Received: 16 May 2018 | First decision: 4 June 2018 | Accepted: 28 June 2018

DOI: 10.1111/apt.14913

WILEY AP&T Alimentary Pharmacology & Therapeutics

Review article: systemic treatment of hepatocellular carcinoma

Matthias Pinter[1,2] | Markus Peck-Radosavljevic[3]

[1]Division of Gastroenterology & Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria

[2]Liver Cancer (HCC) Study Group Vienna, Medical University of Vienna, Vienna, Austria

[3]Department of Internal Medicine and Gastroenterology (IMuG), Hepatology, Endocrinology, Rheumatology & Nephrology, Central Emergency Medicine (ZAE), Klinikum Klagenfurt am Wörthersee, Klagenfurt, Austria

Correspondence: Matthias Pinter, Division of Gastroenterology & Hepatology, Department of Internal Medicine III, Medical University of Vienna, Waehringer Gürtel 18-20, A-1090 Vienna, Austria (matthias.pinter@meduniwien.ac.at) and Markus Peck-Radosavljevic, Department of Internal Medicine and Gastroenterology (IMuG), Hepatology, Endocrinology, Rheumatology & Nephrology, Central Emergency Medicine (ZAE), Klinikum Klagenfurt am Wörthersee, Feschnigstraße 11, 9020 Klagenfurt am Wörthersee, Austria (markus@peck.at)

Summary

Background: The approval of the tyrosine kinase inhibitor sorafenib in 2007 marked a milestone in the treatment of hepatocellular carcinoma, as sorafenib was the first systemic therapy to show a survival benefit in patients with advanced hepatocellular carcinoma. Since then many drugs failed in the first- and second-line setting and it took almost another decade until further tyrosine kinase inhibitors succeeded in phase III trials.

Aim: To summarise the evolving field of systemic therapy of hepatocellular carcinoma.

Methods: We reviewed recently published studies identified from PubMed and data presented at recent meetings. Main search terms included hepatocellular carcinoma, tyrosine kinase inhibitors, immunotherapy, immune checkpoint inhibitors, sorafenib, regorafenib, lenvatinib, cabozantinib, ramucirumab, and nivolumab.

Results: We discuss the evolution of targeted therapies since the approval of sorafenib including failures and recent advances. We also elaborate the unmet need of biomarkers to guide treatment decisions and discuss the emerging field of immunotherapy in hepatocellular carcinoma.

Conclusions: The tyrosine kinase inhibitors sorafenib (first line) and regorafenib (second line) have been approved for hepatocellular carcinoma, and the immune checkpoint inhibitor nivolumab obtained conditional approval for sorafenib-experienced patients in the United States. With lenvatinib in the first line, and cabozantinib and ramucirumab in sorafenib-experienced patients, three more targeted therapies reached their primary endpoint in phase III trials and may soon be added to the treatment armamentarium.

The Handling Editor for this article was Professor Peter Hayes, and this uncommissioned review was accepted for publication after full peer-review.

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer,[1] usually develops in patients with liver cirrhosis,[2,3] and represents the second most common cause of cancer-related death.[4]

Potential curative therapies include resection, liver transplantation, and local ablative therapies, but these are reserved for early stages, characterised by small tumours limited to the liver. Transarterial chemoembolzation (TACE) and systemic therapies are the only available treatment options in the palliative setting,[5] while transarterial radioembilisation is struggling (and currently unable) to find a place in the evidence-based treatment landscape.[6-8] Patients with either symptomatic disease (performance status 1-2), macrovascular tumour invasion, or extrahepatic metastases (advanced stage HCC) are classical candidates for systemic treatment according to current guidelines.[5] Patients with multifocal HCC and compensated liver disease (intermediate stage HCC) should be treated with TACE.[5] However, these patients may become candidates for systemic therapies under certain circumstances (Figure 1): if they fail to respond to TACE (failure of 2 rounds of TACE), develop untreatable progression (major intrahepatic progression, macrovascular invasion, metastasis, symptomatic progression), show deterioration of liver function (ascites, decompensation),[9,10] or show unfavourable disease characteristics at baseline (Hepatoma arterial-embolisation prognostic score C or D; Barcelona-Clinic Liver Cancer B subclass 3 or 4; STATE score <18).[11-13] Liver function in particular should be monitored cautiously as even discrete subclinical worsening of liver function is associated with poorer outcome after repeated TACE.[14,15]

To date, only tyrosine kinase inhibitors have been approved globally and additionally an immune checkpoint inhibitor in the United States only.[16] Conventional chemotherapy is not recommended in HCC due to lack of efficacy,[5] and only recently two phase III studies testing chemotherapy in advanced HCC again failed.[17,18] Whether a subset of patients with HCC may have some benefit from chemotherapy[19] needs to be confirmed in larger studies.

This review focuses on the evolution of targeted therapies since the approval of sorafenib, including failures and recent advances, and discusses the unmet need of biomarker-driven treatment strategies as well as the emerging field of immunotherapy in HCC.

2 | TARGETED THERAPIES

2.1 | Sorafenib

For the longest time no effective drug treatment was available for patients with HCC until the unprecedented success of the multity-rosine kinase inhibitor sorafenib. The approval in 2007 was based on the positive results of the well-known SHARP study, a randomised controlled phase III trial, which showed a significant prolongation of median overall survival (OS) for sorafenib vs placebo (10.7 vs 7.9 months; hazard ratio (HR), 0.69), reflecting an extension of OS by 44%.[20] A second phase III trial conducted in the Asia-Pacific region showed similar results regarding HR, even though patients in both groups had a shorter absolute OS compared to patients in the SHARP trial (Table 1). This was probably because of the enrolment of patients with more advanced disease in terms of extrahepatic spread, number of intrahepatic lesions, alpha-Fetoprotein (AFP), and performance status.[21] Hence, sorafenib showed a survival benefit in two independent phase III trials conducted in different geographic regions, and became the standard of care for advanced HCC.[3,5] Side effects were mostly mild to moderate and manageable, with diarrhoea and dermatological side effects (eg hand-foot-skin reaction, rash, pruritus) being the most frequent and troublesome adverse events.[20,21] The occurrence of dermatological events was later shown to be associated with a better outcome.[22,23]

The efficacy of sorafenib is likely a result of the fine balance between its antitumour effects and the mild and manageable toxicity profile.[24] A potential beneficial effect of sorafenib on the portal hypertensive syndrome, which may contribute to the improved survival in HCC patients, was reported in experimental models[25] and small clinical pilot studies[26,27] but not yet confirmed in large prospective trials.

Notably, both phase III trials included only patients with well-preserved liver function, a common practice in HCC studies to avoid a potential masking of a drug-induced antitumour effect by death from underlying liver disease.[3,28] Data from our real-life cohort[29] and that of others[30] showed that the Child-Pugh score was a strong predictor for OS (median OS for Child-Pugh A/B/C, 11.3/5.5/1.6 months[29]). These data were confirmed by the GIDEON study, a large global prospective noninterventional phase IV observational study.[31] Consequently, patients with Child-Pugh stage C are unlikely to derive a clinical meaningful benefit from any systemic therapy and should just receive best supportive care, if not a candidate for liver transplantation.[5] A phase III trial (BOOST, NCT01405573) investigating if Child-Pugh B patients may benefit from sorafenib treatment was unfortunately terminated due to lack of enrolment. Thus, prospective data on sorafenib in Child-Pugh B patients are still missing, hindering clear recommendations for this heterogeneous subgroup of patients.

Given the success of sorafenib in advanced HCC, sorfenib was later on also evaluated in patients with early and intermediate stage tumours. A phase III randomised controlled trial (STORM) investigated sorafenib in the adjuvant setting after curative resection or local ablation. However, the study failed to reach its primary endpoint recurrence-free survival.[32]

A phase II randomised controlled trial (SPACE) investigated the combination of drug-eluting-beads-TACE plus sorafenib or placebo in patients with intermediate HCC.[33] Sorafenib failed to prolong the primary endpoint time to recurrence (TTP) in a clinically relevant manner (sorafenib vs placebo, 169 vs 166 days), partly also due to shortcomings in trial design. As a result of strict TACE discontinuation criteria, more than one-third of patients in the sorafenib group received only one TACE procedure, but at least 30% of these patients received further TACE cycles outside the study. This may have negatively affected the outcome of this study.[33] Two phase III studies testing this combination also failed to show an improved outcome for sorafenib.[34,35] Results of a Japanese phase II study (TACTICS) evaluating conventional lipiodol TACE plus sorafenib vs TACE

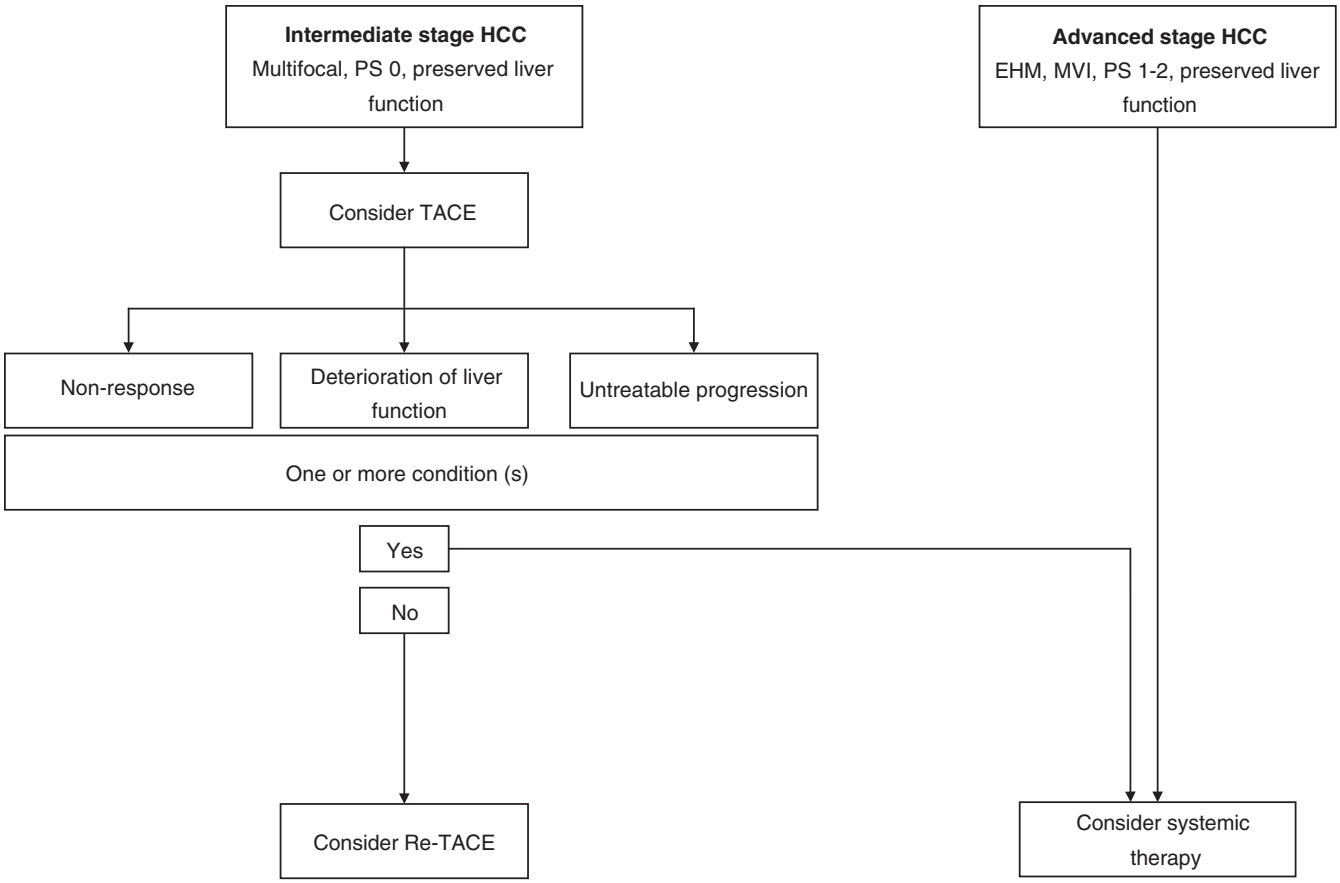

FIGURE 1 Candidates for systemic therapy. HCC, hepatocellular carcinoma; EHM, extrahepatic metastases; MVI, macrovascular invasion; PS, Performance Status; TACE, transarterial chemoembolisation

TABLE 1 Survival data of positive phase III trials in hepatocellular carcinoma

Study	Drug	Setting	Median OS (months)	HR (95% CI)
SHARP[20]	Sorafenib vs placebo	1st-line	10.7 vs 7.9	0.69 (0.55-0.87)
Asia-Pacific[21]	Sorafenib vs placebo	1st-line	6.5 vs 4.2	0.68 (0.50-0.93)
REFLECT[49]	Lenvatinib vs sorafenib[a]	1st-line	13.6 vs 12.3	0.92 (0.79-1.06)
RESORCE[46]	Regorafenib vs placebo	2nd-line	10.6 vs 7.8	0.63 (0.50-0.79)
CELESTIAL[50]	Cabozantinib vs placebo	2nd-/3rd-line	10.2 vs 8.0	0.76 (0.63-0.92)
REACH-2[62]	Ramucirumab vs placebo	2nd-line	8.5 vs 7.3	0.71 (0.53-0.95)

OS, overall survival; HR, hazard ratio; CI, confidence interval.
[a]"Non-inferiority" design.

alone in HCC without macrovascular invasion/extrahepatic metastases were recently presented.[36] The combination significantly prolonged the primary endpoint progression-free survival (PFS) vs TACE alone (25.2 vs 13.5 months; HR 0.59; $P = 0.006$). Possible reasons for the success of this trial are the longer exposure to sorafenib compared to other trials, and the fact that new, previously untreated lesions were not regarded as progressive disease/treatment failure prompting discontinuation of TACE.[36] These positive results may revive the discussion on this almost abandoned strategy in intermediate stage HCC.

Taken together, sorafenib was the first systemic therapy that showed a moderate but significant survival benefit and consequently became the first drug to be approved for HCC. Sorafenib is recommended for patients with advanced stage HCC or those who progressed on TACE. As data on Child-Pugh B patients are still lacking, clear recommendations for its use can only be made for patients with Child-Pugh class A.[5] Large studies failed to show a benefit of sorafenib in the adjuvant setting or in combination with loco-regional therapies.

2.2 | Failed phase III trials

The success of sorafenib has increased the interest to develop drugs in HCC. But instead of seeing more effective drugs being added to

the therapeutic armamentarium, we had to witness several compounds failing in randomised controlled phase III trials, both in the first-line (sunitinib, brivanib, linifanib, erlotinib[37-40]) and second-line (brivanib, everolimus, ramucirumab[41-43]) setting (Figure 2).

Potential reasons for failure have been discussed elsewhere,[24] and include high toxicity (sunitinib[38]), modest efficacy (erlotinib, linifanib, brivanib, everolimus[37,39,40,42]), noninferiority design with a small window of opportunity (linifanib, brivanib[37,39]), and a clinical imbalance between the test and placebo arm (brivanib[41]).

Notably, most drugs proceeded to phase III based on efficacy data obtained from small single-arm phase II studies, often using surrogate endpoints such as radiological response, TTP, or PFS. These surrogate endpoints are only poor predictors of OS in HCC, where even a significant response often does not translate into a survival benefit.[41,43] Additionally, composite endpoints (eg, PFS) are vulnerable, as death from underlying cirrhosis may mask potential drug effects, and are generally discouraged as primary endpoints in HCC trials.[28] It was recently recommended that drugs should be tested in properly powered phase II studies with a control arm or at least with a large enough sample size in order to minimise a potential selection bias and random errors; the use of OS as a primary endpoint should also be considered in these trials.[24] However, with more drugs becoming available in the second- and third-line setting influencing the outcome of HCC patients, OS may not adequately reflect the effect of a tested first-line treatment, making future trial design even more difficult.

Moreover, the pattern of progression during sorafenib therapy influences postprogression survival and could therefore affect the results of second-line trials.[44] Given that the failed second-line phase III trials were designed before the publication of these important findings, none of the studies stratified patients according to the pattern of progression. Thus, it could well be that an enrichment of the worse progression pattern (new extrahepatic lesion/macrovascular invasion) may have occurred in the test arm, masking a potential drug effect.[44,45]

Finally, since HCC can be diagnosed by radiology alone in patients with liver cirrhosis,[5] a tumour biopsy, allowing tissue-based biomarker analysis to potentially rescue a drug at least in a subset of patients, was not mandatory in most phase III trials.[24]

2.3 | Recent advancements

After the approval of sorafenib, it took almost a decade until another drug could succeed in phase III, and again it was a multityrosine kinase inhibitor tested in an unselected "all-comer" cohort. Regorafenib was evaluated in a second-line phase III trial (RESORCE) and demonstrated a significant survival benefit compared to placebo (median OS, 10.6 vs 7.8 months; HR 0.63).[46] Similar to the phase III trials of sorafenib,[20,21] only patients with Child-Pugh stage A were allowed in order to minimise a potential confounding effect of advanced liver cirrhosis on OS. Because of the similar toxicity profile of both drugs, patients intolerant to sorafenib were excluded.[46] Hence, no conclusions can be made about the efficacy of regorafenib in patients intolerant to sorafenib and in those with more advanced liver dysfunction (Child-Pugh B).[46] The most common adverse events were mostly of mild grade and included hand-foot-skin reaction, fatigue, and diarrhoea. However, including only patients who tolerated sorafenib could have reduced the occurrence of severe side effects.[46] As previously shown for sorafenib,[22] development of hand-foot-skin reaction was associated with improved survival with regorafenib in an exploratory retrospective analysis.[47]

Unlike in the negative second-line study of brivanib,[41] stratification was done separately for macrovascular invasion and extrahepatic spread and therefore allowed both prognostic variables to be well balanced between the groups. Even though not a stratification factor, the pattern of progression was equally distributed between both arms,[46] which may have contributed to the positive outcome of this study. Regorafenib was finally approved for the indication "HCC" in 2017 in Europe and the United States.

Based on promising results of a phase II study,[48] the multityrosine kinase inhibitor lenvatinib was tested against sorafenib in a phase III trial with the primary endpoint being noninferiority in OS (noninferiority margin: upper limit of the two-sided 95% confidence interval for HR below 1.08).[49] Only patients with Child-Pugh stage A were included and patients with extensive tumour load (≥50% of the liver), bile duct invasion, or invasion of the main portal vein were excluded. Dosing of lenvatinib was based on body weight (8 mg

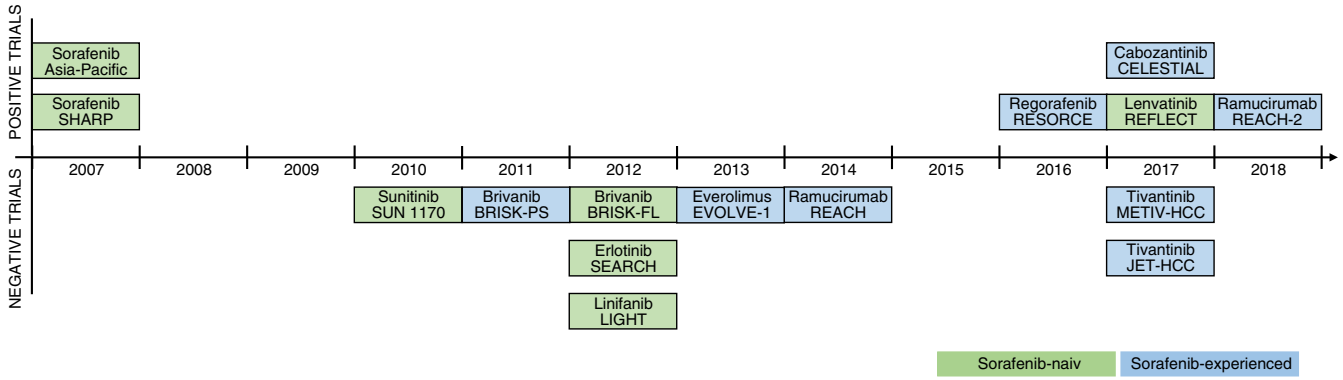

FIGURE 2 Timeline of targeted therapies that succeeded and failed in phase III randomised controlled trials of hepatocellular carcinoma (years refer to date of press announcement)

<60 kg and 12 mg ≥60 kg once daily),[49] as lenvatinib exposure was influenced by body weight in the phase II study.[48]

The study finally reached its primary endpoint with a HR of 0.92 (95% CI, 0.79-1.06) and a median OS of 13.6 months for lenvatinib and 12.3 months for sorafenib.[49] Forest plots for OS revealed that lenvatinib was most effective compared to sorafenib in patients with baseline AFP ≥200 ng/mL (HR, 0.78; 95% CI, 0.63-0.98) and least effective in patients without macrovascular invasion/extrahepatic spread and those from the Western region. The latter is of special note since about two-thirds of the study population came from the Asia-Pacific region and only one-third from Western countries. Secondary endpoints (PFS, TTP, objective response rate) were significantly better with lenvatinib. This observation underlines again that these surrogate endpoints only poorly predict OS in HCC. The rates of treatment-related treatment-emergent adverse events ≥3 (57% vs 49%) and treatment-related serious treatment-emergent adverse events (18% vs 10%) were higher with lenvatinib. Arterial hypertension as the most common adverse event with lenvatinib occurred more often in the lenvatinib arm (42% vs 30%). The frequency of hand-foot-skin reaction—the most common side effect in the sorafenib arm—was higher with sorafenib (52% vs 27%). Notably, as safety was not a predefined study endpoint, both drugs cannot be compared reliably. Health-related quality of life scores for role functioning, pain, diarrhoea, nutrition, and body image worsened earlier with sorafenib.[49] Taken together, based on a manageable safety profile and promising survival data, lenvatinib will likely be approved for HCC in the foreseeable future and become an alternative in the first-line setting of patients with advanced HCC.

Cabozantinib, that targets several tyrosine kinases including MET, vascular endothelial growth factor (VEGF), and AXL, succeeded in a phase III (CELESTIAL) trial in sorafenib-experienced patients with advanced HCC and Child-Pugh class A.[50] Up to two prior systemic therapies were allowed and sorafenib must have been one of them, meaning that cabozantinib was used as second or third-line treatment in this study. Cabozantinib significantly prolonged the primary endpoint median OS compared to placebo (10.2 vs 8.0 months) with a HR of 0.76 (95% CI, 0.63-0.92). The effect on PFS was even more pronounced (5.2 vs 1.9 months), as was the prolongation of median OS in patients who received sorafenib as only prior therapy (11.3 vs 7.2 months). The safety profile was acceptable with hand-foot-skin reaction and arterial hypertension being the most common grade ≥3 adverse events.[50] Unlike in the phase III randomised controlled trial with regorafenib,[46] this study also allowed the inclusion of patients intolerant to sorafenib.[50] Table 1 summarises the survival data of all positive phase III trials of targeted therapies in HCC.

Taken together, lenvatinib was noninferior compared to sorafenib in terms of overall survival in the first-line setting and will be added to the treatment armamentarium shortly. No data are available on the efficacy of lenvatinib in patients with main portal vein invasion or a tumour load ≥50% of the liver as these patients were excluded from the study.

Regorafenib was the first drug to show a prolongation of survival in the second-line setting and has been approved for patients who have been previously treated with sorafenib. The magnitude of benefit was similar to that of sorafenib. Patients who progress on sorafenib are the best candidates for regorafenib while those intolerant to sorafenib may also not tolerate regorafenib very well. As the CELESTIAL trial allowed inclusion of patients who discontinued sorafenib due to adverse events, cabozantinib may become the preferred second-line option in patients intolerant to sorafenib, once approved by regulatory agencies.

Notably, as none of these agents was tested in Child-Pugh B patients, only patients with well-preserved liver function may be treated until data for Child-Pugh B patients become available and support the use of these drugs in this indication. The limited efficacy of the different agents (Table 1) may partly be owed to the lack of a biomarker for treatment selection, as discussed in the next paragraph.

2.4 | Biomarkers for patient selection

Unlike "all-comer" trials, study inclusion based on oncogenic drivers or biomarkers for activated signalling pathways ensures that the molecular target is present in the studied population,[24] which eventually may increase the likelihood of a positive outcome. Biomarker-driven treatment concepts have already been established for several malignancies (eg breast cancer, colorectal cancer, lung cancer) and have helped to improve the outcome of patients receiving systemic therapy.[51-54]

Potential biomarkers in HCC include well-established prognostic markers like AFP, markers of key signalling pathways, or epigenetic markers among others. The RAS, mammalian target of rapamycin (mTOR), MET, and fibroblast growth factor (FGF)-19 signalling represent some of the few potential drivers of HCC progression, for whom selective inhibitors are already available for clinical use.[24]

The mTOR inhibitor everolimus was tested in a phase III trial in the second-line setting against placebo.[42] This pathway is activated in around half of all HCCs and associated with a worse outcome.[55,56] Given the high frequency of aberrant mTOR signalling in HCC, one could expect at least some improvement in OS if everolimus was active, even though the study was performed in "all-comers".[42] Despite this strong theoretical rationale for the use of everolimus in HCC, final results did not even show a trend in survival (everolimus vs placebo, 7.6 vs 7.3 months).[42]

A proof-of-principle trial evaluated the MEK inhibitor refametinib alone or in combination with sorafenib in patients with RAS-mutated HCC.[57] The study was based on promising results of a phase II study showing better response rates for the combination of refametinib plus sorafenib in HCC patients with mutated RAS compared to wild-type RAS.[58] Of 498 patients in the monotherapy and 820 patients in the combination arm included, the prevalence of RAS mutation was 6.5% and 3.3%, respectively, and 16 patients in each group finally received treatment. Given the insufficient efficacy with no confirmed response for refametinib alone and only one confirmed partial response for the combination arm this approach was not further pursued in HCC.[57]

The MET inhibitor tivantinib was investigated in a second-line randomised controlled phase II study where it only improved survival

in patients with high tumoral MET expression but not in cases with MET-low HCC.[59] These results prompted the conduction of a phase III trial (METIV-HCC) testing tivantinib vs placebo only in patients with high MET expression.[60] However, the high expectations for tivantinib to become the first biomarker-driven treatment approach in HCC could not be fulfilled, as recently presented results did not show an improvement of the primary endpoint OS (median OS for tivantinib vs placebo, 8.4 vs 9.1 months).[60] Tivantinib also failed in a similar phase III (JET-HCC) study conducted in Japan only.[61]

While brivanib, a multityrosine kinase inhibitor with activity against FGF receptors, failed in two phase III trials in unselected "all-comers",[39,41] pilot studies using biomarkers for activated FGF signalling are under way. The FGF receptor blocker erdafitinib is currently being evaluated in an early phase study of advanced HCC patients with FGF19 amplification (NCT02421185). Another phase I/II study is testing the FGF receptor-4 inhibitor FGF401 alone or in combination with an antiprogrammed cell death 1 (PD-1) antibody in sorafenib-experienced HCC patients with positive FGF receptor-4 and klotho beta (= co-factor for FGF19 activation) expression (NCT02325739).

Ramucirumab, a monoclonal antibody against VEGF receptor-2, was investigated in a second-line phase III randomised controlled trial (REACH). While ramucirumab failed to improve the primary endpoint OS in the whole cohort, patients with elevated serum AFP did much better on ramucirumab than on placebo (median OS, 7.8 vs 4.2 months).[43] Based on these data, another phase III randomised controlled trial (REACH-2) has been conducted testing ramucirumab vs placebo in sorafenib-experienced patients with AFP of 400 ng/mL or higher. As recently reported, ramucirumab moderately but significantly prolonged survival (median OS, 8.5 vs 7.3 months) with a HR of 0.71 (95% CI, 0.53-0.95), making ramucirumab the first drug that showed a survival benefit in a biomarker-selected population.[62] Hence, ramucirumab—the first biomarker-guided treatment in HCC—will likely become a preferred option in patients with AFP ≥400 ng/mL, and especially in those with poor tolerance to tyrosine kinase inhibitors.

The difficult mission of setting up successful biomarker-enriched trials in HCC is at least in parts a result of the complex tumour biology. HCC is heterogeneous[63] and the molecular profile obtained by a single biopsy does not guarantee that it is actually representative for the whole tumour load, especially in multifocal HCC.[22] Additionally, the expression of a target or the activation of a certain signalling cascade does not categorically imply tumour dependency.[64] These aspects further complicate the identification of tissue biomarkers to guide treatment decisions in HCC. Nevertheless, all efforts towards a personalised HCC therapy should be made and acquiring tissue samples for molecular profiling seems to be indispensable to achieve this goal.[65]

3 | IMMUNOTHERAPY

3.1 | Rationale

Immunotherapy has become a mainstay in the treatment of certain malignancies including melanoma and lung cancer.[66] There are also several reasons why immunotherapy may be feasible and effective in HCC.[67,68] HCC is an immunogenic tumour as spontaneous regressions, often immune mediated,[68,69] and naturally occurring tumour-associated antigen-specific CD8+ T-cell responses, correlating with survival,[70] have been reported. Several mechanisms in the tumour microenvironment create an immunosuppressive milieu (eg cytokines with suppressor function, immune checkpoints, defective antigen presentation, immunosuppressive cell types) which promotes tumour immune evasion,[67,68,71,72] an emerging hallmark of cancer.[73] The tolerogenic liver environment, essential to avoid overreaction to antigens delivered from the intestine,[74] may further facilitate tumour immune escape.[67,68,71] Chronic inflammation, present in most HCC cases due to an underlying liver disease/cirrhosis,[3] also promotes T-cell exhaustion (hyporesponsive cells with impaired cytotoxicity) and immunosuppression.[71] Finally, immunotherapeutic drugs are not metabolised by the liver making their pharmacological profile more predictable in patients with liver cirrhosis,[67] a condition often found in patients with HCC.[3]

Several different approaches of immunotherapy exist, including vaccines, cytokines, oncolytic viruses, adoptive cell therapy, gene therapy, and immune checkpoint inhibitors.[75] The latter ones will be discussed herein, as this strategy is already in advanced clinical testing in HCC and clinical data from early trials have been promising.

3.2 | Immune checkpoint blockers

Immune checkpoint receptors (eg PD-1, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)) and their ligands (eg programmed cell death 1 ligand 1 or 2) are membrane-bound coinhibitory molecules that are expressed on several cell types of the innate and acquired immune system, including T cells, natural killer cells, and dendritic cells. Physiologically, binding of a ligand to its receptor on the surface of T cells inhibits T-cell overactivation during an immune response in order to minimise collateral tissue damage.[72,76,77]

One important mechanism how tumours manage to escape host immunity is the expression of immune checkpoint molecules on the surface of cancer cells and cells of the tumour microenvironment (eg tumour-associated macrophages, regulatory T cells, myeloid-derived suppressor cells).[67] Immune checkpoint blockers are monoclonal antibodies that interfere with the ligand-receptor interaction and thereby promote activation of immune effector cells in order to fight cancer cells.[72]

Several checkpoint inhibitors have already been tested in HCC (Table 2). Tremelimumab, an antibody against CTLA-4, was tested in a small pilot trial of 21 sorafenib-naive or -experienced patients (24%) with HCC and chronic hepatitis C virus infection.[78] Of 17 patients evaluable, three had partial response (PR) and the disease control rate (DCR) was 76%. While median TTP was 6.48 months, the median OS of 8.3 months was less promising, but may be partially explained by a high number of Child-Pugh B patients (43%) included. The safety profile was mild with rash, fatigue, elevated transaminases, and diarrhoea being the most frequent side effects; only a few treatment-related AEs grade 3 or higher were reported.[78]

TABLE 2 Results of selected studies testing immune checkpoint inhibitors in hepatocellular carcinoma

Author, year	Treatment (no. of patients)	Prior sorafenib treatment (%)	ORR/DCR (%)	TTP/PFS (months)	OS (months)
Sangro 2013[78]	Tremelimumab (21)	23.8	17.6/76.4	6.48/NR	8.2
Duffy 2017[93]	Tremelimumab + subtotal ablation (32)	65.6	26.3/NR	7.4/NR	12.3
Crocenzi & Sangro 2017[81,82]	Nivolumab (80)	0	22.5/62.5	NR/NR	28.6
Crocenzi & Sangro 2017[81,82]	Nivolumab (182)	100	18.7/62.6	NR/NR	15.6
Wainberg 2017[79]	Durvalumab (40)	92.5	10/32.5	NR/2.7	13.2
Kelley 2017[85]	Durvalumab + Tremelimumab (40)	75.0	25/57.5	NR/NR	NR
Zhu 2018[83]	Pembrolizumab (104)	100	17.3/61.5	NR/4.9	12.9
Ikeda 2018[91]	Pembrolizumab + lenvatinib	13.3	42.3/100	NR/9.7	NR
Stein 2018[92]	Atezolizumab + bevacizumab (43)	0	65/96%	NR/NR	NR

DCR, disease control rate; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

Preliminary results of a phase I/II trial investigating durvalumab, a mAb against programmed cell death 1 ligand 1 (PD-L1), in 40 patients (92.5% received prior sorafenib) with advanced HCC were recently reported.[79] Four patients had PR (all confirmed), which occurred early and were durable; the DCR at ≥24 weeks was 32.5%. Median PFS and OS were 2.7 months and 13.2 months, respectively. Most common AEs were fatigue, pruritus, and elevated aminotransferases. Eight patients developed treatment-related AEs grade 3 or 4.[79] Based on these data, a decision to develop durvalumab in combination with the CTLA-4 inhibitor tremelimumab as first-line treatment in advanced stage HCC was taken (see below).

The Checkmate 040 study is a phase I/II (dose escalation/dose expansion) trial that investigated nivolumab, a mAb against PD-1, in sorafenib-naive (n = 80) and sorafenib-experienced (n = 182) patients with intermediate-advanced HCC and Child-Pugh stage A. The primary endpoints were safety and investigator-assessed overall response rate (ORR) according to RECISTv1.1.[80] Nivolumab was well tolerated with 29% (sorafenib-naive) and 18% (sorafenib-experienced) of patients experiencing grade 3/4 AEs. Most common side effects were fatigue, pruritus, rash, and diarrhoea. ORR was 22.5% in sorafenib-naive and 18.7% in sorafenib-experienced patients; most notably and different from previous trials with tyrosine kinase inhibitors, seven (2.7%) subjects had complete response (CR). Responses were meaningful and independent of PD-L1 expression and baseline serum AFP levels. Median duration of response was 17.0 months in the dose escalation phase and 9.9 months in the dose expansion cohort. The DCR was around 63%.[80-82] These promising antitumour responses translated into encouraging survival results with a median OS of 28.6 months in sorafenib-naive and about 15 months in sorafenib-experienced patients.[81] Based on these promising data, the United States Food and Drug Administration granted accelerated conditional approval to nivolumab for HCC patients pretreated with sorafenib; conditional indicates the final approval will depend on the results of an ongoing phase III trial of nivolumab vs sorafenib in the first-line in advanced HCC (NCT02576509).

The KEYNOTE-224 is a single-arm study testing pembrolizumab, another PD-1 antibody, in patients with intermediate-advanced HCC and Child-Pugh stage A who were previously treated with sorafenib.[83] Of 104 patients reported to date, 1 patient had CR and 17 subjects had PR (ORR, 17.3%). Median PFS and OS were 4.9 months and 12.9 months respectively. Most common side effects included pruritus, fatigue, diarrhoea, and rash. Twenty-six percent of patients developed AEs ≥3.[83]

Taken together, results from uncontrolled phase I/II studies testing checkpoint inhibitors in HCC are encouraging but need to be confirmed in large randomised controlled trials. Table 3 provides a list of phase III studies evaluating checkpoint inhibitors in HCC.

3.3 | Combination strategies with immune checkpoint inhibitors

Several strategies combining immune checkpoint blockers with other treatment modalities are under investigation for different stages of HCC, and the combination of different checkpoint blockers in advanced stage disease is one of them.

The combined use of nivolumab and ipilimumab (anti-CTLA-4) improves not only the efficacy in melanoma patients compared to ipilimumab alone but also increases toxicity.[84] The combination of these compounds is currently under investigation in HCC (NCT01658878).

Durvalumab combined with tremelimumab is being tested in a large four-arm phase III study as first-line treatment in patients with unresectable HCC (NCT03298451) (Table 3). Preliminary results of a phase I/II study combining durvalumab and tremelimumab in advanced HCC were recently reported. Of 40 patients (75% received prior sorafenib) evaluable, 10 had PR (7 with confirmed PR); the DCR at ≥16 weeks was 57.5%. Most common side effects were manageable and included pruritus, diarrhoea, elevated transaminases, and rash. Ten patients (25%) experienced treatment-related AEs ≥3 or serious AEs.[85]

All tyrosine kinase inhibitors with proven efficacy in HCC[20,46,49,50] target VEGF signalling among other pathways. VEGF can exert immunosuppressive effects on the one hand but anti-VEGF therapy can induce tumour hypoxia on the other hand.[86] Hypoxia supports immunosuppression, *inter alia* by an upregulation of immune checkpoint molecules, and promotes tumour growth and

TABLE 3 Ongoing phase III trials testing immune checkpoint inhibitors in hepatocellular carcinoma

Drug	Target of IT	Setting	ClinicalTrials Identifier	Status	Primary completion
Nivolumab vs placebo	Anti-PD-1	Curative, adjuvant	NCT03383458	Recruiting	Q1 2022
Nivolumab vs sorafenib	Anti-PD-1	Palliative, 1st-line	NCT02576509	Recruiting	Q3 2017
Durvalumab ± tremelimumab vs sorafenib	Anti-PD-L1 + Anti-CTLA-4	Palliative, 1st-line	NCT03298451	Recruiting	Q1 2020
Atezolizumab + bevacizumab vs sorafenib	Anti-PD-L1	Palliative, 1st-line	NCT03434379	Recruiting	Q2 2021
Pembrolizumab vs placebo	Anti-PD-1	Palliative, 2nd-line	NCT02702401	Active, not recruiting	Q1 2019
Pembrolizumab vs placebo	Anti-PD-1	Palliative, 2nd-line	NCT03062358	Recruiting	Q4 2019

IT, immunotherapy; CTLA-4, cytotoxic T lymphocyte-associated protein 4; PD-1, programmed cell death 1; PD-L1, programmed cell death 1 ligand 1.

dissemination.[87,88] Indeed, sorafenib induced tumour hypoxia and up-regulated PD-L1 expression in an experimental model of HCC. Triple combination of sorafenib, AMD3100 (C-X-C chemokine receptor type 4 inhibitor), and anti-PD-1 increased infiltration of cytotoxic T lymphocytes and delayed tumour growth and metastasis.[89,90] Thus, combining targeted therapies with checkpoint blockers may represent a reasonable strategy and is currently tested in several clinical trials (eg PDR001 and sorafenib (NCT02988440), pembrolizumab and lenvatinib (NCT03006926), pembrolizumab and regorafenib (NCT03347292)). Recently presented preliminary data of a phase Ib study testing pembrolizumab plus lenvatinib in unresectable HCC showed a good safety profile, an encouraging ORR of 42.3%, and a median PFS of 9.69 months (Table 2).[91] Similarly, the combination of atezolizumab (anti-PD-L1) and bevacizumab was well tolerated and showed promising preliminary efficacy results (ORR, 65%) as a first-line treatment in advanced HCC (Table 2).[92]

Combination of checkpoint blockers with treatment modalities that increase the release of neoantigens (eg radiotherapy, loco-regional treatment) may further increase the efficacy of immunotherapy.[77] A pilot study investigated the combination of subtotal ablation (local ablation or TACE) and tremelimumab in 32 patients (21 received prior sorafenib) with intermediate-advanced stage HCC, based on the hypothesis that tremelimumab may enhance a peripheral immune response induced by the ablative procedure.[93] Of 19 evaluable patients who had target lesions that were not ablated, five achieved a confirmed PR lasting between 7 and 19 months. Median TTP and OS were 7.4 months and 12.3 months, respectively. Notably, tumour biopsies at week 6 demonstrated increased infiltration of intratumoral CD8+ T cells in responders.[93] To what extent the ablative procedure contributed to the observed clinical effects needs further investigation. The combination of TACE (NCT03143270) or radioembolisation (NCT03033446, NCT02837029) with checkpoint inhibitors is currently studied in pilot studies.

Efficacy of immunotherapy is impaired by a major barrier—the immunosuppressive microenvironment.[94] Renin-angiotensin system inhibitors—partly due to their antifibrotic/antidesmoplastic effects—may have the potential to reprogramme the immunosuppressive tumour microenvironment towards a more immunostimulatory milieu.[88,95] This could enhance the efficacy of immunotherapy. Indeed, experimental models demonstrated that antifibrotic drugs improved the efficacy of anti-PD-1-targeted immunotherapy in HCC[90] and other tumours.[96] This strategy needs prospective evaluation in clinical trials. The transforming growth factor (TGF)-β inhibitor galunisertib, that also has antifibrotic potency,[97] is currently being tested in combination with nivolumab in HCC (NCT02423343). Notably, TGF-β also promotes immunosuppression by inhibiting T-cell responses,[98] which makes this combination particularly attractive.

4 | CONCLUSIONS AND FUTURE PERSPECTIVES

As of today, two tyrosine kinase inhibitors have been approved for the treatment of HCC, namely sorafenib in the first-line and regorafenib in the second-line setting. Additionally, the immune checkpoint inhibitor nivolumab was recently conditionally approved for sorafenib-experienced HCC patients in the Unites States. With lenvatinib in the first-line and cabozantinib and ramucirumab in sorafenib-experienced patients, two more tyrosine kinase inhibitors and one monoclonal VEGF receptor-2 antibody have reached their primary endpoint in phase III randomised controlled trials and may soon be added to the armamentarium of systemic therapies for HCC. Which drug to choose first in each setting will depend on biomarkers like AFP for ramucirumab as the first biomarker-driven approach in HCC, but otherwise will be left to clinicians, further studies, and most importantly real-world data on their true tolerability.

Upcoming results from phase III trials will show if immunotherapy will become a mainstay in the treatment of HCC. Studies investigating immunotherapy as (neo)adjuvant treatment in the curative setting (eg before or after resection or ablation) and approaches combining immunotherapy with other treatment modalities (eg tyrosine kinase inhibitors, loco-regional therapies) may reveal further potential of immunotherapy in HCC. Whether immunotherapy may be an option in patients with HCC recurrence after liver transplantation is also subject to further studies. Notably, a patient with pulmonary recurrence after living donor liver transplantation for HCC, who progressed on sorafenib showed complete radiological remission to pembrolizumab despite ongoing immunosuppression and without signs of graft rejection.[99] However, nivolumab led to fatal

acute liver organ rejection in two patients with recurrent, metastatic fibrolamellar HCC.[100]

Some biomarkers (eg AFP, VEGF, hepatocyte growth factor) may have prognostic implications,[101] but only serum AFP was so far successful as biomarker to guide treatment decisions in HCC.[62]

Biomarkers to monitor treatment efficacy are lacking. Decreases in serum AFP or VEGF under sorafenib treatment were associated with better response and survival in small cohorts,[102-105] but large prospective studies for validation are lacking.

MicroRNAs and exosomes—which often contain microRNAs themselves—have been investigated in HCC in recent years, but mainly as diagnostic biomarkers.[106,107] Some microRNAs may enhance and others decrease sorafenib sensitivity of HCC cells,[108] and the expression of certain microRNAs in tissue[109,110] and serum[111,112] samples correlated with response to sorafenib therapy and survival. Again, these potential biomarkers have not been adopted into routine clinical practice yet, as data were often obtained from small retrospective studies and thus need further prospective validation.

A renaissance of the tumour biopsy may be inevitable to achieve the unmet need of individualised therapy,[65] and acquisition of tumour tissue and serum samples for biomarker analysis should become a routine in clinical HCC trials.

Liquid biopsy could become an alternative to tissue biomarkers as it may provide an even more comprehensive profile of the cancer than that derived from small tumour specimens.[113] However, unlike in other solid tumours such as lung cancer,[114] liquid biopsy is not yet ready for clinical use in HCC, since large-scale studies using standardised techniques and uniform methodology are lacking.[115] It also remains unclear if liquid biopsy can adequately reflect the immune tumour microenvironment.

Biomarkers to predict response to checkpoint blockers are also lacking in HCC. Neither tumoral PD-L1 expression nor baseline AFP predicted response to nivolumab in HCC.[80,81] The intratumoral infiltration of CD8+ T cells during tremelimumab treatment was associated with better outcome in a pilot study; however, only a few patients were evaluable and serial tumour biopsy is required,[93] thus, limiting its use in clinical routine. Other approaches to predict response to immunotherapy including gut microbiota[116,117] or monocytes in the peripheral blood[118] need further prospective evaluation.

ACKNOWLEDGEMENTS

Declaration of personal interests: M.P. is advisory board member of Bayer, BMS, Ipsen, and Eisai, and received travel support from Bayer, and speaking fees from Bayer and BMS. He is also an investigator for Bayer, BMS, and Lilly. M.P.R. received grant support and honoraria from Bayer HealthCare and BMS, and served as a consultant for Bayer HealthCare, BMS, Lilly, ONXEO, Eisai, and Ipsen.

Declaration of funding interests: None.

AUTHORSHIP

Guarantor of the article: Matthias Pinter.

Author contributions: Matthias Pinter: design, literature research, writing of paper; Markus Peck-Radosavljevic: design, intellectual input, writing of paper.

All authors have approved the final version of the paper.

ORCID

Matthias Pinter http://orcid.org/0000-0002-7260-532X

REFERENCES

1. Pinter M, Hucke F, Zielonke N, et al. Epidemiological trends of hepatocellular carcinoma in Austria. *Dig Dis*. 2014;32:664-669.
2. Hucke F, Sieghart W, Schoniger-Hekele M, et al. Clinical characteristics of patients with hepatocellular carcinoma in Austria - is there a need for a structured screening program? *Wien Klin Wochenschr*. 2011;123:542-551.
3. Pinter M, Trauner M, Peck-Radosavljevic M, et al. Cancer and liver cirrhosis: implications on prognosis and management. *ESMO Open*. 2016;1:e000042.
4. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65:87-108.
5. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. *J Hepatol* 2018;69:182-236.
6. Vilgrain V, Bouattour M, Sibert A, et al. SARAH: a randomised controlled trial comparing efficacy and safety of selective internal radiation therapy (with yttrium-90 microspheres) and sorafenib in patients with locally advanced hepatocellular carcinoma. *J Hepatol*. 2017;66 (abstr GS-012).
7. 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(19):1913-1921.
8. Ricke J, Sangro B, Amthauer H, et al. The impact of combining Selective Internal Radiation Therapy (SIRT) with Sorafenib on overall survival in patients with advanced hepatocellular carcinoma: the Soramic trial palliative cohort. *J Hepatol*. 2018;68 (abstr LBO-005).
9. Bruix J, Reig M, Sherman M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. *Gastroenterology*. 2016;150:835-853.
10. Forner A, Gilabert M, Bruix J, et al. Treatment of intermediate-stage hepatocellular carcinoma. *Nat Rev Clin Oncol*. 2014;11:525-535.
11. Bolondi L, Burroughs A, Dufour JF, et al. Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions. *Semin Liver Dis*. 2012;32:348-359.
12. Hucke F, Pinter M, Graziadei I, et al. How to STATE suitability and START transarterial chemoembolization in patients with intermediate stage hepatocellular carcinoma. *J Hepatol*. 2014;61:1287-1296.
13. Kadalayil L, Benini R, Pallan L, et al. A simple prognostic scoring system for patients receiving transarterial embolisation for hepatocellular cancer. *Ann Oncol*. 2013;24:2565-2570.
14. Hucke F, Sieghart W, Pinter M, et al. The ART-strategy: sequential assessment of the ART score predicts outcome of patients with hepatocellular carcinoma re-treated with TACE. *J Hepatol*. 2014;60:118-126.
15. Sieghart W, Hucke F, Pinter M, et al. The ART of decision making: retreatment with transarterial chemoembolization in patients with hepatocellular carcinoma. *Hepatology*. 2013;57:2261-2273.
16. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet* 2018;391(10127):1301-1314.

17. Abou-Alfa GK, Niedzwieski D, Knox J, et al. Phase III randomized study of sorafenib plus doxorubicin versus sorafenib in patients with advanced hepatocellular carcinoma (HCC): CALGB 80802 (Alliance). *J Clin Oncol*. 2016;34 (suppl; abstr 192).
18. Kudo M, Moriguchi M, Numata K, et al. S-1 versus placebo in patients with sorafenib-refractory advanced hepatocellular carcinoma (S-CUBE): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Gastroenterol Hepatol*. 2017;2:407-417.
19. Kohler BC, Waldburger N, Schlamp K, et al. Liver cancers with stem/progenitor-cell features - a rare chemotherapy-sensitive malignancy. *Oncotarget*. 2017;8:59991-59998.
20. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359:378-390.
21. 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.
22. Reig M, Torres F, Rodriguez-Lope C, et al. Early dermatologic adverse events predict better outcome in HCC patients treated with sorafenib. *J Hepatol*. 2014;61:318-324.
23. Howell J, Pinato DJ, Ramaswami R, et al. On-target sorafenib toxicity predicts improved survival in hepatocellular carcinoma: a multicentre, prospective study. *Aliment Pharmacol Ther*. 2017;45:1146-1155.
24. Llovet JM, Hernandez-Gea V. Hepatocellular carcinoma: reasons for phase III failure and novel perspectives on trial design. *Clin Cancer Res*. 2014;20:2072-2079.
25. Reiberger T, Angermayr B, Schwabl P, et al. Sorafenib attenuates the portal hypertensive syndrome in partial portal vein ligated rats. *J Hepatol*. 2009;51:865-873.
26. Coriat R, Gouya H, Mir O, et al. Reversible decrease of portal venous flow in cirrhotic patients: a positive side effect of sorafenib. *PLoS ONE*. 2011;6:e16978.
27. Pinter M, Sieghart W, Reiberger T, et al. The effects of sorafenib on the portal hypertensive syndrome in patients with liver cirrhosis and hepatocellular carcinoma–a pilot study. *Aliment Pharmacol Ther*. 2012;35:83-91.
28. Llovet JM, Di Bisceglie AM, Bruix J, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. *J Natl Cancer Inst*. 2008;100:698-711.
29. Pinter M, Sieghart W, Hucke F, et al. Prognostic factors in patients with advanced hepatocellular carcinoma treated with sorafenib. *Aliment Pharmacol Ther*. 2011;34:949-959.
30. Hollebecque A, Cattan S, Romano O, et al. Safety and efficacy of sorafenib in hepatocellular carcinoma: the impact of the Child-Pugh score. *Aliment Pharmacol Ther*. 2011;34:1193-1201.
31. Marrero JA, Kudo M, Venook AP, et al. Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: The GIDEON study. *J Hepatol*. 2016;65:1140-1147.
32. 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;16:1344-1354.
33. 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;64:1090-1098.
34. Kudo M, Imanaka K, Chida N, et al. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. *Eur J Cancer*. 2011;47:2117-2127.
35. 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;2:565-575.
36. Kudo M, Ueshima K, Ikeda M, et al. Randomized, open label, multicenter, phase II trial comparing transarterial chemoembolization (TACE) plus sorafenib with TACE alone in patients with hepatocellular carcinoma (HCC): TACTICS trial. *J Clin Oncol*. 2018;36 (suppl 4S; abstr 206).
37. Cainap C, Qin S, Huang WT, 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.
38. Cheng AL, Kang YK, Lin DY, et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. *J Clin Oncol*. 2013;31:4067-4075.
39. Johnson PJ, Qin S, Park JW, 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.
40. Zhu AX, Rosmorduc O, Evans TR, 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.
41. Llovet JM, Decaens T, Raoul JL, 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.
42. Zhu AX, Kudo M, Assenat E, 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.
43. 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;16:859-870.
44. Reig M, Rimola J, Torres F, et al. Postprogression survival of patients with advanced hepatocellular carcinoma: rationale for second-line trial design. *Hepatology*. 2013;58:2023-2031.
45. Reig M, Bruix J. Pattern of tumor progression in liver cancer: The missing partner in trial design. *Hepatology*. 2015;62:674-676.
46. 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.
47. Bruix J, Merle P, Granito A, et al. Hand-foot skin reaction (HFSR) and overall survival (OS) in the phase 3 RESORCE trial of regorafenib for treatment of hepatocellular carcinoma (HCC) progressing on sorafenib. *J Clin Oncol*. 2018;36 (suppl 4S; abstr 412).
48. Ikeda K, Kudo M, Kawazoe S, et al. Phase 2 study of lenvatinib in patients with advanced hepatocellular carcinoma. *J Gastroenterol*. 2017;52:512-519.
49. 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;391:1163-1173.
50. Abou-Alfa GK, Meyer T, Cheng AL, 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 (suppl 4S; abstr 207).
51. Cataldo VD, Gibbons DL, Perez-Soler R, et al. Treatment of non-small-cell lung cancer with erlotinib or gefitinib. *N Engl J Med*. 2011;364:947-955.
52. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*. 2005;353:1659-1672.
53. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*. 2014;371:2167-2177.

54. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med*. 2009;360:1408-1417.
55. Sahin F, Kannangai R, Adegbola O, et al. mTOR and P70 S6 kinase expression in primary liver neoplasms. *Clin Cancer Res*. 2004;10:8421-8425.
56. Villanueva A, Chiang DY, Newell P, et al. Pivotal role of mTOR signaling in hepatocellular carcinoma. *Gastroenterology*. 2008;135:1972-1983, 1983, e1971-1911.
57. Llovet JM, Merle P, Weiss KH, et al. Phase II studies with refametinib or refametinib plus sorafenib in patients with mutant RAS hepatocellular carcinoma (HCC). *Hepatology*. 2016;64 (S1; abstr 1237).
58. Lim HY, Heo J, Choi HJ, et al. A phase II study of the efficacy and safety of the combination therapy of the MEK inhibitor refametinib (BAY 86-9766) plus sorafenib for Asian patients with unresectable hepatocellular carcinoma. *Clin Cancer Res*. 2014;20:5976-5985.
59. Santoro A, Rimassa L, Borbath I, et al. Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled phase 2 study. *Lancet Oncol*. 2013;14:55-63.
60. Rimassa L, Assenat E, Peck-Radosavljevic M, et al. Second-line tivantinib (ARQ 197) vs placebo in patients (Pts) with MET-high hepatocellular carcinoma (HCC): results of the METIV-HCC phase III trial. *J Clin Oncol*. 2017;35 (suppl; abstr 4000).
61. Kobayashi S, Ueshima K, Moriguchi M, et al. JET-HCC: a phase 3 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 (suppl_5; abstr 6190).
62. Zhu AX, Kang YK, Yen CJ, et al. REACH-2: a randomized, double-blind, placebo-controlled phase 3 study of ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated baseline alpha-fetoprotein (AFP) following first-line sorafenib. *J Clin Oncol*. 2018;36 (suppl; abstr 4003).
63. Xue R, Li R, Guo H, et al. Variable intra-tumor genomic heterogeneity of multiple lesions in patients with hepatocellular carcinoma. *Gastroenterology*. 2016;150:998-1008.
64. Zhang B, Finn RS. Personalized clinical trials in hepatocellular carcinoma based on biomarker selection. *Liver Cancer*. 2016;5:221-232.
65. Schirmacher P, Bedossa P, Roskams T, et al. Fighting the bushfire in HCC trials. *J Hepatol*. 2011;55:276-277.
66. Smyth MJ, Ngiow SF, Ribas A, et al. Combination cancer immunotherapies tailored to the tumour microenvironment. *Nat Rev Clin Oncol*. 2016;13:143-158.
67. Hato T, Goyal L, Greten TF, et al. Immune checkpoint blockade in hepatocellular carcinoma: current progress and future directions. *Hepatology*. 2014;60:1776-1782.
68. Greten TF, Wang XW, Korangy F. Current concepts of immune based treatments for patients with HCC: from basic science to novel treatment approaches. *Gut*. 2015;64:842-848.
69. Huz JI, Melis M, Sarpel U. Spontaneous regression of hepatocellular carcinoma is most often associated with tumour hypoxia or a systemic inflammatory response. *HPB (Oxford)*. 2012;14:500-505.
70. Flecken T, Schmidt N, Hild S, et al. Immunodominance and functional alterations of tumor-associated antigen-specific CD8 + T-cell responses in hepatocellular carcinoma. *Hepatology*. 2014;59:1415-1426.
71. Harding JJ, El Dika I, Abou-Alfa GK. Immunotherapy in hepatocellular carcinoma: primed to make a difference? *Cancer*. 2016;122:367-377.
72. Inarrairaegui M, Melero I, Sangro B. Immunotherapy of hepatocellular carcinoma: facts and hopes. *Clin Cancer Res* 2018;24(7):1518-1524.
73. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144:646-674.
74. Thomson AW, Knolle PA. Antigen-presenting cell function in the tolerogenic liver environment. *Nat Rev Immunol*. 2010;10:753-766.
75. Prieto J, Melero I, Sangro B. Immunological landscape and immunotherapy of hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol*. 2015;12:681-700.
76. Chen L, Flies DB. Molecular mechanisms of T cell co-stimulation and co-inhibition. *Nat Rev Immunol*. 2013;13:227-242.
77. Greten TF, Sangro B. Targets for immunotherapy of liver cancer. *J Hepatol* 2018;68:157-166.
78. Sangro B, Gomez-Martin C, de la Mata M, 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.
79. Wainberg ZA, Segal NH, Jaeger D, et al. Safety and clinical activity of durvalumab monotherapy in patients with hepatocellular carcinoma (HCC). *J Clin Oncol*. 2017;35 (suppl; abstr 4071).
80. 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;389:2492-2502.
81. Sangro B, Melero I, Yau T, et al. Nivolumab in sorafenib-naive and -experienced patients with advanced hepatocellular carcinoma (HCC): survival, hepatic safety, and biomarker assessments in CheckMate 040. *Hepatology*. 2017;66 (S1):abstract #141.
82. Crocenzi TS, El-Khoueiry AB, Yau TC, et al. Nivolumab (nivo) in sorafenib (sor)-naive and -experienced pts with advanced hepatocellular carcinoma (HCC): CheckMate 040 study. *J Clin Oncol*. 2017;35 (suppl; abstr 4013).
83. Zhu A, Finn R, Cattan S, et al. Pembrolizumab (pembro) in patients with advanced hepatocellular carcinoma (HCC): KEYNOTE-224 update. *J Clin Oncol*. 2018;36 (suppl; abstr 4020).
84. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med*. 2015;373:23-34.
85. Kelley RK, Abou-Alfa GK, Bendell JC, et al. Phase I/II study of durvalumab and tremelimumab in patients with unresectable hepatocellular carcinoma (HCC): phase I safety and efficacy analyses. *J Clin Oncol*. 2017;35 (suppl; abstr 4073).
86. Hato T, Zhu AX, Duda DG. Rationally combining anti-VEGF therapy with checkpoint inhibitors in hepatocellular carcinoma. *Immunotherapy*. 2016;8:299-313.
87. Jain RK. Antiangiogenesis strategies revisited: from starving tumors to alleviating hypoxia. *Cancer Cell*. 2014;26:605-622.
88. Pinter M, Jain RK. Targeting the renin-angiotensin system to improve cancer treatment: implications for immunotherapy. *Sci Transl Med* 2017;9:eaan5616.
89. Chen Y, Huang Y, Reiberger T, et al. Differential effects of sorafenib on liver versus tumor fibrosis mediated by stromal-derived factor 1 alpha/C-X-C receptor type 4 axis and myeloid differentiation antigen-positive myeloid cell infiltration in mice. *Hepatology*. 2014;59:1435-1447.
90. Chen Y, Ramjiawan RR, Reiberger T, et al. CXCR4 inhibition in tumor microenvironment facilitates anti-programmed death receptor-1 immunotherapy in sorafenib-treated hepatocellular carcinoma in mice. *Hepatology*. 2015;61:1591-1602.
91. Ikeda M, Sung MW, Kudo M, 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 (suppl; abstr 4076).
92. Stein S, Pishvaian MJ, Lee MS, et al. Safety and clinical activity of 1L atezolizumab + bevacizumab in a phase Ib study in hepatocellular carcinoma (HCC). *J Clin Oncol*. 2018;36 (suppl; abstr 4074).
93. Duffy AG, Ulahannan SV, Makorova-Rusher O, et al. Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma. *J Hepatol*. 2017;66:545-551.

94. Munn DH, Bronte V. Immune suppressive mechanisms in the tumor microenvironment. *Curr Opin Immunol*. 2016;39:1-6.
95. Liu H, Naxerova K, Pinter M, et al. Use of Angiotensin System Inhibitors Is Associated with Immune Activation and Longer Survival in Nonmetastatic Pancreatic Ductal Adenocarcinoma. *Clin Cancer Res*. 2017;23:5959-5969.
96. Jiang H, Hegde S, Knolhoff BL, et al. Targeting focal adhesion kinase renders pancreatic cancers responsive to checkpoint immunotherapy. *Nat Med*. 2016;22:851-860.
97. Luangmonkong T, Suriguga S, Bigaeva E, et al. Evaluating the antifibrotic potency of galunisertib in a human ex vivo model of liver fibrosis. *Br J Pharmacol*. 2017;174:3107-3117.
98. Li MO, Flavell RA. TGF-beta: a master of all T cell trades. *Cell*. 2008;134:392-404.
99. Rammohan A, Reddy MS, Farouk M, et al. Pembrolizumab for metastatic hepatocellular carcinoma following live donor liver transplantation: the silver bullet? *Hepatology* 2018;67:1166-1168.
100. Friend BD, Venick RS, McDiarmid SV, et al. Fatal orthotopic liver transplant organ rejection induced by a checkpoint inhibitor in two patients with refractory, metastatic hepatocellular carcinoma. *Pediatr Blood Cancer* 2017;64: https://doi.org/10.1002/pbc.26682
101. Llovet JM, Pena CE, Lathia CD, et al. Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. *Clin Cancer Res*. 2012;18:2290-2300.
102. Personeni N, Bozzarelli S, Pressiani T, et al. Usefulness of alpha-fetoprotein response in patients treated with sorafenib for advanced hepatocellular carcinoma. *J Hepatol*. 2012;57:101-107.
103. Shao YY, Lin ZZ, Hsu C, et al. Early alpha-fetoprotein response predicts treatment efficacy of antiangiogenic systemic therapy in patients with advanced hepatocellular carcinoma. *Cancer*. 2010;116:4590-4596.
104. Tsuchiya K, Asahina Y, Matsuda S, et al. Changes in plasma vascular endothelial growth factor at 8 weeks after sorafenib administration as predictors of survival for advanced hepatocellular carcinoma. *Cancer*. 2014;120:229-237.
105. Yau T, Yao TJ, Chan P, et al. The significance of early alpha-fetoprotein level changes in predicting clinical and survival benefits in advanced hepatocellular carcinoma patients receiving sorafenib. *Oncologist*. 2011;16:1270-1279.
106. Borel F, Konstantinova P, Jansen PL. Diagnostic and therapeutic potential of miRNA signatures in patients with hepatocellular carcinoma. *J Hepatol*. 2012;56:1371-1383.
107. Wu Z, Zeng Q, Cao K, et al. Exosomes: small vesicles with big roles in hepatocellular carcinoma. *Oncotarget*. 2016;7:60687-60697.
108. Kanthaje S, Makol A, Chakraborti A. Sorafenib response in hepatocellular carcinoma: microRNAs as tuning forks. *Hepatol Res*. 2018;48:5-14.
109. Gyongyosi B, Vegh E, Jaray B, et al. Pretreatment MicroRNA Level and Outcome in Sorafenib-treated Hepatocellular Carcinoma. *J Histochem Cytochem*. 2014;62:547-555.
110. Vaira V, Roncalli M, Carnaghi C, et al. MicroRNA-425-3p predicts response to sorafenib therapy in patients with hepatocellular carcinoma. *Liver Int*. 2015;35:1077-1086.
111. Nishida N, Arizumi T, Hagiwara S, et al. MicroRNAs for the prediction of early response to sorafenib treatment in human hepatocellular carcinoma. *Liver Cancer*. 2017;6:113-125.
112. Stiuso P, Potenza N, Lombardi A, et al. MicroRNA-423-5p promotes autophagy in cancer cells and is increased in serum from hepatocarcinoma patients treated with sorafenib. *Mol Ther Nucleic Acids*. 2015;4:e233.
113. Yong E. Cancer biomarkers: written in blood. *Nature*. 2014;511:524-526.
114. Hofman P. Liquid biopsy and therapeutic targets: present and future issues in thoracic oncology. *Cancers (Basel)* 2017;9:E154.
115. Okajima W, Komatsu S, Ichikawa D, et al. Liquid biopsy in patients with hepatocellular carcinoma: circulating tumor cells and cell-free nucleic acids. *World J Gastroenterol*. 2017;23:5650-5668.
116. Hampton T. Gut Microbes May Shape Response to Cancer Immunotherapy. *JAMA*. 2018;319:430-431.
117. Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. *Science*. 2018;359:91-97.
118. Krieg C, Nowicka M, Guglietta S, et al. High-dimensional single-cell analysis predicts response to anti-PD-1 immunotherapy. *Nat Med*. 2018;24:144-153.

How to cite this article: Pinter M, Peck-Radosavljevic M. Review article: systemic treatment of hepatocellular carcinoma. *Aliment Pharmacol Ther*. 2018;48:598–609. https://doi.org/10.1111/apt.14913