sup> Similarly, LEAP-012 demonstrated improved PFS with TACE–pembrolizumab–lenvatinib versus TACE–placebo.<sup>82</sup> While no OS data have been reported for EMERALD-1, TACE–pembrolizumab–lenvatinib was not associated with

improved OS at first interim analysis of LEAP-012.<sup>82</sup> In EMERALD-1, the rate of any grade 3-4 adverse events (AEs) increased from 23% in patients receiving TACE–placebo to 45.5% in those receiving TACE–durvalumab–bevacizumab.<sup>81</sup> The rate of grade 5 AEs increased from 5.5% with TACE–placebo to 10.4% with TACE–durvalumab–bevacizumab. Similarly, the rate of grade  $\geq 3$  AEs increased from 31% with TACE–placebo to 71% TACE–pembrolizumab–lenvatinib in LEAP-012.<sup>82</sup> Considering the immature OS data and increased risk of toxicity, shared decision making is recommended when considering adding durvalumab–bevacizumab or pembrolizumab–lenvatinib to TACE in patients with intermediate-stage HCC.

**TARE.** TARE (injection of <sup>90</sup>Y-loaded microspheres into the liver via the hepatic artery with no or minimal ischaemia) has demonstrated tumour response and high disease control rates with an acceptable safety profile in phase II studies and registries.<sup>83</sup> LEGACY and RASER reported clinically meaningful response rates after selective or segmental TARE (radiation segmentectomy) in single tumours  $\leq 8$  cm.<sup>84,85</sup> Use of TARE is based on successful selective tumour uptake during angiographic technetium-99m macroaggregated albumin evaluation to preserve liver function.<sup>86</sup>

Phase II RCTs have compared TARE with TACE in early- and intermediate-stage HCC, reporting favourable time to progression (TTP) with TARE over TACE.<sup>87,88</sup> The TRACE trial was halted at interim analysis as the HR for TTP (primary endpoint) was  $<0.39$  in favour of TARE.<sup>89</sup> Median OS was 30.2 months with TARE and 15.6 months with DEB-TACE (HR 0.48). Details of trials comparing TARE with sorafenib are provided in **Supplementary Material Section 3**.

### **Recommendations**

- Multidisciplinary team (MDT) management is strongly recommended for patients with early- and intermediate-stage HCC [II, A].

### **Liver resection**

- Liver resection is recommended for patients with a single tumour  $>2$  cm and no evidence of portal hypertension (BCLC 0-A) [II, A].



- Liver resection is recommended for patients with Child–Pugh A liver function without significant portal hypertension or other contraindications [III, A]
- Liver resection can be considered for well-selected patients with stable Child–Pugh B liver function and/or a minor degree of portal hypertension, with careful consideration of the risk of decompensation [III, B].
- Liver resection is recommended as an option in patients with intermediate-stage HCC (BCLC B) who are not suitable for intra-arterial therapies [II, A].
- In patients with liver cirrhosis, minimally invasive resection is the recommended method [III, A].

### **Thermal tumour ablation**

- MWA or RFA is recommended in very early-stage HCC (BCLC 0) [II, A].
- MWA or RFA is recommended as an alternative to resection in early-stage HCC (BCLC A) [II, A].
  - The choice of resection or ablation should consider technical limitations and should be discussed by an MDT [III, A].
- MWA or RFA can be recommended for solitary tumours 3-5 cm in diameter or multifocal disease ( $\leq 3$  tumours  $\leq 3$  cm) (BCLC A) in patients who are not candidates for surgical resection or as a bridge to OLT [II, B].

### **Adjuvant treatment**

- Adjuvant systemic treatment with TKIs or ICI-based combinations after resection or ablation is not recommended [I, E].
- Adjuvant anticancer therapy is not recommended following OLT [IV, E].

### **Liver transplantation**

- OLT is recommended for patients that fit the Milan criteria, when a recurrence rate of <10% and a 5-year survival rate of 70% are expected [II, A].
- UCSF criteria can also be considered in patients with HCC beyond the Milan criteria [III, B].
- OLT can be recommended over locoregional therapy in patients with an expected 5-year OS rate >50% [II, B].
- When a prolonged waiting time (>3 months) is anticipated, patients can be offered local HDR brachytherapy, SBRT, TACE, TARE or thermal ablation as a bridge to OLT [III, B]. TARE is recommended over TACE for small tumours in patients waiting for OLT [II, A].
- OLT can be considered in transplant-eligible patients with liver-limited disease following downstaging with systemic therapy, including ICIs, although there may be a higher risk for acute rejection with shorter time since last dose [IV, C].
- Switching to mTOR inhibitors cannot be routinely recommended in patients undergoing OLT for HCC [I, D].
- For patients with solitary metastases occurring  $\geq 1$  year after OLT, resection is recommended [IV, A]. Locoregional therapy can also be recommended based on size and location of the metastasis [IV, B].
- TKIs can be recommended as first-line systemic therapy for patients with multifocal HCC recurrence or metastases after OLT [IV, B].
- Ramucirumab can be considered post-TKI for patients with AFP  $\geq 400$  ng/ml [IV, B; only European Medicines Agency (EMA) and Food and Drug Administration (FDA) approved after first-line sorafenib].

## RT

- In early-stage HCC, SBRT, proton therapy and image-guided HDR brachytherapy can be considered as alternatives to thermal ablation for

tumours that are not well suited for or are recurrent following thermal ablation (BCLC A) [II, B].

### **Transarterial therapies**

- In single tumours  $\leq 8$  cm, selective or segmental TARE can be an alternative option for patients who are unfavourable for resection (BCLC A) [III, B].
- DEB-TACE or conventional lipiodol-based TACE can be recommended for patients with intermediate-stage HCC (BCLC B), although DEB-TACE can minimise the systemic side-effects of ChT [I, B].
- TARE [II, B] or bland embolisation [II, C] can be considered as alternatives to TACE in intermediate-stage HCC (BCLC B).
- TACE–durvalumab–bevacizumab or TACE–pembrolizumab–lenvatinib may be considered in patients with intermediate-stage HCC (BCLC B), but the long-term benefit has not been established [I, C; not EMA or FDA approved].
- The combination of TACE with a TKI is not recommended [I, E].
- If substantial necrosis is not achieved after the second session, TACE treatment should be stopped [III, A].
- Outside of clinical trials, therapeutic algorithms based on prognostic scores of unknown predictive value cannot be recommended for selecting patients for initial and repeated TACE [III, D].
- Modified RECIST (mRECIST) criteria should be used to assess the efficacy of locoregional therapies in intermediate-stage HCC [III, A].

### **MANAGEMENT OF ADVANCED HCC**

Systemic therapy is recommended for patients with intermediate-stage disease who are not suitable for, or who have progressed despite, local therapies (BCLC B) and

for patients with advanced HCC and good liver function (BCLC C). An algorithm for systemic treatment of advanced HCC is shown in **Figure 2**. External beam RT (EBRT) has demonstrated benefits in patients with painful bone metastases or hepatic pain due to high HCC burden.<sup>90</sup>

### ***First-line treatment***

**Atezolizumab–bevacizumab.** IMbrave150, which evaluated atezolizumab–bevacizumab in unresectable HCC, was the first phase III study to demonstrate a survival advantage for any agent over sorafenib. Median OS was 19.2 months with atezolizumab–bevacizumab versus 13.4 months with sorafenib (HR 0.66).<sup>91</sup> Atezolizumab–bevacizumab achieved an objective response rate (ORR) of 30% versus 11% with sorafenib, including an 8% complete response rate with atezolizumab–bevacizumab versus <1% with sorafenib.<sup>91</sup> Treatment-related grade 3-4 AEs were consistent with the known side-effects of each drug and were comparable between arms. There was also a notable delay in the deterioration of quality of life measures in the atezolizumab–bevacizumab group compared with the sorafenib group.<sup>92</sup> Due to the increased risk of bleeding associated with bevacizumab, endoscopies were required within 6 months before enrolment.<sup>92</sup> ORIENT-32, evaluating a bevacizumab biosimilar in combination with the anti-programmed cell death protein 1 (PD-1) inhibitor sintilimab, has provided confirmatory evidence for the findings of IMbrave150 in an exclusively Chinese population.<sup>93</sup>

**Durvalumab–tremelimumab.** HIMALAYA was the first trial to report the effectiveness of dual ICI therapy. The study compared durvalumab–tremelimumab, durvalumab monotherapy and sorafenib monotherapy.<sup>94</sup> Improved median OS was observed with the single tremelimumab regular interval durvalumab (STRIDE) regimen (tremelimumab 300 mg in one dose plus durvalumab 1500 mg every four weeks) compared with sorafenib alone (16.4 versus 13.8 months; HR 0.78).<sup>94</sup> The trial also demonstrated that durvalumab monotherapy was non-inferior to sorafenib (secondary endpoint; median OS 16.6 versus 13.8 months; HR 0.86).<sup>94</sup> STRIDE and durvalumab monotherapy resulted in 5-year OS rates of 19.6% and 14.4%, respectively, compared with 9.4% for sorafenib.<sup>95</sup> Treatment-related AEs (TRAEs) of

any grade were less common with durvalumab versus sorafenib, but serious TRAEs occurred with similar frequency.<sup>94</sup> Adding tremelimumab doubled serious TRAEs, including immune AEs (35.8% in the durvalumab–tremelimumab arm versus 16.5% in the durvalumab monotherapy arm across all grades). Grade 3-4 AEs occurred in 12.5% of patients in the durvalumab–tremelimumab arm versus 6.4% in the durvalumab monotherapy arm. High-dose steroids were required to treat immune AEs in 20.1% of patients receiving durvalumab–tremelimumab compared with 9.5% receiving durvalumab monotherapy.

**Nivolumab–ipilimumab.** Nivolumab–ipilimumab versus lenvatinib (in 90% of patients) or sorafenib was evaluated in the global phase III CheckMate-9DW study.<sup>96</sup> OS was improved with nivolumab–ipilimumab versus TKIs (median OS 23.7 versus 20.6 months; HR 0.79). The OS benefit was generally consistent across patient subgroups; however, the Kaplan–Meier curves crossed after ~12 months, suggesting a potential early detrimental effect of the ICI-based combination. There was no improvement in PFS, but ORR was 36% with nivolumab–ipilimumab compared with 13% for the TKIs. TRAEs of any grade were reported in 84% of patients receiving nivolumab–ipilimumab and 91% of patients receiving a TKI. Grade 3-4 TRAEs, including immune AEs, occurred in 41% and 42% of patients, respectively. Treatment-related death occurred in 4% of patients receiving nivolumab–ipilimumab. Treatment was discontinued in 18% of patients receiving nivolumab–ipilimumab due to AEs and high-dose steroids were required to treat immune AEs in 28%. The B grade of recommendation assigned to nivolumab–ipilimumab reflects the opinion of 66% of authors, whereas 34% favoured an A grade.

**Camrelizumab–rivoceranib.** CARES-310 evaluated the anti-PD-1 antibody camrelizumab and the vascular endothelial growth factor receptor 2-targeted TKI rivoceranib versus sorafenib for the first-line treatment of unresectable HCC.<sup>97</sup> To date, this is the only phase III trial to demonstrate significant improvements in both PFS and OS with an ICI–TKI combination versus single-agent TKI in the first-line setting. Median OS was significantly improved with camrelizumab–rivoceranib versus sorafenib (23.8 versus 15.2 months; HR 0.64).<sup>98</sup> ORR was also improved with

camrelizumab–rivoceranib (27% versus 6% using RECIST v1.1). Grade 3-4 TRAEs occurred in 81% of patients receiving camrelizumab–rivoceranib and in 52% of those receiving sorafenib.<sup>97</sup> Common TRAEs included hypertension, hand-foot syndrome and elevated aspartate aminotransferase levels. TRAEs led to discontinuation of camrelizumab in 17.6% and rivoceranib in 16.9% of patients in the camrelizumab–rivoceranib group; discontinuation of both agents occurred in 4.4% of patients. Sorafenib was discontinued due to TRAEs in 4.8% of patients. The B grade of recommendation assigned to camrelizumab–rivoceranib reflects the opinion of 83% of authors, whereas 17% favoured an A grade.

**Tislelizumab.** The phase III RATIONALE-301 trial evaluated tislelizumab, a monoclonal antibody with high affinity and specificity for PD-1, versus sorafenib.<sup>99</sup> The primary endpoint of non-inferiority was met with a median OS of 15.9 versus 14.1 months, respectively (HR 0.85). ORR was 14.3% in the tislelizumab arm. Tislelizumab was associated with fewer TRAEs leading to discontinuation (6.2% versus 10.2% with sorafenib) and fewer grade  $\geq 3$  TRAEs (22.2% versus 53.4%, respectively).

**Lenvatinib.** Lenvatinib was compared with sorafenib as first-line therapy in the open-label, global, phase III REFLECT trial.<sup>100</sup> The primary endpoint was met, demonstrating non-inferiority for lenvatinib with a median OS of 13.6 months compared with 12.3 months for sorafenib (HR 0.92). The secondary endpoints, however, favoured lenvatinib with a superior ORR (24% versus 9% by mRECIST) and PFS (7.4 versus 3.7 months). There were differences in the AE profile of the two drugs with hypertension, proteinuria, dysphonia and hypothyroidism more common with lenvatinib, whilst hand-foot syndrome, diarrhoea and alopecia were more common with sorafenib. Subsequently, lenvatinib was used as the control in the phase III LEAP-002 study in which lenvatinib achieved a median OS of 19.0 months.<sup>101</sup> Lenvatinib has also been combined with TACE and compared with lenvatinib alone in the open-label LAUNCH trial in China.<sup>79</sup> Median OS was 17.8 months with TACE–lenvatinib but only 11.5 months with lenvatinib monotherapy. The global relevance of this study is uncertain.

**Sorafenib.**

Sorafenib was the first systemic therapy to demonstrate a survival benefit in advanced HCC in a placebo-controlled phase III trial.<sup>102</sup> A confirmatory trial conducted in Asia (including mainly patients with a background of HBV infection) resulted in a similar HR in favour of sorafenib.<sup>103</sup> Subsequently, sorafenib has been used as the control arm in multiple trials in the first-line setting, in which the median OS for sorafenib was 13.0-15.5 months, perhaps reflecting the use of second-line agents, patient selection and better management of AEs.<sup>104,105</sup> The most common TRAEs are diarrhoea, fatigue, hand-foot syndrome and rash, and around a quarter of patients require dose reduction due to AEs.<sup>102</sup>

### ***Second-line treatment***

**Regorafenib.** The phase III RESORCE trial compared regorafenib with placebo in patients who had progressed on sorafenib but tolerated sorafenib  $\geq 400$  mg daily for  $\geq 20$  of the 28 days before discontinuation.<sup>106</sup> Regorafenib was associated with improved OS (median 10.6 versus 7.8 months with placebo; HR 0.63). ORR with regorafenib was 11% by mRECIST and PFS was 3.1 months. Regorafenib was discontinued due to AEs in 25% of patients and the most common grade 3-4 AEs included hypertension, hand-foot syndrome, fatigue and diarrhoea.

**Cabozantinib.** Cabozantinib was compared with placebo in the global, phase III CELESTIAL trial in patients who had received one or two prior therapies including sorafenib.<sup>107</sup> Median OS was superior in the cabozantinib arm (10.2 versus 8.0 months with placebo; HR 0.63). PFS was also improved with cabozantinib (5.2 versus 1.9 months). ORR with cabozantinib was 4% by RECIST v1.1. The most common grade 3-4 AEs were hand-foot syndrome, hypertension, fatigue and diarrhoea, and dose reductions were required in 62% of patients. Cabozantinib was subsequently included in COSMIC-312, which evaluated first-line cabozantinib versus sorafenib as a secondary endpoint.<sup>105</sup> The final analysis reported a median PFS of 5.8 months for cabozantinib and 4.3 months for sorafenib. In the absence of data demonstrating non-inferior survival, first-line cabozantinib cannot be recommended. A prospective clinical trial of cabozantinib following prior ICI-based regimens reported a median OS of 9.9 months.<sup>108</sup>

**Ramucirumab.** The phase III REACH trial failed to demonstrate superiority for second-line ramucirumab over placebo in advanced HCC, but a subgroup analysis suggested benefit for patients with serum AFP  $\geq 400$  ng/ml.<sup>109</sup> The subsequent REACH-2 trial restricted enrolment to patients with AFP  $\geq 400$  ng/ml.<sup>110</sup> There was a significant improvement in OS with ramucirumab (median 8.5 versus 7.3 months with placebo; HR 0.71) although absolute survival in both arms was poor, reflecting the adverse prognosis conferred by elevated AFP. ORR by RECIST v1.1 was 5% with ramucirumab.<sup>110</sup> Ramucirumab was generally well tolerated; hypertension was the most common grade 3-4 TRAE (8%). The rate of treatment discontinuation due to TRAEs was 11%, and 5% of patients required dose reductions for AEs.

**Immunotherapy.** The FDA granted accelerated approval for second-line nivolumab–ipilimumab and pembrolizumab, based on efficacy data from CheckMate-040 and KEYNOTE-224.<sup>111,112</sup> Subsequent phase III trials of second-line pembrolizumab failed to meet their primary endpoints, although the KEYNOTE-394 trial recently reported positive results in an Asian population.<sup>104,113</sup> Based on the positive phase III trials, ICI-based combinations are recommended in the first-line setting. There are so far no published data on treatment beyond progression and the continuation of ICI after failure in prior lines.

### **ChT**

Information on ChT trials in HCC is available in **Supplementary Material Section 4.**

### ***Sequencing and decision making for systemic therapy***

Systemic therapy selection is influenced by several considerations including efficacy, toxicity, contraindications and predictive factors. Typically, candidates for systemic therapy should have Child–Pugh A liver function and an Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1, consistent with clinical trial patient demographics. The preferred first-line treatment is usually combination therapy including a PD-1 or programmed death-ligand 1 (PD-L1) inhibitor. Direct comparisons between studies should be avoided due to differences in patient populations. All four ICI combinations are, consequently, regarded as viable first-line options, pending approval from the EMA and FDA for nivolumab–ipilimumab and



camrelizumab–rivoceranib. Consideration of side-effects is crucial; for instance, as bevacizumab carries an increased risk of variceal bleeding, upper endoscopy is recommended for the diagnosis and treatment of any varices.<sup>114</sup> Unlike IMbrave150, HIMALAYA did not require endoscopy; however, it should be noted that patients with advanced portal vein thrombosis classified as Vp4 were excluded from HIMALAYA and CheckMate-9DW, but not from IMbrave150 and CARES-310 (albeit only partial occlusion was permitted in CARES-310). Finally, high rates of TRAEs and treatment discontinuations were observed with nivolumab–ipilimumab and camrelizumab–rivoceranib in pivotal trials. In a network meta-analysis of first-line therapies, camrelizumab–rivoceranib was associated with a significantly higher risk of TRAEs compared with other regimens.<sup>115</sup> Overall, all four ICI regimens can be considered as first-line therapy but atezolizumab–bevacizumab should not be given when there is a risk of bleeding.

To date, no validated predictive markers have been identified for ICI therapy in HCC. Initial data suggested potential negative predictive value of non-alcoholic steatohepatitis or non-viral liver disease for ICI efficacy, but this was not confirmed in a meta-analysis of eight randomised trials.<sup>116</sup> For patients with contraindications to ICIs, sorafenib or lenvatinib remain suitable first-line treatments.<sup>100</sup> Between these two options, lenvatinib is favoured for its higher ORR, better PFS and longer OS in recent phase III trials.<sup>96,100,101</sup>

In the second-line setting, the only treatments with evidence-based sequencing are regorafenib, cabozantinib or ramucirumab following sorafenib. There is no apparent difference in efficacy between these agents and optimal treatment sequences have yet to be defined, with ramucirumab reserved for patients with AFP >400 ng/ml. The effectiveness of second-line therapies after lenvatinib or ICI combinations remains under investigation. Prospective data collection and registries may also provide further data in due course.

## ***Recommendations***

### **First-line treatment**

- For patients with well-preserved liver function and ECOG PS 0-1 (BCLC B-C):

- Atezolizumab–bevacizumab [I, A; ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 5] or durvalumab–tremelimumab [I, A; ESMO-MCBS v1.1 score: 5] are recommended.
- In patients with portal hypertension, screening for varices is strongly recommended before initiation of atezolizumab–bevacizumab [IV, A].
- Camrelizumab–rivoceranib [I, B; not EMA or FDA approved] or nivolumab–ipilimumab [I, B; not EMA or FDA approved] can be recommended.
- Durvalumab [I, A; ESMO-MCBS v1.1 score: 4; EMA approved, not FDA approved] or tislelizumab [I, A; not EMA or FDA approved] should be considered for patients who have contraindications to ICI combination therapies.
- Lenvatinib [I, A; non-inferiority established versus sorafenib via ESMO-MCBS v1.1] or sorafenib [I, A; ESMO-MCBS v1.1 score: 3] are recommended for patients who have contraindications to ICI therapy.
- For patients with poor liver function and/or ECOG PS  $\geq 2$  (BCLC D), best supportive care is recommended, including SBRT for pain [III, A].

### **Second-line treatment**

- For patients with well-preserved liver function and ECOG PS 0-1 who have progressed on  $\geq 1$  systemic therapies:
  - Regorafenib [I, A; ESMO-MCBS v1.1 score: 4; EMA and FDA approved after first-line sorafenib] or cabozantinib [I, A; ESMO-MCBS v1.1 score: 3; EMA and FDA approved after first-line sorafenib] should be considered.
  - Ramucirumab can be considered for patients with AFP  $\geq 400$  ng/ml [I, B; ESMO-MCBS v1.1 score: 1; EMA and FDA approved after first-line sorafenib].

- Sorafenib should be considered after first-line lenvatinib [IV, A; ESMO-MCBS v1.1 score: 3].
- Lenvatinib should be considered after first-line ICI therapy [IV, A; not EMA or FDA approved for second-line use].
- Sorafenib can be considered after first-line ICI therapy [IV, B; ESMO-MCBS v1.1 score: 3]

## **ChT**

- Systemic ChT has not been shown to improve survival in randomised trials and cannot be recommended [II, D].

## **Sequencing systemic therapy**

- The use of all approved drugs is recommended as sequential therapy following ICI combinations or lenvatinib [III, A].

## **RT**

- EBRT should be used to treat painful bone metastases [III, A] or hepatic pain due to high HCC burden [II, A].

## **ENDPOINTS FOR CLINICAL TRIALS**

Information on endpoints used in HCC trials is available in **Supplementary Material Section 5**.

### ***Recommendations***

- Major pathological response should be the primary endpoint for phase II studies in the neoadjuvant setting, with OS as a secondary endpoint [V, A].
- RFS should be the primary endpoint for phase III studies in the neoadjuvant setting, with major pathological response and OS as secondary endpoints [V, A].

- RFS should be the primary endpoint for RCTs in the adjuvant setting, with OS as a secondary endpoint [V, A].
- OS should be the primary endpoint for RCTs in intermediate-stage HCC [V, A]. Co-primary endpoints of OS and PFS can also be recommended, although less strongly [V, B].
- OS should be the primary endpoint for RCTs in advanced HCC, with PFS as a secondary endpoint [V, A]. The use of co-primary endpoints cannot be recommended [V, D].

## **RESPONSE ASSESSMENT AND FOLLOW-UP**

Information on follow-up for patients with HCC is available in **Supplementary Material Section 6** and **Supplementary Table S4**.

### ***Recommendations***

- Viable tumour should be assessed using CT or MRI and should be defined as uptake of contrast agent in the arterial phase [III, A].
- mRECIST can be recommended for assessment of response or progression after locoregional therapies [III, B].
- mRECIST criteria can be recommended in daily clinical practice to assess lesion viability for therapy decision making [III, B].
- For patients who have received radical treatments (surgery or thermal ablation), with or without adjuvant therapy, follow-up should include clinical evaluation of liver decompensation and early detection of recurrence by multiphasic CECT or CEMRI every 3 months during the first 2 years, followed by surveillance every 6 months for  $\leq 5$  years [III, A].
- For patients with advanced HCC who have received local therapies and/or systemic agents, follow-up should include clinical evaluation of liver

decompensation and assessment of tumour progression by dynamic CT or MRI every 3-4 months to guide therapy decisions [III, A].

## METHODOLOGY

This Clinical Practice Guideline (CPG) was developed in accordance with the ESMO standard operating procedures for CPG development

(<https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology>). All

recommendations provided are based on current scientific evidence and the authors' collective expert opinion. Where recommendations for multiple different treatment options exist, prioritisation is illustrated by ordering these options according to: level of evidence (LoE) and grade of recommendation (GoR); where equal, by ESMO-MCBS score; where equal, by alphabetical order. The relevant literature has been selected by the expert authors. A table of ESMO-MCBS scores is included in

**Supplementary Table S5**. ESMO-MCBS v1.1<sup>117</sup> was used to calculate scores for new therapies/indications approved by the EMA or FDA

(<https://www.esmo.org/Guidelines/ESMO-MCBS>). The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this CPG. LoEs and GoRs have been applied using the system shown in **Supplementary Table S6**.<sup>118</sup> Statements without grading were considered justified standard clinical practice by the authors. For future updates to this CPG, including eUpdates and Living Guidelines, please see the ESMO Guidelines website: <https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-gastrointestinal-cancers/hepatocellular-carcinoma-esmo-clinical-practice-guidelines-for-diagnosis-treatment-and-follow-up>.

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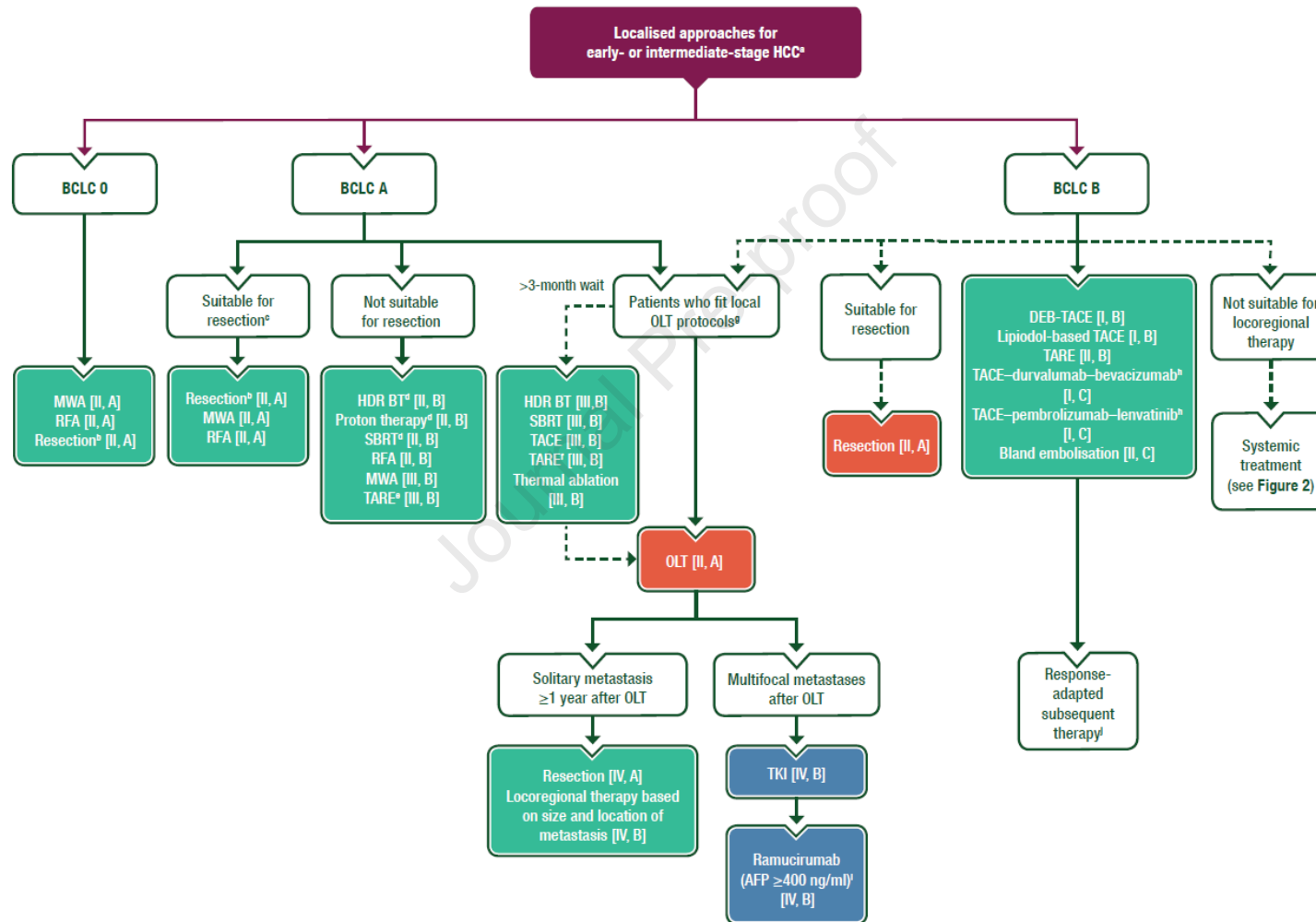
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## FIGURES

Figure 1. Management of early- or intermediate-stage HCC.



Purple: algorithm title; orange: surgery; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects; dashed lines: optional therapy.

AFP,  $\alpha$ -foetoprotein; BCLC, Barcelona Clinic Liver Cancer; DEB-TACE, doxorubicin-eluting beads transarterial chemoembolisation; EMA, European Medicines Agency; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; HDR BT, high-dose rate brachytherapy; ICI, immune checkpoint inhibitor; MDT, multidisciplinary team; MWA, microwave ablation; OLT, orthotopic liver transplantation; RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy; TACE, transarterial chemoembolisation; TARE, transarterial radioembolisation; TKI, tyrosine kinase inhibitor; UCSF, University of California San Francisco.

<sup>a</sup>MDT management is strongly recommended [II, A].

<sup>b</sup>Single tumour >2 cm and no evidence of portal hypertension. Liver resection is also recommended for patients with Child–Pugh A liver function without significant portal hypertension or other contraindications [III, A] and can be considered for well-selected patients with stable Child–Pugh B liver function and/or a minor degree of portal hypertension, with careful consideration of risk of decompensation [III, B].

<sup>c</sup>The choice of resection or ablation should consider technical limitations and should be discussed by an MDT [III, A]

<sup>d</sup>If unsuitable for or recurrent following thermal ablation.

<sup>e</sup>Single tumours  $\leq 8$  cm.



<sup>f</sup>TARE is recommended over TACE for small tumours [II, A].

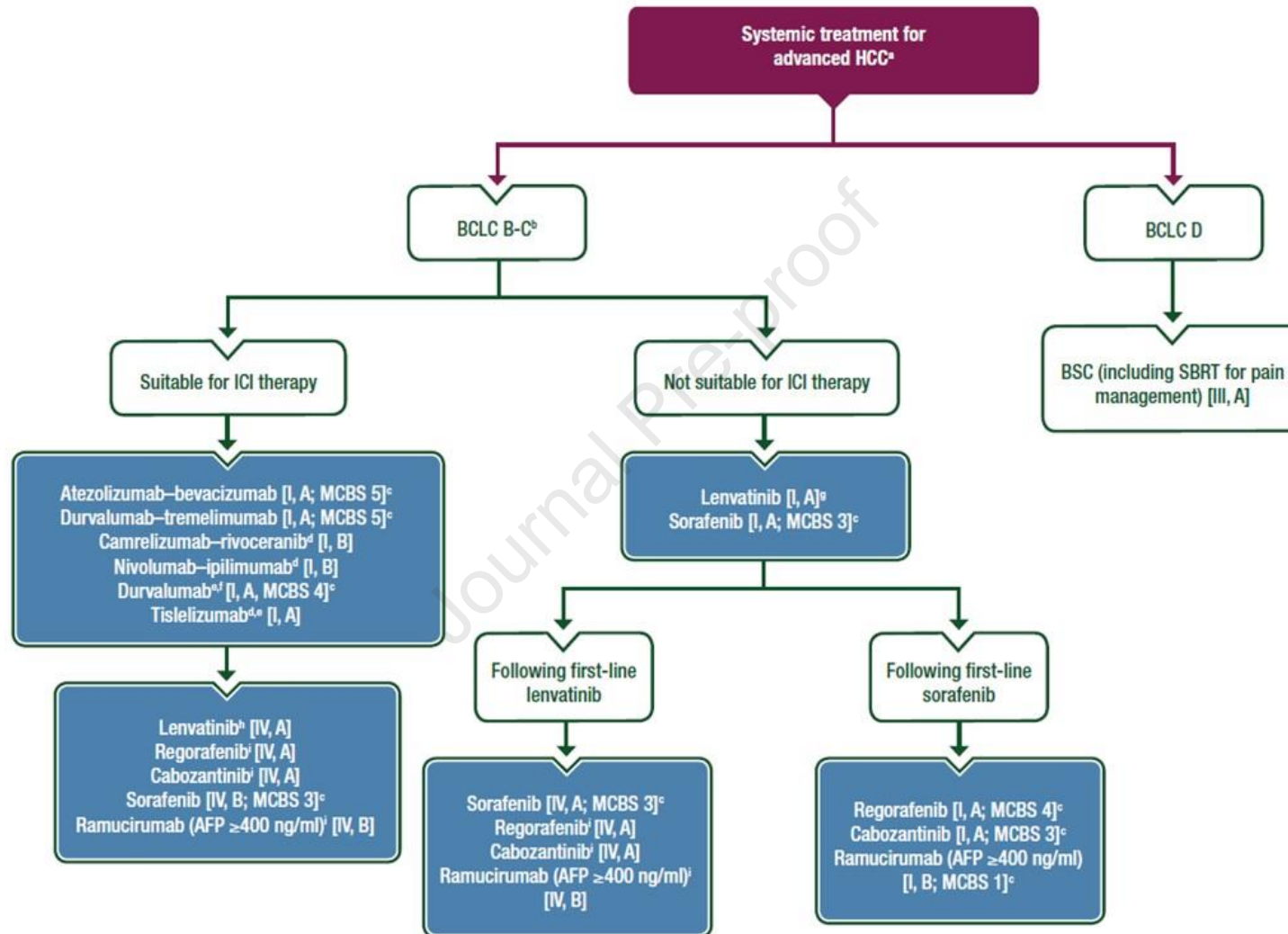
<sup>g</sup>OLT is recommended for patients that fit the Milan criteria, when a recurrence rate of <10% and a 5-year survival rate of 70% are expected [II, A] but UCSF criteria can also be considered [III, B]. OLT can be recommended over locoregional therapy in patients with an expected 5-year survival rate >50% [II, B].

<sup>h</sup>Not EMA or FDA approved.

<sup>i</sup>Only EMA and FDA approved for use after first-line sorafenib.

<sup>j</sup>OLT can be considered in transplant-eligible patients with liver-limited disease following downstaging with systemic therapy, including ICIs, although there may be a higher risk for acute rejection with shorter time since last dose [IV, C].

Figure 2. Management of advanced HCC.



Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.

AFP,  $\alpha$ -foetoprotein; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; EMA, European Medicines Agency; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; MCBS, Magnitude of Clinical Benefit Scale; PS, performance status; SBRT, stereotactic body radiotherapy.

<sup>a</sup>Locoregional therapies may be appropriate for selected patients (see **Figure 1**).

<sup>b</sup>Patients with well-preserved liver function and ECOG PS 0-1

<sup>c</sup>ESMO-MCBS v1.1<sup>117</sup> was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (<https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms>).

<sup>d</sup>Not EMA or FDA approved.

<sup>e</sup>In patients with contraindications to ICI combinations.

<sup>f</sup>EMA approved, not FDA approved.

<sup>g</sup>Non-inferiority established versus sorafenib via ESMO-MCBS v1.1.

<sup>h</sup>Not EMA or FDA approved for second-line use.

<sup>i</sup>Only EMA and FDA approved for use after first-line sorafenib.

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