

Review

Hepatocellular Carcinoma: Reasons for Phase III Failure and Novel Perspectives on Trial Design

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Abstract

Hepatocellular carcinoma (HCC) is a major health problem. Most patients with HCC experience a recurrence after resection/ablation or are diagnosed at advanced stages. Sorafenib remains the only approved systemic drug for these patients. Molecular therapies targeting signaling cascades involved in hepatocarcinogenesis have been explored in phase III clinical trials. However, none of the drugs tested have shown positive results in the first-line (brivanib, sunitinib, erlotinib, and linifanib) or second-line (brivanib, everolimus) setting after sorafenib progression. Reasons for failure are heterogeneous and include lack of understanding of critical drivers of tumor progression/dissemination, liver toxicity, flaws in trial design, or marginal antitumoral potency. These trials are also challenging time to progression as a surrogate endpoint of survival. Trials ongoing testing drugs head-to-head versus sorafenib in "all comers" might have difficulties in achieving superior results in the first line. Novel trials are also designed testing drugs in biomarker-based subpopulations of patients with HCC. Most common mutations, however, are undruggable, such as *p53* and *CTNNB1*. Two types of studies are proposed: (i) phase II pivotal proof-of-concept studies testing drugs blocking potential oncogenic addiction loops, such as the one testing MEK inhibitors in RAS⁺ patients or amplification of *FGF19* as a target; and (ii) phase II to III studies using biomarker-based trial enrichment for defining HCC subpopulations, such as the case of enriching for *MET*-positive tumors. These strategies have been deemed successful in breast, melanoma, and lung cancers, and are expected to change the landscape of trial design of HCC. *Clin Cancer Res*; 20(8); 2072–9. ©2014 AACR.

Introduction

Hepatocellular carcinoma (HCC) is a major public health problem, ranking as the third cause of cancer-related deaths and the 16th absolute cause of deaths globally (1). There has been a net increase of 62% in HCC-related annual death rates (from 463,000 to 752,000) during the past 20 years. In addition, HCC is the most rapidly escalating cause of cancer mortality in the United States with 24,000 new cases annually (1–4).

Approximately 90% of HCCs are associated with underlying cirrhosis (2, 4). In fact, HCC usually arises in a damaged liver with extensive inflammation and fibrosis responsible for the complex pathogenesis with deregulation of several signaling pathways and accumulation of

genetic alterations (5–7). Once HCC has developed, ~30% of cases are diagnosed at an early stage of the disease and are amenable for resection, liver transplantation, or local ablation with radiofrequency (2, 4, 8). Median survival is of 60 months, but 70% of cases recur at 5 years after resection or complete ablation and no adjuvant therapies are available to date (2, 4, 8). Intermediate HCC cases can benefit from loco-regional chemoembolization, while other local therapies, such as internal radiation with Y-90, are currently being tested in phase III studies in order to be considered for standard of care (2, 4, 8). In advanced cases, only one systemic therapy is effective, the multikinase inhibitor sorafenib, for which approval by the U.S. Food and Drug Administration (FDA) represented a breakthrough in the management of the disease (9, 10). The efficacy of sorafenib is probably due to a fine balance between targeting cancer cells/microenvironment as a result of blocking multiple kinases (including VEGF, PDGF, C-KIT, and B-RAF) on the one hand, and manageable toxicity on the other (11). However, the median life expectancy of patients with HCC on sorafenib is only 1 year, indicating the clear need to improve their outcome.

Sorafenib approval paved the way for testing of a wide range of molecular therapies. Unfortunately, none of them (sunitinib, brivanib, erlotinib, linifanib, and everolimus) have resulted in survival benefits. Obvious reasons for

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treatment failure include liver toxicity and lack of substantial antitumoral potency (12, 13). More profound reasons involve clear lack of understanding of the driving mechanisms of tumor progression and dissemination, which should be specific for molecular subclasses (5–7). In other cancers, treating tumors addicted to oncogenic loops (i.e., ELM4–ALK fusion gene in lung cancer with crizotinib) has yielded striking benefits (14, 15). No addiction loops have yet been uncovered in HCC, and trials testing molecular therapies are seldom enriched by biomarkers (16). Therefore, further research is needed to understand HCC biology and to identify key relevant molecular targets. In addition, a deep analysis of the recently reported negative trials is urgent. Herein we analyze the results of phase III trials reported in the past 2 years and explore the new designs proposed to overcome this negative trend.

Reasons for Failure of Phase III Studies

Hepatocellular carcinoma trials are characterized by patient heterogeneity and are complex to interpret and dissect (16). Our purpose is to provide some information on the reasons underlying the fact that phase III pivotal consecutive randomized controlled trials (RCT) in HCC reported during the past 2 years did not meet the primary end point (Table 1). Six phase III trials were reported negative in the first-line (sunitinib, brivanib, linifanib, and erlotinib; refs. 17–20) and second-line setting (brivanib and everolimus; ref. 21). Four of them were designed for superiority and two for noninferiority (brivanib and lini-

fanib; refs. 18 and 19) with a primary endpoint of overall survival (OS). To explore the reasons for these failures, we also comment on (i) ongoing phase III pivotal trials and (ii) phase II trials exploring drugs tested with novel designs (refametinib, tivantinib). Just for clarity, we are not herein exploring ongoing phase III trials with adjuvant therapies or phase II and III trials in the intermediate HCC setting.

Potential reasons for failure

Reasons for failure are heterogeneous and include lack of understanding of critical drivers of tumor progression/dissemination, liver toxicity, flaws in trial design, or marginal antitumoral potency. When dissecting the results of these recent trials (17–21), for which there are only two published articles (17, 21), we can speculate that the main shortcomings for sunitinib have been liver toxicity and issues with trial design (17), for erlotinib lack of efficacy (20), for linifanib lack of efficacy and eventually toxicity (19), and for brivanib lack of efficacy and eventually issues with trial design (18, 21). In addition, a recent press release announced that the phase III trial comparing everolimus versus placebo in the second-line setting did not meet the primary endpoint, but full data have not yet been reported. We are herein focusing on exploring the causes of trial failure, and the concept of drivers, oncogenic addiction, and biomarker-driven trials will be discussed in more detail in a subsequent section of this article.

Drugs tested in HCC: fine balance between efficacy and toxicity. Sorafenib is a drug leading to survival advantages

Table 1. Randomized phase III pivotal clinical trials completed in HCC in the first- and second-line settings (2007–2013)

First-line advanced HCC			
Comparison (reference)	Design	OS ^a	TTP
Sorfenib vs. placebo (9) (SHARP trial)	Superiority	10.7 mo vs. 7.9 mo; HR = 0.69 (95% CI, 0.55–0.87); <i>P</i> = 0.00058	5.5 mo vs. 2.8 mo; HR = 0.58 (95% CI, 0.45–0.74); <i>P</i> < 0.001
Sorfenib vs. placebo (10) (Asia Pacific Trial)	Superiority	6.5 mo vs. 4.2 mo; HR = 0.68 (95% CI, 0.50–0.93); <i>P</i> = 0.014	2.8 mo vs. 1.4 mo; HR = 0.57 (95% CI, 0.42–0.79); <i>P</i> = 0.0005
Sunitinib vs. sorafenib (17) (SUN trial)	Superiority	7.2 mo vs. 10.2 mo; HR = 1.30 (95% CI, 1.13–1.5); <i>P</i> = 0.001	3.8 mo vs. 4.1 mo; HR = 1.13 (95% CI, 0.98–1.31); <i>P</i> = 0.16
Brivanib vs. sorafenib (18) (BRISK-FL trial)	Noninferiority	9.5 mo vs. 9.9 mo; HR = 1.05 (95% CI, 0.94–1.23); <i>P</i> = 0.31	4.1 mo vs. 4.2 mo; HR = 1.01 (95% CI, 0.88–1.16); <i>P</i> = 0.8
Linifanib vs. sorafenib (19) (LIGHT Trial)	Noninferiority	9.1 mo vs. 9.8 mo; HR = 1.04 (95% CI, 0.89–1.22); <i>P</i> = ns	5.4 mo vs. 4 mo; HR = 0.76 (95% CI, 0.64–0.89); <i>P</i> < 0.001
Sorafenib ± erlotinib vs. sorafenib (20) (SEARCH trial)	Superiority	9.5 mo vs. 8.5 mo; HR = 0.92 (95% CI, 0.78–1.1); <i>P</i> = 0.2	3.2 mo vs. 4.0 mo; HR = 0.1.13 (95% CI, 0.94–1.36); <i>P</i> = 0.91
Second-line advanced HCC ^b			
Brivanib vs. placebo (21) (BRISK-PS Trial)	Superiority	9.4 mo vs. 8.2 mo; HR = 0.89 (95% CI, 0.69–1.15); <i>P</i> = 0.33	4.2 mo vs. 2.7 mo; HR = 0.56 (95% CI, 0.42–0.78); <i>P</i> = 0.001

Abbreviation: TTP, time to progression.

^aOverall survival (OS) is the primary endpoint in all studies.

^bResults for everolimus vs. placebo have been reported as negative in a recent press release.

with manageable adverse events, and with near absence of liver toxicity or treatment-related deaths (9, 10). Because of the success of the SHARP trial testing sorafenib (9), its design has been adopted by almost all studies testing molecular therapies in the first-line setting. The main concepts were adopted by guidelines of trial design (8, 16) and are as follows: (i) select only patients with preserved liver function (Child-Pugh A). Only patients with Child-Pugh A should be included in trials to prevent liver failure and death as a result of the natural history of cirrhosis. Patients with Child-Pugh A without HCC are expected to have a 1-year survival rate of 95%, a percentage that is of utmost importance to prevent competing risks for death (the main endpoint). Underlying liver disease highly complicates HCC treatment, as it can be itself responsible for morbidity and mortality. (ii) Select patients with advanced-stage HCC according to the Barcelona Clinic Liver Cancer (BCLC-C) staging system (2, 4, 22), or those with BCLC-B progressing after the standard of care for intermediate cases, chemoembolization. Other classifiers of patients—such as CLIP (Cancer of the Liver Italian Program) score (23)—might not be appropriate for treatment allocation, because the primary purpose of the score was to define prognosis but not to allocate for specific therapies. (iii) Define OS as primary endpoint, and time to progression (TTP) as secondary endpoint. Progression-free survival is a vulnerable endpoint in HCC research (16).

Sunitinib, a drug similar to sorafenib in terms of the inhibitory kinase profile—except for B-RAF inhibition, which is important in HCC signaling—and with better antitumor activity [lower 50% inhibitory concentration (IC_{50}) for almost all of the targets] was approved by the FDA in 2006 for the treatment of renal carcinoma and gastrointestinal stromal tumors. Nonetheless, sunitinib did not meet the survival superiority endpoint versus sorafenib in a phase III study (17) probably as a result of two factors. First, signals of efficacy and toxicity were already present in phase II studies (24, 25). Second, head-to-head comparisons with the standard of care (sorafenib) should only be conducted if the signal of efficacy in phase II is robust. Two phase II single-arm trials testing sunitinib showed liver toxicity (encephalopathy, hepatorenal syndrome) leading to death in the range of 6% to 10% (24, 25). Both studies including less than 40 patients showed median survivals in the range of 8 to 10 months, associated with 10% (50 mg/day; ref. 24) and 6% (37.5 mg/day; ref. 25) treatment-related death, respectively. Based on these data, 37.5-mg dose was used in a subsequent phase III study randomizing 1,074 patients, which was halted for toxicity/futility after a data safety watch at 457 events (17). Results at that point showed median survival of 7.9 months versus 10.2 months (sunitinib vs. sorafenib; HR = 1.30). Treatment-related deaths accounted for 3.2% of cases (17/526 patients) in the sunitinib arm versus 0.3% (2/542) in the sorafenib arm. Subgroup analysis showed higher benefit of sorafenib for hepatitis C virus–related patients with HCC (median survival of 15 months).

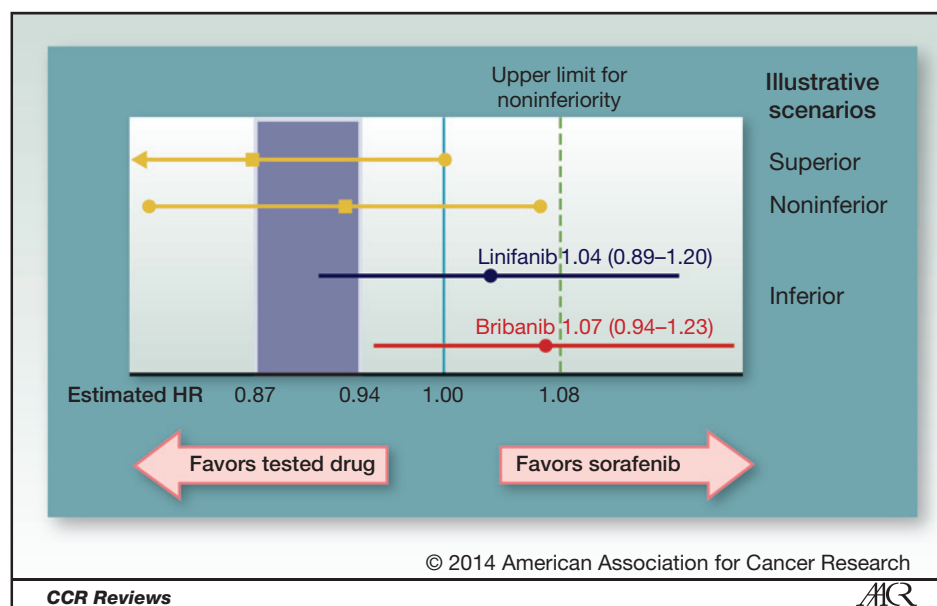
Lack of efficacy. The EGFR tyrosine kinase inhibitor *erlotinib* moved to phase III trial with modest disease control benefit in 2 previous phase II trials (26, 27). These single-arm phase II studies reported median survival of 10 to 13 months associated to marginal response rates (26, 27). There were no data testing the combination of sorafenib+erlotinib in phase II in HCC, but it was estimated that this combination would be able to improve OS in the SEARCH study (20). At the end of the study 720 patients were randomized being the median OS for the combination arm of 9.5 months compared with 8.5 months for the sorafenib arm (HR = 0.9; 95% CI, 0.78–1.1; $P = 0.2$). Considering that trial design, stratification, and execution of the trial was similar to SHARP, the results reported highlighted the fact that erlotinib is not adding outcome benefit in patients on sorafenib. It seems also that adding erlotinib led to cumulative adverse events decreasing sorafenib treatment duration from 4 to 3 months.

Linifanib, a more potent multikinase inhibitor targeting VEGFR and PDGFR than sorafenib, was tested in the first-line setting after a small single-arm phase II study including 44 patients showed median survival of 10.4 months (28). The phase III study with around 1,000 patients did not meet the noninferiority endpoint (OS = 9.1 versus 9.8 months; HR = 1.04; 95% CI 0.89–1.22; $P < 0.001$; ref. 19). The study was halted at the third interim analysis because of futility, although the reported data also suggest that linifanib was more toxic than sorafenib in terms of serious adverse events (54% vs. 38%), grade 3 to 4 hypertension (20% vs. 10%) and grade 3 to 4 liver-related complications (encephalopathy, ascites, and hyperbilirubinemia: 20% vs. 10%).

A better understanding of trial design: the noninferiority scenario. According to guidelines, new molecules tested in the first-line setting need to be combined with the standard of care sorafenib to demonstrate superiority (8, 16). This has only been the case in one RCT, sorafenib + erlotinib (20), while the others were directly testing the candidate drug versus sorafenib. We can estimate that in order to improve sorafenib outcome in the first-line setting for superiority, the drug has to be potent enough to achieve a HR of 0.5 or less if it is theoretically compared with the natural history of the disease or placebo (9, 29). This represents a very challenging scenario that requires a very potent drug able to decrease the risk of death by 50%. Nonetheless, two pivotal RCTs proposed a two-step design, first testing noninferiority and then testing for superiority (18, 19). Despite splitting the α between two analyses—which can be assumed increasing the sample size—it seems that this approach can give chances to drugs that show efficacy similar to that of sorafenib. However, the window of opportunity for these drugs is certainly too narrow.

Brivanib is a multikinase inhibitor with activity against fibroblast growth factor (FGF) signaling that achieved a 10-month OS (95% CI, 6.8–15.2) with a good tolerance and safety profile in a first-line single-arm 55-patient trial (30). The phase III pivotal study was designed as a noninferiority trial under the assumption that brivanib would have equal effects to sorafenib or would not be unacceptably worse

Figure 1. Understanding noninferiority study design and HR boundaries in HCC research. It is estimated that RCTs comparing drugs head-to-head to sorafenib in the first-line setting might have three potential results: (i) the drug is superior to sorafenib, if the HR (95% CI) boundaries do not cross the unity; (ii) the drug is noninferior compared with sorafenib, if the HR (95% CI) boundaries fall between 1 and 1.08; and (iii) the drug is inferior to sorafenib if the HR (95% CI) boundaries cross the 1.08 upper limit for noninferiority. The figure shows the HR and 95% CI of two RCTs, showing that according to this design the drugs are inferior to sorafenib (18, 19).



than sorafenib (assuming a decrease in OS no more than 3 weeks; ref. 18). Figure 1 shows the results of the phase III trial including 1,155 patients where the boundary of the confidence interval of the HR for survival was set at 1.08 following recommendations for noninferiority trial design. In summary, it is estimated that RCT testing drugs head-to-head to sorafenib in first-line might have 3 potential results: (i) drug is superior to sorafenib, if the HR (95% CI) boundaries do not cross the unity; (ii) the drug is noninferior compared with sorafenib, if the HR (95% CI) boundaries fall between 1 and 1.08; and (iii) the drug is inferior to sorafenib if the HR (95% CI) boundaries cross the 1.08 upper limit for noninferiority. Despite using this less risky design, the brivanib trial was not able to meet the primary endpoint (9.5 months with brivanib vs. 9.9 months with sorafenib; HR = 1.07; 95% CI, 0.94–1.23; $P = 0.3$; ref. 18). This new concept points to the question of which methodology would fit better to test drugs in liver oncology as it may really influence the results of the study. Investigators assumed that similar outcomes between two drugs would deem them approved, and then clinical decision making would be based upon toxicity profiles, costs, or even subgroup analysis. Nonetheless, with the small window of opportunity for noninferiority HR 95% upper boundaries (between 1 and 1.08) it seems that there should be a clear nonsignificant trend for superiority in order to have a drug approved with this trial design. The results of the linifanib trial (19) are also reflected in Fig. 1.

The second-line scenario. Brivanib has been the first drug to be tested in the second-line setting after sorafenib progression or intolerance in HCC (21). After promising data with a single-arm phase II study including 46 patients achieving a median survival of 9.2 months (31), a phase III trial testing brivanib versus placebo was conducted. The study did not achieve the primary endpoint of survival (9.4 months with brivanib versus 8.2 months with placebo;

HR = 0.89; 95.8% CI, 0.69–1.15; $P = 0.3307$; ref. 21). Reasons for treatment failure have been discussed previously (32) and include (i) impressive natural history of the placebo arm—because of positive selection bias with an enrichment of indolent HCCs; (ii) potential imbalance in prognostic factors, particularly portal vein invasion, an issue analyzed in the next section of this article. After adjusting for this factor, the HR comparing brivanib versus placebo was 0.82 (21); and (iii) positive signal was not obtained in the setting of a phase II randomized study (31). Another drug, everolimus, also did not meet the primary endpoint in the second-line setting, and the reasons should be thoroughly explored once the data are available.

Lessons learned

After analyzing the results of these trials, we have learned some lessons. First, specific and properly powered phase II studies exploring liver-related toxicity are required in cirrhotic patients with HCC prior to testing drugs in phase III. In fact, liver-induced toxicity might hamper the positive results obtained by potent antitumoral drugs, as can be the case with sunitinib, in which drug-related liver adverse events might have counterbalanced the antitumoral benefits (17). In addition, it has been proposed that these phase II trials incorporate a control arm that would reduce selection bias and allow impartial comparison in secondary analysis (16, 32, 33). This strategy might have diminished the risk of a negative phase III trial. It has to be acknowledged, however, that the positive signal leading to the sorafenib phase III trial was obtained in a large single-arm phase II study including more than 100 patients (34). Large phase II studies might prevent biased results because of the regression-to-the-mean correction effect by which the higher the sample, the lower the risk of random error in estimating a survival outcome. Thus, this approach remains as a valid alternative to randomized phase II studies. Second, trial stratification in the second-line

setting might include portal invasion and metastases as separate variables, as opposed to the first-line, in which metastasis and/or portal invasion can be jointly assessed as a single variable. The fact that more than 70% of patients presented with metastases (ref. 21; as opposed to around 40% to 50% in first-line, ref. 9, 19) masks the stratification effect of portal invasion. Third, secondary endpoints such as TTP and objective response rate (ORR) need to be revisited. The fact that there was a potential correlation in the SHARP study between survival and TTP led to the assumption that this time-to-event endpoint was more mature than objective response assessed by conventional RECIST criteria (16). This was confirmed in the Asian-Pacific trial testing sorafenib versus placebo (10). Nonetheless, the trials analyzed herein reveal some inconsistencies between OS and TTP (Table 1), and thus TTP is challenged as a surrogate endpoint. Eventually, investigators in further studies in the first-line and second-line setting (where median OS for the placebo arm is expected to be 7–8 months) need to consider analyzing OS as a primary endpoint even in the phase II scenario. Alternatively, ORR is currently revisited as an endpoint after the introduction of modified RECIST (mRECIST) assessment (35) in HCC endorsed by the AASLD-JNCI (16) and EASL-EORTC guidelines (8). Unfortunately, data on ORR by mRECIST are only available in one study (second-line brivanib; ref. 21) and the study exploring a correlation between ORR (achieved in 10% of patients on brivanib) as surrogate marker for survival is still ongoing. Finally, none of the studies reported herein has disclosed any biomarker analysis that could rescue the drug in a molecularly selected subgroup of patients. Recent guidelines recommend obtaining tumor biopsies in all clinical research studies in HCC (8). The case of cetuximab in colon cancer (36), for which survival advantages were only observed in wild-type RAS patients as opposed to "all comers," should encourage companion studies with biomarkers in the phase III setting.

Novel Perspectives on Trial Design

Most phase II and III studies currently ongoing in HCC are targeting "all comers." Such is the case of levatinib, Y-90, doxorubicin, or oncolytic virus, which are challenging sorafenib in the first-line setting, and ramucirumab, regorafenib, or cabozantinib versus placebo in second line. Although this strategy remains valid and probably will be the most common approach in the field, it is expected that an increasing number of studies targeting specific molecular subclasses of HCC will emerge. To understand the rationale for trial design based on molecular markers, we first review the molecular classification and drivers as potential targets of therapies in HCC reported so far and then explore the two proposed trial designs: proof-of-concept trials and biomarker-based enrichment trials.

Overview of molecular classification and drivers as targets for therapies in HCC

Molecular classification of cancer should aid in understanding the biologic subclasses and drivers of the disease,

optimize benefits from molecular therapies, and enrich trial populations. In HCC, no molecular subclass has been reported as responding to a specific targeted therapy so far (8). From the biologic standpoint, different tumoral classes have been characterized, including a Wnt subclass (enriched with CTNNB1 mutations), a proliferation class (with two subclasses: S1-TGF- β and S2-*EpCAM* positive) and an inflammation class (37–40). The proliferation subclass accounts for 50% of cases and is enriched with tumors derived from progenitor cells (e.g., "EpCAM"; ref. 38), and these cases tend to have worse prognosis. In addition, RAS, IGF, MET, and mTOR signaling are pathways clearly enriched in this subclass (37).

High-resolution analysis of molecular alterations in human malignancies has allowed the identification of new disease drivers to allow the modification of treatments in some solid malignancies such as lung, breast, or melanoma. Recent studies have provided a broad picture of the mutational profile in HCC and identified an average of 30 to 40 mutations per tumor, among which six to eight are considered drivers (41, 42). The main mutations described are in the promoter region of *TERT*, *p53*, *CTNNB1*, *ARID1A*, and *Axin 1* (see Table 2; ref. 42). Deep-sequencing studies confirmed *TP53* and *CTNNB1* as frequently mutated in HCC (41, 42). Of note, mutations in these genes are mutually exclusive—an indication that they could act as drivers of tumor progression. In addition, these studies revealed novel mutations associated with HCC in different members of the chromatin remodeling pathway (*ARID1A* and *ARID2*), in genes involved in ubiquitination (*KEAP1*), RAS/MAPK signaling (*RPS6KA3*), and oxidative stress (*NFE2L2*), and *JAK1* in 9% of hepatitis B virus (HBV)-related HCC. Functional validation of these novel mutations in experimental models suggests that *JAK1* inhibition represents an attractive new therapeutic target. Furthermore, it is clear that genes commonly mutated in other solid tumors such as *EGFR*, *BRAF*, *PIK3CA*, or *KRAS* are rarely mutated in HCC (<5% of cases; Table 2; ref. 42). High-level amplifications at 5% to 10% prevalence containing oncogenes have been described in 11q13 (*Cyclin D1* and *FGF19*) and 6p21 (*VEGFA*; ref. 37), whereas other more common amplifications reported contain Myc and Met genes. Some of these confirmed drivers represent druggable targets for therapies.

Proof-of-concept trials and trial enrichment

We can distinguish two types of biomarkers defining different trial designs: oncogenic addition loops, defining proof-of-concept trials (the case of refametinib in RAS-positive mutants in phase II; ref. 43), and the activation of signaling cascades leading to trial enrichment based on biomarkers (the case of tivantinib in patients with MET-positive HCC in phase II and III; ref. 44).

Pivotal proof-of-concept phase II trials. Several molecular therapies have been approved in oncology during the past decade targeting oncogenic addiction loops. Oncogenic addiction can be defined as a heightened state of dependency of cancer cells on activated oncogenes or loss of

Table 2. Landscape of most prevalent mutations and high-level amplifications of HCC

Gene	Pathways/gene functions involved	Estimated frequency based on deep-sequencing studies (%)
Genes frequently mutated in HCC		
<i>TERT promoter</i>	Telomere stability	60
<i>TP53</i>	Genome integrity	20–30
<i>CTNNB1</i>	WNT signaling	15–25
<i>ARID1A</i>	Chromatin remodeling	10–16
<i>TTN</i>	Chromosome segregation	4–10
<i>NFE2L2</i>	Oxidative stress	6–10
<i>JAK1</i>	JAK/STAT signaling	0–9
Genes frequently mutated in other solid tumors, but rarely muted in HCC		
<i>IDH1, IDH2</i>	NAPDH metabolism	<5
<i>EGFR</i>	Growth factor signaling	<5
<i>BRAF</i>	RAS/MAPK signaling	<5
<i>KRAS, NRAS</i>	RAS/MAPK signaling	<5
<i>PIK3CA</i>	AKT signaling	<5
<i>PTEN</i>	AKT signaling	<5
Oncogenes contained in high-level amplifications in HCC		
<i>FGF19</i>	FGF signaling	5–10
<i>Cyclin D1</i>	Cell cycle	5–10

Adapted from Villanueva and Llovet (42).

tumor suppressors. Therefore, not all genetic alterations found in cancer genomes are able to establish this dependence. Numerous human cancers highlight the therapeutic perspective of oncogene addiction. For instance, the kinase activity of the BCR–ABL fusion protein is implicated in the pathogenesis of chronic myeloid leukemia, and once this loop is effectively discontinued with imatinib, tumor burden decreases and there is a positive effect in patient survival (45). Similarly, *EGFR* mutations in lung cancer predict responses to erlotinib/ gefitinib (46), and patients with amplification in *HER2/neu* in breast cancer respond to trastuzumab, a monoclonal antibody directed to this receptor (47). More recent examples are melanoma tumors harboring *B-RAF* mutations responding to vemurafenib (48) and *ALK* fusions responding to crizotinib in NSCLC. In these latter cases, proof-of-concept pivotal single-arm trials led to accelerated FDA approval.

Despite being an attractive strategy, there are some issues that need to be addressed when implementing this concept in HCC: (i) discovery of *bona fide* oncogenic addiction loops; (ii) selection of adequate *ad hoc* blockade drugs. For instance, WNT activation occurs in 50% of cases (49), but WNT inhibitors have not yet entered advanced clinical developmental phases; and (iii) HCC has a significant genomic heterogeneity, which facilitates the coexistence of competing loops within the same tumor. Despite these drawbacks, it is time to develop personalized medicine approaches in HCC. A few "druggable" drivers of tumor progression and metastasis have been identified so far, such as *RAS*, *FGF19*, *IGF2*, *NOTCH1*, *MET* and *mTOR* signaling

(42, 50). An example of a proof-of-principle early trial that is ongoing is the one testing the MEK inhibitor refametinib in specific RAS-mutated HCC cases (~5% of patients with HCC). In this trial, 300 patients with HCC will be screened in order to treat around 15 RAS-positive patients (43).

Trial enrichment for activation of signaling pathways. Validated biomarkers predicting response to sorafenib have not been identified. High *c-KIT* or low *HGF* were identified as predictors of survival in patients treated with sorafenib, thus raising the possibility that these markers could identify better drug responders (51). However, none of them ultimately showed predictive value (*P* of interaction: 0.081 and 0.073, respectively; ref. 51). Further efforts should be focused in enriching trial populations with biomarkers defining molecular subclasses. This can be the case with some pathways that are clearly activated in HCC, such as *mTOR*, *IGF*, *MET*, and *WNT* among others. One can speculate that the reasons why trial enrichment has not been implemented in HCC research until very recently might be related to (i) difficulties in obtaining tumor tissue in patients already diagnosed by noninvasive criteria; (ii) lack of effective biomarkers to be applied for the drugs tested so far in phase III; and (iii) limited understanding of the pathogenesis of the disease and primary drivers in selected populations.

Recently, a phase II trial comparing tivantinib (a selective oral inhibitor of *MET*) versus placebo was conducted in the second-line setting. No effect was identified in "all comers," but a significant survival effect was achieved in the *post hoc* analysis of *MET*-positive patients (OS = 7.2 vs 3.8; HR = 0.38;

95% CI, 0.18–0.81; $P = 0.01$; ref. 44). Confirmation of results is ongoing in phase III. From the biologic standpoint, adverse events related to tivantinib, such as neutropenia, suggest that the drug has off-target effects. Another c-Met inhibitor, cabozantinib, is being tested in phase III. This drug is a multikinase inhibitor also targeting VEGF, and the trial is conducted in the second line in all patients progressing to sorafenib.

We are facing a new era for testing drugs in HCC. On one hand, nonspecific drugs that target all patients will still be explored, and there is room for such types of drugs particularly in the second-line (this is the case of ramucirumab and regorafenib) or third-line setting, when there is such unmet need. On the other hand, pivotal proof-of-concept trials or trials with biomarker-based enrichment

will emerge for specific pockets of HCC populations, which can completely change the treatment paradigm not only of advanced cases, but also of early or intermediate stages. In parallel, some etiology-specific activated pathways or oncogenes might be discovered or confirmed in the near future and should be considered for further modeling of trial design. Thus, the dawn of a new era of HCC trials is coming.

Disclosure of Potential Conflicts of Interest

J.M. Llovet is a consultant/advisory board member for Bayer Pharmaceuticals, Boeringher/Ingelheim, Bristol-Myers Squibb, Blueprint, Lilly-Imclone, Novartis, and Jennerex. No potential conflicts of interest were disclosed by the other author.

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