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REVIEW ARTICLE

Goals and targets for personalized therapy for HCC

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Abstract
Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality worldwide and its incidence continues to rise. While cirrhosis underlies most cases of HCC, many molecular pathways are implicated in HCC carcinogenesis, including the TERT promoter mutation, Wnt/β-catenin, P53, Akt/mTOR, vascular endothelial growth factor receptor (VEGFR), and endothelial growth factor receptor (EGFR)/RAS/MAPK pathways. While the most widely used staging and treatment algorithm for HCC—the Barcelona Clinic Liver Cancer (BCLC) system—does not recommend systemic molecular therapy for early HCC, a variety of treatment options are available depending upon the stage of HCC at diagnosis. Determining the best treatment options must take into account not only the burden and extent of HCC, but also the patient's performance status, underlying liver function, extra-hepatic disease and co-morbidities. Radiofrequency or microwave ablation, liver resection, or liver transplantation, all potential curative therapies for HCC, should be the first-line treatments when possible. For patients who are not candidates of curative treatments, locoregional therapies such as transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and stereotactic body radiation (SBRT) can improve survival and quality of life. Sorafenib, a multi-kinase VEGF inhibitor, is the most widely used systemic chemotherapy approved as a first-line agent for unresectable or advanced HCC. Clinical trials are underway directed towards molecular therapies that target different aspects of the hepatocellular carcinogenesis cascade. Ideally, the goal of future therapy should be to target multiple pathways in the HCC cascade with combination treatments to achieve personalized care aimed at improving overall survival.

Keywords Hepatocellular carcinoma · Liver transplant · Locoregional therapy · Molecular drivers · Targeted treatment

Introduction

Surgical, locoregional, and systemic therapies are used in the treatment of HCC. Determining the best treatment for any given patient depends on many parameters, including the degree of underlying liver disease, the size and extent of the tumor, the presence of vascular invasion, and the patient's performance status. With the advent of targeted molecular therapies, treatment tailored to individual patients will be the future of HCC care. In this article, we briefly review the epidemiology, pathogenesis, presentation, diagnosis, and staging of HCC. We then review the evidence-based treatments and focus on goals and targets for personalized therapy for HCC.

Epidemiology and classification

HCC is the sixth most commonly diagnosed cancer worldwide [1]. The incidence of HCC is increasing, with approximately 782,000 new cases in 2012 [1]. An increasing mortality rate parallels HCC's rising incidence, with 745,000 people globally dying of HCC in 2012, making up 9.1% of cancer-related mortality and making it the third leading cause of cancer-related mortality worldwide [1].

An estimated 70–90% of HCC cases arise in the setting of cirrhosis [2]. Genetic mutations, chromosomal aberrations, molecular signaling pathways, and epigenetic deregulation have been implicated in hepatocellular carcinogenesis. Using whole-exome sequencing, Zucman-Rossi and colleagues identified six predominant pathways implicated in HCC [3]:

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(1) Telomere maintenance, aided by telomerase, a protein in which the TERT enzyme is essential, is defective in more than 90% of human HCCs [3]. TERT promoter mutations occur in 60% of HCCs and are one of the earliest recurrent somatic genetic alterations seen; integration of HBV DNA into the TERT promoter region and TERT amplification are other mutations seen in HCC [3–5].
(2) The most common oncogenic mutational pathway in HCC is the Wnt/β-catenin pathway [3]. The CTNNB1 gene encodes for β-catenin, which has been implicated as an activating mutation in 11–47% of HCCs; inactivation of the AXIN1 or APC genes also accounts for initiation of the Wnt/β-catenin pathway [3, 6]. Calderaro et al. classified HCC into two principal distinct phenotypes, the CTNNB1 and the TP53 phenotypes [4]. HCCs classified as CTNNB1 tumors are more likely to be large and well differentiated [4].
(3) The P53 cell-cycle pathway is another commonly affected pathway in HCC carcinogenesis [3–6]. Inactivation of this tumor suppression cascade leads to unregulated cell-cycle activity, and the most common mutation for HCC patients is in the TP53 gene (12–48%) [3]. HCCs classified as TP53 tumors are more likely to be poorly differentiated, associated with vascular invasion, multinucleated, and pleomorphic [4].
(4) Epigenetic modifiers involved in histone methylation (MLL, MLL2, MLL3, and MLL4 genes) and chromatin remodeling (ARID1A, ARID2) are mutated in 2–18% of HCC cases [3].
(5) Mutations involved in the oxidative stress pathway, such as NFE2L2 and KEAP1, lead to prolonged cell life and tumor growth [3].
(6) PI3 K/AKT/mTOR and RAS/RAF/mitogen-activated protein kinase (MAPK) pathway elements are mutated in some HCCs [3]. The PI13 K/AKT signaling pathway, similar to the RAS/MAPK pathway, is downstream of tyrosine kinase receptors and is involved in cell growth, spread, and survival. Dysregulation of this pathway has been associated with hepatocellular carcinogenesis; of note, mammalian target of rapamycin (mTOR) is a molecule involved in the PI13 K/AKT pathway, and inhibition of the mTOR pathway has shown to stop HCC growth in cell lines [7]. Endothelial growth factor receptor (EGFR) is a transmembrane protein that participates in cell proliferation and survival. If upregulation of EGFR occurs by mutation, cell differentiation, proliferation, and survival can be sustained via activation of downstream RAS/MAPK and AKT pathways. EGFR mutation has been variably associated with HCC, in as little as 4% to as much as 66% of cases [7, 8]. Vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) aberration in hepatocellular carcinogenesis, whose expression correlates with HCC and metastatic disease, lead to upregulation of angiogenesis as well as cell proliferation due to downstream upregulation of the RAS/MAPK pathways [8].

Other genetic pathways involved in hepatic differentiation, such as CFH, are estimated to affect 34% of HCCs [5]. Mutations in the IL-6/JAK/STAT and transforming growth factor (TGF)-β are seen in 9% and 5% of HCCs, respectively [5]. Other affected pathways include insulin-like growth factor (IGF), Hedgehog, and mesenchymal epithelial transition (MET) pathways [7–10].

Of note, in addition to classifying HCCs phenotypically, Calderaro and colleagues also created a classification system for HCCs along genetic and clinical features. Six groups exist, labeled G1–G6. G1–G3 subgroups are marked by TP53 mutations, chromosomal instability and marked cell proliferation, and elevated serum alpha-fetoprotein (AFP) levels [4]. G4–G6 subgroups are notable for being well differentiated, having stable chromosomal features, and little cell proliferation [4]. Certain etiologies of HCC have been shown to be associated with distinct genetic aberrations. HCC caused by HBV is more likely to contain TP53 mutations and alcohol-induced HCC is more likely to contain TERT and CTNNB1 mutations [5].

Diagnosis and treatment

Diagnosis

Multiple clinical guidelines for HCC surveillance exist. The most widely accepted is bi-annual imaging with ultrasound (with or without serum AFP level), summarized in Table 1 [11–13]. Table 2 describes the level of evidence of these recommendations based upon the GRADE system [14]. Most HCC diagnoses are attained radiographically because of excellent imaging accuracy and due to the adverse risks of biopsy, including false-negative results and tumor seeding and spread [13]. Initial diagnostic imaging is often performed using ultrasound, which has a sensitivity of 58–70% [15]. Both computed tomography (CT) abdomen and magnetic resonance imaging (MRI) abdomen use arterial and venous phase images to aid in diagnosis and have higher sensitivity and specificity for HCC detection compared to ultrasound. Characteristic findings on CT and MRI include arterial phase hyperenhancement with washout during delayed venous phase [16–18]. The sensitivity and specificity of CT are 81% and 93%, respectively, compared to 91% and 95%, respectively, for MRI [19].

Table 1 HCC surveillance recommendations

Hepatology organization	Imaging	Biochemical markers	Screening interval	Level of evidence for screening high-risk patients
AASLD	Ultrasound	± AFP	Biannually	B1
APASL	Ultrasound	+ AFP	Biannually	B2
EASL	Ultrasound	− AFP	Biannually	A1/2

AASLD American Association for the Study of Liver Diseases, *APASL* Asian Pacific Association for the Study of the Liver, *EASL* European Association for the Study of the Liver

Table 2 The GRADE system of recommendations based upon classification of evidence

evidence grade	Explanation	Symbol
High quality	Further research is unlikely to change our confidence in the estimate of the effect	A
Moderate quality	Further research his likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low or very low quality	Further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate. Any estimate of effect is uncertain	C
Recommendation grading		
Strong	Factors influencing the strength of the recommendation included the quality of the evidence, presumed important patient outcomes, and cost	1
Weaker	Variability in preferences and values, or more uncertainty; more likely a weak recommendation is warranted. Recommendation is made with less certainty; higher costs or resource consumption	2

Staging

Staging is paramount for HCC as it determines proper treatment and prognosis. At least 18 different staging systems have been proposed, and the Barcelona Clinic Liver Cancer (BCLC) system (Fig. 1) is among the most widely accepted [17]. The BCLC staging system takes into account underlying hepatic function as assessed by the Child–Pugh (CP) score (Table 3), performance status (PS) as measured by the Eastern Cooperative Oncology Group (ECOG) (Table 4), and tumor factors including extension into the portal vein or extra-hepatic spread; it also provides treatments and prognoses for each specific sub-classification. These sub-classifications are 0 (very early), A (early), B (intermediate), C (advanced), and D (end or terminal stage) [20–22].

Two studies comparing different staging modalities have shown BCLC's superiority in predicting survival as compared to other systems [18]. Both the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) have recommended BCLC for HCC staging [12, 23]. Figure 2 summarizes other commonly used HCC staging systems [18, 20, 21].

Treatment

Curative treatment

Radiofrequency ablation (RFA), liver resection (LR), and liver transplantation (LT) are the only potential curative treatments for HCC. These treatments are indicated for patients with Stage 0 (very early stage) or Stage A (early stage) disease. Percutaneous treatment options include RFA, microwave ablation and cryoablation. RFA entails inserting a needle into a tumor under imaging guidance and delivering an electric current to induce cell necrosis [24, 25]. Complications, such as intra-abdominal hemorrhage, infection, biliary tract injury, and tumor seeding, occur in approximately 7–9% of cases; mortality rates are less than 0.5% [26, 27]. Limitations of RFA include the heat-sink effect, in which vessels close to the ablation zone reduce the heat delivered to the tumor and, thus, RFA's cytotoxic capacity, and its restriction based upon the location of the tumor [27].

RFA has an approximately 70% 5-year survival rate when employed as the treatment for stage A disease. A large prospective cohort study of almost 1200 patients detailed a 5- and 10-year survival rates of 60.2% and 27.3%, respectively [28]. Debate exists among experts when to use RFA versus LR or LT; however, the BCLC algorithm and Western hepatology associations typically recommend RFA when a patient has either stage 0 or stage A disease with elevated portal pressures and other co-morbidities that make the patient a challenging or unsuitable surgical candidate [21, 29]. Three randomized controlled trials of patients with either solitary or multiple HCC lesions, none greater than 5 cm, compared RFA and LR, with two trials showing no difference in disease-free and overall survival, while one study showed a survival benefit with surgery [30–32]. Two recent meta-analyses, however, have shown improved

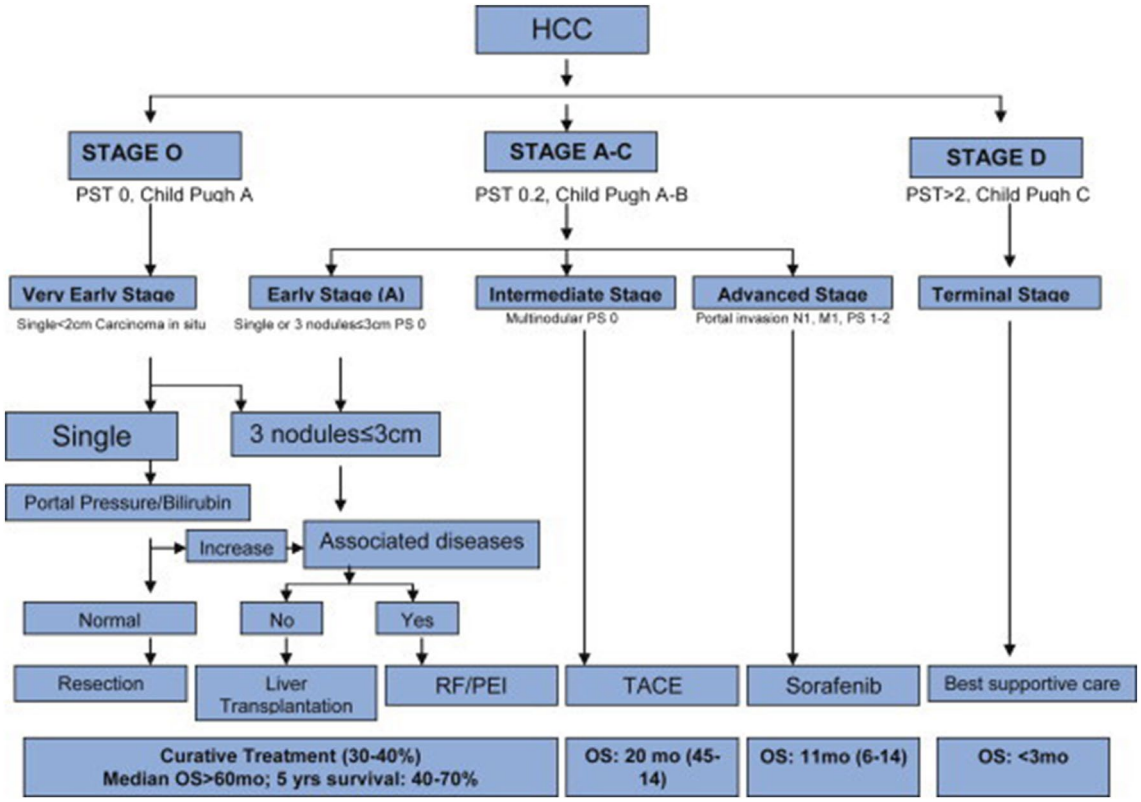

Fig. 1 Barcelona Clinic Liver Cancer (BCLC) staging system with associated treatment recommendations

Table 3 Child–Pugh Score

Clinical/lab criteria	1	2	3
Encephalopathy	None	Mild–moderate (grade 1–2)	Severe (grade 3–4)
Ascites	None	Mild–moderate (diuretic-responsive)	Severe (refractory to diuretics)
Bilirubin (mg/dL)	< 2.0	2–3	> 3
Albumin (g/dL)	> 3.5	2.8–3.5	< 2.8
INR	< 1.7	1.7–2.3	> 2.3

CP Class A: 5–6 points; CP Class B: 7–9 points; CP Class C: 10–15 points

recurrence-free and overall survival with LR versus RFA [33, 34].

For a patient with HCC and either stage 0 or stage A HCC without contraindications to surgery, LR or LT is the preferred therapy. LR is indicated for very early stage HCC (singular tumor focus, < 2 cm in size) without portal hypertension or elevated bilirubin [20, 35–38]. The in-hospital mortality rate after LR is < 3% [35]. Complications include liver failure, infection, thrombosis, and bleeding [36]. Survival rates for LR vary according to techniques and treatments used at the time of analysis as well as HCC characteristics and stage, but 5-year overall survival estimates range from 13 to 81%, with most studies documenting 25–55% [36, 37, 39, 40]. A study of very early stage disease patients with CP class A disease and normal platelet counts showed an overall 5-year survival of 81% after LR [40]. Determining variables affecting survival post-LR include TNM stage, positive resection margins, and microvascular invasion [35]. LR has been consistently associated with a high HCC recurrence rate, estimated at 60–100% within 5 years [36–38].

Patients with stage A disease and underlying cirrhosis who can safely undergo surgery should receive LT as treatment for their HCC. While LT carries the advantage of complete resection of a localized tumor, it also removes the underlying field defect by curing the patient's cirrhosis. The disadvantages of LT include a higher morbidity and early mortality compared to LR and the shortage of available donor grafts. Less than 30% of patients with HCC qualify for LT at diagnosis, largely due to late presentation of disease [34]. Factors influencing survival post-LT include the use of adjuvant treatment, immunosuppression regimens, ischemia time, and tumor burden [41]. Most US transplant centers use the Milan Criteria (Fig. 3) to assess if a patient qualifies for

Table 4 Performance status measurements as assessed by the Eastern Cooperative Oncology Group (ECOG) and Karnofsky Scale

Score (ECOG; Karnofsky)	ECOG	Karnofsky
0, 100–90	Fully active, able to carry on all pre-disease performance without restriction	100: Normal, no complaints, no evidence of disease 90: Able to carry on normal activity, minor signs of symptoms of disease
1, 80–70	Restricted in physically strenuous activities but ambulatory and able to carry out work of a light or sedentary nature	80: Normal activity with effort, some signs of symptoms of disease 70: Cares for self but unable to carry on normal activity or to do active work
2, 60–50	Ambulatory and capable of all self-care but unable to carry out any work activities; Up and about > 50% of waking hours	60: Requires occasional assistance but is able to care for most of personal needs 50: Requires considerable assistance and frequent medical care
3, 40–30	Capable of only limited self-care, confined to bed or chair > 50% of waking hours	40: Disabled; requires special care and assistance 30: Severely disabled; hospitalization is indicated although death not imminent
4, 20–10	Completely disabled; cannot carry on any self-care. Totally confined to bed or chair	20: Very ill; hospitalization and active supportive care necessary 10: Moribund
5, 0	Dead	Dead

HCC based on the tumor size and number of nodules [42]. Other expanded criteria, which demonstrate equivalent survival rates in selected patients, include the UCSF Criteria and Up-to-seven criteria (Fig. 3) [43–46]. Five-year overall survival rates for LT range from 62 to 94%, depending on HCC stage, with most estimates near 70% [36–38, 47–49].

Several studies have been performed to compare the survival and recurrence rates of LR and LT to determine the most efficacious therapy. After adjusting for stage, overall 5-year survival rates do not differ between LR and LT, although one study has shown improved overall survival for LT [36, 37, 48, 49]. While LT offers the additional benefit of curing cirrhosis, in an era of scarce grafts and equivalent survival rates, LR is considered as the first-line treatment for stage 0 disease. On the other hand, LT has consistently proven to have lower 5-year recurrence rates than LR (18% versus 67%) and better longer-term disease-free survival [39].

Palliative treatments

TACE Transarterial chemoembolization (TACE) is the standard of care for BCLC stage B (intermediate stage) HCC. Predominant blood supply to HCCs is via the hepatic artery, as opposed to normal liver parenchyma, which obtains 75% of its blood supply from the portal vein [49]. In patients undergoing conventional TACE, this selective arterial perfusion is taken advantage of by delivering an emulsion or suspension of doxorubicin, cisplatin, or mitomycin C in an iodinated lipid compound locally to the tumor, subsequently followed by injection of an embolic agent [50–52]. The combination of direct cytotoxicity from chemotherapeutic agents and ischemia from selective embolization induces tumor necrosis; embolization also has the added effect of reducing washout and systemic chemotherapy toxicity [52]. TACE is used in patients who have unresectable HCC, defined as larger than 5 cm, and for palliative purposes [53]. Indications include multinodular tumors in patients with CP A or B disease and a performance status of 0 [51, 52, 54–58]. Decompensated cirrhosis, portal vein thrombosis (PVT), large bilobar tumors, GFR less than 30 mL/min, and extra-hepatic spread are contraindications to TACE [52, 53, 59]. The most common side effect, prevalent in 35–100% of patients undergoing TACE, is post-embolization syndrome, a constellation of fever, abdominal pain, nausea, and vomiting. Potential complications include liver failure, biliary or hepatic artery injury, and infection; mortality rates from TACE are less than 2% [51, 60].

TACE has been shown to improve overall survival compared to best supportive care (BCS) for stage B HCC, from a mean of 16 months to 20 months [51, 52, 58, 59]. A randomized controlled trial (RCT) that selected for BCLC stage B patients (70% of whom had CP A disease) showed a 2-year survival of 63% for patients who received TACE, significantly improved from the 2-year survival rate of 27% for patients who received BCS [52]. Drug-eluting beads (DEB)-TACE is another locoregional therapy similar to conventional TACE except for the addition of polyvinyl alcohol hydrogel beads which cause a sustained release of chemotherapy. DEB-TACE has not been shown to improve survival compared to TACE but has demonstrated less systemic and hepatic toxicity due to slow and sustained release of chemotherapy [51, 57].

Fig. 2 Commonly used HCC staging systems (Okuda, TNM, CLIP, French/GRETCH, CUPI, JIS, Tokyo Score). *TNM* tumor-node-metastasis, *CLIP* cancer of the liver Italian program, *GRETCH* Groupe d'Etude et de Traitement du Carcinome Hépatoc ellulaire, *CUPI* Chinese University Prognostic Index, *JIS* Japan Integrated Staging Score

TARE Transarterial radioembolization (TARE) is another locoregional therapy which uses radioactive yttrium-90 (Y-90), iodine-131 (131I), or rhenium-188 (188Re) to selectively inject radioactive microspheres intra-arterially to cause radiation-induced cell necrosis. TARE is a two-staged procedure compared to TACE [61–63]. During the first step, an angiogram is performed to assess vascularity, and coil embolization of non-HCC supplying hepatic artery branches is carried out as necessary to prevent radioactive spread to non-HCC tissue. Technetium-labeled albumin is then injected into the arterial system and its distribution is assessed using single photon emission computed tomography (SPECT). This scintigraphy is mandatory to evaluate for potential spread of radiation outside of the target HCC lesion (i.e., evaluate for shunts to the lung and splanchnic system) and to anticipate treatment response and determine radiation dosing [59, 60, 62]. Shortly after this initial mapping procedure, the second session is performed, which consists of the actual delivery of radioactive-containing microspheres to the tumor [62].

Similar to TACE, TARE is indicated for BCLC Stage B patients. Absolute contraindications include metastatic

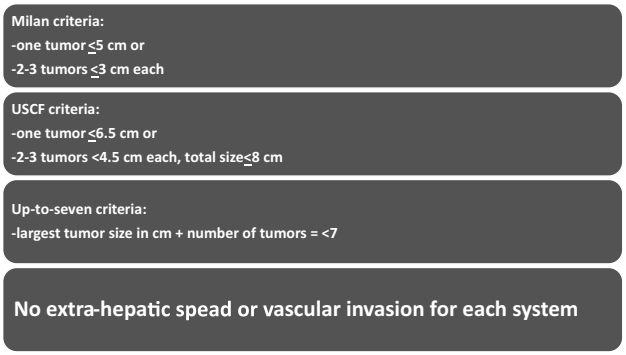

Fig. 3 Composion of the Milan criteria, UCSF criteria, and Up-to-seven criteria, three different standards for assessing whether HCC is transplantable

HCC, ECOG > 2, decompensated cirrhosis, inability to prevent radioactive washout to the gastrointestinal tract, lung shunting of microspheres greater than 20% (as measured by SPECT), and greater than 50 gray of radiation exposure cumulatively to the lungs [63]. In contrast to TACE, TARE can be performed in patients with PVT because of the lack of vascular embolization during the treatment phase of TARE. Furthermore, experts have promoted TARE over TACE in Stage B patients with more than five tumors or those with bilobar disease as well due to improved survival [59, 62]. Most complications of TARE stem from radiation, including radiation-induced liver disease (RILD), liver failure, radiation pneumonitis, post-embolization syndrome, and biliary complications.

Although TARE has proven efficacy for BCLC Stage B HCC in terms of improvement of overall survival, the superiority of TACE or TARE in this patient population has not been established. TARE has been shown to be safe with clear treatment response; in fact, one study showed a 79% tumor response rate [64–66]. Another study revealed a 100% disease control rate but only 23.8% tumor response rate [67]. Survival rates with TARE vary; one study reported median survival of 16.9 months in BCLC Stage B patients, and another retrospective analysis demonstrated a median survival of 14 months when TARE was used as first-line therapy compared to 8 months in patients receiving standard therapy [62, 67]. Although no RCTs have been published comparing TARE to TACE because of the large number of patients who would need to be enrolled to assess superiority, an analysis comparing TACE and TARE with unresectable HCC demonstrated equivalent survival rates but longer time to progression (13.3 months versus 8.4 months) and less side effects with TARE [65].

Radiation

External beam radiation therapy (RT), particularly stereotactic body radiation therapy (SBRT), is another option for treatment of HCC. Patients with non-resectable HCC, portal vein tumor invasion, and extra-hepatic metastases have been shown to benefit from RT [68–72]. Experts have varying recommendations on optimal candidates for this therapy. One group advised using SBRT specifically for patients with non-resectable HCC with ≤ 3 lesions, with largest lesion less than 6 cm and no extra-hepatic metastases, CP A or B disease, and Karnofsky performance score of greater than 70 [69]. Tumors near the gastrointestinal tract should not be irradiated due to the increased risk of radiation-induced inflammation and bleeding [71]. Of note, symptomatic extra-hepatic disease is an indication for SBRT. Palliative radiation has been shown to improve pain from metastatic lesions [70]. While there have not been RCTs comparing SBRT to varying accepted treatments for different stages of HCC, studies have shown 1-year local control rates of 72–100%, complete response rates of 20–60% and 2-year overall survival rates of 21–69% when employing SBRT [66–71].

Downstaging HCC and bridging to transplantation

Two important scenarios for multiple HCC treatment modalities, with clearly proven benefit, are downstaging non-transplantable HCC into either Milan or UCSF Criteria and bridging HCC to transplantation by preventing waitlist drop-out. The most common treatment modality employed for downstaging and bridging is TACE. However, TARE, RFA, ethanol ablation, surgical resection, and radiation have been used as well; up to an estimated 50% of patients on the liver transplant list receive locoregional treatment [73, 74]. An estimated 6–28% of patients who receive downstaging therapies then become candidates for resection [73]. Depending on the criteria used to assess suitability for transplant, downstaging has a 24–90% success rate [73]. One of the first prospective studies examining downstaging demonstrated a 70.5% success rate employing TACE, RFA, ethanol ablation, or resection, with 1- and 4-year post-transplant survival rates of 96.2% and 92.1%, respectively [72]. TACE is frequently used for tumors larger than 3 cm, and has been shown to have a 54% downstaging success rate in one study [74]. RFA is utilized as well, with tumors less than 3 cm being associated with successful downstaging; complete tumor necrosis rates after RFA have been reported as high as 90%, with one study reporting a mean of 58% [74, 75]. Multiple studies document a 3.0–9.3% drop-out rate after TACE and a 0–21% drop-out rate after RFA [76]. TARE has been compared to TACE in downstaging T3 lesions to T2, with TARE having significant more success (58% compared to 31% with TACE) in downstaging. TARE also showed

improved overall survival (censored 35.7–18.7 months, uncensored 41.6–19.2 months) compared to TACE in the same study [75]. TACE has been shown to lead to complete tumor necrosis rates of 27–57%, and one study demonstrated a complete tumor necrosis rate of 77% for DEB-TACE [76]. A systematic review and pooled analysis, however, showed no differences in success or recurrence rates post-transplant between TACE and TARE [77].

Bridging therapies are used with the intent to prevent drop-out on the transplant list. For patients on the wait-list who do not receive any bridging treatments, 1-year drop-out rates are greater than 30% [76]. HCC patients who undergo liver resection prior to liver transplant had similar 3- and 5-year survivals as those who underwent liver transplant alone [78].

Sorafenib

Sorafenib, a multikinase inhibitor, is indicated for BCLC Stage C (advanced stage) HCC, with underlying CP A or B score and PS of 1–2 [18]. Sorafenib has many different molecular targets, including the RAF/MAPK/extra-cellular signal-related kinase (ERK) pathway, which promotes cell growth and survival; the tyrosine kinases vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR), which all promote angiogenesis; and the anti-apoptotic protein Mcl-1 [8, 9, 79]. Advanced-stage HCC correlates with increased activity of the RAF/MAPK/ERK pathway and increased levels of VEGF and FGF-2 [9]. The most common side effects associated with sorafenib are hand–foot syndrome, diarrhea, and fatigue [79–81].

Two multicenter RCTs established the efficacy of sorafenib in advanced HCC. The Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial which enrolled patients from North America, Europe and Australia compared sorafenib to placebo and showed an improved median overall survival of 10.7 months with sorafenib versus 7.9 months with placebo; the median time to radiologic progression was also prolonged, to 5.5 months from 2.8 months, with sorafenib [81]. A similar RCT was carried out in China, South Korea, and Taiwan (the Asia Pacific trial) which again showed a significant improved median overall survival with sorafenib of 6.5 months versus placebo of 4.2 months [82]. The decreased median overall survival in the latter study compared to SHARP may have been secondary to the Asian–Pacific region study having a higher proportion of patients with a PS of 2, more metastatic disease to the lung, and a larger tumor burden [80].

Other molecular therapy

Other small molecule inhibitors have been studied for the treatment of advanced HCC; however, most have failed. Sunitinib, a multikinase inhibitor that targets PDGFR, FLT-3, c-KIT, and VEGFR, was demonstrated to be inferior to sorafenib in advanced HCC, with median overall survival for patients assigned to the sorafenib group 10.2 months versus 7.9 months for sunitinib [79]. Brivanib is a multi-kinase inhibitor that targets FGFR and VEGFR. A RCT comparing brivanib and sorafenib as first-line treatment for advanced HCC did not meet its endpoint of overall survival (median overall survival was 9.9 months for sorafenib and 9.5 months for brivanib), and time to progression was equivalent between both groups [83]. Another RCT that compared brivanib and best supportive care to best supportive care alone in advanced HCC patients who progressed or were intolerant of sorafenib showed that brivanib did not lengthen overall survival [84]. A RCT that compared linifanib, a tyrosine kinase inhibitor that acts on VEGFR and PDGFR, and sorafenib for advanced HCC demonstrated equivalent median overall survival; however, there were significantly more serious adverse events in the linifanib arm [85]. Erlotinib inhibits EGFR as well as the RAF/MEK/ERK signaling pathways; a phase III RCT comparing sorafenib and erlotinib to sorafenib alone did not show improved survival, time to progression, or overall response rate with combination therapy [7, 86]. Cixutumumab, which targets IGF-1R, showed no clinical response in a phase II trial for advanced HCC patients [87]. Two other monoclonal antibodies, AVE1642 and BIIB002, which act on IGF-1/2 and IGF-1R, respectively, have not been studied in the phase II trial stage [9].

Although investigations into advanced HCC treatments have often been marked by lack of efficacy, the advent of personalized medicine tailored to individuals' distinct genetic signatures may lead to an increased number of therapeutic agents. One study of 243 liver tumors showed that 28% of analyzed specimens contained mutations that targeted already approved treatments [5]. These include JAK, FLT, KIT, BRAF, FGF, and PDFGR mutations [5]. Moreover, lenvatinib, a VEGFR, FGFR, PDGFR, RET, and KIT inhibitor, has recently been approved as first-line treatment for advanced HCC [88]. A phase three non-inferiority RCT of 954 patients in 20 countries who had not received previous advanced HCC therapy showed non-inferiority between lenvatinib and sorafenib with regards to median survival (13.6 months and 12.3 months, respectively) [89]. Furthermore, two new agents, regorafenib, a multi-kinase VEGFR inhibitor, and nivolumab, which block the programmed cell death protein-1 (PD-1) pathway, have been FDA-approved as second-line agents for advanced HCC, and studies are ongoing to evaluate nivolumab as a first-line agent [90, 91]. Regorafenib approval was granted upon the basis of a phase

three RCT of 573 patients in 21 countries who progressed on sorafenib; all patients had CP A disease. Median survival for regorafenib was significantly higher (10.6 months) compared to placebo (7.8 months) [92]. Nivolumab approval was based on the CheckMate 040 trial, a phase I and II dose escalation and expansion study, of 262 patients in 11 countries who had CP scores of 7 or less, ECOG of 1 or less, and who did not tolerate sorafenib or progressed on systemic HCC therapy [93]; 20% of patients had an objective response, and 45% of patients had stable disease.

Other potential advanced HCC therapies are currently being studied. Cabozantinib is a tyrosine kinase inhibitor that acts on VEGFR, MET, and AXL [94]. A phase three RCT of 707 HCC patients who were previously treated with sorafenib, received at most two systemic therapies for advanced HCC, or who progressed on one systemic treatment comparing cabozantinib to placebo showed a significantly longer median overall survival (10.2 months versus 8.0 months) on cabozantinib [94]. Ramucirumab is a VEGFR2 inhibitor that was tested in phase three RCT (565 patients) as second-line therapy for advanced HCC patients who progressed on or were intolerant to sorafenib. Overall, there was no difference in median overall survival between placebo and ramucirumab [95]. However, patients who had an AFP level $\geq$ 400 ng/mL had a significantly higher overall median survival with ramucirumab as opposed to placebo; the direct relationship between AFP and VEGFR expression may account for this difference [95]. Many of these agents are expected to request or attain FDA approval in the near future. Figure 4 shows FDA- and non-FDA-approved therapies and where they fit in the spectrum of advanced HCC treatment, and Fig. 5 details molecular receptors, ligands, and pathways as potential targets for therapies studied in HCC treatment.

Epigenetic therapies are also currently being studied for HCC treatment. DNA methyltransferase (DNMT) inhibitors, including zebularine, and histone deacetylases (HDAC) such as belinostat have shown anti-tumor activity in HCC cell lines (Fig. 6) [10]. In addition, microRNA (miRNA)-targeted therapies are under investigation. MiRNA molecules act on messenger RNA (mRNA) molecules to repress gene expression by stopping mRNA translation [10]. MiRNAs have been discovered to act as tumor suppressor regulators via mechanisms such as cell-cycle regulation and inhibition of HBV replication; decreased miRNA activity has been demonstrated in HCC cells [10]. Hepatic cells that lack miRNA-122, a miRNA tumor suppressor molecule linked to HCC development in mice, exhibit oncogenic properties such as migration and invasion. Reconstituting these cells with miRNA-122 inhibits these oncogenic properties [10]. Further investigation is needed to demonstrate efficacy and safety of epigenetic and miRNA targeted therapies.

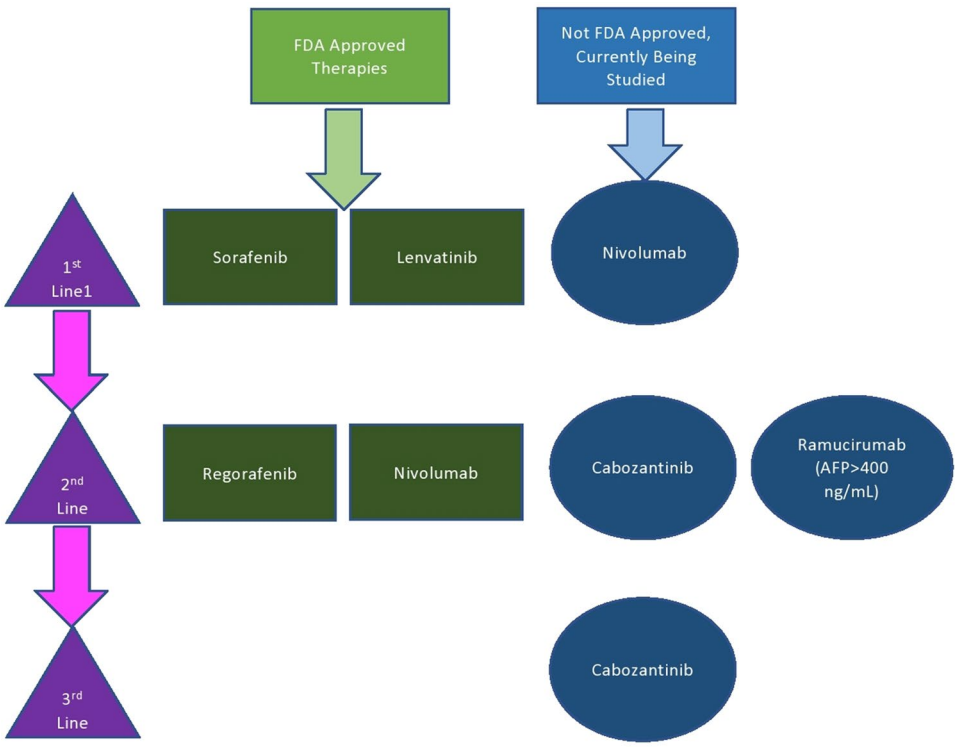

Fig. 4 First, second, and third line FDA approved and non-FDA approved investigational therapies for advanced HCC. Nivolumab and regorafenib are approved for patients who were treated with sorafenib previously. Ramucirumab is currently being studied in patients with a baseline AFP level greater than 400 ng/mL. *FDA* food and drug administration, *AFP* alpha-fetoprotein

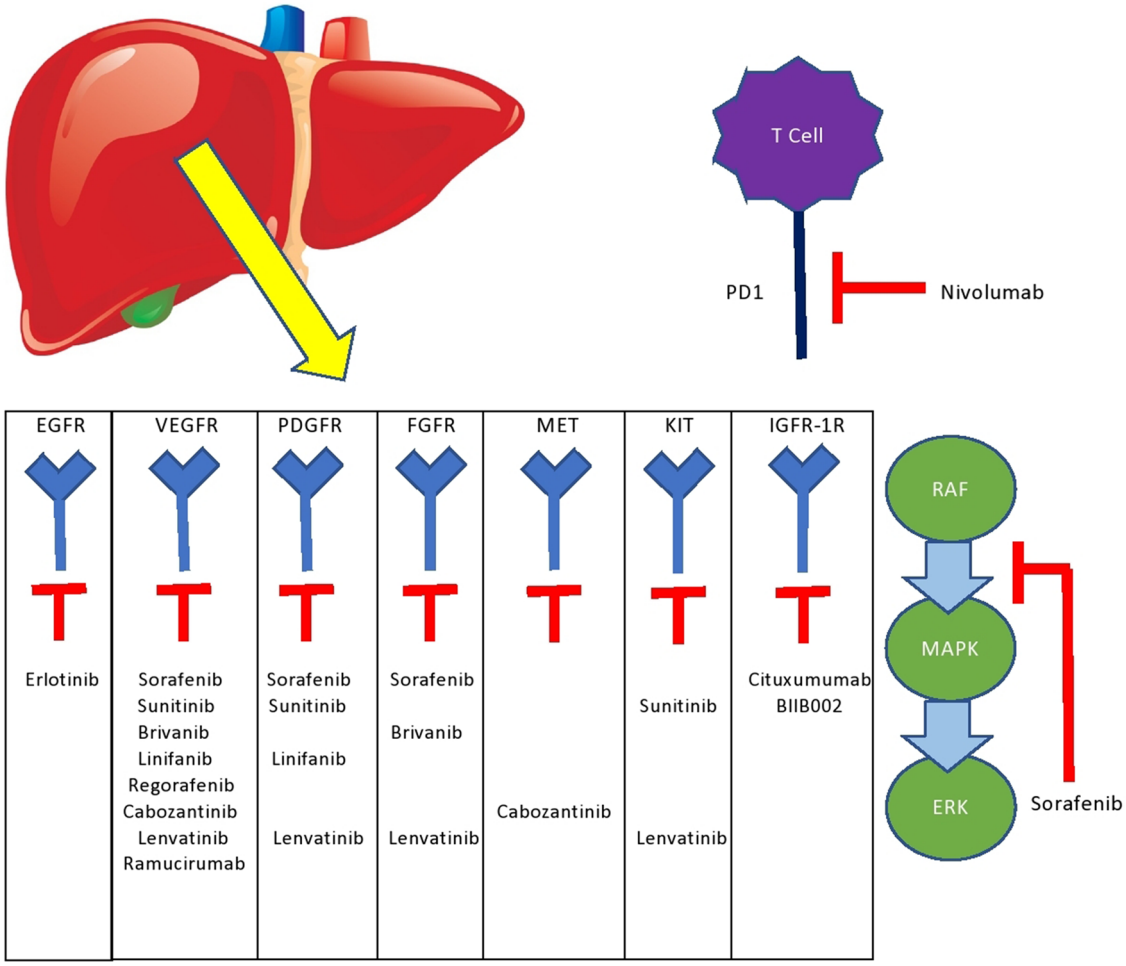

Fig. 5 Approved and non-approved therapies for HCC based upon their molecular targets. Red Ts indicate inhibition of a receptor, ligand, or pathway. Of note, only sorafenib, regorafenib, lenvatinib, and nivolumab have FDA approval for HCC treatment currently. *PD1* programmed death-1, *EGFR* endothelial growth factor receptor, *VEGFR* vascular endothelial growth factor receptor, *PDGFR* platelet-derived growth factor receptor, *FGFR* fibroblast growth factor receptor, *MET* mesenchymal epithelial transition, *IGFR-1R* insulin-like growth factor receptor

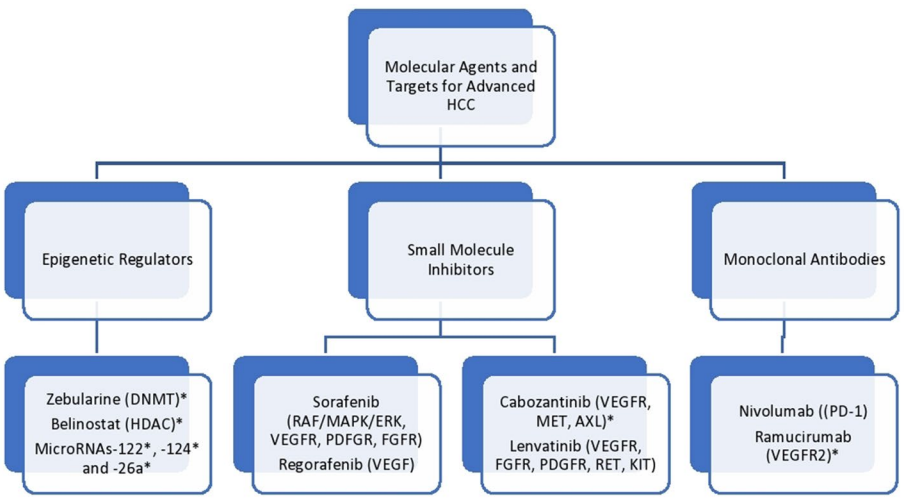

Fig. 6 Molecular therapies for the treatment of HCC according to target class. Targets, if applicable, are in parentheses. An asterisk denotes a therapy that is not FDA approved. *DNMT* DNA methyltransferase, *HDAC* histone deacetylases. See Fig. 5 legend for other abbreviations

Chemotherapy

Chemotherapeutic agents, such as oxaliplatin and gemcitabine, have shown minimal success in HCC treatment and as such are not recommended due to their systemic toxicity and short survival benefits [80]. A retrospective study analyzing 37 patients with HCC who received capecitabine demonstrated an 8.1 month median overall survival [96]. Another retrospective study that examined advanced HCC patients who received combination of gemcitabine and oxaliplatin (GEMOX) showed a median overall survival of 11 months [97]. A phase II RCT comparing doxorubicin and FOLFOX4 (fluorouracil, leucovorin, and oxaliplatin) did not show a significantly different median overall survival with either treatment [98].

Conclusion

While an established staging system with efficacious therapies exists for HCC, many questions remain unanswered regarding the most optimal treatment for each patient with HCC. Liver transplantation, an ideal cure, is currently limited by donor graft availability—and optimization of donors should continue to be investigated, including increasing living donor transplantation and using previously considered marginal grafts, i.e., HCV-positive donor grafts and donation after cardiac death donors. Continued investigations of small molecule inhibitors, monoclonal antibodies, and epigenetic agents will be crucial in prolonging and improving the quality of life for patients with advanced HCC. A particular area of study that should be further explored is combination therapy, including combined LRTs, molecular therapies, and adjuvant systemic therapies with surgical therapy. As more data emerge concerning these treatments, achieving the best personalized therapy for HCC will continue to be the ideal goal.

Compliance with ethical standards

Conflict of interest TC has no conflicts of interest to report. AP is on the speaker's bureau for Eisai and BTG and serves on advisory board for Wako Diagnostics..

Ethical approval Not applicable.

Informed consent Not applicable as this is a review article.

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