Perspective

Systemic treatment for hepatocellular carcinoma

Manushi Aggarwal [a,b,c], Abeer Arain [a,b,c], Zhaohui Jin [a,b,*]

[a] *Carle Cancer Center, Carle Foundation Hospital, 509 W. University Avenue, Urbana, IL 61801, USA*
[b] *Department of Internal Medicine, University of Illinois College of Medicine at Urbana-Champaign, Urbana, IL 61801, USA*

Abstract

Hepatocellular carcinoma (HCC) is one of the most common cancers with high mortality worldwide. Treatment options for patients with advanced stage HCC remain a great challenge. However, novel agents especially small molecule tyrosine kinase inhibitor and innovative immunotherapy demonstrate new promising therapeutic options for these patients. This review article summarizes systemic treatment options evaluated in HCC focusing on the most recently published data and ongoing studies.
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Introduction

Liver cancer is the fifth most common cancer in men and ninth most common cancer in women worldwide.[1] Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver (about 70%−85% of all liver cancers).[2] An estimated 42,220 new cases of liver cancer will be diagnosed in the United States in 2018.[3] The incidence rate of HCC is increasing in many parts of the world including the United States. The incidence rate increased by 3.1% per year from 2008 to 2012 and it is about 3 times more common in men than in women.[4]

HCC is an aggressive and lethal disease in general with the number of deaths per year close to its incidence worldwide.[5,6] The European Association for the Study of the Liver (EASL)−European Organization for Research on Treatment of Cancer (EORTC) Clinical Practice Guidelines report that HCC is a common cause of cancer-related deaths (692,000 cases per year), and accounts for 7% of all cancers throughout the world.[7] In the United States, the rate of HCC deaths appears to have increased by about 40% over the period 1990−2004, whereas the overall rate of cancer deaths has declined by about 18% during this same period. An estimated 30,200 liver cancer deaths will occur in the United States in the year 2018.[3]

HCC has a clear geographical distribution, with the highest incidence rates in East Asia and sub-Saharan Africa, where around 85% of cases occur.[8] This

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* Corresponding author. Carle Cancer Center, Carle Foundation Hospital, 509 W. University Avenue, Urbana, IL, 61801, USA.
E-mail address: Zhaohui.jin@carle.com (Z. Jin).
[c] The first two authors contributed equally to this work.

distribution pattern is considered to be reflective of the high prevalence of hepatitis B virus (HBV) infection and associated liver cirrhosis.[6] Worldwide, approximately 54% of HCC cases are attributed to HBV infection (which affects 400 million people globally) while 31% is attributed to hepatitis C virus (HCV) infection (which affects 170 million people), and approximately 15% is associated with other causes. Other important risk factors for HCC include heavy alcohol consumption, obesity, diabetes, and tobacco smoking.[7]

The diagnosis of HCC can be made by characteristic imaging studies without tissue biopsy which differs from a majority of other cancers that usually require a histological confirmation. HCC shows unique radiologic hallmarks such as hypervascularization in the arterial phase ("wash-in") followed by hypodensity at the portal venous phase ("wash-out"). The EASL panel of experts, the American Association for the Study of Liver Diseases (AASLD), Organ Procurement and Transplantation Network (OPTN), and American College of Radiology (ACR) Liver Imaging Reporting and Data System (LI-RADS) have proposed imaging criteria to diagnose HCC (nodule ≥10 mm).[7,9−11]

The current EASL−EORTC guidelines endorse the Barcelona-Clinic Liver Cancer (BCLC) classification that is followed by most clinicians. The BCLC includes prognostic variables related to tumor size, vascular/nodal invasion, distant metastasis, liver function and health performance status as summarized in Table 1.[12,13]

Various therapeutic options available for HCC include surgical resection, local ablative therapy or transarterial chemoembolization (TACE), radioembolization, radiation treatment and systemic treatment. In the very early stage and early stage, curative treatments such as liver resection, transplantation, or radiofrequency ablation have survival benefits. Local treatment including embolization, external beam radiotherapy (RT) and systemic therapy are the main treatment options for intermediate stage while systemic therapy is used for advanced stage.[14−16] Unfortunately, the role of radio-embolization in locally advanced HCC treatment is debatable due to the recently reported negative data from the SorAfenib versus Radioembolization in Advanced Hepatocellular carcinoma (SARAH), selective internal radiation therapy versus sorafenib (SIR-VENIB) and SORAfenib in combination with local MICro-therapy guided by gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) enhanced MRI (SORAMIC) studies.[17−19] Systemic treatment options for advanced HCC have been very limited historically, however, more novel treatments have become available in the past several years with promising new agents on the horizon. We are summarizing the HCC systemic treatments in this review (Table 2).[20−26]

First-line therapy

Sorafenib

Sorafenib acts by inhibiting multiple intracellular (c-RAF, BRAF, and mutant BRAF) and cell surface kinases [KIT, Fms-related tyrosine kinase (FLT)-3, rearranged during transfection (RET), RET/papillary thyroid carcinoma (PTC), vascular endothelial growth

Table 1
The BCLC classification.

Stage	Criteria
Very early HCC (BCLC stage 0)	Single tumor <2 cm in diameter
	No vascular invasion/satellites
	Patient has good health status (ECOG PS 0) and well-preserved liver function (Child−Pugh A class)
Early HCC (BCLC stage A)	Single tumor >2 cm or 3 nodules <3 cm of diameter
	ECOG PS 0 and preserved liver function (Child−Pugh class A or B)
Intermediate HCC (BCLC stage B)	Multinodular asymptomatic tumors without an invasive pattern, preserved liver function (Child−Pugh class A or B), ECOG PS 0
Advanced HCC (BCLC stage C)	Cancer related-symptoms (symptomatic tumors, preserved liver function, ECOG PS 1−2)
	Macrovascular invasion (either segmental or portal invasion) or extrahepatic spread (lymph node involvement or metastases)
Terminal HCC (BCLC stage D)	End stage liver function
	ECOG PS 3 or 4

BCLC: Barcelona-Clinic Liver Cancer; HCC: hepatocellular carcinoma; ECOG: Eastern Cooperative Oncology Group; PS: performance status.

Table 2
Summary for positive HCC treatment studies.

Name of trial	Patient number	Treatment	Lines of treatment	OR	PFS (months)	OS (months)
SHARP[20]	602	Sorafenib	1st	2% PR, 71% SD	5.5	10.7 (*HR*, 0.69)
		Placebo		1% PR, 67% SD	2.8	7.9
ASIA−PACIFIC[21]	271 enrolled	Sorafenib	1st	3.3% PR, 54.0% SD	2.8	6.5 (*HR*, 0.68)
	226 randomized	Placebo		1.3% PR, 27.6% SD	1.4	4.2
REFLECT[22]	1492 enrolled	Lenvatinib	1st	1% CR, 23% PR, 51% SD	7.4	13.6 (*HR*, 0.92)
	954 randomized	Sorafenib		<1% CR, 9% PR, 51% SD	3.7	12.3
RESORCE[23]	843 screened	Regorafenib	2nd	1% CR, 10% PR, 54% SD	3.1	10.6 (*HR*, 0.63)
	573 randomized	Placebo		0% CR, 4% PR, 32% SD	1.5	7.8
CheckMate-040[24]	262	Nivolumab	2nd	1% CR, 18% PR, 45% SD	3.4	15.0 (dose escalation cohort)
CELESTIAL[25]	707	Carbozantinib	2nd	4%	5.2	10.2 (*HR*, 0.76)
		Placebo		0.40%	1.9	8
REACH-2[26]	292	Ramucirumab	2nd	4.60%	2.8	8.5 (*HR*, 0.71)
		Placebo		1.10%	1.6	7.3

HCC: hepatocellular carcinoma; OR: objective response; PFS: progression-free survival; OS: overall survival; PR: partial response; SD: stable disease; CR: complete response; *HR*: hazard ratio.

factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, and platelet-derived growth factor receptor (PDGFR)-β]. These kinases are involved in tumor cell signaling, angiogenesis, and apoptosis.

The two major landmark placebo-controlled trials that led to approval of sorafenib were the SHARP trial and the Asia−Pacific trial. In the SHARP trial, 602 patients with advanced HCC who had not received previous systemic treatment were divided to receive either sorafenib or placebo. The trial was stopped at the second planned interim analysis as 321 deaths had occurred. The results demonstrated a longer median overall survival (OS) in the sorafenib group compared to placebo group [10.7 *vs*. 7.9 months; *HR*, 0.69; 95% confidence interval (*CI*), 0.55−0.87; *P* < 0.001] and median time to progression (TTP) (5.5 *vs*. 2.8 months). At 1-year post-randomization, 44% of patients on sorafenib were alive, compared with 33% of patients on placebo, with 62% of sorafenib-treated patients progression-free at 4 months compared with 42% of patients in the placebo group. In the subgroup with HCV infection, amongst 167 patients, median OS (14.0 *vs*. 7.4 months), median TTP (7.6 *vs*. 2.8 months), and disease control rate (DCR, 44.2% *vs*. 29.6%) were all higher with sorafenib than the placebo group. Weight loss, diarrhea, hand-foot skin reaction (HFSR), and hypophosphatemia were statistically more frequently seen in the sorafenib group.[20]

The Asia−Pacific region study was a placebo-controlled phase 3 trial that enrolled 271 patients from 23 centers in the mainland and Taiwan of China, and South Korea. The trial showed a significantly longer median OS (6.5 months *vs*. 4.2 months;

HR, 0.68; 95% *CI*, 0.50−0.93; *P* = 0.014), median TTP (2.8 months *vs*. 1.4 months; *HR*, 0.57; 95% *CI*, 0.42−0.79; *P* = 0.0005) in sorafenib treated patients compared with the placebo arm. The most frequently reported grade 3/4 drug-related adverse events (AEs) in the patients treated with sorafenib were HFSR [16 patients (10.7%)], diarrhea [9 patients (6.0%)], and fatigue [5 patients (3.4%)].[21]

Based on these results, sorafenib was approved by U. S. Food and Drug Administration (FDA) in 2007 for the treatment of unresectable HCC and has been the standard systemic treatment for HCC since then.

Lenvatinib

Lenvatinib is a multiple-receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 [kinase insert domain receptor (KDR)], VEGFR3 (FLT4); it also inhibits other RTKs including fibroblast growth factors (FGF) receptors FGFR1, 2, 3, and 4; PDGFRα; KIT; RET.

The REFLECT trial was a phase III trial comparing lenvatinib with sorafenib in the first-line setting for treatment of patients with unresectable HCC. 954 patients were enrolled. The median OS, progression-free survival (PFS) and TTP were 13.6 months (*vs*. 12.3 months), 7.4 months (*vs*. 3.7 months) and 8.9 months (*vs*. 3.7 months) in the lenvatinib group (*vs*. sorafenib). OS for lenvatinib was non-inferior to sorafenib while the PFS and TTP were in favor of lenvatinib. Safety profile of lenvatinib was also comparable to that of sorafenib.[19] Most common AEs associated with

lenvatinib in the study were hypertension (42% compared with 30% with sorafenib group), diarrhea (39% versus 46% with sorafenib group), decreased appetite (34% versus 27% with sorafenib), decreased weight (31% compared with 22% in sorafenib group), and fatigue (30% compared with 25% in the sorafenib group).[22] Lenvatinib was approved by FDA for first-line HCC treatment in July 2018 based on these data.

Second-line therapy

Regorafenib

Regorafenib binds and inhibits VEGFRs 2 and 3, RET, KIT, PDGFR and Raf kinases, which result in the inhibition of tumor angiogenesis and tumor cell proliferation.

The RESORCE trial was a randomized, double-blind, placebo-controlled, phase 3 trial. 573 HCC patients who tolerated sorafenib ($\geq$400 mg/day for $\geq$20 days of last 28 days of treatment), progressed on sorafenib, and had Child-Pugh A liver function were enrolled. Regorafenib improved median OS compared with placebo (10.6 months *vs.* 7.8 months) with a *HR* of 0.63 (95% *CI*, 0.50−0.79; one-sided *P* < 0.0001). Regorafenib was also associated with higher DCR (objective response plus stable disease, 65% *vs.* 36%) and tumor response rate (11% *vs.* 4%, no complete response seen). Adverse events were reported in all regorafenib recipients [374 (100%) of 374] and 179 (93%) of 193 placebo recipients. The most common clinically relevant grade 3 or 4 treatment-emergent events were hypertension (15% in the regorafenib group *vs.* 5% in the placebo group), HFSR (13% *vs.* one 1%), fatigue (9% *vs.* 5%), and diarrhea (3% *vs.* 0%). This study suggested that regorafenib provides survival benefit in HCC patients progressing on sorafenib treatment and led to FDA approval of regorafenib as second-line treatment for HCC after sorafenib in April 2017.[23]

Further exploratory analysis with longer follow up from the RESORCE study revealed that regorafenib provides survival benefits regardless of the patient previous sorafenib dose prior to the regorafenib treatment. However, during the regorafenib treatment, rates of grade $\geq$3 AEs of HFSR, fatigue, anorexia, and bilirubin elevations were higher in patients who received last sorafenib dose <800 mg/day. Regorafenib associated survival benefit was not related to the TTP on previous sorafenib. The median time from the start of sorafenib treatment to death was 26.0 months in the regorafenib group compared with 19.2 months in the placebo group. These data confirmed benefits of sequential systemic treatment with sorafenib followed by regorafenib.[24]

Nivolumab

Nivolumab is an immuno-oncologic agent. It is a fully human immunoglobulin G4 (IgG4) programmed cell death protein-1 (PD-1) immune checkpoint inhibitor antibody that acts by disrupting the interaction between PD-1 and its ligands [programmed cell death protein ligands (PD-Ls), PD-L1/PD-L2]. It restores T-cell antitumor immunity directed against tumor cells.

CheckMate-040 was a phase I/II multicohort trial of nivolumab. The first part of the study is the dose escalation phase and expansion phase that enrolled a total of 262 advanced HCC patients (48 in the dose escalation cohort and 214 in the expansion cohort). Those patients either had disease progression on sorafenib or refused or were intolerant of sorafenib. Nivolumab 3 mg/kg was chosen in the expansion cohort with an objective response rate of 20%. This study results also revealed prolongation of the median survival (sorafenib-naive patients, 28.6 months; sorafenib-experienced patients, 15.6 months). There was a manageable toxicity profile of the drug in HCC patients, including those with no viral infection and those with underlying HCV or HBV infection, and favorable responses were observed across all dose levels and all etiologic cohorts. Based on the promising results of the CheckMate-040 trial, FDA has approved the use of nivolumab for advanced HCC patients who fail to respond to first-line treatment with sorafenib.[25]

Cabozantinib

Cabozantinib is a multiple receptor tyrosine kinases inhibitor, including hepatocyte growth factor (HGF) receptor [mesenchymal-epithelial transition (MET)], RET, and the VEGF receptor.

A phase II trial which included 41 patients with HCC and Child-Pugh A that had progressed on a previous systemic therapy has shown positive results. Patients on cabozantinib showed 5% of partial responses, 78% stable disease, and 7% progressive disease, with a median OS of 15.1 months and median PFS of 4.4 months, regardless of previous treatment with sorafenib. Most frequent side effects of grade 3 or higher were diarrhea, palmar-plantar erythrodysesthesia, and thrombocytopenia.[26]

The CELESTIAL trial was a randomized, double-blind, placebo-controlled study of cabozantinib in patients with advanced HCC conducted at more than 100 sites globally in 19 countries. 707 patients were randomized 2:1 to receive 60 mg of cabozantinib once daily or placebo. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, a Child-Pugh score of A, and had progressed on at least 1 prior systemic therapy for advanced HCC, with 70% having received only prior sorafenib. Stratification was based on etiology of the disease (HCV, HBV or other), geographic region (Asia *vs.* other regions), and presence of extrahepatic spread and/or macrovascular invasion. For cabozantinib *vs.* placebo group, median OS was 10.2 months *vs.* 8.0 months (*HR*, 0.76; 95% *CI*, 0.63−0.92; *P* = 0.005) and median PFS was 5.2 months *vs.* 1.9 months (*HR*, 0.44; 95% *CI*, 0.36−0.52; *P* < 0.0001). More patients discontinued therapy due to treatment-related AEs with cabozantinib (16%) *vs.* placebo (3%). Cabozantinib was associated with higher risk for Grade 3 or 4 AEs (68% *vs.* 36%). The most common grade 3/4 AEs associated with cabozantinib *vs.* placebo were palmar-plantar erythrodysesthesia (17% *vs.* 0%), hypertension (16% *vs.* 2%), increased aspartate aminotransferase (12% *vs.* 7%), fatigue (10% *vs.* 4%), and diarrhea (10% *vs.* 2%). Six patients had a grade 5 AE in the cabozantinib arm, which included hepatic failure, esophagobronchial fistula, portal vein thrombosis, upper gastrointestinal hemorrhage, pulmonary embolism, and hepatorenal syndrome. One patient in the placebo group died of hepatic failure.[27,28]

Subgroup analysis from the CELESTIAL trial evaluated patients in this study who had received sorafenib as the only prior systemic therapy and stratified patients based on duration of prior sorafenib treatment (<3 months, 3 to <6 months, and ≥6 months). Out of the 495 patients who received only prior sorafenib, about 136 (27%) had received prior sorafenib for less than 3 months, 141 (28%) for 3−6 months and 217 (44%) for ≥6 months. OS and PFS were improved with cabozantinib *vs.* placebo in patients who received only prior sorafenib; median survival was 11.3 months for cabozantinib *vs.* 7.2 months for placebo, and median PFS was 5.5 months for cabozantinib *vs.* 1.9 months for placebo. The study concludes that cabozantinib improves OS and PFS in patients with advanced HCC who had received sorafenib as the prior systemic therapy regardless of the duration of prior sorafenib treatment although median OS seemed to be longer for patients who were treated with sorafenib for longer duration.[29]

Ramucirumab

Increased VEGF and VEGFR2 expression is associated with high alpha-fetoprotein (AFP) expression in HCC patients. Ramucirumab is a fully humanized monoclonal antibody targeting VEGFR2 and is currently FDA approved for treatment in gastric cancer, colorectal cancer and non-small cell lung cancer.[30]

REACH-2 study is a phase 3 randomized, double blind, placebo-controlled study of ramucirumab *vs.* placebo as second-line treatment in HCC patients with high AFP expression after first-line sorafenib. The primary endpoint of trial was OS and secondary objective were PFS and objective response rate (ORR). 292 HCC patients with AFP ≥400 ng/ml were enrolled in the study with 2:1 randomization. Ramucirumab treatment significantly improved OS (median OS of 8.5 months *vs.* 7.3 months with placebo; *HR*, 0.710; 95% *CI*, 0.531−0.949; *P* = 0.0199). Ramucirumab also improved PFS (median PFS 2.8 months *vs.* 1.6 months with placebo; *HR*, 0.452; 95% *CI*, 0.339−0.603; *P* < 0.0001). ORR was 4.6% with ramucirumab *vs.* 1.1% with placebo.[31,32]

Future directions in the management of hepatocellular carcinoma

Systemic treatments of advanced HCC are evolving with new medications that demonstrated clinical benefits for patient. Meanwhile, although there are some successes, only a few medications have shown improved OS benefits as discussed above while many others failed to meet the OS endpoints in phase 3 studies (sunitinib,[33] brivanib,[34] linifanib,[35] ramucirumab,[36] everolimus,[37] and tivantinib[38]). There are multiple ongoing clinical studies evaluating novel systemic therapies for HCC patients.

Immunotherapy such as checkpoint inhibitors has already shown positive results in the management of advanced HCC, as seen in the nivolumab study (other cohorts in the CheckMate-040 are still ongoing to further evaluate the efficacy of nivolumab and sorafenib in the treatment of advanced HCC; the safety and efficacy of the combination of nivolumab plus ipilimumab in the treatment of advanced HCC; nivolumab treatment in Child-Pugh B patients, the safety and tolerability of nivolumab in combination with cabozantinib and nivolumab with ipilimumab in combination with cabozantinib). Other checkpoint inhibitor

studies, such as pembrolizumab, are currently enrolling HCC patients for first-line and second-line treatment (Keynote 224 and Keynote 240 trial, clinicaltrials.gov).

The Keynote 224 study is an open label, phase 2 clinical trial studying the effect of pembrolizumab in advanced HCC patients who were previously treated with sorafenib. Most recently updated data revealed that of 104 treated patients, 23 patients are still on treatment (median follow up 8.4 months). ORR was 16.3% with median time to response of 2.1 months. The 6-month PFS and OS rates were 43.1% and 77.9%, respectively. Best responses were reported as complete remission (CR) in 1 patient (1.0%), partial remission (PR) in 16 patients (15.4%), and stable disease (SD) in 47 patients (45.2%), while 34 patients (32.7%) had diseases progression on the treatment. Treatment is overall well tolerated with fatigue and increased aspartate aminotransferase seen in ≥10% patients. One death reported to be due to ulcerative esophagitis. Three patients developed immune medicated hepatitis.[39] The Keynote 240 study is an ongoing randomized, double blind, placebo-controlled phase 3 study comparing pembrolizumab *vs.* placebo in previously treated HCC patients. The primary endpoints of this study are PFS and OS.[40]

Tiselizumab is another humanized monoclonal antibody with high affinity and binding specificity for PD-1. A phase 3, randomized, multicenter study is being conducted to compare the efficacy and safety of tiselizumab *vs.* sorafenib as the first-line treatment in patients with advanced HCC. The primary outcome of this non-inferiority study is OS. The trial is currently enrolling patients (NCT03412773).[41]

There are multiple clinical trials studying the combination therapy with immunotherapy for advanced HCC. PD-1/PD-L1 inhibitor combined with cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor demonstrated better ORR, PFS and OS compared with single agent in other malignancies.[42,43] HIMALAYA study is a randomized, multicenter phase 3 study of durvalumab (D) and tremelimumab (T) as first-line treatment in patients with unresectable HCC. Patients will be randomized in three groups evaluating D monotherapy, D + T combination therapy, or sorafenib monotherapy. The study plans to measure the OS as the primary endpoint. Secondary endpoints include ORR, duration of response, DCR and PFS.[44]

Another trial of combination treatment involving the PD-1 inhibitor also showed promising results. The phase 1 study assessing the safety and efficacy of combination of SHR-1210 (S), a fully humanized IgG4 monoclonal PD-1 antibody plus apatinib (A), a VEGFR2 inhibitor in patients with advanced HCC, gastric cancer (GC) and esophagogastric cancer (EGJ). The trial is ongoing, and preliminary results from 42 enrolled patients reported ORR of 30.6% in 36 evaluable patients. Among 18 HCC patients (all HBV infected), the ORR was 50%. All 7 patients with PR were still on treatment, 5 of them lasted for more than 47 weeks (NCT02942329).[45]

In addition to checkpoint inhibitors, other immunotherapy agents including vaccines are also studied. Preliminary data from a phase II trial of hepcortespenlisimut-L, an oral vaccine made from tumor antigens and pooled alloantigens has shown promising results to date in early phase studies. The vaccine treatment is reported to lower AFP levels after two months of treatment and has been correlated with tumor regression on imaging scans. After 12 months of follow up, preliminary data reported 90.7% of patients were still alive, and the first patient in the study who received treatment more than 5 years ago remained to be in CR. No obvious side effect was observed. Currently a phase III study is ongoing.[46]

Another vaccine, named HepaVac 101 (IMA970A) is a multi-peptide HCC vaccine composed of 16 newly discovered and overexpressed tumor-associated peptides (TUMAPs). In a recent European trial (phase I/II), a total of 40 patients with very early, early and intermediate stage of HCC were enrolled to be treated with this new vaccine. Patients will be treated with pre-vaccination infusion of cyclophosphamide. The primary endpoint of this vaccine is safety, immunogenicity and tolerability. Secondary endpoints include immunological markers such as T-lymphocytes and biomarkers in blood and tissues. The trial is in the process of checking the safety of the novel vaccination in the first 10 patients and is planning to study the checkpoint inhibitors after that.[47]

Another novel treatment of HCC which has been explored is the first-in-human, first-in-class therapy called MTL-CEBPA, a small activating RNA (saRNA) targeting the transcription factor C/enhancer binding protein-α (EBP-α), which acts as a master regulator of liver homeostasis and multiple oncogenic processes. In the preliminary results from a phase I study in patients with advanced liver cancer, 19 patients have been treated and once weekly MTL-CEBPA has been well tolerated. The trial is ongoing and conclusive results will be updated (NCT02716012).[48]

Future development for HCC treatment will largely depend on our better understanding of the pathogenesis of HCC, the immune evasion mechanism of tumor cells, the tumor microenvironment and genetic/

epigenetic modification of the tumor cells. Meanwhile, with more effective treatment on the horizon and given the heterogeneity of HCC, we also expect to identify the biomarkers that could predict the response or resistance to the treatment to help us personalize treatment for individual patient.

Conflicts of interest

The authors declare no conflicts of interest.

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