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HEPATIC CANCER (N PARIKH, SECTION EDITOR)

The Current Landscape of Systemic Therapies for Advanced Hepatocellular Carcinoma

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Abstract

Purpose of review As the global burden of HCC continues to rise, there is an overwhelming need for new systemic therapies for the treatment of advanced-stage HCC. In this review, we explore the current landscape of approved therapies for intermediate-stage HCC after progression with locoregional therapy or in those who present with advanced-stage HCC not amenable to curative options.

Recent findings In the last 10 years, several agents have been studied in the first and second-line treatment of HCC but failed to show clinical benefit. Between 2008 and 2016, sorafenib was the sole agent used in the treatment of advanced-stage HCC. Recent strides have shown success with lenvatinib as an alternative agent for first-line treatment, and regorafenib, cabozantinib, ramucirumab, nivolumab, and pembrolizumab as second- and thrid-line agents in advanced HCC.

Summary The next series of HCC trials are appropriately directed at combination therapies—combining targeted therapy with immunomodulators in the hopes of improving overall survival and ultimately getting closer to finding a cure.

Key Words Hepatocellular carcinoma · Liver cancer · Advanced therapy · Systemic therapy

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third leading cause of cancer related mortality. In 2018 there were estimated to be 841,080 new cases and 781,631 HCC related death worldwide [1]. While the burden of HCC varies by geographic region, race/ethnicity, gender, and age, 80-90% of all cases occur in the setting of cirrhosis and chronic liver disease [2, 3]. The major causes of cirrhosis include hepatitis B (HBV), hepatitis C (HCV), alcoholic liver disease, and nonalcoholic fatty liver disease [2]. While several HCC staging systems exist, the Barcelona Clinic Liver Cancer (BCLC) staging system remains the most widely accepted staging classification used for HCC. Current guidelines according to EASL and AASLD utilize this algorithm for stratification and treatment allocation [4, 5].

Given the lack of stringent surveillance programs in the West, only 5-10% of patients are diagnosed at an early stage (BCLC 0-A) when curative options are available. By contrast, in Asia, specifically Japan, due to the use of strict surveillance programs 30% of patients are diagnosed at an early stage (BCLC 0-A) [4]. Curative options include resection, liver transplantation and radiofrequency or microwave ablation. At present, transarterial chemoembolization (TACE) is the standard of care for intermediate-stage HCC with a median survival of 16 months with untreated disease [4, 5]. Unfortunately given the natural history of the disease, >50% of patients eventually require systemic therapy either due to progression of disease with locoregional therapy or because of advanced-stage HCC (with macrovascular invasion and/or extrahepatic disease).

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In 2007, the landmark Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial introduced sorafenib as the first systemic agent which was FDA approved for first-line treatment of advanced-stage HCC. This multi-target receptor tyrosine kinase (TKI) inhibitor improved median overall survival by 2.8 months compared to placebo [6]. A similar benefit with sorafenib was subsequently observed in Asian patients with mostly HBV-related HCC [7]. Between 2008 and 2016, sorafenib was the sole agent used in the treatment of advanced-stage HCC. In the last 10 years, several agents have been studied in the first and second-line treatment of HCC but failed to show clinical benefit. Recent strides have shown success with lenvatinib [8] as an alternative agent for first-line treatment, and regorafenib [9••], cabozantinib [10••], ramucirumab [11••], nivolumab [12••], and pembrolizumab [13••] as second-line agents in advanced-stage HCC. In this review, we explore the current landscape of approved therapies for intermediate-stage HCC after progression with locoregional therapy or in those who present with advanced-stage HCC not amenable to curative options.

First-line Therapy

In 2007, sorafenib became the only FDA approved systemic agent available for the treatment of advanced-stage HCC. While systemic chemotherapy has shown clear survival benefits in other malignancies, phase III trials with these agents in the treatment of HCC have failed to show similar benefits [14–16]. As our understanding of genomic landscape of HCC expands, attempts are being made to develop agents targeting the molecular pathways involved in the pathogenesis of HCC. Several phase III trials have gone head-to-head with sorafenib but have failed to show superiority - (erlotinib + sorafenib [17], doxorubicin + sorafenib [14]) or non-inferiority - (sunitinib [18], brivanib [19], linifanib [20]) (Table 1). In 2018, the results of REFLECT trial introduced a second agent for first-line treatment of advanced-stage HCC.

Lenvatinib

Lenvatinib is an oral TKI inhibitor of VEGFR1-3, FGFR1-4, PDGFRα, KIT and RET. Success with lenvatinib was initially demonstrated in a phase II trial in patients with advanced-stage HCC. This study showed very favorable results with regards to time to progression (TTP) and overall survival (OS), 7.4 months and 18.7 months, respectively [21]. Based on the promising results of this phase II trial, a phase III multicenter non-inferiority study was conducted to compare the efficacy and safety of lenvatinib compared to sorafenib in patients without prior systemic therapy. In the REFLECT trial, a total of 954 patients were randomly assigned in a 1:1 ratio to receive lenvatinib or sorafenib [8••].

Lenvatinib met its primary endpoint of non-inferiority demonstrating a median OS of 13.6 months compared to 12.3 months in the sorafenib group (HR 0.92, 95% CI 0.79-1.06). Significant outcomes were also noted in all secondary endpoints. Median progression-free survival (PFS) and TTP reported by institutional investigators and masked independent imaging review according to the modified response evaluation criteria in solid tumors (mRECIST) criteria was greater in the lenvatinib group compared to the sorafenib group. The objective response rate (ORR) was higher in the lenvatinib group (24.1%) compared to the sorafenib group (9.2%). Furthermore, upon masked independent review ORR reached 40.6% in the lenvatinib group [8••].

Although baseline alpha-fetoprotein (AFP) concentration was not included as a stratification factor, a subgroup analysis showed favorable outcomes in patients with AFP >200 ng/mL in the lenvatinib group compared to the sorafenib group. In the lenvatinib group, 46% of patients had an AFP ≥ 200 ng/mL compared to 39% in the sorafenib arm. Despite this disadvantage in the lenvatinib arm, median OS was greater with lenvatinib (HR 0.78, 95% CI 0.63–0.98) [8••].

Grade ≥3 treatment-emergent adverse events (AEs) were higher with lenvatinib (57%) versus sorafenib (49%). Discontinuation of therapy due to treatment-related AEs was 9% with lenvatinib and 7% with sorafenib. Despite the higher frequency of AEs, the median duration of treatment was longer in the lenvatinib arm compared to sorafenib, 5.7 months and 3.7 months, respectively, suggesting a superior tolerability [8••].

Based on the above results, lenvatinib has now been approved for first-line treatment in patients with BCLC stage C HCC and BCLC stage B HCC.

Second-Line Therapy

Since the approval of sorafenib, there has been a large unmet clinical need for second-line agents in patients with intolerance to or progression on sorafenib. While sorafenib extended OS, intolerance and resistance to sorafenib have limited its clinical use. Since 2013, multiple phase III trials have attempted but failed to bridge this clinical gap [22–28] (Table 1). The molecular diversity of HCC creates challenges as many patients harbor a primary or acquired resistance to sorafenib. Primary resistance to sorafenib is associated with overexpression of epidermal growth factor receptor (EGFR), which leads to downstream signaling, enhancing cell growth and proliferation. Acquired resistance results from abnormal activation of several pathways - PI3k/Akt and JAK-STAT, epithelial-mesenchymal transition that promotes cell migration and invasion, and activation of hypoxia inducible factor which allows tumor progression in suboptimal tumor microenvironments (TME) [29]. Sequential inhibition after

Table 1 Overview of Phase III Trials for First and Second Line Treatment in Advanced-Stage HCC mo- months, HR- hazard ratio, NS- not significant, BSC- best supportive care, NA- not available

Trial Name	Treatment Line	Drug Studied	Patients	Overall Survival	Positive Result	NCT
SHARP	1st	Sorafenib	299	10.7 mo vs 7.9 mo	Yes	NCT00105443
		Placebo	303	HR 0.69 (0.55–0.87), p < 0.001		
Asia-Pacific	1st	Sorafenib	150	6.5 mo vs 4.2 mo	Yes	NCT00492752
		Placebo	76	HR 0.68 (0.5-0.93), p=0.01		
SUN1170	1st	Sorafenib	544	10.2 mo vs 7.9 mo	No	NCT00699374
		Sunitinib	530	HR 1.3 (1.13-1.5), p=0.001		
SEARCH	1st	Sorafenib + Erlotinib	362	9.5 mo vs 8.5 mo	No	NCT00901901
		Sorafenib	358	HR 0.92 (0.781-1.106), p=0.2		
BRISK-FL	1st	Sorafenib	578	9.9 mo vs 9.5 mo	No	NCT00858871
		Brivanib	577	HR 1.07 (0.94-1.23), p=-0.31		
LiGHT	1st	Sorafenib	519	9.8 mo vs 9.1 mo	No	NCT01009593
		Linifanib	510	HR 1.046 (0.896-1.221), p=NS		
CALGB 80802	1st	Sorafenib + Doxorubicin	173	9.3 mo vs 10.5 mo	No	NCT01015833
		Sorafenib	173	HR 1.06 (0.8-1.4), p=NS		
REFLECT	1st	Sorafenib	476	12.3 mo vs 13.6 mo	Yes	NCT01761266
		Lenvatinib	478	HR 0.92 (0.79–1.06), p<0.05		
CheckMate 459	1st	Sorafenib	NA	HR 0.85 (0.72-1.02), p=0.0752	No	NCT02576509
		Nivolumab				
HIMALAYA	1st	Sorafenib			ongoing	NCT03298451
		Durvalumab + Tremelimumab				
IMbrave150	1st	Sorafenib			ongoing	NCT03434379
		Atezolizumab + Bevacizumab				
	1st	Sorafenib			ongoing	NCT03412773
		BGB-A317				
	1st	Sorafenib			ongoing	NCT02645981
		Donafenib				
PHOCUS	1st	Sorafenib			ongoing	NCT02562755
		Pexa Vec + Sorafenib				
ORIENT-32	1st	Sorafenib			ongoing	NCT03794440
		Sintilimab + IBI305				
COSMIC-312	1st	Sorafenib			ongoing	NCT03755791
		Cabozantinib + Atezolizumab				
	1st	SHR-1210 + FOLFOX4			ongoing	NCT03605706
		Sorafenib				
		FOLFOX4				
	1st	Sorafenib			ongoing	NCT03236649
		Icaritin				
LEAP-002	1st	Lenvatinib			ongoing	NCT03713593
		Lenvatinib + Pembrolizumab				
	1st	Sorafenib			ongoing	NCT03764293
		SHR-1210 + Apatinib				
BRISK-PS	2nd	Brivanib	263	9.4 mo vs 8.2 mo	No	NCT00825955
		Placebo	132	HR 0.89 (0.69-1.15), p=0.33		
EVOLVE-1	2nd	Everolimus	362	7.6 mo vs 7.3 mo	No	NCT01035229
		Placebo	184	HR 1.05 (0.86-1.27), p=0.68		
REACH	2nd	Ramucirumab	283	9.2 mo vs 7.6 mo	No	NCT01140347
		Placebo	282	HR 0.86 (0.72-1.05), p=0.13		
RESORCE	2nd	Regorafenib	379	10.6 mo vs 7.8 mo	Yes	NCT01774344
		Placebo	294	HR 0.63 (0.50-0.79), p<0.01		
METIV-HCC	2nd	Tivantinib	226	8.4 mo vs 9.1 mo	No	NCT01755767
		Placebo	114	HR 0.97 (0.75-1.25), p=NS		
S-CUBE	2nd	S-1	223	11.1 mo vs 11.2 mo	No	JapicCTI-090920
		Placebo	111	HR 0.86 (0.67-1.10), p=0.220		
CELESTIAL	2nd	Cabozantinib	467	10.2 mo vs 8.0 mo	Yes	NCT01908426
		Placebo	237	HR 0.76 (0.63-0.92), p=0.0049		
REACH-II	2nd	Ramucirumab	197	8.5 mo vs 7.3 mo	Yes	NCT02435433
		Placebo	95	HR 0.71 (0.531-0.949), p=0.0199		
ADI-PEG 20	2nd	ADI-PEG 20	424	7.8 mo vs 7.4 mo	No	NCT01287585
		Placebo	211	HR 1.022 (0.847-1.233), p=0.884		

Table 1 (continued)

Trial Name	Treatment Line	Drug Studied	Patients	Overall Survival	Positive Result	NCT
JET-HCC	2nd	Tivantinib Placebo	134 61	9.9 mo vs 8.5 mo HR 0.85 (0.59-1.22), p not reported	No	NCT02029157
ReLive	2nd	Doxorubicin Transdrug BSC	263 134	9.1 mo vs 9.0 mo HR 1.00 (0.78-1.28), p=0.99	No	NCT01655693
KEYNOTE-240	2nd	Pembrolizumab BSC	278 135	HR 0.78 (0.611-0.998), p=0.0238	No	NCT02702401
KEYNOTE-394	2nd	Pembrolizumab + BSC Placebo + BSC			ongoing	NCT03062358
	2nd	Apatinib Placebo			ongoing	NCT02329860

sorafenib is an active area of research and may help overcome these patterns of resistance. Next, we discuss the landmark trials that extended OS after progression on or intolerance to sorafenib. It is important to note that while rapid approval of these agents has provided clinicians alternative second-line agents, comparative studies of these agents are lacking. As such, ultimate treatments options should rely on clinical judgment tailored to the individual requirements of the patient.

Regorafenib

Regorafenib is an oral multi-kinase inhibitor that is structurally homologous to sorafenib. It inhibits activity against anti-angiogenic TKIs (VEGFR1-3, PDGFR-β, FGFR, TIE2), oncogenic TKIs (RET, KIT) and intracellular signaling kinases (RAF-1 and BRAF). The difference in one fluorine atom offers a broader but more toxic biochemical profile [30]. A phase II study to examine the safety of regorafenib in patients with HCC following progression with first-line sorafenib showed acceptable tolerability and antitumor activity [31].

The RESORCE trial was a phase III trial to evaluate the safety and efficacy of regorafenib compared to placebo in patients with HCC after progression with sorafenib. Given the strong toxicity profile of regorafenib, patients were required to have tolerated sorafenib (≥400 mg daily) for at least 20 of the 28 days before discontinuation, thereby preventing dropout rates due to AEs. Patients were randomized in a 2:1 ratio, to regorafenib or placebo. To eliminate confounding variables, patients were matched on their pattern of progression during sorafenib, median time on sorafenib, median time from progression on sorafenib, and median time from discontinuation of sorafenib [9••].

Regorafenib met its primary endpoint and demonstrated an OS benefit of 10.6 months (placebo: 7.8 months, HR 0.63, 95% CI 0.5-0.79, p<0.0001). Regorafenib also significantly improved secondary endpoints. Median PFS and TTP in months by the mRECIST criteria were 3.1 months vs 1.5 months (HR 0.46, 95% CI 0.37-0.56, p<0.0001) and 3.1 months vs 1.5 months (HR 0.44, 95% CI 0.36-0.55, p<0.0001), respectively, with regorafenib compared to placebo. The ORR and disease control rate (DCR) by both mRECIST and RECIST criteria were higher with regorafenib compared to placebo [9••]. A subsequent analysis of median OS from the start of sorafenib showed that sequential therapy with sorafenib-regorafenib prolonged median OS to 26.0 months compared to 19.2 months in the sorafenib-placebo arm [32•].

Grade ≥3 treatment-emergent AEs were observed in all patients treated with regorafenib. Of these, 93% were deemed possibly drug-related. Despite the high incidence of AEs, median treatment duration was longer with regorafenib compared to placebo, 3.6 vs 1.9 months, respectively. Discontinuation of therapy due to treatment-related AEs was 25% with regorafenib and 19% with placebo [9••].

Based on these results, regorafenib was the first agent approved for second-line therapy in patients with advanced-stage HCC. One explanation for this synergistic effect may be attributed to the broader activity profile of regorafenib. Specifically, adaptive responses by the tumor lead to induction of proangiogenic factors like Ang and the TIE2 ligand, further promoting tumor angiogenesis. Sequential inhibition of the Ang/TIE2 pathway after anti-VEGF therapy may exert a more profound inhibition of this pathway and prevent resistance to sorafenib monotherapy [30, 32•]. Lastly, it is important to note that the RESORCE trial excluded patients who were intolerant to sorafenib. Exclusion of this subset of patients created an unmet need for second-line agents suitable for patients in this group. As discussed later, the success of the CELESTIAL and REACH-2 trial investigate this gap.

Cabozantinib

Cabozantinib is an oral TKI inhibitor of VEGF1-3, MET, and AXL. Similar to VEGF, overexpression of MET and AXL are triggered by tumor hypoxia [33, 34]. Preclinical tumor models have shown up-regulation of MET with long-term sorafenib treatment leading to sorafenib resistance [35]. Inhibition of

MET and AXL, in conjunction with VEGF, provides a more comprehensive blockade of this pathway.

In a phase II discontinuation trial, cabozantinib showed preliminary signs of clinical activity with a PFS 5.2 months and DCR 66%, and a modest ORR at 5% [36]. The CELESTIAL trial was a randomized phase III trial to evaluate the safety and efficacy of cabozantinib compared to placebo in patients with advanced HCC after progression on sorafenib. In contrast to other phase III trials, patients who received up to two lines of systemic therapy were eligible to enroll. A total of 707 patients were randomized in a 2:1 ratio to receive cabozantinib or placebo [10••].

The trial was stopped after the second interim analysis revealed a significant survival benefit with cabozantinib compared to the placebo arm. Cabozantinib improved median OS to 10.2 months vs 8.0 months in the placebo group (HR 0.76, 95% CI 0.63-0.92, p<0.005). The ORR by RECIST was numerically modest however statistically significant between the two groups (cabozantinib 4% vs placebo 1%, p=0.009). The median PFS by RECIST was 5.2 months with cabozantinib vs 1.9 months with placebo. Furthermore, cabozantinib showed clinical activity across all subgroup analysis of PFS [10••].

Regarding AEs, grade ≥3 AEs were higher with cabozantinib (68%) compared with placebo (36%). Discontinuation of therapy due to drug related AEs was also higher with cabozantinib (15%) compared with the placebo group (3%). Despite the higher incidence of AE, median duration of treatment was longer with cabozantinib (3.8 months) compared with the placebo (2.0 months) [10••].

Ramucirumab

Ramucirumab is a human IgG1 monoclonal antibody that targets VEGFR-2 thereby preventing interaction with its ligand VEGF. VEGF and its receptor (VEGFR) have been long implicated in tumor angiogenesis, growth and metastasis [37, 38]. Pathological angiogenesis creates an abnormal TME, leading to hypoxia and further perpetuating angiogenesis through up-regulation of VEGF and VEGFR [39]. Inhibition of VEGF and VEGFR plays a crucial role in HCC as increased levels of VEGF portend a poor prognosis [38].

Ramucirumab was initially evaluated as a second line agent in advanced-stage HCC after progression with first-line sorafenib in the REACH trial. While ramucirumab failed to meet its primary endpoint of OS, it did show clinical activity with regards to PFS, TTP, and ORR (all p<0.0001). Importantly, a subgroup analysis of patients with AFP ≥400 ng/mL demonstrated an OS benefit for the ramucirumab group (7.8 months) vs. the placebo group (4.2 months) (HR 0.67, 95% CI 0.51-0.90, p=0.006). Furthermore, subgroup analysis of PFS in patients with AFP ≥400 ng/mL showed similar benefits (HR 0.70, 95% CI 0.53-0.92) [24]. These results paved the way for the landmark REACH-2 trial, which was the first successful phase III trial to show survival benefit in a biomarker selected population [11••].

REACH-2 was randomized phase III study to evaluate the efficacy of ramucirumab in patients with HCC with progression or intolerance to sorafenib and a baseline AFP ≥400 ng/mL. Patients were randomized in a 2:1 ratio to ramucirumab or placebo. A 2:1 ratio for randomization was selected to allocate a larger percentage of patients to ramucirumab. To eliminate confounding variables, the two groups were similar in regards to the median duration of previous sorafenib therapy and time from progression on sorafenib to randomization [11••].

Ramucirumab improved median OS in the ramucirumab group (8.5 months) compared to the placebo group (7.3 months) (HR 0.71, 95% CI 0.531-0.949, p=0.0199). Although the groups did not differ in the ORR (p=0.1697), significant improvements in PFS (p<0.0001), TTP (p<0.0001), and DCR (p=0.0006) were noted in the ramucirumab group [11••].

With regards to toxicity profile, the most common treatment-emergent AEs with ramucirumab were grade 1-2. The most frequent grade ≥3 AEs reported with ramucirumab were hypertension (12.6%) and hyponatremia (5%), which were only observed in 5% of the total group. Discontinuation of therapy due to treatment-related AEs was higher with ramucirumab (11%) compared to placebo (3%) [11••].

Previous trials with biomarker selectivity failed to show similar survival benefits [27]. REACH-2 was the first successful phase III trial to show a survival benefit in a biomarker-selected population. AFP concentration in HCC has been linked with poor prognosis, with levels >400 ng/mL correlating with more aggressive disease [40, 41]. Though AFP has been suggested as a potential prognostic indicator, at this time there is no validated biomarker of prognosis and response to therapy in HCC [42, 43]. The success of the REACH-2 trial underscores the need for further studies with biomarker selectivity.

Immune Checkpoint Inhibitors

Advances in cancer immunology have further characterized the distinct area directly surrounding cancer cells, termed the TME, and the high levels of regulatory T-cells that often surround cancer cells and allow for tumor progression [44•]. Attempts have been successful in other cancers in targeting co-inhibitory molecules on the surface of regulatory T-cells to reduce spread and induce tumor response. These targeted approaches have been designed with a variety of different proteins in mind. However, in this review, we will focus on the two primary immunologic targets used within HCC treatment:

cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) along with its ligand, PD-L1.

CTLA-4 Therapies

CTLA-4 was one of the early targets identified for monoclonal antibody therapy. Current HCC therapies using humanized monoclonal CTLA-4 antibodies include ipilimumab and tremelimumab. While ipilimumab was first approved in 2011 for treatment of metastatic melanoma, most HCC therapy trials involving immune checkpoint markers have studied tremelimumab. A phase II study was conducted among 21 patients with hepatitis C and inoperable HCC with preserved hepatic function (Child Pugh class A or B), with cancer control in 77% and partial response in 17.6% [45]. A combination study of tremelimumab and radiofrequency ablation evaluated 32 patients with HCC treated with two different dose levels followed by ablation on day 36 of therapy. Its results showed promise, with 26% showing partial response [46]. In both studies, use of tremelimumab resulted in reductions in HCV viral load among patients with chronic HCV. An additional phase III study (HIMALAYA, NCT03298451) is currently ongoing comparing combination therapy with tremelimumab with durvalumab (a monoclonal PD-1/PDL-1 antibody) against durvalumab monotherapy and sorafenib monotherapy [47] (Table 2).

PD-1/PD-L1

PD-1 and its associated ligand protein, PD-L1, are inhibitory proteins that are expressed along a variety of different immune cells that inhibit T-cell production and induce apoptosis. Nivolumab, pembrolizumab, atezolizumab and durvalumab are all monoclonal antibodies designed to target PD-1 or both PD-1 and PDL-1. Nivolumab was the first FDA-approved monoclonal antibody against PD-1, and was evaluated against HCC initially during the CheckMate 040 trial, a phase I/II study that evaluated 262 patients diagnosed with HCC and preserved hepatic function, many of whom had already progressed while on sorafenib [12••]. The study showed an objective response rate in 20% of patients. This prompted a follow-up, phase III study (CheckMate 459, NCT02576509), that identified no improvement in survival, although its full study data has not yet been published [48]. Pembrolizumab is an additional monoclonal antibody that has shown promise in early trials. The KEYNOTE 224 trial was a phase II trial involving 104 patients, with objective response in 17% [13••]. A larger study, KEYNOTE 240 was started but failed to meet primary endpoints [49, 50]. Despite the mixed outcomes in larger studies, both nivolimumab and pembrolizumab have been FDA-approved as second-line therapies, primarily based on the outcomes of CheckMate 040 and KEYNOTE 224, respectively. There are multiple ongoing trials involving anti-PD-1/PD-L1 agents, including phase I and III studies for nivolumab (NCT02576509, NCT03383458); neoadjuvant use of pembrolizumab (NCT03337841); studies of new anti-PD-1/PD-L1 agents (NCT02989922, NCT03389126, and NCT02988440) as well as combination therapy (discussed below) (Table 2).

Intracellular kinases

Intracellular kinases are a targeted enzyme class that have been associated with increased tumor growth via the mTOR pathway. The EVOLVE-1 trial was a phase III study conducted on 546 patients who were sorafenib non-responders and randomized to everolimus or placebo, with no differences in OS, or TTP, and only mild improvement in disease control rate [23]. Mitogen-activated protein kinase kinase (MEK) is another intracellular kinase target being studied for HCC treatment. Refametinib is a another small molecular inhibitor that was evaluated in combination with sorafenib for patients with RAS mutations, with an OS of 12.7 months [51]. Sapanisertib is a new small-molecule inhibitor currently being evaluated in a phase I/II study against sorafenib (NCT02575339) (Table 2).

Transforming growth factor beta

Transforming growth factor beta (TGFβ) is a complex signaling pathway with tumor-suppressive and tumor-promoting activities. This multifaceted pathway influences tumor growth, angiogenesis, invasion, metastases, endothelial cell proliferation, and resistance to chemotherapy [52]. Furthermore, activation of TGFβ within the TME allows tumor cells to evade detection by the immune system [52, 53]. TGFβ influences immune dysregulation by shifting the balance of T-helper (Th) 1/Th2 towards Th2 (increasing humoral immunity and decreasing cell-mediated immunity), directly inhibiting Th1 responses, cytotoxic CD8+ T-cells, natural killer cells and dendritic cells and upregulating CD4+ T-regulatory cells (Treg) [52].

Galunisertib (LY2157299), a TGFβRI kinase inhibitor, has progressed furthest in clinical development with results from a phase II study showing a median OS of 36 weeks. Within this group, AFP responders – defined as a decline in serum AFP >20% - had a survival of 93.1 weeks compared to non-responders at 29.6 weeks [54]. Preliminary data from a phase II trial with galunisertib plus sorafenib as first-line therapy showed a median TTP of 4.1 months and median OS of 17.9 months [55].

Table 2 Ongoing Phase 1/2 trials in the treatment of Advanced-stage HCC

Mechanism	Study Phase	Drug	Comparator	Molecular target	NCT
Molecular Targeted	1	Chiauranib	none	VEGFRs, PDGFRa, c-Kit	NCT03245190
	1, 2	Tivozanib	none	VEGFRs	NCT01835223
	2	Anlotinib	none	VEGFRs	NCT02809534
	1	Sorafenib + Navitoclax	none	BCL2	NCT02143401
Immune Checkpoint inhibitors	2	SHR-1210	none	PD-1	NCT02989922
	2	Avelumab	none	PD-L1	NCT03389126
	1, 2	Durvalumab	none	PD-L1	NCT01693562
	1, 2	Nivolumab + Mogamulizumab	none	PD-1 + CCR4	NCT02705105
	1, 2	Pembrolizumab + Epacadostat	none	PD-1+ IDO1	NCT02178722
	1	Pembrolizumab + XL888	none	PD-1 + HSP 90	NCT03095781
	2	SHR-1210 + Apatinib	FOLFOX4, GEMOX	PD-1	NCT03092895
	1	Durvalumab + Guadecitabine	none	PD-L1 + DNA methyltransferase	NCT03257761
	2	Pembrolizumab + Bavituximab	none	PD-1	NCT03519997
Combination Therapy	1, 2	Nivolumab + Bevacizumab	none	PD-1 + VEGF	NCT03382886
	1	Lenvatinib + Pembrolizumab	none	PD-1 + VEGF	NCT03006926
	1	Lenvatinib + Nivolumab	none	PD-1 + VEGF	NCT03418922
	1	Regorafenib + Pembrolizumab	none	PD-1 + VEGF + TIE2	NCT03347292
	1, 2	Sorafenib + Pembrolizumab	none	VEGFR, PDGFRa, RAF inhibitor + PD-1	NCT03211416
	1	Avelumab + Axitinib	none	PD-L1 + VEGFR, c-KIT and PDGFR	NCT03289533
	1	Spartalizumab + Sorafenib	none	VEGFR, PDGFRa, RAF inhibitor + C-MET	NCT02988440
	1	Ramucirumab + Durvalumab	none	VEGFR + PD-1/PD-L1	NCT02572687
	1, 2	Apatinib + SHR-1210	none	VEGFR + PD-1	NCT02942329
	1	Cabozantinib + Durvalumab	none	c-Met, VEGFR, AXL, RET + PD-1/PD-L1	NCT03539822
	1	SF1126 + Nivolumab	none	PI3 kinase inhibitor + PD-1 inhibitor	NCT03059147
	1	Vorolanib + Pembrolizumab	Vorolanib + Nivolumab	VEGFR + PDGFR + PD1	NCT03511222
C-MET	2	Capmatinib	none	c-MET	NCT01737827
	1, 2	Capmatinib + Spartalizumab	Capmatinib	c-MET	NCT02795429
	1, 2	MSC2156119J	none	c-MET	NCT02115373
Intracellular kinases	2	Milciclib maleate	none	cyclin-dependent kinase & tropomyosin receptor kinase A inhibitor	NCT03109886
	1, 2	Tefinostat	none	histone deacetylase inhibitor	NCT02759601
	1, 2	Resminostat + Sorafenib	Sorafenib	histone deacetylase inhibitor + VEGFR, PDGFRa, RAF inhibitor	NCT02400788
	1	Napabucasin + Sorafenib	none	Cancer Stemness Kinase inhibitor + VEGFR, PDGFRa, RAF inhibitor	NCT02358395
	1, 2	Napabucasin + Sorafenib	Amcasertib + Sorafenib	Cancer Stemness Kinase inhibitor + VEGFR, PDGFRa, RAF inhibitor	NCT02279719
	1, 2	Sapanisertib	Sorafenib	mTOR inhibitor	NCT02575339
	2	ABC294640	none	Sphingosine kinase 2 inhibitor	NCT02939807
	2	Palbociclib	none	cyclin-dependent kinase inhibitor	NCT01356628
FGF-FGFR axis	1, 2	BLU-554	none	FGFR4	NCT02508467
	1, 2	INCB062079	none	FGFR4	NCT03144661
	1	H3B-6527	none	FGFR4	NCT02834780
	1	Erdafitinib	none	FGFR1-4	NCT02421185
	1, 2	FGF401+Spartalizumab	FGF401	FGFR4	NCT02325739
TGF-Beta	1, 2	Galunisertib (LY2157299)+ Nivolumab	none	TGFBR1	NCT02423343
	2	Galunisertib (LY2157299) + Sorafenib	Galunisertib (LY2157299)	TGFBR1	NCT02178358

Table 2 (continued)

Mechanism	Study Phase	Drug	Comparator	Molecular target	NCT
	2	Galunisertib (LY2157299)	Sorafinib, Ramucirumab	TGFBR1	NCT01246986
	1	NIS793 + PDR001	none	TGFB	NCT02947165
Oncolytic Virus	1, 2	Pexa Vec + Nivolumab	none	oncolytic virus	NCT03071094
	1	p53MVA + Pembrolizumab	none	oncolytic virus	NCT02432963
	1	Talimogene Laherparepvec + Pembrolizumab	none	oncolytic virus	NCT02509507
Miscellaneous	1, 2	Enzalutamide + Sorafenib	Enzalutamide	Androgen Receptor	NCT02642913
	2	Enzalutamide	Placebo	Androgen Receptor	NCT02528643
	2	CF102	Placebo	A3AR	NCT02128958
	1, 2	Carotuximab + Sorafenib	none	Endoglin	NCT02560779
	1	Sonidegib (LDE225)	none	Hedgehog	NCT02151864
	1, 2	CC-122 + Nivolumab	none	Cereblon	NCT02859324
	2	BBI503	none	Cancer Stemness Kinase inhibitor	NCT02232633

The TGFβ pathway has been implicated in resistance to anti-PD-1/L1 therapy, with preclinical studies with combination therapy showing synergistic effects on immune modulation by upregulating CD8+ T-effector cells [56]. By contrast, combination therapy with anti-VEGF and anti-TGFβ agents has shown synergistic effects on modulating immune tolerance via Treg cells [57]. Combination trials with nivolumab (NCT02423343), PDR001 (NCT02947165), ramucirumab (NCT01246986), and sorafenib (NCT02178358) are currently underway (Table 2).

FGF-FGFR

The TKI fibroblast growth factor receptor (FGFR) and its ligand fibroblast growth factor (FGF) have been long implicated in tumorigenesis and tumor progression, highlighting its role as a potential target in anticancer treatments [58]. FGFR4 is the predominant isoform in the liver, expressed in both HCC and normal liver tissue [59]. Activation of FGFR4 by FGF19 induces hepatocyte proliferation and the potential for malignant transformation [60]. Furthermore, overexpression of FGF19 and activation of the FGFR/FGF19 pathway has been associated with sorafenib resistance [61].

Preliminary results with BLU-554, a potent irreversible kinase inhibitor that selectively targets FGFR4, has shown promising results in patients with FGF19+ tumor expression (defined by immunohistochemistry (IHC) with FGF19 ≥1%). BLU-554 demonstrated clinical benefit with an ORR 16% in FGF19+ versus 0% in FGF19- patients with advanced HCC [62]. Several FGFR4 kinase inhibitors are undergoing clinical development in a biomarker-selected population: BLU-554 (NCT02508467), H3B-6527 (NCT02834780), FGF401 (NCT02325739), and INCB062079 (NCT03144661) (Table 2).

Oncolytic virus

Targeted oncolytic viruses (OV) are being extensively researched for their potential role in cancer treatment. OVs are genetically engineered viruses that trigger antitumor immunity via preferential replication in and lysis of tumor cells. OV mediated destruction releases tumor antigen that not only activates the host's innate immune response but also creates adaptive immune response to create long-lasting responses [63]. While OVs are being studied in a variety of cancer types, the clinical benefit of OV in cancer treatment was first seen with the GM-CSF-expressing herpes virus T-Vec in advanced melanoma [64]. The JX-594 (Pexa-Vec) is a genetically engineered recombinant vaccina virus with inactivation of the thymidine kinase gene and expression of human GM-CSF. The mechanism of action of Pexa-Vec is multimodal and thought to result from direct infection and lysis, induction of antitumor response, and tumor vascular disruption [65].

Early clinical trials with intratumoral injection with Pexa-Vec demonstrated a tolerable safety profile and an early signal of efficacy [66, 67]. However, a subsequent phase IIb study of Pexa-Vec in second-line treatment after sorafenib failed to demonstrate improved OS, as reported by the company, and meet its primary endpoint of OS [68]. A phase III study, PHOCUS, with Pexa-Vec plus sorafenib compared to sorafenib monotherapy for first-line therapy in advanced HCC is currently underway (NCT02562755) [69]. Additional trials

with combination OVs and immune-checkpoint inhibitors are also ongoing (NCT03071094, NCT02432963, NCT02509507) (Table 2).

Combination therapy

Given the multiple pathways upregulated in HCC tumorigenesis, trials studying therapy with combinations of immunotherapy, TKI inhibitors and intracellular kinase inhibitors have become more common. These combinations have been attempted both with the addition of agents to sorafenib for first-line use, as well as combinations of second-line agents for patients with HCC and progression despite sorafenib.

Combinations of immunotherapy with TKI inhibitors are undergoing evaluation. Preliminary data was presented from the IMbrave 150 trial, a phase Ib trial with 68 patients treated with a combination of atezolizumab, an anti-PD-L1 agent, and bevacizumab, a VEGF inhibitor. An objective response rate of 34% was reported, with further data regarding survival and PFS still pending [70]. Studies are in progress to evaluate multiple other combinations (NCT02572687, NCT03347292, NCT02942329, NCT03299946, NCT03289533, NCT03222076, NCT02705105, NCT02178722, NCT02795429) (Table 2).

Conclusions

HCC develops from a complex interaction of genetic and non-genetic factors, generally in the setting of chronic liver disease. This multistep process involves the formation of dysplastic nodules and the sequential accumulation of somatic mutations that vary based on the etiology of the underlying liver disease which eventually leads to the development of hepatocellular carcinoma. Tumor initiation and progression results from an average of 35 to 80 somatic mutations per tumor which makes targeting therapies difficult [71]. Because of its complexity, a number of different molecular pathways are currently being studied to improve disease control. Although many new drugs have been recently approved, none to date have shown superiority to sorafenib.

As the global burden of HCC continues to rise, there is an overwhelming need for new systemic therapies for the treatment of advanced-stage HCC. While alterations in several unique pathways have been linked with hepatic carcinogenesis, development of new agents remains a challenge. The next series of HCC trials are appropriately focusing on combination therapies—targeted therapy with TKIs, often combined with immunomodulators in the hopes of finding curative therapy.

Compliance with ethical standards

Conflict of Interest Prachi Rana and John Heydak each declare no conflicts of interest.

Anjana Pillai is on the speaker's bureau for Eisai and Simply Speaking Hepatitis and served on speaker's bureau for BTG. She is on the medical advisory board for Wako Diagnostics.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the author

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