Molecular therapies for HCC: Looking outside the box

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Summary

Over the past decade, sorafenib has been the only systemic agent with proven clinical efficacy for patients with unresectable hepatocellular carcinoma (HCC). Recently, lenvatinib was shown to be non-inferior to sorafenib, while regorafenib, cabozantinib, and ramucirumab were shown to be superior to placebo in patients failing sorafenib. In addition, trials of immune checkpoint inhibitors reported encouraging efficacy signals. However, apart from alpha-fetoprotein, which is used to select patients for ramucirumab, no biomarkers are available to identify patients that may respond to a specific treatment. Different synergisms have been postulated based on the potential interplay between antiangiogenic drugs and immunotherapy, with several clinical trials currently testing this hypothesis. Indeed, encouraging preliminary results of phase I studies of bevacizumab plus atezolizumab and lenvatinib plus pembrolizumab have led to the design of ongoing phase III trials, including both antiangiogenics and immune checkpoint inhibitors in the front-line setting. Other important phase II studies have tested molecular therapies directed against different novel targets, such as transforming growth factor-beta, MET (hepatocyte growth factor receptor), and fibroblast growth factor receptor 4. These studies integrated translational research with the aim of better defining the biological tumour profile and identifying tumour and blood biomarkers that select patients who may really benefit from a specific molecular therapy. Importantly, good safety profiles make these drugs suitable for future combinations. In this review, we discuss the most recent data on novel combination strategies and targets, as well as looking ahead to the future role of molecular therapies in the treatment of patients with advanced HCC.

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Introduction

Despite its increasing global incidence and status as a leading cause of cancer death, historically, there has been a dearth of new drug developments for hepatocellular carcinoma (HCC). The approval of sorafenib in 2007[1] ushered in a period of robust clinical research that until recently did not yield new drug approvals. This all changed in 2017 with the approval of regorafenib[2] in the second-line setting. Remarkably, what followed was a record number of positive phase III studies including lenvatinib in the first-line[3] and cabozantinib[4] and ramucirumab in the second-line.[5] In addition, the United States Food and Drug Administration (FDA) approved both nivolumab and pembrolizumab, 2 anti-programmed cell death protein 1 (PD-1) monoclonal antibodies for use in the second-line after sorafenib based on an accelerated approval mechanism, using data from single-arm phase II studies (Fig. 1).[6,7]

These robust readouts in a relatively short period have caused a significant shift in the research priorities for advanced HCC. The next phase of studies is focused on combination strategies to improve outcomes in the first-line setting and there are already early clinical data supporting this approach. In addition, we are now discussing studies in the third-line setting and beyond; a concept that would not even have been considered a few years ago. Once again, there are studies evaluating these newly approved drugs in earlier stages of HCC as well.

While we eagerly await the readouts of current phase III studies, it is time to start thinking of additional novel approaches for the treatment of HCC.

Targeted therapies for untargeted populations

The development of molecular targeted therapies in cancer medicine has often followed a rational development plan. That is to say, a molecular alteration or sub-classification of the disease is recognised, a novel therapeutic is selected to be evaluated in this population based on a scientific rationale, and clinical activity is established based on a biomarker, to identify patients that are most likely to respond. In liver cancer research there has been a significant disconnect in this process.

Over the past 20 years, a significant amount of work has been done to define the molecular subgroups of HCC.[8] Broadly speaking, there are 2 large classes of HCC, a proliferation class and a non-proliferation class. The proliferation class is more commonly associated with hepatitis B virus, being poorly differentiated, having higher alpha-fetoprotein (AFP) values and worse outcomes than the non-proliferation class, which is more commonly associated with hepatitis C virus or

alcohol-related HCC. Tumours in the non-proliferation class tend to confer a better outcome, have lower AFP values and be moderately to well differentiated. Within these 2 classes there are various subclasses based on genomic and epigenomic alterations. Despite the availability of assays that identify these groups and alterations, historically this heterogeneity has not played a role in patient selection for clinical trials. Only recently, studies with ramucirumab selected patients with an elevated AFP for inclusion,[5] but this was only after a negative phase III study in an unselected population.[9] Studies of clinical material have also defined "immune activated" phenotypes which may be important for identifying patients that would best respond to immunotherapy-based approaches.[10,11]

Currently approved agents

To understand the challenges involved in the development of new treatment approaches for advanced HCC, we must first appreciate the data supporting currently approved agents, which are summarised in Table 1.[1–7,12,13]

Understanding the mechanisms of action of approved drugs is critical to developing novel strategies. The majority of approved drugs are small molecule multikinase inhibitors of the vascular endothelial growth factor receptor (VEGFR). Increasingly, monoclonal antibodies are becoming important in the HCC landscape, including those aimed at blocking VEGFR, PD-1, and programmed cell death-ligand 1 (PD-L1). While the exact mechanism of action of multikinase inhibitors is not known, the monoclonal antibodies by design are very specific and their activity and side effect profiles result from target engagement. One of the challenges with all of these drugs is the development of biomarkers predictive of response. Except for ramucirumab, for which an elevated AFP is used to select patients, none of these drugs make use of a biomarker to identify patients that respond. Several studies have attempted to identify both blood and tissue biomarkers, but these have generally not yielded robust results or are hypotheses generating at best.[14–16] Studies designed specifically to validate biomarkers are critical for future success. These include novel studies, using tissue acquisition in the pre-surgical setting, where tissue is obtained at baseline, followed by a brief exposure to therapy before surgery. At the time of surgery, post-treatment tissue is obtained for molecular analyses and to determine whether there is a correlation with clinical response. One such study revealed interesting observations when evaluating the combination of the cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody ipilimumab with nivolumab.[17] These so called "window of opportunity" studies not only give us a better understanding of what new drugs are doing *in situ*, but can possibly point to specific new targets for therapy

Algorithm of treatment for advanced HCC

Front-line | Second-line | Beyond
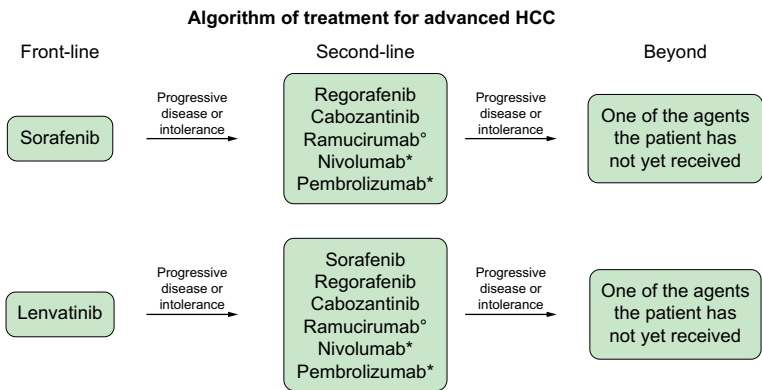
Fig. 1. Algorithm of treatment for advanced HCC. Potential options for sequencing systemic agents. Note that i) lenvatinib has not been studied in patients with liver occupation ≥50%, clear bile duct invasion, main portal vein invasion; ii) all phase III second-line studies to date have been after prior sorafenib, not lenvatinib; iii) regorafenib has been studied only in patients progressing on sorafenib; iv) the CELESTIAL (cabozantinib) trial enrolled also third-line patients; v) this is not evidence-based after second-line as the sequences have not been tested formerly. °If alpha-fetoprotein ≥400 ng/ml; *Approved by the United States Food and Drug Administration based on phase II data, not approved by the European Medicines Agency. HCC, hepatocellular carcinoma.

that are modulated, providing data for rational combination strategies.

Emerging novel combinations of molecular therapies

The definitive role of single-agent immunotherapies is yet to be proven. Recent top-line results from 2 long awaited phase III studies of 2 PD-1 targeted antibodies have been released. In the front-line setting, the CheckMate 459 study compared nivolumab to sorafenib in an open-label phase III study that randomised over 700 patients. This trial did not achieve statistical significance for its primary endpoint of overall survival (OS) per the pre-specified analysis; median OS (95% CI) was 16.4 months (13.9–18.4) for nivolumab versus 14.7 months (11.9–17.2) for sorafenib (hazard ratio [HR] 0.85, 95% CI 0.72–1.02, $p = 0.0752$).[13] In the second-line setting, the phase III KEYNOTE-240 confirmed the clinical activity of pembrolizumab in advanced HCC but did not meet the pre-specified criteria for statistical significance defined in the trial to demonstrate superiority over placebo; median OS (95% CI) was 13.9 months (11.6–16.0) for pembrolizumab versus 10.6 months (8.3–13.5) for placebo (HR 0.781; 95% CI 0.611–0.998; $p = 0.0238$) with a pre-specified p value of 0.0174 required.[12] Data from KEYNOTE-240 demonstrate that this class of agents clearly have activity in HCC with an objective response rate (ORR) of over 18% and a median duration of response (DOR) of over 13 months. These studies highlight the fact that identifying patients that are most likely to derive benefit is critical for success. Whereas in some tumour types PD-L1 expression has been associated with clinical benefit, in HCC this has not yielded robust results. Still, various predictive biomarkers have been proposed, but require

Key points

Recent positive trial results have caused a significant shift in the research priorities for advanced HCC, studies of novel approaches are ongoing, and studies designed to validate biomarkers are critical for future success.

Review

Trial name	Line of therapy	Active agent	Control	Primary endpoints	Results (months or rate)	Ref.
SHARP	First-line	Sorafenib	Placebo	OS	10.7 *vs.* 7.9 HR 0.69 (95% CI 0.55–0.87; *p* <0.001)	1
REFLECT	First-line	Lenvatinib	Sorafenib	OS, non-inferiority	13.6 *vs.* 12.3 HR 0.92 (95% CI 0.79–1.06)	3
RESORCE	Second-line	Regorafenib	Placebo	OS	10.6 *vs.* 7.8 HR 0.63 (95% CI 0.50–0.79; *p* <0.0001)	2
CELESTIAL	Second- and third-line	Cabozantinib	Placebo	OS	10.2 *vs.* 8.0 HR 0.76 (95% CI 0.63–0.92; *p* = 0.005)	4
REACH-2	Second-line and AFP ≥400 ng/ml	Ramucirumab	Placebo	OS	8.5 *vs.* 7.3 HR 0.71 (95% CI 0.531–0.949; *p* = 0.0199)	5
Checkmate 040	Second-line	Nivolumab*	None	ORR, OS, safety	~17%, ~15.0	6
KEYNOTE-224	Second-line	Pembrolizumab*	None	ORR, OS, safety	17%, 12.9	7
KEYNOTE-240	Second-line	Pembrolizumab**	Placebo	PFS, OS	PFS 3.0 *vs.* 2.8 HR 0.718 (95% CI 0.570–0.904; *p* = 0.0022) OS 13.9 *vs.* 10.6 HR 0.781 (95% CI 0.611–0.998; *p* = 0.0238)	12
Checkmate 459	First-line	Nivolumab**	Sorafenib	OS	OS 16.4 *vs.* 14.7 HR 0.85 (95% CI 0.72–1.02; *p* = 0.0752)	13

AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival; ORR, objective response rate; PFS, progression-free survival. *Nivolumab and pembrolizumab currently have accelerated approval in the United States for the second-line treatment of advanced HCC based on phase II results. **Though there were numerical improvements, the *p* values for OS and PFS did not reach the pre-specified cut-offs for statistical significance.

Key points

Combining antiangiogenics and immune checkpoint inhibitors may represent an evolution of current treatment options that is based on a strong preclinical rationale.

clinical validation.[10,11] Short of having a selection marker for patients, another strategy is to combine immune-oncology agents with other drug classes to increase the number of patients that benefit.

One of the factors supporting malignant cell escape from immune surveillance is hypoxia within the tumour microenvironment, resulting from an altered blood supply. Hypoxia also impairs the function of resident and transiting immune effector cells, while in cancer cells, myeloid-derived suppressor cells, and dendritic cells, the activation of hypoxia-inducible factor 1 alpha upregulates PD-L1 expression.[18] However, hypoxia may also result from antiangiogenic treatments such as sorafenib, which in HCC mouse models can induce an increase of PD-L1 expression in HCA-1 tumours after 28 days of treatment. This is consistent with the observation that, in resected human tumours, PD-L1 is preferentially expressed in hypoxic areas and that this can be a key factor in triggering immune evasion.[19]

Also, mounting evidence suggests that the excessive production of VEGF in response to the hypoxic state can exert immunosuppressive effects in tumours through the inhibition of dendritic cell maturation and the priming of immuno-suppressive inflammatory cell subsets.[20,21] Moreover, other findings with anti-VEGF strategies attribute antitumor responses to an improvement in tumour-specific T cell activity. DC101, for instance, an antiangiogenic monoclonal antibody specific for VEGFR-2, can increase tumour-specific CD8+ T cells in mice, thus favouring tumour regression.[22] In addition, a reduction in the proliferation of regulatory T cells has been observed in mouse models of colorectal cancer when targeting the VEGF/VEGFR axis with suni-tinib or bevacizumab. This effect can restore the physiologic density of regulatory T cells within a tumoural environment that is predisposed towards immune tolerance.[23]
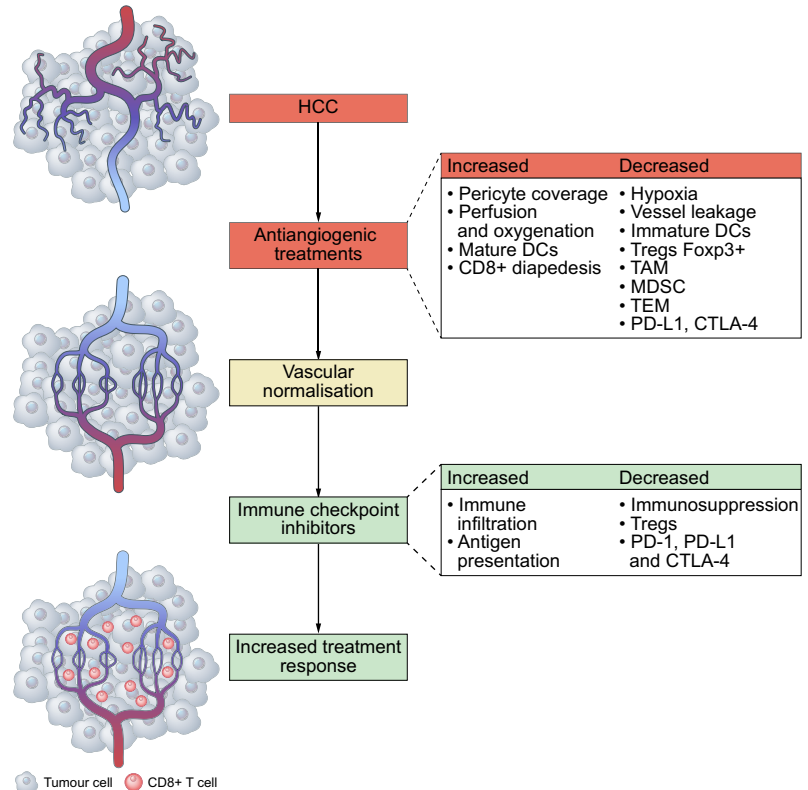
Immune checkpoint inhibitors have been introduced into clinical practice for a number of malignancies, kindling interest in these ground-breaking agents for HCC. While many aspects of these therapies remain poorly understood, it has been hypothesised that alleviating tumour hypoxia could improve the outcomes achieved with current immunotherapies. This constitutes the rationale for the concurrent targeting of VEGF and its cognate receptors and immune check-points, with several preclinical findings supporting this hypothesis. In a mouse model of colorectal cancer, although the combination of DC101 and anti-PD-1 antibody did not show any statistically significant differences in terms of T cell tumour infiltration, when comparing anti-PD-1 antibody (alone or in combination with DC101) to control, or to DC101 alone, an increase in both CD4+ and CD8+ T cell infiltrate in tumours was only observed with anti-PD-1 treatment.[24] Furthermore, in HCC models, immunosuppression promoted by sorafenib may be decreased by blockade of hypoxia-induced pathways, yet only the addition of an anti-PD-1 antibody is capable of stimulating T lymphocyte infiltration.[19]

When tumour cells are treated with cabozantinib the expression of major histocompatibility complex class 1 antigen increases, which is associated with a greater sensitivity of tumour cells to T cell-mediated killing.[25] A further preclinical study showed that lenvatinib has more potent antitumor activity when combined with PD-1 inhibition, decreasing the number of tumour-associated macrophages and therefore affecting antitumor immune responses.[26] Since both reduced and increased immunosuppression may result from blockade of the VEGF/VEGFR axis, combining antiangiogenics and immune checkpoint inhibitors may represent an evolution of current treatment options that is based on a sound preclinical rationale (Fig. 2).[27]

Several clinical trials are currently testing this hypothesis (Table 2). Updated results of a phase Ib study of bevacizumab combined with the anti-PD-L1 antibody atezolizumab in patients with advanced HCC and well-preserved liver function (Child-Pugh class A) (ClinicalTrials.gov NCT02715531) reported an ORR of 32% by investigator assessment according to RECIST 1.1, among 73 evaluable patients.[28] Objective responses were observed in all subgroups of patients regardless of aetiology, region, baseline AFP levels, and tumour burden (extrahepatic spread and/or macrovascular invasion). At a median follow-up of 7.2 months, 18 responses (78%) were ongoing for ≥6 months, including 6 (26%) that were ongoing for ≥1 year. Median progression-free survival (PFS) was 14.9 months (range 0.5–23.9+), and the 6-month PFS rate was 65%, while median DOR and median OS were not reached at the time of presentation. The ORR based on investigator assessment per RECIST 1.1 was confirmed by an independent review facility (IRF) assessment according to RECIST 1.1 (27%) and mRECIST (34%). Among 103 safety-evaluable patients, the most common any-grade adverse events (AEs) were decreased appetite (28%), fatigue, rash, and pyrexia (20% each), and the most common grade 3/4 AE was hypertension (10%). Five grade 5 AEs were reported, and 2 of them were considered treatment-related (1 case of grade 4 drug-induced liver injury, followed by sepsis and hepatic decompensation, and 1 case of pneumonitis). Serious AEs (SAEs) occurred in 35% of the patients, and treatment-related SAEs in 18% of the patients. AEs leading to treatment withdrawal from bevacizumab, atezolizumab, or both treatments occurred in 10%, 8%, 6% of the patients, respectively. Overall, AEs were in line with the safety profile of each drug and no new safety signals were identified (Table 3).[28] According to earlier data[29] this combination has been granted breakthrough therapy designation by the FDA[30] and has been further assessed in the IMbrave150 phase III trial (ClinicalTrials.gov NCT03434379).

The IMbrave150 is a multicentre, open-label, randomised phase III study evaluating the efficacy and safety of bevacizumab and atezolizumab compared to sorafenib in patients with untreated locally advanced or metastatic HCC and well-preserved liver function (Child-Pugh class A). The updated co-primary endpoints of this study are OS and PFS, as determined by an IRF according to RECIST 1.1. Updated secondary endpoints include ORR, PFS, time to progression (TTP), and DOR as determined by the investigator according to RECIST 1.1; ORR, TTP, and DOR as determined by an IRF according to RECIST 1.1; ORR, PFS, TTP, and DOR as determined by an IRF according to mRECIST; quality of life (QOL), OS and PFS according to baseline AFP levels, pharmacokinetics (PK), anti-drug antibodies to atezolizumab, and AEs. This trial randomised approximately 480 patients

Signalling pathways targeted by immune checkpoint inhibitors and antiangiogenics

Fig. 2. Signalling pathways targeted by immune checkpoint inhibitors and antiangiogenics. CTLA-4, cytotoxic T-lymphocyte antigen 4; DCs, dendritic cells; MDSCs, myeloid-derived stem cells; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; TAMs, tumour-associated macrophages; TEM, TIE-2 (angiopoietin receptor) expressing monocytes; Tregs, regulatory T lymphocytes. Adapted from Mossenta M, *et al.*[27]. Note: This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited (CC BY 4.0).

in a 2:1 ratio. Patients in the experimental arm received bevacizumab at a dose of 15 mg/kg and atezolizumab at a dose of 1,200 mg by i.v. infusion on day 1 of each 21-day cycle, patients in the control arm received sorafenib at the standard dose of 400 mg orally twice a day on days 1–21 of each 21-day cycle. A press release stated that "the phase III IMbrave150 study met its co-primary endpoints demonstrating statistically significant and clinically meaningful improvements in OS and PFS compared with standard-of-care sorafenib".[31]

All antiangiogenic agents with positive phase III results in HCC (sorafenib, lenvatinib, regorafenib, cabozantinib and ramucirumab) target VEGFR-2 signalling to varying degrees, along with other receptors involved in the angiogenic process (except for ramucirumab which selectively targets VEGFR-2). Based on this evidence, all agents could be synergistically associated with immune checkpoint inhibitors. Preliminary data from a phase Ib study testing the combination of lenvatinib and the anti-PD-1 antibody pembrolizumab for first-line treatment of unresectable HCC (ClinicalTrials.gov NCT03006926) reported an ORR of 42.3%,

Key points

Preliminary results of phase I studies of bevacizumab plus atezolizumab and lenvatinib plus pembrolizumab are encouraging and have led to the design of ongoing phase III trials of antiangiogenics plus immune checkpoint inhibitors.

including unconfirmed responses and of 26.9% excluding unconfirmed responses, and a median PFS of 9.69 months (95% CI 5.55–not evaluable) per investigator assessment by mRECIST, among 26 evaluable patients.[32] Among 30 safety-evaluable patients, AEs were consistent with known safety profiles of lenvatinib and pembrolizumab. Decreased appetite and hypertension (53.3% each) were the most common any-grade AEs, followed by diarrhoea (43.3%) and fatigue (40%). The most common grade ≥3 AEs were hypertension (16.7%), aspartate aminotransferase increase (16.7%), decreased white blood cell count (13.3%), and hyponatremia (10.0%). There were 8 SAEs (26.7%) and 3 grade 5 AEs including 2 that were deemed to be treatment-related (acute respiratory distress syndrome and intestinal perforation). Sixty percent of patients had a dose interruption or reduction and 16.7% discontinued lenvatinib and/or pembrolizumab due to AEs. Overall, toxicities were manageable and no new unexpected safety signals were observed (Table 3).[32] In addition, a phase Ib trial of lenvatinib plus nivolumab in patients with HCC is ongoing in Japan (ClinicalTrials.gov NCT03418922), and a single-arm phase IIb study is exploring the combination of lenvatinib and pembrolizumab as second-line treatment in patients with advanced hepatobiliary tumours, while also analysing potential biomarkers of response (ClinicalTrials.gov NCT03895970).

Based on the phase Ib results, the phase III multicentre, randomised, double-blinded, active-controlled, LEAP-002 trial (ClinicalTrials.gov NCT03713593) is assessing the efficacy and safety of lenvatinib in combination with pembrolizumab versus lenvatinib in combination with placebo as first-line therapy in patients with advanced HCC and well-preserved liver function (Child-Pugh class A). The co-primary endpoints are OS and PFS according to RECIST 1.1 as assessed by blinded independent central review (BICR). Secondary endpoints include ORR, DOR, disease control rate (DCR), TTP per RECIST 1.1 as assessed by BICR; PFS, ORR, DOR, DCR, TTP per mRECIST as assessed by BICR; AEs and PK. This trial will randomise approximately 750 patients: patients in the experimental arm will receive lenvatinib 12 mg (for patients with body weight ≥60 kg) or 8 mg (for patients with body weight < 60 kg) orally once daily, plus pembrolizumab 200 mg i.v. on day 1 of each 21-day cycle; patients in the control arm will receive lenvatinib 12 mg (for patients with body weight ≥60 kg) or 8 mg (for patients with body weight < 60 kg) orally once daily, plus placebo i.v. on day 1 of each 21-day cycle.[33]

Given the results emerging from the aforementioned phase I trials it is possible that some agents may also move from the second- to the front-line setting. This is the case for the ongoing phase I/II and III studies of combinations of cabozantinib with immune checkpoint inhibitors. In the earlier phases of clinical development, the CheckMate 040 is a multicohort phase I/II trial (ClinicalTrials.gov NCT01658878) exploring possible synergistic activities of cabozantinib combined with the anti-PD-1 antibody nivolumab, with or without the anti-CTLA-4 antibody ipilimumab, in patients with advanced HCC and well-preserved liver function (Child-Pugh class A). Primary endpoints of the study are safety and efficacy in terms of ORR. The multicohort phase Ib COSMIC-021 study (ClinicalTrials.gov NCT03170960) is testing the combination of cabozantinib and atezolizumab in patients with advanced HCC, well-preserved liver function (Child-Pugh class A), and no prior systemic therapy, with the primary objectives of safety and preliminary efficacy (ORR per RECIST 1.1) of the combination.[34] Other ongoing phase I/II trials are testing the combination of regorafenib plus pembrolizumab in first-line (ClinicalTrials.gov NCT03347292), regorafenib plus the anti-PD-L1 antibody avelumab in patients with advanced or metastatic digestive solid tumours including HCC (ClinicalTrials.gov NCT03475953), cabozantinib plus nivolumab as neoadjuvant treatment in locally advanced HCC (ClinicalTrials.gov NCT03299946), cabozantinib plus the anti-PD-L1 antibody durvalumab (ClinicalTrials.gov NCT03539822), or ramucirumab plus durvalumab (ClinicalTrials.gov NCT02572687) in previously treated patients with advanced malignancies including HCC. In the phase III space the multicentre, randomised, open-label, controlled COSMIC-312 trial (ClinicalTrials.gov NCT03755791) is evaluating the efficacy and safety of cabozantinib in combination with atezolizumab versus sorafenib in the first-line treatment of patients with advanced HCC and well-preserved liver function (Child-Pugh class A). The 2 primary endpoints of this study are OS and PFS, according to RECIST 1.1 as determined by a blinded independent radiology committee (BIRC), for comparisons of cabozantinib + atezolizumab versus sorafenib. The secondary endpoint is PFS according to RECIST 1.1 as assessed by BIRC for cabozantinib versus sorafenib. Additional endpoints include PFS, ORR, TTP, and DOR per RECIST 1.1 by BIRC and by the investigator; radiographic response according to mRECIST; AEs, PK, immunogenicity of atezolizumab, biomarker analyses including AFP, and QOL. The trial will randomise approximately 740 patients in a 2:1:1 ratio. Patients in the experimental arm receive cabozantinib orally at a dose of 40 mg once daily, plus atezolizumab at the dose of 1,200 mg i.v. every 3 weeks; patients in the control arm receive sorafenib at the standard dose of 400 mg orally twice a day, and patients in the cabozantinib arm receive single-agent cabozantinib orally at a dose of 60 mg once daily.[35]

Finally, in the context of different combination approaches, ramucirumab combined with emibetuzumab, a bivalent MET antibody (ClinicalTrials.gov NCT02082210), and nivolumab combined

Table 2. Ongoing trials of novel combinations of molecular therapies for HCC.

Trial name/ identifier	Setting	Treatment	Primary endpoints	Study type	Planned enrollment, n
Phase I/II trials					
GO30140/ NCT02715531*	Advanced HCC/first-line	Bevacizumab + atezolizumab	Safety, ORR, PFS	Phase Ib	430 (across all cohorts)
NCT03006926	Advanced HCC/first-line	Lenvatinib + pembrolizumab	Dose escalation: Safety, DLTs Dose expansion: ORR, DOR	Phase Ib (dose-escalation and dose-expansion)	97
NCT03418922	Advanced HCC/first-line	Lenvatinib + nivolumab	Part 1: DLTs, safety Part 2: Safety	Phase Ib (part 1 and part 2)	26
NCT03895970	Advanced hepatobiliary tumors/second-line	Lenvatinib + pembrolizumab	ORR, DCR, PFS	Phase IIb	50
CheckMate 040/ NCT01658878*	Advanced HCC/first- or second-line	Cabozantinib + nivolumab +/− ipilimumab	Safety, ORR	Phase I/II (dose-escalation, dose-expansion)	620 (across all cohorts)
COSMIC-021/ NCT03170960	Advanced solid tumors, HCC/first-line	Cabozantinib + atezolizumab	Dose escalation: MTD, Recommended dose Dose expansion: ORR	Phase Ib (dose-escalation and dose-expansion)	1000 (across all cohorts)
CaboNivo/ NCT03299946	Locally advanced HCC/neoadjuvant	Cabozantinib + nivolumab	Safety, number of patients who complete preoperative treatment and proceed to surgery	Phase Ib	15
CAMILLA/ NCT03539822	Advanced GI tumors, HCC/second-line	Cabozantinib + durvalumab	MTD	Phase Ib	30
NCT03347292	Advanced HCC/first-line	Regorafenib + pembrolizumab	Safety, DLTs	Phase Ib (dose-escalation and dose-expansion	40
REGOMUNE/ NCT03475953	Advanced GI tumors, HCC/second-line	Regorafenib + avelumab	Part 1: Recommended phase II dose of regorafenib art 2: ORR	Phase I/II (part 1 and part 2)	212
NCT02572687	Advanced solid tumors, HCC/second-line and AFP ≥1.5x upper limit of normal	Ramucirumab + durvalumab	DLTs	Phase I	114
NCT02082210	Advanced solid tumors, HCC/second-line	Ramucirumab + emibetuzumab	Part A: DLTs Part B: ORR	Phase I/II	97
NCT02423343	Advanced solid tumors, HCC/second-line and AFP ≥200 ng/mL	Galunisertib + nivolumab	Phase Ib: MTD	Phase Ib/II (dose escalation and cohort expansion)	75
Phase III trials					
IMbrave150/ NCT03434379	Advanced HCC/first-line	Atezolizumab + bevacizumab *vs.* sorafenib	OS, PFS	Phase III, randomised, open-label	480
LEAP-002/ NCT03713593	Advanced HCC/first-line	Lenvatinib + pembrolizumab *vs.* lenvatinib + placebo	PFS, OS	Phase III, randomised, double-blinded	750
COSMIC-312/ NCT03755791	Advanced HCC/first-line	Cabozantinib + atezolizumab *vs.* sorafenib *vs.* cabozantinib	PFS, OS	Phase III randomised, open-label	740

AFP, alpha-fetoprotein; DCR, disease control rate; DLTs, dose-limiting toxicities; DOR, duration of response; GI, gastrointestinal; HCC, hepatocellular carcinoma; MTD, maximum tolerated dose; ORR, objective response rate; OS, overall survival; PFS, progression-free survival. *Trials include other cohorts.

Table 3. Results of phase I trials of antiangiogenics plus immune checkpoint inhibitors for HCC.

	Bevacizumab + atezolizumab	Lenvatinib + pembrolizumab
Efficacy results (INV-assessed)*	n = 73 (%)	n = 26 (%)
Overall response rate	23 (32)	11 (42.3 incl. unconfirmed responses)
		7 (26.9 excl. unconfirmed responses)
Complete response	1 (1)	1 (3.8)/0 (0)
Partial response	22 (30)	10 (38.5)/7 (26.9)
Disease control rate	56 (77)	n.a.
≥16 weeks	48 (66)	
≥24 weeks	34 (47)	
Median DOR, months	NR (1.6–22.0)	n.a.
≥6 months	12 (52)	
≥12 months	6 (26)	
Median PFS, months	14.9 (range 0.5–23.9+)	9.69 (95% CI 5.55–NE)
6-month PFS, %	65	n.a.
Median OS, months	NR (0.8–24.0 +)	n.a.
Safety results	n = 103 (%)	n = 30 (%)
Any AEs	95 (92)	30 (100)
Treatment-related AEs	84 (82)	28 (93.3)
Grade ≥3	46 (45)	18 (60)
Serious AEs	36 (35)	8 (26.7)
Grade 5	5 (5)**	3 (10)**
Dose modifications due to AEs		
Dose interruptions/reductions	n.a.	18 (60)/18 (60)
Discontinuation	24 (24)	5 (16.7)

AEs, adverse events; DOR, duration of response; HCC, hepatocellular carcinoma; INV, investigator; n.a., not available; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival. *Investigator-assessed, per RECIST 1.1 in the bevacizumab plus atezolizumab trial, per modified RECIST in the lenvatinib plus pembrolizumab trial; **2 grade 5 AEs in each trial were deemed treatment-related.

with galunisertib, a transforming growth factor-beta (TGF-β) receptor I kinase inhibitor (ClinicalTrials.gov NCT02423343), are being tested in phase I/II trials in patients with different types of advanced cancer including HCC.

In principle, robust preclinical data and early phase clinical data support combining antiangiogenic agents with immune checkpoint inhibitors in HCC and this approach, aiming to revert an immunosuppressive milieu into an immunosupportive one, could ultimately lead to improved clinical outcomes.[36]

Novel targets for molecular therapies

The recent development of immunotherapy in the field of HCC has overshadowed the results of important phase II studies using molecular therapies, with efforts to better define the biological tumour profile for which those therapies could be appropriate. Given HCC heterogeneity, such trials have integrated translational research, investigating both tumour and blood biomarkers to decipher which patient subgroup might be the best candidate for a specific molecular therapy. This section summarises the main approaches that have generated promising results with well-tolerated active compounds suitable for future combinations, as well as highlighting key findings from ancillary translational studies.

TGF-β inhibition

The role of the TGF-β pathway has been extensively reported in HCC. Importantly, the TGF-β pathway has dual and opposite functions: the ligand TFG-β1 could be beneficial at early tumour stages by inhibiting cell proliferation, while at late stages it promotes cell invasion, angiogenesis, epithelial-to-mesenchymal transition, and drug resistance.[37,38] For example, a preclinical study using hepatic sinusoidal endothelial cells and malignant hepatocytes to investigate hepatocellular transmigration suggests that TGF-β is crucially involved in blood vessel invasion of HCC cells, amongst more general cell–cell interactions between transmigrating hepatocytes and endothelial cells, revealed by significant changes in proteome profiling.[39] In addition, experiments using HCC cell lines show that TGF-β promotes cell proliferation and invasion and may induce fibroblast growth factor receptor 4 (FGFR4) expression through the extracellular-signal-regulated kinase (ERK) pathway *in vitro*, while TGF-β collaborates with FGFR4 to promote the metastatic dissemination of HCC *in vivo*.[40] Moreover, recent works report that TGF-β attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells.[41] The aforementioned findings provide an important rationale for inhibiting the TGF-β pathway in order to circumvent HCC aggressiveness and resistance to therapies, especially in the era of immune-oncology.

Most TGF-β inhibitors that have reached the clinics are small molecules designed to inhibit TFG-β receptors.[42] Among them, galunisertib (LY2157299 Monohydrate) is a TGF-β receptor 1 inhibitor[43] that has been investigated as a single drug or in combination with sorafenib across a

wide phase I-II programme in HCC, involving several cohorts with biomarker monitoring. In cohort A, which included 109 patients with AFP elevated to >1.5x the upper limit of normal (58–65% of patients with AFP ≥400 ng/ml), galunisertib was given orally as a single second-line agent following sorafenib failure, with patients achieving a median OS of 7.5 months, with no safety concerns. Interestingly, patients under exposure to galunisertib who had a reduction of >20% of AFP or TGF-β1 in the first 6 cycles of treatment had longer survival than those without a biological response (21.5 vs. 6.8 months for AFP, 11.2 vs. 5.3 months for TGF-β1, respectively), suggesting that galunisertib had a pronounced effect on a subgroup of this population with a particularly poor prognosis.[44] Galunisertib is currently being further investigated in combination with sorafenib.[45,46] Given the favourable safety profile, TGF-β pathway inhibition could be attractive for future combinations with other approaches such as PD-1/PD-L1 inhibitors, or using bifunctional fusion proteins targeting both TGF-β and PD-L1, such as the M7824 compound.[47,48]

MET inhibitors

c-MET (MET) is a tyrosine kinase receptor with a single known ligand, hepatocyte growth factor (HGF). The MET/HGF pathway is involved in HCC progression by promoting cellular proliferation, survival and invasion.[49,50] The MET/HGF axis is also associated with tyrosine kinase inhibitor resistance,[51] as patients with high plasma HGF concentrations above 3,279.1 pg/ml derived no obvious benefit from sorafenib compared to placebo in the pivotal phase III SHARP trial.[13] Several generations of MET inhibitors have been investigated in HCC, including selective or non-selective compounds. The latter group could hit a wide spectrum of targets (tivantinib), mimicking cytotoxic agents,[52] or inhibit mainly VEGFR (cabozantinib).[4] In practice, data on non-selective MET inhibitors reflect that their antitumor activity may be predominantly due to their activity against non-MET targets; those compounds associated with related off-target AEs.[53] In contrast, more recent selective oral compounds such as tepotinib[54] and capmatinib[55] have been developed in HCC, with a focus on reducing toxicity and identifying patient subgroups with MET abnormalities during phase II programmes.[53] As an example, tepotinib has been assessed in preclinical models[54] and as a second-line single agent in Western patients with MET-positive HCC who have failed on sorafenib (ClinicalTrials.gov NCT02115373). The tolerance was favourable at the recommended dose of 500 mg daily, peripheral oedema being the most frequent AE in 39% of patients (grade 3 in 6%). The objective of the trial was met with 31 out of 49 patients (63.3%) progression-free at 12 weeks. However, the limited ORR (8%) and DCR (27%) suggest that only a minority of patients are sensitive to selective MET inhibition despite being enrolled based on MET positivity using immunohistochemistry.[56] Our team and others have shown that MET amplification, a rare genetic alteration present in only 1% of HCC, was associated with complete response to tepotinib in preclinical models and in patients.[57] In contrast, MET overexpression at the protein level seems to be insufficient to identify patients who will respond to this selective approach, which warrants better characterisation of the appropriate biological profile.[57] Selective MET inhibition with tepotinib is currently being compared to sorafenib in Asian patients (ClinicalTrials.gov NCT01988493).

FGFR4 inhibitors

Blocking the FGF19/FGFR4 axis is another promising approach in HCC that illustrates the concept of biological selection of patients. There is a strong preclinical rationale to inhibit this pathway since FGF19/FGFR4 signalling enhances HCC cell invasion by suppressing E-cadherin expression and promoting the expression of epithelial-to-mesenchymal transition-related genes.[58] While there was no significant difference in FGFR4 expression between HCC and surrounding liver parenchyma, FGF19 was significantly overexpressed in HCC specimens and was an independent prognostic factor for overall and disease-free survival.[59] Moreover, FGF19 expression has been correlated with early recurrence and shorter disease-specific recurrence in a cohort of patients with HCC who underwent hepatectomy.[60] The role of FGF19 has also been highlighted in resistance to sorafenib[61] making this pathway of particular interest given the current wide use of multikinase inhibitors in HCC.

Following the first in class FGFR4 inhibitor BLU9931, other drugs have been investigated in HCC. BLU-554 is the most advanced of these compounds, following completion of a phase I dose escalation/dose expansion study, which assessed FGF19 expression using immunohistochemistry in parallel.[62] BLU-554 was well tolerated, with most AEs being mild to moderate gastrointestinal events. Thus, the maximum tolerated dose of 600 mg once daily was expanded in 81 patients. The ORR was 17% in FGF19-positive patients and 0% in FGF19-negative patients.[63] This important trial highlights the role of the FGF19/FGFR4 pathway as a relevant therapeutic target in advanced HCC and demonstrates that FGF19 could be used as a biomarker for patient selection. BLU-554 is currently being further investigated as single agent in HCC.

Conclusion

It is clear that the results of current trials are changing survival for patients with advanced HCC. While important questions, such as the opti-

> **Key points**
>
> Translational studies suggest that inhibitors of TGF-β, MET, and FGFR4 counteract HCC aggressiveness when used in patients with the appropriate biological tumour profile.

mal sequence strategy for these new agents and how best to assess imaging response to systemic therapies, still need to be answered, they are unlikely to provide the significant advances that the field requires. The empiric development of new drugs in HCC has not yielded the significant outcomes that we have seen in other malignancies. To really move the field forward, we will need to continue to "think outside the box", adopting novel combination strategies and to continue to pursue new targets in HCC. The success of these strategies will rely on the successful translation of laboratory studies into the clinic. Specifically, developing biomarkers that identify patients most likely to respond to a given treatment is critical. To do so, we must capitalise on the recent clinical successes that have established that HCC is not a "one drug disease" and use this momentum to drive the next generation of research studies.

Abbreviations

AEs, adverse events; AFP, alpha-fetoprotein; BICR, blinded independent central review; BIRC, blinded independent radiology committee; CTLA-4, cytotoxic T-lymphocyte antigen 4; DCs, dendritic cells; DCR, disease control rate; DOR, duration of response; ERK, extracellular-signal-regulated kinase; FGFR4, fibroblast growth factor receptor 4; HCC, hepatocellular carcinoma; HGF, hepatocyte growth factor; HR, hazard ratio; IRF, independent review facility; MDSCs, myeloid-derived stem cells; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; QOL, quality of life; TAMs, tumour-associated macrophages; TEM, TIE-2 (angiopoietin receptor) expressing monocytes; TGF-β, transforming growth factor-beta; TTP, time to progression; Tregs, regulatory T lymphocytes; VEGFR, vascular endothelial growth factor receptor.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.09.010.

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Author names in bold designate shared co-first authorship

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