Hepatocellular carcinoma

Arndt Vogel, Tim Meyer, Gonzalo Sapisochin, Riad Salem, Anna Saborowski

Hepatocellular carcinoma is one of the most common cancers worldwide and represents a major global health-care challenge. Although viral hepatitis and alcohol remain important risk factors, non-alcoholic fatty liver disease is rapidly becoming a dominant cause of hepatocellular carcinoma. A broad range of treatment options are available for patients with hepatocellular carcinoma, including liver transplantation, surgical resection, percutaneous ablation, and radiation, as well as transarterial and systemic therapies. As such, clinical decision making requires a multidisciplinary team that longitudinally adapts the individual treatment strategy according to the patient's tumour stage, liver function, and performance status. With the approval of new first-line agents and second-line agents, as well as the establishment of immune checkpoint inhibitor-based therapies as standard of care, the treatment landscape of advanced hepatocellular carcinoma is more diversified than ever. Consequently, the outlook for patients with hepatocellular carcinoma has improved. However, the optimal sequencing of drugs remains to be defined, and predictive biomarkers are urgently needed to inform treatment selection. In this Seminar, we present an update on the causes, diagnosis, molecular classification, and treatment of hepatocellular carcinoma.

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Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany (Prof A Vogel MD, A Saborowski MD); **Research Department of Oncology, UCL Cancer Institute, University College London, Royal Free Hospital, London, UK** (T Meyer PhD FRCP); **Abdominal Transplant & HPB Surgical Oncology, University Health Network, University of Toronto, ON, Canada** (G Sapisochin MD PhD); **Department of Radiology, Northwestern University, Chicago, IL, USA** (R Salem MD MBA)

Correspondence to:
Prof Arndt Vogel, Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, 30625 Hannover, Germany
vogel.arndt@mh-hannover.de

Introduction

Hepatocellular carcinoma is one of the most common malignancies and a leading cause of cancer-related mortality worldwide. In this Seminar, we discuss the epidemiology, risk factors, prognostic factors, diagnosis, and treatment (from surgery, liver transplantation, and local ablative and intra-arterial therapies to the latest developments in molecular and immune-based therapies for advanced disease) and provide perspectives for future developments.

Epidemiology and risk factors

In 2020, almost 906000 people were diagnosed with liver cancer globally, the most common form of which was hepatocellular carcinoma (figure 1).[1] Hepatocellular carcinoma is the third leading cause of cancer deaths worldwide, with a relative 5-year survival rate of approximately 18%. The similarity between incidence and mortality (830000 deaths per year) underlines the dismal prognosis associated with this disease.[2]

The diagnosis of hepatocellular carcinoma peaks in people aged between 60 and 70 years, and predominantly affects men.[3] The incidence of hepatocellular carcinoma varies by geographical region and ethnicity, which is largely attributed to the prevalence of (and the age of exposure to) major risk factors. Most patients with hepatocellular carcinoma have a background of chronic liver disease as a consequence of chronic infections with the hepatitis B virus (HBV) or hepatitis C virus (HCV), alcohol abuse or alcoholic steatohepatitis (ASH), and non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH). Obesity, diabetes, and nicotine use are also associated with increased incidence of hepatocellular carcinoma, as are rare conditions such as haemochromatosis or hereditary tyrosinaemia type 1. Additionally, rates of hepatocellular carcinoma in patients with HIV have increased, specifically in those who are co-infected with HBV or HCV.[4] Exposure to aflatoxin B1 is especially relevant in Asia, where it overlaps with HBV infection.[5] The prevalence of risk factors for hepatocellular carcinoma varies globally, with a predominance of HBV in Asia, HCV in Japan, and NAFLD and NASH and alcohol in Europe and North America. In many cases, the risks of developing hepatocellular carcinoma are multifactorial and include demographic factors (age, sex, and ethnicity), severity and activity of underlying disease (fibrosis stage, inflammatory activity, and treatment), metabolic factors (diabetes and obesity), and lifestyle factors (alcohol intake and smoking). The global incidence of viral hepatitis-related malignancies has declined since the 2000s because of the implementation of neonatal HBV vaccination programmes and the availability of highly effective antiviral treatments for HBV and HCV.[6–10] To predict the remaining risk of hepatocellular carcinoma in these patients, several scores have been established and validated that help to guide surveillance strategies, specifically for patients with liver cirrhosis.[11–13] Of note, antiviral treatment improves survival in patients with HBV-related hepatocellular carcinoma, and most likely also in HCV-related hepatocellular carcinoma. However, the long-term effect of successful anti-HCV therapy on the recurrence risk of hepatocellular carcinoma remains inconclusive.[14–17]

Although the prevalence of virally driven hepatocellular carcinoma has declined, the incidence of NAFLD and NASH-related liver cancer has increased.[18] NAFLD is part of a multisystem disease and is considered the hepatic manifestation of the metabolic syndrome,[19] although it

Search strategy and selection criteria

We searched MEDLINE and PubMed databases for all articles published in English using the terms "hepatocellular carcinoma" or "liver cancer", focusing on randomised trials and other high-quality studies from Jan, 2000, up to March, 2022. Publications within the past 5 years were prioritised, although older, relevant studies that were high quality were also selected. Meeting abstracts from peer-reviewed congresses were also included if they were deemed to be of high quality and could potentially change practice.

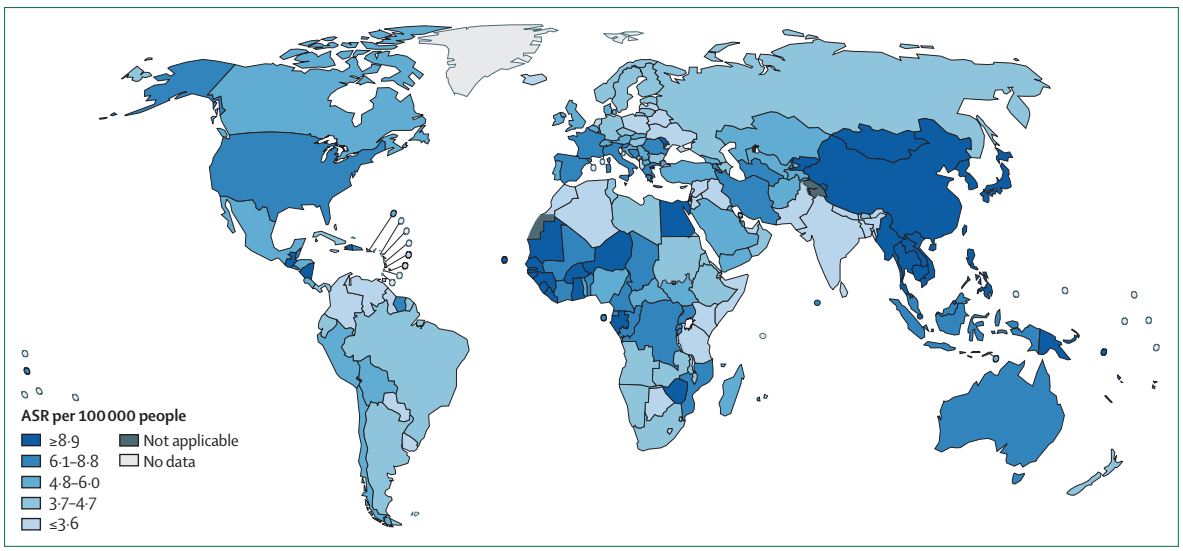

Figure 1: **ASR of liver cancer, 2020**
Reproduced from Globocan, by permission of the International Agency for Research on Cancer. ASR=age-standardised rate.

For more on **Globocan** see https://gco.iarc.fr/today/home

can also occur in people who are not obese, especially in Asian people.[20] NAFLD is now the most common chronic liver disease, with a worldwide prevalence of 25% (ranging from 14% in Africa to 32% in the Middle East, and approximately 25% in Europe and the USA).[21] Of note, optimisation of both glycaemic control and bodyweight are desirable, as they appear to be independently associated with an increased risk of liver cancer.[22] 20% to 30% of NAFLD and NASH-related hepatocellular carcinomas develop in the absence of cirrhosis. However, prospective studies that define the risk of hepatocellular carcinoma in patients with NAFLD and NASH are not yet available.[23,24] Of note, variants in patatin-like phospholipase domain containing 3 (*PNPLA3*; rs738409), transmembrane 6 superfamily member 2 (*TM6SF2*; rs58542926), and hydroxysteroid 17-beta dehydrogenase 13 (*HSD17B13*) are associated with the development of hepatocellular carcinoma in people with NAFLD and NASH, but also in people with alcoholic liver disease.[25,26] Alcohol consumption is a well-established risk factor for several diseases and accounts for approximately 5% of the global burden of cancer.[27] Alcohol-related liver disease is significantly more common in men, but the relative risk of developing hepatocellular carcinoma is higher in women compared with men.[28,29] Coffee has been consistently associated with a decreased risk of liver cancer. A meta-analysis published in 2017 showed that two cups of coffee per day could reduce risk of hepatocellular carcinoma by 35%,[30] but the mechanisms underlying the protective effects of coffee were not clear.

Prevention and screening

Chronic liver disease predisposes people to hepatocellular carcinoma. The prevention of chronic liver disease, therefore, reduces the population at risk. The effect of this approach has been clearly shown in Taiwan, where the introduction of a national HBV vaccination programme for newborn babies in 1984 resulted in a 35·9% reduction in the incidence of hepatocellular carcinoma in those younger than 30 years.[31] Although no equivalent vaccination for HCV is available, the advent of direct-acting antivirals offers the prospect of eliminating HCV in line with the aims of the global health sector strategy for viral hepatitis.[32] Meanwhile, ASH, NAFLD, and NASH are emerging as dominant risk factors, and public health measures are urgently needed to react to this epidemiological transition. There are, however, only few data to support the efficacy of hepatocellular carcinoma surveillance in these patients.

In those with established liver disease, chemopreventive measures that show promise include low dose aspirin,[33] statins,[34–36] and metformin.[37,38] In addition to preventing disease, early detection remains key to improving outcomes. The only randomised trial was conducted in China and there are not yet any robust data supporting the general application of screening.[39] Nevertheless, international guidelines recommend surveillance of populations at high risk with six-monthly abdominal ultrasound with or without alpha fetoprotein (AFP).[40,41] However, controversies exist regarding the value of AFP. Although some studies suggest that AFP is the best single biomarker for hepatocellular carcinoma and complements the use of ultrasound, others have questioned the sensitivity, specificity, and predictive value of AFP testing.[42] At a cutoff value of 20 ng/mL, AFP was found to have a sensitivity between 49% and 71% and a specificity between 49% and 86% in detecting hepatocellular carcinomas smaller than 5 cm.[43] In addition to a better implementation of surveillance for patients at risk, novel surveillance tests are needed,[44] particularly for the increasing number of

patients with NAFLD, for whom ultrasound performance is frequently impaired in the setting of obesity.[45] Although there is little evidence to support screening of subgroups, it should be applied in those for whom the incidence of hepatocellular carcinoma makes it cost-effective and in those for whom a competing risk of death would not prevent the benefit of early detection. This scenario is particularly relevant for patients with NAFLD and NASH without cirrhosis, for whom the incidence of hepatocellular carcinoma is low but the competing risk of death from diabetes or ischaemic heart disease is high.

Diagnosis

Hepatocellular carcinoma can be diagnosed on the basis of validated imaging criteria (in people who have liver cirrhosis) or tissue biopsy. Commonly used imaging modalities include multiphasic CT or MRI, in which hepatocellular carcinoma typically shows enhancement (brightness compared with surrounding parenchyma) in the early arterial phase, and washout (temporal decrease in enhancement relative to surrounding parenchyma) in the delayed phase. The latter creates a peripheral rim of enhancement around the tumour, resulting in the formation of a capsule; an observation highly specific for hepatocellular carcinoma.[46] This imaging feature has been prospectively confirmed and universally adopted by guidelines.[40,41,46]

Usually, solid hepatic nodules raise suspicion for hepatocellular carcinoma once they are ≥1 cm, especially in patients with liver cirrhosis. Lesions that are identified incidentally or through regular screening by ultrasound, dynamic contrast-enhanced CT or MRI of the abdomen should be obtained for further assessment. As not all tumours present with classic enhancement patterns, the liver imaging reporting and data system (LI-RADS, LR) was developed to help guide the diagnosis of hepatocellular carcinoma in patients at high risk without the need for tissue biopsy. LI-RADS is based on tumour size, contrast dynamics, capsule appearance, and threshold growth, and categorises nodules into the following categories: LI-RADS non-categorisable due to inadequate imaging; LR-1: definitely benign; LR-2: probably benign; LR-3: intermediate risk of hepatocellular carcinoma (confidence risk 12–50%); LR-4: probably hepatocellular carcinoma (47–80%); LR-5: definitely hepatocellular carcinoma (93–96%), and LR-M: a probably malignant lesion but not definitely hepatocellular carcinoma.[47]

Pathological diagnosis of hepatocellular carcinoma is typically based on the examination of a resection or explant specimen, or from a biopsy sample. Historically, biopsy has been reserved for lesions in which non-invasive imaging criteria for diagnosis are not met or are not applicable (for patients without cirrhosis). Especially in the setting of advanced disease, biopsy is now increasingly done because diagnostic certainty is needed to ensure appropriate use of systemic therapy. The routine application of biopsy in advanced disease has been shown to be safe and overcomes the limitations of non-invasive criteria.[48] Of note, a prospective multicentre audit evaluated biopsy in the setting of advanced disease and showed that the positive predictive value of non-invasive criteria for diagnosis of hepatocellular carcinoma is 91·4%. This finding shows that up to 9% of patients would receive inappropriate therapy in the absence of a biopsy.[48]

The histological classification and criteria for diagnosis of hepatocellular carcinoma have been defined by WHO and the International Consensus Group for Hepatocellular Neoplasia.[49,50] In resection and explant specimens, pathological staging is done according to the TNM classification and grade is typically defined as well, moderate, or poor.[51] Within a cirrhotic liver, the differentiation of hepatocellular carcinoma from a dysplastic nodule is supported by the presence of architectural and cellular atypia (trabecular disarray and an increased nuclear to cytoplasmic ratio), and the presence of stromal or vascular invasion. Diagnosis is further supported by immunohistochemistry for markers including glypican 3, heat shock protein 70, and glutamine synthetase. The presence of two or more of these markers increases the diagnostic specificity to 100%.[52,53] In the non-cirrhotic liver, well differentiated tumours need to be distinguished from hepatocellular adenomas. Less well differentiated tumours might need to be distinguished from other liver tumours by evidence of hepatocellular differentiation markers (eg, arginase). The morphology of hepatocellular carcinoma has been associated with specific molecular alterations. For instance, the histological subtype macrotrabecular-massive, observed in 12% of early hepatocellular carcinomas, has an aggressive phenotype with high levels of AFP and specific molecular features (ie, G3 transcriptomic subgroup, *TP53* mutations, and *FGF19* amplifications).[54] Tumours that display both hepatocytic and cholangiocytic differentiation represent a distinct entity, termed combined hepatocellular carcinoma-cholangiocarcinoma. Combined hepatocellular carcinoma-cholangiocarcinoma represents fewer than 5% of primary liver tumours and evidence suggests that this entity is associated with a worse prognosis than hepatocellular carcinoma.[55] Particular subtypes of hepatocellular carcinoma can be distinguished by pathological features, and the presence of a specific fusion transcript (DNAJB1-PRKACA) is pathognomonic for fibrolamellar hepatocellular carcinoma.

Clinical and biochemical biomarkers in hepatocellular carcinoma

To improve outcomes in hepatocellular carcinoma, it will be essential to decipher how key clinical and molecular characteristics influence disease course and treatment response. The prognosis for hepatocellular carcinoma depends not only on tumour characteristics, such as tumour burden, extrahepatic spread, vascular infiltration, or tumour differentiation, but is heavily influenced by

the underlying liver disease. Additionally, higher levels of serum AFP are significantly associated with increased mortality, independent of demographic and clinical factors or treatment, and have been shown to predict the risk of tumour recurrence after resection and liver transplantation.[56–60]

Several models and scores have been developed to evaluate the hepatic functional reserve as an independent prognostic factor for survival in patients with hepatocellular carcinoma. The Child-Pugh score, which is based on clinical and laboratory parameters, was initially conceived to assess prognosis in patients with portal hypertension undergoing surgery for variceal bleeding and is now broadly used to evaluate liver function in clinical practice. The albumin-and-bilirubin (ALBI) grading system, introduced in 2015, is based only on serum albumin and bilirubin, and consequently facilitates a more objective assessment of liver function compared with the Child-Pugh system.[61] Post-hoc analyses of several phase 3 trials have confirmed the strong prognostic role of liver function during systemic therapy in advanced hepatocellular carcinoma.[62–64]

Apart from prognostic biomarkers, predictive biomarkers to guide treatment decisions are urgently needed. Efforts in biomarker discovery must consider the substantial transcriptional and genetic heterogeneity of hepatocellular carcinoma. Several molecular signatures have been published that converge on at least two major pathway classifications: the proliferation class, characterised by chromosomal instability, and the non-proliferation class, which is associated with a better prognosis.[65–67] Although these molecular classifications (which combine transcriptomic analyses, somatic genetic alterations, and clinical and biological features) define the inter-patient hepatocellular carcinoma heterogeneity and link molecular characteristics to disease causes,[68,69] their use in clinical practice is limited and the predictive power of any of the proposed signatures has not yet been established in prospective trials.[70] With regards to atezolizumab plus bevacizumab as the current standard of care in patients with advanced hepatocellular carcinoma, a post-hoc analysis of the pivotal IMbrave150 phase 3 trial identified molecular correlates, including gene signatures for T-cell subsets and for myeloid inflammation that were positively associated with clinical outcome.[71]

See Online for appendix

Patients with hepatocellular carcinoma typically have a low to moderate tumour mutational burden, with an average of 2·9 mutations per megabase, corresponding to approximately 40 to 60 somatic coding mutations.[72] Recurrent genetic alterations include TERT promoter (50–60%), *TP53* (20–40%), *CTNNB1* (15–40%), and *ARID1A* mutations (10–20%), for which no targeted therapies are yet available.[68] As an emerging diagnostic approach, liquid biopsy, which encompasses the analysis of circulating tumour cells, cell free DNA, or exosomes, has the potential to complement and even substitute for tissue analysis. The key advantage of liquid-based diagnostics is the ability to conduct non-invasive, longitudinal sampling.[73–75] Initial data show that the presence and abundance of circulating tumour cells can predict disease prognosis and response to therapy in patients with hepatocellular carcinoma,[76] but their use in clinical management needs to be validated in prospective cohorts. In addition, high serum levels of several angiogenesis biomarkers (eg, VEGF A and ANG-2) have been associated with poor prognosis in hepatocellular carcinoma,[77] but none of these markers is able to predict response to treatment, specifically for the currently used multi-target tyrosine kinase inhibitors (TKIs).[78–82] Finally, several inflammatory markers, including the neutrophil-to-lymphocyte ratio and the C-reactive protein-based and AFP-based CRAFITY score, might be of interest in respect to the rapidly evolving field of immuno-oncology. Moreover, these markers might not only predict survival, but also identify patients who will have a greater overall survival benefit under systemic therapy.[83–86]

Treatment

Treatment options for patients with hepatocellular carcinoma are outlined in national and international guidelines, with slight differences in the therapeutic approach between Asia, Europe, and North America.[87–91] The Barcelona Clinic of Liver Cancer (BCLC) algorithm is the most widely used staging system and subdivides patients with hepatocellular carcinoma 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).[92]

Surgery

Surgery (liver resection or liver transplantation) represents the main curative treatment option for patients with hepatocellular carcinoma. Ideal candidates for liver surgery are those with single tumours and maintained liver function. Liver transplantation is generally recommended for patients with multifocal disease or decompensated cirrhosis (appendix p 1). The surgical management of patients with hepatocellular carcinoma who have cirrhosis is complex. Patients should therefore be assessed by multidisciplinary teams in experienced centres and both resection and transplantation should be considered.

When treating a patient with hepatocellular carcinoma with liver resection it is important to determine the patient's underlying liver function. Hepatocellular carcinoma in non-cirrhotic liver is less common but, in this population, liver resection should be the first treatment option if the tumour is technically resectable.[93,94] The goal of liver resection in patients with hepatocellular carcinoma is to achieve a complete R0 outcome, with clear resection margins. However, given that most patients with hepatocellular carcinoma will have underlying liver disease, liver resection should also aim to preserve as much parenchyma as possible to decrease the risk of liver

decompensation. Several refinements in surgical techniques have been made to achieve minimal morbidity and mortality after liver resection. Minimally invasive techniques have also been developed for liver surgery and represent the first option for resection of hepatocellular carcinoma in most centres worldwide due to equivalent oncological results to open surgery and better short-term outcomes.[95,96] Classically, liver resection has been recommended to patients with compensated liver cirrhosis without portal hypertension. Indirect evidence of portal hypertension is based on the presence of varices and enlarged spleen and low platelet count (<100 000 per µl). In patients that have direct measurements taken, those with a hepatic venous pressure gradient over 10 mm Hg are generally not considered for surgical resection because of the greater risk of poor outcomes.[97] However, with advancements in minimally invasive techniques, some patients with portal hypertension could benefit from liver resection with minimal risk of liver decompensation.[98,99] Pre-surgical liver function can be evaluated by model for end-stage liver disease score or ALBI score, indocyanine green clearance, or by ultrasound-based assessment of liver stiffness.[100–103] Several risk factors for poor outcome have been identified and are related to multifocality, satellitosis, and the presence of vascular invasion.[104]

There is still debate on the best type of resection, and comparisons between anatomical and non-anatomical resections in hepatocellular carcinoma have produced discrepant results.[105,106] Theoretically, anatomical liver resections should improve clinical outcomes due to the risk of satellite lesion distribution through the anatomical pedicle. Although the 5-year overall survival following surgical resection is around 70%,[107] a main drawback of resection is the high incidence of tumour recurrence in the liver, which occurs in up to 80% of patients. Concerning adjuvant treatment, evidence from the STORM trial[108] did not show a benefit of sorafenib over placebo, and no adjuvant therapy can yet be recommended. Ongoing trials aim to address the efficacy of immunotherapy as adjuvant or neo-adjuvant treatment, with initial promising results from phase 2 trials.[109–111]

Liver transplantation

A post-transplantation 5-year survival rate of 75–80%, with low risk of recurrence (approximately 15%), can be achieved in patients with hepatocellular carcinoma undergoing liver transplantation. The reason behind these superior outcomes is that liver transplantation treats both the hepatocellular carcinoma with the widest surgical margins as well as the underlying liver cirrhosis, which is a key risk factor for tumour recurrence. The main limitation for liver transplantation is the shortage of available organs for all patients in need and, therefore, efforts have been made to select patients with the best outcomes from liver transplantation. The selection of patients for liver transplantation is frequently based on criteria that strictly take the size and the number of tumours into account. However, several studies have shown that these parameters alone might not be the best predictors of outcomes, and therefore other biological markers and surrogates of tumour biology are increasingly being used to select patients for liver transplantation (appendix pp 1–2).

Owing to the imbalance between patients in need of liver transplantation and the availability of organs, patients with hepatocellular carcinoma are required to wait between 6 and 9 months in many jurisdictions around the world until they receive a liver transplant. To avoid tumour progression, patients are treated while waiting for transplantation, which is referred to as bridging therapy. Individual patients might also receive treatment to reduce tumour mass to fulfil a particular criterion for transplantation, which is known as downsizing or downstaging.[112] The most commonly applied bridging modality is transarterial chemoembolisation (TACE), but ablation and radiation are also used. In this context, living donor liver transplantation has emerged as a good option for patients with hepatocellular carcinoma and is, in experienced centres, associated with superior outcomes compared with liver transplantation from deceased donors when outcomes are assessed from the time of listing.[113,114] This result is due to a decrease in drop-out. However, a note of caution should be made when using living donors in this context to avoid fast-tracking patients with a recent hepatocellular carcinoma diagnosis to transplantation.

Ablation

Thermal ablation is recommended for patients with early-stage hepatocellular carcinoma (≤2 cm), as well as for patients with 2–4 cm lesions that are not suitable for surgical resection because of anatomical reasons or patient conditions. Radiofrequency ablation (RFA) is the most commonly used ablation technique for the treatment of hepatocellular carcinoma. The technique entails inducing thermal injury to the tumour tissue through electromagnetic energy deposition. By applying the RFA probe to the tumour, a closed-loop circuit is formed through which alternating electric fields pass. This process results in a high level of heat with ultimate damage to the target tissue. To achieve necrosis, a temperature of 50–100°C should be maintained to the entire tumour volume for 4–6 min.[115] With contemporary data, local ablation is now considered a potentially curative therapy for small hepatocellular carcinomas (<3 cm),[116,117] and most guidelines recommend RFA as first-line therapy for single tumours smaller than 2 cm.[40,118,119] In these patients, response rates of 70–90% can be achieved after 1–2 treatment sessions (appendix p 4). Superior outcomes have been shown in patients with at least a 1 cm margin. Multiple studies have compared the effectiveness of RFA to surgical resection. One trial that compared no touch multibipolar RFA to surgical resection in solitary hepatocellular carcinoma

(2–5 cm) showed similar overall survival for both methods, despite the higher rates of recurrence in the cohort that received ablation.[120] Microwave ablation (MWA) was originally developed to help achieve intraoperative haemostasis. The advantages of MWA over RFA, including higher ablative temperatures, shorter interventional times, and overcoming the heat sink effect (the cooling effect due to flowing blood that leads to a smaller ablation volume), have resulted in MWA overtaking RFA as the preferred ablation technique in early-stage hepatocellular carcinoma.[121] In a phase 2 trial[122] of 152 patients, no differences between RFA and MWA were observed in terms of local tumour progression at 2 years. Other hepatic ablation techniques, including cryoablation and irreversible electroporation, are still under investigation. Emerging data for cryoablation show similar outcomes to RFA in hepatocellular carcinoma tumours smaller than 4 cm.[123] However, a study that used propensity score matching showed a survival benefit in patients treated with RFA compared with cryoablation.[124] There have been some recent trends combining local ablation with other locoregional therapies (eg, TACE-RFA), as well as radiotherapies and immunotherapies (appendix p 4). One study that added iodine-125 to RFA was found to significantly lower recurrence of hepatocellular carcinoma and improve overall survival.[125] However, overall, these data were largely premature, with further investigations needed, and there are no guidelines that recommend ablation with systemic therapies outside of a clinical trial.

Intra-arterial therapies

As hepatocellular carcinoma tumours are hypervascular and derive most of their blood supply from the hepatic artery, intra-arterial therapy represents a mainstay of treatment for intermediate stage hepatocellular carcinoma. Intra-arterial therapy involves the direct intra-arterial injection of particles (with or without chemotherapeutic agents) within the tumour vascularity. In general, intra-arterial therapy is categorised into bland particle embolisation (TAE), chemoembolisation (conventional trans-arterial chemoembolisation [cTACE] or drug-eluting bead [DEB]-TACE), or radioembolisation. In all cases, the hepatic artery is accessed with microcatheters via groin access. Depending on the treatment, overnight hospitalisation might be necessary to manage post-embolisation syndrome for TAE and TACE.

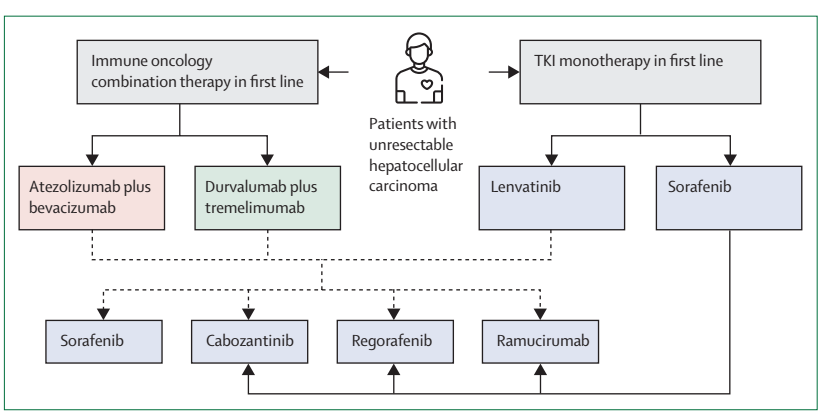

Figure 2: **Systemic therapy options for patients with hepatocellular carcinoma**
Dashed lines represent treatment sequences that are recommended without phase 3 evidence. Cabozantinib, regorafenib, and ramucirumab have been evaluated after first-line treatment with sorafenib. TKI=tyrosine kinase inhibitor.

TAE involves the injection of 100–500 micron-sized particles until stasis is reached. The rationale for this approach involves the arterial dependence of hepatocellular carcinoma tumours, with subsequent hypoxia and necrosis. The seminal TACE study[126] from 2002, which randomly assigned patients to receive cTACE, TAE, or placebo, was stopped when it was shown that cTACE had survival benefits compared with placebo. Although TAE also showed survival benefits, the study was stopped before reaching significance. Hence, no conclusion could be made about TAE in this study. Since the publication of this study, cTACE has been considered the international standard of care for intermediate stage disease, with survival rates ranging from 20 months to 36 months (appendix p 4). This procedure has been markedly improved using the principles of selectivity during injection, minimising the risk of non-target embolisation and liver decompensation. In an attempt to better standardise drug delivery and decrease post-embolisation syndrome, DEB-TACE was developed to ensure more constant and tumour-specific drug delivery. In 2010, PRECISION V,[127] an international, randomised phase 2 study that compared cTACE and DEB-TACE was published. Although the study did not meet its primary endpoint of improving objective response rate, DEB-TACE was associated with significantly fewer side-effects than cTACE that were related to the leakage of doxorubicin into the systemic circulation. Two randomised trials did not show any benefit of cTACE or DEB-TACE over TAE.[128,129] Despite these results, cTACE remains the most widely used intra-arterial therapy for intermediate stage hepatocellular carcinoma.

The technical approach for radioembolisation is identical to other intra-arterial therapies, whereby hepatic arterial access is obtained and a therapeutic is injected. Although the mechanism of action for traditional intra-aterial therapy includes ischaemia (with or without a chemotherapeutic), radioembolisation relies on the delivery of 40 micron-sized radiation particles without ischaemia or alteration in hepatic arterial blood flow. The persistence of hepatic arterial flow results in the near-elimination of post-embolisation syndrome. With fatigue being the most prominent symptom of post-radioembolisation syndrome, this treatment can be given on an outpatient basis.[130] This therapy has also been shown to have a high response rate and a long time to progression (appendix p 4).[131,132] Although early interest in radioembolisation was for locally advanced disease (vascular invasion), two prospective randomised trials[133,134]

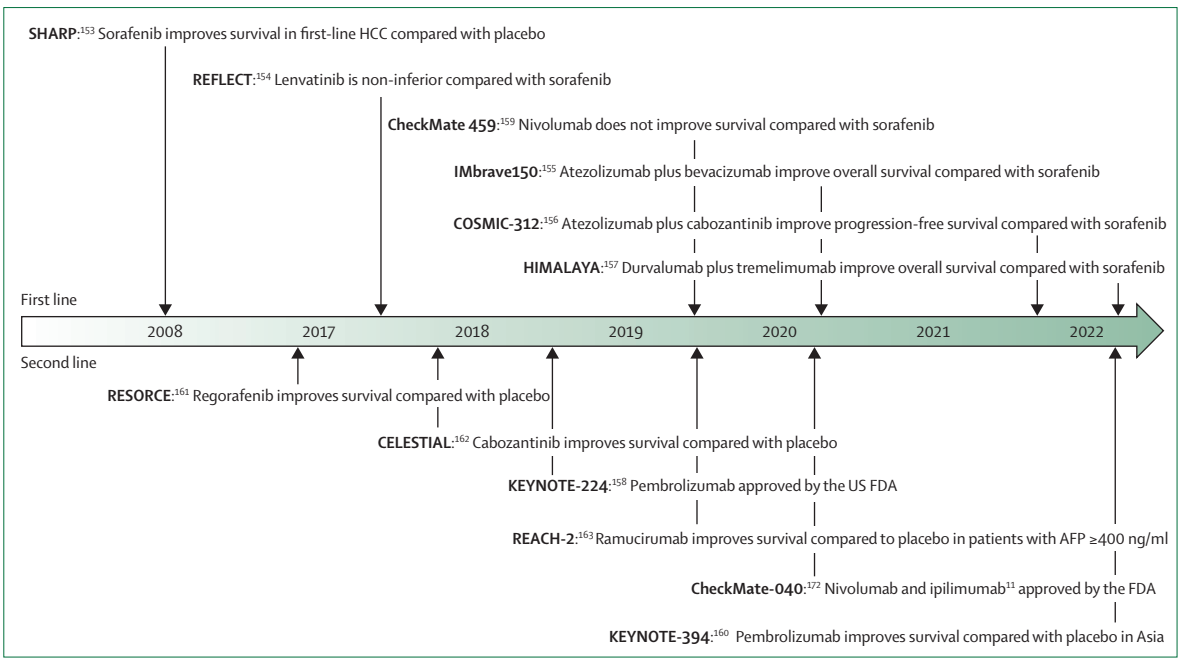

Figure 3: **Milestones in the development of systemic therapy for HCC**
AFP=alpha-fetoprotein. FDA=Food and Drug Administration. HCC=hepatocellular carcinoma.

did not provide evidence to show a survival benefit over sorafenib. In a randomised phase 2 study,[135] the importance of personalised dosimetry was confirmed when significantly higher responses were observed compared with standard dosimetry. In 2021, radioembolisation was included in the curative arm of the BCLC algorithm, with median survival exceeding 50 months.[92]

Several randomised trials have been conducted to evaluate TACE combined with TKIs to improve the efficacy of TACE. Although there were differences in trial design, agent used (sorafenib in SPACE and TACE 2; brivanib in BRISK TA; and orantinib in ORIENTAL), location (SPACE was done in Asia and the USA; BRISK TA was done globally; TACE 2 was done in the UK; and ORIENTAL was done in Japan, South Korea, and Taiwan), and primary endpoint (time to progression in SPACE; overall survival in BRISK TA and ORIENTAL; and progression-free survival in TACE 2), the results of these trials were all negative (appendix p 4).[136–139] With adapted criteria of progression, including time to untreatable progression and progression to TACE refractoriness, the TACTICS trial[140] met one of the coprimary endpoints, in which median progression-free survival significantly increased from 13·5 months with TACE to 25·2 months in patients receiving TACE plus sorafenib (equating to a 41% [p=0·006] reduction in the risk of progression with the addition of the targeted therapy). However, the longer progression-free survival did not translate into a longer overall survival in the experimental arm. Based on promising data from phase 2 studies that evaluated the combination of immune checkpoint inhibitor(ICI)-based therapies with TACE and radioembolisation, this concept is further explored in randomised phase 3 studies.[141–143] Contemporarily, the principles of safely administering intra-arterial therapies are based on angiographic selectivity (preserving hepatic parenchyma) and optimisation of local drug or radiation delivery, as well as a multidisciplinary approach of stage migration to systemic treatments.

Radiotherapy

The main radiotherapy techniques for hepatocellular carcinoma are stereotactic body radiotherapy (SBRT), proton therapy, and interstitial brachytherapy. The local precision of these strategies allows for a high tumour dose and reduces the risk of radiation-induced liver disease. A number of small prospective studies of SBRT in hepatocellular carcinoma reported local control rates of 75–95% 1 year after treatment.[144] These data are supported by large cohort studies and meta-analyses of retrospective studies not only in early hepatocellular carcinoma, but also in patients at high risk with portal vein infiltration.[145–150] SBRT can therefore be considered as a treatment option in palliative settings when other local therapies are not feasible (eg, if there is a high probability of treatment failure, limited liver function, and technical obstacles), but additional prospective trials are required to better define the role of these treatment modalities.[151] In view of the high local tumour control rate, SBRT might also be an interesting alternative to conventional bridging therapies in the context of liver transplantation to reduce the risk of waiting list dropout.[144,152]

Advanced stage

Systemic therapies

Systemic therapy is the preferred treatment modality for patients with advanced stage hepatocellular carcinoma, as well as for patients with intermediate stage hepatocellular carcinoma who do not qualify for local therapies. The survival of patients treated with systemic agents has significantly improved since 2017. With the approval of six treatment regimens by the European Medicines Agency (EMA) and eight regimens by the US Food and Drug Administration (FDA), sequential therapy should be routinely considered for patients with advanced hepatocellular carcinoma (figures 2, 3). Baseline characteristics of the pivotal trials and key efficacy parameters of approved systemic agents are summarised in tables 1 and 2.

First-line therapies

Sorafenib was the first targeted therapy to show efficacy in patients with advanced hepatocellular carcinoma. This TKI targets VEGF receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), rapidly accelerated fibrosarcoma (RAF), and several other tyrosine kinases. In the pivotal SHARP study,[153] median overall survival in the sorafenib arm was 10·7 months versus 7·9 months in patients who were given placebo. Similar results were also shown in a parallel phase 3 study involving patients who were mainly Asian and predominantly affected by HBV.[164] Of note, despite similar data for progression-free survival, overall survival in other phase 3 trials has increased over time in the sorafenib arm, peaking at 15·5 months in the COSMIC-312 study.[156] The reasons for the extended survival are likely to be multifactorial, including differences in inclusion criteria and the use of effective sequential therapies.

Lenvatinib is an oral TKI with activity against VEGFR1–3, FGFR1–4, PDGF, RET, and KIT. In the phase 3 REFLECT study,[154] which mainly enrolled Asian patients, non-inferiority of lenvatinib in comparison to sorafenib was shown in the first-line setting with a median overall survival of 13·6 months in the experimental lenvatinib arm versus 12·3 months in the control (sorafenib) arm. Concerning the key secondary endpoints, median progression-free survival and overall response rate, lenvatinib was superior to sorafenib. Adverse effects were overall slightly more pronounced in patients treated with lenvatinib, particularly hypertension and proteinuria, whereas patients who received sorafenib had more hand foot skin reactions and diarrhoea. Quality of life scores declined with both treatments, but were slightly in favour of lenvatinib.[165] Based on the data from the REFLECT study, lenvatinib has been approved by the EMA and the FDA for the first-line treatment of advanced hepatocellular carcinoma.

IMbrave150 was not only the first phase 3 study to show a significant survival benefit compared with sorafenib, but also the first positive phase 3 study with an ICI-based regimen. The study was interrupted at the first interim analysis having met its primary endpoint by showing improved overall survival with the combination of the VEGF-A antibody bevacizumab with the PD-L1 antibody atezolizumab compared with sorafenib (19·2 months versus 13·4 months in the final analysis).[155,166] Additionally, the confirmed overall response rate and progression-free survival were significantly improved in the atezolizumab plus bevacizumab arm. Despite a similar number of patients with serious adverse events, tolerability and patient reported outcomes were also favourable for the combination arm with a median time to deterioration of quality of life of 11·2 months versus 3·6 months.[167] Because of the increased risk of bleeding associated with the administration of bevacizumab, endoscopies were required within the 6 months before enrolment and screening for varices is strongly advised before treatment initiation in patients with portal hypertension. The IMbrave150 trial marked the transition towards ICI-based therapy for patients with hepatocellular carcinoma and international guidelines endorsed the combination regimen as the new standard of care in front-line treatment of advanced hepatocellular carcinoma.[87–89]

Several promising combinatorial treatment strategies involving ICIs are currently under investigation and data from two additional phase 3 trials[156,157] for first-line treatment of hepatocellular carcinoma have been reported. Based on the unique immunomodulatory and anti-angiogenic profile of the multikinase inhibitor cabozantinib, the COSMIC-312 trial[156] evaluated the efficacy of cabozantinib plus atezolizumab versus sorafenib (with overall survival and progression-free survival as dual primary endpoints) and sorafenib versus cabozantinib single agent (with progression-free survival as a secondary endpoint). The study met one of its dual primary endpoints, and showed a significant improvement in progression-free survival in the combination arm compared with sorafenib in first-line hepatocellular carcinoma (in the final analysis), which, however, did not translate into prolonged median overall survival in the interim analysis. For the secondary endpoint, the evaluation of progression-free survival with the single agents, median progression-free survival was 5·8 months with cabozantinib versus 4·3 months with sorafenib, which also did not reach the threshold of significance at this interim analysis. Grade 3 or 4 toxicities were in line with the side-effect profiles previously reported for cabozantinib, sorafenib, and atezolizumab.

The HIMALAYA trial[157] is the largest phase-3 first-line study conducted in patients with advanced hepatocellular carcinoma, and the first to report outcomes for dual ICI therapy. An initial four-arm design was used to assess the efficacy of combined checkpoint inhibition with durvalumab and tremelimumab (two different treatment regimens) or durvalumab monotherapy compared with sorafenib alone. One of the two dual therapy arms was discontinued and the remaining regimen comprised a

	IMbrave150[155] (n=501)		SHARP[153] (n=602)		REFLECT[154] (n=954)		COSMIC-312[156] (n=649)		HIMALAYA[157] (n=1171)		
	Atezolizumab plus bevacizumab (n=336)	Sorafenib (n=165)	Sorafenib (n=299)	Placebo (n=303)	Lenvatinib (n=478)	Sorafenib (n=476)	Atezolizumab plus cabozantinib (n=432)	Sorafenib (n=217)	Stride (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
Baseline characteristics (%)											
ECOG 0	209 (62%)	103 (62%)	161 (54%)	164 (54%)	304 (64%)	301 (63%)	277 (64%)	144 (66%)	244 (62%)	237 (61%)	241 (62%)
ECOG 1	127 (38%)	62 (38%)	114 (38%)	117 (39%)	174 (36%)	175 (37%)	153 (36%)	73 (34%)	148 (38%)	150 (39%)	147 (38%)
BCLC A	8 (2%)	6 (4%)	0	0	0	0	0	0	0	0	0
BCLC B	52 (15%)	26 (16%)	54 (18%)	51 (17%)	104 (22%)	92 (19%)	140 (32%)	72 (33%)	77 (20%)	80 (21%)	66 (17%)
BCLC C	276 (82%)	133 (81%)	244 (82%)	252 (83%)	374 (78%)	384 (81%)	292 (68%)	145 (67%)	316 (80%)	309 (79%)	323 (83%)
EHS	212 (63%)	93 (56%)	159 (53%)	150 (50%)	291 (61%)	295 (62%)	232 (54%)	122 (56%)	209 (53%)	212 (54%)	203 (52%)
MVI	129 (38%)	71 (43%)	108 (36%)	123 (41%)	109 (23%)	90 (19%)	136 (31%)	61 (28%)	103 (26%)	94 (24%)	100 (25%)
VP4	48 (14%)	25 (15%)	NA	NA	Excluded	Excluded	NA	NA	Excluded	Excluded	Excluded
CP A	333 (100%)	165 (100%)	284 (95%)	297 (98%)	475 (99%)	471 (99%)	432 (100%)	217 (100%)	387 (98%)	380 (98%)	379 (97%)
ALBI 1	189 (57%)	81 (52%)	NA	NA	318 (66%)	340 (72%)	NA	NA	217 (55%)	198 (51%)	203 (52%)
ALBI 2	140 (43%)	75 (48%)	NA	NA	158 (34%)	134 (28%)	NA	NA	174 (44%)	189 (49%)	185 (48%)
AFP >400 ng/ml	126 (38%)	62 (37%)	93 (31%)	109 (36%)	163 (46%)*	157 (39%)*	163 (38%)	65 (30%)	145 (37%)	137 (35%)	124 (32%)
Efficacy data											
Median overall survival (months)	19·2	13·4	10·7	7·9	13·6	12·3	15·4	15·5	16·4	16·6	13·8
Progression-free survival (months)	6·9	4·3	5·5	2·8	7·3	3·6	6·8	4·2	3·8	3·7	4·1
Overall survival: HR (95% CI)	0·66 (0·52–0·85)	0·66 (0·52–0·85)	0·69 (0·55–0·87)	0·69 (0·55–0·87)	0·92 (0·79–1·06)	0·92 (0·79–1·06)	0·90 (0·69–1·18)	0·90 (0·69–1·18)	0·78 (0·65–0·93)†	0·78 (0·65–0·93);† 0·86 (0·73–1·03)‡	0·86 (0·73–1·03)‡
Progression-free survival: HR (95% CI)	0·65 (0·53–0·81)	0·65 (0·53–0·81)	0·58 (0·45–0·74)	0·58 (0·45–0·74)	0·66 (0·57–0·77)	0·66 (0·57–0·77)	0·63 (0·44–0·91)	0·63 (0·44–0·91)	0·90 (0·77–1·05)	0·90 (0·77–1·05); 1·02 (0·88–1·19)	1·02 (0·88–1·19)
Overall response rate (RECIST 1.1 criteria)	97 (30%)	18 (11%)	6 (2%	3 (1%)	90 (19%)	31 (7%)	47 (11%)	8 (4%)	79 (20%)	66 (17%)	20 (5%)
Overall response rate (modified RECIST 1.1 criteria)	114 (35%)	22 (14%)	NA	NA	194 (41%)	59 (12%)	NA	NA	NA	NA	NA
Complete responses (RECIST 1.1 criteria)	25 (8%)	2 (<1%)	0	0	2 (<1%)	1 (<1%)	1 (<1%)	0	12 (3%)	6 (2%)	0
Disease control rate (modified RECIST 1.1 criteria)	241 (74%)	87 (55%)	129 (43%)	97 (32%)	348 (73%)	281 (59%)	337 (78%)	140 (65%)	236 (60%)	213 (55%)	236 (61%)
Safety											
≥3 adverse events	Hypertension: 39 (12%); AST increase: 17 (5%); proteinuria: 13 (4%)	Hypertension: 14 (9%); AST increase: 5 (3%); proteinuria: 1 (<1%)	HFSR: 24 (8%); diarrhoea: 24 (8%); fatigue: 12 (4%)	HFSR: 1 (<1%); diarrhoea: 6 (2%); fatigue: 7 (3%)	Hypertension: 111 (23%); bilirubin increase: 31 (7%); proteinuria: 27 (6%)	Hypertension: 68 (14%); bilirubin increase: 23 (5%); proteinuria: 28 (2%)	Hepatic events: 37 (9%); diarrhoea: 18 (4%); rash: 1 (<1%)	Hepatic events: 7 (3%); diarrhoea: 4 (2%); rash: 1 (<1%)	Hepatic events: 23 (6%); diarrhoea: 17 (4%); rash: 6 (2%)	Hepatic events: 17 (5%); diarrhoea: 6 (2%); rash: 1 (<1%)	Hepatic events: 15 (10%); diarrhoea: 16 (4%); rash: 0 (0%)
Subsequent therapies	121 (36%)	86 (52%)	NA	NA	156 (33%)	184 (39%)	87 (20%)	80 (37%)	160 (41%)	168 (43%)	175 (45%)

ALBI=albumin-bilirubin. AFP= alpha fetoprotein. BCLC=Barcelona Clinic of Liver Cancer. CP A=Child-Pugh A. ECOG=Eastern Cooperative Oncology Group. EHS=extrahepatic spread. HFSR=hand foot skin reaction. HR=hazard ratio. MVI=macrovascular infiltration. NA=not applicable. RECIST=Response Evaluation Criteria In Solid Tumors. VP4=vena porta main trunk infiltration. *AFP levels ≥200 ng/ml were reported only in the REFLECT study. In all other studies, the AFP cutoff was 400 ng/ml. †Value refers to comparison of STRIDE *vs* sorafenib. ‡Value refers to comparison of durvalumab *vs* sorafenib.

Table 1: **Baseline characteristics and key efficacy outcome data from positive phase 3 studies (first line)**

	RESORCE[161]		CELESTIAL[162]		REACH-2[163]	
	Regorafenib (n=379)	Placebo (n=194)	Cabozantinib (n=470)	Placebo (n=237)	Ramucirumab (n=197)	Placebo (n=95)
Baseline characteristics (%)						
ECOG 0	247 (65%)	130 (67%)	245 (52%)	131 (55%)	113 (57%)	55 (58%)
ECOG 1	132 (35%)	64 (33%)	224 (48%)	106 (45%)	84 (43%)	40 (42%)
BCLC A	1 (<1%)	0	0	0	0	0
BCLC B	53 (14%)	22 (11%)	42 (9%)	24 (10%)	34 (17%)	20 (21%)
BCLC C	325 (86%)	172 (89%)	427 (91%)	213 (90%)	163 (83%)	75 (97%)
EHS	264 (70%)	147 (76%)	369 (79%)	182 (77%)	141 (72%)	70 (74%)
MVI	110 (29%)	54 (28%)	129 (27%)	81 (34%)	70 (36%)	30 (35%)
VP4	NA	NA	NA	NA	NA	NA
CP A	373 (98%)	188 (97%)	465 (99%)	235 (99%)	197 (100%)	95 (100%)
ALBI 1	164 (43%)	81 (42%)	186 (39%)	102 (43%)	85 (43%)	42 (44%)
ALBI 2	213 (56%)	112 (58%)	282 (61%)	133 (57%)	112 (57%)	53 (56%)
AFP >400 ng/ml	162 (43%)	87 (45%)	192 (41%)	101 (43%)	197 (100%)	95 (100%)
Efficacy data						
Median overall survival (months)	10·6	7·8	10·2	8·0	8·1	5·3
Progression-free survival (months)	3·1	1·5	5·2	1·9	2·8	1·5
Overall survival: HR (95% CI)	0·63 (0·50–0·79)	0·63 (0·50–0·79)	0·76 (0·63–0·92)	0·76 (0·63–0·92)	0·71 (0·53–0·95)	0·71 (0·53–0·95)
Progression-free survival: HR (95% CI)	0·46 (0·37–0·56)	0·46 (0·37–0·56)	0·44 (0·36–0·52)	0·44 (0·36–0·52)	0·45 (0·34–0·60)	0·45 (0·34–0·60)
Overall response rate (RECIST 1.1 criteria)	27 (7%)	6 (3%)	18 (4%)	1 (<1%)	9 (5%)	1 (1%)
Overall response rate (modified RECIST 1.1 criteria)	40 (11%)	8 (4%)	NA	NA	NA	NA
Complete response (modified RECIST 1.1 criteria)	2 (1%)	0%	0%	0%	0%	0%
Disease control rate	247 (65%)	70 (36%)	300 (64%)	79 (33%)	118 (60%)	37 (39%)
Safety						
≥3 adverse events	Hypertension: 57 (16%); HFSR: 47 (13%); bilirubin increase: 39 (11%)	Hypertension: 9 (5%); HFSR: 1 (1%); bilirubin increase: 21 (11%)	HFSR: 79 (17%); hypertension: 74 (16%); diarrhoea: 46 (10%)	HFSR: 0 (0%); hypertension: 4 (2%); diarrhoea: 4 (2%)	Liver failure: 36 (18%); hypertension: 25 (13%); bleeding: 10 (6%)	Liver failure: 15 (16%); hypertension: 5 (5%); bleeding: 3 (3%)
Subsequent therapies	76 (20%)	54 (28%)	118 (25%)	71 (30%)	53 (27%)	27 (27%)

AFP=alpha fetoprotein. ALBI=albumin-bilirubin. BCLC=Barcelona clinic liver cancer. CP A=Child-Pugh A. ECOG=Eastern Cooperative Oncology Group. EHS=extrahepatic spread. HFSR=hand foot skin reaction. HR=hazard ratio. MVI=macrovascular infiltration. NA=not applicable. RECIST=Response Evaluation Criteria In Solid Tumors. VP4=vena porta main trunk infiltration.

Table 2: **Baseline characteristics and key efficacy outcome data from positive phase 3 studies (second line)**

single priming dose of tremelimumab and durvalumab every 4 weeks (the single tremelimumab regular interval durvalumab [STRIDE] regimen). The trial showed that there was a significant improvement in overall survival for the combination arm compared with sorafenib, thus meeting its primary endpoint. In addition, non-inferiority of durvalumab compared with sorafenib as front-line therapy in patients with advanced hepatocellular carcinoma was reported. Although overall response rate was higher with durvalumab and tremelimumab and durvalumab compared with sorafenib, data for progression-free survival were nearly identical, suggesting that progression-free survival is not a reliable surrogate for overall survival for patients with hepatocellular carcinoma treated with ICIs, as in other cancers.

The single dose of tremelimumab doubled the rate of grade 3 and 4 treatment-related adverse events, as well as the number of patients who required treatment with high dose steroids (20·0%) in comparison to durvalumab monotherapy (9·5%). Currently, neither the STRIDE regimen or durvalumab monotherapy is approved, and atezolizumab plus bevacizumab remains the only ICI-based therapy for hepatocellular carcinoma approved by both the EMA and FDA. In addition, the FDA granted accelerated approval for nivolumab (in March, 2020) and ipilimumab and pembrolizumab (in November, 2018) for second-line therapy based on phase 1 and 2 efficacy data from KEYNOTE-224 and CheckMate 040.[158, 168] Subsequent phase 3 trials of first-line nivolumab and second-line pembrolizumab did not meet their primary endpoints,

although the KEYNOTE-394 trial reported positive results for pembrolizumab in an Asian population.[159,160,169]

Second-line therapies

Regorafenib is an oral fluorinated sorafenib analog with a similar spectrum of molecular targets. The randomised controlled RESORCE phase 3 trial[161] evaluated the role of regorafenib in patients after progression on sorafenib and was the first positive trial in the second-line setting for patients with advanced hepatocellular carcinoma. In contrast to other phase 3 trials in second-line, tolerability of sorafenib was required for enrolment. The trial reached its primary endpoint by showing a significant improvement in median overall survival for regorafenib over placebo. The spectrum of adverse events was similar to the side-effect profile for sorafenib. Based on the results of the study, regorafenib was approved in 2017 by the FDA and EMA for the treatment of patients with advanced hepatocellular carcinoma who tolerated, but progressed, on sorafenib.

Cabozantinib, a tyrosine kinase inhibitor with activity against multiple targets including MET, VEGFR, and the TAM kinase family (TYRO-3, AXL, and MER), is endorsed by both the EMA and the FDA as a second-line treatment for patients with advanced hepatocellular carcinoma. The approval of cabozantinib was based on the improved overall survival (10·2 months for cabozantinib *vs* 8·0 months for placebo), that was shown in the phase 3 CELESTIAL trial,[162] which compared cabozantinib to placebo in second-line and third-line patients with preserved liver function and good performance status. Despite a low overall response rate, median progression-free survival was extended and a quality of life analysis favoured cabozantinib over placebo.[170] In contrast to the other second-line trials, the CELESTIAL study included patients who had more than one previous therapy, and provided preliminary evidence in the third-line setting.

Ramucirumab, a recombinant monoclonal antibody that binds to and inhibits VEGFR-2, was the first intravenous, non-TKI to become available for the treatment of advanced hepatocellular carcinoma. Although the initial phase 3 REACH study[171] did not provide evidence that ramucirumab improves median overall survival for patients who received previous therapy with sorafenib, a subgroup analysis showed an overall survival benefit, specifically in patients with a baseline AFP level ≥400 ng/ml; a finding that could be confirmed in the subsequent REACH-2 study.[163] An additional pooled meta-analysis of prospectively collected quality of life data showed that there was a statistically significant benefit of ramucirumab over placebo, and was notable for being the first comprehensive analysis of phase 3 data that shifted quality of life into the focus of clinical decision making in advanced hepatocellular carcinoma.[173] Overall, although ramucirumab is an option for patients with hepatocellular carcinoma with an AFP ≥400 ng/ml, it is not necessarily the agent of choice for this population, considering the treatment benefit of TKIs independent of AFP.

Assessment of response

Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 is the gold standard for radiologic response assessment.[174] In brief, RECIST 1.1. measures the sums of the maximum diameters of target lesions at baseline, and subsequently measures the change during follow-up. Although RECIST 1.1 criteria were developed to capture response assessment under systemic therapies that impart cytostatic or cytotoxic effects, modified RECIST (mRECIST) criteria were developed specifically for hepatocellular carcinoma in the setting of molecular-targeted therapies or locoregional therapies.[175,176] The development of the mRECIST criteria stemmed from two key assumptions related to hepatocellular carcinoma: first, hepatocellular carcinoma is a hypervascular tumour, and response might not only be manifested by lesional size reduction, but also by loss of vascularity (representing necrosis). Furthermore, it was previously thought that hepatocellular carcinoma tumours occurring in a background of liver cirrhosis would be less likely to undergo anatomical reduction despite effective treatment. As a result, mRECIST criteria have become an ancillary method of reporting response in addition to RECIST 1.1, particularly when attempting to adequately capture the necrosis-inducing treatment effect from local and systemic therapies.[177,178] The extent of reduction of enhancement translates to the response declared in a manner analogous to RECIST 1.1 (eg, a 20% decrease in enhancement is considered a partial response). In the era of immunotherapy, which induces radiological shrinkage, RECIST 1.1 has been the standard method of response assessment in clinical trials. Immune RECIST, that mandates confirmation of PD, has not been widely adopted in hepatocellular carcinoma and would benefit from inclusion as an exploratory endpoint to provide validation of its use.

Of note, response to preoperative therapies could be used as a dynamic biomarker of improved outcomes following surgery and transplantation. In addition, response to therapies also correlates with longer survival after locoregional and systemic therapies in more advanced disease.[177–179]

Transition between local and systemic therapies for intermediate stage hepatocellular carcinoma

To ensure that patients are matched with the optimal therapy, clinical decision making requires a multidisciplinary team that longitudinally re-evaluates and adapts therapeutic strategies. Although local therapies remain the mainstay of early disease stages, there is currently a paradigm shift in patients with intermediate hepatocellular carcinoma. As a result of the substantial progress in systemic treatments, a critical review of the indication for locoregional therapies is mandatory. Studies have provided evidence that median overall survival with

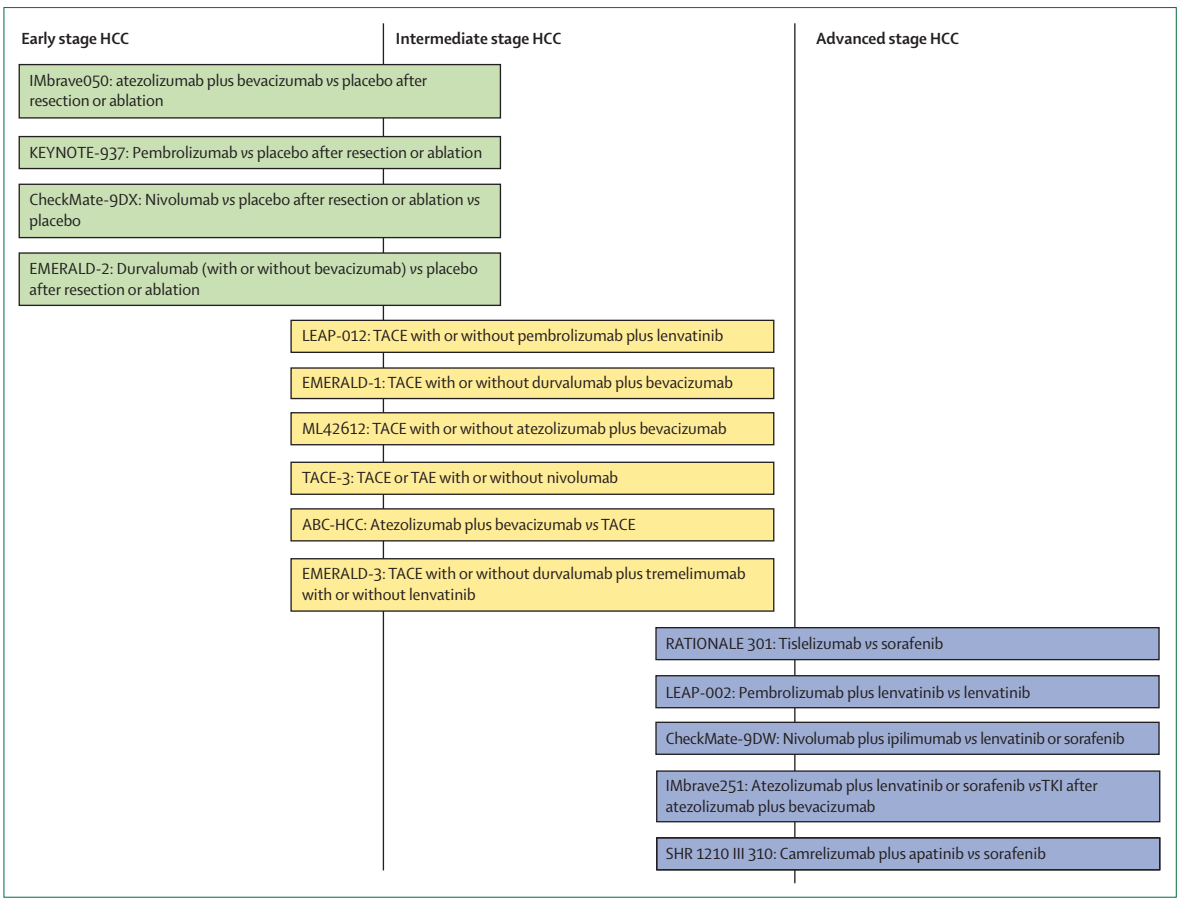

Figure 4: **Ongoing immunotherapy-based phase 3 trials in HCC**
HCC=hepatocellular carcinoma. TAE=bland particle embolisation. TACE=transarterial chemoembolisation. TKI=tyrosine kinase inhibitor.

TACE is significantly worse in unselected patient populations (median overall survival <20 months) compared with selected patients with maintained liver function and small tumours (30–45 months).[180,181] Guidelines therefore recommend TACE in patients with liver-limited disease, a tumour size <7 cm, no macrovascular infiltration, a preserved liver function, and a good Eastern Cooperative Oncology Group (ECOG) performance status. Prognostic scores, such as the hepatoma arterial-embolisation prognostic score, could also help to select patients that are most likely to benefit from treatment.[181–183]

Apart from the identification of optimal candidates for local therapies, the appropriate time to transition from local to systemic therapies must not be missed. Although repeated use of locoregional therapies is possible, by doing so, patients are at risk of cumulative liver injury and acute and chronic deterioration of liver function, thereby jeopardising options for subsequent systemic treatment.[184–186] Increasing evidence suggests that patients who only reach disease stabilisation after TACE, but do not reach a deep response, are likely to have a poor prognosis and are not likely to benefit from additional local therapies.[181]

Earlier conversion towards systemic therapies, rather than repetitive use of embolisation, is advocated in the event of the development of extrahepatic spread, or progressive venous involvement, particularly in patients without a radiological response.[187] A longitudinal response assessment and close monitoring of liver function is mandatory to allocate patients to either local or systemic therapies.

Sequencing and decision making for systemic therapy

The selection of systemic therapy for an individual patient is influenced by several factors, including efficacy, and toxicity, as well as the presence of contraindications or predictive factors. Special populations (eg, people living with HIV, patients on haemodialysis, or patients with cardiovascular events) are usually excluded from clinical trials, and the standard of care for these patients is poorly defined. In general, patients should have Child-Pugh A liver disease and an ECOG performance status of 0 to 1, consistent with the population in which the evidence base was generated. Although treatment might be tolerated outside of these criteria, there is no evidence of benefit and

outcomes are generally poor.[188–190] For most patients, combination therapy, including a PD1 or PD-L1 inhibitor, represents the first-line treatment of choice. Hence, the combinations of both atezolizumab plus bevacizumab, and durvalumab plus tremelimumab, if approved by the FDA and the EMA, could be considered.[155,157] Atezolizumab plus cabozantinib did not show an overall survival benefit compared with sorafenib, which makes this combination a less attractive option compared with other ICI-based regimens.[156] Although atezolizumab plus bevacizumab was associated with a higher response rate and more impressive hazard ratio than durvalumab plus tremelimumab, cross-trial comparisons are unreliable because of distinct patient populations included in these trials, and both regimens should be considered as effective first-line options. Additional considerations include the side-effect profile; for example, bevacizumab is associated with an increased risk of variceal haemorrhage and upper endoscopy is recommended to ensure varices are adequately treated.[191] Despite esophagogastroduodenoscopy (EGD) and treatment of varices being mandated in the IMbrave 150 trial,[155] 8 (2·4%) patients had a variceal haemorrhage and four patients died of gastrointestinal bleeding. The HIMALAYA trial[157] did not mandate EGD and no variceal bleeding was reported. However, it should be noted that patients with advanced portal vein thrombosis classified as Vp4 were excluded from the HIMALAYA trial but not from the IMbrave150 trial. Thus, for patients deemed to be at risk of bleeding, the dual checkpoint regimen might be preferred. Regarding quality of life assessment, a significant delay in deterioration of patient reported outcomes has been reported for atezolizumab plus bevacizumab as well as for durvalumab plus tremelimumab and for durvalumab compared with sorafenib.[157,167] As of July, 2022, no validated predictive markers have been identified for ICI therapy in hepatocellular carcinoma. On the basis of pre-clinical data and a meta-analysis of three clinical trials, a potential negative predictive value of NASH and non-viral liver disease for ICI efficacy in patients with hepatocellular carcinoma was suggested,[192] but could not be confirmed in subgroup analyses from the HIMALAYA trial or other trials in the preoperative setting.[61,111] Therefore, at this point, there are no conclusive data that advocate for clinical decision making based on underlying liver disease.

Despite the success of recent trials, some patients have contraindications to ICI therapy, including patients who have severe autoimmune disorders and patients living with an essential organ transplant. For these patients, treatment with single agent sorafenib or lenvatinib are appropriate first-line agents. Given their equivalent efficacy in terms of survival, additional factors, such as the higher response rate and superior progression-free survival for lenvatinib compared with sorafenib, can be considered when choosing a first-line strategy.[154]

In the second-line setting, the only evidence-based sequences are for regorafenib, cabozantinib, or ramucirumab following first-line sorafenib. There are no meaningful differences in efficacy for any of these drugs evaluated in the second-line setting and the best treatment sequences of the available drugs have not been established. As of July, 2022, second-line therapy after lenvatinib or ICI-based combinations has not been systematically evaluated, but trials are ongoing to help to address this evidence gap (figure 4). In the meantime, international guidelines recommend the use of approved drugs following ICI-based combinations and lenvatinib, and prospective data collection or registries could provide further data in due course.[87]

Current developments

ICI-based therapies are now an integral part of systemic treatment for advanced hepatocellular carcinoma and are currently being explored in all disease stages, from neoadjuvant therapy[109,110] and adjuvant therapy in early hepatocellular carcinoma, over head-to-head comparisons and combinations with local therapies in intermediate stage disease, to treatment-beyond-progression concepts in advanced disease (figure 4). In addition to ICI-based therapies, current strategies are exploring biomarker-driven approaches (eg, that target the FGF19-FGFR4 pathway)[193] or combination therapies that inhibit compensatory signalling pathways that are suspected to cause therapy resistance (eg, feedback activation of the EGFR-PAK2-ERK5 pathway as a mediator of resistance to lenvatinib).[194] Synthetic lethality concepts (eg, combining LXRα activation and RAF inhibition)[195] or strategies to induce vulnerabilities (eg, combining CDC7 and mTOR inhibitors)[196] could further diversify hepatocellular carcinoma therapies. To realise precision medicine in hepatocellular carcinoma in the future, biomarkers need to be established that guide treatment decisions in all stages of hepatocellular carcinoma.

Future perspectives

The epidemiology of liver cancer is changing and will increasingly be dominated by non-viral causes. Innovative surveillance and preventive strategies will be needed to address the rising incidence of hepatocellular carcinoma in patients with fatty liver disease. Despite substantial progress made in locoregional and systemic therapy, most patients are likely to not respond and ultimately succumb to their disease. Consequently, more effective systemic therapies are still required, along with predictive biomarkers that enable personalised and cost-effective treatment stratification. The dynamic interplay between locoregional and systemic therapy is also being explored. Having been one of the most challenging cancers with the poorest outlook, there are reasons to be optimistic that the coming years will continue to lead to improved outcomes.

Contributors

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References

1 Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; **71:** 209–49.

2 Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin* 2022; **72:** 7–33.

3 Petrick JL, Florio AA, Znaor A, et al. International trends in hepatocellular carcinoma incidence, 1978–2012. *Int J Cancer* 2020; **147:** 317–30.

4 Sun J, Althoff KN, Jing Y, et al. Trends in hepatocellular carcinoma incidence and risk among persons with HIV in the US and Canada, 1996–2015. *JAMA Netw Open* 2021; **4:** e2037512.

5 Chen T, Liu J, Li Y, Wei S. Burden of disease associated with dietary exposure to aflatoxins in China in 2020. *Nutrients* 2022; **14:** 1027.

6 Romano A, Angeli P, Piovesan S, et al. Newly diagnosed hepatocellular carcinoma in patients with advanced hepatitis C treated with DAAs: a prospective population study. *J Hepatol* 2018; **69:** 345–52.

7 Dave S, Park S, Murad MH, et al. Comparative effectiveness of entecavir versus tenofovir for preventing hepatocellular carcinoma in patients with chronic hepatitis B: a systematic review and meta-analysis. *Hepatology* 2021; **73:** 68–78.

8 Papatheodoridis GV, Idilman R, Dalekos GN, et al. The risk of hepatocellular carcinoma decreases after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. *Hepatology* 2017; **66:** 1444–53.

9 Chiang CJ, Yang YW, You SL, Lai MS, Chen CJ. Thirty-year outcomes of the national hepatitis B immunization program in Taiwan. *JAMA* 2013; **310:** 974–76.

10 Kanwal F, Kramer JR, Asch SM, Cao Y, Li L, El-Serag HB. Long-term risk of hepatocellular carcinoma in HCV patients treated with direct acting antiviral agents. *Hepatology* 2020; **71:** 44–55.

11 Kim HY, Lampertico P, Nam JY, et al. An artificial intelligence model to predict hepatocellular carcinoma risk in Korean and Caucasian patients with chronic hepatitis B. *J Hepatol* 2022; **76:** 311–18.

12 Kim HS, Yu X, Kramer J, et al. Comparative performance of risk prediction models for hepatitis B-related hepatocellular carcinoma in the United States. *J Hepatol* 2022; **76:** 294–301.

13 Ioannou GN, Green PK, Beste LA, Mun EJ, Kerr KF, Berry K. Development of models estimating the risk of hepatocellular carcinoma after antiviral treatment for hepatitis C. *J Hepatol* 2018; **69:** 1088–98.

14 Dang H, Yeo YH, Yasuda S, et al. Cure with interferon-free direct-acting antiviral is associated with increased survival in patients with hepatitis C virus-related hepatocellular carcinoma from both east and west. *Hepatology* 2020; **71:** 1910–22.

15 Yin J, Li N, Han Y, et al. Effect of antiviral treatment with nucleotide/nucleoside analogs on postoperative prognosis of hepatitis B virus-related hepatocellular carcinoma: a two-stage longitudinal clinical study. *J Clin Oncol* 2013; **31:** 3647–55.

16 Jiang E, Shangguan AJ, Chen S, Tang L, Zhao S, Yu Z. The progress and prospects of routine prophylactic antiviral treatment in hepatitis B-related hepatocellular carcinoma. *Cancer Lett* 2016; **379:** 262–67.

17 Sapena V, Enea M, Torres F, et al. Hepatocellular carcinoma recurrence after direct-acting antiviral therapy: an individual patient data meta-analysis. *Gut* 2022; **71:** 593–604.

18 Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol* 2018; **15:** 11–20.

19 Jinjuvadia R, Patel S, Liangpunsakul S. The association between metabolic syndrome and hepatocellular carcinoma: systemic review and meta-analysis. *J Clin Gastroenterol* 2014; **48:** 172–77.

20 Lazarus JV, Mark HE, Anstee QM, et al. Advancing the global public health agenda for NAFLD: a consensus statement. *Nat Rev Gastroenterol Hepatol* 2022; **19:** 60–78.

21 GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; **396:** 1204–22.

22 Mao D, Lau ESH, Wu H, et al. Risk associations of glycemic burden and obesity with liver cancer–a 10-year analysis of 15,280 patients with type 2 diabetes. *Hepatol Commun* 2022; **6:** 1350–60.

23 Kanwal F, Kramer JR, Mapakshi S, et al. Risk of hepatocellular cancer in patients with non-alcoholic fatty liver disease. *Gastroenterology* 2018; **155:** 1828–1837.e2.

24 Gawrieh S, Dakhoul L, Miller E, et al. Characteristics, aetiologies and trends of hepatocellular carcinoma in patients without cirrhosis: a United States multicentre study. *Aliment Pharmacol Ther* 2019; **50:** 809–21.

25 Gellert-Kristensen H, Richardson TG, Davey Smith G, Nordestgaard BG, Tybjaerg-Hansen A, Stender S. Combined effect of PNPLA3, TM6SF2, and HSD17B13 variants on risk of cirrhosis and hepatocellular carcinoma in the general population. *Hepatology* 2020; **72:** 845–56.

26 Abul-Husn NS, Cheng X, Li AH, et al. A protein-truncating HSD17B13 variant and protection from chronic liver disease. *N Engl J Med* 2018; **378:** 1096–106.

27 Safiri S, Nejadghaderi SA, Karamzad N, et al. Global, regional, and national cancer deaths and disability-adjusted life-years (DALYs) attributable to alcohol consumption in 204 countries and territories, 1990–2019. *Cancer* 2022; **128:** 1840–52.

28 Frezza M, di Padova C, Pozzato G, Terpin M, Baraona E, Lieber CS. High blood alcohol levels in women. The role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. *N Engl J Med* 1990; **322:** 95–99.

29 Turati F, Galeone C, Rota M, et al. Alcohol and liver cancer: a systematic review and meta-analysis of prospective studies. *Ann Oncol* 2014; **25:** 1526–35.

30 Kennedy OJ, Roderick P, Buchanan R, Fallowfield JA, Hayes PC, Parkes J. Coffee, including caffeinated and decaffeinated coffee, and the risk of hepatocellular carcinoma: a systematic review and dose-response meta-analysis. *BMJ Open* 2017; **7:** e013739.

31 Liao SH, Chen CL, Hsu CY, et al. Long-term effectiveness of population-wide multifaceted interventions for hepatocellular carcinoma in Taiwan. *J Hepatol* 2021; **75:** 132–41.

32 WHO. Global health sector strategy on viral hepatitis 2016–2021. Towards ending viral hepatitis. Geneva: World Health Organization, 2016.

33 Simon TG, Duberg AS, Aleman S, Chung RT, Chan AT, Ludvigsson JF. Association of aspirin with hepatocellular carcinoma and liver-related mortality. *N Engl J Med* 2020; **382:** 1018–28.

34 Simon TG, Duberg AS, Aleman S, et al. Lipophilic statins and risk for hepatocellular carcinoma and death in patients with chronic viral hepatitis: results from a nationwide Swedish population. *Ann Intern Med* 2019; **171:** 318–27.

35 Hsiang JC, Wong GL, Tse YK, Wong VW, Yip TC, Chan HL. Statin and the risk of hepatocellular carcinoma and death in a hospital-based hepatitis B-infected population: a propensity score landmark analysis. *J Hepatol* 2015; **63:** 1190–97.

36 Singh S, Singh PP, Singh AG, Murad MH, Sanchez W. Statins are associated with a reduced risk of hepatocellular cancer: a systematic review and meta-analysis. *Gastroenterology* 2013; **144:** 323–32.

37 Chen HP, Shieh JJ, Chang CC, et al. Metformin decreases hepatocellular carcinoma risk in a dose-dependent manner: population-based and in vitro studies. *Gut* 2013; **62:** 606–15.

38 Singh S, Singh PP, Singh AG, Murad MH, Sanchez W. Anti-diabetic medications and the risk of hepatocellular cancer: a systematic review and meta-analysis. *Am J Gastroenterol* 2013; **108:** 881–91.

39 Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2004; **130:** 417–22.

40 Vogel A, Cervantes A, Chau I, et al. Hepatocellular carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2019; **30**: 871–73.

41 Galle PR, Forner A, Llovet JM, et al. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2018; **69:** 182–236.

42 Ahmed Mohammed HF, Roberts LR. Should AFP (or any biomarkers) be used for HCC surveillance? *Curr Hepatol Rep* 2017; **16:** 137–45.

43 Song PP, Xia JF, Inagaki Y, et al. Controversies regarding and perspectives on clinical utility of biomarkers in hepatocellular carcinoma. *World J Gastroenterol* 2016; **22:** 262–74.

44 Adeniji N, Dhanasekaran R. Current and emerging tools for hepatocellular carcinoma surveillance. *Hepatol Commun* 2021; **5:** 1972–86.

45 Singal AG, El-Serag HB. Rational HCC screening approaches for patients with NAFLD. *J Hepatol* 2022; **76:** 195–201.

46 Forner A, Vilana R, Ayuso C, et al. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. *Hepatology* 2008; **47:** 97–104.

47 Kim YY, Kim MJ, Kim EH, Roh YH, An C. Hepatocellular carcinoma versus other hepatic malignancy in cirrhosis: performance of LI-RADS version 2018. *Radiology* 2019; **291:** 72–80.

48 Childs A, Zakeri N, Ma YT, et al. Biopsy for advanced hepatocellular carcinoma: results of a multicentre UK audit. *Br J Cancer* 2021; **125:** 1350–55.

49 Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. *Histopathology* 2020; **76:** 182–88.

50 International Consensus Group for Hepatocellular Neoplasia. The International Consensus Group for Hepatocellular Neoplasia. Pathologic diagnosis of early hepatocellular carcinoma: a report of the international consensus group for hepatocellular neoplasia. *Hepatology* 2009; **49:** 658–64.

51 Amin MB, Greene FL, Edge SB, et al. The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin* 2017; **67**: 93–99.

52 Di Tommaso L, Destro A, Seok JY, et al. The application of markers (HSP70 GPC3 and GS) in liver biopsies is useful for detection of hepatocellular carcinoma. *J Hepatol* 2009; **50:** 746–54.

53 Tremosini S, Forner A, Boix L, et al. Prospective validation of an immunohistochemical panel (glypican 3, heat shock protein 70 and glutamine synthetase) in liver biopsies for diagnosis of very early hepatocellular carcinoma. *Gut* 2012; **61:** 1481–87.

54 Ziol M, Poté N, Amaddeo G, et al. Macrotrabecular-massive hepatocellular carcinoma: a distinctive histological subtype with clinical relevance. *Hepatology* 2018; **68:** 103–12.

55 Beaufrère A, Calderaro J, Paradis V. Combined hepatocellular-cholangiocarcinoma: an update. *J Hepatol* 2021; **74:** 1212–24.

56 Tyson GL, Duan Z, Kramer JR, Davila JA, Richardson PA, El-Serag HB. Level of α-fetoprotein predicts mortality among patients with hepatitis C-related hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 2011; **9:** 989–94.

57 Wang Y, Chen Y, Ge N, et al. Prognostic significance of alpha-fetoprotein status in the outcome of hepatocellular carcinoma after treatment of transarterial chemoembolization. *Ann Surg Oncol* 2012; **19:** 3540–46.

58 Kudo M, Izumi N, Sakamoto M, et al. Survival analysis over 28 years of 173,378 patients with hepatocellular carcinoma in Japan. *Liver Cancer* 2016; **5:** 190–97.

59 Toso C, Meeberg G, Hernandez-Alejandro R, et al. Total tumor volume and alpha-fetoprotein for selection of transplant candidates with hepatocellular carcinoma: a prospective validation. *Hepatology* 2015; **62:** 158–65.

60 Halazun KJ, Rosenblatt RE, Mehta N, et al. Dynamic α-fetoprotein response and outcomes after liver transplant for hepatocellular carcinoma. *JAMA Surg* 2021; **156:** 559–67.

61 Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. *J Clin Oncol* 2015; **33:** 550–58.

62 Vogel A, Merle P, Verslype C, et al. ALBI score and outcomes in patients with hepatocellular carcinoma: post hoc analysis of the randomized controlled trial KEYNOTE-240. *Ther Adv Med Oncol* 2021; **13:** 17588359211039928.

63 Vogel A, Frenette C, Sung M, et al. Baseline liver function and subsequent outcomes in the phase 3 REFLECT study of patients with unresectable hepatocellular carcinoma. *Liver Cancer* 2021; **10:** 510–21.

64 Kudo M, Galle PR, Brandi G, et al. Effect of ramucirumab on ALBI grade in patients with advanced HCC: results from REACH and REACH-2. *JHEP Rep* 2020; **3:** 100215.

65 Hoshida Y, Nijman SM, Kobayashi M, et al. Integrative transcriptome analysis reveals common molecular subclasses of human hepatocellular carcinoma. *Cancer Res* 2009; **69:** 7385–92.

66 Chiang DY, Villanueva A, Hoshida Y, et al. Focal gains of VEGFA and molecular classification of hepatocellular carcinoma. *Cancer Res* 2008; **68:** 6779–88.

67 Boyault S, Rickman DS, de Reyniès A, et al. Transcriptome classification of HCC is related to gene alterations and to new therapeutic targets. *Hepatology* 2007; **45:** 42–52.

68 Calderaro J, Couchy G, Imbeaud S, et al. Histological subtypes of hepatocellular carcinoma are related to gene mutations and molecular tumour classification. *J Hepatol* 2017; **67:** 727–38.

69 Pinyol R, Torrecilla S, Wang H, et al. Molecular characterisation of hepatocellular carcinoma in patients with non-alcoholic steatohepatitis. *J Hepatol* 2021; **75:** 865–78.

70 Pinyol R, Montal R, Bassaganyas L, et al. Molecular predictors of prevention of recurrence in HCC with sorafenib as adjuvant treatment and prognostic factors in the phase 3 STORM trial. *Gut* 2019; **68:** 1065–75.

71 Zhu AX, Abbas AR, de Galarreta MR, et al. Molecular correlates of clinical response and resistance to atezolizumab in combination with bevacizumab in advanced hepatocellular carcinoma. *Nat Med* 2022; published online June 23. https://doi.org/10.1038/s41591-022-01868-2.

72 Sanchez-Vega F, Mina M, Armenia J, et al. Oncogenic signaling pathways in the Cancer Genome Atlas. *Cell* 2018; **173:** 321–337.e10.

73 Labgaa I, Villacorta-Martin C, D'Avola D, et al. A pilot study of ultra-deep targeted sequencing of plasma DNA identifies driver mutations in hepatocellular carcinoma. *Oncogene* 2018; **37:** 3740–52.

74 von Felden J, Craig AJ, Garcia-Lezana T, et al. Mutations in circulating tumor DNA predict primary resistance to systemic therapies in advanced hepatocellular carcinoma. *Oncogene* 2021; **40:** 140–51.

75 von Felden J, Garcia-Lezana T, Dogra N, et al. Unannotated small RNA clusters associated with circulating extracellular vesicles detect early stage liver cancer. *Gut* 2021; gutjnl-2021-325036.

76 Ahn JC, Teng PC, Chen PJ, et al. Detection of circulating tumor cells and their implications as a biomarker for diagnosis, prognostication, and therapeutic monitoring in hepatocellular carcinoma. *Hepatology* 2021; **73:** 422–36.

77 Llovet JM, Peña CEA, Lathia CD, Shan M, Meinhardt G, Bruix J. Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. *Clin Cancer Res* 2012; **18:** 2290–300.

78 Schoenleber SJ, Kurtz DM, Talwalkar JA, Roberts LR, Gores GJ. Prognostic role of vascular endothelial growth factor in hepatocellular carcinoma: systematic review and meta-analysis. *Br J Cancer* 2009; **100:** 1385–92.

79 Zhu AX, Kang YK, Rosmorduc O, et al. Biomarker analyses of clinical outcomes in patients with advanced hepatocellular carcinoma treated with sorafenib with or without erlotinib in the SEARCH Trial. *Clin Cancer Res* 2016; **22:** 4870–79.

80 Teufel M, Seidel H, Köchert K, et al. Biomarkers associated with response to regorafenib in patients with hepatocellular carcinoma. *Gastroenterology* 2019; **156:** 1731–41.

81 Zhu AX, Chen D, He W, et al. Integrative biomarker analyses indicate etiological variations in hepatocellular carcinoma. *J Hepatol* 2016; **65:** 296–304.

82 Rimassa L, Kelley RK, Meyer T, et al. Outcomes based on plasma biomarkers for the phase 3 CELESTIAL trial of cabozantinib versus placebo in advanced hepatocellular carcinoma. *Liver Cancer* 2021; **11:** 38–47.

83 Zheng J, Seier K, Gonen M, et al. Utility of serum inflammatory markers for predicting microvascular invasion and survival for patients with hepatocellular carcinoma. *Ann Surg Oncol* 2017; **24:** 3706–14.

84 Johnson PJ, Dhanaraj S, Berhane S, Bonnett L, Ma YT. The prognostic and diagnostic significance of the neutrophil-to-lymphocyte ratio in hepatocellular carcinoma: a prospective controlled study. *Br J Cancer* 2021; **125:** 714–16.

85 Bruix J, Cheng AL, Meinhardt G, Nakajima K, De Sanctis Y, Llovet J. Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: analysis of two phase III studies. *J Hepatol* 2017; **67:** 999–1008.

86 Scheiner B, Pomej K, Kirstein MM, et al. Prognosis of patients with hepatocellular carcinoma treated with immunotherapy—development and validation of the CRAFITY score. *J Hepatol* 2022; **76:** 353–63.

87 Vogel A, Martinelli E, ESMO Guidelines Committe. Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO Clinical Practice guidelines. *Ann Oncol* 2021; **32:** 801–05.

88 Bruix J, Chan SL, Galle PR, Rimassa L, Sangro B. Systemic treatment of hepatocellular carcinoma: an EASL position paper. *J Hepatol* 2021; **75:** 960–74.

89 The International Liver Cancer Association. ILCA systemic therapy guidance. https://ilca-online.org/wp-content/uploads/2020/06/Systemic-therapy-guidelines-V1.2.pdf (accessed July 26, 2022).

90 Kudo M, Kawamura Y, Hasegawa K, et al. Management of hepatocellular carcinoma in Japan: JSH consensus statements and recommendations 2021 update. *Liver Cancer* 2021; **10:** 181–223.

91 Chen LT, Martinelli E, Cheng AL, et al. Pan-Asian adapted ESMO clinical practice guidelines for the management of patients with intermediate and advanced/relapsed hepatocellular carcinoma: a TOS-ESMO initiative endorsed by CSCO, ISMPO, JSMO, KSMO, MOS and SSO. *Ann Oncol* 2020; **31:** 334–51.

92 Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. *J Hepatol* 2021; **76:** 681–93.

93 Lang H, Sotiropoulos GC, Dömland M, et al. Liver resection for hepatocellular carcinoma in non-cirrhotic liver without underlying viral hepatitis. *Br J Surg* 2005; **92:** 198–202.

94 Viganò L, Conci S, Cescon M, et al. Liver resection for hepatocellular carcinoma in patients with metabolic syndrome: a multicenter matched analysis with HCV-related HCC. *J Hepatol* 2015; **63:** 93–101.

95 Kabir T, Tan ZZ, Syn NL, et al. Laparoscopic versus open resection of hepatocellular carcinoma in patients with cirrhosis: meta-analysis. *Br J Surg* 2021; **109:** 21–29.

96 Ivanics T, Claasen MP, Patel MS, et al. Long-term outcomes of laparoscopic liver resection for hepatocellular carcinoma: a propensity score matched analysis of a high-volume North American center. *Surgery* 2021; **171:** 982–91.

97 Berzigotti A, Reig M, Abraldes JG, Bosch J, Bruix J. Portal hypertension and the outcome of surgery for hepatocellular carcinoma in compensated cirrhosis: a systematic review and meta-analysis. *Hepatology* 2015; **61:** 526–36.

98 Berardi G, Morise Z, Sposito C, et al. Development of a nomogram to predict outcome after liver resection for hepatocellular carcinoma in Child-Pugh B cirrhosis. *J Hepatol* 2020; **72:** 75–84.

99 Azoulay D, Ramos E, Casellas-Robert M, et al. Liver resection for hepatocellular carcinoma in patients with clinically significant portal hypertension. *JHEP Rep* 2020; **3:** 100190.

100 Citterio D, Facciorusso A, Sposito C, Rota R, Bhoori S, Mazzaferro V. Hierarchic interaction of factors associated with liver decompensation after resection for hepatocellular carcinoma. *JAMA Surg* 2016; **151:** 846–53.

101 Serenari M, Han KH, Ravaioli F, et al. A nomogram based on liver stiffness predicts postoperative complications in patients with hepatocellular carcinoma. *J Hepatol* 2020; **73:** 855–62.

102 Allaire M, Goumard C, Lim C, Le Cleach A, Wagner M, Scatton O. New frontiers in liver resection for hepatocellular carcinoma. *JHEP Rep* 2020; **2:** 100134.

103 Marasco G, Alemanni LV, Colecchia A, et al. Prognostic value of the albumin-bilirubin grade for the prediction of post-hepatectomy liver failure: a systematic review and meta-analysis. *J Clin Med* 2021; **10:** 2011.

104 Ivanics T, Murillo Perez CF, Claasen MP, et al. Dynamic risk profiling of hepatocellular carcinoma recurrence after curative intent liver resection. *Hepatology* 2022; published online Feb 18. https://doi.org/10.1002/hep.32411.

105 Moris D, Tsilimigras DI, Kostakis ID, et al. Anatomic versus non-anatomic resection for hepatocellular carcinoma: a systematic review and meta-analysis. *Eur J Surg Oncol* 2018; **44:** 927–38.

106 Su CM, Chou CC, Yang TH, Lin YJ. Comparison of anatomic and non-anatomic resections for very early-stage hepatocellular carcinoma: the importance of surgical resection margin width in non-anatomic resection. *Surg Oncol* 2021; **36:** 15–22.

107 Pinna AD, Yang T, Mazzaferro V, et al. Liver transplantation and hepatic resection can achieve cure for hepatocellular carcinoma. *Ann Surg* 2018; **268:** 868–75.

108 Bruix J, Takayama T, Mazzaferro V, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2015; **16:** 1344–54.

109 Ho WJ, Zhu QF, Durham J, et al. Neoadjuvant cabozantinib and nivolumab convert locally advanced hepatocellular carcinoma into resectable disease with enhanced antitumor immunity. *Nat Can* 2021; **2:** 891–903.

110 Kaseb AO, Hasanov E, Cao HST, et al. Perioperative nivolumab monotherapy versus nivolumab plus ipilimumab in resectable hepatocellular carcinoma: a randomised, open-label, phase 2 trial. *Lancet Gastroenterol Hepatol* 2022; **7:** 208–18.

111 Marron TU, Fiel MI, Hamon P, et al. Neoadjuvant cemiplimab for resectable hepatocellular carcinoma: a single-arm, open-label, phase 2 trial. *Lancet Gastroenterol Hepatol* 2022; **7:** 219–29.

112 Mazzaferro V, Citterio D, Bhoori S, et al. Liver transplantation in hepatocellular carcinoma after tumour downstaging (XXL): a randomised, controlled, phase 2b/3 trial. *Lancet Oncol* 2020; **21:** 947–56.

113 Lai Q, Sapisochin G, Gorgen A, et al. Evaluation of the intention-to-treat benefit of living donation in patients with hepatocellular carcinoma awaiting a liver transplant. *JAMA Surg* 2021; **156:** e213112.

114 Goldaracena N, Gorgen A, Doyle A, et al. Live donor liver transplantation for patients with hepatocellular carcinoma offers increased survival vs. deceased donation. *J Hepatol* 2019; **70:** 666–73.

115 Lencioni R, Crocetti L. Radiofrequency ablation of liver cancer. *Tech Vasc Interv Radiol* 2007; **10:** 38–46.

116 Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. *Nat Rev Dis Primers* 2021; **7:** 6.

117 Kudo M, Hasegawa K, Kawaguchi Y, et al. A multicenter randomized controlled trial to evaluate the efficacy of surgery versus radiofrequency ablation for small hepatocellular carcinoma (SURF trial): analysis of overall survival. *J Clin Oncol* 2021; **39** (suppl): 4093.

118 Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018; **67:** 358–80.

119 Omata M, Cheng AL, Kokudo N, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. *Hepatol Int* 2017; **11:** 317–70.

120 Mohkam K, Dumont PN, Manichon AF, et al. No-touch multibipolar radiofrequency ablation vs. surgical resection for solitary hepatocellular carcinoma ranging from 2 to 5 cm. *J Hepatol* 2018; **68:** 1172–80.

121 Harari CM, Magagna M, Bedoya M, et al. Microwave ablation: comparison of simultaneous and sequential activation of multiple antennas in liver model systems. *Radiology* 2016; **278:** 95–103.

122 Vietti Violi N, Duran R, Guiu B, et al. Efficacy of microwave ablation versus radiofrequency ablation for the treatment of hepatocellular carcinoma in patients with chronic liver disease: a randomised controlled phase 2 trial. *Lancet Gastroenterol Hepatol* 2018; **3:** 317–25.

123 Gupta P, Maralakunte M, Kumar-M P, et al. Overall survival and local recurrence following RFA, MWA, and cryoablation of very early and early HCC: a systematic review and Bayesian network meta-analysis. *Eur Radiol* 2021; **31:** 5400–08.

124 Xu J, Noda C, Erickson A, et al. Radiofrequency ablation *vs.* cryoablation for localized hepatocellular carcinoma: a propensity-matched population study. *Anticancer Res* 2018; **38:** 6381–86.

125 Bian H, Zheng JS, Nan G, et al. Randomized trial of [131I] metuximab in treatment of hepatocellular carcinoma after percutaneous radiofrequency ablation. *J Natl Cancer Inst* 2014; **106:** dju239.

126 Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; **359:** 1734–39.

127 Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. *Cardiovasc Intervent Radiol* 2010; **33:** 41–52.

128 Brown KT, Do RK, Gonen M, et al. Randomized trial of hepatic artery embolization for hepatocellular carcinoma using doxorubicin-eluting microspheres compared with embolization with microspheres alone. *J Clin Oncol* 2016; **34:** 2046–53.

129 Meyer T, Kirkwood A, Roughton M, et al. A randomised phase II/III trial of 3-weekly cisplatin-based sequential transarterial chemoembolisation vs embolisation alone for hepatocellular carcinoma. *Br J Cancer* 2013; **108:** 1252–59.

130 Salem R, Gabr A, Riaz A, et al. Institutional decision to adopt Y90 as primary treatment for hepatocellular carcinoma informed by a 1,000-patient 15-year experience. *Hepatology* 2018; **68:** 1429–40.

131 Salem R, Johnson GE, Kim E, et al. Yttrium-90 radioembolization for the treatment of solitary, unresectable hcc: the LEGACY study. *Hepatology* 2021; **74:** 2342–52.

132 Salem R, Gordon AC, Mouli S, et al. Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology* 2016; **151:** 1155–1163.e2.

133 Chow PKH, Gandhi M, Tan SB, et al. SIRveNIB: selective internal radiation therapy versus sorafenib in Asia-Pacific patients with hepatocellular carcinoma. *J Clin Oncol* 2018; **36:** 1913–21.

134 Vilgrain V, Pereira H, Assenat E, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *Lancet Oncol* 2017; **18:** 1624–36.

135 Garin E, Tselikas L, Guiu B, et al. Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. *Lancet Gastroenterol Hepatol* 2021; **6:** 17–29.

136 Kudo M, Han G, Finn RS, et al. Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: a randomized phase III trial. *Hepatology* 2014; **60:** 1697–707.

137 Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: the SPACE trial. *J Hepatol* 2016; **64:** 1090–98.

138 Kudo M, Cheng AL, Park JW, et al. Orantinib versus placebo combined with transcatheter arterial chemoembolisation in patients with unresectable hepatocellular carcinoma (ORIENTAL): a randomised, double-blind, placebo-controlled, multicentre, phase 3 study. *Lancet Gastroenterol Hepatol* 2018; **3:** 37–46.

139 Meyer T, Fox R, Ma YT, et al. Sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma (TACE 2): a randomised placebo-controlled, double-blind, phase 3 trial. *Lancet Gastroenterol Hepatol* 2017; **2:** 565–75.

140 Kudo M, Ueshima K, Ikeda M, et al. Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. *Gut* 2020; **69:** 1492–501.

141 Vogel A, Saborowski A, Hinrichs J, et al. IMMUTACE: a biomarker-orientated, multi center phase II AIO study of transarterial chemoembolization (TACE) in combination with nivolumab performed for intermediate stage hepatocellular carcinoma (HCC). *Ann Oncol* 2021; **32**: S1312-S.

142 Llovet JM, Vogel A, Madoff DC, et al. Randomized phase 3 LEAP-012 study: transarterial chemoembolization with or without lenvatinib plus pembrolizumab for intermediate-stage hepatocellular carcinoma not amenable to curative treatment. *Cardiovasc Intervent Radiol* 2022; **45:** 405–12.

143 Tai D, Loke K, Gogna A, et al. Radioembolisation with Y90-resin microspheres followed by nivolumab for advanced hepatocellular carcinoma (CA 209-678): a single arm, single centre, phase 2 trial. *Lancet Gastroenterol Hepatol* 2021; **6:** 1025–35.

144 Wong TC, Lee VH, Law AL, et al. Prospective study of stereotactic body radiation therapy for hepatocellular carcinoma on waitlist for liver transplant. *Hepatology* 2021; **74:** 2580–94.

145 Shanker MD, Moodaley P, Soon W, Liu HY, Lee YY, Pryor DI. Stereotactic ablative radiotherapy for hepatocellular carcinoma: a systematic review and meta-analysis of local control, survival and toxicity outcomes. *J Med Imaging Radiat Oncol* 2021; **65:** 956–68.

146 Kim N, Cheng J, Jung I, et al. Stereotactic body radiation therapy vs. radiofrequency ablation in Asian patients with hepatocellular carcinoma. *J Hepatol* 2020; **73:** 121–29.

147 Hara K, Takeda A, Tsurugai Y, et al. Radiotherapy for hepatocellular carcinoma results in comparable survival to radiofrequency ablation: a propensity score analysis. *Hepatology* 2019; **69:** 2533–45.

148 Zhang H, Chang N, Han T, et al. Radiofrequency ablation versus stereotactic body radiotherapy for hepatocellular carcinoma: a meta-analysis. *Future Oncol* 2021; **17:** 4027–40.

149 Wahl DR, Stenmark MH, Tao Y, et al. Outcomes after stereotactic body radiotherapy or radiofrequency ablation for hepatocellular carcinoma. *J Clin Oncol* 2016; **34:** 452–59.

150 Rajyaguru DJ, Borgert AJ, Smith AL, et al. Radiofrequency ablation versus stereotactic body radiotherapy for localized hepatocellular carcinoma in nonsurgically managed patients: analysis of the national cancer database. *J Clin Oncol* 2018; **36:** 600–08.

151 Apisarnthanarax S, Barry A, Cao M, et al. External beam radiation therapy for primary liver cancers: an ASTRO clinical practice guideline. *Pract Radiat Oncol* 2022; **12:** 28–51.

152 Durand-Labrunie J, Baumann AS, Ayav A, et al. Curative irradiation treatment of hepatocellular carcinoma: a multicenter phase 2 trial. *Int J Radiat Oncol Biol Phys* 2020; **107:** 116–25.

153 Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359:** 378–90.

154 Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018; **391:** 1163–73.

155 Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med* 2020; **382:** 1894–905.

156 Kelley RK, Rimassa L, Cheng A-L, et al. Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2022; **8:** 995–1008.

157 Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *NEJM Evid* 2022; published online June 6. https://doi.org/10.1056/EVIDoa2100070.

158 Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol* 2018; **19:** 940–52.

159 Yau T, Park JW, Finn RS, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol* 2022; **23:** 77–90.

160 Qin S, Chen Z, Fang W, et al. Pembrolizumab plus best supportive care versus placebo plus best supportive care as second-line therapy in patients in Asia with advanced hepatocellular carcinoma (HCC): phase 3 KEYNOTE-394 study. *J Clin Oncol* 2022; **40** (suppl)**:** 383.

161 Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; **389:** 56–66.

162 Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med* 2018; **379:** 54–63.

163 Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2019; **20:** 282–96.

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

165 Vogel A, Qin S, Kudo M, et al. Lenvatinib versus sorafenib for first-line treatment of unresectable hepatocellular carcinoma: patient-reported outcomes from a randomised, open-label, non-inferiority, phase 3 trial. *Lancet Gastroenterol Hepatol* 2021; **6:** 649–58.

166 Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol* 2022; **76:** 862–73.

167 Galle PR, Finn RS, Qin S, et al. Patient-reported outcomes with atezolizumab plus bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma (IMbrave150): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2021; **22:** 991–1001.

168 El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* 2017; **389:** 2492–502.

169 Finn RS, Ryoo BY, Merle P, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial. *J Clin Oncol* 2020; **38:** 193–202.

170 Freemantle N, Mollon P, Meyer T, et al. Quality of life assessment of cabozantinib in patients with advanced hepatocellular carcinoma in the CELESTIAL trial. *Eur J Cancer* 2022; **168:** 91–98.

171 Zhu AX, Park JO, Ryoo BY, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol* 2015; **16:** 859–70.

172 Yau T, Kang Y-K, Kim T-Y, et al. Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib. *JAMA Oncol* 2020; **6:** e204564.

173 Zhu AX, Nipp RD, Finn RS, et al. Ramucirumab in the second-line for patients with hepatocellular carcinoma and elevated alpha-fetoprotein: patient-reported outcomes across two randomised clinical trials. *ESMO Open* 2020; **5:** e000797.

174 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45:** 228–47.

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

176 Vincenzi B, Di Maio M, Silletta M, et al. Prognostic relevance of objective response according to EASL criteria and mRECIST criteria in hepatocellular carcinoma patients treated with loco-regional therapies: a literature-based meta-analysis. *PLoS One* 2015; **10:** e0133488.

177 Kudo M, Montal R, Finn RS, et al. Objective response predicts survival in advanced hepatocellular carcinoma treated with systemic therapies. *Clin Cancer Res* 2021; **28:** 3443–51.

178 Memon K, Kulik L, Lewandowski RJ, et al. Radiographic response to locoregional therapy in hepatocellular carcinoma predicts patient survival times. *Gastroenterology* 2011; **141:** 526–35.

179 Llovet JM, Montal R, Villanueva A. Randomized trials and endpoints in advanced HCC: role of PFS as a surrogate of survival. *J Hepatol* 2019; **70:** 1262–77.

180 Lencioni R, de Baere T, Soulen MC, Rilling WS, Geschwind JFH. Lipiodol transarterial chemoembolization for hepatocellular carcinoma: a systematic review of efficacy and safety data. *Hepatology* 2016; **64:** 106–16.

181 Han G, Berhane S, Toyoda H, et al. Prediction of survival among patients receiving transarterial chemoembolization for hepatocellular carcinoma: a response-based approach. *Hepatology* 2020; **72:** 198–212.

182 Kadalayil L, Benini R, Pallan L, et al. A simple prognostic scoring system for patients receiving transarterial embolisation for hepatocellular cancer. *Ann Oncol* 2013; **24:** 2565–70.

183 Waked I, Berhane S, Toyoda H, et al. Transarterial chemo-embolisation of hepatocellular carcinoma: impact of liver function and vascular invasion. *Br J Cancer* 2017; **116:** 448–54.

184 Lencioni R, Kudo M, Ye SL, et al. GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib): second interim analysis. *Int J Clin Pract* 2014; **68:** 609–17.

185 Park JW, Chen M, Colombo M, et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. *Liver Int* 2015; **35:** 2155–66.

186 Kudo M, Raoul J-L, Lee HC, Cheng A-L, Nakajima K, Peck-Radosavljevic M. Deterioration of liver function after transarterial chemoembolization (TACE) in hepatocellular carcinoma (HCC): an exploratory analysis of OPTIMIS—an international observational study assessing the use of sorafenib after TACE. *J Clin Oncol* 2018; **36** (suppl)**:** 368.

187 Llovet JM, De Baere T, Kulik L, et al. Locoregional therapies in the era of molecular and immune treatments for hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol* 2021; **18:** 293–313.

188 Marrero JA, Kudo M, Venook AP, et al. Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: ThxDEON study. *J Hepatol* 2016; **65:** 1140–47.

189 King J, Palmer DH, Johnson P, et al. Sorafenib for the treatment of advanced hepatocellular cancer–a UK audit. *Clin Oncol (R Coll Radiol)* 2017; **29:** 256–62.

190 Kudo M, Matilla A, Santoro A, et al. CheckMate 040 cohort 5: a phase I/II study of nivolumab in patients with advanced hepatocellular carcinoma and Child-Pugh B cirrhosis. *J Hepatol* 2021; **75:** 600–09.

191 Siegel AB, Cohen EI, Ocean A. Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. *J Clin Oncol* 2008; **26:** 2992–98.

192 Pfister D, Núñez NG, Pinyol R, et al. NASH limits anti-tumour surveillance in immunotherapy-treated HCC. *Nature* 2021; **592:** 450–56.

193 Kim RD, Sarker D, Meyer T, et al. First-in-human phase I study of fisogatinib (BLU-554) validates aberrant FGF19 signaling as a driver event in hepatocellular carcinoma. *Cancer Discov* 2019; **9:** 1696–707.

194 Jin H, Shi Y, Lv Y, et al. EGFR activation limits the response of liver cancer to lenvatinib. *Nature* 2021; **595:** 730–34.

195 Rudalska R, Harbig J, Snaebjornsson MT, et al. LXRα activation and Raf inhibition trigger lethal lipotoxicity in liver cancer. *Nat Can* 2021; **2:** 201–17.

196 Wang C, Vegna S, Jin H, et al. Inducing and exploiting vulnerabilities for the treatment of liver cancer. *Nature* 2019; **574:** 268–72.