




## REVIEW

# Hepatocellular carcinoma: recent advances and emerging medical therapies [version 1; peer review: 2 approved]

Kwan-Lung Ko <sup>1</sup>, Lung-Yi Mak<sup>1</sup>, Ka-Shing Cheung<sup>1</sup>, Man-Fung Yuen<sup>1,2</sup>

<sup>1</sup>Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong, Hong Kong

<sup>2</sup>State Key Laboratory of Liver Research, The University of Hong Kong, Hong Kong, Hong Kong

**V1** First published: 17 Jun 2020, 9(F1000 Faculty Rev):620  
<https://doi.org/10.12688/f1000research.24543.1>

Latest published: 17 Jun 2020, 9(F1000 Faculty Rev):620  
<https://doi.org/10.12688/f1000research.24543.1>

## Abstract

Hepatocellular carcinoma remains a deadly disease with poor prognosis in patients with unresectable cancer. Trans-arterial chemoembolization is the primary locoregional therapy for intermediate-stage hepatocellular carcinoma, with an estimated median overall survival of less than two years. For almost a decade, sorafenib has been the only standard systemic treatment for metastatic disease or tumors which progress or are considered unsuitable for locoregional therapy. Major breakthroughs have been made over the past few years in the management of hepatocellular carcinoma, especially in medical therapies for advanced disease. In this article, recent advances in intra-arterial therapy, multi-kinase inhibitors, and immunotherapy will be reviewed.

## Keywords

hepatocellular carcinoma, medical therapy

## Open Peer Review

Approval Status  

	1	2
<b>version 1</b> 17 Jun 2020		

**Faculty Reviews** are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

1. **Guohong Han**, Fourth Military Medical University, Xi'an, China
2. **Tim F. Greten**, National Institutes of Health, Bethesda, USA

Any comments on the article can be found at the end of the article.

**Corresponding author:** Man-Fung Yuen ([mfyuen@hkucc.hku.hk](mailto:mfyuen@hkucc.hku.hk))

**Author roles:** **Ko KL:** Writing – Original Draft Preparation, Writing – Review & Editing; **Mak LY:** Writing – Original Draft Preparation, Writing – Review & Editing; **Cheung KS:** Writing – Original Draft Preparation, Writing – Review & Editing; **Yuen MF:** Conceptualization, Project Administration, Supervision, Writing – Review & Editing

**Competing interests:** No competing interests were disclosed.

**Grant information:** The author(s) declared that no grants were involved in supporting this work.

**Copyright:** © 2020 Ko KL *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**How to cite this article:** Ko KL, Mak LY, Cheung KS and Yuen MF. **Hepatocellular carcinoma: recent advances and emerging medical therapies [version 1; peer review: 2 approved]** F1000Research 2020, 9(F1000 Faculty Rev):620  
<https://doi.org/10.12688/f1000research.24543.1>

**First published:** 17 Jun 2020, 9(F1000 Faculty Rev):620 <https://doi.org/10.12688/f1000research.24543.1>

## Introduction

Among all cancers globally, liver cancer ranked the sixth in incidence and the fourth in mortality, accounting for 841,080 new cases and 781,631 deaths worldwide in 2018<sup>1</sup>. Hepatocellular carcinoma (HCC) is the predominant form of primary liver cancer, with risk factors including hepatitis B virus (HBV) and hepatitis C virus (HCV) infection as well as cirrhosis of any etiology such as alcoholic liver disease, non-alcoholic steatohepatitis, and primary biliary cholangitis. Diagnosis of HCC is usually made by contrast enhanced imaging. Barcelona Clinic Liver Cancer (BCLC) staging remains the most commonly used staging system<sup>2,3</sup>. BCLC staging incorporates tumor burden, liver reserve, and performance status and classifies HCC into very early stage (0), early stage (A), intermediate stage (B), advanced stage (C), and terminal stage (D)<sup>4</sup>. The management strategy can then be recommended according to different stages of disease<sup>2</sup>. Recently, a popular staging system, the Hong Kong liver cancer staging system (HKLC), which is derived from a group of Hong Kong experts<sup>5</sup>, was introduced. According to this study, it has a better discriminating power than BCLC<sup>6</sup>. Nevertheless, it is noteworthy that BCLC is derived from mostly HCV-related HCC cases, while HKLC is derived from an Asian cohort where HBV is the predominant risk factor for HCC. Surgical resection, tumor ablation, and liver transplantation are curative treatments indicated for very early and early stage HCC. Owing to a lack of widely implemented HCC surveillance programs in many parts of the world, most patients are unfortunately diagnosed at an advanced stage, precluding curative therapy<sup>7</sup>.

Non-surgical management for HCC includes locoregional intra-arterial therapy, systemic treatment with multi-kinase inhibitors, and immunotherapy. Recent advances and emerging strategies in these modalities to improve the outcome of HCC will be reviewed.

## Intra-arterial therapy

### Trans-arterial chemoembolization

Trans-arterial chemoembolization (TACE) is the most popular form of intra-arterial therapy and is the established first-line treatment for intermediate-stage HCC<sup>2,3</sup>. It involves arterial catheterization, usually via the femoral artery, to cannulate the hepatic arterial branches. Cytotoxic agent, usually doxorubicin or cisplatin, is then delivered to the highly vascularized liver tumor. It is followed by blocking of the feeding vessel with an embolization agent, commonly lipiodol, to induce ischemic necrosis of the tumor. The rest of the liver parenchyma is relatively preserved as a result of dual blood supply from both the portal vein and the hepatic artery<sup>8</sup>. Significant improvement of survival was shown in patients with locally advanced HCC and Child-Pugh A or B cirrhosis treated with TACE as compared with best supportive care, with relative risk of death reduction more than 50%<sup>9-11</sup> (Table 1). Post-embolization syndrome, liver failure due to ischemic damage, biliary injury, gastroduodenal ulceration, and renal dysfunction are potential complications of TACE. Acute liver decompensation may occur in up to one-fifth of patients undergoing TACE<sup>12</sup>. Dosage of cytotoxic agent, baseline liver function as reflected by bilirubin and prothrombin time, and stage of cirrhosis are identified risk factors. Absolute contraindications to TACE include

decompensated cirrhosis, renal failure, main portal vein obstruction, extensive tumor burden, and technical difficulties<sup>13</sup>. Despite gradual improvement in efficacy and survival, patient selection for the initiation of TACE, the evaluation of tumor response, and the decision on the frequency and duration of therapy are not standardized because of marked heterogeneity within the group of intermediate-stage HCC<sup>14</sup>. The Hepatoma Arterial-Embolization Prognostic (HAP) score, Assessment for Retreatment with TACE (ART) score, and selection for TACE treatment (STATE) score are prognostic scores derived from combinations of tumor diameter, radiological response, alpha-fetoprotein (AFP) level, and liver biochemistry (bilirubin, aspartate aminotransferase [AST], and C-reactive protein) to better stratify and select patients for the initiation of or subsequent TACE<sup>15-18</sup>. However, controlled studies are required to determine whether implementing the prognostic scores in addition to BCLC staging can further improve treatment response and survival in patients receiving TACE. In addition, better definition of TACE failure is also needed, as it correlates with patient survival and mandates switching TACE to an alternative treatment strategy.

### Other forms of intra-arterial therapy

TACE with drug-eluting beads (DEB-TACE) and trans-arterial radio-embolization (TARE) are alternative intra-arterial locoregional therapies for HCC (Table 1). In DEB-TACE, cytotoxic-carrying microspheres are used instead of lipiodol, allowing simultaneous delivery of chemotherapeutic and embolization agents. The potential advantage of DEB-TACE is more sustained and selective drug delivery to the tumor with less systemic absorption and toxicity. However, evidence thus far does not show a clear benefit of DEB-TACE over conventional TACE. The PRECISION V trial is a phase II randomized trial comparing tumor response between DEB-TACE and TACE in 212 patients with unresectable HCC. Superiority in the primary endpoint of tumor response rate at 6 months was not met (51.6% for DEB-TACE versus 43.5% for TACE,  $P = 0.110$  for superiority), but a significant reduction in liver toxicity and doxorubicin-related side effects was seen in the DEB-TACE arm<sup>19</sup>. TARE is a form of selective internal radiation therapy (SIRT), in which radioactive Yttrium-90 (Y90) microspheres are introduced into the tumor vasculature. The main anti-tumor effect in TARE is achieved by radiation instead of embolization. As the patency of the hepatic artery is maintained, TARE can be used in HCC with main portal vein invasion or thrombosis, which is considered a contraindication for conventional TACE. A meta-analysis of eight studies involving 1,500 patients demonstrated superiority of TARE over TACE in overall survival (OS), 3-year OS, time to progression (TTP), and hospitalization days<sup>20</sup>. A subsequent phase II randomized trial also showed significantly longer TTP in the TARE group compared with conventional TACE (>26 months versus 6.8 months,  $P < 0.01$ )<sup>21</sup>. However, improvement of OS was not shown. A randomized controlled trial comparing DEB-TACE and TARE is currently underway (NCT01381211).

### Multi-kinase inhibitors

Tumor cell proliferation, differentiation, and angiogenesis are postulated to be mediated by multiple intracellular and cell surface protein kinases with their downstream pathways, as depicted

**Table 1. Trials on intra-arterial therapies for hepatocellular carcinoma.**

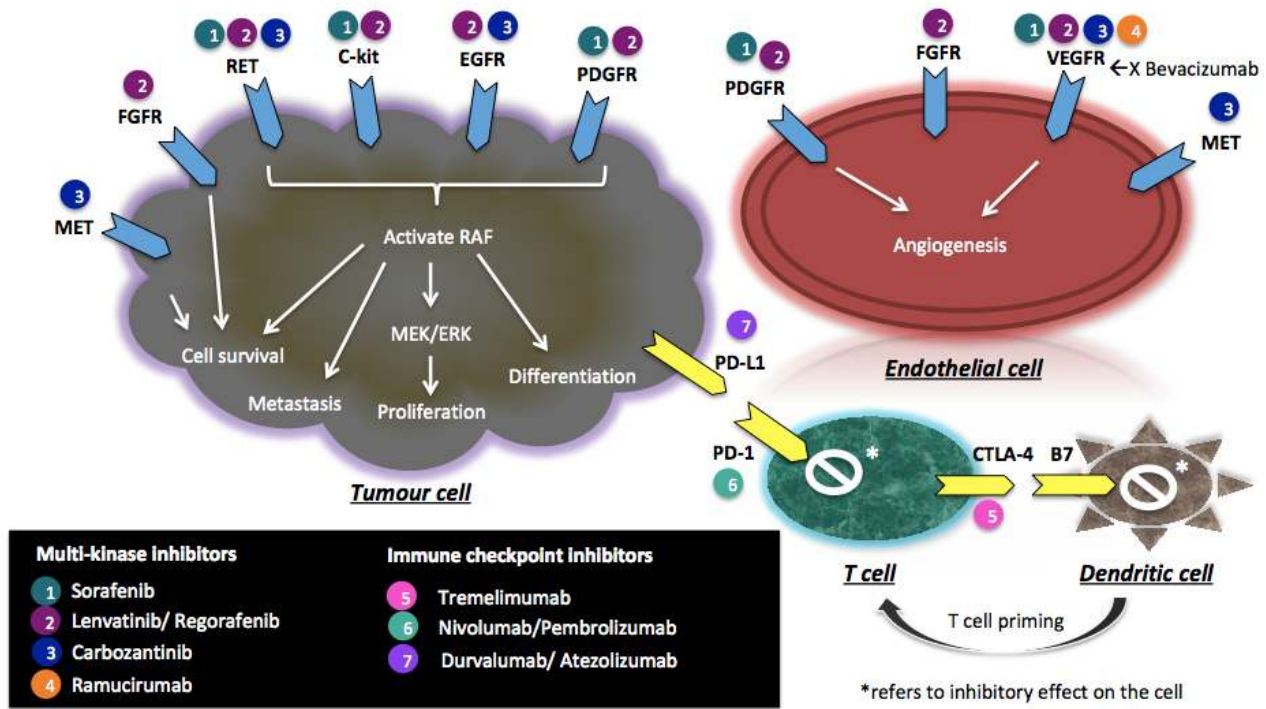
	Study arm	Control arm	No. of patients	Outcome	Major side effects for study arm
Llovet <i>et al.</i> <sup>9</sup>	Embolization arm: gelatin sponge Chemoembolization arm: gelatin sponge plus doxorubicin	Placebo	112	Mean survival 25.3 versus 28.7 versus 17.9 months; HR 0.47, 95% CI 0.25–0.91, $P = 0.025$ for chemoembolization versus placebo	Cholecystitis, leucopenia, ischemic biliary and liver injury, infection, allergic dermatitis, alopecia
Lo <i>et al.</i> <sup>10</sup>	TACE	Placebo	79	Estimated 1-, 2-, and 3-year survival 57%, 31%, and 26% versus 32%, 11%, and 3% RR of death 0.50, 95% CI 0.31–0.81, $P = 0.005$	Fever, abdominal pain, vomiting, ascites
Yuen <i>et al.</i> <sup>11</sup>	TACE	Conservative care	96	Mean survival 31.2 versus 14.1 months, $P = 0.0126$	Hepatic decompensation
Lammer <i>et al.</i> <sup>19</sup>	DEB-TACE	TACE	212	Tumor response at 6 months 51.6% versus 43.5%, $P = 0.110$ for superiority	Significant reduction in liver toxicity and doxorubicin-related side effects in DEB-TACE arm
Salem <i>et al.</i> <sup>21</sup>	Y90 radioembolization	TACE	179	Time to progression >26 versus 6.8 months, $P = 0.001$	Less diarrhea and hypoalbuminemia in Y90 arm
Kudo <i>et al.</i> <sup>22</sup>	TACE plus sorafenib	TACE	156	Median PFS 25.2 versus 13.5 months, $P = 0.006$ Median TTUP 26.7 versus 20.6 months, $P = 0.020$	Thrombocytopenia, hand-foot-skin reaction, hypertension, increased lipase and amylase, neutropenia, fatigue, diarrhea, erythema multiforme more common in study arm
Ricke <i>et al.</i> <sup>23</sup>	SIRT plus sorafenib	Sorafenib	424	Median survival 12.1 versus 11.4 months; HR 1.01, 95% CI 0.81–1.25, $P = 0.953$	Hyperbilirubinemia and fatigue more common in study arm

CI, confidence interval; DEB-TACE, TACE with drug-eluting beads; HR, hazard ratio; PFS, progression-free survival; RR, relative risk; TACE, trans-arterial chemoembolization; TTUP, time to TACE untreatable progression; SIRT, selective internal radiation therapy; Y90, yttrium-90.

in [Figure 1](#)<sup>24</sup>. Sorafenib, an inhibitor of platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), rearrange during transfection (RET), and C-kit, is the first multi-kinase inhibitor proved to be beneficial in unresectable, advanced-stage HCC. The SHARP trial is the first phase III, placebo-controlled trial of the use of sorafenib in HCC. In this landmark study involving 602 patients with advanced disease naïve to systemic treatment, median OS was significantly improved in the sorafenib group compared to the placebo group (10.7 versus 7.9 months,  $P < 0.001$ )<sup>25</sup>. Another multi-national randomized controlled trial in the Asia-Pacific region, where chronic hepatitis B is the major risk factor for HCC, also confirmed the findings in the SHARP study<sup>26</sup>. Further analysis of the two randomized controlled trials identified HCV-related HCC, absence of extrahepatic spread, and low neutrophil-to-lymphocyte ratio as predictors of greater survival benefit with sorafenib<sup>27</sup>. The remarkable result with sorafenib is considered a major breakthrough in more than 30 years of pursuing a systemic treatment for HCC. However, the therapeutic window is narrow with sorafenib, with restrictions to patients with good performance status and compensated cirrhosis. Also, dose-limiting side effects including hand-foot-skin reaction, diarrhea, and weight loss are not uncommon. However, recent studies have shown an association between dermatological adverse

effects with sorafenib with better treatment outcomes<sup>28,29</sup>. Over subsequent years, other agents have been studied as alternative first-line treatments against sorafenib or as second-line treatments against placebo in patients intolerant to or who have progressed while on sorafenib. Sunitinib, brivanib, linifanib, everolimus, and tivantinib were unable to meet their respective study end points as either non-inferior or superior to sorafenib or show survival benefit in those who failed sorafenib<sup>30–34</sup>.

Lenvatinib, an inhibitor of epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), VEGFR, PDGFR, RET, and C-kit, emerged almost a decade after sorafenib as an alternative first-line treatment for advanced HCC. Non-inferiority to sorafenib in terms of OS (13.6 versus 12.3 months, 95% confidence interval [CI] 0.79–1.06) was demonstrated in the REFLECT trial<sup>35</sup>. In patients who progressed while on sorafenib, regorafenib and cabozantinib prolonged survival in their respective phase III randomized controlled trials ([Table 2](#)). Bruix *et al.* demonstrated that regorafenib treatment resulted in longer median survival than placebo (10.6 versus 7.8 months; hazard ratio [HR] 0.63,  $P < 0.001$ )<sup>36</sup>. Comparable improvement in median OS was shown with cabozantinib by Abou-Alfa *et al.* (10.2 versus 8.0 months; HR 0.76,  $P = 0.005$ )<sup>37</sup>.



**Figure 1. Potential treatment targets for systemic therapy in hepatocellular carcinoma.** CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; ERK, extracellular-signal-regulated kinase; FGFR, fibroblast growth factor receptor; MEK, mitogen-activated protein kinase/ERK kinase; PD-1, programmed cell death protein 1; PDGFR, platelet-derived growth factor receptor; PD-L1, programmed death ligand-1; RET, rearrange during transfection; VEGFR, vascular endothelial growth factor receptor.

**Table 2. Phase III trials on first- and second-line systemic therapy in hepatocellular carcinoma.**

Trial name	Study drug	Control	No. of patients	Median overall survival (months)	Major side effects of study drug
<b>First line</b>					
SHARP	Sorafenib	Placebo	602	10.7 versus 7.9 HR 0.69, 95% CI 0.55–0.87, $p < 0.001$	Diarrhea, weight loss, hand-foot-skin reaction, and hypophosphatemia
REFLECT	Lenvatinib	Sorafenib	954	13.6 versus 12.3 HR 0.92, 95% CI 0.79–1.06, non-inferiority met	Hypertension, diarrhea, decreased appetite, and decreased weight
IMbrave150	Atezolizumab plus bevacizumab	Sorafenib	501	Not estimated versus 13.2 HR 0.58, 95% CI 0.42–0.79, $p < 0.001$	Hypertension, proteinuria, Increase AST, decrease platelet
Checkmate-459	Nivolumab	Sorafenib	743	16.4 versus 14.7 HR 0.85, 95% CI 0.72–1.0, $p = 0.0752$	Not yet published
HIMALAYA	Durvalumab plus tremelimumab	Sorafenib	Ongoing	–	–
LEAP-002	Lenvatinib plus pembrolizumab	Lenvatinib	Ongoing	–	–
COSMIC-312	Cabozantinib plus atezolizumab	Sorafenib	Ongoing	–	–
ORIENT-32	Sintilimab plus IBI305	Sorafenib	Ongoing	–	–
NCT03764293	Apatinib plus SHR-1210	Sorafenib	Ongoing	–	–

Trial name	Study drug	Control	No. of patients	Median overall survival (months)	Major side effects of study drug
<b>Second line</b>					
RESORCE	Regorafenib	Placebo	573	10.6 versus 7.8 HR 0.63, 95% CI 0.50–0.79, <i>p</i> <0.001	Hypertension, hand-foot-skin reaction, fatigue, diarrhea
CELESTIAL	Cabozantinib	Placebo	707	10.2 versus 8.0 HR 0.76, 95% CI 0.63–0.92, <i>p</i> =0.005	Palmar-plantar erythrodysesthesia, hypertension, increased AST, fatigue, diarrhea
REACH-2	Ramucirumab	Placebo	292	8.5 versus 7.3 HR 0.71, 95% CI 0.531–0.949, <i>p</i> =0.0199	Hypertension, hyponatremia, increased AST
KEYNOTE-240	Pembrolizumab	Placebo	413	13.9 versus 10.6 HR 0.781, 95% CI 0.611–0.998, non-significant at prespecified threshold	Increased ALT/AST, increased bilirubin
KEYNOTE-394	Pembrolizumab	Placebo	Ongoing	–	–

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CI, confidence interval; HR, hazard ratio.

The recombinant IgG1 monoclonal antibody ramucirumab, which inhibits type 2 VEGFR-mediated angiogenesis, is the latest approved agent for advanced HCC. The initial REACH trial using ramucirumab failed to demonstrate benefit over placebo in patients with BCLC stage B and C disease not amenable to locoregional therapy and treated with first-line sorafenib<sup>38</sup>. However, the effect of ramucirumab was noted to correlate with baseline AFP level, and benefit in OS was seen in the subgroup of patients with baseline AFP concentration above 400 ng/ml. The finding formed the basis of the follow-up REACH-2 trial, in which only sorafenib-treated patients with baseline serum AFP concentration over 400 ng/ml were recruited. Median OS (8.5 versus 7.3 months; HR 0.71, *P* = 0.020) and progression-free survival (PFS) (2.8 versus 1.6 months; HR 0.45, *P* <0.001) were significantly improved in the ramucirumab group compared with the placebo group<sup>39</sup>. The study also highlighted that HCC is a heterogeneous disease and that stratification with biomarkers such as AFP is important in the future development of cancer therapy.

### Immunotherapy

The past decade has witnessed major breakthroughs in cancer immunotherapy, which has demonstrated benefit in various solid organ and hematological malignancies<sup>40</sup>. HCC develops in an inflammatory milieu, and immune tolerance is reported to play an important role in tumor pathogenesis<sup>41,42</sup>. Immune checkpoint inhibitors (ICPIs) targeting the programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) pathway and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) pathway are the two most studied immunotherapy mechanisms in HCC (Figure 1). The two pathways are believed to act at different stages of the immune response. The PD-1/PD-L1 pathway promotes immune tolerance by suppressing the activity of T cells and mediating the differentiation of regulatory

T cells, while the CTLA-4 pathway prevents autoimmunity by inhibiting the proliferation of potential autoreactive T cells<sup>43,44</sup>. By inhibiting these immune checkpoints, self-tolerance to malignant cells is lost, resulting in immune-mediated clearance of tumor tissue.

### CTLA-4 inhibitors

CTLA-4 blockage with tremelimumab is the first checkpoint inhibitor being evaluated as a potential treatment for hepatitis C-related HCC. A phase II study found that tremelimumab exhibits both anti-tumor and antiviral activities, with an acceptable safety profile<sup>45</sup>.

### PD-1/PD-L1 inhibitors

Nivolumab is a monoclonal antibody inhibiting PD-1 receptor and demonstrated a favorable response rate of 20% in the dose expansion and escalation study (CheckMate 040)<sup>46</sup>. The median OS in sorafenib-experienced patients in this phase II study was 16.7 months with an overall response rate of 14.5%. A similar response rate and improvements in OS, objective response rate, and complete response rate were confirmed in the subsequent head-to-head comparison against sorafenib as first-line therapy in advanced HCC (CheckMate 459), but the primary endpoint of OS did not reach statistical significance<sup>47</sup>.

Pembrolizumab is another anti-PD-1 monoclonal antibody being investigated as a potential treatment for advanced HCC. In the phase II Keynote-224 trial, an objective response was observed in 18 of 104 sorafenib-experienced patients (17%), including one complete and 17 partial responses<sup>48</sup>. A consistent result was seen in the Keynote-240 study, a follow-up phase III randomized controlled trial comparing pembrolizumab with best supportive care as second-line therapy after

sorafenib, but the co-primary endpoint of improvement in OS and PFS was not met<sup>49</sup>. A similar phase III study using pembrolizumab in Asian subjects is being conducted (Keynote-394, NCT03062358).

### CTLA-4 and PD-1/PD-L1 combination

Studies have also looked into a potential synergistic effect with combined inhibition of PD-1 and CTLA-4 pathways. Tremelimumab together with the anti-PD-L1 monoclonal antibody durvalumab have demonstrated favorable anti-tumor activity with acceptable tolerability in a small pilot study involving patients with advanced HCC or biliary tract carcinomas<sup>50</sup>. A phase III multicenter randomized study (HIMALAYA, NCT03298451) is currently underway testing the dual therapy against sorafenib as first-line treatment in patients with unresectable HCC. The combination of nivolumab and the CTLA-4-inhibiting antibody ipilimumab also showed efficacy with a median OS of 23 months in its dose-finding study<sup>51</sup>.

The side effect profile of ICPIs is diverse and distinctive from conventional cytotoxic chemotherapy. The immune-related adverse reactions can affect virtually any organ but most commonly involve the endocrine system, skin, gastrointestinal tract, and liver. For grade 1 toxicity, such as mild endocrinopathy, ICPIs can be continued with close monitoring and hormone replacement. Grade 2 or above toxicity usually mandates interruption of ICPIs with or without the need for steroids and immunosuppressants<sup>52</sup>. Compared with patients with melanoma and non-small-cell lung cancer, HCC patients tend to have more elevation of AST/alanine aminotransferase when given ICPIs<sup>53</sup>. It can be difficult to differentiate hepatitis associated with ICPIs from other causes of deranged liver function such as disease progression, reactivation of concurrent viral hepatitis, or decompensation of underlying cirrhosis.

### Combination of therapies of different mechanisms

Investigators have brought together locoregional therapy with systemic therapy or systemic therapy of different classes with the hope of augmenting tumor response. The initial experience with adding sorafenib or other molecular targeted therapy to TACE was disappointing<sup>54</sup>. Inadequate dose and duration of sorafenib in these trials were identified as key reasons for failure. The Japanese TACTICS trial eventually demonstrated superiority of TACE plus sorafenib over TACE alone in terms of longer PFS (25.2 versus 13.5 months,  $P = 0.006$ ) and longer time to TACE untreatable progression (26.7 versus

20.6 months,  $P = 0.020$ )<sup>22</sup>. The SORAMIC study looked into the combination of sorafenib and SIRT with Y90 compared with sorafenib alone for advanced HCC. The primary endpoint of OS was not met, but subgroup analysis of non-cirrhotic patients or patients aged under 65 years did show a survival benefit with combination therapy<sup>23</sup>. Future trials should address issues such as timing of sorafenib administration in relation to intra-arterial therapy, patient selection for such combination therapy by balancing potential benefits with incremental adverse effects, and more precise definition of both treatment efficacy and failure.



The combination of atezolizumab, an anti-PD-L1 antibody, and bevacizumab, an anti-VEGF antibody, has been investigated as a first-line systemic therapy in unresectable or metastatic HCC. It is postulated that the anti-angiogenic and immunomodulatory effect of bevacizumab can augment the anti-tumor immune activity of atezolizumab, as shown by a partial response rate of 62% in the phase I trial<sup>55</sup>. Encouraging results were recently reported from the phase III IMbrave 150 trial comparing the dual therapy with sorafenib, in which statistically significant improvement in both OS and PFS was shown (HR of OS 0.58,  $P < 0.001$  and HR of PFS 0.59,  $P < 0.001$ )<sup>56</sup>.

Additional phase III trials on combinations of systemic therapies including lenvatinib and pembrolizumab (NCT03713593), cabozantinib and atezolizumab (NCT03755791), sintilimab and IBI305 (NCT0379440), and apatinib and SHR1210 (NCT03764293) are currently ongoing (Table 2).


### Conclusion

HCC remains a deadly disease, and unresectable HCC is associated with limited survival. Considerable advancement in local and systemic therapies has been achieved in recent years owing to better understanding of the tumor microenvironment and the interplay between the tumor and the host immune system. With the latest breakthrough achieved with ICPIs, the armamentarium of treatment for HCC is rapidly expanding. However, heterogeneity in patient selection and definition of treatment response in the existing literature make the application of trial results to real-world practice difficult. With the standardization of trial design, prognostic markers of treatment response can be identified, allowing the selection of patients for the most appropriate anti-tumor therapy. Future studies should also continue to utilize therapeutic agents of different classes to achieve synergistic activity while minimizing toxicity.

## References

1.  Bray F, Ferlay J, Soerjomataram I, et al.: **Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.** *CA Cancer J Clin.* 2018; **68**(6): 394–424. [PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
2.  Marrero JA, Kulik LM, Sirlin CB, et al.: **Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American**

**Association for the Study of Liver Diseases.** *Hepatology.* 2018; **68**(2): 723–50. [PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)

3.  European Association for the Study of the Liver, Peter R Galle, Alejandro Forner: **EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma.** *J Hepatol.* 2018; **69**(1): 182–236. [PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)



4. Llovet JM, Fuster J, Bruix J: **The Barcelona approach: Diagnosis, staging, and treatment of hepatocellular carcinoma.** *Liver Transpl.* 2004; 10(2 Suppl 1): S115–20.  
[PubMed Abstract](#) | [Publisher Full Text](#)
5. Yau T, Tang VYF, Yao TJ, *et al.*: **Development of Hong Kong Liver Cancer Staging System With Treatment Stratification for Patients With Hepatocellular Carcinoma.** *Gastroenterology.* 2014; 146(7): 1691–1700.e3.  
[PubMed Abstract](#) | [Publisher Full Text](#)
6. **F** Parikh ND, Scaglione S, Li Y, *et al.*: **A Comparison of Staging Systems for Hepatocellular Carcinoma in a Multicenter US Cohort.** *Clin Gastroenterol Hepatol.* 2018; 16(5): 781–2.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [Faculty Opinions Recommendation](#)
7. **F** Francica G, Borzio M: **Status of, and strategies for improving, adherence to HCC screening and surveillance.** *J Hepatocell Carcinoma.* 2019; 6: 131–41.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [Faculty Opinions Recommendation](#)
8. Shin SW: **The current practice of transarterial chemoembolization for the treatment of hepatocellular carcinoma.** *Korean J Radiol.* 2009; 10(5): 425–34.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
9. Llovet JM, Real MI, Montaña X, *et al.*: **Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: A randomised controlled trial.** *Lancet.* 2002; 359(9319): 1734–9.  
[PubMed Abstract](#) | [Publisher Full Text](#)
10. Lo CM, Ngan H, Tso WK, *et al.*: **Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma.** *Hepatology.* 2002; 35(5): 1164–71.  
[PubMed Abstract](#) | [Publisher Full Text](#)
11. Yuen MF, Chan AO, Wong BC, *et al.*: **Transarterial chemoembolization for inoperable, early stage hepatocellular carcinoma in patients with Child-Pugh grade A and B results of a comparative study in 96 Chinese patients.** *Am J Gastroenterol.* 2003; 98(5): 1181–5.  
[PubMed Abstract](#) | [Publisher Full Text](#)
12. Chan AO, Yuen MF, Hui CK, *et al.*: **A prospective study regarding the complications of transcatheter intraarterial lipiodol chemoembolization in patients with hepatocellular carcinoma.** *Cancer.* 2002; 94(6): 1747–52.  
[PubMed Abstract](#) | [Publisher Full Text](#)
13. **F** Vogel A, Cervantes A, Chau I, *et al.*: **Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.** *Ann Oncol.* 2018; 29(Suppl 4): iv238–iv255.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
14. Sieghart W, Hucke F, Peck-Radosavljevic M: **Transarterial chemoembolization: Modalities, indication, and patient selection.** *J Hepatol.* 2015; 62(5): 1187–95.  
[PubMed Abstract](#) | [Publisher Full Text](#)
15. 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(10): 2565–70.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
16. Sieghart W, Hucke F, Pinter M, *et al.*: **The ART of decision making: Retreatment with transarterial chemoembolization in patients with hepatocellular carcinoma.** *Hepatology.* 2013; 57(6): 2261–73.  
[PubMed Abstract](#) | [Publisher Full Text](#)
17. Hucke F, Sieghart W, Pinter M, *et al.*: **The ART-strategy: Sequential assessment of the ART score predicts outcome of patients with hepatocellular carcinoma re-treated with TACE.** *J Hepatol.* 2014; 60(1): 118–26.  
[PubMed Abstract](#) | [Publisher Full Text](#)
18. Hucke F, Pinter M, Graziadei I, *et al.*: **How to STATE suitability and START transarterial chemoembolization in patients with intermediate stage hepatocellular carcinoma.** *J Hepatol.* 2014; 61(6): 1287–96.  
[PubMed Abstract](#) | [Publisher Full Text](#)
19. Lammer J, Malagari K, Vogl T, *et al.*: **Prospective Randomized Study of Doxorubicin-Eluting-Bead Embolization in the Treatment of Hepatocellular Carcinoma: Results of the PRECISION V Study.** *Cardiovasc Intervent Radiol.* 2010; 33(1): 41–52.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
20. Zhang Y, Li Y, Ji H, *et al.*: **Transarterial Y90 radioembolization versus chemoembolization for patients with hepatocellular carcinoma: A meta-analysis.** *Biosci Trends.* 2015; 9(5): 289–98.  
[PubMed Abstract](#) | [Publisher Full Text](#)
21. Salem R, Gordon AC, Mouli S, *et al.*: **Y90 Radioembolization Significantly Prolongs Time to Progression Compared With Chemoembolization in Patients With Hepatocellular Carcinoma.** *Gastroenterology.* 2016; 151(6): 1155–1163.e2.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
22. **F** Kudo M, Ueshima K, Ikeda M, *et al.*: **Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial.** *Gut.* 2019.  
[PubMed Abstract](#) | [Faculty Opinions Recommendation](#)
23. **F** Ricke J, Klumpen HJ, Amthauer H, *et al.*: **Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma.** *J Hepatol.* 2019; 71(6): 1164–74.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
24. Cervello M, Bachvarov D, Lampiasi N, *et al.*: **Molecular mechanisms of sorafenib action in liver cancer cells.** *Cell Cycle.* 2014; 11(15): 2843–55.  
[PubMed Abstract](#) | [Publisher Full Text](#)
25. **F** Llovet JM, Ricci S, Mazzaferro V, *et al.*: **Sorafenib in advanced hepatocellular carcinoma.** *N Engl J Med.* 2008; 359(4): 378–90.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
26. 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(1): 25–34.  
[PubMed Abstract](#) | [Publisher Full Text](#)
27. Bruix J, Cheng AL, Meinhardt G, *et al.*: **Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: Analysis of two phase III studies.** *J Hepatol.* 2017; 67(5): 999–1008.  
[PubMed Abstract](#) | [Publisher Full Text](#)
28. Reig M, Torres F, Rodriguez-Lope C, *et al.*: **Early dermatologic adverse events predict better outcome in HCC patients treated with sorafenib.** *J Hepatol.* 2014; 61(2): 318–24.  
[PubMed Abstract](#) | [Publisher Full Text](#)
29. **F** Rimola J, Díaz-González A, Darnell A, *et al.*: **Complete response under sorafenib in patients with hepatocellular carcinoma: Relationship with dermatologic adverse events.** *Hepatology.* 2018; 67(2): 612–22.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
30. 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(32): 4067–75.  
[PubMed Abstract](#) | [Publisher Full Text](#)
31. 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.** *JCO.* 2013; 31(28): 3517–24.  
[PubMed Abstract](#) | [Publisher Full Text](#)
32. 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(2): 172–9.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
33. Zhu AX, Kudo M, Assenat E, *et al.*: **Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial.** *JAMA.* 2014; 312(1): 57–67.  
[PubMed Abstract](#) | [Publisher Full Text](#)
34. **F** Rimassa L, Assenat E, Peck-Radosavljevic M, *et al.*: **Tivantinib for second-line treatment of MET-high, advanced hepatocellular carcinoma (METIV-HCC): A final analysis of a phase 3, randomised, placebo-controlled study.** *Lancet Oncol.* 2018; 19(5): 682–93.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
35. **F** 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(10126): 1163–73.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
36. Bruix J, Qin S, Merle P, *et al.*: **Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): A randomised, double-blind, placebo-controlled, phase 3 trial.** *Lancet.* 2017; 389(10064): 56–66.  
[PubMed Abstract](#) | [Publisher Full Text](#)
37. **F** Abou-Alfa GK, Meyer T, Cheng AL, *et al.*: **Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma.** *N Engl J Med.* 2018; 379(1): 54–63.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
38. Zhu AX, Park JO, Ryou BY, *et al.*: **Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): A randomised, double-blind, multicentre, phase 3 trial.** *Lancet Oncol.* 2015; 16(7): 859–70.  
[PubMed Abstract](#) | [Publisher Full Text](#)
39. **F** Zhu AX, Kang YK, Yen CJ, *et al.*: **Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased  $\alpha$ -fetoprotein concentrations (REACH-2): A randomised, double-blind, placebo-controlled, phase 3 trial.** *Lancet Oncol.* 2019; 20(2): 282–96.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
40. Kruger S, Ilmer M, Kobold S, *et al.*: **Advances in cancer immunotherapy 2019 - latest trends.** *J Exp Clin Cancer Res.* 2019; 38(1): 268.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
41. **F** Iñárraiegui M, Melero I, Sangro B: **Immunotherapy of Hepatocellular Carcinoma: Facts and Hopes.** *Clin Cancer Res.* 2018; 24(7): 1518–24.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
42. Yarchoan M, Xing D, Luan L, *et al.*: **Characterization of the Immune Microenvironment in Hepatocellular Carcinoma.** *Clin Cancer Res.* 2017; 23(23): 7333–9.  
[PubMed Abstract](#) | [Publisher Full Text](#)



43. **F** Salmaninejad A, Valilou SF, Shabgah AG, *et al.*: **PD-1/PD-L1 pathway: Basic biology and role in cancer immunotherapy.** *J Cell Physiol.* 2019; **234**(10): 16824–37.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
44. Buchbinder EI, Desai A: **CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition.** *Am J Clin Oncol.* 2016; **39**(1): 98–106.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
45. Sangro B, Gomez-Martin C, de La Mata M, *et al.*: **A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C.** *J Hepatol.* 2013; **59**(1): 81–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
46. 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**(10088): 2492–502.  
[PubMed Abstract](#) | [Publisher Full Text](#)
47. 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).** *Ann Oncol.* 2019; **30**(Supplement 5): v874–v875.  
[Publisher Full Text](#)
48. **F** Zhu AX, Finn RS, Edeline J, *et al.*: **Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): A non-randomised, open-label phase 2 trial.** *Lancet Oncol.* 2018; **19**(7): 940–52.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
49. **F** 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**(3): 193–202.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
50. Floudas CS, Xie C, Brar G, *et al.*: **Combined immune checkpoint inhibition (ICI) with tremelimumab and durvalumab in patients with advanced hepatocellular carcinoma (HCC) or biliary tract carcinomas (BTC).** *JCO.* 2019; **37**(4\_suppl): 336.  
[Publisher Full Text](#)
51. Yau T, Kang YK, Kim TY, *et al.*: **Nivolumab (NIVO) + ipilimumab (IPI) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): Results from CheckMate 040.** *JCO.* 2019; **37**(15\_suppl): 4012.  
[Publisher Full Text](#)
52. **F** Brahmer JR, Lacchetti C, Schneider BJ, *et al.*: **Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline.** *J Clin Oncol.* 2018; **36**(17): 1714–68.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [Faculty Opinions Recommendation](#)
53. Brown ZJ, Heinrich B, Steinberg SM, *et al.*: **Safety in treatment of hepatocellular carcinoma with immune checkpoint inhibitors as compared to melanoma and non-small cell lung cancer.** *J Immunother Cancer.* 2017; **5**(1): 93.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
54. Kudo M, Arizumi T: **Transarterial Chemoembolization in Combination with a Molecular Targeted Agent: Lessons Learned from Negative Trials (Post-TACE, BRISK-TA, SPACE, ORIENTAL, and TACE-2).** *Oncology.* 2017; **93**(Suppl 1): 127–34.  
[PubMed Abstract](#) | [Publisher Full Text](#)
55. Stein S, Pishvaian MJ, Lee MS, *et al.*: **Safety and clinical activity of 1L atezolizumab + bevacizumab in a phase Ib study in hepatocellular carcinoma (HCC).** *JCO.* 2018; **36**(15\_suppl): 4074.  
[Publisher Full Text](#)
56. Cheng AL, Qin S, Ikeda M, *et al.*: **IMbrave150: Efficacy and safety results from a phase III study evaluating atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (Sor) as first treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC).** *Ann Oncol.* 2019; **30**(Supplement 9): ix186–ix187.  
[Publisher Full Text](#)

# Open Peer Review

Current Peer Review Status:  

---

## Editorial Note on the Review Process

**Faculty Reviews** are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

---

## The reviewers who approved this article are:

### Version 1

#### 1. Tim F. Greten

Liver Cancer Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

**Competing Interests:** No competing interests were disclosed.

#### 2. Guohong Han

Department of Liver Diseases and Digestive Interventional Radiology, Xijing Hospital of Digestive Diseases, Xijing Hospital, Fourth Military Medical University, Xi'an, China

**Competing Interests:** No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact [research@f1000.com](mailto:research@f1000.com)

**F1000Research**