



Systemic therapy for advanced hepatocellular carcinoma: targeted therapies

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Abstract: Therapeutic options for advanced, unresectable hepatocellular carcinoma (HCC) have changed dramatically over the last 3 years. While surgical resection, orthotopic liver transplantation, and localized therapeutic options such as ablation, radiation therapy, and embolization remain therapeutics of choice in localized disease, systemic therapy is the only option in advanced, metastatic HCC. Since the United States Food and Drug Administration (US FDA) approval of sorafenib in 2008, targeted therapies such as sunitinib, tivantinib, brivanib, erlotinib, and linifanib; monoclonal antibody- bevacizumab showed no meaningful improvement in treatment of HCC. However, with improved understanding on the molecular pathophysiology and tumor heterogeneity of HCC, we have made progress in expanding the therapeutic options in advanced HCC. Targeted therapy with lenvatinib, cabozantinib, and regorafenib; monoclonal antibody ramucirumab; immunotherapies nivolumab and pembrolizumab have demonstrated promising results in the clinical trials. The current work outlines the molecular mechanisms and tumorigenesis of HCC, a detailed discussion of the trial results of the approved therapies in HCC, future perspectives and potential options to overcome the challenges of systemic therapy in HCC.

Keywords: Liver cancer; targeted therapy; sorafenib; lenvatinib

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy attributing to third highest cancer-related deaths globally (1). While majority of cases were reported in Asia-Pacific and sub-Saharan region historically, rising incidence is seen in the Western World due to higher rates of non-alcoholic fatty liver disease (NAFLD) (2). The incidence of HCC is closely related to advanced liver disease with various risk factors such as infections, toxins, and metabolic factors all leading to cirrhosis (3-5). The chronic inflammation and immunosuppressive environment in cirrhotic liver has been shown to promote

HCC tumorigenesis. Given the heterogeneity in the risk factors and molecular pathways contributing to HCC tumorigenesis, it poses a major therapeutic challenge especially at advanced stages of diagnosis.

Management of HCC is primarily based on the stage at diagnosis, underlying liver function, patient's age, and medical comorbidities (6). Surgical resection is the preferred therapy of choice for patients in localized disease without any macrovascular invasion. Alternatively, in surgically unresectable patients with solitary lesion less than 5 cm or three lesions each less than 3 cm (no macrovascular invasion; no nodal or distant metastases), liver transplantation can be potentially curative. In patients

with liver confined disease with no macrovascular invasion who are not candidates for surgical resection or orthotopic liver transplantation, liver directed therapies are preferred approach (6). Liver directed therapies may also aid in downstaging the tumor rendering the patients potentially resectable or eligible for transplantation (7).

Unfortunately, >50% patients with HCC are diagnosed at advanced stage rendering systemic therapy as the only therapeutic option (8). In addition, approximately 70% of the patients who undergo surgical resection of the primary tumor develop recurrences (9). Systemic therapy is preferred in patients who had extensive recurrence or in those liver-directed therapies may not be an option. Currently, sorafenib and lenvatinib are United States Food and Drug Administration (US FDA) approved first-line therapies for advanced HCC. In patients who progressed or did not tolerate sorafenib, second-line options include cabozantinib, regorafenib, ramucirumab [for patients with alpha-fetoprotein (AFP) levels > 400 ng/mL], nivolumab, and pembrolizumab. Most recently, US FDA approved the use of NTRK inhibitors larotrectinib or entrectinib in patients with *NTRK* fusion-positive solid malignancies, which include advanced HCC. Although cytokine therapy (interferon alpha-2b, interleukin-12) yielded not so encouraging results (10,11), nivolumab and pembrolizumab have shown encouraging results in terms of PFS in phase II trials (12,13). Unfortunately, phase III trials of nivolumab in first line setting and pembrolizumab in second line setting did not meet their primary end points (14,15). Preliminary results of phase III trial demonstrated OS and PFS benefit with atezolizumab plus bevacizumab compared to sorafenib as first line treatment for HCC (16).

Development of effective therapies for HCC is hampered by the tumor heterogeneity stemming from multifactorial risk factors. A better understanding on the heterogenic tumorigenic pathways will hopefully shed light on tumor biomarkers, genomics and other tumor factors that predict targeted therapy response in HCC. In the present work, we sought to discuss the tumorigenesis of HCC, clinical trials that evaluated the drugs targeting these tumorigenic pathways, and outline future directions of targeted therapy in advanced HCC.

HCC tumorigenesis

Next generation whole exome and RNA sequencing have demonstrated that HCC is a complex and heterogenous tumor. Despite the presence of various risk factors, majority

of HCC tumors are preceded by common tumorigenic pathway of chronic inflammation and fibrosis. Histological examination of these lesions has shown the background of cirrhosis and islands of dysplastic lesions (both low- and high-grade) (17). Interestingly, HCC exhibits significant heterogeneity both clinically and histopathologically ranging from well- to poorly differentiated lesions even within the same liver. As in any other solid organ malignancies, gene mutations, copy number variations, gene rearrangements, and epigenetic modifications were shown to play a key role in HCC tumorigenesis. Unlike melanoma and lung cancer, HCC is known to harbor 20–100 genetic mutations per genome (intermediate-range) (18). Most common genetic mutations implicated in HCC tumorigenesis are TERT promoter mutations (30–60%), *TP53* (18–50%), *AXIN1/2*, *ARID1A/2*, and β -catenin gene (18–40%) (17). The gene mutation number and the type of gene involved is primarily dependent on the underlying etiological factor. For instance, hepatitis B virus (HBV) associated HCC is known to have high number of mutations per genome given the RNA mediated replication of HBV. HCC tissue samples integrated with HBV were shown to have increased TERT promoter mutations (19). Notably, genetic aberrations in TERT has been implicated in premature liver fibrosis (20). In contrast, HCV causes gene mutations by causing DNA breaks especially in *TP53*, *CTNNB*, and *BCL-6* genes (17). A considerable high number of *TP53* mutation harboring HCC are seen in the geographical areas with high prevalence of HCV (17,21,22). In addition to *TP53* mutations, HCV infection is known to target mitogen-activated protein kinase (RAS/MAPK) pathways and JAK/STAT contributing to tumorigenesis (21).

Molecular studies identified DNA methylation defects especially in the genes *RASSF1A*, *SOCS-3*, *CDKN2A*, *MGMT*, and *GSTP1* as one of the potential contributors of HCC tumorigenesis (23–26). While both HBV and HCV are generally implicated in DNA methylation defects, Wnt-signaling pathway is particularly targeted by HCV (27–29). HCV proteins NS3 and NS5 need a special mention here as they were shown to alter micro-RNA-155 expression, which potentiates tumor necrosis factor-alpha (TNF- α) levels thereby contributing to tumorigenesis (30).

Chronic viral infection (HBV, HCV) and exposure to toxins such as aflatoxin and alcohol results in upregulation of cellular signaling pathways especially epidermal growth factor (EGF), hepatocyte growth factor (HGF/c-Met), insulin-like growth factor, and platelet-derived growth factor (PDGF). These ligands are particularly implicated

in cell differentiation pathways (Notch, Wnt-signaling). In addition, angiogenic pathways such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) mediated pathways are also upregulated by activating receptor tyrosine kinases in P13K/AKT/mTOR and Ras/Raf/MEK/ERK (MAPK) cascades (31).

In general, hepatic tissue is exposed to higher degree of antigens from gastrointestinal tract. To survive this massive antigen exposure, augmented interleukins 4, 5, 8, and 10 aid in creating an immunosuppressive environment in hepatic tissue. This immune suppressive environment results from an inhibition of myeloid cell arginase-1 and galectin-9 activity and increased expression of check points (programmed-cell death pathway) (32). In addition, immune-activating cytokines (interleukin 1, TNF, interferon-gamma) are suppressed (17). This intrinsic immune suppressive environment helps in creating a fertile soil for carcinogenesis and tumor progression. Further, higher percentage of myeloid-derived suppressor cells (MDSCs) and regulatory T-cells are seen in HCC (33).

Interestingly, a higher percent of intratumor heterogeneity especially in terms of histology, proliferation, genomic mutations and activated receptor tyrosine kinases (64% and 25–47% in HCC measuring 3–5, <2 cm in diameter, respectively) (34). A single institution analysis of 120 HCC tumors from 23 patients showed intratumoral heterogeneity in 87% (20 of 23 patients). Among these patients, 26% had morphologic heterogeneity whereas morphologic and immunohistochemical heterogeneity was seen in 39% (35). This inter- and intratumor heterogeneity represents a major challenge potentially attributing to drug resistance and treatment failure. This tumor heterogeneity also makes things harder to develop a predictable tissue biomarker in HCC. As detailed earlier, approximately 70% of early stage HCC recur after curative resection. It is possible that this recurrent cancerous lesion may be a metastatic lesion of the primary tumor or may be a new second primary HCC. Moreover, given the multifactorial etiology, “field cancerization” effect has been well-documented in HCC resulting in multiple synchronous primary lesions in HCC (36). This is of particular concern in developing effective targeted therapy as we may be missing the activated downstream signaling pathway in unbiopsied lesion (37). In the subsequent sections, we discuss the various targeted therapies evaluated in phase II and III clinical trials in HCC with a special focus on challenges and future directions that potentially help in improving outcomes.

Targeted therapy in advanced, inoperable HCC

Sorafenib

Sorafenib, a multi-kinase inhibitor that primarily targets VEGFRs 1, 2, and 3, PDGFR, c-kit, STAT3 pathway (38), and cell cycle (39) was approved by the US FDA in 2008. The drug showed encouraging results in terms of median OS in advanced HCC in two landmark randomized trials (40,41). In a phase III trial, patients with advanced HCC who are treatment naïve were randomized to receive either sorafenib or placebo (SHARP trial). Compared to placebo, sorafenib resulted in significantly better median OS (10.7 *vs.* 7.9 months; $P=0.001$). Similar promising results were seen in another randomized trial in Asia-Pacific region that showed a better median OS (6.5 *vs.* 4.2 months, $P=0.01$). Interestingly, on sub-group analysis, the participants in Asia-Pacific region study that harbored HCV had a better response with sorafenib. In both the trials (SHARP and Asia-Pacific trials), sorafenib benefit was much more evident in patients that had no extra-hepatic spread, HCV infection, and lower neutrophil-to-lymphocyte ratio. Both the trials demonstrated similar side effect profile of sorafenib, which included fatigue, weight loss, diarrhea, palmar-plantar skin reaction, and low phosphorous levels. Notably, none of the participants in sorafenib cohort had a complete response and 1% of the active drug cohort demonstrated overall response per as evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Interestingly, both the trials included only the patients with good performance status of Eastern Cooperative Oncology Group (ECOG) 0 or 1 (90%) and good hepatic function (95% and 5% of patients in sorafenib group were of Child-Pugh class A and class B, respectively). An observational registry evaluated the safety of sorafenib in higher Child-Pugh scores, which showed that the drug had a tolerable safety profile in high Child-Pugh groups, too (42). However, median OS was only 5.2 months in patients with Child-Pugh B status demonstrating limited benefit (43).

Given the encouraging results seen with sorafenib monotherapy, the drug was evaluated in combination with doxorubicin in the patients with advanced HCC ($n=96$) (44). Compared to doxorubicin monotherapy, the combination group resulted in delayed time to progression (6.4 *vs.* 2.8 months; $P=0.02$) and median OS (13.7 *vs.* 6.7 months; $P=0.006$) (44). Unfortunately, these encouraging results were not replicated in a phase III trial (Table 1) (45). Similar disappointing results were seen in another phase III trial (SEARCH) that evaluated the combination sorafenib and

Table 1 Selected phase III trials of the agents approved targeted therapies in advanced HCC

Agent	Study (n)	Dose evaluated	Targets	Patients with portal vein invasion	ORR	PFS	OS
Sorafenib	SHARP (n=602) (40)	Sorafenib 400 mg twice daily vs. placebo	VEGFRs 1, 2, and 3, PDGFR, (RAF) kinases, and c-kit	Included	2%	4.1 months	10.7 months
	Asia-Pacific (n=226) (41)	Sorafenib 400 mg twice daily vs. placebo		Included	3.3%	2.8 months	6.5 months
	Abou-Alfa <i>et al.</i> , CALGB 80802 (Alliance) (n=356) (45)	Sorafenib 400 mg twice daily vs. placebo in combination with Doxorubicin 60 mg/m ² (21-day cycle)		Included	9.3% vs. 5.4%	4 months (sorafenib + doxorubicin); 3.9 months (sorafenib)	9.3 months (sorafenib + doxorubicin); 9.4 months (sorafenib)
Lenvatinib	Kudo <i>et al.</i> , (n=954) (46)	Lenvatinib 12 mg once daily (>60 kg body weight), 8 mg (<60 kg body weight) vs. sorafenib 400 mg twice daily	EGFR1-3, FGFR 1-4, PDGFR, and c-kit	Excluded	24.1% vs. 9.2%	7.4 vs. 3.7 months	13.6 vs. 12.3 months
Cabozantinib	CELESTIAL trial (n=707) (47)	Cabozantinib 60 mg once daily vs. placebo	AXL, MET, and VEGFR2	Included	4% vs. 0.4%	5.2 months	10.2 months
Regorafenib	RESORCE trial (n=573) (48)	Regorafenib 160 mg once daily vs. placebo	VEGFR1, 2 and 3; PDGFR, c-kit, and FGFR	Included	11% vs. 4%	3 months	10.6 months
Ramucirumab	REACH trial (n=565) (49)	Ramucirumab (8 mg/kg) or placebo	VEGFR-2	Included	7%	2.8 months	9.2 months
	REACH-2 trial (n=292) (50)	Ramucirumab (8 mg/kg) or placebo		Included	5%	2.8 months	8.5 months

HCC, hepatocellular carcinoma; ORR, overall response rate; PFS, progression free survival; OS, overall survival of active drug therapy cohort; VEGFR, vascular endothelial growth factor receptors; RAF, rapidly accelerated fibrosarcoma; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; PDGFR, platelet derived growth factor receptor.

erlotinib (51). The combination did not show any benefit in terms of median OS (9.5 *vs.* 8.5 months, $P=0.41$) and PFS (3.2 *vs.* 4 months, $P=0.18$).

Despite the encouraging results as monotherapy, sorafenib did not show OS benefit when combined with trans-arterial chemoembolization (TACE) (52-54). In addition, a phase III trial (STORM) showed no benefit of sorafenib in adjuvant setting in terms of recurrence free survival and median OS (55). Moreover, a recent meta-analysis that evaluated sorafenib as an adjuvant therapy in patients with localized HCC demonstrated no significant benefit in terms of recurrence and median OS (56).

Lenvatinib

After the US FDA approval of sorafenib in 2008, there has

been a sad saga of 10 years in which no targeted therapy has shown clinically significant OS benefit in advanced HCC. After a decade, lenvatinib received approval from the US FDA as a first-line therapy in advanced, inoperable HCC given its impressive outcomes in terms of OS and PFS. Lenvatinib is a small molecule tyrosine kinase inhibitor targeting EGFR 1-3, FGFR 1-4, PDGFR, RET and c-kit. In a phase II trial involving patients with advanced, inoperable HCC (n=46), lenvatinib resulted in a median OS and PFS of 18.7 and 12.8 months, respectively and 47% of the patients had stable disease as best response (57). Lenvatinib was compared to sorafenib in a phase III non-inferiority trial which showed a better PFS (7.4 *vs.* 3.7 months; $P<0.0001$) and time to progression (8.9 *vs.* 3.7 months; $P<0.0001$) as compared to that of sorafenib arm (46). In addition, lenvatinib was shown to be non-inferior

to sorafenib in advanced HCC in terms of OS (13.6 *vs.* 12.3 months). Objective response rate was higher in lenvatinib group as compared to that of sorafenib group (24% *vs.* 9% as per modified RECIST criteria). While treatment-related adverse events were similar in both the arms, serious adverse events were higher in lenvatinib group. Proteinuria was the most common treatment related adverse event leading to treatment discontinuation. Given the non-inferiority nature of lenvatinib (as compared to sorafenib) and a tolerable safety profile—the drug is approved for the use in advanced, inoperable HCC by various regulatory medical agencies across the World.

Although lenvatinib resulted in non-inferiority results as compared to sorafenib, a number of questions are yet to be answered. For instance, there is a lack of specific data or biomarkers that would help the practicing physicians choose between lenvatinib *vs.* sorafenib. Moreover, recently, US FDA approved regorafenib, cabozantinib, ramucirumab (in AFP >400 ng/mL), nivolumab, pembrolizumab in the patients who progressed on sorafenib. It is yet to be determined if these agents would be beneficial in the patients who used lenvatinib as first-line therapy as lenvatinib targets FGFR, KIT, and RET pathways, which was not the case with sorafenib (58). Moreover, patients with invasion of main portal vein and bile ducts and >50% involvement of liver were excluded from the clinical trial. It is yet to be determined how the drug is tolerated by all advanced HCC patients across the World. Lenvatinib is also currently being evaluated in combination with pembrolizumab in a phase III trial in patients with advanced HCC (59).

Cabozantinib

Cabozantinib, a tyrosine kinase inhibitor acts by targeting AXL, MET, and VEGFR2 proteins. The drug has shown promising results in advanced HCC patients who progressed on first-line sorafenib therapy (47,60). In a phase II trial (n=41), the drug resulted in median PFS and OS of 5.2 and 11.5 months, respectively, with a tumor regression rate and objective response rate of 78% and 5%, respectively. The drug was tolerated well with most common grade ≥ 3 adverse events being diarrhea (20%), palmar-plantar syndrome (15%), and low platelet count (15%) (60). Given the promising results, the drug was further evaluated in a phase III trial (CELESTIAL trial) (47) (n=707) in advanced HCC patients who progressed on sorafenib. The trial allowed receipt of up to two prior

systemic therapy. The drug showed encouraging results in reducing the risk of death by 24% as compared to that of placebo. The drug resulted in statistically and clinically meaningful benefit in terms of PFS (5.2 *vs.* 1.9 months; $P < 0.0001$ and median OS (10.2 *vs.* 8 months, $P = 0.004$). Cabozantinib group had higher percentage of grade ≥ 3 adverse events including hand-foot syndrome (17%), high blood pressure (16%), and elevated liver enzyme- aspartate aminotransferase (12%), loose stools (10%), and fatigue (10%). Given the encouraging results in terms of PFS and OS and tolerable safety profile, the drug was approved by the US FDA for the use in advanced HCC that progressed on first-line sorafenib therapy.

Recently, results of cabozantinib in combination with immunotherapy (nivolumab and ipilimumab) were presented in annual gastrointestinal oncology symposium, 2020 (61). Cabozantinib was evaluated as a doublet therapy (in combination with nivolumab, n=36) or as a triple therapy (in combination with nivolumab and ipilimumab, n=35). The double therapy and triple therapy resulted in overall response rate of 17% and 26%, respectively. The triple therapy had higher rates of grade > 3 adverse events as compared to the combination of cabozantinib and nivolumab (42% *vs.* 71%). Cabozantinib is currently being evaluated in combination with atezolizumab as a first-line therapy in advanced, inoperable HCC (NCT03755791). These combination therapies will hopefully provide valuable therapeutic options in advanced HCC.

Regorafenib

Regorafenib is a multi-tyrosine kinase inhibitor that targets VEGFR 1, 2, and 3, PDGFR, FGFR, RAF, RET, and c-kit. The drug was evaluated in a phase II trial in patients with advanced HCC that progressed on sorafenib therapy (n=36) with Barcelona Clinic Liver Cancer Stage B or C HCC and Child-Pugh class A (62). In this phase II trial, regorafenib resulted in median time to progression and OS of 4.3 and 13.8 months, respectively. Most common adverse events noted were hand-foot syndrome (53%), diarrhea (53%), fatigue (53%), decreased thyroid function (42%) and high blood pressure (36%). In a phase III trial that randomized advanced, inoperable HCC patients that progressed on sorafenib (n=573) into best supportive care plus either regorafenib 160 mg once daily (a cycle of 3 weeks on/1 week off) arm or placebo (n=194) arm (48). Regorafenib resulted in promising results in terms of median time to progression (3 *vs.* 1.5 months; $P < 0.001$),

PFS (3 *vs.* 1.5 months; $P < 0.001$) and median OS (10.6 *vs.* 7.8 months; $P < 0.0001$) (48).

Ramucirumab

Ramucirumab is a human IgG1 monoclonal antibody blocking VEGFR-2 that has been approved by the US FDA for the use in advanced HCC that progressed on sorafenib. In a phase II trial ($n=42$), ramucirumab yielded a median OS of 12 months (63). While the drug was tolerated well, the most common grade ≥ 3 adverse events were high blood pressure, gastrointestinal bleeding, infusion-related reaction, and fatigue. In a phase III trial (REACH) involving advanced HCC who progressed or did not tolerate sorafenib ($n=563$), ramucirumab resulted in a non-significant benefit in median OS (9.2 *vs.* 7.6 months, compared to placebo, $P=0.14$) (49). However, on sub-group analysis in patients with Child-Pugh A class and AFP level >400 ng/mL (or >1.5 times the upper limit), ramucirumab showed OS advantage as compared to that of placebo (HR: 0.67; $P=0.01$). REACH-2 phase III trial evaluated ramucirumab in advanced HCC patients with elevated AFP levels (>400 ng/mL) (50). Ramucirumab arm had a significantly better median OS (8.5 *vs.* 7 months; $P=0.01$) and PFS (3 *vs.* 1.6 months, $P < 0.01$) as compared to that of placebo. Given the promising results in this particular subgroup of AFP >400 ng/mL, the drug is approved by the US FDA for the use in this subset of advanced HCC who progressed on sorafenib therapy.

Table 1 summarizes the phase III clinical trials of currently approved targeted therapies in advanced HCC.

Current management

Lenvatinib and sorafenib are FDA approved for first-line treatment of HCC. Lenvatinib does have higher PFS and response rates. In patients where response may be required such as impending liver failure, lenvatinib may be preferred over sorafenib. However, the cost of the drug also needs to be considered. Preliminary results suggest that combination of atezolizumab plus bevacizumab has better survival compared to sorafenib. Thus, atezolizumab plus bevacizumab will likely become standard first line treatment for HCC. However, patients who have untreated varices, high risk of bleeding, severe autoimmune disease or other contraindications to immunotherapy may benefit from treatment with tyrosine kinase inhibitors. Multiple agents are approved for patients who have progressed

on sorafenib including cabozantinib, regorafenib, and ramucirumab. Unfortunately, there is no good biomarker to determine optimal treatment strategy. Though lenvatinib is approved as a first-line agent in advanced HCC, no data exists on the second-line therapies that progressed on lenvatinib. Encouragingly, multiple trials are also evaluating combination of immunotherapy and tyrosine kinase inhibitors.

Future directions

The incidence of HCC tripled since 1980 and is forecasted to rise until 2030 in all patient cohorts except Asians (64). Thanks to next generation sequencing and other molecular studies that improved our understanding on the carcinogenesis of HCC. Despite this improved understanding on the tumorigenesis, advanced HCC continues to represent a major challenge due to its tumor heterogeneity that was evident on DNA ploidy analysis and DNA fingerprinting (36). This tumor heterogeneity is of a major challenge to develop an effective targeted therapy. It is clinically not feasible to biopsy all the lesions in multi-centric tumors. One potential option is evaluating the role of circulating tumor cells (CTCs) and ctDNA, which may help in identifying more tumor types or heterogeneity as the therapy proceeds. However, we need more data to standardize the CTCs and ctDNA in HCC.

One potential option is evaluating the combination of combination therapies that may target the tumorigenesis at multiple levels. The role of hypoxia-inducible factor 1α (HIF- 1α) in HCC tumorigenesis has been well-established, especially in the tumors that have rapid growth. Such tumors with high level of HIF- 1α expression were shown to have poor prognosis. Preclinical studies have shown that tumor hypoxia considerably increase the PD-L1 expression on tumor and immune cells especially on MDSCs, dendritic cells, and monocytes. Hence, one of the potential areas for exploration would be evaluating the combination of immune check point inhibitors and check point inhibitors, which help in targeting the two primary mechanisms of HCC tumorigenesis. The other potential barrier is lack of predictive biomarkers, which help the clinicians in picking the right drug of choice in the right clinical scenario. For instance, ramucirumab may be an option especially in the patients with AFP levels >400 ng/mL but no such clear-cut criteria are available for other agents. Developing such criteria and biomarkers would help clinicians to choose therapy in appropriate clinical context.

In conclusion, improved understanding of HCC tumorigenesis, developing standard biomarkers, evaluating the role of CTCs and finally evaluating the combination of various treatment modalities may potentially help us in targeting this dismal tumor, especially in advanced stages.

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