Current and Future Systemic Therapies for Hepatocellular Carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is a common cancer with unmet needs and limited effective therapeutic options. The management strategy for diagnosed HCC is based on Barcelona Clinic Liver Cancer (BCLC) staging. Advanced HCC is treated with systemic therapy comprising oral tyrosine kinase inhibitors (TKIs) and intravenous immune checkpoint inhibitors, provided that liver function is reasonable. Five new agents have been approved by the US Food and Drug Administration (FDA) in the past 2 years for the treatment of HCC: lenvatinib in the first-line setting, and regorafenib, nivolumab, pembrolizumab, and cabozantinib as second-line therapies. The FDA is considering a label expansion of ramucirumab to include its use in HCC. These therapies have all been shown to extend overall patient survival and appear to have a reasonable safety profile. Multiple ongoing trials are studying immune checkpoint inhibition alone or in combination with TKIs. The results of these trials will help determine the optimal choice, timing, and sequence of agents. This article reviews the role of currently approved systemic therapies for HCC and highlights potential future combination therapeutic strategies. The article also brings forward the concept of a developing shift to the left for therapy, as mapped out in the BCLC staging and treatment algorithm, marking earlier use of systemic therapy prior to advanced progression of the disease.

Primary liver cancer is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer death worldwide.[1] The incidence of hepatocellular carcinoma (HCC), the most common type of primary liver cancer (75% of cases), is on the rise.[2] It has been estimated that disease incidence has almost tripled during the past 3 decades, with a shift toward occurrence at younger ages.[3,4] The most common risk factors for developing HCC are chronic hepatitis B virus infection, chronic hepatitis C virus infection, heavy alcohol intake, and metabolic syndrome with nonalcoholic fatty liver disease. Hepatitis B virus infection is the most common etiology in Southeast Asia and sub-Saharan Africa, whereas nonalcoholic fatty

liver disease and hepatitis C virus infection are more prominent in the United States.[5] The treatment paradigm for HCC underwent a major overhaul starting in 2007 with the advent of the small molecule inhibitor sorafenib (Nexavar, Bayer). Prior to sorafenib's approval, no agent had shown improvement in overall survival (OS) in this difficult-to-treat patient population.[6] Systemic therapy based on tyrosine kinase inhibitors (TKIs), antiangiogenesis agents, and, recently, immunotherapy has since become the cornerstone of advanced HCC management.[7] Accordingly, in parallel with the increased understanding of disease pathogenesis, positive trials over the past 2 years have translated into approval by the US Food and Drug Administration (FDA) of 5 additional agents for the treatment of advanced HCC. This article reviews the rapidly expanding role of systemic therapy in HCC treatment and highlights emerging medication combinations that are paving the way for future therapeutic options.

Barcelona Clinic Liver Cancer Staging and Treatment Strategies

The Barcelona Clinic Liver Cancer (BCLC) staging system was developed by Llovet and colleagues in the late 1990s to help stratify patients with HCC based on survival outcomes and to direct patients to the best available therapy.[8] The classification system combines multiple variables (eg, tumor stage, liver function, performance status, cancer-related symptoms) in an algorithm and recognizes 5 stages for the disease. The BCLC staging system has been adopted as a standard by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver. Patients with very early HCC (stage 0) are candidates for tumor resection or radiofrequency ablation (Figure). Early-stage HCC (stage A) can be treated with curative-intent radical therapies such as resection, liver transplantation, percutaneous ethanol injection, or radiofrequency ablation. Intermediate-stage HCC (stage B) is generally treated with transarterial chemoembolization. Advanced HCC (stage C) is treated with systemic agents. End-stage HCC (stage D) patients have a survival of less than 3 months either due to poor liver function or very advanced HCC and may benefit from palliative care. Patients who fail or are not eligible for a certain treatment modality should be offered an alternative option within the same stage or the next BCLC stage.[7]

Assessing Response to Therapy

Designing clinical trials for systemic HCC therapy has been challenging due to the heterogeneity of the population with the disease and the difficulties faced when evaluating tumor response. In an attempt to standardize trial design, an expert panel convened by the AASLD in 2008 recommended using time-to-progression as the primary endpoint in phase 2 trials and OS as the primary endpoint in phase 3 trials when studying agents in the advanced HCC setting.[9] Disease and progression-free survival are believed to be unreliable endpoints in HCC studies because of the natural history of cirrhosis that might confound detection of any benefit from the medication.

Unlike cytotoxic chemotherapy, targeted agents may act as cytostatic agents, with a possible increase in inflammation leading to a tumor response without a measurable change in size.[9] The Response Evaluation Criteria in Solid Tumors (RECIST) assess changes in tumor size but ignore tumor necrosis, which is a common phenomenon after locoregional and systemic therapy. Thus, RECIST were thought to underestimate the response to some treatment modalities in HCC.[10] Modified RECIST (mRECIST) were developed in 2010 to overcome this limitation and to focus on the measurement of the viable portions of the tumor.[10] mRECIST take into consideration changes in the degree of tumor arterial enhancement in contrast-enhanced, multiphasic computed tomography or magnetic resonance imaging. Complete remission is defined as the disappearance of any intratumoral arterial enhancement in all target lesions. Lencioni and colleagues found that a higher objective response rate (ORR) by mRECIST to the systemic targeted therapy brivanib in patients with advanced HCC predicted OS benefit.[11] Although not universally validated and accepted as a standard, ORR by mRECIST could be considered a potential surrogate endpoint for OS in patients with HCC treated with systemic therapy.[11] Further research is required to confirm this observation.

The recent introduction of immune-targeted therapy added another layer of complexity to HCC response evaluation. While some patients have expected shrinkage or stabilization of their disease, others experience an initial increase in their tumor burden, known as pseudoprogression, related to an infiltration of cancer stroma by inflammatory cells. The immune-related response criteria have been proposed as an alternative to RECIST for the evaluation of response to immunotherapy, but they are yet to be validated or commonly used in ongoing clinical trials.[12]

Sorafenib as a Prototype Targeted Agent

Sorafenib is an oral multikinase inhibitor with antiproliferative and antiangiogenic properties that works by inhibiting vascular endothelial growth factor receptor (VEGFR) -2 and -3 tyrosine kinases, platelet-derived

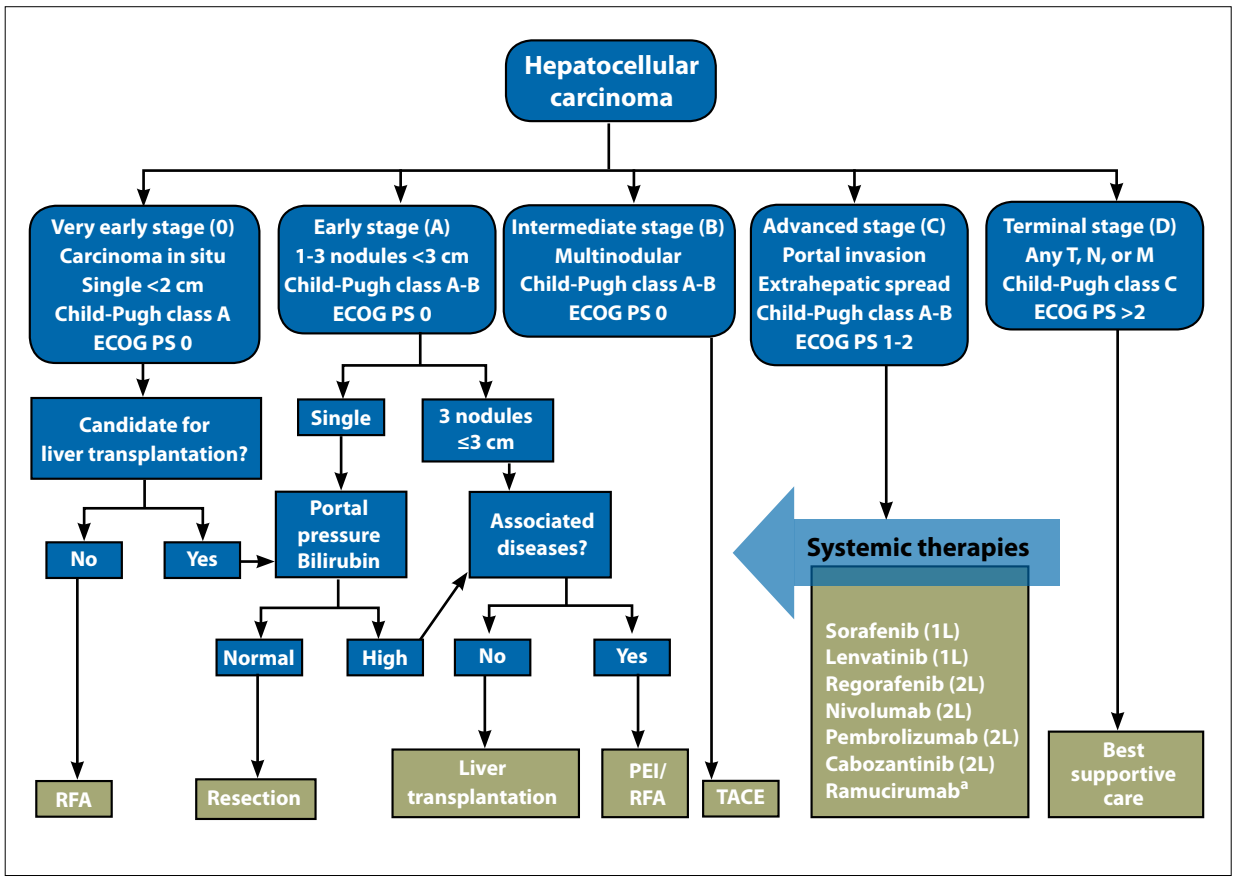

Figure. Barcelona Clinic Liver Cancer staging system and corresponding treatment options. Adapted from Llovet et al.[42]

1L, first-line; 2L, second-line; ECOG, Eastern Cooperative Oncology Group; M, metastasis stage; N, nodal stage; PEI, percutaneous ethanol injection; PS, performance status; RFA, radiofrequency ablation; T, tumor stage; TACE, transarterial chemoembolization.

[a]Under review by the US Food and Drug Administration.

growth factor receptor (PDGFR) -β tyrosine kinases, and rapidly accelerated fibrosarcoma kinases.[13] Sorafenib was approved in 2007 by the FDA as first-line therapy for unresectable HCC (BCLC stage C with Child-Pugh class A or BCLC stage B progressing after locoregional therapy) based on OS benefit in the phase 3 SHARP (Sorafenib in Advanced Hepatocellular Carcinoma) trial.[6] Compared with placebo in advanced HCC, sorafenib prolonged OS by 2.8 months (median OS, 10.7 months vs 7.9 months; hazard ratio [HR], 0.69; 95% CI, 0.55-0.87; *P*<.001) and was the first agent to demonstrate survival benefit.[6] Sorafenib was well tolerated, with diarrhea, fatigue, and hand-foot skin reaction reported as the main treatment-related adverse events. The patient population was mainly recruited from Europe and North America. Results of the Asia-Pacific trial published in 2009 confirmed sorafenib's efficacy in an Asian population.[14] The magnitude of benefit was comparable with that seen in the SHARP trial (HR, 0.68; 95% CI, 0.50-0.93; *P*=.014).[14] Sorafenib was initially approved for patients with well-preserved liver function; however, final results from the GIDEON (Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of its Treatment With Sorafenib) trial—a large prospective, observational, registry study evaluating the efficacy and tolerability of sorafenib in patients with liver dysfunction—highlighted a similar safety profile irrespective of Child-Pugh staging.[15] However, routine use of sorafenib in patients with underlying liver dysfunction is not recommended based on these noninterventional data alone, and, when opted for, the benefits and risks of therapy should be weighed carefully prior to initiation.

Combinations of sorafenib with other agents in the first-line setting have not yielded positive results to date. The SoraDox (Sorafenib Plus Doxorubicin Versus Sorafenib Alone for the Treatment of Advanced Hepatocellular Carcinoma) and SEARCH (Sorafenib Plus Erlotinib in Patients With Advanced Hepatocellular

Carcinoma) trials, which compared sorafenib in tandem with doxorubicin and erlotinib, respectively, to sorafenib monotherapy, failed to meet their primary efficacy endpoints.[16,17] Studies exploring earlier use of sorafenib with locoregional therapies in intermediate-stage HCC[18-20] and as adjuvant therapy after curative-intent local therapy[21] also did not meet their primary endpoints. Sorafenib remained the only available systemic therapy for advanced HCC until new therapies were approved in 2017.

New Systemic Therapies

Multikinase Inhibitors and Antiangiogenic Agents

Lenvatinib (Lenvima, Eisai) is an oral TKI of fibroblast growth factor receptor (FGFR), VEGFR, PDGFR-α, rearranged during transfection (RET), and KIT. In a phase 3 noninferiority trial,[22] lenvatinib was found to be noninferior but not statistically superior to sorafenib regarding OS (median OS, 13.6 months vs 12.3 months; HR, 0.92; 95% CI, 0.79-1.06). Additionally, lenvatinib demonstrated a statistically significant increase in ORR compared with sorafenib (ORR, 24.1% vs 9.2%; odds ratio, 3.13; 95% CI, 2.15-4.56; *P*<.001), the largest difference being driven by partial response rate (23% vs 9%).[22] Patients with more than 50% of the liver involved by HCC, obvious invasion of the bile duct, and/or invasion of the main portal vein were excluded from the study. Adverse effects including hypertension, diarrhea, low appetite, and weight loss occurred in a third of the patients. The results of this study led to the approval of lenvatinib for first-line therapy of unresectable HCC in August 2018.

Regorafenib (Stivarga, Bayer) is a potent oral inhibitor of angiopoietin-1 receptor (Tie2), VEGFR, PDGFR, and FGFR that was studied by Bruix and colleagues in patients who have progressed on and were tolerant to sorafenib.[23] The phase 3 RESORCE (Regorafenib for Patients With Hepatocellular Carcinoma Who Progressed on Sorafenib Treatment) trial demonstrated improvement in median OS with regorafenib compared with placebo in a second-line setting (10.6 months vs 7.8 months; HR, 0.63; 95% CI, 0.5-0.79; *P*<.001). Hypertension was the most common adverse effect, occurring in 15% of patients on regorafenib, followed by hand-foot skin reaction. Regorafenib was approved by the FDA based on this multinational study in patients who had previously been treated with sorafenib.

Cabozantinib (Cabometyx, Exelixis) is a small-molecule TKI with activity against c-Met, VEGFR-2, AXL, and RET.[24] Abou-Alfa and colleagues studied the use of cabozantinib vs placebo in patients with advanced HCC who progressed on sorafenib.[25] They noted an improvement in median OS (10.2 months vs 8.0 months; HR, 0.76; 95% CI, 0.63-0.92; *P*=.005). Hand-foot syndrome and hypertension were the most common adverse effects in the treated population. This trial led to the approval of cabozantinib in advanced HCC after progression on sorafenib. It is worth noting that 27% of the patients had received 2 previous systemic agents, including sorafenib, prior to testing cabozantinib. This in particular makes cabozantinib an agent of choice beyond second-line therapy in advanced HCC.

Ramucirumab (Cyramza, Lilly), an intravenous human monoclonal antibody directed against VEGFR-2, was evaluated in a population of patients with advanced HCC who had progressed on or been intolerant of sorafenib.[26,27] Zhu and colleagues initially found no statistically significant change in OS when comparing ramucirumab with placebo in the REACH (Ramucirumab After Sorafenib in Patients With Advanced Hepatocellular Carcinoma) trial (median OS, 9.2 months vs 7.6 months; HR, 0.87; 95% CI, 0.72-1.05; *P*=.14).[27] However, a post-hoc subgroup analysis of the REACH trial revealed improved survival in patients with a baseline α-fetoprotein serum level above 400 ng/mL compared with less than 400 ng/mL (median OS, 7.8 months vs 4.2 months; HR, 0.67; 95% CI, 0.51-0.9; *P*=.006).[27] Results of the confirmatory randomized, controlled REACH-2 trial were published in 2018. This study investigated the efficacy of ramucirumab vs placebo in 292 patients with advanced HCC and an α-fetoprotein serum level above 400 ng/mL.[28] Findings were similar to previous observations with ramucirumab, extending OS in this particular subset of patients (median OS, 8.5 months vs 7.3 months; HR, 0.71; 95% CI, 0.53-0.95; *P*=.0199).[28] Hypertension and hyponatremia were the only grade 3 adverse effects occurring in more than 5% of patients. Based on the REACH-2 trial findings, ramucirumab remains the only systemic agent to demonstrate clinical benefit in a biomarker-selected population in HCC. FDA approval of ramucirumab for HCC is currently pending.

Immunotherapy Agents

HCC is an immunogenic cancer, which is demonstrated in part by the presence of tumor-infiltrating lymphocytes in the tumor microenvironment.[29] Conversely, studies have also shown the presence of an immunosuppressive intratumoral milieu driven by constant exposure of the liver to antigens via the portal system and immune dysfunction related to cirrhosis.[30,31] These changes are responsible for a phenomenon of immune escape and make HCC an attractive target for immunotherapy, and for immune checkpoint inhibitors in particular. Monoclonal antibodies targeting cytotoxic T-lymphocyte protein 4, programmed cell death-1 (PD-1), and programmed death-ligand 1 (PD-L1) have shown activity

Table 1. Systemic Therapies Currently Approved or in Advanced Development for Hepatocellular Carcinoma

Therapy	Mechanism of Action	Target(s)	Phase of Development
Sorafenib	Oral multikinase inhibitor	VEGFR-2, VEGFR-3, PDGFR-β, RAF kinases	Approved in 2007
Lenvatinib	Oral multikinase inhibitor	FGFR, VEGFR, PDGFR-α, RET, KIT	Approved in 2018
Regorafenib	Oral multikinase inhibitor	Tie2, VEGFR, PDGFR, FGFR	Approved in 2017
Cabozantinib	Oral multikinase inhibitor	c-Met, VEGFR-2, AXL, RET	Approved in 2019
Nivolumab	Immune checkpoint inhibitor	PD-1	Approved in 2017
Pembrolizumab	Immune checkpoint inhibitor	PD-1	Approved in 2018
Ramucirumab	Intravenous monoclonal antibody	VEGFR-2	Under review by the US Food and Drug Administration

c-MET, tyrosine-protein kinase Met; FGFR, fibroblast growth factor receptor; PD-1, programmed cell death-1; PDGFR, platelet-derived growth factor receptor; RAF, rapidly accelerated fibrosarcoma; RET, rearranged during transfection; VEGFR, vascular endothelial growth factor receptor.

across multiple malignancies, including gastrointestinal cancers.[32]

Nivolumab (Opdivo, Bristol-Myers Squibb), a PD-1 inhibitor, received a conditional accelerated approval by the FDA in September 2017 for the treatment of HCC following prior sorafenib therapy. Approval was based on the results of a phase 1/2 dose escalation and expansion trial (CheckMate-040), in which nivolumab was tested in patients with advanced HCC with or without prior exposure to sorafenib.[33] This study showed an ORR of 15% (95% CI, 6%-28%) and 20% (95% CI, 15%-26%) in the escalation and expansion phases, respectively. Three complete and numerous partial responses were noted in each of the 2 phases. Tumor response was prolonged with a median OS of 15.6 months (95% CI, 13.2-18.9 months) in the treatment expansion cohort. Baseline tumor PD-L1 expression did not predict response to therapy. The most common treatment-related adverse events included rash, pruritus, and fatigue. Further trials are required to verify the clinical benefit of nivolumab in HCC. A confirmatory phase 3 trial (CheckMate-459) is currently testing nivolumab against sorafenib in the frontline setting.[34]

Pembrolizumab (Keytruda, Merck), another PD-1 inhibitor, has been tested in a global phase 2 trial after progression on or intolerance for sorafenib.[35] ORR was similar to nivolumab (17%; 95% CI, 11%-26%), with 1 complete and 17 partial responses. The median duration of response was not reached, and, at the time of this article, some responses were still ongoing. Twenty-four percent of patients experienced grade 3, treatment-related adverse effects, including transaminitis and fatigue. Based on the KEYNOTE-224 trial findings, the FDA approved pembrolizumab in November 2018 for patients who have previously received sorafenib. Results are undergoing confirmation in large phase 3 studies (KEYNOTE-240 and -394).[36,37] A summary of the systemic therapies for HCC that are currently available and under review can be found in Tables 1 and 2.

Table 2. Recommended Systemic Treatments for Hepatocellular Carcinoma Including Line of Therapy

Therapy	First-Line	Second-Line	Adjuvant
Sorafenib	Yes	N/A	No
Lenvatinib	Yes	N/A	N/A
Regorafenib	N/A	Yes	N/A
Cabozantinib	N/A	Yes	N/A
Nivolumab	N/A	Yes	N/A
Pembrolizumab	N/A	Yes	N/A
Ramucirumab	N/A	Under review	N/A

N/A, not applicable.

Future Perspectives

With the addition of multiple TKIs and immune checkpoint inhibitors to the armamentarium of agents directed against advanced HCC, the next logical step in drug development involves combination therapies and finding the right way to sequence medications in order to maximize survival benefit. Combinations currently being studied include 2 immune checkpoint inhibitors, an immune checkpoint inhibitor backbone with a TKI, immunotherapy with locoregional therapy, as well as an association of a TKI with transarterial chemoembolization. Recent data from a phase 1 trial combining atezolizumab (Tecentriq, Genentech; a PD-L1 inhibitor)

with bevacizumab (Avastin, Genentech; an anti-VEGF antibody) tested against sorafenib in the frontline setting showed an improved ORR of 34%.[38] The combination of durvalumab (Imfinzi, AstraZeneca; a PD-L1 inhibitor) and tremelimumab (a cytotoxic T-lymphocyte–associated protein 4 inhibitor) was well tolerated in a phase 1/2 study in advanced unresectable disease.[39] Safety and efficacy are being confirmed in the phase 3 HIMALAYA (Study of Durvalumab and Tremelimumab as First-line Treatment in Patients With Advanced Hepatocellular Carcinoma) trial.[40]

It is safe to predict an upcoming shift to the left for systemic therapy in the treatment of HCC (Figure). Immune-modulating drugs appear to be safe and may rapidly become integrated in first-line regimens of advanced or intermediate-stage HCC. Furthermore, with the increased insight into liver cancer biology and genomics, classification of HCC is actively evolving[41] with the hope of fulfilling the promise of precision medicine in a cancer that is known for poor prognosis and limited responsiveness to systemic therapy.

Summary

The treatment landscape of HCC is changing at a rapid pace. Multiple oral kinase inhibitors and 2 immunotherapy agents are now available for treatment of advanced HCC. Phase 3 trials are studying different combinations of drugs in various lines of therapy with the hope of extending OS of patients beyond current standards. Further drug approvals and earlier use of systemic therapy are expected in the field of HCC management. However, despite all of these pharmacologic advances, prevention of HCC remains essential. Hepatitis B virus vaccination, hepatitis C virus screening and treatment, alcohol abstinence, weight loss in obese patients, and active surveillance of cirrhotic patients for the development of suspicious liver lesions are all important measures proven to help decrease the burden of advanced HCC. HCC might be on the rise, but improved understanding of its genesis, its early detection, and its management may contribute to curbing the epidemic.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. 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.
2. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med*. 1999;340(10):745-750.
3. El-Serag HB. Hepatocellular carcinoma. *N Engl J Med*. 2011;365(12):1118-1127.
4. El-Serag HB, Kanwal F. Epidemiology of hepatocellular carcinoma in the United States: where are we? Where do we go? *Hepatology*. 2014;60(5):1767-1775.
5. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology*. 2004;127(5)(suppl 1):S35-S50.
6. Llovet JM, Ricci S, Mazzaferro V, et al; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359(4):378-390.
7. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2018;69(1):182-236.
8. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis*. 1999;19(3):329-338.
9. Llovet JM, Di Bisceglie AM, Bruix J, et al; Panel of Experts in HCC-Design Clinical Trials. Design and endpoints of clinical trials in hepatocellular carcinoma. *J Natl Cancer Inst*. 2008;100(10):698-711.
10. Kim MN, Kim BK, Han K-H, Kim SU. Evolution from WHO to EASL and mRECIST for hepatocellular carcinoma: considerations for tumor response assessment. *Expert Rev Gastroenterol Hepatol*. 2015;9(3):335-348.
11. Lencioni R, Montal R, Torres F, et al. Objective response by mRECIST as a predictor and potential surrogate end-point of overall survival in advanced HCC. *J Hepatol*. 2017;66(6):1166-1172.
12. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res*. 2009;15(23):7412-7420.
13. Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res*. 2004;64(19):7099-7109.
14. Cheng A-L, Kang Y-K, 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.
15. 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(6):1140-1147.
16. Ettrich T, Perkofer L, Berger AW, et al. Sorafenib plus doxorubicin versus sorafenib alone for advanced hepatocellular carcinoma (Soradox trial): final results of a prospective, randomized, open-label, multicenter phase IIb trial. *Eur J Cancer*. 2015;51(suppl 3):S457.
17. Zhu AX, Rosmorduc O, Evans TRJ, 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(6):559-566.
18. Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: the SPACE trial. *J Hepatol*. 2016;64(5):1090-1098.
19. Kudo M, Imanaka K, Chida N, et al. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. *Eur J Cancer*. 2011;47(14):2117-2127.
20. Meyer T, Fox R, Ma YT, et al. Sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma (TACE 2): a randomised placebo-controlled, double-blind, phase 3 trial. *Lancet Gastroenterol Hepatol*. 2017;2(8):565-575.
21. Bruix J, Takayama T, Mazzaferro V, et al; STORM investigators. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2015;16(13):1344-1354.
22. 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):1163-1173.
23. Bruix J, Qin S, Merle P, et al; RESORCE Investigators. 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.
24. Yakes FM, Chen J, Tan J, et al. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. *Mol Cancer Ther*. 2011;10(12):2298-2308.
25. Abou-Alfa GK, Meyer T, Cheng A-L, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med*. 2018;379(1):54-63.
26. Spratlin JL, Cohen RB, Eadens M, et al. Phase I pharmacologic and biologic

study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. *J Clin Oncol*. 2010;28(5):780-787.
27. Zhu AX, Park JO, Ryoo B-Y, et al; REACH Trial Investigators. 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):859-870.
28. Zhu AX, Kang Y-K, Yen C-J, et al. REACH-2: a randomized, double-blind, placebo-controlled phase 3 study of ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated baseline alpha-fetoprotein (AFP) following first-line sorafenib [published online June 1, 2018]. *J Clin Oncol*. doi:10.1200/JCO.2018.36.15_suppl.4003.
29. Yoong KF, McNab G, Hübscher SG, Adams DH. Vascular adhesion protein-1 and ICAM-1 support the adhesion of tumor-infiltrating lymphocytes to tumor endothelium in human hepatocellular carcinoma. *J Immunol*. 1998;160(8): 3978-3988.
30. Thomson AW, Knolle PA. Antigen-presenting cell function in the tolerogenic liver environment. *Nat Rev Immunol*. 2010;10(11):753-766.
31. Albillos A, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. *J Hepatol*. 2014;61(6):1385-1396.
32. Jindal V. Immune checkpoint inhibitors in gastrointestinal malignancies. *J Gastrointest Oncol*. 2018;9(2):390-403.
33. 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): 2492-2502.
34. Sangro B, Park J-W, Dela Cruz CM, et al. A randomized, multicenter, phase 3 study of nivolumab vs sorafenib as first-line treatment in patients (pts) with advanced hepatocellular carcinoma (HCC): CheckMate-459 [published online May 11, 2017]. *J Clin Oncol*. doi:10.1200/JCO.2016.34.15_suppl.TPS4147.
35. Zhu AX, Finn RS, Edeline J, et al; KEYNOTE-224 Investigators. 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):940-952.
36. Finn RS, Chan SL, Zhu AX, et al. KEYNOTE-240: randomized phase III study of pembrolizumab versus best supportive care for second-line advanced hepatocellular carcinoma [published online March 21, 2017]. *J Clin Oncol*. doi:10.1200/JCO.2017.35.4_suppl.TPS503.
37. ClinicalTrials.gov. Study of pembrolizumab (MK-3475) or placebo given with best supportive care in Asian participants with previously treated advanced hepatocellular carcinoma (MK-3475-394/KEYNOTE-394). https://clinicaltrials.gov/ct2/show/NCT03062358. Identifier: NCT03062358. Accessed April 18, 2019.
38. Pishvaian MJ, Lee MS, Ryoo B-Y, et al. LBA26 Updated safety and clinical activity results from a phase Ib study of atezolizumab + bevacizumab in hepatocellular carcinoma (HCC) [published online October 23, 2018]. *Ann Oncol*. doi:10.193/annonc/mdy424.028.
39. Kelley RK, Abou-Alfa GK, Bendell JC, et al. Phase I/II study of durvalumab and tremelimumab in patients with unresectable hepatocellular carcinoma (HCC): phase I safety and efficacy analyses [published online May 30, 2017]. *J Clin Oncol*. doi:10.1200/JCO.2017.35.15_suppl.4073.
40. Abou-Alfa GK, Chan SL, Furuse J, et al. A randomized, multicenter phase 3 study of durvalumab (D) and tremelimumab (T) as first-line treatment in patients with unresectable hepatocellular carcinoma (HCC): HIMALAYA study [published online June 1, 2018]. *J Clin Oncol*. doi:10.1200.JCO.2018.36.15_suppl. TPS4144.
41. Hoshida Y, Toffanin S, Lachenmayer A, Villanueva A, Minguez B, Llovet JM. Molecular classification and novel targets in hepatocellular carcinoma: recent advancements. *Semin Liver Dis*. 2010;30(1):35-51.
42. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet*. 2003;362(9399):1907-1917.