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Upper Gastrointestinal Cancers (L Rajdev, Section Editor)

Systemic Therapy for Advanced Hepatocellular Carcinoma in an Evolving Landscape

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Opinion statement

Globally, hepatocellular carcinoma (HCC) is a leading cause of cancer-related death and a malignancy with rising incidence. After sorafenib remaining the one and only FDA-approved therapy for the disease for many years, the past 2 years has seen the landscape of available treatments change dramatically. Multiple multi-targeted tyrosine kinases (TKIs) have demonstrated success and garnered FDA approval both in the first- (lenvatinib) and second-line (regorafenib) settings. Now, various questions regarding the sequencing of these therapies remain for investigation. Effective positioning of these TKIs will be crucial to optimization of outcomes for patients with HCC. Additionally, promising outcomes have been seen with a number of immunotherapies, and one such agent has been approved (nivolumab). Positioning of these immunotherapies in the landscape may or may not have impacts upon sequencing of all of the available therapies. Further studies are ongoing investigating such sequencing questions, in addition to more novel agents to combat this devastating disease.

Introduction

Liver cancers, worldwide, account for more than 850,000 new cancer cases annually, and approximately 90% of these are hepatocellular carcinoma (HCC) [1, 2]. HCC is a lethal malignancy arising from hepatocytes. In the USA, HCC-related deaths represent 3 and 6% of all cancer-related deaths in females and males, respectively [3]. HCC is the second leading cause of cancer-related death globally, and there is a recognizable increase in the mortality rates from HCC in most countries, including the USA [4, 5].

There are several well-defined risk factors for the disease including cirrhosis, hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, alcohol abuse, and nonalcoholic steatohepatitis (NASH) [2] (Fig. 1). Other well-known and characterized colluding factors for development of the disease include intake of aflatoxin B1, and certain metabolic disorders including hemochromatosis. Newer studies have suggested that infection with adeno-associated virus 2 (AAV2) may be a novel cause of the disease, particularly in individuals without cirrhosis [6] (Fig. 1).

HCC is often diagnosed at advanced stages for which curative therapy options are not valid, with a 5-year survival rate of just 3% [3]. Sorafenib arose as the singular standard in 2007 and remained the sole standard until recently. Since 2017, we have witnessed a dynamically changing treatment landscape for patients with advanced HCC, including the emergence of a number of novel tyrosine kinase inhibitors and checkpoint inhibitors. We discuss herein recent literature highlighting recently emergent options for management of this disease, as relevant to management of our patients as medical oncologists.

Treatment

First-line therapy

Sorafenib

The first therapeutic to demonstrate efficacy and garner FDA approval in 2007 for treatment of HCC was sorafenib [7]. This agent is a multi-tyrosine kinase inhibitor (TKI) inhibiting the serine–threonine kinases Raf-1 and B-Raf and the

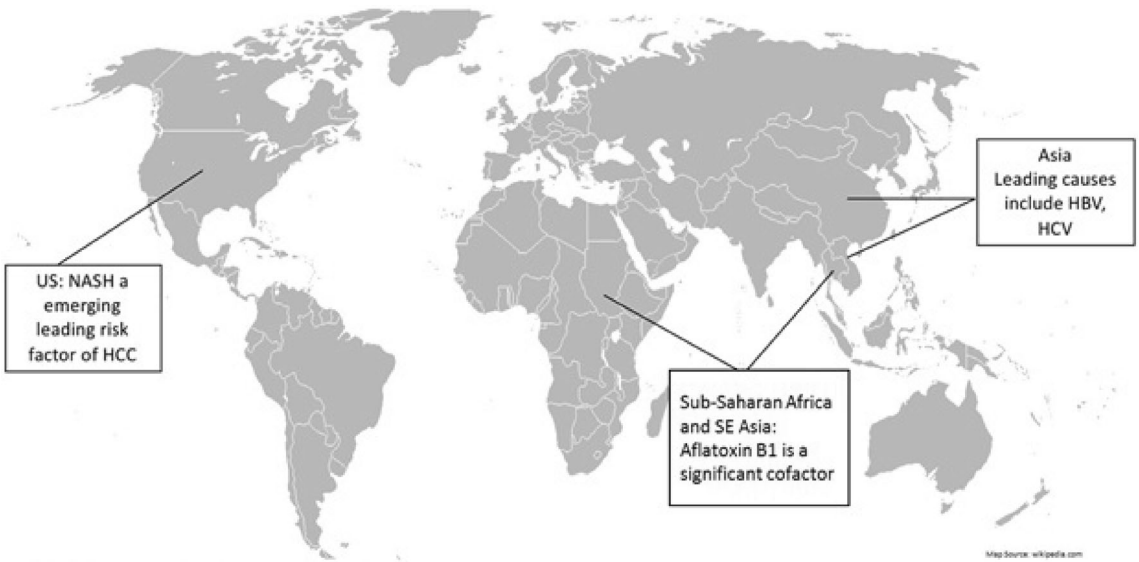

Fig. 1. Global risk factors for HCC.

receptor tyrosine kinase activity of vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3 and platelet-derived growth factor receptor β (PDGFR-β) [8, 9]. In the phase III multicenter, double-blind, placebo-controlled SHARP trial, 602 patients with advanced HCC and no previous systemic treatment were randomly assigned to receive either sorafenib or placebo [10] (Table 1). Sorafenib demonstrated a significant improvement in median survival at 10.7 months, compared to 7.9 months for patients in the placebo group,

Table 1. First-line studies and outcomes

	Sorafenib (Llovet et al)	Sorafenib (Kudo et al)	Lenvatinib
Median age	64.9	62	63
Male:female (%)	87/13	84/16	85/15
Global region			
Western (Europe, North America, Australia)	97	33	33
Asia	0	67	67
Risk factor (%)			
Alcohol	26	4	8
Hepatitis B	19	48	53
Hepatitis C	29	26	19
Other/unknown	25	21	21
ECOG performance status			
0	54	63	64
1	38	37	36
BCLC stage (%)			
B	18	19	22
C	82	81	78
Macroscopic vascular invasion, extrahepatic spread, or both	70	71	69
Macroscopic portal vein	36	23	19
Extrahepatic spread	53	61	62
Child-Pugh class (%)	95	99	99
Concomitant systemic antiviral therapy (%)	2	31	34
Previous anticancer procedures/surgery	63	72	68
Responses (RECIST; independent review (%)			
CR	0	< 1	< 1
PR	2	6	18
SD54	71	53	54
Disease control rate (%)	43	59	73
Median time to progression (months)	5.5	3.7	7.4
Median PFS (months)	NR	3.6	7.3
Median OS (months)	10.6	12.3	13.6

(HR = 0.69; $p < 0.001$) [10]. In the Asia Pacific region, Sorafenib also proved itself in a phase 3 randomized, double-blind, placebo-controlled trial [11]. In this trial, 226 patients with HCC who had not received prior systemic therapy, and with Child-Pugh A liver function, from centers in China, South Korea, and Taiwan, were randomized 2:1 to sorafenib or placebo. Median OS was 6.5 months compared with 4.2 months, respectively (hazard ratio [HR] 0.68; $p = 0.014$). Median time to progression (TTP) was 2.8 months compared with 1.4 months (HR 0.57 [0.42–0.79]; $p = 0.0005$). The most common adverse reactions (≥ 20%) considered to be related to sorafenib are fatigue, weight loss, rash/desquamation, hand-foot skin reaction, alopecia, diarrhea, anorexia, nausea, and abdominal pain.

Given the varied etiologies for patients' underlying liver disease and risk factors for HCC, the question of sorafenib's benefit in each of these different subgroups has been explored too. As noted above, the survival advantage was not to the same magnitude as that seen in the SHARP trial (10.7 vs. 6.5 months) [11]. This difference could be related to a multitude of reasons including variances in patterns of care between the two regions, significantly higher percentage of poorer performance status (ECOG PS 1) pts. in AP study compared with the SHARP trial (69% vs 38%), a higher number of patients with metastatic disease in the AP study (69% vs 53%), or also a significantly higher percentage of patients with hepatitis B (HBV) as the etiology of their liver disease in the AP study (71%) compared with the low percentage of these patients in the SHARP trial (19%). Alongside this, patients with hepatitis C (HCV)–related liver disease represented just 11% of patients in the AP study and at least 29% in the SHARP trial. Subgroup analyses of phase II and III studies of sorafenib in HCC have shown greater benefit from the treatment in those with HCV-induced HCC versus other causes [12, 13]. In one particular phase II study of sorafenib in patients with advanced HCC, it was noted that there was a significant difference in time to progression (TTP) in patients with higher (2 to 4+) pERK staining compared with those with lower (0 to 1+) intensity ($p = 0.00034$), suggesting an important contribution from Raf inhibition by sorafenib [13]. In the case of hepatitis C, HCV-1 core protein may result in high activity of Raf-1, thus increasing the possibility of oncogenesis [14]. In the above phase II study, in fact, retrospective analysis revealed that patients with hepatitis C as a risk factor had improved median TTP of 6.5 months compared with 4 months in hepatitis B patients [15]. Supportive of these results, as it relates to hepatitis as an etiology for liver disease and an HCC risk factor, a meta-analysis of phase III trial results demonstrated improved overall survival (OS) for sorafenib in patients who are both HBV negative and HCV positive [16].

After almost a decade of suboptimal results of trials evaluating agents in the first-line setting in an effort to improve outcomes above and beyond sorafenib, recent data have offered a potential alternative, and data from ongoing trials to emerge in the coming months to years seeks to raise bar.

Lenvatinib

Lenvatinib, a molecule with a different and more varied target profile compared with sorafenib, is an inhibitor of VEGF receptors 1–3, FGF receptors 1–4, PDGF receptor α, RET, and KIT, initially showed activity in a phase 2 study of patients

Table 2. Second-line studies and outcomes

	Regorafenib (RESORCE)	Nivolumab (CheckMate 040)	Pembrolizumab (KEYNOTE-224)	Cabozantinib (CELESTIAL)
Median age	64	64	68	64
Male:female (%)	88/12	80/20	83/17	81/19
Global region (%)		NR	NR	
Rest of world	62			75
Asia	38			25
Risk factor (%)				
Alcohol	24	NR	NR	24
Hepatitis B	38	24	21	38
Hepatitis C	21	23	26	24
NASH	7	NR	NR	9
Other/unknown	24	53	NR	23
ECOG performance status				
0	65	64	61	52
1	35	36	39	48
BCLC stage (%)				
B	14	NR	19	
C	86	NR	81	
Macroscopic vascular invasion, extrahepatic spread, or both (%)	80	NR	NR	85
Macroscopic portal vein invasion (%)	29	29	17	27
Extrahepatic spread	70	67	63	79
Child-Pugh class A (%)	98	99	94	100
Concomitant systemic antiviral therapy (%)	NR	NR	NR	NR
Responses (RECIST; independent review (%)				
CR	1	1	1	0
PR	10	18	15	4
SD54	54	45	45	61
Disease control rate (%)	65	64	61	65
Median time to progression (months)	3.2	3.4	NR	NR
Median PFS (months)	3.1	4	4.8	5.2
Median OS (months)	10.6	NR	NR	10.2

with hepatocellular carcinoma [17]. In the phase 3 open-label, multicenter non-inferiority trial, REFLECT study, overall survival was compared in patients treated with lenvatinib (12 mg/day for bodyweight ≥ 60 kg or 8 mg/day for bodyweight < 60 kg) versus sorafenib as a first-line treatment for unresectable, systemic treatment naïve hepatocellular carcinoma [18••].(Table 1) Over the

course of about 2 years, 954 eligible patients were randomly assigned to lenvatinib or sorafenib. Median overall survival for lenvatinib was 13.6 months compared to sorafenib at 12.3 months (hazard ratio 0.92, 95% CI 0.79–1.06), meeting the study primary criteria for non-inferiority. Treatment was generally well tolerated. The most common any-grade adverse events were hypertension, diarrhea, decreased appetite, decreased weight, fatigue, nausea, palmar-plantar erythrodysesthesia, dysphonia, and proteinuria for lenvatinib. For sorafenib, the most common any-grade adverse events were alopecia, palmar-plantar erythrodysesthesia, diarrhea, hypertension, decreased appetite, and fatigue. The objective response rate, per RECIST 1.1 by independent reviewer, for patients on lenvatinib was 18%, versus 6% for those in the sorafenib group. However, interestingly, the response rate as assessed per modified RECIST (mRECIST) criteria by independent reviewer was different from that done by investigator. By independent evaluator, the objective response rate was 40.6% versus 12.4%, respectively. By investigator, the objective response rate was 24.1% versus 9.2%, respectively. As assessed by independent reviewer per mRECIST criteria, the disease control rate was 74% and 58%, respectively ($p < 0.0001$). While OS was non-inferior to sorafenib, median PFS did not differ between that assessed by independent reviewer or investigator. By independent reviewer, the median PFS was 7.3 months for the lenvatinib arm, compared with 3.6 months for those on sorafenib. Similar progression-free survival and time-to-progression results were observed for mRECIST and RECIST 1.1 based on masked independent imaging review. The median duration on treatment was 5.7 months for patients on lenvatinib and 3.7 months for those on sorafenib. Subgroup analysis revealed no significant differences in overall survival among subgroups of patients receiving lenvatinib. Based upon this data, the FDA approved lenvatinib in August 2018 for use in the first-line setting for those patients with unresectable, advanced HCC.

Second-line therapy

In the second-line setting, a string of randomized phase 3 trials utilizing several agents failed to show a benefit over placebo. This impasse was broken in 2017 with the publication of both the RESORCE and CheckMate 040 trials, and the eventual FDA approval of regorafenib and conditional approval nivolumab [19••, 20••].

Regorafenib

The RESORCE trial was a randomized, double-blind, global phase 3 trial evaluating regorafenib (160 mg daily on days 1–21 of 28-day cycle) versus placebo in adults with HCC who had tolerated sorafenib (≥ 400 mg/day for ≥ 20 of the last 28 days of treatment), progressed on sorafenib, and had Child-Pugh A liver function [19••] (Table 2). Over a two-and-a-half-year period, 573 were randomized. Regorafenib demonstrated improved overall survival compared with placebo with a hazard ratio of 0.63 ($p < 0.0001$) and a median overall survival of 10.6 months versus 7.8 months, respectively. Median progression-free survival was 3.1 months and 1.5 months, respectively. Interestingly, analysis of survival for the sequencing of sorafenib followed by regorafenib versus placebo shows significantly improved survival at 26 months versus 19.2 months [21]. Adverse events were seen in all patients on

regorafenib, with the most common clinically relevant grade 3 or 4 treatment-emergent events being similar to those seen in prior studies of regorafenib: hypertension, hand–foot skin reaction, fatigue, and diarrhea.

Cabozantinib

Other than targeting angiogenesis and immune-related targets, other targets are demonstrating some value too and seek to establish their role in the management strategy in the coming years. One such target has been the c-met pathway which has been a target of much interest in HCC in recent prior years, with strong preclinical support. Increased c-met activity can initiate, drive, or contribute to the development and progression of HCC. Aberrant c-met activity is associated with rapid tumor growth, aggressively invasive disease, and poor patient prognosis [22, 23]. C-met aberrations occur in approximately 50% of patients with HCC and can arise through gene mutation (4%), gene amplification (24%), increased mRNA expression (50%), and receptor overexpression (28%) [24–26]. Unfortunately, here again, we have seen a number of failed studies, until recently.

Tivantinib, an agent targeting the c-met kinase, was studied in a phase 3 METIV-HCC study, based on a prior phase 2 study. In the phase 2 study, c-met overexpression was noted to be associated with a more intriguing response rate to tivantinib. The subgroup of patients with MET overexpression showed an improvement in median OS from 3.8 to 7.2 months (HR 0.38, $p = 0.01$) In the METIV-HCC study, 340 patients with c-met-high HCC (staining intensity score ≥ 2 in $\geq 50\%$ of tumor cells), following treatment with sorafenib, were randomized to tivantinib or placebo. Median OS was 8.4 months in the tivantinib arm compared with 9.1 months in the placebo arm (HR = 0.97, $p = 0.81$). Median PFS was 2.1 months and 2 months, respectively (HR-0.96, $p = 0.81$). The JET-HCC study in Japan also recently demonstrated no significant clinical benefit with very similar results in patients randomized to tivantinib versus placebo in the second-line setting [27]. Median PFS was 2.8 versus 2.3 months (HR = 0.72, $p = 0.065$), respectively. Median OS was 9.9 versus 8.5 months (HR = 0.85).

In a counter argument about the necessity of c-met expression, another c-met inhibitor, cabozantinib, which targets c-met, in addition to RET, VEGFR2, AXL-1, and TIE-2, was studied in a phase 2 study [28] Based on these results, the phase 3 CELESTIAL trial randomized 707 patients with advanced HCC who had received at least one prior systemic therapy to cabozantinib or placebo regardless of c-met expression [29, 30••] (Table 2). The study demonstrated cabozantinib' s efficacy compared with placebo with a median OS of 10.2 vs 8.0 months, respectively (HR 0.76, $p = 0.0049$), and a median PFS of 5.2 vs 1.9 months (HR 0.44, $p < 0.001$). The drug was generally well tolerated with the more common adverse effects being hand–foot skin reaction, hypertension, increased aspartate aminotransferase, fatigue, and diarrhea.

Ramucirumab

Ramucirumab, targeting VEGFR2, was evaluated in the REACH study in which 565 patients with advanced HCC were randomized to ramucirumab or placebo [31]. Median OS for the ramucirumab group was 9.2 months versus 7.6 months

for the placebo group (HR 0.87; $p = 0.14$) [31]. In a prespecified subgroup of patients with a baseline α-fetoprotein (AFP) concentration of ≥ 400 ng/mL, median OS was 7.8 versus 4.2 months, respectively (HR 0.67; $p = 0.006$). On such basis, the follow-up multicenter phase 3 REACH-2 study was launched evaluating 292 patients with advanced HCC with baseline AFP > 400 ng/mL with progression during or after sorafenib, randomized to ramucirumab versus placebo. Ramucirumab significantly improved overall survival at 8.5 months, versus 7.3 months for placebo (HR 0.710; $p = 0.0199$). The 12- and 18-month OS rates both favored ramucirumab at 36.8% versus 30.3% and 24.5% versus 11.3%, respectively. Median PFS was also significantly improved for ramucirumab at 2.8 months versus 1.6 months (HR 0.452; $p < 0.0001$). Overall response rates were 4.6% and 1.1%, respectively, with disease.

Checkpoint inhibitors

Nivolumab

Of course, other options in the second-line setting also include immunotherapy agents. HCC, given its development in the setting of chronic inflammation and metabolic disorders, is nurtured in an immunosuppressive environment. This includes T cell exhaustion, rampant immunosuppressive signaling, and atypical immune checkpoint expression by tumor. Prior preclinical data have demonstrated that several immunologic mechanisms play a role in HCC development and progression, and in thwarting effective patients' antitumor immune surveillance capabilities [32]. The first study exploring the potential of immunotherapy in HCC was a small 20 patient phase 2 trial of the anti-CTLA4 tremelimumab in patients with heavily pretreated, advanced disease, many with impaired liver function [33]. This study demonstrated antitumor activity with a partial response rate of 17.6% and 58.8% with stable disease. One third of patients experienced clinical benefit for more than 12 months. Given such an immunosuppressive environment, and these initial phase 2 results demonstrating a manageable safety profile and preliminary evidence of

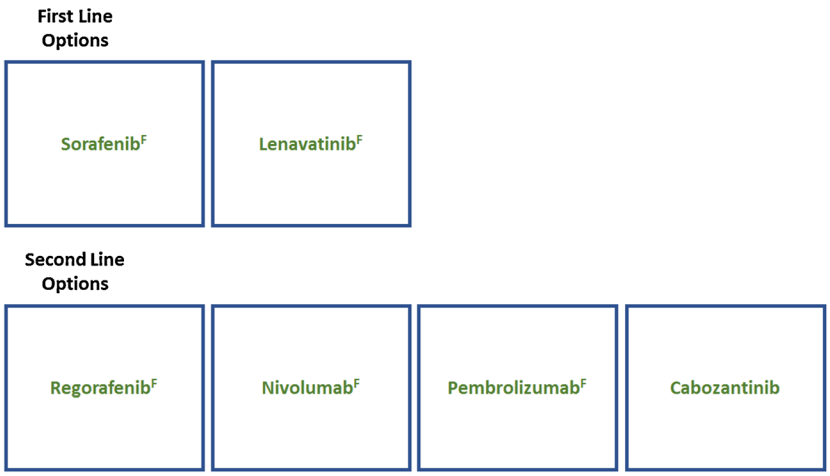

Fig. 2. Current landscape of therapeutics for HCC. Superscript letter F = FDA approved for HCC.

antitumor activity, further studies have gone on to establish immunotherapy agents as a standard in the landscape of therapy for patients with HCC. The CheckMate 040 study, a phase 1/2, open-label, dose escalation and expansion trial of nivolumab in 262 patients with advanced hepatocellular carcinoma with or without hepatitis C or B infection showed a manageable safety profile for nivolumab [20••] (Table 2). The ORR was approximately 20% in all patients treated with nivolumab, regardless of HBV or HCV infection status, or of whether patients had or had not previously been treated with sorafenib. Objective responses were seen regardless of PD-L1 expression on tumor cells, with PD-L1-positive patients demonstrating an objective response rate of 26% and PD-L1-negative patients demonstrating an objective response rate of 19%. Disease control rates ranged from 55 to 75% depending on the subgroup. Median duration of response was 9.9 months in the overall population, with responses ongoing in 67% of patients at the time of data cutoff. Median OS had not yet been reached at time of publication. Based on the CheckMate-040 data, the FDA granted accelerated approval to the drug, condition upon further trials being required to verify the clinical benefit of nivolumab for this indication. As such, nivolumab is also being evaluated in the first-line setting, compared to sorafenib, in the CheckMate 459 study (NCT02576509).

Pembrolizumab

In the KEYNOTE-224 trial, 104 patients with advanced HCC who had had progression on or intolerance to sorafenib received pembrolizumab 200 mg every 3 weeks [34••] (Table 2). For the primary endpoint, objective response rate, the study demonstrated that 17% of patients had responses and 44% of patients at stable disease. This response rate was similar across all etiology subgroups evaluated. Median duration of treatment had not been reached, with 77% of responding patients having a response duration ≥9 months. Median PFS was 4.9 months, and median OS was 12.9 months. Checkpoint inhibitors continue to be evaluated in a number of different forms, most commonly as combination therapies, as it seeks to move earlier in the treatment paradigm. One example is the HIMALAYA study which seeks to durvalumab (anti-PD-L1) with tremelimumab (anti-CTLA4) in the first-line setting, compared with durvalumab alone or sorafenib (NCT03298451).

Conclusion

HCC is one of the world's most prevalent malignancies and many cases are still diagnosed in an advanced stage. Glimmers of real hope with the advent of different therapeutic approaches have emerged and the progress of ongoing work should be followed closely.

In the realm of management of advanced HCC, sorafenib is no longer the sole kid on the block. Recent new FDA approvals of three new drugs have occurred in quick succession (Fig. 2). First-line therapy options now number

two, and with results of CheckMate-459 anxiously awaited, a game-changing third option may be on the horizon. Lenvatinib, the newest FDA approval for HCC patients, though non-inferior to sorafenib in terms of OS, did demonstrate significantly improved PFS and objective response rates, while also being generally well tolerated. Either option is a reasonable one or selection by the treating physician may depend on outcome priorities, physician comfort with the drug, and the patient's underlying liver disease including a consideration of hepatitis C status based on prior data discussed. Second-line options are also now plenty. Regorafenib garnered approval after it demonstrated improvements in OS and PFS, in addition to significant improvements in survival for the sequence of sorafenib followed by regorafenib. Nivolumab was conditionally approved on the basis of significant and promising survival outcomes, in addition to a very pleasing safety profile. While these agents provide a myriad of opportunities and options for our patients, many questions remain to be addressed. The data on each is reported in cohorts of patients who had prior sorafenib therapy, not lenvatinib. The choice of agent used in the second-line setting should again be based upon physician comfort with the drug, the patient's underlying liver disease, and patient choice after education about the data and safety profile. The most pressing challenge will be the optimal sequencing of first-line and second-line agents. Intense correlative efforts will also be needed to elucidate predictive biomarkers and evidence-based sequencing pathways.

Finally, the impact of various combinations of agents in the advanced disease setting is already being investigated. These include many studies involving immunotherapies such as the HIMALAYA trial (NCT03298451) evaluating durvalumab and tremelimumab in the first-line setting compared with sorafenib; the IMbrave 50 trial (NCT03434379) investigating atezolizumab and bevacizumab in the first-line setting compared with sorafenib; and the PHOCUS trial (NCT02562755) evaluating PexaVec followed by sorafenib versus Sorafenib alone. Exciting combinations are also being explored in earlier stages of disease, including evaulations of locoregional therapies such as chemoembolization or radioembolization with immunotherapies. These ongoing evaluations will certainly go a long way to informing us regarding the best management strategies for patients with HCC, but will undoubtedly introduce questions. Though great strides have been made, significant improvements are still needed and yet to come.

Compliance with Ethical Standards

Conflict of Interest

Kabir Mody has received research funding from Agios, Senwha Biosciences, Taiho, ArQule, Astra Zeneca, Genentech, Incyte, Tracon Pharmaceuticals, Medimmune, and Puma Biotechnology; and has received compensation from AstraZeneca, Bayer, Celgene, Eisai, Exelixis, Merrimack, and Vicus for service as a consultant.

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

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