Controversies in the management of hepatocellular carcinoma

Alejandro Forner,[1,2,*] Leonardo G Da Fonseca,[1] Álvaro Díaz-González,[1] Marco Sanduzzi-Zamparelli,[1] María Reig,[1,2] Jordi Bruix[1,2]

Summary

The management of hepatocellular carcinoma (HCC) has evolved considerably over the last decade. Surveillance of cirrhotic patients and refinements to imaging techniques have enabled a relevant proportion of patients to be diagnosed at an early stage, when effective therapies are feasible. Resection, transplantation and ablation are all options in patients with early stage HCC. Thus, there is some controversy regarding which is the best treatment approach in challenging scenarios. There have also been major developments in locoregional therapies, particularly in intra-arterial approaches. Finally, the systemic treatment for HCC has changed dramatically following the demonstration of a survival benefit with sorafenib; there are currently several first-line (sorafenib and lenvatinib) and second-line (regorafenib, cabozantinib and ramucirumab) treatments that have shown a survival benefit. Expectations for immune checkpoint inhibitors are high, with the results of the ongoing phase III trials eagerly awaited. In this review we discuss some of the controversies in the management of HCC, focussing in particular on systemic therapy.

Keywords: Hepatocelullar carcinoma; Diagnosis; Surgery; Liver transplantation; Locoregional therapy; Systemic therapy.

Received 12 December 2018; received in revised form 11 January 2019; accepted 13 January 2019; available online 18 March 2019

Introduction

Decades ago, hepatocellular carcinoma (HCC) was usually diagnosed at an advanced stage, upon the presence of symptoms and liver decompensation, resulting in a dismal outcome with no chance for curative therapies. This scenario has completely changed; the acceptance of surveillance in patients at risk of developing HCC has enabled diagnosis of the disease at earlier stages, when potentially curative treatments are feasible. In addition, HCC is recognised as a chemoresistant tumour and until 2007, no systemic therapy had conferred any survival benefit in HCC, leaving a relevant proportion of patients without effective therapy. This grave situation completely changed with the emergence of sorafenib as the first effective systemic treatment in HCC.[1,2] The positive results of sorafenib in advanced HCC triggered the evaluation of several agents for first- and second-line treatment, but it took 10 years from the approval of sorafenib for a second phase III trial to be positive. Currently, in addition to sorafenib, lenvatinib has shown non-inferiority to sorafenib in first-line treatment, and 3 agents (regorafenib, cabozantinib, and ramucirumab) have demonstrated a survival benefit compared to placebo after sorafenib failure. In this review we will discuss the most controversial aspects and challenging scenarios in the management of HCC, with particular focus on the available systemic options.

Diagnosis of HCC: Any room for improvement?

The accurate characterization of a small nodule detected by surveillance abdominal ultrasound is a clinical challenge. HCC is a major exception in oncology as a conclusive diagnosis can be obtained in a relevant proportion of patients by imaging techniques, with no need for histological confirmation. Since the first non-invasive criteria were published in 2001, based on the coincidental finding by 2 dynamic imaging techniques of arterial phase hyperenhancement in nodules >2 cm (or in 1 technique if alpha-fetoprotein [AFP] >400 ng/ml),[3] these criteria have been refined. The most important advance was the recognition of a specific vascular profile consisting of non-peripheral contrast uptake in the arterial phase and washout of contrast in venous phases. The near absolute specificity of that typical enhancement pattern based on multi-detector computed tomography (CT) and/or extracellular, contrast-enhanced magnetic resonance (MR) has been validated extensively in Europe, North America and Asia[4–7] and is the cornerstone of the non-invasive criteria for HCC diagnosis endorsed by several scientific societies.[8–10] Disappointingly, non-invasive imaging criteria are hampered by their limited sensitivity, achieving 60–70% sensitivity and a negative predictive value below 50% in highly experienced centres when applied on nodules between 1 and 2 cm.[4–7] Accordingly, in a relevant proportion of

[1]*Barcelona Clinic Liver Cancer (BCLC) group, Liver Unit, Hospital Clínic of Barcelona, Fundació Clínic per a la Recerca Biomédica (FCRB), IDIBAPS, University of Barcelona, Spain*
[2]*Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Spain*

* Corresponding author. Address: BCLC Hospital Clínic Barcelona, Villarroel 170, Escala 11, 4ª planta, 08036 Barcelona, Spain. Tel.: +34 932273303/+34 932279803. *E-mail address:* aforner@clinic.ub.es (A. Forner).

cases, the only way to obtain a conclusive HCC diagnosis is by pathological assessment of a tumour sample obtained by percutaneous biopsy. Regrettably, in some cases a biopsy is not feasible because of the location of the tumour, clotting disorders, or ascites. Also, although infrequent, biopsy is not free of complications such as bleeding. Finally, small nodules are susceptible to false-negative results, in some cases because sampling is inadequate and/or not sufficiently representative to allow for a confident pathological diagnosis and, in other cases, because it is unfeasible to perform a reliable differential diagnosis between high-grade dysplastic nodules and very well-differentiated HCC.[11,12] This highlights the need to explore new strategies for improving the sensitivity of imaging diagnosis without impairing the near absolute specificity of the current non-invasive criteria. In the last years, a major advance in liver imaging has been the development of organ-specific contrast agents. Among them, the most widely used is gadoxetic acid.[13–15] After intravenous injection, gadoxetic acid distributes into the vascular and extravascular spaces during the arterial, and portal phases, and progressively into the hepatocytes and bile ducts during the transitional phase and the hepatobiliary phase. Up to now, several retrospective studies have been published reporting sensitivities ranging from 70–100%,[16–27] and no prospective assessment of the diagnostic accuracy of this contrast agent has been conducted so far. Regrettably, in all these studies the imaging criteria for HCC diagnosis was not uniform, as some authors considered the finding of hypo-intensity in the hepatobiliary phase to be equivalent to portal washout[17,21,25] or even diagnostic of HCC, regardless of the presence of arterial contrast enhancement in patients with cirrhosis.[21,28,29] In addition, the retrospective design of the studies[19,20,22] may lead to an overestimation of the sensitivity of the technique since the population included in those analyses might be biased by excluding those with non-typical or technically suboptimal imaging. Finally, most of the studies evaluating the accuracy of MR with gadoxetic acid were conducted in Eastern Asia, where HCC frequently arises in patients with chronic HBV infection without advanced cirrhosis. The recently published European Association for the Study of the Liver (EASL) clinical practice guidelines have accepted the use of gadoxetic acid MR as a diagnostic imaging modality, but aimed to assure a near absolute specificity, they clearly stated that the contrast washout can only be read in the portal phase, and hypo-intensity in the hepatobiliary phase should only be considered an ancillary finding favouring malignancy.[8] With these restrictions, the sensitivity dramatically falls to 40–45%,[30,31] figures below those reported with extracellular contrast media.[4–7] Finally, other ancillary features such as hyperintensity on diffusion-weighted MRI may improve the detection of HCCs,[32] but their real impact on specificity should be validated in large-scale, prospective studies.

Key points

HCC management has evolved considerably over the last decade. This cancer was usually diagnosed at advanced stages with no chance of curative therapy. The implementation of surveillance and the improvements in imaging techniques have allowed the diagnosis at earlier stages, when effective therapies are available and long-term survival is achievable.

Ten years ago, no systemic treatment was able to demonstrate survival benefit. Fortunately, at this moment 5 agents have shown efficacy in phase III trials and immune checkpoints inhibitors have surged forward as a promising strategy against this devasting neoplasia.

The complexity of HCC management demands its management in centres involving hepatologists, liver surgeons, radiologists and interventional radiologists, pathologists and oncologists working in multidisciplinary teams to fully capture and tailor individualised treatment approaches.

Another controversy is the convenience of contrast-enhanced ultrasound (CEUS) as a reliable tool for HCC diagnosis. Its use was questioned because of the potential risk of misdiagnosis with intrahepatic cholangiocarcinoma (ICC), since the pattern of homogeneous arterial hyperenhancement followed by washout on CEUS is present in about 50% of ICCs in cirrhosis.[33,34] However, in a relevant proportion of ICC cases, the onset of washout takes place earlier than 60 s after contrast injection,[33–35] while this is rarely observed in HCC, and the intensity of washout in the portal phase is more marked in ICC than in HCC.[36] Thus, the definition of this typical hallmark of HCC on CEUS has been refined to: global arterial contrast enhancement followed by late (>60 s) washout of mild degree.[37] This pattern was adopted by the EASL clinical practice guidelines for the diagnosis of non-invasive HCC by CEUS, but only as a second-line approach when both CT and MR are contraindicated or are inconclusive for the HCC diagnosis.[8]

Finally, the Liver Imaging Reporting and Data System (LI-RADS) proposed by the American College of Radiology was developed and repeatedly updated to enable the homogeneous reporting of imaging techniques for the diagnosis of hepatic nodules in patients at risk of HCC.[38,39] LI-RADS addresses the full spectrum of liver lesions, classifying the observations into 5 categories, from LR-1 (definitely benign) to LR-5 (definitely HCC). Between both of them we find LR-2 (probably benign), LR-3 (intermediate probability of HCC) and LR-4 (probably HCC) with a progressive increase of HCC risk through the different categories.[40] The aim of this classification is to link the likelihood of an indeterminate nodule being an HCC with clinical management. Regrettably, this stratification for clinical decision making is hampered by the excessive risk of HCC in those indeterminate lesions, since even the lowest risk group (LR-2) bears a cancer risk of at least 10%, which is sufficiently high to pursue diagnosis by biopsy rather than to wait for 3–6 months to register evolutionary changes, as suggested in the last

American Association for the Study of Liver Diseases (AASLD) guidelines following the LI-RADS recommendations.[9,41] Accordingly, biopsy should be indicated when the imaging-based diagnosis remains inconclusive, especially in lesions smaller than 2 cm in diameter where the diagnostic performance of contrast-enhanced imaging is lower. Furthermore, a more active biopsy strategy is encouraged in the setting of research, since potential complications of liver biopsy are rare and manageable and do not justify abstaining from diagnostic biopsy. The broader availability of liver biopsy in HCC will allow patients to access experimental treatment options, while improving clinicians' understanding of the molecular pathophysiology of the disease, which will ultimately improve the therapeutic approach to this cancer in the future.

Surgical resection: Where are the limits?

Surgical resection is the recommended upfront therapy for patients with single HCC, achieving the highest effectiveness in terms of disease control and overall survival (OS) in well selected patients.[8–10] Ideally, the best candidates are those patients with solitary lesions in the absence of underlying cirrhosis. Regrettably, in a relevant proportion of cases, HCC arises in the setting of cirrhosis and in those patients with impaired liver function and/or decompensation, surgical resection should be avoided.[42] The presence of clinically significant portal hypertension (CSPH), defined as hepatic venous pressure gradient >10 mmHg, has consistently been demonstrated to be one of the most powerful predictive factors for liver decompensation and death after resection.[43] Series from centres of excellence in Asia, Europe and the US have shown that the 5-year survival after resection drops from 70–80% to 50–60% when CSPH is present.[44–47] These figures should be compared with the better outcome offered by liver transplantation (LT) or the competitive survival achieved by thermal ablation with a lower cost and safer profile. In the most recent update of the EASL clinical practice guidelines on the management of HCC, the panel suggested extended criteria based not only on the presence of CSPH, but also on the accurate assessment of liver function and the extent of hepatectomy and surgical invasiveness, the latter closely depending on tumour size and localization.[8] The emergence of a minimally invasive laparoscopic approach has been associated with less surgical-related complications and similar survival outcomes.[48,49] In selected peripherally located cases, in which a percutaneous approach is suboptimal, surgical resection emerges as a safe and effective treatment strategy even in the presence of CSPH.[47,50,51] Another unresolved question is the potential superiority of surgical resection over locoregional therapies, particularly transarterial chemoembolization (TACE), in patients with multifocal disease. Several retrospective analyses have shown survival benefit of resection compared to TACE in intermediate patients, but these studies suffered from unintentional selection bias because those patients who are selected for hepatic resection rather than TACE have features that gave the surgeon confidence that a good outcome would be achieved, whereas those selected for TACE probably lacked such characteristics, immediately introducing a bias against TACE.[52] Finally, despite the accurate selection of patients with early tumours and the success of resection for the complete tumour removal, the patients are at high risk of tumour recurrence. Unfortunately, none of the molecular classifications of HCC that have been proposed so far predict disease progression or recurrence after resection.[53] Several agents and procedures have been evaluated for preventing and/or delaying tumour recurrence,[54] including sorafenib,[55] but all trials to date have failed to demonstrate any survival benefit. There is an ongoing, randomized phase II trial evaluating the usefulness of immune checkpoint inhibitors in this scenario,[56] the results of which are eagerly awaited.

Liver transplantation: Surpassing Milan criteria

The excellent outcomes achieved with LT in the last years were at the expense of the worldwide acceptance of the restrictive Milan criteria[57] imposed in part because of the organ shortage.[8] Nowadays, this situation has dramatically changed because of the high efficacy of direct-acting antivirals (DAAs) for hepatitis C virus (HCV) treatment, which have led to a dramatic decrease in the number of patients at need of LT for decompensated cirrhosis in areas with a high prevalence of HCV infection, thus increasing organ availability.[58,59] This evolving scenario has motivated referral centres to consider criteria beyond Milan, expanding the pool of patients who can benefit from LT and achieve acceptable long-term outcomes. The expanded criteria published during the last decade considered only the morphologic features of the tumour defined by the size and number of nodules.[60–65] Very recently, several authors have proposed considering the biological tumour behaviour. In that sense, some criteria take into consideration the use of tumour grading as a tool for patient selection (LT is contraindicated in patients with poorly differentiated tumours), but its real applicability is hampered by the tumour heterogeneity that prevents a reliable assessment of tumour degree by pre-LT biopsy.[66,67] More clinically appealing is the use of tumour markers such as AFP as a surrogate of tumour aggressiveness. In that regard, several proposals have been reported that combine different AFP cut-offs with morphological characteristics.[68–70] Regrettably, no consensus

has been reached on which AFP cut-off value is the most appropriate and how to combine them with the tumour burden, but all proposals agree that regardless of the morphological characteristics, AFP beyond 1,000 ng/ml is associated with a dismal prognosis that discourage the LT indication.[69,70]

Controversies in intra-arterial treatments

There are 2 TACE techniques, namely conventional TACE (cTACE), which uses lipiodol as a vehicle for chemotherapy (mainly doxorubicin or cisplatin) followed by embolization with particles (more frequently gelfoam), and drug-eluting bead (DEB)-TACE, which uses non-resorbable and embolic microspheres preloaded with chemotherapy that enable the slow release of the cytotoxic agent into the tumour and a calibrated embolization.[52,71] The OS benefit of cTACE over best supportive care was firstly demonstrated by 2 randomized clinical trials in 2002[72,73] and then confirmed by a meta-analysis[74] showing the superiority of cTACE with higher 2-year OS (odds ratio 0.53; 95% CI 0.32–0.89; $p = 0.017$). Accordingly, the EASL and European Society for Medical Oncology guidelines recommend, with the highest level of evidence, the use of TACE as the first-line therapy in intermediate stage or, according to the stage migration principle, in early stage HCC when resection, ablation or LT have failed or are not feasible.[8,10] TACE is able to offer median survival beyond 30–40 months with both cTACE[75,76] and DEB-TACE.[77,78]

Despite the current evidence supporting the use of TACE, there are still some critical questions that remain unanswered. Firstly, there are controversies regarding the real benefit of adding chemotherapy to the embolization. The trial by Llovet *et al.*[72] was a 3-arm study including cTACE, transarterial-embolization without chemotherapy (TAE) and best supportive care arms. The study was prematurely stopped in an interim analysis because cTACE was shown to be superior to best supportive care, but at that point no differences were observed between cTACE *vs.* TAE and TAE *vs.* best supportive care. In the study of Malagari *et al.*,[79] 84 patients were randomized to receive DEB-TACE or TAE with a fixed schedule and the 9-month overall response rate (ORR) and time to progression (TTP) were higher in the DEB-TACE group than the TAE group (42.4 *vs.* 36.2 months; $p = 0.008$), but there was no difference in the 1-year survival rate. In the phase II/III trial conducted by Meyer *et al.*,[80] and more recently in the phase II trial conducted by Brown *et al.*,[81] no differences in survival were observed between cTACE and TAE and DEB-TACE and TAE respectively, suggesting the equivalence of both techniques. Unfortunately, the median OS of patients treated with TACE (17.3[80] and 20.8[81] months) was far from the current expected survival with TACE,[75,77,78] undoubtedly because of the inclusion of patients who are not candidates for TACE (BCLC C or D stage or decompensated patients), thus limiting the interpretability of these results. Another controversial point is whether combining TACE with thermal ablation improves outcomes based on the theoretically higher tumour response obtained by the combination of both approaches.[82] Two single-centre randomized clinical trials[83,84] from the same group in Asia, and a recent meta-analysis,[85] showed that the combination of cTACE and radiofrequency ablation (RFA) was superior to RFA alone in terms of OS rate and recurrence-free survival, without a significant difference in major complications. In 2012, Peng *et al.*[83] included 139 patients with recurrent solitary tumours of up to 5 cm or 3 nodules <3 cm and the reported 1-, 3-, and 5-year survival rates were 94%, 69%, and 46%, *vs.* 82%, 47%, and 36% in the combination and the RFA alone group, respectively ($p = 0.037$). In the subgroup analysis, no significant difference was observed in small HCC <3 cm, mainly because of the high rate of complete necrosis after RFA alone. In 2013, in the study by Peng *et al.*[84] 189 patients with solitary tumours of up to 7 cm or 3 nodules <3 cm were randomized; the combination arm was associated with better OS (hazard ratio [HR] 0.53; $p = 0.002$) and recurrence-free survival (HR 0.58; $p = 0.009$). Regrettably, trials evaluating combined TACE and RFA have either recruited patients with early stage disease, and/or compared TACE and RFA with RFA alone, instead of TACE and RFA *vs.* TACE alone, making it impossible to evaluate the real impact of adding RFA to TACE in intermediate HCC. In addition, these promising results have not yet been validated in Western countries and the combination of the 2 techniques on the same occasion is quite demanding in terms of resources, so cost-effective analysis should be required before accepting this approach.

Since the local hypoxia and ischaemic necrosis achieved by TACE triggers the activation of pro-angiogenic factors, the combination of TACE with anti-angiogenic agents might constitute an effective strategy to improve outcomes. Sorafenib[86–88] and brivanib[89] have been evaluated in combination with TACE but both failed to demonstrate a survival benefit.

Finally, one of the most controversial issues in the field of intra-arterial treatments is the clinical value of selective internal radiation therapy (SIRT) with yttrium-90 (Y90), also known as radioembolization.[90] Several groups have reported the outcome of patients treated with SIRT with some promising signs of efficacy in terms of tumour response and OS,[91–94] but up to now, no randomized clinical trial has been able to show a survival benefit in advanced HCC. In that regard, 2 phase III trials designed to demonstrate survival superiority of SIRT over sorafenib have recently been reported.[95,96] In both of them, despite radiologic tumour response and TTP being better in

the SIRT arm, the primary objective (survival benefit) was not achieved in the intention-to-treat analysis. Furthermore, both studies showed that the treatment applicability of these techniques was around 75% despite the inclusion of patients theoretically suitable for SIRT.[95,96] Additionally, a recent phase III trial failed to demonstrate a survival benefit of the combination of SIRT with sorafenib over sorafenib alone (SORAMIC trial).[97] There is still an ongoing trial evaluating if SIRT combined with sorafenib offers better survival than sorafenib alone (STOP HCC trial, NCT01556490), and the preliminary results of the 2 first interim analyses support the continuation of the study.[98] Therefore, according to the available evidence, SIRT cannot be recommended in advanced HCC.[8] More controversial is the data on intermediate HCC. There are no phase III trials evaluating the efficacy of SIRT in this scenario so far, and all available data come from prospective studies and phase II trials. For instance, Salem *et al.*[99] conducted a randomized, phase II trial including 179 BCLC A or B patients who were randomly assigned to SIRT with Y90 or cTACE, with TTP and OS as primary and secondary aims, respectively. The TTP was significantly longer in the SIRT than in the cTACE group (26 *vs.* 6.8 months; $p = 0.012$) while OS was similar (18.6 and 17.7 months; $p = 0.99$), thus reinforcing the perception that radiological response does not necessarily translate into better survival. Similarly, a multicentric cohort study[100] including 86 BCLC B stage patients treated with SIRT or cTACE reported no difference in terms of OS (16.4 *vs.* 18 months; $p = 0.4$) and TTP (13.3 *vs.* 6.8 month; $p = 0.12$). Noticeably, in both studies the median survival in the cTACE group was far from the expected survival between 30 and 40 months achieved in well selected candidates with both DEB-TACE[77,78] and cTACE,[75,76] limiting the significance of these results. Although well-designed phase III trials are needed to demonstrate the superiority of SIRT over TACE, the complexity of the technique and the need for a large number of patients (probably more than 1,000 patients) to demonstrate a significant and clinically relevant survival advantage make these requested trials unaffordable.

Systemic therapy in HCC: Current scenario

Systemic therapy should be considered in patients with advanced disease, defined as presence of extrahepatic spread, macrovascular invasion and/or mild cancer-related symptoms, and for those who are not candidates for locoregional modalities, if the patient has preserved liver function. Over the last decade, drug development has broken paradigms. The systemic treatment for HCC changed dramatically after the demonstration of a survival benefit with sorafenib in 2007.[1,2] Until this landmark, no effective option was available. Efforts to test cytotoxic drugs used for other solid tumours, such as doxorubicin, platinum salts and 5-fluorouracil, provided disappointing results characterized by prohibitive treatment-related toxicities.[101–103] Meanwhile, increasing knowledge of the hallmarks that drive hepatocarcinogenesis, including angiogenesis and molecular signalling pathways, provided the basis for the design of clinical trials.

Sorafenib, a multikinase inhibitor that exerts antiproliferative and anti-angiogenic effects, became the standard of care after the results of 2 phase III randomized placebo-controlled trials; the SHARP trial[1] and the Asia-Pacific trial.[2] Both consistently demonstrated that sorafenib improved OS with a manageable toxicity profile. In the following years after its approval, real-practice data validated the efficacy and safety of sorafenib and consolidated this drug as the cornerstone of systemic therapy for advanced HCC.[104–107] The search for a predictive biomarker of sorafenib response was justified by the weak correlation between response rate and OS. Sorafenib extended survival without any measurable sight of tumour shrinkage, once the response rate by conventional radiologic criteria was less than 5%. Angiopoietin-2, KIT and vascular endothelial growth factor (VEGF) seem to be prognostic rather than a tool to guide treatment decisions.[108] A better prognosis was reported for patients who present early dermatologic adverse events within the firsts 2 months of treatment.[109,110] Additionally, the definition of sorafenib failure surpasses the simplistic evaluation of radiological progression by conventional criteria. The SHARP trial allowed patients to be treated until symptomatic and beyond radiological progression. Prospective data showed that new extrahepatic lesions confer a worse prognosis than the growth of pre-existing lesions or new intrahepatic nodules.[107,111–113]

Several drugs tested in phase III trials published after sorafenib approval did not reproduce the promising results of their earlier development phases[114–119] (Table 1). These failures can probably be explained by a lack of anti-tumoral activity, unsuitable trial designs and impaired safety profiles.[120]

In the second-line setting, regorafenib, an oral multikinase inhibitor targeting angiogenesis and oncogenesis,[121] exhibited a survival improvement. The RESORCE trial was a phase III placebo-controlled trial that enrolled patients who progressed on sorafenib, had preserved liver function and tolerated sorafenib at least 400 mg/day for 20 or more of the last 28 days of treatment.[111] Regorafenib was shown to significantly prolong survival and became the standard second-line therapy in HCC. Treatment-related adverse events were similar to those described for sorafenib and included hypertension, hand-foot skin reaction, fatigue and diarrhoea.

These results led to an unprecedented scenario in the treatment of HCC. The sequence sorafenib-

regorafenib extended survival beyond what has been previously reported. In an exploratory analysis of the patients treated with regorafenib in the RESORCE trial, the median OS was 26 months (95% CI 22.6–28.1), independently of the TTP on sorafenib and the last sorafenib dose.[122] Notably, this advance laid the foundation for the development of new strategies and, recently, novel drugs were tested in successful trials.

Lenvatinib a multikinase inhibitor targeting VEGF receptor 1-3, fibroblast growth factor receptor 1-4, platelet-derived growth factor receptor, RET and KIT, has recently shown to be non-inferior to sorafenib, according to the results of the REFLECT trial, and represents an alternative to sorafenib in the first-line setting.[123] It is noteworthy that patients with main portal vein thrombosis, bile duct invasion or more than half of the liver affected were not included in this trial. The median OS for the lenvatinib arm was 13.6 months, non-inferior to 12.3 months in the sorafenib arm (HR 0.92; 95% CI 0.79–1.06). The toxicity profile was slightly different between the 2 arms. Sorafenib was more commonly associated with hand-foot reaction while lenvatinib led to higher rates of hypertension. Secondary, the ORR with lenvatinib was 24.1% (*vs.* 9.2% with sorafenib) based on modified RECIST criteria (mRECIST), and progression-free survival (PFS) was 7.4 *vs.* 3.7 months, respectively. The median TTP of lenvatinib was 7.4 months *vs.* 3.7 months with sorafenib (HR 0.60; 95% CI 0.51–0.71). However, median lenvatinib treatment duration was 5.7 months *vs.* 3.7 months for sorafenib. The gap between median TTP and treatment duration observed in the lenvatinib arm suggest the occurrence of early discontinuations, probably due to adverse events. Moreover, the mRECIST evaluation may be distorted by the effect of vasoconstriction induced by the tyrosine-kinase inhibitors directed to VEGFR,[124–126] since the vasoconstrictor effect reduces the contrast uptake without necessarily reflecting effective response to therapy. As a consequence, all endpoints based on mRECIST response are potentially faulty. The defence of mRECIST as a tool to detect response not captured by RECIST was never properly validated,[127,128] and there is a weak correlation between TTP and OS in HCC.[129]

For patients who progressed on sorafenib, cabozantinib (a MET and VEGF receptor inhibitor) was tested in a placebo-controlled phase III trial.[130] The CELESTIAL trial analysed patients who received at least 1 prior systemic therapy, with 72% having received only sorafenib and 28% having been previously treated beyond second-line. For cabozantinib *vs.* placebo group, median OS was 10.2 months *vs.* 8.0 months (HR 0.76; 95% CI 0.63–0.92). Treatment-related adverse events were comparable to those of other multikinase inhibitors, with hand-foot reaction and hypertension the most frequent grade 3-4 adverse events. The PFS also favoured cabozantinib *vs.* placebo (5.2 *vs.* 1.9 months). A subgroup analysis of the CELESTIAL trial with patients treated with the sequence sorafenib-cabozantinib reported benefit in survival with cabozantinib regardless of the duration of sorafenib treatment.[131]

As no predictive factor is recognised in advanced HCC, a biomarker-driven approach was analysed in patients with tumoral overexpression of c-MET. C-MET is the receptor of the hepatocyte growth factor, which is overexpressed more often after sorafenib exposure and represents a negative prognostic factor.[112] Tivantinib, a drug developed as a selective inhibitor of c-MET, was tested in placebo-controlled trials enriched with patients with c-MET overexpression after sorafenib. The METIV trial[112] did not meet the primary endpoint of improved OS, and the JET-HCC trial in Japan[132] did not demonstrate a benefit in PFS.

The subset of patients who present with AFP ≥400 ng/ml benefit from second-line ramucirumab, a monoclonal antibody that selectively inhibits VEGF receptor 2. This was recently depicted by the sub-analysis of the REACH trial, that compared ramucirumab *vs.* placebo.[133] Although the trial did not prove survival benefit for ramucirumab, the subgroup of patients with AFP ≥400 ng/ml had better OS. This result was further confirmed with the phase III REACH-2 trial that exclusively included patients with AFP ≥400 ng/ml.[134] The molecular mechanism explaining why this benefit was only observed in this subset of patients is unknown.

It is crucial to critically analyse the phase III results already available, as we are facing a shift

Table 1. Targeted therapies evaluated in phase III – overall survival results.

Study	Randomisation	Survival, months	*p* value
First-line			
SHARP[1]	Sorafenib *vs.* placebo	10.7 *vs.* 7.9	<0.001
Asia-Pacific[2]	Sorafenib *vs.* placebo	6.5 *vs.* 4.2	0.001
SUN1170[117]	Sunitinib *vs.* sorafenib	7.9 *vs.* 10.2	n.s.
BRISK-FL[114]	Brivanib *vs.* sorafenib	9.5 *vs.* 9.9	n.s.
SEARCH[119]	Sorafenib + erlotinib *vs.* sorafenib	9.5 *vs.* 8.5	n.s.
LIGHT[118]	Linifanib *vs.* sorafenib	9.1 *vs.* 9.8	n.s.
REFLECT[123]	Lenvatinib *vs.* sorafenib	13.6 *vs.* 12.3	<0.001*
Second-line			
RESORCE[111]	Regorafenib *vs.* placebo	10.6 *vs.* 7.8	<0.0001
CELESTIAL[130]	Cabozantinib *vs.* placebo	10.2 *vs.* 8.0	0.005
BRISK-PS[115]	Brivanib *vs.* placebo	9.4 *vs.* 8.2	n.s.
EVOLVE[116]	Everolimus *vs.* placebo	7.6 *vs.* 7.3	n.s.
METIV[112]	Tivantinib *vs.* placebo	8.4 *vs.* 9.1	n.s.
REACH[133]	Ramucirumab *vs.* placebo	9.2 *vs.* 7.6	n.s.
REACH-2[134]	Ramucirumab *vs.* placebo (AFP ≥400 ng/ml)	8.5 *vs.* 7.3	0.0199

AFP, alpha-fetoprotein. n.s., non-significant.
*non-inferiority

towards incorporation and approval of new therapies with different oncologic targets. Sorafenib and regorafenib are widely used, yet physicians dispose of sufficient data to guide treatment management and patient selection. The most recent agents, such as lenvatinib, cabozantinib and ramucirumab are rapidly being incorporated into clinical management worldwide. Thus, establishing the optimal strategy and selecting the most suitable treatment for the appropriate subgroup will become major issues.

Immunotherapy in HCC: Hopes and facts

The concept that immune activation inhibits tumour growth is not new.[135] But it was the finding that blocking immune checkpoints induces an anti-tumour response that formed the basis for the development of novel immunotherapies.[136] In several solid tumours, the blockage of programmed death-1 (PD-1)/programmed death 1 ligand-1 (PDL-1) or cytotoxic T-lymphocyte associated protein-4 (CTLA-4) has produced outstanding improvement in clinical outcomes, making it a key part of the treatment paradigm for a number of cancers.

HCC is unique not only because of the underlying cirrhosis but also because of the particular immunobiology of the liver. In response to the continued antigen exposure, the liver has evolved a myriad of mechanisms of immune regulation and tolerance. The coexistence of hepatitis B or C virus infection driving chronic inflammation are suggested to result in an immunosuppressive phenotype, and some mechanisms of immune evasion are present in the HCC microenvironment.[136]

The interest in studying immune checkpoint inhibitors such as PD-1/PDL-1 and CTLA-4 in HCC promptly translated into clinical phases and, actually, early data have already been published[137] (Table 2). In the CHECKMATE 040 trial, a phase I/II trial that enrolled patients with advanced HCC, both sorafenib-naïve and -experienced as well as with or without HBV/HCV, nivolumab (an anti-PD1 agent) showed a manageable safety profile and a response rate of 20% with a median duration of response of 9.9 months (95% CI 8.3-not calculable) in the dose expansion phase compared to a response rate of 15% for a median duration of 17 months (95% CI 6–24) in the dose-escalation phase.[138] Based on these results, nivolumab was granted accelerated approval by the FDA for sorafenib-experienced HCC.[139] By the same token, pembrolizumab, an anti-PD1 agent, received accelerated approval based on an ORR of 17%, with a duration of response of ≥9 months reported in 77% of patients in KEYNOTE 224, a single-arm phase II trial that included patients after sorafenib progression or intolerance.[140,141] Although the toxicity profile of the anti-PD-1 agents seems favourable with about 10% of patients experiencing grade 3-4 adverse events, the risk of immune-mediated toxicities warrants strict vigilance concerning symptoms of colitis,

Table 2. Efficacy and safety data of immune checkpoint inhibitors in advanced hepatocellular carcinoma.

Agent (mechanism)	Trial	Phase	Design	n	Target population	Response rate		Median survival		Grade 3/4 AEs
						ORR	DCR	OS	PFS	
Monotherapy										
Nivolumab (anti-PD1)	CHECKMATE 040[138] (NCT 01658878)	I/II	Cohort 1 (dose escalation)/ Cohort 2 (dose expansion)	48/ 214	Advanced HCC: HCV, HBV or non-infected; sorafenib-naïve or treated	15% /20%	58% /64%	15 /NR	NR /4	25%/ 19%
Pembrolizumab (anti-PD1)	KEYNOTE 224[140] (NCT02702414)	II	Non-randomised, single-arm	104	Advanced HCC: sorafenib-treated	17%	62%	12.9	4.9	25%
Tremelimumab (anti-CTLA4)	NCT01008358[151]	II	Non-randomised, single-arm	21	Inoperable HCC: Naïve or previously treated	17.6%	76.4%	8.2	NR	45%
Durvalumab (anti-PDL1)	NCT01693562*,[152]	II	Non-randomised, single arm	40	Stage III or IV Fail, ineligible, refusal or progression to first-line	10.3	NR	13.2	2.7	20%
Combination										
Atezolizumab (anti-PDL1)+ Bevacizumab (anti-VEGF)	NCT02715531*,[144]	Ib	Non-randomised, single-arm	103	Unresectable HCC: Non-previous treated; HBV, HCV or non-infected	32%	96%	NR	14.9	28%
Lenvatinib (kinase inhibitor)+ Pembrolizumab (anti-PD1)	NCT03006926*,[143]	Ib	Non-randomised, single arm	30	Unresectable HCC: sorafenib-naïve or treated; HCV, HBV or non-infected.	46% 26.9	92%	NR	9.69	60%

AEs, adverse events; DCR, disease control rate; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; NR, not reported; ORR, overall response rate; PFS, progression-free survival; PD1, programmed cell-death.
Median survival given in months
*non-published data.

pneumonitis and especially hepatitis in patients with HCC.[142] In February 2019, the company responsible for pembrolizumab development announced that the phase III KEYNOTE-240 trial failed to show an increase in survival of this agent compared to placebo in patients previously treated with sorafenib. The presentation of the final results is pending.

Final results of the CHECKMATE 040 (NCT01658878) are pending, with an estimated completion date of late 2019. This study also evaluated cohorts on Child-Pugh B, HBV/HCV infected, combinations of ipilimumab (anti-CTLA-4) and nivolumab, nivolumab and cabozantinib and nivolumab plus ipilimumab and cabozantinib.

Combination therapy using an immune checkpoint inhibitor and a targeted therapy is also an approach currently under investigation. The rational for combinations relies not only on the additive therapeutic effect, but also on the potential immunomodulatory property of targeted agents and their impact on the immunosuppressive tumour microenvironment. In that sense, results of an open-label phase Ib trial that assessed the efficacy of lenvatinib plus pembrolizumab in 94 patients were recently reported. The combination induced a confirmed response rate of 26.9%, with a median PFS of 9.69 months (95% CI 5.55-not calculable). Sixty percent of the patients had dose interruptions or reductions, 5 patients experienced serious adverse events and there were 2 treatment-related deaths.[143] Further survival analyses are pending. In 2018, the combination of atezolizumab, an anti-PDL1 inhibitor, and bevacizumab, a monoclonal antibody against VEGF, was designated a breakthrough therapy for first-line HCC treatment by the FDA. The designation was based on a phase Ib study in which, after a median follow-up of 10.3 months, the combination induced an ORR of 65% among 23 evaluable patients (11 of them with extrahepatic spread). The safety analysis included 43 patients and treatment-related grade 3-4 adverse events occurred in 28%.[144] The data was further updated showing a 32% (23/73) ORR and a median PFS of 14.9 months.[145] Actually, the ongoing phase III IMbrave150 trial (NCT03434379) is comparing this combination with sorafenib in the frontline setting. The most relevant ongoing clinical trials on immune checkpoint inhibitors for advanced HCC are summarized in Table 3.

Open questions: Challenges in interpreting upcoming data

Radical changes in therapeutic modalities require innovative concepts. The positive results of first- and second-line treatments for HCC stress the importance of evaluating pre and post-trial treatment, which is a relevant issue in malignancies with several active treatment lines.

Table 3. Clinical trials on immune checkpoint inhibitors for advanced hepatocellular carcinoma.

Agent	Clinical trial number	Phase, design	Primary end point	Status*
Phase II and III trials with immune checkpoint inhibitors				
Nivolumab *vs.* sorafenib	NCT02576509	Phase III, first-line	Overall survival	Active, not recruiting
Pembrolizumab *vs.* best supportive care	NCT02702401	Phase III, after sorafenib	Overall survival and progression-free survival	Active, not recruiting
Atezolizumab + bevacizumab *vs.* sorafenib	NCT03434379	Phase III, first-line	Overall survival and progression-free survival	Recruiting
Durvalumab ± tremelimumab *vs.* sorafenib	NCT03298451	Phase III, first-line	Overall survival	Recruiting
BGB-A317 *vs.* sorafenib	NCT03412773	Phase III, first-line	Overall survival	Recruiting
Avelumab	NCT03389126	Phase II, after sorafenib	Response rate	Recruiting
Targeted therapy + immune checkpoint inhibitor combinations				
Nivolumab + cabozantinib	NCT01658878	Phase I/II, multicohort	Safety and response rate	Active, not recruiting
Nivolumab + lenvatinib	NCT03418922	Phase I	Safety	Recruiting
Nivolumab + sorafenib	NCT03439891	Phase I/II	Safety and response rate	Recruiting
Nivolumab + bevacizumab	NCT03382886	Phase I	Safety	Recruiting
Pembrolizumab + lenvatinib	NCT03006926	Phase I	Safety	Recruiting
Pembrolizumab + regorafenib	NCT03347292	Phase I	Safety	Recruiting
Avelumab + axitinib	NCT03289533	Phase I	Safety	Recruiting
PDR001 + sorafenib	NCT02988440	Phase I	Safety	Recruiting
Immuno-oncology agents in combination				
Nivolumab + ipilimumab	NCT01658878	Phase I/II, multicohort	Safety and response rate	Active, not recruiting
Durvalumab ± tremelimumab	NCT02519348	Phase I/II	Safety and response rate	Recruiting
Nivolumab + galunisertib	NCT02423343	Phase I/II	Safety, response rate, progression-free and overall survival	Recruiting
Nivolumab + pexastimogene devacirepvec	NCT03071094	Phase I/II	Safety and response rate	Recruiting

*Status on December 1st, 2018 at clinicaltrial.gov.

While the final results of the ongoing immunotherapy-based clinical trials for HCC are eagerly awaited, accumulated experience in other solid tumours allows us to anticipate future challenges in HCC. Patients who receive immunotherapy might develop atypical response patterns, wherein they initially meet conventional criteria for progressive disease, but later show a decrease or stabilization in tumour burden. This phenomenon, called pseudoprogression, can be explained by immune-cell infiltration and delayed antitumoral activity.[144] The use of adapted immune criteria to define progression revealed that patients who met this definition of pseudoprogression can have similar outcomes as those who did not progress according to conventional radiological criteria.[146] However, a reliable marker to discriminate which mechanism is behind the increase in tumour burden remains to be identified, precluding a formal recommendation regarding continuation of treatment beyond progression.

Meanwhile, a subset of patients may experience accelerated progression after immune checkpoint inhibitors, resulting in poor short-term survival. This is referred to as hyperprogression, which is estimated to occur in around 10% of patients treated for lung cancer, but there is no clear understanding of its pathophysiology.[147] As reported in lung cancer, hyperprogression in HCC may be a devastating event due to the short liver reserve capacity, as well as being an important determinant of treatment efficacy.

An interesting finding in melanoma and renal cell carcinoma is that around 10–30% of the patients present long-term disease control, resulting in unprecedented survival figures. It suggests that there is a subgroup of outlier patients that probably have a sensitive tumoral phenotype or a specific predictive biomarker. Improved PFS and OS have been shown in patients with advanced melanoma and lung cancer when comparing PD-L1-positive *vs.* PD-L1-negative subgroups.[148,149] Mutation burden, tumour-infiltrating lymphocytes and immune gene signatures are also being investigated as potential tools.[150] For HCC, the PDL-1 expression seems to be around 20–25%, but no correlation between PDL-1 expression and better response has been established so far.[138]

Considering that regulatory agencies are prioritizing accelerated approval based on response rates and duration of response, it is important to state that survival improvements should be the real endpoint to be pursued. Since we still do not have final results from the ongoing phase III studies, it is not possible to correlate the available results of response rate with real survival benefit. Early phase studies do not always reflect the population enrolled in controlled trials, particularly regarding the pattern of tumour progression rate and whether tumours are stable or under recent progression at the point of trial inclusion. Both parameters are relevant and may justify discrepant results between suggestive early phase data and negative phase III trial outcomes.

The current scenario of systemic therapy in HCC is likely to change in the near future. If the encouraging data on immunotherapy materializes, a major challenge would be to evaluate the potential benefit of sequenced strategies or combination between active agents. Undoubtedly, proper patient selection and an accurate and critical interpretation of trials results will remain crucial.

Financial support

Alejandro Forner has been supported by grants from ISCIII (PI13/01229 and PI18/00542). Álvaro Diaz-González is supported by a grant from the ISCIII (CM15/00050) and Ayuda Clínico Junior 2018 from the Asociación Española Contra el Cáncer (AECC). María Reig: Received grant support from Instituto de Salud Carlos III (PI15/00145 and PI18/00358). Jordi Bruix: received grant support from Instituto de Salud Carlos III (PI14/00962 and PI18/00768), AECC (PI044031), Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2014 SGR 605) and WCR (AICR) 16-0026. CIBERehd is funded by the Instituto de Salud Carlos III.

Conflict of interest

Alejandro Forner: Speaker fees from Bayer, Gilead and MSD; consultancy fees from Bayer and Guerbert. Leonardo Gomes da Fonseca: Speaker fees and travel grants from Bayer and IPSEN. Álvaro Díaz-González: Speaker fees and travel grants from Bayer. Travel grants from BTG. Marco Sanduzzi-Zamparelli: Speaker fees and travel grants from Bayer. Travel grants from BTG. María Reig: Consultancy from Bayer, BMS, Roche, Ipsen, AstraZeneca and Lilly. Lecture fees from Bayer, BTG, BMS, Gilead, and Lilly. Research grants from Bayer. Jordi Bruix: Consultancy from Arqule, Bayer, Novartis, BMS, BTG- Biocompatibles, Eisai, Kowa, Terumo, Gilead, Bio-Alliance, Roche, AbbVie, Merck, Sirtex, Ipsen, AstraMedimmune, Incyte, Quirem, Adaptimmune, Lilly. Research grants from Bayer and BTG. Educational grants from Bayer and BTG. Lecture fees from Bayer, BTG- Biocompatibles, Eisai, Terumo, Sirtex, Ipsen.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2019.02.003.

References

[1] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc J-F, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–390.
[2] Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25–34.
[3] Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001;35:421–430.
[4] Forner A, Vilana R, Ayuso C, Bianchi L, Solé M, Ayuso JR, 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.
[5] Sangiovanni A, Manini MA, Iavarone M, Romeo R, Forzenigo LV, Fraquelli M, et al. The diagnostic and economic impact of contrast imaging technique in the diagnosis of small hepatocellular carcinoma in cirrhosis. Gut 2010;59:638–644.

[6] Khalili KT, Kim TK, Jang HJ, Haider MA, Khan L, Guindi M, et al. Optimization of imaging diagnosis of 1-2 cm hepatocellular carcinoma: An analysis of diagnostic performance and resource utilization. J Hepatol 2011;54:723–728.

[7] Kim SE, Lee HC, Shim JH, Park HJ, Kim KM, Kim PN, et al. Noninvasive diagnostic criteria for hepatocellular carcinoma in hepatic masses larger than 2 cm in a hepatitis B virus-endemic area. Liver Int 2011;31:1468–1476.

[8] Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul J-L, et al. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182–236.

[9] Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67:358–380.

[10] Vogel A, Cervantes A, Chau I, Daniele B, Llovet J, Meyer T, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol 2018;29:iv238–iv255.

[11] Tremosini S, Forner A, Boix L, Vilana R, Bianchi L, Reig M, 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;61:1481–1487.

[12] Roskams T, Kojiro M. Pathology of Early Hepatocellular Carcinoma: Conventional and Molecular Diagnosis. Semin Liver Dis 2010;30:17–25.

[13] Van Beers BE, Pastor CM, Hussain HK. Primovist, Eovist: What to expect? J Hepatol 2012;57:421–429.

[14] Kitao A, Zen Y, Matsui O, Gabata T, Kobayashi S, Koda W, et al. Hepatocellular carcinoma: signal intensity at gadoxetic acid-enhanced MR Imaging–correlation with molecular transporters and histopathologic features. Radiology 2010;256:817–826.

[15] Choi JW, Lee JM, Kim SJ, Yoon J-H, Baek JH, Han JK, et al. Hepatocellular carcinoma: imaging patterns on gadoxetic acid-enhanced MR Images and their value as an imaging biomarker. Radiology 2013;267:776–786.

[16] Kim SH, Kim SH, Lee J, Kim MJ, Jeon YH, Park Y, et al. Gadoxetic Acid–Enhanced MRI Versus Triple-Phase MDCT for the Preoperative Detection of Hepatocellular Carcinoma. Am J Roentgenol 2009;192:1675–1681.

[17] Granito A, Galassi M, Piscaglia F, Romanini L, Lucidi V, Renzulli M, et al. Impact of gadoxetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance on the non-invasive diagnosis of small hepatocellular carcinoma: a prospective study. Aliment Pharmacol Ther 2013;37:355–363.

[18] Duncan JK, Ma N, Vreugdenburg TD, Cameron AL, Maddern G. Gadoxetic acid-enhanced MRI for the characterization of hepatocellular carcinoma: A systematic review and meta-analysis. J Magn Reson Imaging 2017;45:281–290.

[19] Kim BR, Lee JM, Lee DH, Yoon JH, Hur BY, Suh KS, et al. Diagnostic Performance of Gadoxetic Acid-enhanced Liver MR Imaging versus Multidetector CT in the Detection of Dysplastic Nodules and Early Hepatocellular Carcinoma. Radiology 2017;285:134–146.

[20] Baek C-K, Choi J-Y, Kim K-A, Park M-S, Lim JS, Chung YE, et al. Hepatocellular carcinoma in patients with chronic liver disease: a comparison of gadoxetic acid-enhanced MRI and multiphasic MDCT. Clin Radiol 2012;67:148–156.

[21] Bartolozzi C, Battaglia V, Bargellini I, Bozzi E, Campani D, Pollina LE, et al. Contrast-enhanced magnetic resonance imaging of 102 nodules in cirrhosis: correlation with histological findings on explanted livers. Abdom Imaging 2013;38:290–296.

[22] Ichikawa T, Sano K, Morisaka H. Diagnosis of Pathologically Early HCC with EOB-MRI: Experiences and Current Consensus. Liver Cancer 2014;3:97–107.

[23] Joo I, Lee JM, Lee DH, Jeon JH, Han JK, Choi BI. Noninvasive diagnosis of hepatocellular carcinoma on gadoxetic acid-enhanced MRI: can hypointensity on the hepatobiliary phase be used as an alternative to washout? Eur Radiol 2015;25:2859–2868.

[24] Lee YJ, Lee JM, Lee JS, Lee HY, Park BH, Kim YH, et al. Hepatocellular carcinoma: diagnostic performance of multidetector CT and MR imaging-a systematic review and meta-analysis. Radiology 2015;275:97–109.

[25] Choi SH, Byun JH, Lim Y-S, Yu E, Lee SJ, Kim SY, et al. Diagnostic criteria for hepatocellular carcinoma <=3 cm with hepatocyte-specific contrast-enhanced magnetic resonance imaging. J Hepatol 2016;64:1099–1107.

[26] Guo J, Seo Y, Ren S, Hong S, Lee D, Kim S, et al. Diagnostic performance of contrast-enhanced multidetector computed tomography and gadoxetic acid disodium-enhanced magnetic resonance imaging in detecting hepatocellular carcinoma: direct comparison and a meta-analysis. Abdom Radiol (New York) 2016;41:1960–1972.

[27] Joo I, Lee JM, Lee DH, Ahn SJ, Lee ES, Han JK. Liver imaging reporting and data system v2014 categorization of hepatocellular carcinoma on gadoxetic acid-enhanced MRI: Comparison with multiphasic multidetector computed tomography. J Magn Reson Imaging 2017;45:731–740.

[28] Golfieri R, Renzulli M, Lucidi V, Corcioni B, Trevisani F, Bolondi L. Contribution of the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI to Dynamic MRI in the detection of hypovascular small (≤ 2 cm) HCC in cirrhosis. Eur Radiol 2011;21:1233–1242.

[29] Sugimoto K, Kim SR, Imoto S, Tohyama M, Kim SK, Matsuoka T, et al. Characteristics of Hypovascular versus Hypervascular Well-Differentiated Hepatocellular Carcinoma Smaller Than 2 cm - Focus on Tumor Size, Markers and Imaging Detectability. Dig Dis 2015;33:721–727.

[30] Kim Y-Y, An C, Kim S, Kim M-J. Diagnostic accuracy of prospective application of the Liver Imaging Reporting and Data System (LI-RADS) in gadoxetate-enhanced MRI. Eur Radiol 2018;28:2038–2046.

[31] Ayuso C, Darnell A, Rimola J, Garcia-Criado M, Vilana R, Forner A, et al. Prospective evaluation of dynamic MR with gadoxetic acid for the non-invasive diagnosis of HCC in newly detected nodules. ESGAR, 2018. B Abstr n.d.;9:S659.

[32] Li X, Li C, Wang R, Ren J, Yang J, Zhang Y. Combined Application of Gadoxetic Acid Disodium-Enhanced Magnetic Resonance Imaging (MRI) and Diffusion-Weighted Imaging (DWI) in the Diagnosis of Chronic Liver Disease-Induced Hepatocellular Carcinoma: A Meta-Analysis. PLoS One 2015;10e0144247.

[33] Vilana R, Forner A, Bianchi L, García-Criado A, Rimola J, de Lope CR, et al. Intrahepatic peripheral cholangiocarcinoma in cirrhosis patients may display a vascular pattern similar to hepatocellular carcinoma on contrast-enhanced ultrasound. Hepatology 2010;51:2020–2029.

[34] Galassi M, Iavarone M, Rossi S, Bota S, Vavassori S, Rosa L, et al. Patterns of appearance and risk of misdiagnosis of intrahepatic cholangiocarcinoma in cirrhosis at contrast enhanced ultrasound. Liver Int 2013;33:771–779.

[35] Wildner D, Bernatik T, Greis C, Seitz K, Neurath MF, Strobel D. CEUS in hepatocellular carcinoma and intrahepatic cholangiocellular carcinoma in 320 patients - early or late washout matters: a subanalysis of the DEGUM multicenter trial. Ultraschall Med 2015;36:132–139.

[36] Wildner D, Pfeifer L, Goertz R, Bernatik T, Sturm J, Neurath M, et al. Dynamic Contrast-Enhanced Ultrasound (DCE-US) for the Characterization of Hepatocellular Carcinoma and Cholangiocellular Carcinoma. Ultraschall Der Medizin - Eur J Ultrasound 2014;35:522–527.

[37] American College of Radiology . CEUS-LI-RADS version 2017. , https://www.acr.org/-/media/ACR/Files/RADS/LI-RADS/CEUS-LI-RADS-2017-Core.pdf?la=en [n.d.].

[38] Chernyak V, Fowler KJ, Kamaya A, Kielar AZ, Elsayes KM, Bashir MR, et al. Liver Imaging Reporting and Data System (LI-RADS) Version 2018: Imaging of Hepatocellular Carcinoma in At-Risk Patients. Radiology 2018;:181494.

[39] Tang A, Singal AG, Mitchell DG, Hecht EM, Fowler KJ, Kulik L, et al. Introduction to the Liver Imaging Reporting and Data System (LI-RADS) for hepatocellular carcinoma. Clin Gastroenterol Hepatol 2018;S1542-3565(18) 31135–2. [Epub ahead of print].

[40] van der Pol CB, Lim CS, Sirlin CB, McGrath TA, Salameh J-P, Bashir MR, et al. Accuracy of the Liver Imaging Reporting and Data System in Computed Tomography and Magnetic Resonance Image Analysis of Hepatocellular Carcinoma or Overall Malignancy—A Systematic Review. Gastroenterology 2018;S0016-5085(18):35262–35264 [Epub ahead of print].

[41] Bruix J, Ayuso C. Diagnosis of hepatic nodules in patients at risk for hepatocellular carcinoma: LIRADS probability vs certainty. Gastroenterology 2019;S0016-5085(19):30381–30386 [Epub ahead of print].

[42] Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;31:1301–1314.

[43] 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;61:526–536.

[44] Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 1999;30:1434–1440.

[45] Ishizawa T, Hasegawa K, Aoki T, Takahashi M, Inoue Y, Sano K, et al. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. Gastroenterology 2008;134:1908–1916.

[46] Cucchetti A, Piscaglia F, Cescon M, Ercolani G, Terzi E, Bolondi L, et al. Conditional survival after hepatic resection for hepatocellular carcinoma in cirrhotic patients. Clin Cancer Res 2012;18:4397–4405.

[47] Roayaie S, Jibara G, Tabrizian P, Park J-W, Yang J, Yan L, et al. The role of hepatic resection in the treatment of hepatocellular cancer. Hepatology 2015;62:440–451.
[48] Han H-S, Shehta A, Ahn S, Yoon Y-S, Cho JY, Choi Y. Laparoscopic versus open liver resection for hepatocellular carcinoma: Case-matched study with propensity score matching. J Hepatol 2015;63:643–650.
[49] Sposito C, Battiston C, Facciorusso A, Mazzola M, Muscarà C, Scotti M, et al. Propensity score analysis of outcomes following laparoscopic or open liver resection for hepatocellular carcinoma. Br J Surg 2016;103:871–880.
[50] Cucchetti A, Ercolani G, Vivarelli M, Cescon M, Ravaioli M, Ramacciato G, et al. Is Portal Hypertension a Contraindication to Hepatic Resection? Ann Surg 2009;250:922–928.
[51] Molina V, Sampson-Dávila J, Ferrer J, Fondevila C, Díaz del Gobbo R, Calatayud D, et al. Benefits of laparoscopic liver resection in patients with hepatocellular carcinoma and portal hypertension: a case-matched study. Surg Endosc 2018;32:2345–2354.
[52] Forner A, Gilabert M, Bruix J, Raoul J-L. Treatment of intermediate-stage hepatocellular carcinoma. Nat Rev Clin Oncol 2014;11:525–535.
[53] Pinyol R, Montal R, Bassaganyas L, Sia D, Takayama T, Chau G-Y, et al. Molecular predictors of prevention of recurrence in HCC with sorafenib as adjuvant treatment and prognostic factors in the phase III STORM trial. Gut 2018; gutjnl-2018-316408. [Epub ahead of print].
[54] Lu L-C, Cheng A-L, Poon RTP. Recent advances in the prevention of hepatocellular carcinoma recurrence. Semin Liver Dis 2014;34:427–434.
[55] Bruix J, Takayama T, Mazzaferro V, Chau G-Y, Yang J, Kudo M, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase III, randomised, double-blind, placebo-controlled trial. Lancet Oncol 2015;16:1344–1354.
[56] Study Evaluating Nivolumab (Anti-PD-1 Antibody) Alone Versus Nivolumab Plus Ipilimumab (Anti-CTLA-4 Antibody) in Patients With Resectable and Potentially Resectable Hepatocellular Carcinoma (HCC) (CA209-956) - Full Text View - ClinicalTrials.gov, n.d.
[57] Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–699.
[58] Pascasio JM, Vinaixa C, Ferrer MT, Colmenero J, Rubin A, Castells L, et al. Clinical outcomes of patients undergoing antiviral therapy while awaiting liver transplantation. J Hepatol 2017;67:1168–1176.
[59] Belli LS, Perricone G, Adam R, Cortesi PA, Strazzabosco M, Facchetti R, et al. Impact of DAAs on liver transplantation: Major effects on the evolution of indications and results. An ELITA study based on the ELTR registry. J Hepatol 2018;69:810–817.
[60] Yao FY, Xiao L, Bass NM, Kerlan R, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: validation of the UCSF-expanded criteria based on preoperative imaging. Am J Transpl 2007;7:2587–2596.
[61] Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 2009;10.
[62] Duffy JP, Vardanian A, Benjamin E, Watson M, Farmer DG, Ghobrial RM, et al. Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. Ann Surg 2007;246:502–511.
[63] Onaca N, Davis GL, Goldstein RM, Jennings LW, Klintmalm GB. Expanded criteria for liver transplantation in patients with hepatocellular carcinoma: a report from the International Registry of Hepatic Tumors in Liver Transplantation. Liver Transpl 2007;13:391–399.
[64] Herrero JI, Sangro B, Pardo F, Quiroga J, Inarrairaegui M, Rotellar F, et al. Liver transplantation in patients with hepatocellular carcinoma across Milan criteria. Liver Transpl 2008;14:272–278.
[65] Lee SG, Hwang S, Moon DB, Ahn CS, Kim KH, Sung KB, et al. Expanded indication criteria of living donor liver transplantation for hepatocellular carcinoma at one large-volume center. Liver Transpl 2008;14:935–945.
[66] Cillo U, Vitale A, Bassanello M, Boccagni P, Brolese A, Zanus G, et al. Liver transplantation for the treatment of moderately or well-differentiated hepatocellular carcinoma. Ann Surg 2004;239:150–159.
[67] Sapisochin G, Goldaracena N, Laurence JM, Dib M, Barbas A, Ghanekar A, et al. The Extended Toronto Criteria for Liver Transplantation in Patients With Hepatocellular Carcinoma: A Prospective Validation Study. Hepatology 2016;64:2077–2088.
[68] Toso C, Meeberg G, Hernandez-Alejandro R, Dufour J-F, Marotta P, Majno P, et al. Total tumor volume and alpha-fetoprotein for selection of transplant candidates with hepatocellular carcinoma: A prospective validation. Hepatology 2015;62:158–165.
[69] Duvoux C, Roudot-Thoraval F, Decaens T, Pessione F, Badran H, Piardi T, et al. Liver transplantation for hepatocellular carcinoma: a model including alpha-fetoprotein improves the performance of Milan criteria. Gastroenterology 2012;143:985–986.
[70] Mazzaferro V, Sposito C, Zhou J, Pinna AD, De Carlis L, Fan J, et al. Metroticket 2.0 Model for Analysis of Competing Risks of Death Following Liver Transplantation for Hepatocellular Carcinoma. Gastroenterology 2018;154:128–139.
[71] Raoul J-L, Forner A, Bolondi L, Cheung TT, Kloeckner R, de Baere T. Updated use of TACE for hepatocellular carcinoma treatment: How and when to use it based on clinical evidence. Cancer Treat Rev 2019;72:28–36.
[72] Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002;359:1734–1739.
[73] Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164–1171.
[74] Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology 2003;37:429–442.
[75] Takayasu K, Arii S, Kudo M, Ichida T, Matsui O, Izumi N, et al. Superselective transarterial chemoembolization for hepatocellular carcinoma. Validation of treatment algorithm proposed by Japanese guidelines. J Hepatol 2012;56:886–892.
[76] Zhang Y, Zhang M, Chen M, Mei J, Xu L, Guo R, et al. Association of Sustained Response Duration With Survival After Conventional Transarterial Chemoembolization in Patients With Hepatocellular Carcinoma. JAMA Netw Open 2018;1e183213.
[77] Burrel M, Reig M, Forner A, Barrufet M, Lope CRD, Tremosini S, et al. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. J Hepatol 2012;56:1330–1335.
[78] Malagari K, Pomoni M, Moschouris H, Bouma E, Koskinas J, Stefaniotou A, et al. Chemoembolization With Doxorubicin-Eluting Beads for Unresectable Hepatocellular Carcinoma: Five-Year Survival Analysis. Cardiovasc Interv Radiol 2012;35:1119–1128.
[79] Malagari K, Pomoni M, Kelekis A, Pomoni A, Dourakis S, Spyridopoulos T, et al. Prospective Randomized Comparison of Chemoembolization with Doxorubicin-Eluting Beads and Bland Embolization with BeadBlock for Hepatocellular Carcinoma. Cardiovasc Intervent Radiol 2010;33:541–551.
[80] Meyer T, Kirkwood A, Roughton M, Beare S, Tsochatzis E, Yu D, 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;108:1252–1259.
[81] Brown KT, Do RK, Gonen M, Covey AM, Getrajdman GI, Sofocleous CT, 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;34:2046–2053.
[82] Nault J-C, Sutter O, Nahon P, Ganne-Carrié N, Séror O. Percutaneous treatment of hepatocellular carcinoma: State of the art and innovations. J Hepatol 2018;68:783–797.
[83] Peng Z-W, Zhang Y-J, Liang H-H, Lin X-J, Guo R-P, Chen M-S. Recurrent hepatocellular carcinoma treated with sequential transcatheter arterial chemoembolization and RF ablation versus RF ablation alone: a prospective randomized trial. Radiology 2012;262:689–700.
[84] Peng Z-W, Zhang Y-J, Chen M-S, Xu L, Liang H-H, Lin X-J, et al. Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial. J Clin Oncol 2013;31:426–432.
[85] Wang X, Hu Y, Ren M, Lu X, Lu G, He S. Efficacy and Safety of Radiofrequency Ablation Combined with Transcatheter Arterial Chemoembolization for Hepatocellular Carcinomas Compared with Radiofrequency Ablation Alone: A Time-to-Event Meta-Analysis. Korean J Radiol 2016;17:93.
[86] Lencioni R, Llovet JM, Han G, Tak WY, Yang J, Guglielmi A, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial. J Hepatol 2016;64:1090–1098.

[87] Chao Y, Chung Y-H, Han G, Yoon J-H, Yang J, Wang J, et al. The combination of transcatheter arterial chemoembolization and sorafenib is well tolerated and effective in Asian patients with hepatocellular carcinoma: Final results of the START trial. Int J Cancer 2015;136:1458–1467.
[88] Meyer T, Fox R, Ma YT, Ross PJ, James MW, Sturgess R, et al. Sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma (TACE 2): a randomised placebo-controlled, double-blind, phase III trial. Lancet Gastroenterol Hepatol 2017;2:565–575.
[89] Kudo M, Han G, Finn RS, Poon RTP, Blanc J-F, Yan L, et al. Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: A randomized phase III trial. Hepatology 2014;60:1697–1707.
[90] Sangro B, Salem R. Transarterial Chemoembolization and Radioembolization. Semin Liver Dis 2014;34:435–443.
[91] Sangro B, Carpanese L, Cianni R, Golfieri R, Gasparini D, Ezziddin S, et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. Hepatology 2011;54:868–878.
[92] Kulik LM, Carr BI, Mulcahy MF, Lewandowski RJ, Atassi B, Ryu RK, et al. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. Hepatology 2008;47:71–81.
[93] Hilgard P, Hamami M, El Fouly A, Scherag A, Müller S, Ertle J, et al. Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. Hepatology 2010;52:1741–1749.
[94] Salem R, Gabr A, Riaz A, Mora R, Ali R, Abecassis M, et al. Institutional decision to adopt Y90 as primary treatment for hepatocellular carcinoma informed by a 1,000-patient 15-year experience. Hepatology 2018;68:1429–1440.
[95] Chow PKH, Gandhi M, Tan S-B, Khin MW, Khasbazar A, Ong J, et al. SIRveNIB: Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients With Hepatocellular Carcinoma. J Clin Oncol 2018;36 (19):1913–1921.
[96] Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux G-P, 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 III trial. Lancet Oncol 2017;18:1624–1636.
[97] Ricke J, Bulla K, Walecki J, Schott E, Sangro B, Kolligs F, Amthauer H, et al. Safety and toxicity of the combination of Y90-radioembolization and sorafenib in advanced HCC: an interim analysis of the European multicenter trial SORAMIC. J Hepatol 2013;58:S114.
[98] Chauhan N, Bukovcan J, Boucher E, Cosgrove D, Edeline J, Hamilton B, et al. Intra-Arterial TheraSphere Yttrium-90 Glass Microspheres in the Treatment of Patients With Unresectable Hepatocellular Carcinoma: Protocol for the STOP-HCC Phase III Randomized Controlled Trial. JMIR Res Protoc 2018;7e11234.
[99] Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, et al. Y90 Radioembolization Significantly Prolongs Time to Progression Compared With Chemoembolization in Patients With Hepatocellular Carcinoma. Gastroenterology 2016;151 [1155-1163.e2].
[100] El Fouly A, Ertle J, El Dorry A, Shaker MK, Dechêne A, Abdella H, et al. In intermediate stage hepatocellular carcinoma: radioembolization with yttrium 90 or chemoembolization? Liver Int 2015;35:627–635.
[101] Kaseb AO, Shindoh J, Patt YZ, Roses RE, Zimmitti G, Lozano RD, et al. Modified cisplatin/interferon α-2b/doxorubicin/5-fluorouracil (PIAF) chemotherapy in patients with no hepatitis or cirrhosis is associated with improved response rate, resectability, and survival of initially unresectable hepatocellular carcinoma. Cancer 2013;119:3334–3342.
[102] Gish RG, Porta C, Lazar L, Ruff P, Feld R, Croitoru A, et al. Phase III randomized controlled trial comparing the survival of patients with unresectable hepatocellular carcinoma treated with nolatrexed or doxorubicin. J Clin Oncol 2007;25:3069–3075.
[103] Lai CL, Wu PC, Chan GC, Lok AS, Lin HJ. Doxorubicin versus no antitumor therapy in inoperable hepatocellular carcinoma. A prospective randomized trial. Cancer 1988;62:479–483.
[104] Iavarone M, Cabibbo G, Piscaglia F, Zavaglia C, Grieco A, Villa E, et al. Field-practice study of sorafenib therapy for hepatocellular carcinoma: a prospective multicenter study in Italy. Hepatology 2011;54:2055–2063.
[105] Lencioni R, Kudo M, Ye S-L, Bronowicki J-P, Chen X-P, Dagher L, 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;68:609–617.
[106] Ganten TM, Stauber RE, Schott E, Malfertheiner P, Buder R, Galle PR, et al. Sorafenib in Patients with Hepatocellular Carcinoma-Results of the Observational INSIGHT Study. Clin Cancer Res 2017;23:5720–5728.
[107] Reig M, Rimola J, Torres F, Darnell A, Rodriguez-Lope C, Forner A, et al. Postprogression survival of patients with advanced hepatocellular carcinoma: Rationale for second-line trial design. Hepatology 2013;58:2023–2031.
[108] 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;18:2290–2300.
[109] Reig M, Torres F, Rodriguez-Lope C, Forner A, Llarch N, Rimola J, et al. Early dermatologic adverse events predict better outcome in HCC patients treated with sorafenib. J Hepatol 2014;61:318–324.
[110] Branco F, Alencar R, Volt F, Sartori G, Dode A, Kikuchi L, et al. The Impact of Early Dermatologic Events in the Survival of Patients with Hepatocellular Carcinoma Treated with Sorafenib. Ann Hepatol 2017;16:263–268.
[111] Bruix J, Qin S, Merle P, Granito A, Huang Y-H, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase III trial. Lancet 2017;389:56–66.
[112] Rimassa L, Assenat E, Peck-Radosavljevic M, Pracht M, Zagonel V, Mathurin P, et al. Tivantinib for second-line treatment of MET-high, advanced hepatocellular carcinoma (METIV-HCC): a final analysis of a phase III, randomised, placebo-controlled study. Lancet Oncol 2018;19:682–693.
[113] Iavarone M, Cabibbo G, Biolato M, Della Corte C, Maida M, Barbara M, et al. Predictors of survival of patients with advanced hepatocellular carcinoma who permanently discontinued sorafenib. Hepatology 2015;62:784–791.
[114] Johnson PJ, Qin S, Park JW, Poon RT, Raoul JL, Philip PA, et al. Brivanib Versus Sorafenib As First-Line Therapy in Patients With Unresectable, Advanced Hepatocellular Carcinoma: Results From the Randomized Phase III BRISK-FL Study. J Clin Oncol 2013;31:3517–3524.
[115] Llovet JM, Decaens T, Raoul JL, Boucher E, Kudo M, Chang C, et al. Brivanib in Patients With Advanced Hepatocellular Carcinoma Who Were Intolerant to Sorafenib or for Whom Sorafenib Failed: Results From the Randomized Phase III BRISK-PS Study. J Clin Oncol 2013;31:3509–3516.
[116] Zhu AX, Kudo M, Assenat E, Cattan S, Kang Y-K, Lim HY, et al. Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial. JAMA 2014;312:57–67.
[117] Cheng AL, Kang YK, Lin DY, Park JW, Kudo M, Qin S, et al. Sunitinib Versus Sorafenib in Advanced Hepatocellular Cancer: Results of a Randomized Phase III Trial. J Clin Oncol 2013;31:4067–4075.
[118] Cainap C, Qin S, Huang W-T, Chung IJ, Pan H, Cheng Y, et al. Linifanib Versus Sorafenib in Patients With Advanced Hepatocellular Carcinoma: Results of a Randomized Phase III Trial. J Clin Oncol 2015;33:172–179.
[119] Zhu AX, Rosmorduc O, Evans TRJ, Ross PJ, Santoro A, Carrilho FJ, et al. SEARCH: a phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. J Clin Oncol 2015;33:559–566.
[120] Da Fonseca LG, Reig M, Bruix J. Systemic therapy for hepatocellular carcinoma: trial enrichment does not guarantee success. Oncotarget 2018;9:33741–33742.
[121] Wilhelm SM, Dumas J, Adnane L, Lynch M, Carter CA, Schütz G, et al. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer 2011;129:245–255.
[122] Finn RS, Merle P, Granito A, Huang Y-H, Bodoky G, Pracht M, et al. Outcomes of sequential treatment with sorafenib followed by regorafenib for HCC: Additional analyses from the phase III RESORCE trial. J Hepatol 2018;69:353–358.
[123] Kudo M, Finn RS, Qin S, Han K-H, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase III non-inferiority trial. Lancet 2018;391:1163–1173.
[124] Tugues S, Fernandez-Varo G, Muñoz-Luque J, Ros J, Arroyo V, Rodés J, et al. Antiangiogenic treatment with Sunitinib ameliorates inflammatory infiltrate, fibrosis, and portal pressure in cirrhotic rats. Hepatology 2007;46:1919–1926.

[125] Mejias M, Garcia-Pras E, Tiani C, Miquel R, Bosch J, Fernandez M. Beneficial effects of sorafenib on splanchnic, intrahepatic, and portocollateral circulations in portal hypertensive and cirrhotic rats. Hepatology 2009;49:1245–1256.
[126] Fernandez M, Mejias M, Garcia-Pras E, Mendez R, Garcia-Pagan JC, Bosch J. Reversal of portal hypertension and hyperdynamic splanchnic circulation by combined vascular endothelial growth factor and platelet-derived growth factor blockade in rats. Hepatology 2007;46:1208–1217.
[127] Lencioni R, Montal R, Torres F, Park J-W, Decaens T, Raoul J-L, et al. Objective response by mRECIST as a predictor and potential surrogate endpoint of overall survival in advanced HCC. J Hepatol 2017;66:1166–1172.
[128] Bruix J, Reig M, Sangro B. Assessment of treatment efficacy in hepatocellular carcinoma: Response rate, delay in progression or none of them. J Hepatol 2017;66:1114–1117.
[129] Huang L, De Sanctis Y, Shan M, Bruix J, Llovet J, Cheng A-L, et al. Weak correlation of overall survival and time to progression in advanced hepatocellular carcinoma. J Clin Oncol 2017;35:233.
[130] Abou-Alfa GK, Meyer T, Cheng A-L, El-Khoueiry AB, Rimassa L, Ryoo B-Y, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med 2018;379:54–63.
[131] Abou-Alfa Ghassan K, Meyer T, Cheng A-L, El-Khoueiry AB, Rimassa L, Ryoo B-Y, Cicin I, et al. Cabozantinib (C) versus placebo (P) in patients (pts) with advanced hepatocellular carcinoma (HCC) who have received prior sorafenib: Results from the randomized phase III CELESTIAL trial. J Clin Oncol 2018;36:207.
[132] Kobayashi S, Ueshima K, Moriguchi M, Takayama T, Izumi N, Yoshiji H, et al. JET-HCC: A phase III randomized, double-blind, placebo-controlled study of tivantinib as a second-line therapy in patients with c-Met high hepatocellular carcinoma. Ann Oncol 2017;28.
[133] Zhu AX, Park JO, Ryoo B-Y, Yen C-J, Poon R, Pastorelli D, 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 III trial. Lancet Oncol 2015;16:859–870.
[134] Zhu AX, Kang Y-K, Yen C-J, 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(2):282–296.
[135] Hanahan D, Weinberg A. Hallmarks of Cancer: The Next Generation. Cell 2011;144:646–674.
[136] Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. Int Immunol 2007;19:813–824.
[137] Sangro B, Palmer D, Melero I. Immunotherapy of hepatocellular carcinoma. Hepatic Oncol 2014;1:433–446.
[138] El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, 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;6736:1–11.
[139] Research C for DE and. Approved Drugs - FDA grants accelerated approval to nivolumab for HCC previously treated with sorafenib, n.d.
[140] Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase II trial. Lancet Oncol 2018;19:940–952.
[141] Research C for DE and. Approved Drugs - FDA grants accelerated approval to pembrolizumab for hepatocellular carcinoma, n.d.
[142] Nadeau B, Fecher L, Owens S, Razumilava N. Liver Toxicity with Cancer Checkpoint Inhibitor Therapy. Semin Liver Dis 2018;38:366–378.
[143] Ikeda M, Sung MW, Kudo M, Kobayashi M, David Baron A, Finn RS, et al. A phase 1b trial of lenvatinib (LEN) plus pembrolizumab (PEM) in patients (pts) with unresectable hepatocellular carcinoma (uHCC). J Clin Oncol 2018;36 [abstr 4076].
[144] Stein S, Pishvaian MJ, Lee MS, Lee K-H, Hernandez S, Kwan A, et al. Safety and clinical activity of 1L atezolizumab + bevacizumab in a phase Ib study in hepatocellular carcinoma (HCC). J Clin Oncol 2018;36:4074.
[145] Pishvaian MJ, Lee MS, Ryoo B, Stein S, Lee K, Verret W, et al. Updated safety and clinical activity results from a phase Ib study of atezolizumab + bevacizumab in hepatocellular carcinoma (HCC). Munich, Ger: ESMO2018.
[146] George S, Motzer RJ, Hammers HJ, Redman BG, Kuzel TM, Tykodi SS, et al. Safety and Efficacy of Nivolumab in Patients With Metastatic Renal Cell Carcinoma Treated Beyond Progression: A Subgroup Analysis of a Randomized Clinical Trial. JAMA Oncol 2016;2:1179–1186.
[147] Ferrara R, Mezquita L, Texier M, Lahmar J, Audigier-Valette C, Tessonnier L, et al. Hyperprogressive Disease in Patients With Advanced Non-Small Cell Lung Cancer Treated With PD-1/PD-L1 Inhibitors or With Single-Agent Chemotherapy. JAMA Oncol 2018;4:1543.
[148] Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:1627–1639.
[149] Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015;373:23–34.
[150] Gibney GT, Weiner LM, Atkins MB. Predictive biomarkers for checkpoint inhibitor-based immunotherapy. Lancet Oncol 2016;17:e542–e551.
[151] Sangro B, Gomez-Martin C, de la Mata M, Iñarrairaegui M, Garralda E, Barrera P, et al. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. J Hepatol 2013;59:81–88.
[152] Wainberg ZA, Segal NH, Jaeger D, Lee K-H, Marshall J, Antonia SJ, et al. Safety and clinical activity of durvalumab monotherapy in patients with hepatocellular carcinoma (HCC). J Clin Oncol 2017;35:4071.