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

Running title: Reasons for phase III failure in HCC

Josep M Llovet1-3, * and Virginia Hernandez-Gea1

1 HCC Translational Research Laboratory, Barcelona-Clinic Liver Cancer Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic de Barcelona, Universitat de Barcelona (UB), Barcelona, Catalonia, Spain.

2 Mount Sinai Liver Cancer Program, Division of Liver Diseases, Tisch Cancer Institute, Ichan School of Medicine at Mount Sinai, New York, New York, USA.

3 Institució Catalana de Recerca i Estudis Avançats, Barcelona, Catalonia, Spain

*Corresponding author. HCC Translational Research Laboratory, BCLC, IDIBAPS-Hospital Clinic, Rosello 153 (Centre Esther Koplowitz, 3rd Floor); 08036 Barcelona, Spain. Tel.: +34932279155, fax: +34932275792. E-mail address: jmllovet@clinic.cat

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Abstract

Hepatocellular carcinoma (HCC) is a major health problem. Most HCC patients recur 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 first (brivanib, sunitinib, erlotinib and linifanib) or second line (brivanib, everolimus) 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 end-point of survival. Trials ongoing testing drugs head-to-head vs. sorafenib in “all comers” might have difficulties in achieving superior results in first line. Novel trials are also designed testing drugs in biomarker-based subpopulations of HCC patients. Most common mutations, however, are undruggable such p53 and CTNNB1. Two types of studies are proposed: 1) 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, 2) Phase II-III studies using biomarker-based trial enrichment for defining HCC subpopulations, such as the case of enriching for MET-positive tumors. These strategies have deemed successful in breast, melanoma and lung cancer, and are expected to change the landscape of trial design of HCC.

Keywords: Hepatocellular carcinoma, targeted therapies, phase III trials, randomized controlled trials, clinical trials, oncogenic addiction, biomarkers, trial enrichment, survival
INTRODUCTION

Hepatocellular carcinoma (HCC) is a major public health problem, ranking as the 3rd cause of cancer-related death and the 16th absolute cause of death globally (1). There has been a net increase of 62% in HCC-related annual death rates (from 463,000 to 752,000) during the last 20 years. In addition, HCC is the most rapidly escalating cause of cancer mortality in the US 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 early stage of the disease and are amenable for resection, liver transplantation or local ablation with radiofrequency (2, 4, 8). Median survival is of 60mo, 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 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 which approval 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 HCC patients on sorafenib is only 1 year indicating the clear need to improve their outcome.

Sorafenib approval paved the way for testing a wide range of molecular therapies. Unfortunately, none of them (sunitinib, brivanib, erlotinib, linifanib and everolimus) have resulted in survival benefits. Obvious reasons for treatment failure include liver toxicity and lack of substantial anti-tumoral 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. We herein are dissecting the
results of phase III trials reported in the last 2 years and explore the new designs proposed to overcome this negative trend.

**REASONS FOR FAILURE OF PHASE III STUDIES**

HCC 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 last 2 years did not meet the primary end point (Table 1). Six phase III trials were reported negative in first-line (sunitinib, brivavib, linifanib and erlotinib) (17-20) and second line (brivanib and everolimus) (21). Four of them were designed for superiority and two for non-inferiority (brivanib and linifanib) (18, 19) with a primary end-point of overall survival. In order to explore the reasons for these failures we are also commenting 1) Phase III pivotal trials currently ongoing 2) 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-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 is only one full published paper (brivanib vs placebo in second-line) (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 released announced that the phase III trial comparing everolimus vs placebo in 2nd line did not meet the primary end-point, but full data has not yet reported. We are herein focusing on exploring the causes of trial failure, whereas the concept of drivers, oncogenic addiction and biomarker-driven trials will be discussed in more detail below, in the section of opportunities for the future.

1. **Drugs tested in HCC: fine balance between efficacy and toxicity**

Sorafenib is a drug leading to survival advantages with manageable adverse events, and with almost absence of liver toxicity or treatment-related deaths (9, 10). Due to the success of the SHARP trial testing sorafenib (9), its design has been adopted by almost all studies testing molecular therapies in first line. The main concepts were adopted by guidelines of trial design.
(8, 16) and are as following 1) Select only patients with preserved liver function (Child-Pugh A). Only Child Pugh A patients should be included in trials to prevent liver failure and death as a result of the natural history of cirrhosis. Child-Pugh A patients without HCC are expected to have a 1-yr survival rate of 95%, a figure that is of utmost importance to prevent competing risks for death (the main end-point). Underlying liver disease highly complicates HCC treatment, as it can be itself responsible for morbi-mortality. 2. Select patients with advanced stage of HCC according to the Barcelona Clinic Liver Cancer (BCLC) 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 score (23)- might not be appropriate for treatment allocation, since the primary purpose of the score was to define prognosis but not to allocate for specific therapies. 3) Define overall survival as primary end-point, and time to progression (TTP) as secondary end point. Progression–free survival is a vulnerable end-point 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 (IC₅₀) for almost all of the targets) was approved by the FDA in 2006 for the treatment of renal carcinoma and GIST. Nonetheless, sunitinib did not meet the survival superiority end-point vs sorafenib in a phase III study (17) probably as a result of two factors. First, signals of efficacy/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, hepato-renal Sd.) leading to death in the range of 6-10% (24, 25). Both studies including less than 40 patients showed median survivals in the range of 8-10 mo, associated to 10% (50mg/day) (24) and 6% (37.5 mg day) (25) treatment-related death, respectively. Based on this data, 37.5 mg dose was used in a subsequent phase III study randomizing 1074 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 mo vs 10.2 mo (sunitinib vs sorafenib, hazard ratio (HR): 1.30). Treatment-related deaths accounted for 3.2% of cases (17/526 patients) in sunitinib arm vs 0.3% (2/542) in the sorafenib arm. Subgroup analysis showed higher benefit of sorafenib for HCV-related HCC patients (median survival of 15 mo).

2. **Lack of efficacy**

The EGFR tyrosine kinase inhibitor **erlotinib**, moved to phase III trial with modest disease
control benefit in two previous phase II trials (26, 27). These single-arm phase II studies reported median survival of 10-13 mo associated to marginal response rates (26, 27). There was 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 overall survival 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 mo compared with 8.5 mo 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 mo.

**Linifanib**, a more potent multikinase inhibitor targeting VEGFR and PDGFR than sorafenib, was tested in first line after a small single-arm phase II study including 44 patients showed median survival of 10.4mo (28). The phase III study with around 1000 patients did not meet the non-inferiority end-point (OS 9.1 vs 9.8 months; HR 1.04; 95% CI 0.89-1.22; P <0.001) (19). The study was halted at the 3rd interim analysis due to futility, although the reported data also suggest that linifanib was more toxic than sorafenib in terms of serious adverse events (54% vs 38%), grade 3-4 hypertension (20% vs 10%) and grade 3-4 liver-related complications (encephalopathy, ascites, hiperbilirubinemia: 20% vs 10%).

3. A better understanding of trial design

3A The non-inferiority scenario. According to guidelines, new molecules tested in first line need to be combined with the standard of care sorafenib to demonstrate superiority (8, 16). This has only been the case of one RCT, sorafenib+erlotinib (20), whereas the others were directly testing the candidate drug vs sorafenib. We can estimate that in order to improve sorafenib outcome in first line for superiority the drug has to be potent enough to achieve a HR of 0.5 or less if theoretically compared to 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 50% the risk of death. Nonetheless, two pivotal RCT proposed a two-step design, first testing non-inferiority and then testing for superiority (18, 19). Despite splitting the alpha between two analysis—which can be assumed increasing the sample size—, it seems that this approach can give chances to drugs that show efficacy similar to sorafenib. However, the window of opportunity for these drugs is certainly too narrow.

**Brivanib** is a multikinase inhibitor with activity against FGF signaling that achieved a 10 months OS (95% CI 6.8-15.2) with a good tolerance and safety profile in a first line single-arm 55 patients trial (30). The phase III pivotal study was designed as a non-inferiority trial under
the assumption that brivanib would have equal effects to sorafenib or would not be unacceptable worse than sorafenib (assuming a decrease in OS no more than 3 weeks) (18). Figure 1 shows the results of the phase III trial including 1155 patients where the boundary of the confidence interval of the hazard ratio for survival was set at 1.08 following recommendations for non-inferiority trial design. In summary, it is estimated that RCT testing drugs head-to-head to sorafenib in first line might have three potential results 1) drug is superior to sorafenib, if the HR (95%CI) boundaries do not cross the unity. 2) The drug is non-inferior compared to sorafenib, if the HR (95%CI) boundaries fall between 1 and 1.08, and 3) the drug is inferior to sorafenib if the HR (95%CI) boundaries cross the 1.08 upper limit for non-inferiority. Despite taking this less risky design, brivanib was not able to meet the primary end point (9.5 m brivanib vs 9.9 m sorafenib; HR 1.07 95% CI 0.94-1.23; P = 0.3) (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 2 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 non-inferiority HR 95% upper boundaries (between 1 and 1.08) it seems that there should be a clear non-significant 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 Figure 1.

3.B. The second line scenario. Brivanib has been the first drug to be tested in second-line 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 9.2mo (31), a phase III trial testing brivanib vs placebo was conducted. The study did not achieved the primary end-point of survival (9.4 months brivanib vs 8.2 months placebo; HR: 0.89; 95.8% CI, 0.69–1.15; p: 0.3307) (21). Reasons for treatment failure have been previously discussed (32) and include a) impressive natural history of placebo arm- due to positive selection bias with an enrichment of indolent HCCs, b) Potential unbalance in prognostic factors, particularly portal vein invasion, an issue analyzed in the next section. After adjusting for this factor the HR comparing brivanib vs placebo was 0.82 (21), and c) positive signal was not obtained in the setting of a phase II randomized study (31). Another drug, everolimus, also did not meet the primary end-point in 2nd line, and the reasons should be thoroughly explored once the data is available.

Lessons learned
After dissecting 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 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 of sunitinib where drug-related liver adverse events might have counterbalance 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 due to 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 second line** might include portal invasion and metastases as separate variables as opposed to first line where metastasis and/or portal invasion can be jointly assessed as a single variable. The fact that more than 70% of patients present metastases (21) (as opposed to around 40-50% in first line (9, 19)) is able to mask the stratification effect of portal invasion. Third, **secondary end-points such as TTP and Objective response rate (ORR) need to be revisited.** The fact that there was a correlation in the SHARP study between survival and TTP led to assume this time-to-event end point as more mature than objective response assessed by conventional RECIST (16). This was confirmed in the Asian-Pacific trial testing sorafenib vs placebo (10). Nonetheless, the trials analyzed herein reveal some inconsistencies between OS and TTP (Table 1), and thus TTP is challenged as a surrogate end-point. Eventually, further studies in first and 2nd–line (where median OS for the placebo arm is expected to be 7-8 mo) need to consider analyzing overall survival as a primary end-point even in the phase II scenario. Alternatively, ORR is currently revisited as an end-point after the introduction of mRECIST assessment (35) in HCC endorsed by the AASLD-JNCI (16) and EASL-EORTC guidelines (8). Unfortunately, data on ORR by mRECIST is only available in one study (2nd line brivanib) (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 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), where 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 the HCC field are targeting “all comers”. Such is the case of levantinib, Y-90, doxorubicin or oncolytic virus that are challenging sorafenib in first line and ramucirumab, regorafenib or cabozantinib vs 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. In order to understand the rationale for trial design based on molecular markers, we will first review the molecular classification and drivers as potential targets of therapies in HCC reported so far and then will 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 biological subclasses and drivers of the disease and optimize benefits from molecular therapies and enrich trial populations. In HCC, no molecular subclass has been reported as responding to specific targeted therapy so far (8). From the biological standpoint, different tumoral classes have been characterized including a Wnt subclass (enriched with CTNNB1 mutations), a proliferation class (with two subclasses: S1-TGF-beta 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” (38)) and tend to have worse prognosis. In addition, RAS, IGF, MET and mTOR signalling 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 30–40 mutations per tumour, among which 6-8 are considered drivers (41, 42). The main mutations described are in the promoter region of TERT, p53, CTNNB1, ARIDA1A and Axin 1 (see Table 2 (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 tumour progression. In addition, these studies discovered novel mutations associated with HCC in different members of the chromatin remodelling pathway (ARID1A and ARID2), in genes involved in ubiquitination (KEAP1), RAS/MAPK signalling (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 suggested that JAK1 inhibition...
represents an attractive new therapeutic target. Furthermore, it is clear that genes commonly mutated in other solid tumours such as EGFR, BRAF, PIK3CA or KRAS are rarely mutated in HCC (<5% of cases, Table 2 (42)). High level amplifications at 5-10% prevalence containing oncogenes have been described in 11q13 (Cyclin D1 and FGF19) and 6p21 (VEGFA) (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+ mutants in phase II) (43) and the activation of signaling cascades leading to trial enrichment based on biomarkers (the case of tivantinib in MET-positive HCC patients in phase II-III) (44).

1. **Pivotal proof-of-concept phase II trials.** Several molecular therapies have been approved in oncology during the last decade targeting oncogenic addiction loops. Oncogene addiction can be defined as a heightened state of dependency of cancer cells on activated oncogenes or loss of tumor suppressors. Therefore, not all genetic alterations found in cancer genomes are able to establish this dependence. There are numerous human cancers that 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), amplification in HER2/neu in breast cancer respond to trastuzumab, a monoclonal antibody directed to this receptor (47). More recent examples are melanoma tumors harbouring B-RAF mutations responding to vemurafenib (48), and ALK fusions responding to crizotinib in NSCLC. In these later 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: 1) Discovery of bona fide oncogenic addiction loops; 2) 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; 3) HCC has a significant genomic heterogeneity, what facilitates the co-existence of competing loops within the same tumor. Despite these drawbacks, it is about time to develop personalized medicine approaches in HCC. Few “druggable” drivers of tumor progression and metastasis have been identified so far, such as RAS, FGF19, IGF2, NOTCH1, MET and mTOR.
signalling (42, 50). An example of a proof-of-principle early trial ongoing is the one testing refametinib MEK inhibitor in specific RAS-mutated HCC cases (~5% of HCC patients). In this trial, 300 HCC patients will be screened in order to treat around 15 RAS+ patients (43).

2. Trial enrichment for activation of signaling pathways. Validated biomarkers predicting response to sorafenib have not been identified. Patients with high c-KIT or low HGF were identified as predictors of survival in patients treated with sorafenib, thus raising the concept 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) (51). Further efforts should be focused in enriching trial population with biomarkers defining molecular subclasses. This can be the case with some pathways that are clearly activated in HCC, such as mTOR, IGF, MET, 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 a) difficulties in obtaining tumor tissue in patients already diagnosed by non-invasive criteria b) lack of effective biomarkers to be applied for the drugs tested so far in phase III and c) 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+ patients (OS 7.2 vs 3.8; HR 0.38 95% IC 0.18-0.81; P= 0.01) (44). Confirmation of results is ongoing in phase III. From the biological standpoint, adverse events related to tivantinib such as neutropenia suggests that the drug has off-target effects. Another c-Met inhibitor, cabozatinib, is being tested in phase III. This drug is a multikinase inhibitor also targeting VEGF and the trial is conducted in second line in all patients progressing to sorafenib.

We are facing a new era for testing drugs in the HCC field. On one hand, non-specific drugs will be still explored targeting all patients, and there is room for such type of drugs particularly in second-line (this is the case of ramucirumab and regorafenib) or 3rd line, when there is such unmet need. On the other hand, pivotal proof-of-concept trials or those 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 modelling trial design. Thus, the dawn of a new era of HCC trials is coming.
References


14
43. Refametinib in Ras mutant HCC. In Clinical trials.gov. (Identifier: NCT01915589) and Refametinib in combination with sorafenib in Ras mutant HCC (identifier:NCT01915602).
<table>
<thead>
<tr>
<th>First-line advanced HCC</th>
<th>Design</th>
<th>Overall survival (OS)*</th>
<th>Time to Progression (TTP)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sorafenib vs Placebo</strong> (9) (SHARP trial)</td>
<td>Superiority</td>
<td>10.7 mo vs 7.9 mo; HR 0.69 (95% CI 0.55-0.87) P= 0.00058</td>
<td>5.5 mo vs 2.8 mo; HR 0.58 (95% CI, 0.45 to 0.74) P&lt;0.001</td>
</tr>
<tr>
<td><strong>Sorafenib vs Placebo</strong> (10) (Asia Pacific trial)</td>
<td>Superiority</td>
<td>6.5 mo vs 4.2 mo; HR 0.68 (95% CI 0.50-0.93) P=0.014</td>
<td>2.8 mo vs 1.4 mo; HR 0.57 (95% CI 0.42-0.79) P=0.0005</td>
</tr>
<tr>
<td><strong>Sunitinib vs Sorafenib</strong> (17) (SUN trial)</td>
<td>Superiority</td>
<td>7.2 mo vs 10.2 mo; HR 1.30 (95% CI 1.13-1.5) P= 0.001</td>
<td>3.8 mo vs 4.1 mo; HR 1.13 (95% CI 0.98-1.31) P=0.16</td>
</tr>
<tr>
<td><strong>Brivanib vs Sorafenib</strong> (18) (BRISK-FL trial)</td>
<td>Non-inferiority</td>
<td>9.5 mo vs 9.9 mo; HR 1.05 (95% CI 0.94-1.23) P=0.31</td>
<td>4.1 mo vs 4.2 mo; HR 1.01 (95% CI 0.88-1.16) P=0.8</td>
</tr>
<tr>
<td><strong>Linifanib vs Sorafenib</strong> (19) (LIGHT trial)</td>
<td>Non-inferiority</td>
<td>9.1 mo vs 9.8 mo; HR 1.04 (95% CI 0.89-1.22) P=ns</td>
<td>5.4 mo vs 4 mo; HR 0.76 (95% CI 0.64-0.89) P &lt;0.001</td>
</tr>
<tr>
<td><strong>Sorafenib + erlotinib vs sorafenib</strong> (20) (SEARCH trial)</td>
<td>Superiority</td>
<td>9.5 vs 8.5 mo; HR 0.92 (95% CI 0.78-1.1) P=0.2</td>
<td>3.2 mo vs 4.0 mo; HR 0.113 (95% CI 0.94-1.36) P=0.91</td>
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</table>

**Setting: Second line advanced HCC**

| Brivanib vs Placebo (21) (BRISK-PS trial) | Superiority | 9.4 mo vs 8.2 mo; HR 0.89 (95% CI 0.69-1.15) P=0.33  | 4.2 mo vs 2.7 mo; HR 0.56 (95% CI 0.42-0.78) P=0.001 |

*Overall survival is the primary end-point in all studies; ** Everolimus vs placebo has been reported negative in a recent press release.
Table 2 Landscape of most prevalent mutations and high-level amplifications of human hepatocellular carcinoma. Adapted from Villanueva and Llovet (42).

<table>
<thead>
<tr>
<th>Gene</th>
<th>Pathways/gene functions involved</th>
<th>Estimated frequency based on deep-sequencing studies (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genes frequently mutated in HCC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TERT promoter</td>
<td>Telomere stability</td>
<td>60</td>
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<tr>
<td>TP53</td>
<td>Genome integrity</td>
<td>20–30</td>
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<td>CTNNB1</td>
<td>WNT signalling</td>
<td>15–25</td>
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<td>ARID1A</td>
<td>Chromatin remodelling</td>
<td>10–16</td>
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<tr>
<td>TTN</td>
<td>Chromosome segregation</td>
<td>4–10</td>
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<td>NFE2L2</td>
<td>Oxidative stress</td>
<td>6–10</td>
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<tr>
<td>JAK1</td>
<td>JAK/STAT signalling</td>
<td>0–9</td>
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<tr>
<td><strong>Genes frequently mutated in other solid tumours, but rarely mutated in HCC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDH1, IDH2</td>
<td>NAPDH metabolism</td>
<td>&lt;5</td>
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<tr>
<td>EGFR</td>
<td>Growth factor signalling</td>
<td>&lt;5</td>
</tr>
<tr>
<td>BRAF</td>
<td>RAS/MAPK signalling</td>
<td>&lt;5</td>
</tr>
<tr>
<td>KRAS, NRAS</td>
<td>RAS/MAPK signalling</td>
<td>&lt;5</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>AKT signalling</td>
<td>&lt;5</td>
</tr>
<tr>
<td>PTEN</td>
<td>AKT signalling</td>
<td>&lt;5</td>
</tr>
<tr>
<td><strong>Oncogenes contained in high-level amplifications in HCC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FGF19</td>
<td>FGF signalling</td>
<td>5–10</td>
</tr>
<tr>
<td>Cyclin D1</td>
<td>Cell cycle</td>
<td>5–10</td>
</tr>
</tbody>
</table>
Figure 1: Understanding non-inferiority study design and HR boundaries in HCC research. It is estimated that RCT testing drugs head-to-head to sorafenib in first line might have three potential results 1) drug is superior to sorafenib, if the HR (95%CI) boundaries do not cross the unity. 2) The drugs is non-inferior compared to sorafenib, if the HR (95%CI) boundaries fall between 1 and 1.08, and 3) the drug is inferior to sorafenib if the HR (95%CI) boundaries cross the 1.08 upper limit for non-inferiority. The figure shows the HR and 95%CI of two RCT showing that according to this design the drugs are inferior to sorafenib (18, 19).
Figure 1:

<table>
<thead>
<tr>
<th>Estimated HR</th>
<th>0.87</th>
<th>0.94</th>
<th>1.00</th>
<th>1.08</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favors sorafenib</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favors tested drug</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Illustrative scenarios:
- Superior
- Noninferior
- Inferior†

Upper limit for noninferiority:
- Linifanib: 1.04 (0.89–1.20)
- Bribanib: 1.07 (0.94–1.23)
Hepatocellular Carcinoma: Reasons for Phase III Failure and Novel Perspectives on Trial Design

Josep M Llovet and Virginia Hernandez-Gea

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