CURRENT ONCOLOGY
A Canadian Cancer Research Journal

REVIEW ARTICLE

Non-immunotherapy options for the first-line management of hepatocellular carcinoma: exploring the evolving role of sorafenib and lenvatinib in advanced disease

S. Perera MD PhD,*† D. Kelly MB BCh BAO MRCPI,*† and G.M. O'Kane MB BCh BAO MD MRCPI*†

ABSTRACT

The results of the SHARP trial established sorafenib, a tyrosine kinase inhibitor (TKI), as the sole first-line treatment option in advanced hepatocellular carcinoma (HCC) for more than a decade. In 2020, there has been a surge in new therapies for HCC, including immunotherapeutic strategies and the approval of a number of novel TKIs. In addition to sorafenib, lenvatinib and combination atezolizumab–bevacizumab now represent standard first-line treatment options. As those systemic therapy options begin to be better utilized, assurance of adequate liver function and optimal timing are required to improve patient outcomes. Furthermore, sequencing of the agents will have to be carefully tailored, given the increasing armamentarium of choices. Here, we discuss the role of lenvatinib and sorafenib in the first-line management of HCC.

Key Words Hepatocellular carcinoma, immunotherapy, checkpoint inhibitors, nivolumab, pembrolizumab, atezolizumab, lenvatinib, sorafenib, systemic therapy, tyrosine kinase inhibitors

Curr Oncol. 2020 November:27(S3)165–172 www.current-oncology.com

INTRODUCTION

Globally, hepatocellular carcinoma (HCC) accounts for more than 745,000 deaths per year, and its incidence has been rising in Canada[1]. From 2003–2007 to 2028–2032, the Canadian age-standardized incidence rates for liver cancer are projected to increase by 43% in men and by 15% in women[2]. Hepatocellular carcinoma usually arises in the setting of chronic liver disease and cirrhosis, with varying causes of liver disease being linked to different geographic regions[3]. The overall incidence of cirrhosis in Canada is 89.6 per 100,000 person–years, with the most common cause being viral hepatitis, followed by non-alcoholic fatty liver disease[4]. Modelling suggests that by 2030, there will be 9,305,000 cases of non-alcoholic fatty liver disease associated with a 95% increase in HCC[5]. That increasing trend of HCC related to non-alcoholic fatty liver disease is expected to negate the gains from hepatitis B vaccination[6], indicating a clear need for continued research investment in this disease.

The treatment of HCC can be divided into surgical approaches (resection and transplantation) and nonsurgical approaches, including locoregional therapies (LRTs) and systemic therapies. The most widely accepted algorithm to direct treatment options and provide prognostic information remains the Barcelona Clinic Liver Cancer (BCLC) staging system, which incorporates both Childs–Pugh liver function and performance status. Early-stage disease (BCLC 0/A) represents patients who can be cured with surgical and nonsurgical approaches such as radiofrequency ablation. In a more advanced stage (BCLC C), in which major vascular invasion or extrahepatic spread is evident, systemic treatment is indicated. Most controversies arise from the management of heterogeneous intermediate-stage disease (BCLC B), in which patients have multinodular disease, with varying disease burden and liver function. As a result, those patients could be eligible for liver transplantation or LRTs, most commonly transarterial chemoembolization (TACE)[7,8]. Historically, patients in that group transitioned to systemic treatment only at failure of LRT or when LRT is contraindicated; however, the treatments in this cohort of patients are rapidly evolving.

DISCUSSION

Pathogenesis of HCC and Its Influence on Treatment

A complete overview of the molecular pathogeneses of HCC is beyond the scope of this article, but we aim to highlight

Correspondence to: Grainne M. O'Kane, University of Toronto, 700 University Avenue, 7th Floor, Room 7-712, Toronto, Ontario M5G 1Z5.
E-mail: grainne.o'kane@uhn.ca ■ **DOI:** https://doi.org/10.3747/co.27.7159

features of HCC that are important considerations for the development of effective therapeutic strategies. The pathogenesis of advanced HCC is a multistep process associated with genomic instability, copy-number alterations, mutations of protein coding genes, epigenetic and transcriptomic alterations, and adapted cell metabolism. Previous work has demonstrated alterations in specific genes that are for the most part nontargetable and that include amplifications in oncogenes such as *MET, MYC, TERT, CCND1, FGF19,* and deletions in tumour-suppressor genes such as *PTEN, TP53, CDKN2A,* and *CDKN2B*[9].

Dysregulation of cell signalling pathways—including the vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and Wnt pathways—is essential in HCC development and progression[10]. Most of the tyrosine kinase inhibitors (TKIs) approved in HCC target the VEGF pathway and therefore angiogenesis, a pathway critical in the pathogenesis of this hypervascular tumour[11]. The FGF19/FGF receptor 4 signalling pathway is further associated with cell proliferation, differentiation, and tissue repair; and mutated FGF receptor 4 causes increased local growth and metastasis. Crosstalk between FGF2 and VEGF-A is evident in the early stages of HCC growth[12–14]. Activation of FGF19/FGF receptor 4 leads to downstream signalling, which initiates the Ras/Raf/ERK1/2/MAPK and PI3K/AKT pathways involved in tumour proliferation and replicative immortality. Notably, lenvatinib targets receptors of FGF receptors 1–4 together with VEGF1–3, platelet-derived growth factor receptor α, RET, and KIT[15]. Sorafenib, on the other hand, is a multikinase inhibitor targeting mainly the VEGF1–3 and downstream Raf pathways. Additionally, recognizing the potential targets for TKI resistance is important. For example, sorafenib resistance has been linked to the activation of oncogenic AKT[16].

Not unexpectedly, many hallmarks of inflammation have been detected in HCC, including increased stromal matrix stiffness and increased expression of pro-inflammatory cytokines (interleukin 6)[17,18]. The immune landscape of HCC has a robust suppressive component. "Exhaustion" of antitumour immunity occurs and can lead to tumour tolerance and disease progression. The HCC tumour microenvironment, the accumulation of immunosuppressive cell populations defective in antigen-presenting, and inhibitory receptor–ligand pathways all contribute to immune evasion. The degree of immunosuppression in the tumour microenvironment reflects a worse prognosis in patients with HCC[19]. Understanding the crosstalk between signalling pathways, molecular alterations, and the tumour microenvironment is likely to be critical to further drug development in HCC.

When Should the Oncologist Consider Systemic Treatment?

Systemic therapy is standard for individuals with advanced-stage HCC (BCLC C) who have a good performance status (Eastern Cooperative Oncology Group 0–2) and well-compensated liver function (Child–Pugh A). In patients with intermediate-stage disease, systemic treatment should be considered when the disease becomes refractory to LRTs such as TACE or when patients are LRT-ineligible from the outset. Chemoembolization became an established practice after two randomized trials demonstrated 2-year survival rates of 63% and 31%[7,20]. A subsequent meta-analysis confirmed the superiority of TACE compared with placebo or other approaches, and the BCLC guidelines recommending TACE for intermediate disease have therefore been endorsed by the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, and the European Society for Medical Oncology. A systematic review of 34,137 patients treated with TACE documented a median overall survival (OS) of 19.4 months [95% confidence interval (CI): 16.2 months to 22.6 months][21]. The heterogeneity in patients treated with TACE has led to the development of several prognostic scores based on liver function and tumour burden that attempt to determine who might benefit most. They include the ALBI (albumin–bilirubin) grade, the HAP (hepatoma arterial embolization prognostic) score, the Kinki criteria, and the up-to-seven criteria[22–25]. However, none are currently in use in clinical practice. The decision for TACE or other LRTs in patients with intermediate-stage disease should always take place after multidisciplinary discussion.

Aside from identifying patients who might not benefit from upfront TACE, identifying those with TACE-refractory disease is critical. A prospective international trial characterizing the use of TACE in a real-world setting (OPTIMIS) found that, in patients who became TACE-ineligible, survival was superior for those who received sorafenib (9%) compared with those who continued TACE (median OS: 16.2 months vs. 12.1 months)[26]. The definition of "TACE-refractory" was reached by consensus as 2 or more consecutive insufficient responses of the treated tumour, or clear evidence on computed tomography or magnetic resonance imaging of consecutive progression at 1–3 months after adequately performed TACE. Additionally, evidence of continuous elevation of tumour markers after TACE, the appearance of vascular invasion, or extrahepatic spread also meet the criteria for TACE refractoriness[27]. It is clear that timely and appropriate commencement of systemic therapy is critical to optimize patient outcomes.

TKIs for the Treatment of HCC

In the landmark phase III SHARP trial, median OS was 10.7 months in the sorafenib group and 7.9 months in the placebo group, with a hazard ratio (HR) of 0.69 (95% CI: 0.55 to 0.87; $p < 0.001$)[28]. The median time to symptomatic progression was 4.1 months for sorafenib compared with 4.9 months for placebo (HR: 1.08; 95% CI: 0.88 to 1.31). Of the 299 patients included in the sorafenib arm, 244 (82%) had BCLC stage C disease. Notably, only 2% of patients receiving sorafenib, compared with 1% of patients receiving placebo, experienced a partial response according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumors 1.1). No complete responses were seen in the study. The almost 3-month improvement in survival came at the cost of increased adverse events: a dose reduction or interruption was required in 26% and 44% of patients in the sorafenib group and in 7% and 30% of patients in the placebo group respectively. The most frequent adverse events leading to dose reductions in the sorafenib group were diarrhea (8%), hand–foot skin reaction (5%), and rash or desquamation (3%). Drug-related adverse events leading to permanent treatment discontinuation occurred in 11% of the sorafenib

group and in 5% of the placebo group. Shortly thereafter, the Asia–Pacific study, which evaluated sorafenib in a predominantly Asian population, demonstrated a similar OS benefit[29]. The median OS in that study was 6.5 months in those who received sorafenib and 4.2 months in those who received placebo (HR: 0.68; 95% CI: 0.50 to 0.93; $p = 0{\cdot}014$), highlighting the poorer outcomes in patients of Asian ethnicity, regardless of treatment arm.

Recognition of the side effects of sorafenib and the need for dose modifications has led to improved experiences with this TKI. In a retrospective analysis, patients initiated on a reduced dose of sorafenib demonstrated no significant differences in OS after propensity score matching and adjustment for potential confounders[30]. Furthermore, the study found that starting patients at a lower dose of sorafenib was associated with reduced pill burden, lower treatment costs, and a trend toward a decreased rate of drug discontinuation.

Since the SHARP trial, several studies have attempted to improve outcomes in HCC. Table I summarizes the key findings of all phase III studies comparing sorafenib with other treatments in the first-line setting. The improvements in the objective response rates seen with sorafenib over the years partly reflects the creation of the modified RECIST (mRECIST) in 2010. The mRECIST incorporates the concept of viable tumour, which is defined as the portions of a tumour showing arterial enhancement[43], a change that has led to an improvement in the sensitivity to quantify tumour response with targeted therapies in HCC[44].

It was only in 2018 that the phase III randomized controlled REFLECT trial demonstrated the noninferiority of lenvatinib compared with sorafenib[37]. The median OS was 13.6 months for patients treated with lenvatinib compared with 12.3 months for patients treated with sorafenib (HR: 0.92; 95% CI: 0.79 to 1.06). The PFS (7.4 months vs. 3.7 months)

TABLE I Summary of phase III trials in the first-line management of advanced hepatocellular carcinoma (comparison with sorafenib)

Reference (trial name)	Study treatment	ORR (%)	Progression-free survival (months)[a]			Overall survival (months)[a]		
			Median	HR	95% CI	Median	HR	95% CI
Llovet *et al.*, 2008[28] (SHARP)	Sorafenib	2.0	NR			10.7	**0.69**	**0.55 to 0.87**
	Placebo	1.0	NR			7.9		
Cheng *et al.*, 2009[29] (Asia–Pacific)	Sorafenib	3.3	NR			6.5	**0.68**	**0.50 to 0.93**
	Placebo	1.3	NR			4.2		
Cheng *et al.*, 2013[31] (SUN1170)	Sunitinib	6.6	3.6	1.13	0.99 to 1.30	7.9	1.30	1.13 to 1.50
	Sorafenib	6.1	3			10.2		
Johnson *et al.*, 2013[32] (BRISK-FL)	Brivanib	12	NR			9.5	1.07	0.94 to 1.23[b]
	Sorafenib	9	NR			9.9		
Cainap *et al.*, 2015[33] (LIGHT)	Linifanib	10.1	4.2	**0.81**	**0.70 to 0.95**	9.1	1.05	0.90 to 1.22
	Sorafenib	6.1	2.9			9.8		
Zhu *et al.*, 2015[34] (SEARCH)	Sorafenib–erlotinib	6.6	NR			9.5	0.93	0.78 to 1.11
	Sorafenib	3.9	NR			8.5		
Vilgrain *et al.*, 2017[35] (SARAH)	^{90}Y microspheres	19.0	4.1	1.03	0.85 to 1.25	8	1.15	0.94 to 1.41
	Sorafenib	12.0	3.7			9.9		
Chow *et al.*, 2018[36] (SIRveNIB)	^{90}Y microspheres	16.5	5.8	0.89	0.70 to 1.10	8.8	1.12	0.90 to 1.40
	Sorafenib	1.7	5.1			10		
Kudo *et al.*, 2018[37] (REFLECT)	Lenvatinib	24.1	7.4	**0.66**	**0.57 to 0.77**	13.6	**0.92**	**0.79 to 1.06**
	Sorafenib	9.2	3.7			12.3		
Kudo *et al.*, 2018[38] (SILIUS)	Sorafenib–HAIC	36.3	4.8	0.75	0.57 to 1.00	11.8	1.01	0.74 to 1.37
	Sorafenib	17.5	3.5			11.5		
Abou-Alfa *et al.*, 2019[39] (CALGB80802)	Sorafenib–doxorubicin	10	4.0	0.93	0.75 to 1.16	9.3	1.05	0.83 to 1.31
	Sorafenib	5.4	3.7			9.4		
Yau *et al.*, 2019[40] (CheckMate 459)	Nivolumab	15	NR			16.4	0.85	0.72 to 1.02
	Sorafenib	7	NR			14.7		
Bi *et al.*, 2020[41] (ZGDH3)	Donafenib	4.6	3.7	NR		12	**0.84**	**0.706 to 0.996**[b]
	Sorafenib	2.7	3.6			10.1		
Finn *et al.*, 2020[42] (IMbrave150)	Atezolizumab–bevacizumab	33.2	6.8	**0.59**	**0.47 to 0.76**	NR		
	Sorafenib	13.3	4.3			NR		

[a] Statistically significant results appear in boldface type.
[b] Overall survival for the intention-to-treat population.

ORR = objective response rate, per the modified Response Evaluation Criteria in Solid Tumors; HR = hazard ratio; CI = confidence interval; NR = not reported; HAIC = hepatic arterial infusion chemotherapy.

and the time to progression (8.9 months vs. 3.7 months) were both higher with lenvatinib than with sorafenib (Table I). Advanced or BCLC C HCC accounted for 374 patients (78%) in the lenvatinib arm, and 384 patients (81%) in the sorafenib arm.

Sorafenib or Lenvatinib in the Setting of Advanced Disease: Which Option to Choose?

The availability of both sorafenib and lenvatinib as potential treatment options has provided a choice of 2 TKIs in the first-line setting. In the REFLECT trial, the response rate was 24% for lenvatinib and 9% for sorafenib per mRECIST[37]. That advantage persisted even with the use of the RECIST 1.1. The disease control rates were 75.5% and 60.5% respectively, and 15% of patients in the lenvatinib arm and 31% in the sorafenib arm experienced disease progression. The higher response rates and improved disease control seen with lenvatinib might therefore present reasons to consider choosing first-line lenvatinib in the clinical setting.

Patients receiving lenvatinib experienced more hypertension, proteinuria, dysphonia, and hypothyroidism, but fewer instances of hand–foot skin reactions, diarrhea, and alopecia. In the lenvatinib and sorafenib arms, treatment-related treatment-emergent adverse events led to drug interruption in 40% compared with 32% of patients, dose reduction in 37% compared with 38%, and drug withdrawal in 9% compared with 7%. When adjusted for treatment duration, which was 1.5 times longer in the lenvatinib arm, almost all adverse event episodes were comparable for the lenvatinib and sorafenib arms.

Baseline quality-of-life scores on the health questionnaires in the REFLECT study were similar in the lenvatinib and sorafenib treatment groups. However, the analysis of time to clinically meaningful deterioration showed that role functioning (nominal $p = 0.0193$), pain (nominal $p = 0.0105$), and diarrhea (nominal $p < 0.0001$) on the European Organisation for Research and Treatment of Cancer's 30-question core quality of life questionnaire, as well as nutrition (nominal $p = 0.0113$) and body image (nominal $p = 0.0051$) on its 18-question HCC-specific questionnaire, were observed earlier in patients receiving sorafenib than in those receiving lenvatinib.

Furthermore, the risk of hypertension, the most common high-grade adverse effect seen with lenvatinib can often be appropriately managed with careful monitoring. However, in patients with poorly controlled hypertension, sorafenib might be a better choice of therapy. Notably, a recent multicentre retrospective study of patients started on first-line lenvatinib in Japan showed that OS was improved in patients who developed hypertension and hand–foot skin reaction compared with those who did not experience those adverse effects[45]. Consistent with that observation, an exploratory *post hoc* analysis of the REFLECT trial showed that, in patients treated with lenvatinib, the development of any of the adverse effects of hypertension, diarrhea, proteinuria, and hypothyroidism was associated with longer OS[46], and that hypertension was most strongly associated with better OS (HR: 0.64; 95% CI: 0.52 to 0.80; $p = 0.00005$).

In keeping with REFLECT's phase 2 protocol, the study did not enrol patients with more than 50% liver involvement or those whose tumours had invaded the main portal vein[37]. Those factors were not exclusion criteria in the SHARP study and might constitute grounds for considering sorafenib in such patients[28]. However, a single-institute retrospective analysis evaluated outcomes with lenvatinib or sorafenib in patients with major portal vein thrombosis[47], demonstrating an improved objective response rate, disease control rate, and, importantly, median OS in patients treated with lenvatinib compared with those treated with sorafenib. Those results suggest that lenvatinib can potentially be safely and effectively used in that subset of patients.

Initial Treatment of Intermediate-Stage Disease

As already described, there is increasing interest in initiating systemic treatment earlier, accompanied by a need for identifying predictive biomarkers to determine which patients are unlikely to benefit from TACE. Given the higher response rate seen with lenvatinib, such an approach is being further explored. The Kinki criteria classify patients with BCLC stage B (intermediate HCC) into the substages B1, B2, and B3[24]. Previous studies have shown that stage B2 cancers might not benefit from TACE and are more likely to become TACE-refractory[48]. In a recent proof-of-concept study in patients with Child–Pugh A liver function who were beyond the up-to-seven criteria [that is, the sum of the diameter (in centimetres) of the largest tumour plus the total number of tumours exceeds 7], treatment with lenvatinib (compared with TACE) was associated with a significantly higher objective response rate (73.3% vs. 33.3%, $p < 0.001$) and longer median PFS (16.0 months vs. 3.0 months, $p < 0.001$)[49]. The OS was also significantly longer in the lenvatinib group than in the TACE group (37.9 months vs. 21.3 months; HR: 0.48; $p < 0.01$).

Child–Pugh B Disease

Trials of sorafenib and lenvatinib both primarily included patients classified Child–Pugh A. The prospective GIDEON study demonstrated that median OS was 13.6 months in patients classed Child–Pugh A and 5.2 months in those classed Child–Pugh B[50]. Nevertheless, treatment-related adverse effects and discontinuation rates were similar in the two groups. An analysis of the U.S. Surveillance, Epidemiology, and End Results–Medicare database found that sorafenib use was associated with a survival benefit for patients with decompensated cirrhosis (HR: 0.61; 95% CI: 0.47 to 0.79); however, the median benefit was 31 days and was not cost-effective, given its incremental cost-effectiveness ratio of $224,914 per life–year gained[51]. Taken together, those data suggest that sorafenib can potentially be used in select patients classed Child–Pugh B, with careful monitoring for further hepatic decompensation. Small studies have also suggested a role for lenvatinib in highly selected patients with Child–Pugh B disease[52].

Other First-Line TKIs

More recently, donafenib, a novel multikinase inhibitor, became the first TKI to demonstrate superiority when compared with sorafenib in the first-line setting in HCC[41]. The phase II/III ZGDH3 study enrolled only patients from China, most of whom had HCC in the setting of hepatitis B. Nevertheless, donafenib has been the only TKI to be associated with a median OS superior to that with

sorafenib in both the full analysis set (12.1 months vs. 10.3 months; HR: 0.831; 95% CI: 0.699 to 0.988; $p = 0.0363$) and in the intention-to-treat population (12.0 months vs. 10.1 months; HR: 0.839; 95% CI: 0.706 to 0.996; $p = 0.0446$). Grade 3 or worse adverse events occurred in 57.4% of the donafenib treatment group and in 67.5% of the sorafenib treatment group ($p = 0.0082$). Common adverse effects with donafenib included hand–foot skin reaction (50.5%), aspartate aminotransferase elevation (40.5%), serum bilirubin elevation (39.0%), platelet count reduction (37.8%), and diarrhea (36.6%). Full study results and regulatory approval for donafenib are currently pending. Cabozantinib is also currently being evaluated in the first-line setting, but in combination with atezolizumab, in a comparison with single-agent sorafenib (see NCT03755791 at https://ClinicalTrials.gov/)[53].

When to Consider TKIs Over Immune Checkpoint Inhibitors in the Front-Line Setting for HCC

Immune checkpoint inhibitors (ICIs) have rapidly transformed the treatment landscape for most common malignancies. Single-agent ICIs have shown promise in the treatment of HCC, with several trials demonstrating efficacy in the second-line setting, after sorafenib[54,55]. The recently published IMbrave150 trial[42], which demonstrated the superiority of atezolizumab (a PD-L1 inhibitor) and bevacizumab (an anti-VEGF monoclonal antibody) compared with single-agent sorafenib, has revolutionized the approach to HCC management. Its estimated HR for progression or death at 12 months was 0.58 (95% CI: 0.42 to 0.79; $p < 0.001$) for the atezolizumab–bevacizumab arm compared with the sorafenib arm. IMbrave150 also demonstrated a significant improvement in PFS of almost 2.5 months (6.8 months for atezolizumab–bevacizumab vs. 4.3 months for sorafenib; HR: 0.59: 95% CI: 0.47 to 0.76).The PFS for lenvatinib in the REFLECT trial was comparable at 7.4 months[37]. However, serious adverse events occurred more frequently with atezolizumab–bevacizumab (38%) than with sorafenib (30.8%). Notably, the incidence of upper gastrointestinal bleeding observed in the atezolizumab–bevacizumab arm was 7% compared with 4.5% in the sorafenib arm.

Moreover, a number of eligibility criteria are important to highlight. Patients who have a history of an autoimmune disorder cannot receive ICIs. Furthermore, because bevacizumab is known to be associated with an increased risk of bleeding, IMbrave150 required all patients undergo esophagogastroduodenoscopy within 6 months of their treatment start date to screen for and treat varices. During the current COVID-19 pandemic, access to such diagnostics has been limited[56]. Patients considered to be at high risk of bleeding were excluded from the study, and patients were also required to have had a platelet count of 75×10^9/L or greater, similar to the eligibility criteria in the REFLECT trial. The IMbrave150 study also required that patients with hepatitis B be started on appropriate treatment at least 14 days before study entry and that the level of hepatitis B DNA be below 500 IU/mL before initiation of study treatment. That requirement for suppression of the hepatitis B DNA level could delay and potentially prevent treatment in a subgroup of patients.

Another important distinction between the two study populations are the percentages of older patients included in the study. In IMbrave150, patients more than 65 years of age constituted 48% of the atezolizumab–bevacizumab group and 55% of the sorafenib group.[42] The oldest patient enrolled in the study was 71 years of age. In contrast, in REFLECT, 43% of all patients were older than 65 years, and 12% of the patients receiving lenvatinib and 14% of those receiving sorafenib were more than 75 years of age, with the maximum age being 88.[37]

Within Canada, transplantation remains an important curative option for a number of patients with extended Toronto criteria (includes intermediate-stage patients)[57]. Such patients are eligible to be listed for transplantation, and bridging therapies with TACE are typically used. A recent randomized clinical trial demonstrated improvements in tumour event-free survival and OS for liver transplantation compared with non-transplantation therapies in patients with HCC beyond the Milan criteria who had been treated using effective and sustained downstaging strategies[58]. The study allowed systemic therapies such as sorafenib in addition to LRTs to enable tumour downstaging. Downstaging to transplantation is therefore another important consideration that might necessitate the upfront use of TKIs.

Importantly, patients with a history of transplantation were excluded from IMbrave150 given the use of ICIs in the protocol. While the REFLECT trial also excluded patients with a history of transplantation, TKIs have been successfully used to treat patients in the post-transplantation setting[59]. Therefore, for the subset of patients who develop recurrent disease ineligible for local therapies after liver transplantation, TKIs remain the only potential treatment option at present.

Future Directions in the Treatment of HCC and the Need for Biomarkers

The identification of biomarkers that predict response to TKIs will be important for the selection of patients more likely to benefit from TKI therapy, while at the same time minimizing exposure to treatment-related toxicities. Analysis of plasma biomarkers from the SHARP study population did not identify any significant predictors of sorafenib response[60]. However, in the sorafenib cohort, a trend toward enhanced survival with sorafenib was observed in patients with high soluble c-KIT or a low hepatocyte growth factor concentration at baseline. Serum biomarker analysis from the REFLECT study suggested that, in patients with high baseline FGF21, median OS was longer for treatment with lenvatinib than with sorafenib (10.9 months vs. 6.8 months; HR: 0.528; 95% CI: 0.328 to 0.849; $p = 0.0075$)[61]. But none of those markers have been validated in prospective studies to date. Additionally, given that tumour mutational burden and PD-L1 level are not predictive of treatment response in HCC, recognition of markers of response to ICIs will enable clinicians to more confidently navigate therapies for patients.

An exploratory pooled analysis of data from two phase III studies, SHARP and Asia-Pacific, demonstrated that sorafenib was significantly more effective in patients with hepatitis C virus infection, liver-only disease, and

a low neutrophil-to-leucocyte ratio[62]. The authors proposed that the predictive effect of hepatitis C infection is likely secondary to persistent inflammation as a result of ongoing viral replication, a situation unlikely to arise in patients with hepatitis B given current therapies. Further studies are needed to determine if those or other clinical and biochemical characteristics are indicative of improved response to lenvatinib or the new TKIs.

As highlighted earlier, the pathogenesis of HCC is variable, with alterations present in multiple genes and signalling pathways. A more personalized approach and an improved understanding of each patient's tumour molecular profile will aid in decision-making. Additionally, the combination of TKIs and ICIs offers promise in the management of HCC. The early phase IB results of lenvatinib–pembrolizumab treatment have shown response rates of 46% by mRECIST[63], and the results from the phase III LEAP-002 trial (see NCT03713593 at https://ClinicalTrials.gov/)[64] are eagerly anticipated.

Another important consideration in deciding between TKI therapies is cost. A recent cost–utility analysis from Canada showed similar clinical effectiveness for lenvatinib at a cost lower than that for sorafenib[65]. The study suggested that the use of lenvatinib could lead to savings of approximately $23,719 per patient with advanced HCC. Similarly, an analysis from Japan demonstrated the cost-effectiveness of lenvatinib compared with sorafenib in the first-line treatment of unresectable HCC[66].

SUMMARY

With the rapid growth in the armamentarium of systemic therapies available to treat HCC, the role of sorafenib is becoming increasingly limited. Lenvatinib and atezolizumab–bevacizumab have been established as additional first-line standards, and the results seen with TKI–ICI combinations are promising. Important clinical factors can dictate the choice between lenvatinib, sorafenib, and atezolizumab–bevacizumab. Given that an opportunity to sequence agents is now available, better biomarkers of response must be established, while also considering the side-effect profile and cost of those agents.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: GMO has received honoraria from Eisai and Roche. The remaining authors have no conflicts to disclose.

AUTHOR AFFILIATIONS

*Princess Margaret Cancer Centre, University Health Network, and †Division of Medical Oncology and Hematology, Department of Medicine, University of Toronto, Toronto, ON.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, *et al.* Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359–86.
2. Xie L, Semenciw R, Mery L. Cancer incidence in Canada: trends and projections (1983–2032). *Health Promot Chronic Dis Prev Can* 2015;35(suppl 1):2–186.
3. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003;362:1907–17.
4. Flemming JA, Dewit Y, Mah JM, *et al.* Incidence of cirrhosis in young birth cohorts in Canada from 1997 to 2016: a retrospective population-based study. *Lancet Gastroenterol Hepatol* 2019;4:217–26.
5. Swain MG, Ramji A, Patel K, *et al.* Burden of nonalcoholic fatty liver disease in Canada, 2019–2030: a modelling study. *CMAJ Open* 2020;8:E429–36.
6. Choo SP, Tan WL, Goh BKP, Tai WM, Zhu AX. Comparison of hepatocellular carcinoma in Eastern versus Western populations. *Cancer* 2016;122:3430–46.
7. Llovet JM, Real MI, Montana X, *et al.* Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002;359:1734–9.
8. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology* 2003;37:429–42.
9. Shibata T, Aburatani H. Exploration of liver cancer genomes. *Nat Rev Gastroenterol Hepatol* 2014;11:340–9.
10. Khemlina G, Ikeda S, Kurzrock R. The biology of hepatocellular carcinoma: implications for genomic and immune therapies. *Mol Cancer* 2017;16:149.
11. Morse MA, Sun W, Kim R, *et al.* The role of angiogenesis in hepatocellular carcinoma. *Clin Cancer Res* 2019;25:912–20.
12. Greenman C, Stephens P, Smith R, *et al.* Patterns of somatic mutation in human cancer genomes. *Nature* 2007;446:153–8.
13. Wilkie AO, Morriss-Kay GM, Jones EY, Heath JK. Functions of fibroblast growth factors and their receptors. *Curr Biol* 1995;5:500–7.
14. Tsunoda S, Nakamura T, Sakurai H, Saiki I. Fibroblast growth factor-2–induced host stroma reaction during initial tumor growth promotes progression of mouse melanoma via vascular endothelial growth factor A–dependent neovascularization. *Cancer Sci* 2007;98:541–8.
15. Yamamoto Y, Matsui J, Matsushima T, *et al.* Lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, shows broad antitumour activity in human tumor xenograft models associated with microvessel density and pericyte coverage. *Vasc Cell* 2014;6:18.
16. Zhai B, Hu F, Jiang X, *et al.* Inhibition of AKT reverses the acquired resistance to sorafenib by switching protective autophagy to autophagic cell death in hepatocellular carcinoma. *Mol Cancer Ther* 2014;13:1589–98.
17. Schrader J, Gordon-Walker TT, Aucott RL, *et al.* Matrix stiffness modulates proliferation, chemotherapeutic response, and dormancy in hepatocellular carcinoma cells. *Hepatology* 2011;53:1192–205.
18. Wan S, Zhao E, Kryczek I, *et al.* Tumor-associated macrophages produce interleukin 6 and signal via STAT3 to promote expansion of human hepatocellular carcinoma stem cells. *Gastroenterology* 2014;147:1393–404.
19. Fu Y, Liu S, Zeng S, Shen H. From bench to bed: the tumor immune microenvironment and current immunotherapeutic strategies for hepatocellular carcinoma. *J Exp Clin Cancer Res* 2019;38:396.
20. Lo CM, Ngan H, Tso WK, *et al.* Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002;35:1164–71.
21. Lencioni R, de Baere T, Soulen MC, Rilling W, Geschwind JFH. Lipiodol transarterial chemoembolization for hepatocellular carcinoma: a systematic review of efficacy and safety data. *Hepatology* 2016;64:106–16.
22. Johnson PJ, Berhane S, Kagebayashi C, *et al.* Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach—the ALBI grade. *J Clin Oncol* 2015;33:550–8.

23. Kadalayil L, Benini R, Pallan L, *et al.* A simple prognostic scoring system for patients receiving transarterial embolisation for hepatocellular cancer. *Ann Oncol* 2013;24:2565–70.
24. Kudo M, Arizumi T, Ueshima K, Sakuri T, Kitano M, Nishida N. Subclassification of BCLC B stage hepatocellular carcinoma and treatment strategies: proposal of modified Bolondi's subclassification (Kinki criteria). *Dig Dis* 2015;33:751–8.
25. Bolondi L, Burroughs A, Dufour JF, *et al.* Heterogeneity of patients with intermediate (BCLC B) hepatocellular carcinoma: proposal for a subclassification to facilitate treatment decisions. *Semin Liver Dis* 2012;32:348–59.
26. Kudo M, Raoul JL, Lee HC, *et al.* Deterioration of liver function after transarterial chemoembolization (TACE) in hepatocellular carcinoma (HCC): an exploratory analysis of OPTIMIS—an international observational study assessing the use of sorafenib after TACE [abstract 368]. *J Clin Oncol* 2018;36:. [Available online at: https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.4_suppl.368; cited 15 October 2020]
27. Kudo M, Matsui O, Izumi N, *et al.* Transarterial chemoembolization failure/refractoriness: JSH–LCSGJ criteria 2014 update. *Oncology* 2014;87(suppl 1):22–31.
28. Llovet JM, Ricci S, Mazzaferro V, *et al.* Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378–90.
29. Cheng AL, Kang YK, Chen Z, *et al.* Efficacy and safety of sorafenib in patients in the Asia–Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009;10:25–34.
30. Reiss KA, Yu S, Mamtani R, *et al.* Starting dose of sorafenib for the treatment of hepatocellular carcinoma: a retrospective, multi-institutional study. *J Clin Oncol* 2017;35:3575–81.
31. Cheng AL, Kang YK, Lin DY, *et al.* Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. *J Clin Oncol* 2013;31:4067–75.
32. Johnson PJ, Qin S, Park JW, *et al.* Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. *J Clin Oncol* 2013;31:3517–24.
33. Cainap C, Qin S, Huang WT, *et al.* Linifanib versus sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2015;33:172–9.
34. Zhu AX, Rosmorduc O, Jeffry Evans TR, *et al.* SEARCH: a phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2015;33:559–66.
35. Vilgrain V, Pereira H, Assenat E, *et al.* Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *Lancet Oncol* 2017;18:1624–36.
36. Chow PKH, Gandhi M, Tan SB, *et al.* SIRveNIB: selective internal radiation therapy versus sorafenib in Asia–Pacific patients with hepatocellular carcinoma. *J Clin Oncol* 2018;36:1913–21.
37. Kudo M, Finn RS, Qin S, *et al.* Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018;391:1163–73.
38. Kudo M, Ueshima K, Yokosuka O, *et al.* Sorafenib plus low-dose cisplatin and fluorouracil hepatic arterial infusion chemotherapy versus sorafenib alone in patients with advanced hepatocellular carcinoma (SILIUS): a randomised, open label, phase 3 trial. *Lancet Gastroenterol Hepatol* 2018;3:424–32.
39. Abou-Alfa GK, Shi Q, Knox JJ, *et al.* Assessment of treatment with sorafenib plus doxorubicin vs sorafenib alone in patients with advanced hepatocellular carcinoma: phase 3 CALGB 80802 randomized clinical trial. *JAMA Oncol* 2019;5:1582–8.
40. Yau T, Park JW, Finn RS, *et al.* CheckMate 459: a randomized, multi-center phase III study of nivolumab (NIVO) vs sorafenib (SOR) as first-line (1L) treatment in patients (pts) with advanced hepatocellular carcinoma (aHCC) [abstract 6572]. *Ann Oncol* 2019;30(suppl 5):v874–5.
41. Bi F, Qin S, Gu S, *et al.* Donafenib versus sorafenib as first-line therapy in advanced hepatocellular carcinoma: an open-label, randomized, multicenter phase II/III trial [abstract 4506]. *J Clin Oncol* 2020;38:. [Available online at: https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.4506; cited 15 October 2020]
42. Finn RS, Qin S, Ikeda M, *et al.* on behalf of the IMbrave150 investigators. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med* 2020;382:1894–905.
43. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010;30:52–60.
44. Llovet JM, Montal R, Villanueva A. Randomized trials and endpoints in advanced HCC: role of PFS as a surrogate of survival. *J Hepatol* 2019;70:1262–77.
45. Shimose S, Iwamoto H, Niizeki T, *et al.* Clinical significance of adverse events for patients with unresectable hepatocellular carcinoma treated with lenvatinib: a multicenter retrospective study. *Cancers (Basel)* 2020;12:1867.
46. Sung MW, Finn RS, Qin S, *et al.* Association between overall survival and adverse events with lenvatinib treatment in patients with hepatocellular carcinoma (REFLECT) [abstract 317]. *J Clin Oncol* 2019;37:. [Available online at: https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.4_suppl.317; cited 15 October 2020]
47. Kuzuya T, Ishigami M, Ito T, *et al.* Sorafenib vs. lenvatinib as first-line therapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis. *Anticancer Res* 2020;40:2283–90.
48. Arizumi T, Minami T, Chishina H, *et al.* Time to transcatheter arterial chemoembolization refractoriness in patients with hepatocellular carcinoma in Kinki criteria stages B1 and B2. *Dig Dis* 2017;35:589–97.
49. Kudo M, Ueshima K, Chan S, *et al.* Lenvatinib as an initial treatment in patients with intermediate-stage hepatocellular carcinoma beyond up-to-seven criteria and Child–Pugh A liver function: a proof-of-concept study. *Cancers (Basel)* 2019;11:1084.
50. Marrero JA, Kudo M, Venook AP, *et al.* Observational registry of sorafenib use in clinical practice across Child–Pugh subgroups: the GIDEON study. *J Hepatol* 2016;65:1140–7.
51. Parikh ND, Marshall VD, Singal AG, *et al.* Survival and cost-effectiveness of sorafenib therapy in advanced hepatocellular carcinoma: an analysis of the SEER–Medicare database. *Hepatology* 2017;65:122–33.
52. Komatsu S, Yano Y, Sofue K, *et al.* Assessment of lenvatinib treatment for unresectable hepatocellular carcinoma with liver cirrhosis. *HPB (Oxford)* 2020;22:1450–6.
53. Kelley RK, Cheng AL, Braiteh FS, *et al.* Phase 3 (COSMIC-312) study of cabozantinib (C) in combination with atezolizumab (A) versus sorafenib (S) in patients (pts) with advanced hepatocellular carcinoma (aHCC) who have not received previous systemic anticancer therapy [abstract TPS4157]. *J Clin Oncol* 2019;37:. [Available online at: https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.TPS4157; cited 15 October 2020]
54. Finn RS, Ryoo BY, Merle P, *et al.* Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial. *J Clin Oncol* 2020;38:193–202.
55. El-Khoueiry AB, Sangro B, Yau T, *et al.* Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040):

an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* 2017;389:2492–502.
56. Barry A, Apisarnthanarax S, O'Kane GM, *et al.* Management of primary hepatic malignancies during the COVID-19 pandemic: recommendations for risk mitigation from a multidisciplinary perspective. *Lancet Gastroenterol Hepatol* 2020;5:765–75.
57. Sapisochin G, Goldaracena N, Laurence JM, *et al.* The extended Toronto criteria for liver transplantation in patients with hepatocellular carcinoma: a prospective validation study. *Hepatology* 2016;64:2077–88.
58. Mazzaferro V, Citterio D, Bhoori S, *et al.* Liver transplantation in hepatocellular carcinoma after tumour downstaging (XXL): a randomised, controlled, phase 2b/3 trial. *Lancet Oncol* 2020; 21:947–56.
59. Siegel AB, El-Khoueiry AB, Finn RS, *et al.* Phase I trial of sorafenib following liver transplantation in patients with high-risk hepatocellular carcinoma. *Liver Cancer* 2015;4:115–25.
60. Llovet JM, Peña CE, Lathia CD, *et al.* Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. *Clin Cancer Res* 2012;18:2290–300.
61. Finn RS, Kodo M, Cheng AL, *et al.* Final analysis of serum biomarkers in patients (pts) from the phase III study of lenvatinib (LEN) vs sorafenib (SOR) in unresectable hepatocellular carcinoma (uHCC) [REFLECT]. *Ann Oncol* 2018;29(suppl 8):viii17–18.
62. Bruix J, Cheng AL, Meinhardt G, Nakajima K, De Sanctis Y, Llovet J. Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: analysis of two phase III studies. *J Hepatol* 2017;67:999–1008.
63. Finn RS, Ikeda M, Zhu AX, *et al.* Phase IB study of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma. *J Clin Oncol* 2020;38:2960–70.
64. Llovet JM, Kudo M, Cheng AL, *et al.* Lenvatinib (len) plus pembrolizumab (pembro) for the first-line treatment of patients (pts) with advanced hepatocellular carcinoma (HCC): Phase 3 LEAP-002 study [abstract TPS4152]. *J Clin Oncol* 2019;37:. [Available online at: https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.TPS4152; cited 15 October 2020]
65. Kim JJ, McFarlane T, Tully S, Wong WWL. Lenvatinib versus sorafenib as first-line treatment of unresectable hepatocellular carcinoma: a cost–utility analysis. *Oncologist* 2020;25:e512–19.
66. Kobayashi M, Kudo M, Izumi N, *et al.* Cost-effectiveness analysis of lenvatinib treatment for patients with unresectable hepatocellular carcinoma (uHCC) compared with sorafenib in Japan. *J Gastroenterol* 2019;54:558–70.