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Systemic treatment of hepatocellular carcinoma: why so many failures in the development of new drugs?

ABSTRACT

Introduction: The increasing knowledge of the genomic landscape of hepatocellular carcinoma (HCC) and the development of molecular targeted therapies are a promising background for increasing the number of effective drugs for HCC patients. In recent years, many new drugs have been tested as an alternative to sorafenib or after sorafenib failure.

Areas covered: In this review, our aim is to describe the randomized trials recently conducted in HCC patients, in order to understand the main reasons potentially related to the failures of many drugs. In addition, we briefly describe the main ongoing trials, that could potentially change the scenario of HCC treatment in the next years.

Expert Commentary: Heterogeneity of study populations, lack of understanding of critical drivers of tumor progression, risk of liver toxicity associated with experimental agents, flaws in trial design and marginal antitumoral potency can be considered the main reasons for failure of phase III clinical trials in HCC. Most ongoing trials are conducted without any molecular selection criteria, although many drugs could be probably better tested in a molecularly selected population. The knowledge of potential predictive factors for drug efficacy in patients with advanced HCC could improve the chance of obtaining positive results in clinical trials.

Key-words: hepatocellular carcinoma, clinical trials, regorafenib, ramucirumab, cabozantinib, nivolumab.

1. INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide and represents the second cause of cancer-related death, causing an estimated number of 700000 deaths every year [1]. Chronic liver injury and inflammation due to viral or non-viral causes are the major etiologies, with the majority of cases occurring in the setting of cirrhosis.

The Child-Turcotte-Pugh score, that is the most widely used classification for the evaluation of underlying hepatic impairment, is commonly applied in clinical practice, because hepatic function is associated with prognosis, risk of toxicity and feasibility of the different treatment options of HCC patients [2]. Treatment selection for HCC patients is guided by the stage of the disease, but in contrast to most solid tumors, where the TNM staging system is universally recommended and used, there are several different classifications [3]. Among these systems, Barcelona Clinic Liver Cancer (BCLC) staging system is the most widely applied, because it has been conceived not only to address different prognosis but also to confer a specific therapeutic indication for each stage [4].

While local treatments represent standard therapy for HCC patients when the disease is diagnosed in early or intermediate stages, the oral multikinase inhibitor sorafenib is currently the only approved systemic drug for patients with advanced HCC. This agent demonstrated an overall survival benefit within two randomized, placebo-controlled trials, conducted in both Western and Asian patients eligible for first-line treatment [5,6]. The SHARP trial was designed in 2004: at that time, there was no drug of proven efficacy for patients with advanced HCC, and placebo was considered an acceptable control arm [5]. The SHARP study showed an improvement in survival with the administration of sorafenib, extending median overall survival from 7.9 with placebo to 10.7 months with the experimental drug [Hazard Ratio (HR) 0.69, 95% Confidence Interval

(CI) 0.55 – 0.87; $p=0.02$], with manageable adverse events. In the second randomized trial, conducted in Asian subjects, patients receiving sorafenib had a median overall survival of 6.5 months, compared with 4.2 months for those receiving placebo [HR 0.68; 95% CI 0.50–0.93; $p=0.014$] [6]. As reported above, although the absolute life expectancy was longer in the SHARP trial for both study arms compared to the Asian study, the HRs for survival were comparable between the two studies. The discrepancy between the overall survival in the two control arms may reflect different etiologies and ethnicities across two studies, and more advanced disease in Asian-Pacific Study than those in the SHARP trial.

Following the results of those two trials, sorafenib has been included in international guidelines and it represents standard treatment for patients with advanced HCC and well-preserved liver function (Child-Pugh A). Of note, the evidence about its effectiveness in patients with more severe liver impairment is less robust, because Child-Pugh B patients were not eligible in both trials. Although sorafenib is widely used in clinical practice in Child-Pugh B patients (also due to the lack of effective alternatives), it is not possible to robustly define the optimal management of HCC in this clinically relevant subgroup [7-9].

However, even in HCC patients with well preserved liver function, the median life expectancy is shorter than 1 year, while the incidence of drug-related adverse events and the economic costs are not negligible. This emphasizes the urgent need of developing novel medical approaches to improve the outcome of these patients. Interestingly, the increasing knowledge of the genomic landscape of HCC and the development of molecular targeted therapies represent a promising background for the expansion of the number of effective drugs for HCC patients. In recent years, many new drugs have been tested in HCC patients as an alternative to sorafenib or after sorafenib failure. In detail, first-line trials have compared new drugs as single-agents, or in combination with

sorafenib, compared to sorafenib alone, while second-line trials have compared new drugs vs. no active treatment (placebo or best supportive care) in patients experiencing progressive disease with sorafenib. Unfortunately, to date, none of the first-line trials resulted in a positive result. Similarly, with the exception of the trial testing regorafenib [10], none of the second-line trials has documented the efficacy of another drug after sorafenib failure.

Therefore, further research is urgently needed to identify effective strategies to improve the prognosis of patients with advanced HCC. In this review, our aim is to describe the randomized trials recently conducted in HCC patients, in order to understand the main reasons potentially related to these failures. In addition, we briefly describe the main ongoing trials, that could potentially change the scenario of HCC treatment in the next years.

2. Main phase III trials performed in the first-line setting

2.1 Sunitinib

Sunitinib is an oral multitargeted tyrosine-kinase inhibitor of Vascular Endothelial Growth Factor receptor 1 (VEGFR1), VEGFR-2, VEGFR-3, Platelet-Derived Growth Factor receptor A (PDGFR-A), PDGFR-B, and several other related tyrosine kinases with anti-angiogenic and antitumor activity [11]. Differently from sorafenib, however, sunitinib does not inhibit Raf-1: this could be potentially relevant, because HCC progression is associated with Raf-1/MAP kinase pathway activation, and Raf-1 kinase activity is relevant for HCV replication. Before the conduction of a randomized phase III trial in the first-line setting, sunitinib had shown antitumor activity in three phase II studies in patients with advanced HCC [12-14]. Two of these trials showed a median overall survival in the range of 9 to 10 months, representing an interesting background for the conduction of a randomized trial comparing sunitinib versus sorafenib as first-line treatment. Of note, the phase II trials evaluated different doses and schedules of treatment: 37.5 mg/die on a 4 week-on-2 week off schedule (schedule 4/2), 50 mg/die on schedule 4/2, or 37.5 mg via continuous daily dosing (CDD). In those series of patients, the 50 mg/die schedule 4/2 was associated with relevant toxicity (with a non-negligible incidence of treatment-related deaths), while the 37.5 mg CDD schedule was selected for the phase III trial. The randomized, double-blind, phase III study was designed to test if sunitinib was superior (or at least non inferior) to sorafenib, in terms of overall survival, in patients with advanced HCC [15]. As detailed in **Table 1**, a total of 1074 patients were randomized. Unfortunately, after an interim analysis, the trial was stopped, due to both futility reasons (sunitinib did not meet the criteria to demonstrate that it was either superior or non-inferior to sorafenib) and safety reasons (higher incidence of serious adverse events in the sunitinib arm compared to the sorafenib arm). Disappointingly, although progression-free survival was comparable, overall survival

was substantially worse for patients assigned to experimental arm: in detail, median OS was 7.9 months for sunitinib arm and 10.2 months for sorafenib arm. Subgroup analysis showed that OS was similar among Asian patients and among HBV-infected patients, but was shorter with sunitinib in the subgroup of HCV-infected patients (median OS 9.2 vs 17.6 months), although the difference was not statistically significant. This difference in HCV-infected patients may be related to the specific inhibition of Raf-1 by sorafenib (and not by sunitinib); indeed, Raf-1 kinase activity is crucial for HCV replication and this could contribute to the efficacy of sorafenib. Despite the non-inferiority hypothesis could be considered clinically reasonable when the experimental drug is less toxic than the standard one, patients assigned to sunitinib reported more frequent and severe toxicity compared to those treated with sorafenib. Of note, treatment-related deaths accounted for 3.2% of cases in the sunitinib group compared to 0.3% of cases in the sorafenib group. Furthermore, grade 3-4 adverse events and temporary treatment discontinuation related to adverse events were more frequent in sunitinib group than sorafenib group (82.1% and 76.6% versus 74.4% and 58.7%, respectively). Based on these completely negative results, sunitinib has not been further developed in HCC patients.

2.2 Brivanib

Brivanib is a selective dual inhibitor of fibroblast growth factor receptor (FGFR) and VEGF signaling [16]. In a phase II study, designed as a single-arm trial for patients with advanced HCC, brivanib was administered orally at a dose of 800 mg once daily [17]. The primary endpoint was 6-month progression-free survival, and treatment activity was assessed using modified World Health Organization criteria. The 6-month progression-free survival rate was 18.2%, median PFS was 2.7 months and median overall survival was 10 months. Based on this preliminary results, along with the manageable toxicity profile,

brivanib was judged worth to be tested as first-line treatment versus sorafenib, within the randomized phase III trial Brisk-FL [18]. As shown in **Table 1**, this phase III study randomly assigned 1155 patients to receive sorafenib (at the standard dose of 400 mg twice daily) or brivanib (at the same dose tested in the previous phase II study, 800 mg daily). The study was designed to test the non-inferiority of brivanib in terms of overall survival. This primary end-point was not met: median overall survival in the per-protocol analysis was 9.9 month for sorafenib and 9.5 month for brivanib arm (HR = 1.06, 95% CI 0.93 - 1.22; p = 0.311), while the prespecified margin for declaring non-inferiority was an upper limit for 95% confidence interval less or equal to 1.08. Secondary end-points (TTP, PFS and DCR) were similar between the two arms. Similarly to the case of sunitinib, although the study had been designed to test the non-inferiority of brivanib, tolerability of the experimental drug was worse than sorafenib: most frequent grade 3/4 adverse events were hyponatremia (9% vs. 23%, with sorafenib and brivanib respectively), AST elevation (17% vs. 14%), fatigue (7% vs. 15%), hand-foot-skin reaction (15% vs. 2%), and hypertension (5% vs. 13%). Furthermore, discontinuation as a result of adverse events was higher with brivanib (43%), than with sorafenib (33%).

2.3 Linifanib

Linifanib is an ATP-competitive inhibitor of all VEGF and PDGF receptor tyrosine kinase [19]. In a phase II trial conducted in patients with unresectable or metastatic HCC, who had received no more than 1 prior systemic therapy, patients received oral linifanib at a dose of 0.25 mg/kg [20]. Primary endpoint of the trial was the progression-free rate at 16 weeks. The study was conducted mostly in Asian patients (89%), the majority of patients (82%) had received no prior systemic treatment, and most patients (86%) had a well preserved liver function, with Child-Pugh class A. In this study, linifanib showed promising

clinical activity, with a median overall survival of 9.7 months (reaching a median of 10.4 months in the selected subgroup of patients with Child-Pugh A hepatic function). With all the limitations of indirect comparisons, this survival compared favorably with the outcome of patients treated with sorafenib in the randomized phase III trial conducted in the Asia-Pacific region. Based on this background, a randomized phase III trial was designed, to compare linifanib versus sorafenib as first-line treatment [21]. Aim of the study was to demonstrate the superiority, or at least the non-inferiority, of linifanib compared to sorafenib, in terms of overall survival. As shown in **Table 1**, the study enrolled 1035 patients, but it did not meet neither the superiority nor the non-inferiority end-point (median overall survival was 9.1 months for patients assigned to linifanib vs. 9.8 months for patients assigned to sorafenib arm, HR = 1.046, 95% CI 0.896 - 1.22; p=ns). Secondary end-point (time to progression and objective response rate) were in favour of linifanib (median TTP 5.4 months, ORR 13% with linifanib vs. median TTP 4.0 months and ORR 6.9% with sorafenib). Again, similarly to what observed with sunitinib and brivanib, despite the non-inferiority hypothesis, safety results were in favour of sorafenib: grade 3/4 adverse events, serious adverse events, adverse events leading to discontinuation, dose interruption, and reduction were significantly more frequent with linifanib.

2.4 Erlotinib

Erlotinib is an oral active, potent elective inhibitor of the EGFR/HER1 related tyrosine kinase enzyme, currently used in the treatment of patients with advanced non-small-cell lung cancer [22]. In two previous phase II trials, erlotinib as a single agent showed a modest disease control rate in patients with advanced HCC, and obtained a median overall survival of 10 to 13 months [23,24]. In both studies, evaluation of EGFR status was performed by immunohistochemistry and the patients was stratified into EGFR

high and EGFR low expression cohorts, but there were no significant difference in term of overall survival between the high-EGFR and low-EGFR groups. Of note, within a phase I trial, the combination of erlotinib plus sorafenib showed promising antitumor activity in patients with solid tumors, including hepatocellular carcinoma. Based on these promising but scanty data, despite the absence of phase II trials testing the combination of sorafenib plus erlotinib in HCC patients, the phase III trial (SEARCH) randomized 720 patients to receive the combination vs. sorafenib alone [25]. As reported in **Table 1**, the study showed no significant differences in overall survival (median OS 9.5 months vs. 8.5 months, HR = 0.929, 95% CI 0.78 - 1.10; p = 0.408). The conclusion of the trial was disappointing: the addition of erlotinib did not show any improvement in efficacy, caused an increase in adverse events, and caused a reduction in the treatment duration of sorafenib (median 4 months in the single-agent arm vs. 3 months in the combination arm).

3. Phase III trials performed in second-line setting

3.1 Brivanib

Brivanib has been the first targeted drug tested in a phase III trial in the second-line setting of patients with advanced HCC, after disease progression or intolerance with sorafenib. In a phase II study, conducted in patients with advanced HCC who had progressed after prior anti-angiogenic therapy (mostly sorafenib), brivanib produced an objective response rate of 11%, disease control rate equal to 72%, based on *post hoc* analysis using modified Response Evaluation Criteria in Solid Tumors (mRECIST) for HCC, and a median overall survival of 9.8 months [26]. Subsequently, the randomized phase III trial (BRISK-PS) evaluated the efficacy and safety of brivanib in patients with advanced HCC, whose tumor had progressed on/after or who were intolerant to sorafenib [27]. As reported in **Table 2**, the study randomized 395 patients (in a 2:1 ratio) to receive brivanib 800 mg/die plus best supportive care or placebo plus best supportive care. Brivanib was associated with an improvement in secondary endpoints, such as time to progression (4.7 vs. 2.7 months), objective response rate (10% vs. 2%) and disease control rate based on mRECIST criteria (61% vs. 40%). Unfortunately, brivanib did not significantly improve survival: median overall survival was 9.4 months for patients assigned to experimental treatment and 8.2 months with placebo (HR = 0.89, 95% CI 0.69 - 1.15; $p = 0.33$). Authors discussed a potential selection bias with an enrichment of indolent cases of HCCs (as suggested by the impressive life expectancy of the placebo arm), and a potential imbalance in some prognostic factors (particularly portal vein invasion) as possible reasons of the negative results.

3.2 Everolimus

Everolimus is an oral, selective mTOR (mammalian target of rapamycin) inhibitor [28]. This target is a key regulator of cellular growth, proliferation, angiogenesis and survival. Furthermore, the mTOR pathway is implicated in hepato-carcinogenesis, with activation occurring in up to 45% of HCC and associated with less differentiated tumor and poor prognosis. In a phase I/II trial, everolimus demonstrated a disease control rate for at least 12 week of 44%, a median time-to-progression of 3.9 months and a median overall survival of 8.4 months, with a 10 mg/die schedule [29]. Based on these preliminary results, the phase III trial (EVOLVE-1) randomized 546 patients, in a 2:1 ratio, to receive everolimus (at the dose of 7.5 mg/die) or placebo as second-line treatment after sorafenib failure (**Table 2**) [30]. No significant difference in overall survival was described between the two treatment arms: median overall survival was 7.6 months for patients assigned to everolimus and 7.3 months for patients assigned to placebo (Hazard Ratio 1.05, 95% confidence interval 0.86 - 1.27; p=0.68). Similarly, time-to-progression was not significantly different (median 3.0 months with everolimus vs. 2.6 months with placebo). In a subgroup analysis, patients with HBV appeared to have prolonged overall survival with everolimus (HR 0.64, 95% CI 0.45-0.93), although it was not clear if this finding could truly represent a benefit in this subgroup or rather reflected an imbalance of prognostic factor between groups.

Based on preclinical evidence suggesting that the combination of everolimus and sorafenib could be associated with additive effects, a randomized phase II trial has tested the combination of sorafenib and everolimus compared to sorafenib alone, as first-line treatment [31]. Primary endpoint of this trial was the progression-free rate at 12 weeks. Patients assigned to combination received sorafenib at full dose, combined with

everolimus at the dose of 5 mg/die. Unfortunately, no improvement in primary endpoint and no suggestion of benefit in other outcomes was shown.

3.3 Ramucirumab

Ramucirumab is a human IgG1 monoclonal antibody that specifically binds with high affinity to the extracellular domain of the human Vascular Endothelial Growth Factor receptor 2 (VEGFR-2) [32]. Ramucirumab is able to block the interaction of VEGFR-2 with its ligand, determining the inhibition of endothelial proliferation and migration. This antibody was tested in a phase II study, showing antitumor activity in first-line treatment of HCC, with a median PFS of 4.0 month and a promising median overall survival of 12 months [33]. Of note, in patients with Child-Pugh A cirrhosis, a median OS of 18 months was reported. Based on these preliminary, interesting results, a phase III trial (REACH) was designed to test the efficacy of ramucirumab [34]. However, although patients enrolled in the phase II trial were treatment-naïve, the phase III trial was designed to compare ramucirumab versus placebo in the second-line setting, after sorafenib failure. Disappointingly, as reported in **Table 2**, ramucirumab did not significantly improve survival over placebo: median overall survival was 9.2 months for patients assigned to ramucirumab versus 7.6 months for patients assigned to placebo (Hazard Ratio 0.87, 95% confidence interval 0.72-1.05; p=0.14). In subgroup analysis, ramucirumab was associated with an improvement in overall survival in patients with high baseline alpha-fetoprotein (median overall survival 7.8 months versus 4.2 months, Hazard Ratio 0.67, 95% confidence interval 0.51-0.90; p=0.006), while there was no evidence of benefit with ramucirumab in patients with low baseline alpha-fetoprotein. As all subgroup analyses, this analysis needs further confirmation, that may come from the results of the ongoing phase

III trial REACH-2, which is comparing ramucirumab vs placebo in patients with high baseline AFP values (see below).

3.4 Regorafenib

Regorafenib is a multi-kinase inhibitor that targets kinases involved in angiogenesis (e.g. VEGFR-1–3), oncogenesis (e.g. c-kit, RET and BRAF) and the tumor microenvironment (e.g. PDGFR and FGFR) [35]. Regorafenib, at the daily dose of 160 mg, was tested in a single-arm phase II study in patients with advanced HCC after failure of prior sorafenib therapy [36]. Interestingly, median time-to-progression was 4.3 months, and median overall survival was 13.8 months. The most common grade 3/4 adverse events included fatigue (17%), hand–foot skin reaction (14%) and diarrhea (6%). Based on these data, a phase III randomized controlled trial, the RESORCE [REgorafenib after SORafenib in patients with hepatoCEllular carcinoma] study (ClinicalTrials.gov Identifier NCT01774344) has been designed [10]. This trial was a double blind, placebo-controlled, multicenter phase III study conducted in patients with HCC whose disease had progressed after treatment with sorafenib. As detailed in **Table 2**, the trial enrolled 573 patients, who were randomized in a 2:1 ratio to receive either regorafenib (at the standard dose of 160 mg daily, 3 weeks on / 1 week off) plus best supportive care (BSC) or placebo plus BSC. The primary endpoint of the study was overall survival, and secondary efficacy endpoints were time to progression, progression-free survival, objective tumor response rate and disease control rate. The RESORCE trial met its primary endpoint of a statistically significant improvement in overall survival: median overall survival was 10.6 months for patients assigned to regorafenib and 7.8 months for patients assigned to placebo. Safety profile of regorafenib was similar to what expected with sorafenib: hypertension, hand-foot

skin reaction, fatigue and diarrhea were significantly more common in patients assigned to regorafenib compared to placebo.

4. Main ongoing phase III trials in advanced HCC

In this section, we briefly describe selected drugs currently tested in phase III trials in patients with advanced HCC.

4.1 Tivantinib

Tivantinib is a non-ATP competitive inhibitor of the tyrosine kinase c-Met, which is implicated in cancer cell proliferation, migration, invasion, and metastasis. The c-Met receptor is the only known high-affinity receptor for hepatocyte growth factor (HGF), also known as scatter factor. Binding of HGF to the c-Met extracellular ligand-binding domain results in receptor multimerization and phosphorylation of multiple tyrosine residues in the intracellular portion of c-Met. Activation of c-Met results in subsequent activation of signal transducers such as PI3K, PLC- γ , STATs, ERK1 and 2, and FAK. N-Methyl-N'-nitro-N-nitroso-guanidine human steogenic sarcoma cell line transforming protein (gene) (MET) gene amplification and/or mutations are found in many human malignancies [37,38].

In a phase II randomized controlled study, tivantinib improved PFS in comparison to placebo (HR 0.64, 90% CI 0.43 - 0.94; $p = 0.04$) [39]. Of note, subgroup analysis suggested that patients with high MET expression had a significant benefit from tivantinib. In detail, median overall survival was 7.2 months (95% CI 3.9 - 14.6) in patients with high MET expressing tumors who received tivantinib versus 3.8 months (95% CI 2.1 - 6.8) for MET-high patients who were on placebo (HR 0.38, 95% CI 0.18 - 0.81; $p = 0.01$). Following these intriguing results suggested by subgroup analysis, a randomized, placebo-controlled, double-blind phase 3 study designed to compare tivantinib versus placebo in subjects with MET Diagnostic-High (MET-High), advanced HCC has been designed (ARQ 197-A-U303, ClinicalTrials.gov Identifier NCT01755767). As of June 2016, results are still not available. Recently, a second randomized phase III trial has been started, evaluating

tivantinib in Japanese patients with c-MET diagnostic-high inoperable HCC (ClinicalTrials.gov Identifier NCT02029157).

4.2 Nivolumab

Programmed cell death protein 1 (PD-1) and its ligands, programmed cell death ligand 1 (PD-L1) and 2 (PD-L2), play important roles in the regulation of immune responses [40]. This inhibitory action might help in immune evasion by cancer cells as PD-1, PD-L1 and PD-L2 are abnormally expressed by tumor cells and tumor infiltrating lymphocytes. Nivolumab and pembrolizumab, both PD-1 antibodies, have been approved for advanced melanoma, for advanced non-small cell lung cancer and for an increasing number of solid tumors. For HCC, no results have been reported yet. A Phase I/II trial with nivolumab in advanced HCC has been designed to produce evidence about tolerability and activity of the drug [41]. The first part of this trial was a dose-escalation phase designed to establish the safety of the drug at different dose levels for three cohorts: HCC patients without viral hepatitis, HCC patients with chronic hepatitis C virus infection and HCC patients with chronic hepatitis B virus infection. The second part of the study is an expansion phase designed to generate additional clinical data at specified doses for each of the three cohorts. Of note, a randomized phase III trial is currently testing the efficacy of nivolumab as first-line treatment of patients with HCC: patients assigned to experimental arm receive nivolumab, and patients assigned to control arm are treated with sorafenib (CheckMate 459: CHECKpoint Pathway and nivoluMAb Clinical Trial Evaluation 459, ClinicalTrials.gov Identifier NCT02576509). Primary outcome measures are time-to-progression and overall survival.

4.3 Ramucirumab

As described above, a recent phase III study (REACH) comparing ramucirumab to placebo in patients after failure to sorafenib missed its primary end point [34]. The overall survival in the intention to treat (ITT) population (n = 565) was not significant different between the ramucirumab and the placebo arm (HR 0.866, 95% confidence interval [CI] 0.717 – 1.046; p = 0.1391; median overall survival 9.2 months for ramucirumab versus 7.6 months for placebo). However, in the subgroup of patients with baseline AFP $\geq$ 400 ng/ml (n = 250) the overall survival was significantly longer for the patients treated with ramucirumab (HR 0.67, 95% CI 0.51 – 0.90; p = 0.0059) with a median overall survival of 7.8 months for ramucirumab and 4.2 months for placebo. The reason why ramucirumab is more active in this situation is not clear, yet. Thus, ramucirumab will be further developed in the same population with elevated AFP after failure of sorafenib (either progression or intolerance), within the ongoing phase III REACH-2 trial is comparing ramucirumab to placebo (ClinicalTrials.gov Identifier NCT02435433).

4.4 Cabozantinib

Cabozantinib is a novel oral multiple tyrosine-kinase targeted agent that can inhibit both VEGFR2 and c-Met simultaneously. Cabozantinib can also downregulate KIT, RET, FLT3, and Tie-2 [42]. In the trial reported by Cohn et al [43], 41 patients with advanced HCC and Child-Pugh class A who received $\leq$ 1 prior systemic regimen were enrolled. Half of them had received prior sorafenib. In the lead-in stage, the patients received 100 mg daily over 12 weeks. According to the original RECIST criteria, 2 of 36 patients who were evaluable for the tumor assessment at 12 weeks achieved a confirmed partial response. The overall disease control rate (partial response + stable disease) at 12 weeks was 68%. Based on these results, a randomized phase III trial is currently comparing cabozantinib

versus placebo as second-line treatment of patients with advanced HCC (ClinicalTrials.gov Identifier NCT01908426).

5. Expert commentary: potential reasons for the failure of clinical trials in advanced HCC

The failure of chemotherapy in patients with advanced HCC has been traditionally related to the intrinsic resistance of tumor cells to cytotoxic agents, paired with the high risk of toxicity in these patients with impaired liver function [44]. After the demonstration of efficacy obtained with sorafenib, most clinical oncologists hoped that many “new generation” drugs would have proven effective in this setting, rapidly expanding the list of treatment options for patients with advanced HCC. Unfortunately, as shown in previous paragraphs, this was not the case.

A comprehensive analysis of the results obtained in phase III trials conducted in the era of targeted agents in HCC patients was recently published [45]. The authors suggest that heterogeneity of study populations, lack of understanding of critical drivers of tumor progression/dissemination, risk of liver toxicity associated with experimental agents, flaws in trial design and marginal antitumoral potency are the main reasons for failure of phase III clinical trial on HCC.

We agree that several reasons have potentially contributed to the failure of recent clinical trials [46]. In principle, even if the drug is active and effective, inadequate methodology and study design could be the reason for a negative result in a clinical trial. Obviously, a study could produce a false negative result if the sample size is too small and the statistical power is inadequate to exclude potentially relevant differences between treatment arms. However, as shown in **Table 1 and Table 2**, most trials discussed in previous paragraphs were adequately powered to detect clinically relevant differences in favor of the experimental treatment.

Subgroup analyses are commonly conducted to explore the heterogeneity of treatment efficacy according to known patients' characteristics. In some cases, this

exploration can suggest the existence of interaction between treatment and a specific factor. This was the case for the subgroup analysis of the REACH trial, suggesting a significant effect of ramucirumab in patients with high baseline levels of alpha-fetoprotein [34]. Of course, subgroup analyses cannot provide definitive evidence (especially when they show a positive result in a subgroup within a globally negative trial), but the generated hypothesis can be worth to be tested in a prospective trial [47].

The adequate sample size of the trial, however, does not “preserve” the study from the potential impact of heterogeneity of patients in terms of characteristics and sensitivity to experimental drug. From this point of view, one reason substantially contributing to failure of new drugs tested in clinical trials is our limited knowledge, if any, about biomarkers and predictive factors of drug activity and efficacy. Of note, according to current clinical practice guidelines, diagnosis of hepatocellular carcinoma is often based on the typical imaging pattern alone, without the need for tissue sample and cytological / histological confirmation [48]. Compared to other solid tumors, where the availability of tissue is the rule, this reduces the amount of tumor material available for correlative studies in the setting of advanced HCC. If this is reasonable for patients receiving standard treatment in clinical practice, we strongly believe that tissue collection for patients enrolled in clinical trials should be mandatory, in order to allow prospective (or even retrospective) correlation of patients’ outcome with specific molecular characteristics. Unfortunately, this is not the case for most ongoing clinical trials: in order to describe the proportion of trials for patients with advanced HCC including only patients with tissue diagnosis, in 2015 we analyzed the description of clinical trials included in the ClinicalTrials.gov registry of the U.S. National Institutes of Health, classified as ongoing as of June 2015 (**Figure 1**). Out of 69 trials testing experimental drugs in advanced HCC, 40 trials (58%) did not ask for cytological / histological diagnosis, that was mandatory in the remaining 29 trials (42%). As

expected, most of the ongoing trials are conducted without any molecular selection criteria, that was explicit in only 8 trials (12%). This is disappointing, because many drugs could be probably better tested in a molecularly selected population. For instance, the exome sequencing analysis of 243 liver tumors allowed the identification of 161 putative driver genes associated with 11 recurrently altered pathways [49]. The authors emphasized that their analysis identified genetic alterations potentially targetable by US Food and Drug Administration (FDA)-approved drugs in 28% of the HCCs tested. Given the high molecular heterogeneity of advanced HCC, when one of these drugs is tested in unselected patients, the activity in the subgroup of potentially sensitive patients could be diluted and masked by the absence of activity in the remaining subjects, leading to a negative result in the whole study population. The recent history of molecularly targeted drugs approved in other solid tumors (for instance, Epidermal Growth Factor receptor or ALK tyrosine-kinase inhibitors in advanced non-small cell lung cancer) shows that some drugs have a very high activity but in a very limited proportion of patients. Under these conditions, biomarker-driven trials are essential for demonstration of benefit and subsequent approval.

Another reason for the failure of potentially active drugs could be the impairment of liver function, that is very common in these patients, due to the underlying liver disease. This could disappointingly increase the risk of poor tolerability of experimental drugs. In order to optimize the development of new drugs in this risky setting of patients, in 2008 an International expert panel discussed the methodology of clinical trials in patients with hepatocellular carcinoma, stating that experimental drugs should be mostly tested in patients with well-preserved liver function (Child-Pugh A) [50]. As emphasized by Llovet and colleagues in their position paper, the reason for the exclusion of more impaired liver function was that their inclusion would increase the risk of treatment-emergent adverse

events and the impact of poor liver function on patients' prognosis, potentially compromising the interpretation of results. So it is not surprising that, out of the 69 clinical trials included in the ClinicalTrials.gov registry of the U.S. National Institutes of Health classified as ongoing as of June 2015, 58 (84%) had Child-Pugh stage among inclusion criteria (**Figure 2, Panel A**). In detail, the vast majority of trials include only patients with well preserved or only slightly impaired liver function: 34 trials for Child A patients only (59%) and 12 trials (21%) for Child A and Child B7 patients only (**Figure 2, Panel B**). This restriction should avoid the unintended dilution of treatment activity due to the occurrence of toxicity and to the rapid progression of liver failure. However, if we consider the unselected population of patients with advanced HCC in the "real-life" clinical practice, Child-Pugh A patients represent only a limited proportion of those who are candidates for systemic treatment. We must consider that excluding patients with Child-Pugh B from frontline drug development will greatly reduce the generalizability of results [51]. However, once a drug becomes available in clinical practice, physicians with Child-Pugh B patients will face the difficult decision of whether to deny them the new therapy or expose them to the risk of unacceptable toxicity against an unconfirmed potential benefit. The story of sorafenib represents a good example of the above described risk: both phase 3 trials were limited to Child-Pugh A patients [5,6], and no formal demonstration of efficacy is available in Child-Pugh B patients, despite the urgent need for effective systemic treatments in clinical practice [8].

6. Five-year perspective

Five years ago, soon after the approval of sorafenib for patients with advanced HCC, the majority of experts were relatively sure that one or more drugs that were tested in ongoing clinical trials would have shown efficacy and would have subsequently been approved for the treatment of patients with advanced HCC. Unfortunately, we now know that this was not the case. Regorafenib has been the first drug, after sorafenib, to produce a positive result in a phase III trial, while many drugs produced negative results despite the interesting background and rationale.

This number of failures reminds us that, beyond any good scientific rationale, results of clinical trials can be disappointing. Hopefully, in the near future, the knowledge of potential predictive factors for drug efficacy in patients with advanced HCC will increase, and we are convinced that this could improve the chance of obtaining positive results in clinical trials. For instance, we currently do not know if tivantinib will produce a positive result in the phase III trial, that is limited to cases with high expression of c-MET, based on the hypothesis-generating subgroup analysis of the previous randomized phase II trial [39]. However, if the phase III trial will be positive, the development of tivantinib in HCC could be a good example of the importance of identifying efficacy biomarkers in the early phases of drug development. The risk that a randomized phase III trial could produce a negative result despite using an effective drug can be substantially increased if a beneficial effect in the proportion of responding patients is “diluted” by a large number of non-responding patients [52]. Along with the risk of a false negative result, the other relevant risk, when a drug is tested in a phase III trial without sufficient knowledge of predictive factors, is that the “dilution” of efficacy produced by the large proportion of non-responding patients can determine a statistically significant, but clinically modest improvement. However, the identification of molecular biomarkers needs the availability of tumor tissue to be studied.

Unfortunately, at the moment, the real issue is the poor availability of tumor tissue in patients with HCC compared to other solid tumors. Many efforts are currently made to obtain relevant information about tumor molecular profile with “liquid biopsy”, that means testing the status of biomarkers in plasma or serum. Probably, in the near future, the role of “liquid biopsy” in clinical practice will increase, but currently it cannot be considered a substitute of tumor tissue. We strongly recommend that tumor tissue collection should be mandatory for patients enrolled in clinical trials.

Beyond molecularly targeted agents, immune checkpoint inhibitors represent another relevant category of promising drugs, not only in HCC but in all solid tumors. In the next five years, the number of tumor types where immune checkpoint inhibitors will prove efficacy will rapidly grow. Will HCC be among these cancers? The randomized phase III trial comparing nivolumab vs. sorafenib, currently ongoing, will provide evidence about the efficacy of this promising anti-tumor strategy. At the beginning of the clinical development of nivolumab in this setting, there were many concerns about the tolerability: immune response has a role in the severity of chronic hepatitis, and there is a risk of liver toxicity when immune-checkpoint inhibitors are administered to patients with HCC. However, safety of nivolumab in the phase I-II study was manageable, and it should not represent a major obstacle for the use of this drug in HCC patients. To date, we are not able to predict if the knowledge about predictive factors of efficacy (for nivolumab as well as for other immune-checkpoint inhibitors) will be significantly improved in the near future. At the moment, the predictive role of PD-L1 expression on tumor tissue is not clear: coherently, the randomized trial is being conducted without any molecular selection for the eligibility of patients.

7. Key issues

- Regorafenib has been the first drug, after sorafenib, to produce a positive result in a phase III trial conducted in patients with advanced hepatocellular carcinoma, while many drugs produced negative results despite the interesting background and rationale.
- Heterogeneity of study populations, lack of understanding of critical drivers of tumor progression/dissemination, risk of liver toxicity associated with experimental agents, flaws in trial design and marginal antitumoral potency can be considered the main reasons for failure of phase III clinical trials in HCC.
- Most of the ongoing trials are conducted without any molecular selection criteria. This is disappointing, because many drugs could be probably better tested in a molecularly selected population.
- Hopefully, in the near future, the knowledge of potential predictive factors for drug efficacy in patients with advanced HCC will increase, and this could improve the chance of obtaining positive results in clinical trials.
- The randomized phase III trial comparing nivolumab vs. sorafenib, that is currently ongoing, will provide evidence about the efficacy of the immune checkpoint inhibition strategy in advanced HCC.

Figure legends

Figure 1. Characteristics of clinical trials for patients with advanced hepatocellular carcinoma, ongoing as of June 2015. **Panel A:** absence or presence of cyto/histological diagnosis among eligibility criteria. **Panel B:** absence or presence of molecular selection among eligibility criteria. *Source: ClinicalTrials.gov registry of the U.S. National Institutes of Health, www.clinicaltrials.gov*

Figure 2. Characteristics of clinical trials for patients with advanced hepatocellular carcinoma, ongoing as of June 2015. **Panel A:** number of trials allowing inclusion of each Child-Pugh category, out of 58 trials with information available. **Panel B:** distribution of trials according to Child-Pugh category eligible for inclusion. *Source: ClinicalTrials.gov registry of the U.S. National Institutes of Health, www.clinicaltrials.gov*

References

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108
2. Child CG, Turcotte JG. Surgery and portal hypertension. Major Probl Clin Surg 1964;1:1-85
3. Daniele B, Perrone F. Staging for liver cancer. Clin Liver Dis 2005;9:213-23, vi.
4. Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. Hepatology. 2002;35:519-24
5. Llovet JM, Ricci S, Mazzaferro V, et al. SHARP Investigators Study Group: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–390
*** The first randomized trial demonstrating a survival improvement with a systemic treatment in patients with advanced HCC*
6. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25–34
** The second randomized trial demonstrating the efficacy of sorafenib, specifically in a population of Asian patients.*

7. Lencioni R, Kudo M, Ye SL, et al. GIDEON (Global Investigation of therapeutic Decisions in hepatocellular carcinoma and Of its treatment with sorafenib): second interim analysis. *Int J Clin Pract* 2014;68:609-17
8. Di Maio M, Daniele B, Perrone F. Targeted therapies: Role of sorafenib in HCC patients with compromised liver function. *Nat Rev Clin Oncol* 2009;6:505-6
9. Di Maio M, Daniele G, Piccirillo MC, et al. Potentiality and boundaries of use of sorafenib in patients with hepatocellular carcinoma: awaiting the results of ongoing clinical trials. *Cancers (Basel)* 2012;4:549-65
10. Bruix J, Merle P, Granito A, et al, on behalf of the RESORCE Investigators. Efficacy and safety of regorafenib versus placebo in patients with hepatocellular carcinoma (HCC) progressing on sorafenib: Results of the international, randomized phase 3 RESORCE trial. Presented at ESMO World GI 2016 [abstr. LBA3].
11. Mendel DB, Laird AD, Xin X, et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: Determination of a pharmacokinetic/pharmacodynamic relationship. *Clin Cancer Res* 2003; 9:327–337
12. Faivre S, Raymond E, Boucher E, et al. Safety and efficacy of sunitinib in patients with advanced hepatocellular carcinoma: An open-label, multicentre, phase II study. *Lancet Oncol* 2009; 10:794-800

13. Zhu AX, Sahani DV, Duda DG, et al: Efficacy, safety, and potential biomarkers of sunitinib monotherapy in advanced hepatocellular carcinoma: A phase II study. *J Clin Oncol* 2009; 27:3027-3035
14. Koeberle D, Montemurro M, Samaras P, et al: Continuous sunitinib treatment in patients with advanced hepatocellular carcinoma: A Swiss Group for Clinical Cancer Res (SAKK) and Swiss Association for the Study of the Liver (SASL) multicenter phase II trial (SAKK 77/06). *Oncologist* 2010; 15:285-292
15. Cheng AL, Kang YK, Lin DY, et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. *J Clin Oncol* 2013; 31:4067-75
- * *Negative randomized trial, comparing sunitinib versus sorafenib as first-line treatment of patients with advanced HCC.*
16. Cai ZW, Zhang Y, Borzilleri RM, et al. Discovery of brivanib alaninate ((S)-((R)-1-(4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-5-methylpyrrolo[2,1-f][1,2,4] triazin-6-yloxy)propan-2-yl)2-aminopropanoate), a novel prodrug of dual vascular endothelial growth factor receptor-2 and fibroblast growth factor receptor-1 kinase inhibitor (BMS-540215). *J Med Chem* 2008; 51:1976–80
17. Park JW, Finn RS, Kim JS, et al: Phase II, open-label study of brivanib as first-line therapy in patients with advanced hepatocellular carcinoma. *Clin Cancer Res* 2011; 17:1973-83

18. Johnson PJ, Qin S, Won-Park J, et al. Brivanib Versus Sorafenib As First-Line Therapy in Patients With Unresectable, Advanced Hepatocellular Carcinoma: Results From the Randomized Phase III BRISK-FL Study. *J Clin Oncol* 2013; 28:3517-24
19. Zhou J, Goh BC, Albert DH, et al. ABT-869, a promising multi-targeted tyrosine kinase inhibitor: From bench to bedside. *J Hematol Oncol* 2009; 2:33.
20. Toh HC, Chen PJ, Carr BI, et al: Phase 2 trial of linifanib (ABT-869) in patients with unresectable or metastatic hepatocellular carcinoma. *Cancer* 2013; 119: 380-7
21. Cainap C, Qin S, Huang WT, Chung IJ, Pan H, Cheng Y, et al. Linifanib versus sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2015;33:172-9
22. Silvestri GA, Rivera MP. Targeted therapy for the treatment of advanced non-small cell lung cancer: a review of the epidermal growth factor receptor antagonists. *Chest* 2005; 128:3975-84
23. Philip PA, Mahoney MR, Allmer C, et al. Phase II study of erlotinib (OSI-774) in patients with advanced hepatocellular cancer. *J Clin Oncol* 2005;23:6657–63
24. Thomas MB, Chadha R, Glover K, et al. Phase 2 study of erlotinib in patients with unresectable hepatocellular carcinoma. *Cancer* 2007; 110:1059–67

25. Zhu AX, Rosmorduc O, Evans TR, et al. SEARCH: a phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2015;33:559-66
26. Finn RS, Kang YK, Mulcahy M, et al: Phase II, open-label study of brivanib as second-line therapy in patients with advanced hepatocellular carcinoma. *Clin Cancer Res* 2012;18:2090-98
27. Llovet JM, Decaens T, Raoul JL, et al. Brivanib in Patients With Advanced Hepatocellular Carcinoma Who Were Intolerant to Sorafenib or for Whom Sorafenib Failed: Results From the Randomized Phase III BRISK-PS Study. *J Clin Oncol* 2013;31:3509-16
28. Huynh H, Chow KH, Soo KC, et al. RAD001 (everolimus) inhibits tumour growth in xenograft models of human hepatocellular carcinoma. *J Cell Mol Med.* 2009; 13:1371-80.
29. Zhu AX, Abrams TA, Miksad R, et al. Phase 1/2 study of everolimus in advanced hepatocellular carcinoma. *Cancer* 2011;117:5094-102
30. Zhu AX, Kudo M, Assenat E, et al. Effect of Everolimus on Survival in Advanced Hepatocellular Carcinoma After Failure of Sorafenib The EVOLVE-1 Randomized Clinical Trial. *JAMA* 2014,312:57-67

31. Koeberle D, Dufour JF, Demeter G, et al; Swiss Group for Clinical Cancer Research (SAKK). Sorafenib with or without everolimus in patients with advanced hepatocellular carcinoma (HCC): a randomized multicenter, multinational phase II trial (SAKK 77/08 and SASL 29). *Ann Oncol* 2016;27:856-61
32. Spratlin JL, Cohen RB, Eadens M, et al. Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. *J Clin Oncol* 2010; 28:780–7
33. Zhu AX, Finn RS, Mulcahy M, et al. A phase II and biomarker study of ramucirumab, a human monoclonal antibody targeting the VEGF receptor-2, as first-line monotherapy in patients with advanced hepatocellular cancer. *Clin Cancer Res* 2013; 19: 6614–23
34. Zhu AX, Park JO, Ryoo BY, et al; REACH Trial Investigators. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol* 2015;16:859-70
- * A negative randomized trial testing ramucirumab as second-line treatment of patients with advanced HCC, with a subgroup analysis suggesting the potential efficacy of the drug in patients with high baseline AFP*

35. Mross K, Frost A, Steinbild S, et al. A phase I dose-escalation study of regorafenib (BAY 73-4506), an inhibitor of oncogenic, angiogenic, and stromal kinases, in patients with advanced solid tumors. Clin Cancer Res 2012;18: 2658–67
36. Bruix J, Tak WY, Gasbarrini A, et al. Regorafenib as second-line therapy for intermediate or advanced hepatocellular carcinoma: multicentre, open-label, phase II safety study. Eur J Cancer 2013; 49: 3412–19
37. Trusolino L, Bertotti A, Comoglio PM. A signaling adapter function for $\alpha 6 \beta 4$ integrin in the control of HGF-dependent invasive growth. Cell 2001;107:643-54
38. Taviani D, De PG, Benetti A, et al. u_Pa and c-Met mRNA expression is coordinately enhanced while hepatocyte growth factor mRNA is down-regulated in human hepatocellular carcinoma. Int J Cancer 2000;87:644-9
39. Santoro A, Rimassa L, Borbath I, et al. Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled phase 2 study. Lancet Oncol 2013;14:55-63
- * An interesting randomized phase II trial suggesting the efficacy of tivantinib in patients selected for the high expression of MET*
40. Pennock GK, Chow LQ. The Evolving Role of Immune Checkpoint Inhibitors in Cancer Treatment. Oncologist 2015;20:812-22

41. El-Khoueiry AB, Melero I, Crocenzi TS, et al. Phase I/II safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma (HCC): CA209-040. J Clin Oncol 33, 2015 (suppl; abstr LBA101)
42. Xiang Q, Chen W, Ren M, et al. Cabozantinib suppresses tumor growth and metastasis in hepatocellular carcinoma by a dual blockade of VEGFR2 and MET. Clin Cancer Res 2014; 20:2959-70.
43. Cohn AL, Kelley RK, Yang TS, et al. Activity of cabozantinib (XL184) in hepatocellular carcinoma patients (pts): Results from a phase II randomized discontinuation trial (RDT). J Clin Oncol. 2012; 30: 261.
44. Di Maio M, De Maio E, Perrone F, Pignata S, Daniele B. Hepatocellular carcinoma: systemic treatments. J Clin Gastroenterol. 2002;35(5 Suppl 2):S109-14
45. Llovet JM, Hernandez-Gea V. Hepatocellular Carcinoma: Reasons for Phase III Failure and Novel Perspectives on Trial Design. Clin Cancer Res 2014;20:2072-79
- ** An interesting analysis of the potential reasons of the failure of many clinical trials in advanced HCC*
46. Llovet JM, Villanueva A, Lachenmayer A, Finn RS. Advances in targeted therapies for hepatocellular carcinoma in the genomic era. Nat Rev Clin Oncol 2015;12:408-24

47. Di Maio M, Perrone F. Subgroup Analysis: Refining a Positive Result or Trying to Rescue a Negative One? *J Clin Oncol* 2015;33:4310
48. Bota S, Piscaglia F, Marinelli S, et al. Comparison of international guidelines for noninvasive diagnosis of hepatocellular carcinoma. *Liver Cancer* 2012;1:190-200
49. Schulze K, Imbeaud S, Letouzé E, et al. Exome sequencing of hepatocellular carcinomas identifies new mutational signatures and potential therapeutic targets. *Nat Genet* 2015;47:505-11
50. Llovet JM, Di Bisceglie AM, Bruix J, et al; Panel of Experts in HCC-Design Clinical Trials. Design and endpoints of clinical trials in hepatocellular carcinoma. *J Natl Cancer Inst* 2008;100:698-711
51. Di Maio M, Daniele B, Gallo C, Perrone F. Re: Design and endpoints of clinical trials in hepatocellular carcinoma. *J Natl Cancer Inst* 2008;100(21):1557; author reply 1557-8.
52. Betensky RA, Louis DN, Cairncross JG. Influence of unrecognized molecular heterogeneity on randomized clinical trials. *J Clin Oncol* 2002;20:2495-9

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