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Trial Design and Endpoints in hepatocellular carcinoma: AASLD Consensus Conference

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Abstract

Proper trial design is critical for the success of clinical investigations. Hepatocellular carcinoma (HCC) is a complex disease that has several unique properties. In 2008, after the approval of sorafenib, a panel of experts proposed guidelines for trial design and endpoints in HCC that have been instrumental during the last decade and provided a framework to allow an homogeneous analysis of reported investigations. Since then, several phase III studies have been reported and novel challenges have emerged. A panel of experts conveyed by AASLD organized a Special Topic Conference on trial design and endpoints to address those emerging challenges. This review summarizes the analysis and conclusions of those discussions and provides novel recommendations on the selection endpoints, stratification variables and targeted populations in the complex arena of HCC. We have covered the full spectrum of the disease, from surveillance/ chemoprevention, to neoadjuvant and adjuvant trials after curative therapies, and trials in intermediate and advanced stages of HCC. We explore the prospects for incorporating biomarkers and liquid biopsy into conventional clinical trials. In addition, we address the need for obtaining tissue and blood samples in all investigations and propose novel primary endpoints such as progression free survival with restrictive rules and patient reported outcomes. This up-dated set of recommendations is timely considering the advent of more potent combination therapies in all areas of HCC management, the increase in adverse events associated with those combinations, and the evidence that several lines of effective treatments will benefit a given patient. We herein articulate a framework to facilitate capturing the efficacy of novel therapeutic strategies with the goal of improving the outcomes of patients suffering from this disease.

Introduction

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related mortality worldwide(1,2). This neoplasm has some unique characteristics. It occurs in most cases complicating underlying cirrhosis, has specific non-invasive criteria for diagnosis, follows a unique staging system and historically has been resistant to conventional chemotherapy. Several treatments have achieved adoption as standard of care according to clinical practice guidelines, including potentially curative therapies (i.e. resection, liver transplantation and local ablation) for early tumors, transarterial chemoembolization (TACE) for intermediate stage tumors, and systemic drugs for advanced tumors in front line (sorafenib and lenvatinib) and second line (regorafenib, cabozantinib and ramucirumab)(3–5). Life expectancy has improved progressively in all stages of the disease. Effective implementation of surveillance for patients at risk of developing HCC and access to current proven therapies has been a milestone. Overall, median survival times beyond 5 years are expected for early stages, about 20-30 months for intermediate stages, and between 10-16 months for advanced stage HCC [**Fig. 1**(3,4,6)]. Novel drugs and combinations continue to enter the research arena to address unmet medical needs. All these research activities require precise endpoints and tools for measuring clinical benefits.

Thus, clinical trial design has become a major focus of attention in HCC research. Since randomized controlled trials are the main source of evidence for drug approvals in oncology, it is of paramount relevance to understand the critical endpoints and tools for measuring them, as well as optimal strategies for identifying and enrolling target populations and for patient stratification. It has become evident that a deep understanding of factors determining HCC outcomes and trial design is required to achieve optimal results. There are trials with a non-inferiority design that have been positive, and lead to drug approval, while others demonstrate superior outcomes in surrogate end-points, such as progression free survival (PFS) or patient reported outcomes but not in the primary endpoint of overall survival. Some recent trials have also been reported to be statistically negative but “clinically positive”. It is important to understand the reasons for the failure or success of a trial in order to move the field forward. In addition, while several positive phase III trials for advanced HCC have recently changed clinical practice (7–11), no major advances have occurred in the area of surveillance and early detection, adjuvant therapies after resection/ablation or management of intermediate stage HCC over the last 15 years. The lack of effective novel drugs/devices may be the cause of negative studies in these areas, but suboptimal trial design may also have jeopardized the likelihood of a positive result. With this challenge in mind, the Hepatobiliary Neoplasia Special Interest Group of the American Association for the Study of Liver Disease (AASLD) organized a Single Topic Conference in Atlanta in 2019 to address these issues. This position paper summarizes the major concepts discussed in the conference with the aim of updating the proposals previously reported by a similar AASLD panel in 2008(12).

Overview on trial design and endpoints

Clinical trials are essential to establish the clinical efficacy of new therapeutic interventions. They are instrumental in developing clinical practice guidelines and form the basis for evidence-based medicine(13). An adequate clinical trial design is crucial, as an effective drug can be discarded due to a poor trial design and *vice-versa*. The main considerations when designing a clinical trial are to: a) select a well-defined target patient population (i.e., inclusion and exclusion criteria), b) pre-specify clear endpoints (primary and secondary) and data analysis plan, c) specify randomization and allocation method; and d) secure efficacy of randomization (stratification at enrollment for prognostic variables). Based on these and other variables, the quality of clinical trials can be quantified using different scores such as

the Jadad score(14), the Delphi List(15), the CONSORT statement(16,17), and the Cochrane Back Review Group criteria(18). Until the SHARP trial(11), which established the benefit of sorafenib in advanced stages HCC patients, the quality of the trials conducted in HCC was commonly modest. A systematic review found that only 50% of the clinical trials reported between 2002 and 2005 in HCC were deemed high quality as per the modified Jadad score(19). The 2008 position paper resulting from the AASLD conference provided a useful framework for academic centers, industry partners and regulators on the design of trials in HCC(12). Subsequently, the quality of clinical trials assessing systemic therapies has significantly improved. There has been less activity in terms of high-end clinical trials in other treatment areas. This position paper will extensively discuss the singularities of trial design in every clinical aspect of HCC management.

In clinical trials, the benefit of an intervention is quantified using endpoints, which are predefined events that once reached exclude the patient from further evaluation within the trial. There are 3 main types of endpoints: hard, surrogate and patient-reported, all extensively described elsewhere(20). Hard endpoints are well defined and easy to measure objectively. The archetypes of a hard endpoint are overall survival (OS) or cancer-related survival. Surrogate endpoints, such as progression-free survival or time to progression, partially rely on the quantification of tumor response, generally using imaging techniques and pre-specified criteria(21). Surrogate endpoints are more vulnerable than hard endpoints, but they have several advantages including their convenience in terms of event accumulation and trial feasibility. Patient-reported endpoints, sometimes referred as soft endpoints, are subjective measures such as quality of life (QoL), in most instances obtained from questionnaires. Overall recommendations of trial design and endpoints in HCC are detailed in **Table 1**, whereas expected outcomes for standard of care therapeutic interventions within these trials are summarized in **Table 2**.

Endpoints

OS is defined by the time between patient randomization and death from any cause. OS is usually recommended as the primary endpoint for randomized phase III clinical trials(12). OS is the endpoint most frequently used by regulatory agencies to approve drugs as it is objective and clinically relevant. In HCC, as most patients suffer from concomitant cirrhosis, death can result from competing risks, mainly liver toxicity and failure. This fact underscores the need for detailed assessments of safety with any intervention in this population. It is important to capture adverse events in early phase clinical studies as well as in larger randomized studies. Failures in phase 3 studies have been seen from new agents that are more toxic in an HCC population than in other tumor types(22). The competing risk of cirrhosis can introduce bias when evaluating the anti-tumoral activity of a therapeutic intervention, but it can be easily controlled by imposing stringent inclusion criteria in terms of liver function (i.e., Child-Pugh score A without hepatic decompensation). OS has some limitations such as the long follow-up time required to capture the number of events needed to verify significantly improved survival in the experimental arm(23). This can be a critical limitation when exploring interventions at early or intermediate stages. Also, OS can be confounded by sequential therapies received by patients after tumor progression, which for instance affected 30% of patients enrolled in the lenvatinib trial(7) and up to 50% of patients in the Checkmate 459 comparing nivolumab vs sorafenib(24). Hence, there is a need to develop surrogate endpoints, which are defined as outcomes not inherently meaningful from the clinical standpoint, but thought to accurately predict hard outcomes such as OS(25).

The main surrogate endpoints in oncology are progression-free survival (PFS), time-to-progression (TTP) and objective response rate (ORR). PFS is the time between patient

randomization and death or radiological tumor progression, whichever occurs first. There are different tools assessing tumor response with imaging. The most established tool for measuring tumor response in oncology are the RECIST criteria(26), initially developed to evaluate response to cytotoxic drugs. These criteria were adapted to account for HCC singularities in the modified RECIST (mRECIST) version, which incorporates viable tumour detected with arterial enhancement as a key component to evaluate response(21,27). Using mRECIST criteria increases the percentage of subjects who achieve objective response compared to standard RECIST, as shown in different studies of systemic therapies (28–32). A recent meta-analysis evaluated the power of PFS to predict OS in phase 3 trials testing systemic therapies in advanced HCC(20). The study found a moderate correlation between PFS and OS in 21 RCTs. The authors proposed a conservative surrogate threshold of $\leq$0.6 for hazard ratio of PFS to predict clinically relevant improvements in OS(33). TTP is defined as the time elapsed between patient randomization and radiological tumor progression. Scheduling repeated radiological assessment of response every 6-8 weeks is mandatory for patients included in trials. Data from SHARP and subsequent studies challenges the implied correlation between TTP and OS. The type of progression may also have clinical implications (34). Survival is worse if patients develop a new extrahepatic lesion and/or vascular invasion as opposed to tumor progression resulting from growth of an existing lesion or a new intrahepatic lesion. Lastly, ORR is the percentage of patients with an objective tumor response, and its correlation with OS is worse than for PFS or TTP(20). This is partially inherent to the use of odds ratios instead of hazard ratios for ORR and also to the fact that only a small proportion of patients achieve an objective response (<25%, for approved drugs in advanced HCC), which is the event that correlates with OS(31). Nonetheless, ORR has been reported as an independent predictor of survival in early HCC treated with radiofrequency ablation, intermediate treated with TACE and advanced HCC treated with TKI(27). The impact of the duration of response, which has been reported to be around 12 months for checkpoint inhibitors vs. less than 6 months for TKIs, has not yet been properly incorporated into response assessment. The same is true to small reductions in tumor size not reaching standard thresholds for objective response. In some cases, duration of disease control may be more clinically relevant than the extent of reduction in tumor size. Also, in the case of immune checkpoint inhibitors, tumor response can have a longer lag-time compared to other molecular therapies and can even mimic progression shortly after treatment initiation (*i.e.*, pseudo-progression(35)). This has led to the development of immune-related response criteria(36), which require confirmation of progression at least 4 weeks after progressive disease is first documented.

Surrogate endpoints are frequently used by the Food and Drug Administration (FDA) to approve drugs under the accelerated program, which was initially developed to facilitate early access to new antivirals during the worst years of the HIV epidemic(37). In HCC, the FDA has used ORR and duration of response to grant accelerated approval of the immune checkpoint inhibitors (CPI) nivolumab(38), pembrolizumab(39) and recently the combination of ipilimumab and nivolumab(40). Accelerated approval is not universal and includes some subjectivity from regulators in regards to the strength of the evidence to support approval without a randomized phase 3 study(24,41). In addition, while the use of ORR and other surrogate endpoints may be used to support regulatory approval, they do not necessarily support inclusion in guidelines which often adhere to a higher level of evidence. Despite their common use, surrogate endpoints are vulnerable to interpretation bias. Besides the strength of the endpoint, it is key to determine when the benefit provided by a new therapy is really clinically meaningful. This can be controversial , depending on factors such as the perceptions of patients, providers, health insurers and regulators. In HCC, there is no set threshold that defines a clinically meaningful benefit, but some authors have suggested a hazard ratio cutoff of OS $\leq$0.8 as a starting point for clinical trial design(42). In fact, all

positive trials in HCC have led to significant differences in survival with HR below this threshold.

Surveillance for Hepatocellular Carcinoma: design and endpoints

Surveillance for HCC is one of the milestones advancing the management of HCC, despite that there is not unquestionable data directly supporting a decrease in cancer-related death in persons on surveillance(43). Ultrasound (US), with or without alpha-fetoprotein (AFP), performed every six months is the current standard and is recommended for surveillance of patients with cirrhosis of any cause or chronic hepatitis B without cirrhosis above a regional and gender appropriate age cut-off determined by expert liver societies(3,4). Overall, the implementation of those programs to all targeted populations is modest, and current data report detection of HCC in the setting of surveillance in between 30-50% of cases(44). In meta-analysis, the pooled sensitivity and specificity of US alone has been shown to be 53% (95% CI: 35-70) and 91% (95% CI:86-94), respectively, while the combination of US and AFP has a sensitivity of 63% (95% CI:48-75) and a specificity of 85% (95%CI:77-89)(45). Due to the relatively low sensitivity and specificity of this approach for detecting early stage HCC, particularly in North America, where high rates of central obesity decrease the performance of ultrasound, a recent study showed that this strategy leads to 27% of patients with cirrhosis experiencing harms such as follow up testing (CT, MRI, liver biopsy) performed for false-positive or indeterminate results(46). Further, due to low implementation of comprehensive strategies for HCC surveillance, more than 60% of HCCs in North America, Europe, Africa and large parts of Asia, excepting Taiwan and Japan, are diagnosed with intermediate or advanced stage HCC(47). There is, therefore, an urgent need for better performing, low cost surveillance strategies in HCC, and accounting for both the benefits and harms of surveillance strategies is important.

Within this overriding context, there is excitement time because advances in genetic, epigenetic, proteomic, glycoproteomic and metabolomic analyses in have enabled large scale multi-omic analyses of HCC tissues, circulating tumor DNA, plasma and serum, resulting in the accelerated identification of novel biomarkers(48–51). Models using standard biostatistical and machine learning and artificial intelligence (AI) approaches are using biomarkers combined with clinical parameters to identify persons at highest risk for HCC. Models and biomarkers under active exploration include the GALAD (Gender, Age, AFP-L3, AFP, and Des-carboxy-prothrombin) score(52), novel glycoproteins (fucosylated kininogen)(53), liquid biopsy analyses of circulating tumor DNA for differentially methylated regions(54)(55), and imaging with abbreviated MRI(56). Creating the framework for validation of future surveillance is critically important.

To guide the development and evaluation of new surveillance strategies for clinical utilization, a 5-phase program has been developed by the NCI- Early Detection Research Network (EDRN) for biomarker that uses human samples (blood or human tissue) as well as imaging tests (57). **Table 3** shows recommended phases of surveillance test validation, including trial design for studies for HCC surveillance. *Phase 1* are biomarker discovery or exploratory studies. *Phase 2* studies estimate the ability of a test to distinguish early stage HCC from those with cirrhosis without HCC. It is important to test for confounders such as age, etiology of liver disease, and liver function; and to have adequate sample size and power. *Phase 3* studies enroll at risk individuals and follow them for clinical diagnosis of HCC using prospective-specimen collection, retrospective-blinded evaluation (PRoBE) design (58). The aim is to evaluate, as a function of time before clinical diagnosis, the capacity of the test to detect preclinical HCC; and also, to define the criteria for a positive surveillance test in preparation for phase 4 and 5 studies. Thus, Phases 1-3 rely on retrospective analysis of stored data and specimens. *Phase 4* studies require the new test

be applied to patients with cirrhosis in the clinical setting to assess test performance in HCC detection and false positive and negative rates. Depending on the test under study it may be possible to skip *Phase 4* if the test is already used for patient care, for example, evaluating an MRI for surveillance of HCC. *Phase 5* studies are randomized trials comparing the new surveillance tests against the standard of care, in the case of HCC the standard should be US with or without AFP, with the aim of determining whether the test can reduce mortality at the population level.

When performing surveillance studies in patients with cirrhosis it is important to enrich the *at risk* population in order to achieve a sufficient number of incident HCCs in a reasonable time period. Enriching cohorts with patients of older age, viral hepatitis, male sex, Hispanic ethnicity, history of diabetes, and family history of HCC should be considered (59,60). Alternatively, known independent factors associated with HCC development are abnormal bilirubin and platelet count <100,000/mm^3. There is also a need to study currently important populations such as those with non-alcoholic fatty liver disease-related cirrhosis, those with hepatitis C-related cirrhosis who have achieved a sustained virological response after antiviral treatment, and those with suppressed hepatitis B infection on antiviral treatment. These three specific populations will be the most important etiological risk factors in the next decade and their HCC incidence rates (around 1%/year) appear lower than in previous at risk populations(61). Methods for risk stratification within these populations will therefore become increasingly important for improving the effectiveness of surveillance strategies and programs. Models such as the REAL-B and PAGE-B scores, incorporating male sex, age, alcohol use, baseline cirrhosis, diabetes, platelet count and AFP, allow improved risk stratification of patients on oral antiviral therapy for chronic hepatitis B and could potentially be incorporated into surveillance programs(62).

An important potential confounder in studies that compare the performance of novel biomarkers to current surveillance strategies is the incorporation of imaging by ultrasound or other radiologic modalities into the standard of care. This may confound the results if ultrasound is also used as part of the control arm for the study, as ultrasonography is itself typically part of the gold standard process for determining whether a patient has HCC. Thus, patients with HCCs that are not visible by ultrasound may be falsely determined to be negative for cancer and a positive biomarker test erroneously labeled as a false positive. It is therefore important to use a different high-accuracy imaging modality such as multiphasic MRI as a gold standard in studies for which ultrasonography is part of the surveillance strategy. However, use of MRI may add substantial cost to the study and may also result in visualization of a number of small indeterminate false positive lesions that are seen on MRI and require follow up investigation, a component of the harms associated with surveillance. While studies of the performance of ultrasound with or without AFP in the clinical care setting have shown suboptimal performance in detection of HCC in at risk individuals, it is not clear what the performance characteristics are for phase 2, 3 or 4 biomarker studies that would meet the threshold for FDA approval as a surveillance test. In general, the FDA guidelines for supporting biomarker qualification recommend that analyses intended to support biomarker qualification should be specified in an analysis plan with a prospective-retrospective design before analyzing the data. The FDA provides no set quantitative criteria for determining the relationship between the biomarker and clinical outcome, such as diagnosis of HCC, within a particular context of use. Overall, the goals for *in vitro* diagnostic biomarker studies are that they should produce valid scientific evidence demonstrating reasonable assurance of the safety and effectiveness of the product, and protect the rights and welfare of study subjects(63,64).

Key unmet needs in the field of chemoprevention include an improved understanding of the potential for HCC risk reduction by chemoprevention using commonly used medications

such as aspirin and other antiplatelet agents, statins, metformin and similar agents(65–68). In order to build a robust evidence base through chemoprevention trials, a number of key hurdles need to be crossed, including better definition of target populations, trial enrichment or stratification prior to randomization using clinical, genetic, or other molecular risk stratifying strategies, and careful delineation of appropriate and clinically meaningful end-points for both biomarker-based and chemoprevention trials. Enrichment of populations included in chemopreventive trials should aim to a reasonable time-to event (occurrence of HCC) endpoint, certainly within the threshold of 5 years. Stratification factors for at risk populations have been outlined below and are mandatory to prevent imbalances. Finally, one of the bottlenecks of these trials is that the accepted adverse events for maximum tolerated doses (grade 3 toxicities are unacceptable) are completely different compared to those accepted for primary treatments of advanced tumors, where grade 3-4 adverse events at the level of 30-50% are common for currently accepted drug treatments.

Early HCC stages: design of trials for resection, transplantation and local ablation

Hepatic resection is the treatment of choice for patients with preserved liver function (Child's class A, bilirubin < 1.0 mg/dl, no evidence of portal hypertension) who have a solitary HCC > 2 cm without macrovascular invasion(3,4,69) (**Fig 1, Table 4)**. Outcomes of ideal candidates treated following these criteria are significantly better compared with outcomes not following the guidelines (70). Recent guidelines accepted expanding criteria to include patients with HCC within Milan criteria (3). While 5-year survival rates are in the range of 70% after resection, recurrence of HCC is also around 70% at 5 years)(71). Early (within 2 years) recurrence is most commonly due to the appearance of preexisting undetected metastatic disease, with the most common site in the remaining liver; late recurrence is predominantly the result of *de novo* development of HCC in the remaining liver. There is, thus, a critical unmet need for therapy that can reduce the incidence of HCC recurrence after resection.. A study demonstrating benefit of retinoid administration(72) was not confirmed in a subsequent multicenter trial(73), and small studies suggesting benefit from adoptive immunotherapy(74) and I-131 lipiodol embolization of the liver remnant(75) the results of which have not been duplicated. To this point, all phase III high-quality adjuvant trials conducted so far in this area have been negative, A large randomized, controlled trial of sorafenib after resection or thermal ablation demonstrated no benefit(76). Current attention is largely focused on immunotherapy. Treatment of advanced HCC with anti-PD-1 or PD-L1 antibodies has consistently yielded responses in the range of 15-20%((38,39,41) that are often quite durable. In non-small cell lung cancer similar response rates are seen in advanced disease, and a neoadjuvant trial for resectable tumors resulted in a roughly doubled response rate(77).

Phase 3 trials are currently underway with single-agent immunotherapy or combination therapies. In advanced disease combination therapy, an anti-PD-1/PD-L1 plus either a tyrosine kinase inhibitor (e.g. sorafenib, lenvatinib), an anti-VEGF antibody (e.g. bevacizumab), or a second checkpoint inhibitor (e.g., anti-CTLA-4 antibody) appears to significantly raise response rates, and if established in the advanced setting combination therapy will no doubt be studied in adjuvant/neoadjuvant trials. The ultimate hope is that effective adjuvant/neoadjuvant therapy will be able to substantially improve recurrence-free survival. It is the consensus of the panel that entry criteria for adjuvant/neoadjuvant studies in HCC resection should conform to the criteria for resectability currently espoused in AASLD guidelines(4,69), and prevent a broadening of the tumor eligibility for resection (e.g., multiple tumors, presence of vascular invasion) observed in some currently-running adjuvant trials. While all patients undergoing resection for HCC have significant risk of recurrence, studies should stratify for known risk factors including tumor size (>3cm), microvascular invasion, differentiation degree and serum AFP>400 ng/mL. Neoadjuvant

studies provide a unique opportunity to better understand what factors are associated with response to immunotherapy or lack thereof. Pretreatment biopsy should be mandatory, and thorough characterization of the tumor immune microenvironment should be built into these trials.

Liver transplantation is the treatment of choice for HCC within Milan criteria in patients who are not candidates for resection (78) **(Fig.1, Table 4).** These criteria lead to median OS of 10 years and recurrence rate of < 20%. In the US it has been accepted that patients with more extensive disease (one nodule between 5-8cm, 2-3 nodules ≤ 5cm or 4-5 nodules < 3cm with sum of diameters < 8cm) down-staged to Milan criteria are acceptable for transplantation (79)**.** Downstaging is not accepted by European guidelines, although performed in some countries such as Italy. A significant number of patients who enter the waiting list or a down-staging protocol drop out and do not ultimately undergo transplantation. Locoregional therapy using thermal ablation or transarterial chemoembolization have been the modalities traditionally applied to maintain HCC within Milan criteria while awaiting transplant or to down-stage patients to eligibility. With the advent of effective systemic therapies, their role in the pretransplant setting vis-à-vis locoregional treatment warrants exploration in clinical trials. Locoregional treatment should be the control arm, compared to systemic therapy either alone or in combination with locoregional, with the primary endpoint of drop-out / transplantability. Stratification should be according to whether patients were initially within or beyond Milan criteria, or down-staged to Milan, and base-line AFP levels >400ng/ml.

Treatment of HCC recurrence following transplantation is largely unstudied. The rate of recurrence in properly selected patients is low (10-20%) and these patients have been routinely excluded from studies of systemic therapies. Tyrosine kinase inhibitors have been shown to be safe and are commonly used in an uncontrolled manner(80). There is considerable reluctance to use immunotherapy with anti-PD-1/L1 antibodies due to reports of treatment-related organ rejection, though there are reports of successful treatment(81). As HCC now accounts for nearly 25% of liver transplants in the US, it is time for trials to be implemented studying treatment of post-transplant HCC recurrence.

Local ablation is the mainstay treatment for nonsurgical candidates with early stage HCC (3,4) **(Fig 1, Table 4)**. Tumor size (up to 4-5 cm), number (up to 3 tumors) and location (accessiblility with ultrasound, CT or MRI guidance) limit the applicability of percutaneous ablation. Several randomized studies have demonstrated a significant benefit of radiofrequency ablation (RFA) over percutaneous ethanol injection in terms of complete response rate, and time to recurrence(82,83). Consequently, RFA is the standard ablative therapy at early stages **(Table 1)**. Median OS with RFA is of 60 months, with a recurrence rate ranging from 50-70% (3,4,82,83). AASLD and EASL guidelines have adopted radiofrequency ablation as front line therapy for single tumors <2cm, but in tumors beyond this threshold resection remains as first treatment option(3,4). Randomized phase III trials are scarce in this arena, and are mostly currently focused on adjuvant therapies to prevent recurrence than in challenging the abaltive treatment. Microwave ablation has largely supplanted RFA in the United States(84), whereas ethanol injection is restricted to HCC < 2cm in difficult locations. Cryoablation and irreversible electroporation are still under investigation(3,4,85). Clinical benefit associated with the use of thermally-sensitive carriers loaded with liposomal doxorubicin in conjunction with radiofrequency ablation is currently tested in phase III.

Overall, the main criteria for trial design in the neo-adjuvant/adjuvant after resection/local ablation or liver transplantation setting are as follows (**Table 1**):

1. Target populations for neoadjuvant and adjuvant trials: For resection, trials should include patients meeting current AASLD guidelines, and should not include patients with more advanced HCC, e.g. macrovascular invasion. For transplantation, trials should include patients meeting criteria for listing (i.e., Milan criteria), or meeting established criteria for entry into downstaging protocols. For local ablation the target population should follow AASLD guidelines.

2. Endpoints: The appropriate end-point for adjuvant trials in the setting of either resection or transplant is recurrence-free or time to recurrence. For neo-adjuvant trials, pathological response or 1-yr recurrence can also be considered. For treatments challenging loco-regional therapies, OS remains the primary endpoint, but PFS is also recommended as co-primary end point. Secondary endpoints should at least include objective response rates.

3. Stratification prior to randomization: Appropriate stratification parameters for neoadjuvant/adjuvant studies in the setting of early-stage HCC should include geographical region, tumor size and number, AFP >400ng/mL, type of curative treatment, and pathological features of high risk (size >3cm, microvascular invasion, differentiation degree and tumor satellites).

4. Control arms: For neoadjuvant/adjuvant studies in the setting of resection, a placebo control arm is appropriate. Adjuvant studies in transplantation should also include placebo controls. Defining the control arm for neoadjuvant studies in transplantation remains problematic as there is no evidence-based standard, but there is a general acceptance of the need to include loco-regional therapies to limit tumor progression in patients awaiting transplant that precludes including placebo or untreated patients. Control arms for devices or drugs challenging local ablation should be radiofrequency. Of note, since RFA has been considered effective in nodules up to 4cm, trials exploring treatments for single nodules beyond this size should consider chemoembolization as the best standard control.

5. Unmet needs: HCC recurrence rates after resection or local ablation are unacceptably high. Key needs include biomarkers to improve case selection, and effective neoadjuvant/adjuvant therapies. With regard to transplantation for HCC key needs include definition of optimal neoadjuvant (waiting list) strategies, and identification of useful biomarkers to refine candidate selection beyond algorithms based on tumor size and number.

Trial design and endpoints in intermediate stage HCC

TACE was established as the standard of care for intermediate stage HCC in 2002 following the publication of two small, randomized controlled trials for which OS was the primary endpoint (**Table 4**). The first trial, conducted in Barcelona, demonstrated a hazard ratio of 0.47 [95% CI 0·25–0·91], p=0·025) in favor of TACE, and a 2 year survival of 63% compared with 23% for supportive care(86). In the second, TACE was associated with an improvement in 2 year survival from 11% with supportive care to 31% with TACE, and a reduction in relative risk of death; 0.49 (95% CI, 0.29-0.81; P = 0.006)(87). Response using WHO criteria, was evaluated as a secondary endpoint and was shown to be associated with a better survival(86). On the basis of these trials and a subsequent meta-analysis(88), the BCLC algorithm recommends TACE for those with intermediate stage disease HCC defined by liver confined, multinodular disease, in those patients with a performance status of 0, Child Pugh A or B cirrhosis and in the absence of portal vein invasion(3,5) **(Fig 1)**. Chemoembolization was subsequently adopted by AASLD and EASL guidelines of management of HCC, and no other therapy has so far replaced this standard of care. However, since 2003(86,88) there have been further innovations, guidelines and therapeutic advances which need to be considered in the design of current and future trials. Finally, radioembolization with Y90 for intermediate HCC has produced positive efficacy

signals coming from phase 2 investigations(89), but they have not been adopted by guidelines awaiting phase 3 positive data for this specific population.

Eligibility criteria and stratification factors.

It is increasingly recognized that the BCLC B stage is heterogeneous and this likely accounts for the wide spectrum of reported survival outcomes, which range from 12-48 months. Consequently, there have been several proposals to subdivide the BCLC group but to date, none have been widely adopted(90,91). Additionally, patients who have a performance status of 1 but otherwise conform to the BCLC criteria, are routinely treated with TACE, and many clinicians regard Child-Pugh B disease as a relative contraindication. Applicability of TACE in BCLC-B is 50%, with the excluded patients having relative contraindications for the procedure due to advanced liver dysfunction or technical issues(92). Recent large RCTs have included patients with PS 0-1, Child-Pugh A, and absence of portal vein thrombosis (**Table 1,2**)(93–96). Stratification factors have been less consistent with the exception of AFP for which a threshold of 400ng/ml has been commonly applied. Composite and fully objective prognostic systems may provide a more feasible and consistent method by which to stratify patients. The ALBI score allocates a grade based on bilirubin and albumin and provides a more objective measure of liver function as compared with Child-Pugh class(97). A direct comparison between ALBI and Child Pugh has shown that the ALBI grade 1 is 92% Child-Pugh A5, ALBI 2 spans a wide range from A5 to B9 and ALBI 3 is B7 and above(98). However, tumor characteristics such as size and AFP are also prognostic and this has been addressed by the HAP score which provides a four class prognostic system using bilirubin, albumin, tumour size and AFP as categorical variables(99). The HAP score has been validated in the TACE-treated population, most recently within a cohort of 3000 patients(100). Applying the HAP score resulted in four distinct groups with survival ranging from 33 months for HAP A to 12 months for HAP D. HAP appears to be a simple and robust stratification factor that might be incorporated into TACE trials

TACE procedure

The TACE technique provides another source of heterogeneity and potential bias(101). There remains no consensus regarding the optimal embolic particle, the role of lipiodol or the type of chemotherapy used. Indeed, there are no trials demonstrating the superiority of TACE over bland particle embolization (TAE) and a meta-analysis of five trials including 582 patients showed no difference in survival(102). It is unlikely that further technical innovation to the TACE procedure will result in significantly improved outcomes and the future generation of TACE trials will continue to evaluate the combination of TACE and systemic therapy or to compare TACE with systemic therapy. In both cases, TACE will be the control arm and it is important that this is standardized. To achieve this, some of the recent randomized trials have mandated use of drug-eluting beads (DEB TACE)(93,94). Trials comparing DEB TACE with conventional TACE (cTACE) have failed to show a survival benefit but systemic toxicity from chemotherapy is reduced with DEB TACE(103) (104). If technique is not standardized, stratification according to center is an alternative way to reduce bias. Another area of contention is the schedule of TACE administration. In clinical practice, TACE is usually performed on demand according to radiological response rather than according to a fixed interval, and it is reasonable to recapitulate this in clinical trials. However, an effective systemic therapy may reduce the requirement for TACE. In the TACE-2 trial, there were 18% fewer TACE procedures performed in 12 months in the sorafenib arm compared with the placebo arm(93), and in the Oriental trial, the median number of procedures was 3.2 versus 3.7 in the orantinib and placebo arm respectively(96). Recording the number of procedures over the first 12 months or the mean number of procedures should be considered as a secondary endpoint for randomized trials of TACE

versus TACE plus systemic therapy. In this sense, the reduction in frequency and number of TACE procedures may have implications for health economics and preservation of liver function.

Response assessment

Radiological response is an important indicator of therapeutic activity and can be a surrogate marker of long-term outcomes. Response assessment has been addressed in the next section, but few concepts regarding loco-regional therapies are summarized here. In TACE-related population, mRECIST demonstrated a higher response rate compared with RECIST 1.1(105). Moreover, there was a significant association between survival and overall response according to mRECIST but not with RECIST 1.1. The association between mRECIST response and survival has subsequently been confirmed in multiple other studies and a recent meta-analysis of seven studies including 1357 patients reported a hazard ratio for survival of 0.39 (95% CI; 0.26,0.61) for those with mRECIST response(106). Unfortunately, not all the recently reported phase 3 studies reported response and only TACE-2 ascertained response by both RECIST 1.1 and mRECIST. Best response by RECIST 1.1 was higher than first response but still less than response by mRECIST. Guidelines recommend capturing response as per mRECIST in clinical practice and both RECIST 1.1 and mRECIST as secondary endpoints trials targeting intermediate stage tumors(3).

Primary endpoints

In recent trials, OS for intermediate stage patients receiving TACE was of 21-33 months(93–96) **(Table 2)**. Over the past 10 years, there have been major advances in systemic therapy and many patients now transition from TACE to first and increasingly second line systemic therapy. In TACE-2, patients were unblinded on progression and 36% of those on placebo subsequently received sorafenib(93). Similarly, in the BRISK TA trial, 21% of placebo treated patients had post-progression systemic therapy (95) trial, and in the ORIENTAL trial, 66% of patients in the placebo arm received post-study therapy (96). Use of post-progression therapy may confound OS as an endpoint and increases the duration of follow-up required to meet the survival endpoint. To address this, a variety of surrogate endpoints have been proposed including progression free survival (PFS), time to progression (TTP), time to disease progression (TTDP), time to extrahepatic spread and vascular invasion (TTES/VI) and time to unTACEable progression (TTUP). Recent trials reporting these potential surrogates in addition to survival has allowed evaluation of their performance. The BRISK TA trial reported a promising hazard ratio of 0.61 for TTP but the trial missed its primary endpoint for survival (HR 0.9)(95). Overall, the correlation coefficient of TTP and OS is 0.77. A major limitation of TTP is that it fails to capture death, which is an important indication of toxicity as well as lack of efficacy. By contrast, PFS, which is the most commonly applied surrogate endpoint used in oncology, captures disease progression and death, and has been reported to correlate with OS in the TACE 2 trial. Novel composite endpoints have also been explored. Time to appearance of extrahepatic spread or vascular invasion (TTES/VI or MVI/EHS) showed a promising HRs of 0.64 and 0.62 in the BRISKT TA and SPACE trial that did not correlate with OS benefit(94,95). Particularly, TTUP (time to untreatable progression), a composite end point defined as failure of response after to treatments, or emerging contraindications for TACE was tested in the SPACE trial, but failed to identified benefits for the combo of TACE plus sorafenib vs TACE (HR: 1.586). Recently, other novel endpoints were incorporated into the TACTICS trial comparing TACE plus sorafenib vs TACE alone(107) (108). In this study, PFS and OS were co-primary end points but progression was defined as unTACEable progression and Response Evaluation Criteria in Cancer of the Liver (RECICL)(109) was used to define progression rather than RECSIT 1.1 or mRECIST. Applying these criteria, PFS was superior in the combination arm

(HR=0.59; 95% CI, 0.41 to 0.87; p=0.006) but further follow-up is required to establish wether this translates into a survival benefit. In the meantime, for RCT testing devices alone or in combination with systemic therapies it is recommended that PFS should be the co-primary endpoint along with OS, while ORR should be included as a secondary endpoint **(Table 1 & 2)**. Additional composite endpoints can be included as exploratory endpoints until they are properly validated.

A challenging question for the future is how TACE compares to systemic therapy. TACE was developed at a time when systemic therapy was virtually non-existent. With the advent of first, second and even third line systemic therapies and achieved OS beyond 2 years in selected patients receiving two lines of therapy(23), systemic therapy can be discussed not only following TACE but as an alternative to TACE. This is particularly relevant as transarterial therapies impair liver function and may render many patients no longer eligible for systemic therapy. For patients with limited tumor burden and nodules accessible super-selectively by TACE, locoregional TACE may still be the best approach. In contrast, patients exceeding the up-to-seven criteria may be better suited for clinical trials exploring upfront systemic therapy(110). To answer this question a head-to-head comparison of TACE vs. systemic therapy (or vs. TACE plus systemic therapy) in defined patient subgroups will be needed, making the endpoint discussion even more complex.

Radiologic assessment of response

The RECIST criteria are the standard imaging approach for assessing tumor response in oncology. The original RECIST panel acknowledged that amendments could be needed for tumors with unique complexities and for evaluating non-cytotoxic drugs(111). Both issues are highly relevant for HCC: (a) the association of HCC with an underlying chronic liver disease complicates image assessment, since pathologic and hemodynamic changes in cirrhosis and extrahepatic manifestations of chronic liver disease may mimic tumor progression; (b) nonsurgical treatments for HCC, including loco-regional and systemic therapies, achieve improvements in survival without inducing sizeable tumor shrinkage, frustrating attempts to capture tumor response using standard RECIST metrics(12).

In 2010, modified RECIST (mRECIST) criteria for HCC were proposed(21) addressing confounding factors related to cirrhosis using specific amendments for the assessment of lymph nodes, ascites, portal vein thrombosis, and newly detected hepatic nodules (**Table 5**). These recommendations were made primarily to prevent “overcalls” of progressive disease. In addition, the absence of substantial tumor shrinkage was addressed by introducing the concept of “viable tumor” in the measurement of intrahepatic HCC lesions, enabling the classification of treatment induced intratumoral necrosis in the absence of significant changes in overall tumor diameter as objective responses (21).

During the past decade, mRECIST for HCC has been used extensively in HCC clinical research and its performance has been reviewed elsewhere(27).The proposed mRECIST refinements for assessment of lymph nodes, ascites, portal vein thrombosis, and newly detected hepatic nodules, were progressively incorporated into radiology charters of HCC clinical trials, even when the criteria were named RECIST or RECIST 1.1(112). This process homogenized radiologic interpretation of these findings, improving consistency and reliability in assessment of tumor progression. Consequently, recent studies reported similar results for standard RECIST 1.1 and mRECIST in assessment of progression-driven endpoints, such as PFS and TTP(7,8). Currently, the main difference between standard RECIST and mRECIST is the approach to measurement of intrahepatic lesions, which primarily affects the ability to capture an objective response (OR). Use of the mRECIST viable tumor concept results in identification of 2-3 times more responders than standard

RECIST, not only in patients receiving loco-regional treatments but also those receiving systemic therapies(7,32).

With the advent of immune checkpoint inhibitors, changes to the RECIST model have been proposed(35,36,113–115). Response to immunotherapy can manifest after imaging features that meet current RECIST criteria for progression. Pseudo-progression has been defined as increase in tumor size of existing lesions or the appearance of new lesions, followed by a response(35). Differentiating pseudo-progression from true progression is a challenging but important: while early discontinuation of an effective drug is not desirable, continued long-term treatment with a non-effective drug past true progression might delay the initiation of potentially effective therapies. Pseudo-progression has been described as a marginal event in phase III investigations with anti PDL1/PD1 check point inhibitors in HCC. The incidence of this phenomenon with anti- CTLA-4 and other inhibitors is unknown.

Limited information is available on use of immune-related criteria in HCC. In a phase II study of 104 patients who received pembrolizumab in second line after sorafenib, the use of immune-related RECIST (irRECIST) did not affect response rate or time to response as compared to mRECIST; however median PFS was 7.0 months (95% CI, 4.9-8.0) when assessed by irRECIST vs 3.2 months (95% CI, 2.2-4.1) when assessed by mRECIST(116). In phase IIb study(117) investigating a vaccinia virus-based oncolytic immunotherapy - pexastimogene devacirepvec- in advanced HCC changes to mRECIST were implemented because the treatment induces a flare with swelling and edema(118). These changes included the confirmation of progression at 4 weeks, either by further increase in size or additional signs of progression such as emergence of new lesions(117). Overall, to assess response to checkpoint inhibitors or immunotherapies in HCC, evaluation by CT/MRI at 8-12 weeks after treatment can be recommended, as opposed to the usual interval of 6-8 weeks for tyrosine kinase inhibitors. This window was used in phase II studies testing nivolumab (12 weeks)(38) and pembrolizumab (9 weeks)(116), where the phenomenon of pseudo-progression was reported as a marginal event.

Design and endpoints for systemic therapies in HCC

Standard of care with systemic therapies in HCC

Current estimates suggest that around 50% of HCC patients will receive effective systemic therapies during their lifespan(3,119,120). Several trials have tried to show survival benefits of systemic agents in advanced disease **(Table 2,4)**, a traditionally challenging setting due to the limited efficacy and high toxicity of conventional systemic chemotherapy(121–124). Randomized studies for anti-estrogen therapies also failed to prove any clinical efficacy (125). In 2008, the landmark SHARP trial assessing the multi-tyrosine kinase inhibitor sorafenib was the first to significantly improve survival with manageable adverse events(11). Afterwards, five treatments have succeeded, while several other drugs failed (126,127),(22),(128)(129)(122)(130)(131)(132)(133)-. In first line, atezolizumab (anti-PD-L1 inhibitor) plus bevacizumab (VEGFA inhibitor) have shown to be superior to sorafenib in a recently reported RCT(134). The study was stopped at the first interim analysis by showing a HR of 0.58 for OS (median not reached for combo vs 13.2 mo for sorafenib) and HR of 0.59 for PFS (median 6.8 mo for combo vs 4.3 for sorafenib). These results will pose this combination as standard of care first-line therapy for advanced HCC. Second, lenvatinib (multikinase inhibitor: VEGFRs, FGFRs, RET, KIT and PDGFRA) has become an option equal to sorafenib, after the positive result of the non-inferiority REFLECT study (HR of 0.92; 95% CI 0.79-1.06) (**Table 2, Fig 2A**). Because this trial excludes patients with main portal vein invasion, tumor involvement >50% of the liver and clear bile duct invasion, the relative benefit of lenvatinib vs sorafenib in these patients remain uncertain.

In second line, the phase III trial testing regorafenib (VEGFRs, PDGFRs, KIT and Tie2) improved OS compared to placebo from 7.8 to 10.6 months (HR of 0.63) in patients who progressed and were tolerant to sorafenib(8). The sequential treatment sorafenib-regorafenib led to a median OS of 26 months compared to 19 months for sorafenib-placebo (23). These results need to be taken with caution since they will not apply to all patients receiving sorafenib, but only those able to receive the sequential treatment. The CELESTIAL study, showed median OS of 10.2 months with cabozantinib (VEGFRs, MET and AXL) vs. 8 months with placebo (HR of 0.76)(9); and the REACH-2 study, where ramucirumab (VEGFR2 monoclonal antibody) provided a median OS of 8.5 months in patients with AFP $\geq$ 400 ng/ml vs. 7.3 months with placebo (HR of 0.71)(10,135). AFP is well-known for its independent prognostic capacity in HCC(136). As such, REACH-2 was the first and only positive phase III trial in a biomarker-driven population of patients with HCC (**Fig 2B**). In contrast, 3 phase III trials testing internal radiation with Y-90 for advanced HCC, either as single treatment [SARAH(137) and SIRveNIB(138)] or in combination Y-90 with sorafenib(139) did not meet the primary endpoint of improved OS compared to sorafenib (**Fig. 2A**). As a result, Y-90 was discouraged for the management of advanced HCC in the EASL guidelines (**Fig. 1**)(3). Despite appealing ORR of 15% with durable response for nivolumab and 18% for pembrolizumab, phase III trials comparing the former with sorafenib(24) in front-line and the latter with placebo in second-line resulted negative. Particularly, the latter trial showed a HR of 0.78 with upper boundary of 95CI below 1, but the pre-specified p value ($p<0.0178$) was not hit(41).

Trial design in advanced HCC

Overall survival remains as the primary end-point for advanced HCC research(1,3) **(Table 4)**. It has driven clinical research in HCC for more than 40 years and has been the gold-standard for measuring benefits at all stages of the disease. Nonetheless, the emergence of several effective drugs in advanced HCC has exposed the need for alternative end-points that can capture the benefits of a treatment before they can be diluted by post-progression therapy(3). Progression-free survival (PFS), time to progression (TTP) and objective response rate (ORR) are now emerging as tools to a) identify early strong signals of efficacy that led to accelerated regulatory approval (particularly ORR and PFS)(6,88) and b) test interventions which benefit can be assessed prior additional sequential drugs received beyond progression might mask the actual benefit of the tested drug. In this sense, a recent investigation analyzing 21 reported phase III studies(7–11,121–123,126–131,133,135,137,138,140) in advanced HCC proposed PFS (with a restrictive hazard ratio criteria <= 0.6) as a surrogate end-point for survival when testing kinase inhibitors or monoclonal antibodies, and thus as potential primary end-point in advanced HCC trials(3) **(Table 4)**. Subsequently, six phase III studies have been released that confirm the hypothesis: two positive studies, one testing atezolizumab plus bevacizumab vs sorafenib(134) and the second sorafenib plus hepatic arterial infusion of Folfox vs sorafenib(141), both show HR for PFS $\leq$0.6 and significant survival benefits, and four negative trials for survival testing nivolumab(24), sorafenib plus pravastatin(142), sorafenib plus doxorubicin(143) and pembrolizumab(41), in which the HR for PFS in all cases was >0.6 (**Fig 3**). Considering the special circumstances of the 2 negative trials testing anti-PD1 inhibitors, we should be cautious when applying this rule for testing immune therapies as single agents or for combinations of immune regimes.

Trial design in HCC has been evolving, and new challenges emerge as novel therapies become standard of care. Although there might be distinct approaches to trial design in HCC, there has been a consensus on the basic principles that have been recently reported in guidelines and critical appraisals (3,139,144,145). The key points are summarized below (**Table 1**):

1. *Phase II and Phase III trials*: The panel recommends assessing drugs in the setting of randomized phase II studies before moving to phase III trials. Nonetheless, for some therapies, a large single arm phase II with a strong signal of efficacy might suffice to justify a phase III study. Thresholds for defining signals of efficacy are not clearly established, but for molecular therapies the ORR should likely be above 20-30%(146).

2. *Selection of the target population*: Clinical trials should consider BCLC staging system, Child-Pugh class and ECOG performance status for selection of the target population. In principle, for advanced HCC almost all RCT include patients with well-preserved liver function (Child-Pugh A) and good performance status (ECOG 0 and 1).

3. *Control arm:* The control arm of randomized phase II and III studies should be the standard of care established according to guidelines. Although sorafenib and lenvatinib in front-line (7,11) and regorafenib (8), cabozantinib(9) and ramucirumab (in patients with AFP $\geq$ 400 ng/ml)(10) are accepted as standard of care, this will change when atezolizumab plus bevacizumab are approved by regulatory agencies. At that time, this combination will become the standard of care for comparison in front-line, and subsequence lines of therapy will move downwards. Double-blind trials (as opposed to open label trials) are recommended to prevent selection and allocation biases.

4. *Stratification for prognostic factors prior to randomization*: Stratification is critical in randomized studies to warrant balanced comparisons. For advanced HCC the recommendation is as follows: region, macrovascular invasion, extrahepatic spread, AFP > 400 ng/ml and ECOG 0 vs 1-2. Etiology should also be considered as studies with sorafenib and atezolizumab and bevacizumab suggest an influence of this factor in response.

5. End points: Overall survival: For systemic therapies the primary endpoint should be OS, and PFS is proposed as co-primary endpoint. To date, all regular FDA and EMA drug conventional approvals in advanced HCC were based upon improvements in OS. *Surrogate endpoints:* OS has limitations as a sole endpoint in cancer research: it might require a long follow-up to capture adequate numbers and can be affected by sequential therapies. Thus, surrogate endpoints that are more practical for trial execution are needed. There are no optimal surrogate endpoints able to recapitulate OS in HCC, and thus clinical practice guidelines do not recommend ORR, TTP and PFS as primary endpoints in phase III investigations(144,145). ORR is an independent predictor of OS in three phase II and III trials(7,123,127), but is still considered a suboptimal primary end-point for phase III investigations. Nonetheless, ORR of 16-18% resulted in accelerated FDA approval of nivolumab and pembrolizumab in second line treatment of advanced HCC(38,39). PFS was formerly discarded as a primary end-point of phase III investigations due to the concept of competing risk of survival (competing between death due to tumor progression and due to the natural history of cirrhosis)(12). However, this competing risk drawback has been reduced by the universal selection of Child-Pugh A patients for these investigations, thus reducing the 1-yr risk of death due to decompensation to <5%. Stringent criteria for accepting PFS as primary endpoint have been proposed (HR$\leq$0.6) and it is adopted in the current guidelines **(Table 1)**, but this point is still controversial. Regarding ORR, use of both RECIST1.1. and mRECIST are proposed for the assessment of response in HCC treated with systemic therapy, whereas changes in serum biomarker levels (*i.e.* AFP levels) are not supported(3).

6. *Magnitude of benefit:* In HCC, there is no consensus on what absolute survival benefit (or magnitude of benefit in OS according to HR) is clinically relevant. Reported thresholds of OS with HR <0.8 are sound for capturing the benefit of patients in advanced HCC trials(20). This figure needs to be taken with caution, since other variables can impact

the overall benefit of a given drug, such as quality of life, safety profile and availability of alternative therapies in distinct countries.

7. Checkpoint inhibitors and other immunotherapies have unique features and generally produce higher ORR and longer duration of response, as measured by RECIST1.1. The values of mRECIST and irRECIST in assessing checkpoint inhibitor mediated responses remain investigational.

Immune treatments: Overview of results andspecific endpoints

The initial clinical experience with checkpoint inhibitors in HCC was with a phase II study testing tremelimumab, a CTLA-4 antibody leading to objective response of 18% of patients and time to tumor progression was 6.5 months (147). Immunotherapy has drawn significant attention in HCC with the approval of nivolumab and pembrolizumab by the FDA based on promising results obtained in different phase II studies(38,39). A phase I/II open-label, non-comparative trial (CheckMate 040) assessing the efficacy of nivolumab in advanced HCC reported objective response rate (ORR) of 20% in the dose-expansion phase (n=214) and 15% in the dose-escalation phase (n=48). Duration of response (DOR) was 9.9 months and median PFS as 4.0 months in the dose-expansion cohort. Nivolumab treatment was well tolerated (38). Pembrolizumab, another PD1 specific antibody, was tested in phase II in patients with HCC progressing or intolerant to sorafenib (Keynote 224). Pembrolizumab was effective and tolerable with one complete response (CR) and 17 PR out of 104 patients. The median progression free survival was 4.9 months, and median OS was 12.9 months(39). Camrelizumab, another fully humanized anti-PD-1 antibody, was evaluated in a randomized phase 2 trial in Chinese patients with advanced HCC after failure of at least one line of therapy(148). The ORR was 13.8% and the 6-month OS was 74.7%.

Nivolumab and pembrolizumab failed in phase III trials (**Fig. 2A-B**). Pembrolizumab was tested in a randomized, double-blind phase III trial against placebo in 443 patients with HCC that progressed on or were intolerant to sorafenib (Keynote-240). The co-primary endpoints of PFS and OS failed to reach the prespecified level of statistical significance although median OS was prolonged from 10.6 to 13.9 months (HR: 0.781; 95% CI: 0.611-0.998; P = .0238)(149). Nivolumab was tested against sorafenib in a Phase 3 trial (CheckMate 459), but did not reach survival differences for superiority (24).In this RCT including around 750 patients, median OS for nivolumab was 16.4mo vs 14.7mo for the sorafenib arm (HR: 0.85; 95%CI 0.72-1.02). Objective response rate was 15% and 7%, respectively.

Anti-CTLA4 antibodies have been tested as single agent(147) or in combination with locoregional therapies(150) and are under investigation in combination with anti-PD1 drugs(151). In this regard, very recently the combination ipilimumab and nivolumab received FDA approval based on a ORR of 31% (40). Currently phase III trials are ongoing which either test the combination of two immune checkpoint inhibitors, immune checkpoint inhibitors plus TACE, immune checkpoint blockade in the adjuvant setting or immune checkpoint inhibitors plus vascular targeting agents(152). While the overall response to immune checkpoint inhibition (15-20%) may not be as dramatic as initially hoped, complete responses are seen in a small number of cases in almost every trial. This observation together with the recent results from two phase III trial testing anti-PD1 antibodies in the first- and second-line setting rise up the important question of what endpoint to use in future trials. While OS remains the “gold standard” it should be noted that HCC is not the only cancer where this question is being asked. Due to the unique mechanism of action of immune checkpoint inhibitors(153), new endpoints such as ORR and surrogate biomarkers have been tested and new immune related RECIST criteria devised to capture distinctive

patterns and timing of response to immunotherapy(35,115). Finally, while immunological endpoints may be helpful as surrogates(154), they cannot be recommended at this time.

A systematic review and meta-analysis of 87 phase 2 trials with the foal of defining the most appropriate primary endpoint in phase 2 trials of immune checkpoint inhibitors for advanced solid cancers has been reported. Correlations between ORR odds ratios and hazard ratios (HRs) for PFS and OS were examined for randomized comparisons. Within checkpoint-inhibitor treatment arms, correlations of ORR with 6-month PFS and 12-month OS rates were examined. All analyses were weighted by trial size. Multivariable models to predict 6-month PFS and 12-month OS rates from ORR were developed and their performance validated in an independent sample of trials. The authors demonstrated that ORR correlated poorly with OS and recommended 6-month PFS rate as an endpoint for future phase 2 studies,(155). Thus, PFS endpoint can also be recommended for studies evaluating immune checkpoint inhibitors in HCC **(Table 1)**.

Biomarker-Driven Trials in HCC: Results and Endpoints

Recent clinical trials in advanced HCC are demonstrating that the sequential use of systemic agents is changing the natural history of the disease. Still, these results are incremental and the incorporation of biomarker driven strategies have generally been unsuccessful. Unlike other solid tumors such as breast, lung, colon cancer, and others, where therapeutic decisions are driven by an understanding of a patient given molecular features, in HCC a "one-size-fits-all approach" is still the usual approach to patients. This applies to all therapies so far accepted in guidelines, except for ramucirumab.

Biomarkers provide the distinct possibility of supplementing existing anatomic and/or pathologic information to provide a more accurate assessment of prognosis (to be used for patient stratification) and/or to identify individuals who are more likely to respond to specific therapy (predictive of response) (156–158) There is a plethora of literature on the different predictive biomarker validation designs (159). The NCI defines a biomarker as *a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease*. A biomarker may be used to determine how well the body responds to a treatment for a disease or condition (160).

In HCC, numerous studies have defined the molecular heterogeneity of the disease and specific genetic alterations and subtypes. These data are fertile ground for testing biomarker hypotheses as both prognostic and/ or predictive markers in prospective studies but so far these data have largely been ignored in clinical development in HCC (6). To date, two phase 3 studies have tested biomarker driven approaches. Firstly, tivantinib, a small molecule inhibitor of the hepatocyte growth factor/ c-MET was evaluated in patients that had progressed on sorafenib and had elevated expression of c-MET in their tissue. This was a placebo-controlled study that yielded negative results(131). The possible reasons for failure highlight the challenges with this approach including: 1) validity of the target, 2) robustness of the assay for patient selection, and 3) ability of the agent to inhibit the target successfully in tumor tissue. The latter may be a plausible reason for failure of the trial, considering that the anti-MET activity of this drug has been challenged in experimental studies(161). Conversely, ramucirumab, which initially failed in an "all comers" study(162), demonstrated an improvement in OS for selected patients with AFP$\geq$ 400 ng/ ml. Proof-of-concept studies testing small molecule inhibitors of FGFR-4 using biomarker enriched populations based on FGF-19 expression have been reported with ORR of 16% (163).

Recently, immunotherapy approaches have garnered high interest in the management of HCC and the PD-1 directed antibodies nivolumab and pembrolizumab received accelerated approval by the US FDA(38,39). However, unlike in other cancers, PD-1 and / or PD-L1

expression has not correlated with outcome. This has likely contributed to the recent negative results from phase 3 studies with these agents(149). Ongoing work is focused on further refining biomarker development evaluating other inflammatory markers including incorporation of more broad based assessment tools such as an immune-enriched signature identified through molecular profiling of HCC (164).

Several studies have incorporated biomarker assessments into the trial design. While tissue collection is often optional and therefore limited, serum assays have served to generate hypotheses for further study. In the pivotal SHARP study, baseline levels of angiopoietin 2 and VEGF were prognostic but not predictive of benefit from sorafenib(136). Relevant biomarkers in the FGF and VEGF pathways were analyzed in the REFLECT study and identified differences in the modulation of these pathways by lenvatinib and sorafenib, but no biomarker could define a group receiving differential benefit from either compound(165). In the REACH-2 study, decreases in AFP correlated with better outcome from ramucirumab(10). Novel study designs evaluating biomarker assessments pre-and post-treatment are being performed. These so-called “pre-surgical” studies are designed to acquire tissue at baseline, from patients with resectable tumors, expose the patient to a novel agent for a short period, and then collect tissue at the time of resection. Molecular studies comparing the pre-and post-treatment tissue provide an opportunity to understand the effects of novel therapeutics on relevant pathways in the tumor. These studies can provide critical information that could guide a patient selection strategy in conventional efficacy studies. One such study with nivolumab is producing interesting insights into tumor characteristics that may correlate to response to this drug(166).

Despite the recent successes in clinical trials of new agents for HCC, the improvements in survival are modest. Throughout cancer medicine, the largest impacts in outcomes have been by biomarker driven drug development. Examples include ALK(167) and EGFR(168) testing in lung cancer, HER-2(169) and estrogen receptor(170) testing in breast cancer, c-KIT testing in gastrointestinal tumors(171), and BCR-ABL testing in chronic myelogenous leukemia(172). By enriching for the population most likely to benefit, studies can be conducted with smaller numbers of patients and minimize risk for failure. While historically predictive marker testing is done on tumor tissue obtained by biopsy, newer technologies are now allowing biomarker detection in peripheral blood. The practice of not obtaining biopsies for diagnosis of HCC, the fact that most common driver mutations in HCC are non-actionable and the observation that only 25% of HCCs harbor at least one actionable mutation(172), in contrast to the majority of solid tumors(173), have hindered development of biomarker driven precision treatment to date. Nonetheless, there is now renewed interest in incorporating tissue acquisition into clinical trials, not only in the early part of drug development, but in later studies as well. Clinical trial designs for predictive marker validation are inherently complex and require data from a randomized controlled clinical trial (RCT)(153). There is a plethora of literature on the different predictive biomarker validation designs, including articles that specifically focus on the statistical and clinical properties and assumptions of these different trial designs (156).

Trial design in the precision medicine era require a platform for biomarker profiling (173)(174). The ultimate clinical utility of a biomarker will depend on: 1) its added value in every patient in the context of the markers prevalence, 2) its incremental benefit for treatment selection when considering the added costs and complexity induced by the use of the marker, and 3) the added effectiveness of the new treatment option in all patients versus biomarker-defined subgroups.

Liquid biopsy in early HCC detection, prediction of response and tumor relapse

Liquid biopsy entails the analysis of tumor components released by cancer cells to biological fluids such as blood, saliva or cerebrospinal fluid(175). The concept includes the analysis of actual cancer cells (i.e., circulating tumor cells [CTCs]), fragments of DNA from necrotic or apoptotic cancer cells (i.e., circulating tumor DNA [ctDNA]) and extracellular vesicles(176). Compared to conventional tissue biopsies, the main advantages of liquid biopsy using samples from peripheral blood are: 1) it is minimally invasive, which eliminates the complications associated with invasive tissue biopsies; 2) it facilitates sequential sampling, which is crucial to better select therapies in patients receiving multiple lines of treatment; 3) it enables tracking tumor clonal composition in heterogeneous tumors, a feature that allows earlier detection mechanisms of treatment resistance; and 4) it can be implemented as a point-of-care diagnostic. Potential clinical applications include cancer surveillance, early detection of minimal residual disease after curative therapies, prognostic prediction and molecular monitoring of therapeutic response(177). In an early sign of impact on patient care, the FDA recently approved the use of a ctDNA-based test to detect mutations of EGFR in lung cancer patients who are candidates to receive EGFR-based tyrosine kinase inhibitors(178).

In HCC, liquid biopsy has been evaluated for three clinical applications: early HCC detection in the context of surveillance, as a prognostic biomarker after surgical resection and to predict response to systemic therapies. Mutation profiling of ctDNA is feasible and confidently detects tissue mutations in early stage HCC(179). A recent report combining data from ctDNA and protein markers had a sensitivity and specificity of 85% and 93% respectively for the detection of HCC(180). Also, analysis of DNA methylation alterations in ctDNA has high accuracy for HCC diagnosis(55,181). A study that included a gene signature derived from CTCs was able to accurately discriminate between HCC patients and controls(182). Higher CTC count correlates with a greater risk of tumor recurrence after surgical resection(175). There are few studies using liquid biopsy to predict response to systemic therapies in HCC. A retrospective study suggested that HCC patients with ctDNA detectable *VEGFA* DNA amplifications have better outcomes when treated with sorafenib(183). Also, RAS mutations analysis of ctDNA was used to determine eligibility to receive refametinib in a phase 2 clinical trial(184). Thus, there is increasing interest in applying this technology to predict response to systemic therapies.

Quality of life and patient reported outcomes

Systematic capture of the patient perspective can inform the development of new cancer therapies. The U.S. FDA Office of Hematology and Oncology Products (OHOP) has identified symptomatic adverse events (AEs) as a central Patient Reported Outcome (PRO) using the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) to provide a standard yet flexible method to assess symptomatic AEs from the patient perspective(194,195). The FDA's patient focused drug development program has ongoing efforts to improve methods around the collection, analysis and interpretation of PRO data, as well as initiatives to identify patient-friendly language, and leveraging digital health tools. In 2016, the 21st Century Cures Act tasked the FDA to consider the patient-experience in the risk-benefit determination. The FDA draft guidance outlines the use of PRO to assess symptomatic side effects and the core set of clinical outcomes to measure in cancer trials, including design considerations and assessment frequency(11).

The purpose of measuring quality of life (QOL) should be to compare outcomes between treatment arms, even if one is a placebo. There are two methods of measuring QOL specific to HCC: the European Organization for Research and Treatment of Cancer Quality of Live

Questionnaire (EORTC QLQ)(185) and the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep)(186) questionnaire. Few studies have adequately assessed PRO using these tools in HCC research, a recommendation that is endorsed by the panel.

Most phase III trials for HCC were designed primarily to compare two different treatments in patients with similar stage disease. For example, one study compared QOL after resection with QOL following radiofrequency ablation(187). As expected, QOL was much better after radiofrequency ablation than after resection, and remained superior up to 36 months post-treatment. In addition, QOL following radioembolization has been compared with TACE(188). In this study, there was no overall difference in QOL between the two groups, but the sample size was small. Despite the lack of statistically significant differences, in the TACE group QOL was decreased at 2 and 4 weeks, whereas in the radioembolization group some aspects of QOL actually improved. Similarly, QOL measures favoring Y-90 vs sorafenib have been claimed to support the former treatment in three negative RCT, the SARAH trial (134) and the SIRveNIB trial (135) and SORAMIC trials. However, since indication of a drug/device should be based upon the primary endpoint (survival), no actual indication can be claimed if the result is negative for the primary end-point. Finally, the SHARP trial demonstrating survival benefit of sorafenib also tested time-to-symptomatic progression — as measured by the Functional Assessment of Cancer Therapy–Hepatobiliary Symptom Index 8 (FHSI8) — as a co-primary endpoint. The negative results of this end-point contrasted with the survival benefit obtained by sorafenib, thus challenging the accuracy of the tool used(11). More recently, patient reported outcomes have been tested in the setting of phase III investigations showing significant results in positive RCT in advanced HCC. This is the case of lenvatinib compared to sorafenib, or atezolizumab plus bevacizumab compared to sorafenib, where the tested arms showed better QoL parameters compared with the standard of care. The panel encourage the integration of these endpoints in all investigations in HCC (**Table 6**).

Implications of trial design in Asia

Differences between AASLD, EASL, and Asian guidelines

Recommendations in western guidelines (AASLD and EASL) are based upon evidence from clinical trials (**Table 4**), while Asian guidelines integrate evidence with expert consensus and clinical practice. Applicability of those guidelines varies according to region and treatment stage (47). Asian guidelines (189) in general recommend ablation or resection for very early-stage (stage 0) disease, but differ from western guidelines in the recommendations at other stages of disease. For instance, TACE or yttrium-90 (Y90-SIRT) are recommended for single large tumors, and systemic therapies -i.e Folfox(105), or hepatic arterial infusion chemotherapy - are recommended for advanced stages, along with liver transplantation – mostly living donor transplantation . Similarly, in Asia patients with portal vein invasion and well-preserved liver function might be considered for TACE, resection or radiotherapy (190–194).

Specificities of trial design in Asia

Considering all these guidelines, trial design in Asia has some specificities. For instance, resection in very high-risk patients (multinodular tumors, macrovascular invasion) is common in Asia, and thus adjuvant trials might consider this indication with a recurrence-free survival endpoint. Similarly, studies exploring the role of systemic therapies plus TACE in patients with advanced stages might also be considered in Asia with a primary end point of PFS. Weather these approaches should be tested in specific trials or as part of global trials needs further consideration.

Future prospects

The dawn of a new era: combination therapies

When the report of the first AASLD conference on Design and Endpoints of Clinical Trials in HCC was published(12), the field was still heady with excitement from the first positive trial of a systemic agent for advanced HCC, which established sorafenib as the first FDA approved systemic therapy for HCC (11). However, enthusiasm was also tempered by the subsequent negative results of trials of sorafenib as adjuvant therapy after resection or ablation (STORM)(76) or in combination with TACE (SPACE)(94). It was recognized then that a unique challenge is posed by the combination of underlying chronic liver disease with a very heterogeneous and variably aggressive primary HCC. It is therefore important that treatment strategies account for both the liver disease and malignancy, and thus variables capturing both diseases should be considered in the publication of clinical trials for HCC (**Table 7**). Discussions at the previous AASLD Endpoints conference set the framework for subsequent attempts to bring additional agents to approval, which were met with uniformly disappointing results over the next several years, with trial failures due to unacceptable toxicity or inadequate efficacy(12). While disappointing, these failures led to robust examination of the optimal approach to trial design and catalyzed a more rigorous approach that contributed to the successes in phase 3 HCC clinical trials. With the positive results and approvals of lenvatinib, regorafenib, cabozantinib and ramucirumab based on phase 3 studies, and of the checkpoint inhibitors nivolumab and pembrolizumab based on convincing phase 2 data, we appear to be poised for success in the next most logical treatment paradigms using combination therapies. Indeed, the recent positive phase III study demonstrating superior OS for atezolizumab plus bevacizumab vs sorafenib(134), represents the dawn of a new era of combination therapies in all stages of HCC research (**Fig 1**). This combination is certainly *first in-class* of this approach. Whether other combinations may become *best-in-class* will depend upon the ability of specific TKI and/or MAb to transform “cold tumors”, which are primary resistant to immunotherapy, into “hot-immune-active tumors”, allowing checkpoint inhibitors to optimally unleash immune attack against cancer cells(195–197) .

The advent of combination therapies achieving response rates of 30% and survival rates above 20 months in advanced HCC provides the rationale for testing these combinations in earlier HCC stages. Currently, phase III trials testing combination therapies are ongoing for early stages (neo-adjuvant or adjuvant approaches), intermediate HCC (in combination with TACE or in comparison to TACE) and in front-line trials for advanced HCC (**Table 7**). It is conceivable that systemic therapies may be incorporated in all areas of HCC management in the near future. Thus, the up-dated target population and endpoints described here should be valuable in this endeavor.

Understanding tumor biology remains critical: tissue and blood samples are needed

It is likely that the next key advances in HCC therapy will emanate from an improved understanding of HCC biology and the ability to predict the response of specific HCCs subgroups to particular therapies. Until now, most HCC therapy has been applied in a biologically indiscriminate fashion. The biological heterogeneity of HCC has been evident for many years, demonstrated by differences in phenotypes, tumor growth rates, numbers of tumor nodules, discrete versus infiltrative appearance, propensity for microvascular or macrovascular invasion, propensity for distant metastasis, and association with elevation of AFP, AFP-L3, DCP and other biomarkers. Apart from the limitations that multifocal, invasive or metastatic disease have placed on application of potentially curative treatments such as surgical resection, liver transplantation, and local ablation, we have only recently began to incorporate markers of tumor biology into therapeutic decision making. Applications of tumor

biologic characteristics into therapeutic approaches have been scarce in HCC and mostly focused on using AFP levels for selection policy for transplantation, as an stratification factor in most of trials and finally for selecting candidates to ramucirumab in the management of advanced HCCs in second line.

With the advent of next generation DNA, RNA and non-coding RNA sequencing and similar genome wide methodologies for copy number variation, methylation and proteomic characterization, we now stand ready to translate information from these technologies to the care of HCC patients, transforming the selection of systemic therapy and the selection of optimal candidates for loco-regional therapies. Results suggesting that *CTNNB1*-mutated HCCs are immune excluded and potentially resistant to immune checkpoint inhibitors(198–200) but potentially susceptible to mTOR inhibitors are an early indication of the potential value of genomics in personalizing HCC therapy. These studies may also provide us with tools for better understanding the recent borderline negative results of phase 3 trials with single agent immune checkpoint inhibitors. Personalization of therapy using molecular and genomic signatures will require integration of molecular subclasses into clinical staging systems, to better guide treatment selection. Optimal treatment selection will depend on the ability to target oncogenic signaling pathways that drive tumorigenesis, tumor progression and metastasis. The development of new preclinical tumor models, including organoids, patient derived xenografts, and syngeneic models that preserve aspects of the immune response will be critical for the testing of novel agents and combinations. Ideally, integration of molecular profiling into the HCC treatment paradigm will require genomic data derived in real time from patients, either by tissue biopsy or through liquid biopsy-based access to circulating tumor DNA or other analytes. This will require a cultural change in the care of HCC patients, shifting from a state in which the diagnosis and evaluation of patients is performed non-invasively, to regular use of tissue biopsy and highly sensitive liquid biopsy assays. Development of robust, reproducible predictive biomarkers of high reliability is a key priority to facilitate this transition (**Table 6**). The first implementations of the biomarker-based approaches should be within RCT, which should now routinely require tissue biopsy and liquid biopsy collection as a condition of trial enrollment. Tumor biopsy at screening for trial entry and liquid biopsy at different time points should be mandatory in clinical trials for advanced HCC to allow identification of prognostic and predictive biomarkers, guide clinical decision-making and improve patient outcomes.

Novel endpoints might be adopted

The revolution in drug development in HCC has created the need to revisit established conventions in trial design. OS is regarded as a core endpoint. Nonetheless, the realization that more than 60% of patients progressing after TACE and 50% of patients progressing after first-line systemic therapies receive effective next line therapies may compel the adoption of PFS as an acceptable primary endpoint for major trials (**Table 1)**. In this position paper, we already are recommending PFS as co-primary endpoint for intermediate HCC trials, and for phase II-III trials assessing systemic therapies, with restrictive cut-points. Similarly, patient reported outcomes (PRO) should be pursued as a relevant endpoint in HCC trials, particularly as we enter an era of potent, but seemingly toxic, dual or triple combination therapies possibly associated with serious adverse events. It is important to recognize that currently many HCC patients reach a point in their therapeutic journey when they elect to forgo potentially life extending therapy in favor of approaches that optimize their quality of life. It is therefore critical to extend decisions about HCC trial design and endpoints to incorporate elements that reflect the importance of patient well-being.

FIGURE LEGENDS

Figure 1. Modified BCLC staging system considering new effective therapies in advanced stages [modified and up-dated from EASL Guidelines(3)] Management of patients with HCC is guided by the Barcelona Clinic Liver Cancer (BCLC) staging system, which takes into account both tumor extent and the severity of the underlying liver disease, and defines five prognostic subgroups with respective treatments. Treatment for early stage tumors is with curative intent and options include radiofrequency ablation, hepatic resection, and liver transplantation. Patients with intermediate or advanced HCC are candidates for chemoembolization or systemic therapies, respectively. *Patients with end-stage liver disease if Child-Pugh class C should first be considered for liver transplantation. **Patients with preserved hepatic function Child-Pugh class A with normal bilirubin and no portal hypertension are optimal candidates for hepatic resection. ‡The combination of atezolizumab plus bevacizumab is not yet approved but is set to become the new first-line treatment for advanced HCC(134)- DDLT, deceased donor liver transplantation; ECOG, Eastern Cooperative Oncology Group; LDLT, living donor liver transplantation; M1, distant metastasis; N1, lymph node metastasis; OS, overall survival.

Figure 2. Overall survival outcomes (HR, 95% CI) of phase III clinical trials testing molecular targeted therapies, checkpoint inhibitors and radioembolization in patients with advanced-stage hepatocellular carcinoma. Blue=positive trials for superiority. Orange=positive trials for non-inferiority. Black=negative trials for the primary end-point, Red=tested drug was significantly worse than the standard of care. Vertical red line at HR=1.08 defines the upper boundary of 95% confidence interval accepted by FDA for a positive non-inferior study.

Figure 3. Correlation between progression-free survival and overall survival in 27 phase III trials of advanced HCC (modified from Llovet, J Hep 2019(20)**) .** Trial-level correlation between endpoints using criteria from the Institute for Quality and Efficiency in Health Care (IQWIG). R and R2 refers to the weighted Pearson coefficient between the HR of OS and the HR of the surrogate endpoint. Each dot represents one of the phase III clinical trials conducted on advanced HCC. Size of the dot is proportional to the total number of patients enrolled in the trial. First 21 phase III trials defined a cut-off of 0.6 for PFS to correlate with a significant OS (colored in grey)(20). Afterwards, six additional phase III trials have been reported afterwards: two positive for survival show a HR for PFS <0.6 (green color) and four negative for OS show a PFS HR> 0.6 (red color). X- and Y-axis depict the value of the HR for the surrogate and the hard endpoint, respectively. Gray shaded areas represent the upper and lower limits of the 95% confidence intervals for the regression. HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival.

TABLES

Table 1. Recommendations for Trial design and endpoints in patients with HCC by AASLD panel of experts.

Aim	Factor	Considerations and recommendations
Select the target population	BCLC stage	Include patients according to specific BCLC stage (0–C)
	Child-Pugh classification	Include patients in Child–Pugh class A. Consider ALBI grade and MELD score for refinements on Child A class
	Biomarker-based enrichment	Define rationale for using biomarker and tool
Selection of endpoints	Overall survival (OS)	Primary endpoint for phase II and III studies assessing treatments in intermediate and advanced HCC.
	Progression-free survival (PFS)	Primary endpoint for Phase II studies assessing primary treatments in intermediate and advanced HCC. Consider co-primary in phase III studies in intermediate and advanced HCC, with strict rules for calling superiority Independent centralized blinded review*
	Time to Progression (TTP)	Secondary (or co-primary) endpoint for Phase II studies assessing primary treatments in intermediate and advanced HCC. Independent centralized blinded review*

	Recurrence-free survival (RFS)	Primary endpoint in phase II/III studies assessing adjuvant treatments
	Time to recurrence (TTR)	Primary endpoint (2nd choice) in phase II/III studies assessing adjuvant treatments
	Objective response rate	Phase II co-primary endpoint, Phase III secondary end-point Surrogate endpoint for accelerated approval Independent blinded review assessing mRECIST for interventions at early/ intermediate HCC. Both RECIST 1.1 and mRECIST for interventions at advanced stages
	Patient reported outcomes (PRO)	Recommended as secondary endpoint in all phase III investigations, particularly when testing loco-regional or systemic therapies
	Composite endpoints	OS plus PFS might be considered
Select control arm	Surveillance	Ultrasound with or without AFP
	Adjuvant therapy after resection or local ablation for early stage HCC	Placebo
	Early stage-non surgical	Radiofrequency ablation. Special consideration for single large (>4cm tumoral diameter) when standard of care is TACE as per the stage migration principle.
	Intermediate stage disease	Chemoembolization**
	First line treatment for advanced stage disease	Atezolizumab plus bevacizumab will be considered when

		approved. Sorafenib or lenvatinib plus supportive care Other treatments in Asia**
	Second-line treatment for advanced stage disease	Regorafenib (only in patients tolerant to sorafenib) or cabozantinib. Ramucirumab only in patients with AFP> 400 ng/ml
	Third-line treatment for advanced stage disease	Placebo
To stratify factors before randomization	Adjuvant	A) Geographical region B) Tumor size and number C) Type of curative treatment D) Pathological factors of high risk (size >3cm, microvascular invasion, poor differentiation degree and tumor satellites)
	Intermediate-stage	Child-Pugh class, AFP >400 ng/ ml and geographical region. ALBI score might be considered. Selection of large tumoral burden as per above 7-up-to-7 has been proposed (adopting criteria for extended indications in liver transplantation), but requires validation
	First-line advanced stage	ECOG status, MVI-EHS, AFP >400 ng/ ml and geographical region, Etiology (HCV vs others when testing sorafenib)
	Second-line advanced stage	ECOG status, MVI, EHS, geographical region, AFP >400 ng/ ml. Type of progression might be considered

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HCC; hepatocellular carcinoma; EHS=extrahepatic spread; MVI=macrovascular invasion; RECIST, Response Evaluation Criteria In Solid Tumours.

*= not always recommended

**= Asian guidelines recommend additional treatments for

Intermediate HCC: Japan: HAIC; China: Resection; Taiwan: Resection/Y90

Advanced HCC: Japan : HAIC/Resection/TACE; China: FOLFOX4, resection/TACE; Korea: TACE

Table 2. Expected outcomes reported in phase III trials in HCC research.

Expected outcomes	**Early**	**Intermediate**	**Advanced (1st line) *****	**Advanced (2nd line)**
Overall survival		TACE: 21 mo(93), 26mo (95)-33 mo(96)	Sorafenib: ~11-14(7,11,24) mo Lenvatinib: ~13 mo(7) Atezolizumab+bevacizumab *** (134)	Regorafenib: ~11 mo(8) Cabozantinib: ~10 mo(9) Ramucirumab (only AFP> 400 ng/ml): ~8 mo(10)
PFS	RFS*adjuvant resection /ablation: 33mo	TACE: 7mo (93,95)	Sorafenib: ~4(7) months Lenvatinib: ~7 months(7)	Regorafenib: ~3 mo(8) Cabozantinib: ~5 mo(9) Ramucirumab (only AFP> 400 ng/ml): ~3 mo(10)
ORR*		TACE: ~45-54% (93)	Sorafenib: ~10%(7) Lenvatinib: ~24%(7) Atezolizumab+bevacizumab : 33%; RECIST: 27%(134)	Regorafenib: ~10%(8) Cabozantinib: ~4%(9) Ramucirumab (only AFP> 400 ng/ml): ~5%(10)

*RFS: Recurrence free survival

** ORR as per mRECIST

***Atezolizumab+bevacizumab is expected to be fist line, while sorafenib and lenvatinib will be second line therapies, see **Fig 1**

Table 3. Phases of Surveillance Test Validation in Hepatocellular Carcinoma [(adopted from Pepe et al(57))]**.**

Phases	Type of Study	Design	Aims	Comments
1	Preclinical exploratory	Case-control from biobanked samples	Promising HCC biomarkers identified	Avoid multiple freeze-thaw for blood and tissue samples
2	Clinical Assay and Validation	Large case-controlled accounting for confounders	Biomarker detects clinically established early stage HCC	Appropriate sample size and power essential
3	Retrospective longitudinal	PRoBE	Biomarker detects pre-clinical HCC	Assess benefits and harms of surveillance
4	Prospective screening	Prospective cirrhosis cohort	Confirms the ability of the novel biomarker to detect early stage disease	Assess benefits and harms
5	Cancer control	Randomized study of new biomarker compared to US and AFP	Impact of screening on reducing mortality in patients with cirrhosis (or high-risk populations)	Survival primary endpoint; secondary endpoint early stage detection, assess harms

Table 4. Guidelines recommendations for treatment according to levels of evidence* and strength of recommendation.** *Treatments accepted in guidelines (EASL(3) and AASLD(4)) and level of evidence* (modified from Llovet et al(119))

Category	Treatment	Eligibility criteria or alternative approaches	Evidence level	Recommendation strength
Surgical treatment	Resection	Patient with solitary tumors and well-preserved liver function	2A	Strong
	Liver transplantation	Patients with single tumors of ≤ 5cm or ≤ 3 nodules of ≥ 3cm (Milan criteria) not suitable for resection. Down staging to Milan *.	2A	Strong; Moderate: down staging (US), not recommended in Europe
Loco-regional treatment	Local-ablation	Radiofrequency, BCLC 0-A not suitable for surgery, upper limit 4-5cm Radiofrequency ablation (and alternatively percutaneous ethanol) injection for patients with BCLC 0-A tumours that are not suitable for surgery.	2A 2B	Strong
	Chemoembolization	BCLC B (multinodular asymptomatic tumours without vascular invasion or extra-hepatic spread)	1A	Strong
Systemic treatment	Atezolizumab+ bevacizumab	Child-Pugh A Advanced HCC tumours (BCLC C) or BCLC B progressing upon loco-regional therapies	1A	Strong (not yet included in guidelines)
	Sorafenib	Child-Pugh A	1A	Strong

		Advanced HCC tumours (BCLC C) or BCLC B progressing upon loco-regional therapies		
	Lenvatinib	Child-Pugh A Advanced HCC tumours (BCLC C) or BCLC B progressing upon loco-regional therapies. No Main portal vein invasion	1A	Strong
	Regorafenib	Child-Pugh A Tolerant to sorafenib. Advanced HCC progressing on sorafenib	1A	Strong
	Ramucirumab	Child-Pugh A Advanced HCC progressing on sorafenib AFP> 400 ng/dL	1A	Strong
	Cabozantinib	Child-Pugh A Advanced HCC progressing on sorafenib	1A	Strong
Palliative care	Palliative support	Patients with BCLC D tumours should receive management of pain, nutrition and psychological support	2B	
Treatments under investigation or with further evidence required to be adopted in guidelines				
Surgical treatment	Resection	Patients with multifocal small tumors (≤ 3 nodules ≤ 3cm) or mild portal hypertension)	3A	Moderate
		Adjuvant treatments after resection/local ablation	1D	Strongly not recommended

	Liver transplantation	Up-to-seven criteria in patients without microvascular invasion	2B	Moderate
		Neo-adjuvant loco-regional therapies if the waiting list exceeds 6 months	2D	Moderate
		Living donor liver transplantation in patients with a waiting list exceeding 6-7 months	2A	Moderate
Loco-regional treatment	Other ablative therapies, such cryoablation, laser, irreversible electroporation or high-intensity focused ultrasound	Patients with BCLC 0-A tumours that are not suitable for surgery	N/A	Not recommended
	Chemoembolization	Use of drug-eluting beads, which has shown similar response rates as gelfoam-lipiodol particles associated with less systemic adverse events	1D	Moderate
	Chemoembolization combined with systemic TKis	Multiple RCT failed to show improved outcomes	1A	Not recommended
	Y90-Radioembolization-	In patients at stage BCLC B and in patients BCLC A with a single nodule larger than 4 cm as an alternative to resection	1D	No recommendation
	External 3D conformal radiotherapy (SBRT)	Single tumors at early stages (BCLC A)	3A	No recommendation

Systemic treatment	Molecular targeted therapies and immune-based therapies	- Patients BCLC A as neo-adjuvant therapies. - Patients BCLC B in combination with TACE, Child Pugh A class, ECOG 0-1	1A	No recommendation
Palliative care	Radiotherapy to alleviate pain	Patients with bone metastasis	3A	Moderate

AASLD, American Association for the Study of Liver Diseases; BCLC, Barcelona Clinic Liver Cancer Group; EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma.

*National Cancer Institute classification: **Strength of evidence:** Level #1 (RCT or meta-analysis); #2 non-randomized controlled studies; #3 case series; **Strength of end-point**: A: survival B: cancer-specific survival; C Quality of life, and D: others.**

Table modified from EASL-EORTC guidelines(5)

Table 5. Basic concepts and key points for standard RECIST 1.1 and mRECIST assessment in HCC(27)

Evaluation		RECIST 1.1	mRECIST
Baseline Assessment	**Target lesions**	● Identify up to 2 intrahepatic tumor lesions ≥ 1 cm, that appear suitable for accurate and repeat assessments; measure their longest viable tumor diameter. ● Identify extrahepatic tumor lesions that are ≥ 1 cm in longest diameter and appear suitable for accurate and repeat assessments; measure their longest overall tumor diameter. ● When selecting lymph nodes as extrahepatic target lesions, the short axis must be measured and it must be ≥ 1.5 cm. ● Overall, include a maximum of 2 target lesions per organ and 5 target lesions in total.	● Identify up to 2 intrahepatic tumor lesions ≥ 1 cm, that show typical intratumoral arterial enhancement and appear suitable for accurate and repeat assessments; measure their longest viable tumor diameter. ● Identify extrahepatic tumor lesions (and intrahepatic lesions with atypical enhancement in patients without typical intrahepatic lesions) that are ≥ 1 cm in longest diameter and appear suitable for accurate and repeat assessments; measure their longest overall tumor diameter. ● When selecting lymph nodes as extrahepatic target lesions, the short axis must be measured: it must be ≥ 1.5 cm for all lymph nodes except for porta hepatis lymph nodes where it is required that it is ≥ 2 cm. ● Overall, include a maximum of 2 target lesions per organ and 5 target lesions in total.
	Non-target lesions	● Tumor lesions or sites of disease that have not been selected as target lesions should be recorded at baseline as non-target lesions.	● Tumor lesions or sites of disease that have not been selected as target lesions should be recorded at baseline as non-target lesions. ● Malignant portal vein thrombosis should be considered as a non-target lesions. ● Ascites and pleural effusions should not be considered as tumor lesions, unless associated with unequivocal neoplastic peritoneal or pleural nodules.
		● Measure the longest overall tumor diameter for intrahepatic	● Measure the longest viable tumor diameter of typical intrahepatic

Post-Baseline Assessments	**Target lesions**	and non-nodal extrahepatic target lesions, and the short axis diameter for nodal target lesions.	target lesions avoiding the inclusion of any major intervening areas of necrosis. ● Pay attention in distinguishing areas of tumor necrosis from areas of reduced arterial perfusion caused by changes in local hemodynamics. A change from hypervascularity to hypovascularity does not represent tumor necrosis. Only tumors or tumor areas that show complete absence of contrast enhancement can be assumed to represent necrotic tissue. ● Measure the longest overall tumor diameter for atypical intrahepatic target lesions and non-nodal extrahepatic target lesions, and the short axis diameter for nodal target lesions
	Non-target lesions	● Qualitative assessment of response.	● Qualitative assessment of response, taking into account tumor necrosis for typical intrahepatic non-target lesions. ● Complete disappearance of enhancement inside malignant portal vein thrombus should be considered equivalent to complete regression
	New lesions	· Any new lesion that has no corresponding lesion on baseline imaging and is unequivocally malignant is considered as evidence of PD.	● By definition, a new lesion has no corresponding lesion on the baseline imaging. ● A new liver lesion ≥ 1 cm that shows nonrim-like hypervascularization in the arterial phase with nonperipheral washout in the portal venous or the delayed phase meets the criteria for unequivocal new lesion and declares PD. ● Any new liver lesion <1 cm or any new liver lesion of any size that fails to show the enhancement pattern described above should be considered as equivocal and can only be diagnosed as HCC by evidence of either a change in enhancement pattern (when ≥ 1 cm) or an interval growth ≥ 1 cm in subsequent scans. ● If an equivocal new lesion is later determined to be unequivocal, the timepoint of progression will be the

			timepoint that the lesion was first noted as equivocal. ● Ascites or pleural effusion that appear during treatment should not be assumed to represent PD, unless associated with the emergence of unequivocal neoplastic peritoneal or pleural nodules.

Overall assessment of tumor response by RECIST 1.1 or mRECIST

Target lesions	Non-target lesions	New lesions	**Overall response**
CR	CR	No	CR
CR	Non-CR-NonPD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 6. Unmet needs in trial design in HCC.

1. Clinical trials:
    - Evidence-based data from RCT to provide standard of care in
        a) Adjuvant setting after resection/local ablation
        b) Neo-adjuvant setting prior resection/liver transplantation
        c) Define role of loco-regional therapies or SBRT in large single non-surgical tumors
    - Evidence-based data from RCT to improve the standard of care in
        a) Combination or systemic therapies to improve chemoembolization in intermediate HCC
        b) Combination (or triple) therapies for 1st line advanced HCC
        c) Molecular and immune-based therapies for patients with HCC and impaired liver function (Child-Pugh B).
    - Pivotal proof-of-concept phase II trials and trial enrichment for oncogenic drivers or signaling pathways
    - Systematic inclusion of cost-benefit analyses
2. Identification and validation of biomarkers:
    - Develop biomarkers for early detection in surveillance programs
    - Identify biomarkers predicting treatment response and primary resistance (tissue or liquid biopsy)
3. Quality of life & patient reported outcomes:
    - Incorporate tools for measuring quality of life into clinical trial design as an endpoint
    - Systematic inclusion of patient reported outcomes
4. Molecular pathogenesis and drug development:
    - Integrate molecular subclasses to the clinical staging system in order to better guide treatment allocation
    - Target oncogene addiction loops that result from DNA amplifications and gene mutations or overexpression
    - Improve models for pre-clinical testing of novel drugs

Table 7. Variables to be included in clinical trials assessing treatments for HCC patients

Demographic	Age, sex, ethnicity
	Underlying liver disease (cirrhosis, chronic hepatitis)
	Etiology : define based upon HCV, HBV, alcohol, NASH-NAFLD and others.
Tumor description	Radiological characteristics: size, number of nodules, macroscopic vascular invasion, extrahepatic spread
	Alpha-fetoprotein
	Pathological characteristics in adjuvant trials: size, number, differentiation degree, satellites, micro and macroscopic vascular invasion, pTNM
Staging system	BCLC staging classification
Liver function	Bilirubin, aminotransferases, albumin, alkaline phosphatase, gamma-glutamyl transpeptidase, serum creatinine, serum sodium, prothrombin time, INR, platelet count
	Presence of ascites or encephalopathy
	Child – Pugh score
	ALBI and MELD score
General health	ECOG status, pain, constitutional syndrome

* Modified from Llovet et al, JNCI 2008(12) HCV = hepatitis C virus; HBV = hepatitis B virus; pTNM = pathological tumor–node–metastasis;

BCLC = Barcelona Clinic Liver Cancer; BUN = serum urea nitrogen; MELD: Model of End-Stage Liver Disease; ECOG = Eastern Cooperative

Oncology Group.

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Title: Trial Design and Endpoints in hepatocellular carcinoma: AASLD Consensus Conference.

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Abstract

Proper trial design is critical for the success of clinical investigations. Hepatocellular carcinoma (HCC) is a complex disease that has several unique properties. In 2008, after the approval of sorafenib, a panel of experts proposed guidelines for trial design and endpoints in HCC that have been instrumental during the last decade and provided a framework to allow an homogeneous analysis of reported investigations. Since then, several phase III studies have been reported and novel challenges have emerged. A panel of experts conveyed by AASLD organized a Special Topic Conference on trial design and endpoints to address those emerging challenges. This review summarizes the analysis and conclusions of those discussions and provides novel recommendations on the selection endpoints, stratification variables and targeted populations in the complex arena of HCC. We have covered the full spectrum of the disease, from surveillance/ chemoprevention, to neoadjuvant and adjuvant trials after curative therapies, and trials in intermediate and advanced stages of HCC. We explore the prospects for incorporating biomarkers and liquid biopsy into conventional clinical trials. In addition, we address the need for obtaining tissue and blood samples in all investigations and propose novel primary endpoints such as progression free survival with restrictive rules and patient reported outcomes. This up-dated set of recommendations is timely considering the advent of more potent combination therapies in all areas of HCC management, the increase in adverse events associated with those combinations, and the evidence that several lines of effective treatments will benefit a given patient. We herein articulate a framework to facilitate capturing the efficacy of novel therapeutic strategies with the goal of improving the outcomes of patients suffering from this disease.

Introduction

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related mortality worldwide(1,2). This neoplasm has some unique characteristics. It occurs in most cases complicating underlying cirrhosis, has specific non-invasive criteria for diagnosis, follows a unique staging system and historically has been resistant to conventional chemotherapy. Several treatments have achieved adoption as standard of care according to clinical practice guidelines, including potentially curative therapies (i.e. resection, liver transplantation and local ablation) for early tumors, transarterial chemoembolization (TACE) for intermediate stage tumors, and systemic drugs for advanced tumors in front line (sorafenib and lenvatinib) and second line (regorafenib, cabozantinib and ramucirumab)(3–5). Life expectancy has improved progressively in all stages of the disease. Effective implementation of surveillance for patients at risk of developing HCC and access to current proven therapies has been a milestone. Overall, median survival times beyond 5 years are expected for early stages, about 20-30 months for intermediate stages, and between 10-16 months for advanced stage HCC [**Fig. 1**(3,4,6)]. Novel drugs and combinations continue to enter the research arena to address unmet medical needs. All these research activities require precise endpoints and tools for measuring clinical benefits.

Thus, clinical trial design has become a major focus of attention in HCC research. Since randomized controlled trials are the main source of evidence for drug approvals in oncology, it is of paramount relevance to understand the critical endpoints and tools for measuring them, as well as optimal strategies for identifying and enrolling target populations and for patient stratification. It has become evident that a deep understanding of factors determining HCC outcomes and trial design is required to achieve optimal results. There are trials with a non-inferiority design that have been positive, and lead to drug approval, while others demonstrate superior outcomes in surrogate end-points, such as progression free survival (PFS) or patient reported outcomes but not in the primary endpoint of overall survival. Some recent trials have also been reported to be statistically negative but “clinically positive”. It is important to understand the reasons for the failure or success of a trial in order to move the field forward. In addition, while several positive phase III trials for advanced HCC have recently changed clinical practice (7–11), no major advances have occurred in the area of surveillance and early detection, adjuvant therapies after resection/ablation or management of intermediate stage HCC over the last 15 years. The lack of effective novel drugs/devices may be the cause of negative studies in these areas, but suboptimal trial design may also have jeopardized the likelihood of a positive result. With this challenge in mind, the Hepatobiliary Neoplasia Special Interest Group of the American Association for the Study of Liver Disease (AASLD) organized a Single Topic Conference in Atlanta in 2019 to address these issues. This position paper summarizes the major concepts discussed in the conference with the aim of updating the proposals previously reported by a similar AASLD panel in 2008(12).

Overview on trial design and endpoints

Clinical trials are essential to establish the clinical efficacy of new therapeutic interventions. They are instrumental in developing clinical practice guidelines and form the basis for evidence-based medicine(13). An adequate clinical trial design is crucial, as an effective drug can be discarded due to a poor trial design and *vice-versa*. The main considerations when designing a clinical trial are to: a) select a well-defined target patient population (i.e., inclusion and exclusion criteria), b) pre-specify clear endpoints (primary and secondary) and data analysis plan, c) specify randomization and allocation method; and d) secure efficacy of randomization (stratification at enrollment for prognostic variables). Based on these and other variables, the quality of clinical trials can be quantified using different scores such as

the Jadad score(14), the Delphi List(15), the CONSORT statement(16,17), and the Cochrane Back Review Group criteria(18). Until the SHARP trial(11), which established the benefit of sorafenib in advanced stages HCC patients, the quality of the trials conducted in HCC was commonly modest. A systematic review found that only 50% of the clinical trials reported between 2002 and 2005 in HCC were deemed high quality as per the modified Jadad score(19). The 2008 position paper resulting from the AASLD conference provided a useful framework for academic centers, industry partners and regulators on the design of trials in HCC(12). Subsequently, the quality of clinical trials assessing systemic therapies has significantly improved. There has been less activity in terms of high-end clinical trials in other treatment areas. This position paper will extensively discuss the singularities of trial design in every clinical aspect of HCC management.

In clinical trials, the benefit of an intervention is quantified using endpoints, which are predefined events that once reached exclude the patient from further evaluation within the trial. There are 3 main types of endpoints: hard, surrogate and patient-reported, all extensively described elsewhere(20). Hard endpoints are well defined and easy to measure objectively. The archetypes of a hard endpoint are overall survival (OS) or cancer-related survival. Surrogate endpoints, such as progression-free survival or time to progression, partially rely on the quantification of tumor response, generally using imaging techniques and pre-specified criteria(21). Surrogate endpoints are more vulnerable than hard endpoints, but they have several advantages including their convenience in terms of event accumulation and trial feasibility. Patient-reported endpoints, sometimes referred as soft endpoints, are subjective measures such as quality of life (QoL), in most instances obtained from questionnaires. Overall recommendations of trial design and endpoints in HCC are detailed in **Table 1**, whereas expected outcomes for standard of care therapeutic interventions within these trials are summarized in **Table 2**.

Endpoints

OS is defined by the time between patient randomization and death from any cause. OS is usually recommended as the primary endpoint for randomized phase III clinical trials(12). OS is the endpoint most frequently used by regulatory agencies to approve drugs as it is objective and clinically relevant. In HCC, as most patients suffer from concomitant cirrhosis, death can result from competing risks, mainly liver toxicity and failure. This fact underscores the need for detailed assessments of safety with any intervention in this population. It is important to capture adverse events in early phase clinical studies as well as in larger randomized studies. Failures in phase 3 studies have been seen from new agents that are more toxic in an HCC population than in other tumor types(22). The competing risk of cirrhosis can introduce bias when evaluating the anti-tumoral activity of a therapeutic intervention, but it can be easily controlled by imposing stringent inclusion criteria in terms of liver function (i.e., Child-Pugh score A without hepatic decompensation). OS has some limitations such as the long follow-up time required to capture the number of events needed to verify significantly improved survival in the experimental arm(23). This can be a critical limitation when exploring interventions at early or intermediate stages. Also, OS can be confounded by sequential therapies received by patients after tumor progression, which for instance affected 30% of patients enrolled in the lenvatinib trial(7) and up to 50% of patients in the Checkmate 459 comparing nivolumab vs sorafenib(24). Hence, there is a need to develop surrogate endpoints, which are defined as outcomes not inherently meaningful from the clinical standpoint, but thought to accurately predict hard outcomes such as OS(25).

The main surrogate endpoints in oncology are progression-free survival (PFS), time-to-progression (TTP) and objective response rate (ORR). PFS is the time between patient

randomization and death or radiological tumor progression, whichever occurs first. There are different tools assessing tumor response with imaging. The most established tool for measuring tumor response in oncology are the RECIST criteria(26), initially developed to evaluate response to cytotoxic drugs. These criteria were adapted to account for HCC singularities in the modified RECIST (mRECIST) version, which incorporates viable tumour detected with arterial enhancement as a key component to evaluate response(21,27). Using mRECIST criteria increases the percentage of subjects who achieve objective response compared to standard RECIST, as shown in different studies of systemic therapies (28–32). A recent meta-analysis evaluated the power of PFS to predict OS in phase 3 trials testing systemic therapies in advanced HCC(20). The study found a moderate correlation between PFS and OS in 21 RCTs. The authors proposed a conservative surrogate threshold of ≤0.6 for hazard ratio of PFS to predict clinically relevant improvements in OS(33). TTP is defined as the time elapsed between patient randomization and radiological tumor progression. Scheduling repeated radiological assessment of response every 6-8 weeks is mandatory for patients included in trials. Data from SHARP and subsequent studies challenges the implied correlation between TTP and OS. The type of progression may also have clinical implications (34). Survival is worse if patients develop a new extrahepatic lesion and/or vascular invasion as opposed to tumor progression resulting from growth of an existing lesion or a new intrahepatic lesion. Lastly, ORR is the percentage of patients with an objective tumor response, and its correlation with OS is worse than for PFS or TTP(20). This is partially inherent to the use of odds ratios instead of hazard ratios for ORR and also to the fact that only a small proportion of patients achieve an objective response (<25%, for approved drugs in advanced HCC), which is the event that correlates with OS(31). Nonetheless, ORR has been reported as an independent predictor of survival in early HCC treated with radiofrequency ablation, intermediate treated with TACE and advanced HCC treated with TKI(27). The impact of the duration of response, which has been reported to be around 12 months for checkpoint inhibitors vs. less than 6 months for TKIs, has not yet been properly incorporated into response assessment. The same is true to small reductions in tumor size not reaching standard thresholds for objective response. In some cases, duration of disease control may be more clinically relevant than the extent of reduction in tumor size. Also, in the case of immune checkpoint inhibitors, tumor response can have a longer lag-time compared to other molecular therapies and can even mimic progression shortly after treatment initiation (*i.e.*, pseudo-progression(35)). This has led to the development of immune-related response criteria(36), which require confirmation of progression at least 4 weeks after progressive disease is first documented.

Surrogate endpoints are frequently used by the Food and Drug Administration (FDA) to approve drugs under the accelerated program, which was initially developed to facilitate early access to new antivirals during the worst years of the HIV epidemic(37). In HCC, the FDA has used ORR and duration of response to grant accelerated approval of the immune checkpoint inhibitors (CPI) nivolumab(38), pembrolizumab(39) and recently the combination of ipilimumab and nivolumab(40). Accelerated approval is not universal and includes some subjectivity from regulators in regards to the strength of the evidence to support approval without a randomized phase 3 study(24,41). In addition, while the use of ORR and other surrogate endpoints may be used to support regulatory approval, they do not necessarily support inclusion in guidelines which often adhere to a higher level of evidence. Despite their common use, surrogate endpoints are vulnerable to interpretation bias. Besides the strength of the endpoint, it is key to determine when the benefit provided by a new therapy is really clinically meaningful. This can be controversial , depending on factors such as the perceptions of patients, providers, health insurers and regulators. In HCC, there is no set threshold that defines a clinically meaningful benefit, but some authors have suggested a hazard ratio cutoff of OS ≤0.8 as a starting point for clinical trial design(42). In fact, all

positive trials in HCC have led to significant differences in survival with HR below this threshold.

Surveillance for Hepatocellular Carcinoma: design and endpoints

Surveillance for HCC is one of the milestones advancing the management of HCC, despite that there is not unquestionable data directly supporting a decrease in cancer-related death in persons on surveillance(43). Ultrasound (US), with or without alpha-fetoprotein (AFP), performed every six months is the current standard and is recommended for surveillance of patients with cirrhosis of any cause or chronic hepatitis B without cirrhosis above a regional and gender appropriate age cut-off determined by expert liver societies(3,4). Overall, the implementation of those programs to all targeted populations is modest, and current data report detection of HCC in the setting of surveillance in between 30-50% of cases(44). In meta-analysis, the pooled sensitivity and specificity of US alone has been shown to be 53% (95% CI: 35-70) and 91% (95% CI:86-94), respectively, while the combination of US and AFP has a sensitivity of 63% (95% CI:48-75) and a specificity of 85% (95%CI:77-89)(45). Due to the relatively low sensitivity and specificity of this approach for detecting early stage HCC, particularly in North America, where high rates of central obesity decrease the performance of ultrasound, a recent study showed that this strategy leads to 27% of patients with cirrhosis experiencing harms such as follow up testing (CT, MRI, liver biopsy) performed for false-positive or indeterminate results(46). Further, due to low implementation of comprehensive strategies for HCC surveillance, more than 60% of HCCs in North America, Europe, Africa and large parts of Asia, excepting Taiwan and Japan, are diagnosed with intermediate or advanced stage HCC(47). There is, therefore, an urgent need for better performing, low cost surveillance strategies in HCC, and accounting for both the benefits and harms of surveillance strategies is important.

Within this overriding context, there is excitement time because advances in genetic, epigenetic, proteomic, glycoproteomic and metabolomic analyses in have enabled large scale multi-omic analyses of HCC tissues, circulating tumor DNA, plasma and serum, resulting in the accelerated identification of novel biomarkers(48–51). Models using standard biostatistical and machine learning and artificial intelligence (AI) approaches are using biomarkers combined with clinical parameters to identify persons at highest risk for HCC. Models and biomarkers under active exploration include the GALAD (Gender, Age, AFP-L3, AFP, and Des-carboxy-prothrombin) score(52), novel glycoproteins (fucosylated kininogen)(53), liquid biopsy analyses of circulating tumor DNA for differentially methylated regions(54)(55), and imaging with abbreviated MRI(56). Creating the framework for validation of future surveillance is critically important.

To guide the development and evaluation of new surveillance strategies for clinical utilization, a 5-phase program has been developed by the NCI- Early Detection Research Network (EDRN) for biomarker that uses human samples (blood or human tissue) as well as imaging tests (57). **Table 3** shows recommended phases of surveillance test validation, including trial design for studies for HCC surveillance. *Phase 1* are biomarker discovery or exploratory studies. *Phase 2* studies estimate the ability of a test to distinguish early stage HCC from those with cirrhosis without HCC. It is important to test for confounders such as age, etiology of liver disease, and liver function; and to have adequate sample size and power. *Phase 3* studies enroll at risk individuals and follow them for clinical diagnosis of HCC using prospective-specimen collection, retrospective-blinded evaluation (PRoBE) design (58). The aim is to evaluate, as a function of time before clinical diagnosis, the capacity of the test to detect preclinical HCC; and also, to define the criteria for a positive surveillance test in preparation for phase 4 and 5 studies. Thus, Phases 1-3 rely on retrospective analysis of stored data and specimens. *Phase 4* studies require the new test

be applied to patients with cirrhosis in the clinical setting to assess test performance in HCC detection and false positive and negative rates. Depending on the test under study it may be possible to skip *Phase 4* if the test is already used for patient care, for example, evaluating an MRI for surveillance of HCC. *Phase 5* studies are randomized trials comparing the new surveillance tests against the standard of care, in the case of HCC the standard should be US with or without AFP, with the aim of determining whether the test can reduce mortality at the population level.

When performing surveillance studies in patients with cirrhosis it is important to enrich the *at risk* population in order to achieve a sufficient number of incident HCCs in a reasonable time period. Enriching cohorts with patients of older age, viral hepatitis, male sex, Hispanic ethnicity, history of diabetes, and family history of HCC should be considered (59,60). Alternatively, known independent factors associated with HCC development are abnormal bilirubin and platelet count <100,000/mm^3. There is also a need to study currently important populations such as those with non-alcoholic fatty liver disease-related cirrhosis, those with hepatitis C-related cirrhosis who have achieved a sustained virological response after antiviral treatment, and those with suppressed hepatitis B infection on antiviral treatment. These three specific populations will be the most important etiological risk factors in the next decade and their HCC incidence rates (around 1%/year) appear lower than in previous at risk populations(61). Methods for risk stratification within these populations will therefore become increasingly important for improving the effectiveness of surveillance strategies and programs. Models such as the REAL-B and PAGE-B scores, incorporating male sex, age, alcohol use, baseline cirrhosis, diabetes, platelet count and AFP, allow improved risk stratification of patients on oral antiviral therapy for chronic hepatitis B and could potentially be incorporated into surveillance programs(62).

An important potential confounder in studies that compare the performance of novel biomarkers to current surveillance strategies is the incorporation of imaging by ultrasound or other radiologic modalities into the standard of care. This may confound the results if ultrasound is also used as part of the control arm for the study, as ultrasonography is itself typically part of the gold standard process for determining whether a patient has HCC. Thus, patients with HCCs that are not visible by ultrasound may be falsely determined to be negative for cancer and a positive biomarker test erroneously labeled as a false positive. It is therefore important to use a different high-accuracy imaging modality such as multiphasic MRI as a gold standard in studies for which ultrasonography is part of the surveillance strategy. However, use of MRI may add substantial cost to the study and may also result in visualization of a number of small indeterminate false positive lesions that are seen on MRI and require follow up investigation, a component of the harms associated with surveillance. While studies of the performance of ultrasound with or without AFP in the clinical care setting have shown suboptimal performance in detection of HCC in at risk individuals, it is not clear what the performance characteristics are for phase 2, 3 or 4 biomarker studies that would meet the threshold for FDA approval as a surveillance test. In general, the FDA guidelines for supporting biomarker qualification recommend that analyses intended to support biomarker qualification should be specified in an analysis plan with a prospective-retrospective design before analyzing the data. The FDA provides no set quantitative criteria for determining the relationship between the biomarker and clinical outcome, such as diagnosis of HCC, within a particular context of use. Overall, the goals for *in vitro* diagnostic biomarker studies are that they should produce valid scientific evidence demonstrating reasonable assurance of the safety and effectiveness of the product, and protect the rights and welfare of study subjects(63,64).

Key unmet needs in the field of chemoprevention include an improved understanding of the potential for HCC risk reduction by chemoprevention using commonly used medications

such as aspirin and other antiplatelet agents, statins, metformin and similar agents(65–68). In order to build a robust evidence base through chemoprevention trials, a number of key hurdles need to be crossed, including better definition of target populations, trial enrichment or stratification prior to randomization using clinical, genetic, or other molecular risk stratifying strategies, and careful delineation of appropriate and clinically meaningful end-points for both biomarker-based and chemoprevention trials. Enrichment of populations included in chemopreventive trials should aim to a reasonable time-to event (occurrence of HCC) endpoint, certainly within the threshold of 5 years. Stratification factors for at risk populations have been outlined below and are mandatory to prevent imbalances. Finally, one of the bottlenecks of these trials is that the accepted adverse events for maximum tolerated doses (grade 3 toxicities are unacceptable) are completely different compared to those accepted for primary treatments of advanced tumors, where grade 3-4 adverse events at the level of 30-50% are common for currently accepted drug treatments.

Early HCC stages: design of trials for resection, transplantation and local ablation

Hepatic resection is the treatment of choice for patients with preserved liver function (Child's class A, bilirubin < 1.0 mg/dl, no evidence of portal hypertension) who have a solitary HCC > 2 cm without macrovascular invasion(3,4,69) (**Fig 1, Table 4)**. Outcomes of ideal candidates treated following these criteria are significantly better compared with outcomes not following the guidelines (70). Recent guidelines accepted expanding criteria to include patients with HCC within Milan criteria (3). While 5-year survival rates are in the range of 70% after resection, recurrence of HCC is also around 70% at 5 years)(71). Early (within 2 years) recurrence is most commonly due to the appearance of preexisting undetected metastatic disease, with the most common site in the remaining liver; late recurrence is predominantly the result of *de novo* development of HCC in the remaining liver. There is, thus, a critical unmet need for therapy that can reduce the incidence of HCC recurrence after resection.. A study demonstrating benefit of retinoid administration(72) was not confirmed in a subsequent multicenter trial(73), and small studies suggesting benefit from adoptive immunotherapy(74) and I-131 lipiodol embolization of the liver remnant(75) the results of which have not been duplicated. To this point, all phase III high-quality adjuvant trials conducted so far in this area have been negative, A large randomized, controlled trial of sorafenib after resection or thermal ablation demonstrated no benefit(76). Current attention is largely focused on immunotherapy. Treatment of advanced HCC with anti-PD-1 or PD-L1 antibodies has consistently yielded responses in the range of 15-20%((38,39,41) that are often quite durable. In non-small cell lung cancer similar response rates are seen in advanced disease, and a neoadjuvant trial for resectable tumors resulted in a roughly doubled response rate(77).

Phase 3 trials are currently underway with single-agent immunotherapy or combination therapies. In advanced disease combination therapy, an anti-PD-1/PD-L1 plus either a tyrosine kinase inhibitor (e.g. sorafenib, lenvatinib), an anti-VEGF antibody (e.g. bevacizumab), or a second checkpoint inhibitor (e.g., anti-CTLA-4 antibody) appears to significantly raise response rates, and if established in the advanced setting combination therapy will no doubt be studied in adjuvant/neoadjuvant trials. The ultimate hope is that effective adjuvant/neoadjuvant therapy will be able to substantially improve recurrence-free survival. It is the consensus of the panel that entry criteria for adjuvant/neoadjuvant studies in HCC resection should conform to the criteria for resectability currently espoused in AASLD guidelines(4,69), and prevent a broadening of the tumor eligibility for resection (e.g., multiple tumors, presence of vascular invasion) observed in some currently-running adjuvant trials. While all patients undergoing resection for HCC have significant risk of recurrence, studies should stratify for known risk factors including tumor size (>3cm), microvascular invasion, differentiation degree and serum AFP>400 ng/mL. Neoadjuvant

studies provide a unique opportunity to better understand what factors are associated with response to immunotherapy or lack thereof. Pretreatment biopsy should be mandatory, and thorough characterization of the tumor immune microenvironment should be built into these trials.

Liver transplantation is the treatment of choice for HCC within Milan criteria in patients who are not candidates for resection (78) **(Fig.1, Table 4).** These criteria lead to median OS of 10 years and recurrence rate of < 20%. In the US it has been accepted that patients with more extensive disease (one nodule between 5-8cm, 2-3 nodules ≤ 5cm or 4-5 nodules < 3cm with sum of diameters < 8cm) down-staged to Milan criteria are acceptable for transplantation (79)**.** Downstaging is not accepted by European guidelines, although performed in some countries such as Italy. A significant number of patients who enter the waiting list or a down-staging protocol drop out and do not ultimately undergo transplantation. Locoregional therapy using thermal ablation or transarterial chemoembolization have been the modalities traditionally applied to maintain HCC within Milan criteria while awaiting transplant or to down-stage patients to eligibility. With the advent of effective systemic therapies, their role in the pretransplant setting vis-à-vis locoregional treatment warrants exploration in clinical trials. Locoregional treatment should be the control arm, compared to systemic therapy either alone or in combination with locoregional, with the primary endpoint of drop-out / transplantability. Stratification should be according to whether patients were initially within or beyond Milan criteria, or down-staged to Milan, and base-line AFP levels >400ng/ml.

Treatment of HCC recurrence following transplantation is largely unstudied. The rate of recurrence in properly selected patients is low (10-20%) and these patients have been routinely excluded from studies of systemic therapies. Tyrosine kinase inhibitors have been shown to be safe and are commonly used in an uncontrolled manner(80). There is considerable reluctance to use immunotherapy with anti-PD-1/L1 antibodies due to reports of treatment-related organ rejection, though there are reports of successful treatment(81). As HCC now accounts for nearly 25% of liver transplants in the US, it is time for trials to be implemented studying treatment of post-transplant HCC recurrence.

Local ablation is the mainstay treatment for nonsurgical candidates with early stage HCC (3,4) **(Fig 1, Table 4)**. Tumor size (up to 4-5 cm), number (up to 3 tumors) and location (accessiblility with ultrasound, CT or MRI guidance) limit the applicability of percutaneous ablation. Several randomized studies have demonstrated a significant benefit of radiofrequency ablation (RFA) over percutaneous ethanol injection in terms of complete response rate, and time to recurrence(82,83). Consequently, RFA is the standard ablative therapy at early stages **(Table 1)**. Median OS with RFA is of 60 months, with a recurrence rate ranging from 50-70% (3,4,82,83). AASLD and EASL guidelines have adopted radiofrequency ablation as front line therapy for single tumors <2cm, but in tumors beyond this threshold resection remains as first treatment option(3,4). Randomized phase III trials are scarce in this arena, and are mostly currently focused on adjuvant therapies to prevent recurrence than in challenging the abaltive treatment. Microwave ablation has largely supplanted RFA in the United States(84), whereas ethanol injection is restricted to HCC < 2cm in difficult locations. Cryoablation and irreversible electroporation are still under investigation(3,4,85). Clinical benefit associated with the use of thermally-sensitive carriers loaded with liposomal doxorubicin in conjunction with radiofrequency ablation is currently tested in phase III.

Overall, the main criteria for trial design in the neo-adjuvant/adjuvant after resection/local ablation or liver transplantation setting are as follows (**Table 1**):

1. Target populations for neoadjuvant and adjuvant trials: For resection, trials should include patients meeting current AASLD guidelines, and should not include patients with more advanced HCC, e.g. macrovascular invasion. For transplantation, trials should include patients meeting criteria for listing (i.e., Milan criteria), or meeting established criteria for entry into downstaging protocols. For local ablation the target population should follow AASLD guidelines.

2. Endpoints: The appropriate end-point for adjuvant trials in the setting of either resection or transplant is recurrence-free or time to recurrence. For neo-adjuvant trials, pathological response or 1-yr recurrence can also be considered. For treatments challenging loco-regional therapies, OS remains the primary endpoint, but PFS is also recommended as co-primary end point. Secondary endpoints should at least include objective response rates.

3. Stratification prior to randomization: Appropriate stratification parameters for neoadjuvant/adjuvant studies in the setting of early-stage HCC should include geographical region, tumor size and number, AFP >400ng/mL, type of curative treatment, and pathological features of high risk (size >3cm, microvascular invasion, differentiation degree and tumor satellites).

4. Control arms: For neoadjuvant/adjuvant studies in the setting of resection, a placebo control arm is appropriate. Adjuvant studies in transplantation should also include placebo controls. Defining the control arm for neoadjuvant studies in transplantation remains problematic as there is no evidence-based standard, but there is a general acceptance of the need to include loco-regional therapies to limit tumor progression in patients awaiting transplant that precludes including placebo or untreated patients. Control arms for devices or drugs challenging local ablation should be radiofrequency. Of note, since RFA has been considered effective in nodules up to 4cm, trials exploring treatments for single nodules beyond this size should consider chemoembolization as the best standard control.

5. Unmet needs: HCC recurrence rates after resection or local ablation are unacceptably high. Key needs include biomarkers to improve case selection, and effective neoadjuvant/adjuvant therapies. With regard to transplantation for HCC key needs include definition of optimal neoadjuvant (waiting list) strategies, and identification of useful biomarkers to refine candidate selection beyond algorithms based on tumor size and number.

Trial design and endpoints in intermediate stage HCC

TACE was established as the standard of care for intermediate stage HCC in 2002 following the publication of two small, randomized controlled trials for which OS was the primary endpoint (**Table 4**). The first trial, conducted in Barcelona, demonstrated a hazard ratio of 0.47 [95% CI 0·25–0·91], p=0·025) in favor of TACE, and a 2 year survival of 63% compared with 23% for supportive care(86). In the second, TACE was associated with an improvement in 2 year survival from 11% with supportive care to 31% with TACE, and a reduction in relative risk of death; 0.49 (95% CI, 0.29-0.81; P = 0.006)(87). Response using WHO criteria, was evaluated as a secondary endpoint and was shown to be associated with a better survival(86). On the basis of these trials and a subsequent meta-analysis(88), the BCLC algorithm recommends TACE for those with intermediate stage disease HCC defined by liver confined, multinodular disease, in those patients with a performance status of 0, Child Pugh A or B cirrhosis and in the absence of portal vein invasion(3,5) **(Fig 1)**. Chemoembolization was subsequently adopted by AASLD and EASL guidelines of management of HCC, and no other therapy has so far replaced this standard of care. However, since 2003(86,88) there have been further innovations, guidelines and therapeutic advances which need to be considered in the design of current and future trials. Finally, radioembolization with Y90 for intermediate HCC has produced positive efficacy

signals coming from phase 2 investigations(89), but they have not been adopted by guidelines awaiting phase 3 positive data for this specific population.

Eligibility criteria and stratification factors.

It is increasingly recognized that the BCLC B stage is heterogeneous and this likely accounts for the wide spectrum of reported survival outcomes, which range from 12-48 months. Consequently, there have been several proposals to subdivide the BCLC group but to date, none have been widely adopted(90,91). Additionally, patients who have a performance status of 1 but otherwise conform to the BCLC criteria, are routinely treated with TACE, and many clinicians regard Child-Pugh B disease as a relative contraindication. Applicability of TACE in BCLC-B is 50%, with the excluded patients having relative contraindications for the procedure due to advanced liver dysfunction or technical issues(92). Recent large RCTs have included patients with PS 0-1, Child-Pugh A, and absence of portal vein thrombosis (**Table 1,2**)(93–96). Stratification factors have been less consistent with the exception of AFP for which a threshold of 400ng/ml has been commonly applied. Composite and fully objective prognostic systems may provide a more feasible and consistent method by which to stratify patients. The ALBI score allocates a grade based on bilirubin and albumin and provides a more objective measure of liver function as compared with Child-Pugh class(97). A direct comparison between ALBI and Child Pugh has shown that the ALBI grade 1 is 92% Child-Pugh A5, ALBI 2 spans a wide range from A5 to B9 and ALBI 3 is B7 and above(98). However, tumor characteristics such as size and AFP are also prognostic and this has been addressed by the HAP score which provides a four class prognostic system using bilirubin, albumin, tumour size and AFP as categorical variables(99). The HAP score has been validated in the TACE-treated population, most recently within a cohort of 3000 patients(100). Applying the HAP score resulted in four distinct groups with survival ranging from 33 months for HAP A to 12 months for HAP D. HAP appears to be a simple and robust stratification factor that might be incorporated into TACE trials

TACE procedure

The TACE technique provides another source of heterogeneity and potential bias(101). There remains no consensus regarding the optimal embolic particle, the role of lipiodol or the type of chemotherapy used. Indeed, there are no trials demonstrating the superiority of TACE over bland particle embolization (TAE) and a meta-analysis of five trials including 582 patients showed no difference in survival(102). It is unlikely that further technical innovation to the TACE procedure will result in significantly improved outcomes and the future generation of TACE trials will continue to evaluate the combination of TACE and systemic therapy or to compare TACE with systemic therapy. In both cases, TACE will be the control arm and it is important that this is standardized. To achieve this, some of the recent randomized trials have mandated use of drug-eluting beads (DEB TACE)(93,94). Trials comparing DEB TACE with conventional TACE (cTACE) have failed to show a survival benefit but systemic toxicity from chemotherapy is reduced with DEB TACE(103) (104). If technique is not standardized, stratification according to center is an alternative way to reduce bias. Another area of contention is the schedule of TACE administration. In clinical practice, TACE is usually performed on demand according to radiological response rather than according to a fixed interval, and it is reasonable to recapitulate this in clinical trials. However, an effective systemic therapy may reduce the requirement for TACE. In the TACE-2 trial, there were 18% fewer TACE procedures performed in 12 months in the sorafenib arm compared with the placebo arm(93), and in the Oriental trial, the median number of procedures was 3.2 versus 3.7 in the orantinib and placebo arm respectively(96). Recording the number of procedures over the first 12 months or the mean number of procedures should be considered as a secondary endpoint for randomized trials of TACE

versus TACE plus systemic therapy. In this sense, the reduction in frequency and number of TACE procedures may have implications for health economics and preservation of liver function.

Response assessment

Radiological response is an important indicator of therapeutic activity and can be a surrogate marker of long-term outcomes. Response assessment has been addressed in the next section, but few concepts regarding loco-regional therapies are summarized here. In TACE-related population, mRECIST demonstrated a higher response rate compared with RECIST 1.1(105). Moreover, there was a significant association between survival and overall response according to mRECIST but not with RECIST 1.1. The association between mRECIST response and survival has subsequently been confirmed in multiple other studies and a recent meta-analysis of seven studies including 1357 patients reported a hazard ratio for survival of 0.39 (95% CI; 0.26,0.61) for those with mRECIST response(106). Unfortunately, not all the recently reported phase 3 studies reported response and only TACE-2 ascertained response by both RECIST 1.1 and mRECIST. Best response by RECIST 1.1 was higher than first response but still less than response by mRECIST. Guidelines recommend capturing response as per mRECIST in clinical practice and both RECIST 1.1 and mRECIST as secondary endpoints trials targeting intermediate stage tumors(3).

Primary endpoints

In recent trials, OS for intermediate stage patients receiving TACE was of 21-33 months(93–96) **(Table 2)**. Over the past 10 years, there have been major advances in systemic therapy and many patients now transition from TACE to first and increasingly second line systemic therapy. In TACE-2, patients were unblinded on progression and 36% of those on placebo subsequently received sorafenib(93). Similarly, in the BRISK TA trial, 21% of placebo treated patients had post-progression systemic therapy (95) trial, and in the ORIENTAL trial, 66% of patients in the placebo arm received post-study therapy (96). Use of post-progression therapy may confound OS as an endpoint and increases the duration of follow-up required to meet the survival endpoint. To address this, a variety of surrogate endpoints have been proposed including progression free survival (PFS), time to progression (TTP), time to disease progression (TTDP), time to extrahepatic spread and vascular invasion (TTES/VI) and time to unTACEable progression (TTUP). Recent trials reporting these potential surrogates in addition to survival has allowed evaluation of their performance. The BRISK TA trial reported a promising hazard ratio of 0.61 for TTP but the trial missed its primary endpoint for survival (HR 0.9)(95). Overall, the correlation coefficient of TTP and OS is 0.77. A major limitation of TTP is that it fails to capture death, which is an important indication of toxicity as well as lack of efficacy. By contrast, PFS, which is the most commonly applied surrogate endpoint used in oncology, captures disease progression and death, and has been reported to correlate with OS in the TACE 2 trial. Novel composite endpoints have also been explored. Time to appearance of extrahepatic spread or vascular invasion (TTES/VI or MVI/EHS) showed a promising HRs of 0.64 and 0.62 in the BRISKT TA and SPACE trial that did not correlate with OS benefit(94,95). Particularly, TTUP (time to untreatable progression), a composite end point defined as failure of response after to treatments, or emerging contraindications for TACE was tested in the SPACE trial, but failed to identified benefits for the combo of TACE plus sorafenib vs TACE (HR: 1.586). Recently, other novel endpoints were incorporated into the TACTICS trial comparing TACE plus sorafenib vs TACE alone(107) (108). In this study, PFS and OS were co-primary end points but progression was defined as unTACEable progression and Response Evaluation Criteria in Cancer of the Liver (RECICL)(109) was used to define progression rather than RECSIT 1.1 or mRECIST. Applying these criteria, PFS was superior in the combination arm

(HR=0.59; 95% CI, 0.41 to 0.87; p=0.006) but further follow-up is required to establish wether this translates into a survival benefit. In the meantime, for RCT testing devices alone or in combination with systemic therapies it is recommended that PFS should be the co-primary endpoint along with OS, while ORR should be included as a secondary endpoint **(Table 1 & 2)**. Additional composite endpoints can be included as exploratory endpoints until they are properly validated.

A challenging question for the future is how TACE compares to systemic therapy. TACE was developed at a time when systemic therapy was virtually non-existent. With the advent of first, second and even third line systemic therapies and achieved OS beyond 2 years in selected patients receiving two lines of therapy(23), systemic therapy can be discussed not only following TACE but as an alternative to TACE. This is particularly relevant as transarterial therapies impair liver function and may render many patients no longer eligible for systemic therapy. For patients with limited tumor burden and nodules accessible super-selectively by TACE, locoregional TACE may still be the best approach. In contrast, patients exceeding the up-to-seven criteria may be better suited for clinical trials exploring upfront systemic therapy(110). To answer this question a head-to-head comparison of TACE vs. systemic therapy (or vs. TACE plus systemic therapy) in defined patient subgroups will be needed, making the endpoint discussion even more complex.

Radiologic assessment of response

The RECIST criteria are the standard imaging approach for assessing tumor response in oncology. The original RECIST panel acknowledged that amendments could be needed for tumors with unique complexities and for evaluating non-cytotoxic drugs(111). Both issues are highly relevant for HCC: (a) the association of HCC with an underlying chronic liver disease complicates image assessment, since pathologic and hemodynamic changes in cirrhosis and extrahepatic manifestations of chronic liver disease may mimic tumor progression; (b) nonsurgical treatments for HCC, including loco-regional and systemic therapies, achieve improvements in survival without inducing sizeable tumor shrinkage, frustrating attempts to capture tumor response using standard RECIST metrics(12).

In 2010, modified RECIST (mRECIST) criteria for HCC were proposed(21) addressing confounding factors related to cirrhosis using specific amendments for the assessment of lymph nodes, ascites, portal vein thrombosis, and newly detected hepatic nodules (**Table 5**). These recommendations were made primarily to prevent “overcalls” of progressive disease. In addition, the absence of substantial tumor shrinkage was addressed by introducing the concept of “viable tumor” in the measurement of intrahepatic HCC lesions, enabling the classification of treatment induced intratumoral necrosis in the absence of significant changes in overall tumor diameter as objective responses (21).

During the past decade, mRECIST for HCC has been used extensively in HCC clinical research and its performance has been reviewed elsewhere(27).The proposed mRECIST refinements for assessment of lymph nodes, ascites, portal vein thrombosis, and newly detected hepatic nodules, were progressively incorporated into radiology charters of HCC clinical trials, even when the criteria were named RECIST or RECIST 1.1(112). This process homogenized radiologic interpretation of these findings, improving consistency and reliability in assessment of tumor progression. Consequently, recent studies reported similar results for standard RECIST 1.1 and mRECIST in assessment of progression-driven endpoints, such as PFS and TTP(7,8). Currently, the main difference between standard RECIST and mRECIST is the approach to measurement of intrahepatic lesions, which primarily affects the ability to capture an objective response (OR). Use of the mRECIST viable tumor concept results in identification of 2-3 times more responders than standard

RECIST, not only in patients receiving loco-regional treatments but also those receiving systemic therapies(7,32).

With the advent of immune checkpoint inhibitors, changes to the RECIST model have been proposed(35,36,113–115). Response to immunotherapy can manifest after imaging features that meet current RECIST criteria for progression. Pseudo-progression has been defined as increase in tumor size of existing lesions or the appearance of new lesions, followed by a response(35). Differentiating pseudo-progression from true progression is a challenging but important: while early discontinuation of an effective drug is not desirable, continued long-term treatment with a non-effective drug past true progression might delay the initiation of potentially effective therapies. Pseudo-progression has been described as a marginal event in phase III investigations with anti PDL1/PD1 check point inhibitors in HCC. The incidence of this phenomenon with anti- CTLA-4 and other inhibitors is unknown.

Limited information is available on use of immune-related criteria in HCC. In a phase II study of 104 patients who received pembrolizumab in second line after sorafenib, the use of immune-related RECIST (irRECIST) did not affect response rate or time to response as compared to mRECIST; however median PFS was 7.0 months (95% CI, 4.9-8.0) when assessed by irRECIST vs 3.2 months (95% CI, 2.2-4.1) when assessed by mRECIST(116). In phase IIb study(117) investigating a vaccinia virus-based oncolytic immunotherapy - pexastimogene devacirepvec- in advanced HCC changes to mRECIST were implemented because the treatment induces a flare with swelling and edema(118). These changes included the confirmation of progression at 4 weeks, either by further increase in size or additional signs of progression such as emergence of new lesions(117). Overall, to assess response to checkpoint inhibitors or immunotherapies in HCC, evaluation by CT/MRI at 8-12 weeks after treatment can be recommended, as opposed to the usual interval of 6-8 weeks for tyrosine kinase inhibitors. This window was used in phase II studies testing nivolumab (12 weeks)(38) and pembrolizumab (9 weeks)(116), where the phenomenon of pseudo-progression was reported as a marginal event.

Design and endpoints for systemic therapies in HCC

Standard of care with systemic therapies in HCC

Current estimates suggest that around 50% of HCC patients will receive effective systemic therapies during their lifespan(3,119,120). Several trials have tried to show survival benefits of systemic agents in advanced disease **(Table 2,4)**, a traditionally challenging setting due to the limited efficacy and high toxicity of conventional systemic chemotherapy(121–124). Randomized studies for anti-estrogen therapies also failed to prove any clinical efficacy (125). In 2008, the landmark SHARP trial assessing the multi-tyrosine kinase inhibitor sorafenib was the first to significantly improve survival with manageable adverse events(11). Afterwards, five treatments have succeeded, while several other drugs failed (126,127),(22),(128)(129)(122)(130)(131)(132)(133)-. In first line, atezolizumab (anti-PD-L1 inhibitor) plus bevacizumab (VEGFA inhibitor) have shown to be superior to sorafenib in a recently reported RCT(134). The study was stopped at the first interim analysis by showing a HR of 0.58 for OS (median not reached for combo vs 13.2 mo for sorafenib) and HR of 0.59 for PFS (median 6.8 mo for combo vs 4.3 for sorafenib). These results will pose this combination as standard of care first-line therapy for advanced HCC. Second, lenvatinib (multikinase inhibitor: VEGFRs, FGFRs, RET, KIT and PDGFRA) has become an option equal to sorafenib, after the positive result of the non-inferiority REFLECT study (HR of 0.92; 95% CI 0.79-1.06) (**Table 2, Fig 2A**). Because this trial excludes patients with main portal vein invasion, tumor involvement >50% of the liver and clear bile duct invasion, the relative benefit of lenvatinib vs sorafenib in these patients remain uncertain.

In second line, the phase III trial testing regorafenib (VEGFRs, PDGFRs, KIT and Tie2) improved OS compared to placebo from 7.8 to 10.6 months (HR of 0.63) in patients who progressed and were tolerant to sorafenib(8). The sequential treatment sorafenib-regorafenib led to a median OS of 26 months compared to 19 months for sorafenib-placebo (23). These results need to be taken with caution since they will not apply to all patients receiving sorafenib, but only those able to receive the sequential treatment. The CELESTIAL study, showed median OS of 10.2 months with cabozantinib (VEGFRs, MET and AXL) vs. 8 months with placebo (HR of 0.76)(9); and the REACH-2 study, where ramucirumab (VEGFR2 monoclonal antibody) provided a median OS of 8.5 months in patients with AFP ≥ 400 ng/ml vs. 7.3 months with placebo (HR of 0.71)(10,135). AFP is well-known for its independent prognostic capacity in HCC(136). As such, REACH-2 was the first and only positive phase III trial in a biomarker-driven population of patients with HCC (**Fig 2B**). In contrast, 3 phase III trials testing internal radiation with Y-90 for advanced HCC, either as single treatment [SARAH(137) and SIRveNIB(138)] or in combination Y-90 with sorafenib(139) did not meet the primary endpoint of improved OS compared to sorafenib (**Fig. 2A**). As a result, Y-90 was discouraged for the management of advanced HCC in the EASL guidelines (**Fig. 1**)(3). Despite appealing ORR of 15% with durable response for nivolumab and 18% for pembrolizumab, phase III trials comparing the former with sorafenib(24) in front-line and the latter with placebo in second-line resulted negative. Particularly, the latter trial showed a HR of 0.78 with upper boundary of 95CI below 1, but the pre-specified p value (p<0.0178) was not hit(41).

Trial design in advanced HCC

Overall survival remains as the primary end-point for advanced HCC research(1,3) **(Table 4)**. It has driven clinical research in HCC for more than 40 years and has been the gold-standard for measuring benefits at all stages of the disease. Nonetheless, the emergence of several effective drugs in advanced HCC has exposed the need for alternative end-points that can capture the benefits of a treatment before they can be diluted by post-progression therapy(3). Progression-free survival (PFS), time to progression (TTP) and objective response rate (ORR) are now emerging as tools to a) identify early strong signals of efficacy that led to accelerated regulatory approval (particularly ORR and PFS)(6,88) and b) test interventions which benefit can be assessed prior additional sequential drugs received beyond progression might mask the actual benefit of the tested drug. In this sense, a recent investigation analyzing 21 reported phase III studies(7–11,121–123,126–131,133,135,137,138,140) in advanced HCC proposed PFS (with a restrictive hazard ratio criteria <= 0.6) as a surrogate end-point for survival when testing kinase inhibitors or monoclonal antibodies, and thus as potential primary end-point in advanced HCC trials(3) **(Table 4)**. Subsequently, six phase III studies have been released that confirm the hypothesis: two positive studies, one testing atezolizumab plus bevacizumab vs sorafenib(134) and the second sorafenib plus hepatic arterial infusion of Folfox vs sorafenib(141), both show HR for PFS ≤0.6 and significant survival benefits, and four negative trials for survival testing nivolumab(24), sorafenib plus pravastatin(142), sorafenib plus doxorubicin(143) and pembrolizumab(41), in which the HR for PFS in all cases was >0.6 (**Fig 3**). Considering the special circumstances of the 2 negative trials testing anti-PD1 inhibitors, we should be cautious when applying this rule for testing immune therapies as single agents or for combinations of immune regimes.

Trial design in HCC has been evolving, and new challenges emerge as novel therapies become standard of care. Although there might be distinct approaches to trial design in HCC, there has been a consensus on the basic principles that have been recently reported in guidelines and critical appraisals (3,139,144,145). The key points are summarized below (**Table 1**):

1. *Phase II and Phase III trials*: The panel recommends assessing drugs in the setting of randomized phase II studies before moving to phase III trials. Nonetheless, for some therapies, a large single arm phase II with a strong signal of efficacy might suffice to justify a phase III study. Thresholds for defining signals of efficacy are not clearly established, but for molecular therapies the ORR should likely be above 20-30%(146).

2. *Selection of the target population*: Clinical trials should consider BCLC staging system, Child-Pugh class and ECOG performance status for selection of the target population. In principle, for advanced HCC almost all RCT include patients with well-preserved liver function (Child-Pugh A) and good performance status (ECOG 0 and 1).

3. *Control arm:* The control arm of randomized phase II and III studies should be the standard of care established according to guidelines. Although sorafenib and lenvatinib in front-line (7,11) and regorafenib (8), cabozantinib(9) and ramucirumab (in patients with AFP ≥ 400 ng/ml)(10) are accepted as standard of care, this will change when atezolizumab plus bevacizumab are approved by regulatory agencies. At that time, this combination will become the standard of care for comparison in front-line, and subsequence lines of therapy will move downwards. Double-blind trials (as opposed to open label trials) are recommended to prevent selection and allocation biases.

4. *Stratification for prognostic factors prior to randomization*: Stratification is critical in randomized studies to warrant balanced comparisons. For advanced HCC the recommendation is as follows: region, macrovascular invasion, extrahepatic spread, AFP > 400 ng/ml and ECOG 0 vs 1-2. Etiology should also be considered as studies with sorafenib and atezolizumab and bevacizumab suggest an influence of this factor in response.

5. *End points: Overall survival*: For systemic therapies the primary endpoint should be OS, and PFS is proposed as co-primary endpoint. To date, all regular FDA and EMA drug conventional approvals in advanced HCC were based upon improvements in OS. *Surrogate endpoints:* OS has limitations as a sole endpoint in cancer research: it might require a long follow-up to capture adequate numbers and can be affected by sequential therapies. Thus, surrogate endpoints that are more practical for trial execution are needed. There are no optimal surrogate endpoints able to recapitulate OS in HCC, and thus clinical practice guidelines do not recommend ORR, TTP and PFS as primary endpoints in phase III investigations(144,145). ORR is an independent predictor of OS in three phase II and III trials(7,123,127), but is still considered a suboptimal primary end-point for phase III investigations. Nonetheless, ORR of 16-18% resulted in accelerated FDA approval of nivolumab and pembrolizumab in second line treatment of advanced HCC(38,39). PFS was formerly discarded as a primary end-point of phase III investigations due to the concept of competing risk of survival (competing between death due to tumor progression and due to the natural history of cirrhosis)(12). However, this competing risk drawback has been reduced by the universal selection of Child-Pugh A patients for these investigations, thus reducing the 1-yr risk of death due to decompensation to <5%. Stringent criteria for accepting PFS as primary endpoint have been proposed (HR≤0.6) and it is adopted in the current guidelines **(Table 1)**, but this point is still controversial. Regarding ORR, use of both RECIST1.1. and mRECIST are proposed for the assessment of response in HCC treated with systemic therapy, whereas changes in serum biomarker levels (*i.e.* AFP levels) are not supported(3).

6. *Magnitude of benefit:* In HCC, there is no consensus on what absolute survival benefit (or magnitude of benefit in OS according to HR) is clinically relevant. Reported thresholds of OS with HR <0.8 are sound for capturing the benefit of patients in advanced HCC trials(20). This figure needs to be taken with caution, since other variables can impact

the overall benefit of a given drug, such as quality of life, safety profile and availability of alternative therapies in distinct countries.

7. Checkpoint inhibitors and other immunotherapies have unique features and generally produce higher ORR and longer duration of response, as measured by RECIST1.1. The values of mRECIST and irRECIST in assessing checkpoint inhibitor mediated responses remain investigational.

Immune treatments: Overview of results andspecific endpoints

The initial clinical experience with checkpoint inhibitors in HCC was with a phase II study testing tremelimumab, a CTLA-4 antibody leading to objective response of 18% of patients and time to tumor progression was 6.5 months (147). Immunotherapy has drawn significant attention in HCC with the approval of nivolumab and pembrolizumab by the FDA based on promising results obtained in different phase II studies(38,39). A phase I/II open-label, non-comparative trial (CheckMate 040) assessing the efficacy of nivolumab in advanced HCC reported objective response rate (ORR) of 20% in the dose-expansion phase (n=214) and 15% in the dose-escalation phase (n=48). Duration of response (DOR) was 9.9 months and median PFS as 4.0 months in the dose-expansion cohort. Nivolumab treatment was well tolerated (38). Pembrolizumab, another PD1 specific antibody, was tested in phase II in patients with HCC progressing or intolerant to sorafenib (Keynote 224). Pembrolizumab was effective and tolerable with one complete response (CR) and 17 PR out of 104 patients. The median progression free survival was 4.9 months, and median OS was 12.9 months(39). Camrelizumab, another fully humanized anti-PD-1 antibody, was evaluated in a randomized phase 2 trial in Chinese patients with advanced HCC after failure of at least one line of therapy(148). The ORR was 13.8% and the 6-month OS was 74.7%.

Nivolumab and pembrolizumab failed in phase III trials (**Fig. 2A-B**). Pembrolizumab was tested in a randomized, double-blind phase III trial against placebo in 443 patients with HCC that progressed on or were intolerant to sorafenib (Keynote-240). The co-primary endpoints of PFS and OS failed to reach the prespecified level of statistical significance although median OS was prolonged from 10.6 to 13.9 months (HR: 0.781; 95% CI: 0.611-0.998; P = .0238)(149). Nivolumab was tested against sorafenib in a Phase 3 trial (CheckMate 459), but did not reach survival differences for superiority (24).In this RCT including around 750 patients, median OS for nivolumab was 16.4mo vs 14.7mo for the sorafenib arm (HR: 0.85; 95%CI 0.72-1.02). Objective response rate was 15% and 7%, respectively.

Anti-CTLA4 antibodies have been tested as single agent(147) or in combination with locoregional therapies(150) and are under investigation in combination with anti-PD1 drugs(151). In this regard, very recently the combination ipilimumab and nivolumab received FDA approval based on a ORR of 31% (40). Currently phase III trials are ongoing which either test the combination of two immune checkpoint inhibitors, immune checkpoint inhibitors plus TACE, immune checkpoint blockade in the adjuvant setting or immune checkpoint inhibitors plus vascular targeting agents(152). While the overall response to immune checkpoint inhibition (15-20%) may not be as dramatic as initially hoped, complete responses are seen in a small number of cases in almost every trial. This observation together with the recent results from two phase III trial testing anti-PD1 antibodies in the first- and second-line setting rise up the important question of what endpoint to use in future trials. While OS remains the “gold standard” it should be noted that HCC is not the only cancer where this question is being asked. Due to the unique mechanism of action of immune checkpoint inhibitors(153), new endpoints such as ORR and surrogate biomarkers have been tested and new immune related RECIST criteria devised to capture distinctive

patterns and timing of response to immunotherapy(35,115). Finally, while immunological endpoints may be helpful as surrogates(154), they cannot be recommended at this time.

A systematic review and meta-analysis of 87 phase 2 trials with the foal of defining the most appropriate primary endpoint in phase 2 trials of immune checkpoint inhibitors for advanced solid cancers has been reported. Correlations between ORR odds ratios and hazard ratios (HRs) for PFS and OS were examined for randomized comparisons. Within checkpoint-inhibitor treatment arms, correlations of ORR with 6-month PFS and 12-month OS rates were examined. All analyses were weighted by trial size. Multivariable models to predict 6-month PFS and 12-month OS rates from ORR were developed and their performance validated in an independent sample of trials. The authors demonstrated that ORR correlated poorly with OS and recommended 6-month PFS rate as an endpoint for future phase 2 studies,(155). Thus, PFS endpoint can also be recommended for studies evaluating immune checkpoint inhibitors in HCC **(Table 1)**.

Biomarker-Driven Trials in HCC: Results and Endpoints

Recent clinical trials in advanced HCC are demonstrating that the sequential use of systemic agents is changing the natural history of the disease. Still, these results are incremental and the incorporation of biomarker driven strategies have generally been unsuccessful. Unlike other solid tumors such as breast, lung, colon cancer, and others, where therapeutic decisions are driven by an understanding of a patient given molecular features, in HCC a "one-size-fits-all approach" is still the usual approach to patients. This applies to all therapies so far accepted in guidelines, except for ramucirumab.

Biomarkers provide the distinct possibility of supplementing existing anatomic and/or pathologic information to provide a more accurate assessment of prognosis (to be used for patient stratification) and/or to identify individuals who are more likely to respond to specific therapy (predictive of response) (156–158) There is a plethora of literature on the different predictive biomarker validation designs (159). The NCI defines a biomarker as *a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease*. A biomarker may be used to determine how well the body responds to a treatment for a disease or condition (160).

In HCC, numerous studies have defined the molecular heterogeneity of the disease and specific genetic alterations and subtypes. These data are fertile ground for testing biomarker hypotheses as both prognostic and/ or predictive markers in prospective studies but so far these data have largely been ignored in clinical development in HCC (6). To date, two phase 3 studies have tested biomarker driven approaches. Firstly, tivantinib, a small molecule inhibitor of the hepatocyte growth factor/ c-MET was evaluated in patients that had progressed on sorafenib and had elevated expression of c-MET in their tissue. This was a placebo-controlled study that yielded negative results(131). The possible reasons for failure highlight the challenges with this approach including: 1) validity of the target, 2) robustness of the assay for patient selection, and 3) ability of the agent to inhibit the target successfully in tumor tissue. The latter may be a plausible reason for failure of the trial, considering that the anti-MET activity of this drug has been challenged in experimental studies(161). Conversely, ramucirumab, which initially failed in an "all comers" study(162), demonstrated an improvement in OS for selected patients with AFP$\geq$ 400 ng/ ml. Proof-of-concept studies testing small molecule inhibitors of FGFR-4 using biomarker enriched populations based on FGF-19 expression have been reported with ORR of 16% (163).

Recently, immunotherapy approaches have garnered high interest in the management of HCC and the PD-1 directed antibodies nivolumab and pembrolizumab received accelerated approval by the US FDA(38,39). However, unlike in other cancers, PD-1 and / or PD-L1

expression has not correlated with outcome. This has likely contributed to the recent negative results from phase 3 studies with these agents(149). Ongoing work is focused on further refining biomarker development evaluating other inflammatory markers including incorporation of more broad based assessment tools such as an immune-enriched signature identified through molecular profiling of HCC (164).

Several studies have incorporated biomarker assessments into the trial design. While tissue collection is often optional and therefore limited, serum assays have served to generate hypotheses for further study. In the pivotal SHARP study, baseline levels of angiopoietin 2 and VEGF were prognostic but not predictive of benefit from sorafenib(136). Relevant biomarkers in the FGF and VEGF pathways were analyzed in the REFLECT study and identified differences in the modulation of these pathways by lenvatinib and sorafenib, but no biomarker could define a group receiving differential benefit from either compound(165). In the REACH-2 study, decreases in AFP correlated with better outcome from ramucirumab(10). Novel study designs evaluating biomarker assessments pre-and post-treatment are being performed. These so-called “pre-surgical” studies are designed to acquire tissue at baseline, from patients with resectable tumors, expose the patient to a novel agent for a short period, and then collect tissue at the time of resection. Molecular studies comparing the pre-and post-treatment tissue provide an opportunity to understand the effects of novel therapeutics on relevant pathways in the tumor. These studies can provide critical information that could guide a patient selection strategy in conventional efficacy studies. One such study with nivolumab is producing interesting insights into tumor characteristics that may correlate to response to this drug(166).

Despite the recent successes in clinical trials of new agents for HCC, the improvements in survival are modest. Throughout cancer medicine, the largest impacts in outcomes have been by biomarker driven drug development. Examples include ALK(167) and EGFR(168) testing in lung cancer, HER-2(169) and estrogen receptor(170) testing in breast cancer, c-KIT testing in gastrointestinal tumors(171), and BCR-ABL testing in chronic myelogenous leukemia(172). By enriching for the population most likely to benefit, studies can be conducted with smaller numbers of patients and minimize risk for failure. While historically predictive marker testing is done on tumor tissue obtained by biopsy, newer technologies are now allowing biomarker detection in peripheral blood. The practice of not obtaining biopsies for diagnosis of HCC, the fact that most common driver mutations in HCC are non-actionable and the observation that only 25% of HCCs harbor at least one actionable mutation(172), in contrast to the majority of solid tumors(173), have hindered development of biomarker driven precision treatment to date. Nonetheless, there is now renewed interest in incorporating tissue acquisition into clinical trials, not only in the early part of drug development, but in later studies as well. Clinical trial designs for predictive marker validation are inherently complex and require data from a randomized controlled clinical trial (RCT)(153). There is a plethora of literature on the different predictive biomarker validation designs, including articles that specifically focus on the statistical and clinical properties and assumptions of these different trial designs (156).

Trial design in the precision medicine era require a platform for biomarker profiling (173)(174). The ultimate clinical utility of a biomarker will depend on: 1) its added value in every patient in the context of the markers prevalence, 2) its incremental benefit for treatment selection when considering the added costs and complexity induced by the use of the marker, and 3) the added effectiveness of the new treatment option in all patients versus biomarker-defined subgroups.

Liquid biopsy in early HCC detection, prediction of response and tumor relapse

Liquid biopsy entails the analysis of tumor components released by cancer cells to biological fluids such as blood, saliva or cerebrospinal fluid(175). The concept includes the analysis of actual cancer cells (i.e., circulating tumor cells [CTCs]), fragments of DNA from necrotic or apoptotic cancer cells (i.e., circulating tumor DNA [ctDNA]) and extracellular vesicles(176). Compared to conventional tissue biopsies, the main advantages of liquid biopsy using samples from peripheral blood are: 1) it is minimally invasive, which eliminates the complications associated with invasive tissue biopsies; 2) it facilitates sequential sampling, which is crucial to better select therapies in patients receiving multiple lines of treatment; 3) it enables tracking tumor clonal composition in heterogeneous tumors, a feature that allows earlier detection mechanisms of treatment resistance; and 4) it can be implemented as a point-of-care diagnostic. Potential clinical applications include cancer surveillance, early detection of minimal residual disease after curative therapies, prognostic prediction and molecular monitoring of therapeutic response(177). In an early sign of impact on patient care, the FDA recently approved the use of a ctDNA-based test to detect mutations of EGFR in lung cancer patients who are candidates to receive EGFR-based tyrosine kinase inhibitors(178).

In HCC, liquid biopsy has been evaluated for three clinical applications: early HCC detection in the context of surveillance, as a prognostic biomarker after surgical resection and to predict response to systemic therapies. Mutation profiling of ctDNA is feasible and confidently detects tissue mutations in early stage HCC(179). A recent report combining data from ctDNA and protein markers had a sensitivity and specificity of 85% and 93% respectively for the detection of HCC(180). Also, analysis of DNA methylation alterations in ctDNA has high accuracy for HCC diagnosis(55,181). A study that included a gene signature derived from CTCs was able to accurately discriminate between HCC patients and controls(182). Higher CTC count correlates with a greater risk of tumor recurrence after surgical resection(175). There are few studies using liquid biopsy to predict response to systemic therapies in HCC. A retrospective study suggested that HCC patients with ctDNA detectable *VEGFA* DNA amplifications have better outcomes when treated with sorafenib(183). Also, RAS mutations analysis of ctDNA was used to determine eligibility to receive refametinib in a phase 2 clinical trial(184). Thus, there is increasing interest in applying this technology to predict response to systemic therapies.

Quality of life and patient reported outcomes

Systematic capture of the patient perspective can inform the development of new cancer therapies. The U.S. FDA Office of Hematology and Oncology Products (OHOP) has identified symptomatic adverse events (AEs) as a central Patient Reported Outcome (PRO) using the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) to provide a standard yet flexible method to assess symptomatic AEs from the patient perspective(194,195). The FDA's patient focused drug development program has ongoing efforts to improve methods around the collection, analysis and interpretation of PRO data, as well as initiatives to identify patient-friendly language, and leveraging digital health tools. In 2016, the 21st Century Cures Act tasked the FDA to consider the patient-experience in the risk-benefit determination. The FDA draft guidance outlines the use of PRO to assess symptomatic side effects and the core set of clinical outcomes to measure in cancer trials, including design considerations and assessment frequency(11).

The purpose of measuring quality of life (QOL) should be to compare outcomes between treatment arms, even if one is a placebo. There are two methods of measuring QOL specific to HCC: the European Organization for Research and Treatment of Cancer Quality of Live

Questionnaire (EORTC QLQ)(185) and the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep)(186) questionnaire. Few studies have adequately assessed PRO using these tools in HCC research, a recommendation that is endorsed by the panel.

Most phase III trials for HCC were designed primarily to compare two different treatments in patients with similar stage disease. For example, one study compared QOL after resection with QOL following radiofrequency ablation(187). As expected, QOL was much better after radiofrequency ablation than after resection, and remained superior up to 36 months post-treatment. In addition, QOL following radioembolization has been compared with TACE(188). In this study, there was no overall difference in QOL between the two groups, but the sample size was small. Despite the lack of statistically significant differences, in the TACE group QOL was decreased at 2 and 4 weeks, whereas in the radioembolization group some aspects of QOL actually improved. Similarly, QOL measures favoring Y-90 vs sorafenib have been claimed to support the former treatment in three negative RCT, the SARAH trial (134) and the SIRveNIB trial (135) and SORAMIC trials. However, since indication of a drug/device should be based upon the primary endpoint (survival), no actual indication can be claimed if the result is negative for the primary end-point. Finally, the SHARP trial demonstrating survival benefit of sorafenib also tested time-to-symptomatic progression — as measured by the Functional Assessment of Cancer Therapy–Hepatobiliary Symptom Index 8 (FHSI8) — as a co-primary endpoint. The negative results of this end-point contrasted with the survival benefit obtained by sorafenib, thus challenging the accuracy of the tool used(11). More recently, patient reported outcomes have been tested in the setting of phase III investigations showing significant results in positive RCT in advanced HCC. This is the case of lenvatinib compared to sorafenib, or atezolizumab plus bevacizumab compared to sorafenib, where the tested arms showed better QoL parameters compared with the standard of care. The panel encourage the integration of these endpoints in all investigations in HCC (**Table 6**).

Implications of trial design in Asia

Differences between AASLD, EASL, and Asian guidelines

Recommendations in western guidelines (AASLD and EASL) are based upon evidence from clinical trials (**Table 4**), while Asian guidelines integrate evidence with expert consensus and clinical practice. Applicability of those guidelines varies according to region and treatment stage (47). Asian guidelines (189) in general recommend ablation or resection for very early-stage (stage 0) disease, but differ from western guidelines in the recommendations at other stages of disease. For instance, TACE or yttrium-90 (Y90-SIRT) are recommended for single large tumors, and systemic therapies -i.e Folfox(105), or hepatic arterial infusion chemotherapy - are recommended for advanced stages, along with liver transplantation – mostly living donor transplantation . Similarly, in Asia patients with portal vein invasion and well-preserved liver function might be considered for TACE, resection or radiotherapy (190–194).

Specificities of trial design in Asia

Considering all these guidelines, trial design in Asia has some specificities. For instance, resection in very high-risk patients (multinodular tumors, macrovascular invasion) is common in Asia, and thus adjuvant trials might consider this indication with a recurrence-free survival endpoint. Similarly, studies exploring the role of systemic therapies plus TACE in patients with advanced stages might also be considered in Asia with a primary end point of PFS. Weather these approaches should be tested in specific trials or as part of global trials needs further consideration.

Future prospects

The dawn of a new era: combination therapies

When the report of the first AASLD conference on Design and Endpoints of Clinical Trials in HCC was published(12), the field was still heady with excitement from the first positive trial of a systemic agent for advanced HCC, which established sorafenib as the first FDA approved systemic therapy for HCC (11). However, enthusiasm was also tempered by the subsequent negative results of trials of sorafenib as adjuvant therapy after resection or ablation (STORM)(76) or in combination with TACE (SPACE)(94). It was recognized then that a unique challenge is posed by the combination of underlying chronic liver disease with a very heterogeneous and variably aggressive primary HCC. It is therefore important that treatment strategies account for both the liver disease and malignancy, and thus variables capturing both diseases should be considered in the publication of clinical trials for HCC (**Table 7**). Discussions at the previous AASLD Endpoints conference set the framework for subsequent attempts to bring additional agents to approval, which were met with uniformly disappointing results over the next several years, with trial failures due to unacceptable toxicity or inadequate efficacy(12). While disappointing, these failures led to robust examination of the optimal approach to trial design and catalyzed a more rigorous approach that contributed to the successes in phase 3 HCC clinical trials. With the positive results and approvals of lenvatinib, regorafenib, cabozantinib and ramucirumab based on phase 3 studies, and of the checkpoint inhibitors nivolumab and pembrolizumab based on convincing phase 2 data, we appear to be poised for success in the next most logical treatment paradigms using combination therapies. Indeed, the recent positive phase III study demonstrating superior OS for atezolizumab plus bevacizumab vs sorafenib(134), represents the dawn of a new era of combination therapies in all stages of HCC research (**Fig 1**). This combination is certainly *first in-class* of this approach. Whether other combinations may become *best-in-class* will depend upon the ability of specific TKI and/or MAb to transform “cold tumors”, which are primary resistant to immunotherapy, into “hot-immune-active tumors”, allowing checkpoint inhibitors to optimally unleash immune attack against cancer cells(195–197) .

The advent of combination therapies achieving response rates of 30% and survival rates above 20 months in advanced HCC provides the rationale for testing these combinations in earlier HCC stages. Currently, phase III trials testing combination therapies are ongoing for early stages (neo-adjuvant or adjuvant approaches), intermediate HCC (in combination with TACE or in comparison to TACE) and in front-line trials for advanced HCC (**Table 7**). It is conceivable that systemic therapies may be incorporated in all areas of HCC management in the near future. Thus, the up-dated target population and endpoints described here should be valuable in this endeavor.

Understanding tumor biology remains critical: tissue and blood samples are needed

It is likely that the next key advances in HCC therapy will emanate from an improved understanding of HCC biology and the ability to predict the response of specific HCCs subgroups to particular therapies. Until now, most HCC therapy has been applied in a biologically indiscriminate fashion. The biological heterogeneity of HCC has been evident for many years, demonstrated by differences in phenotypes, tumor growth rates, numbers of tumor nodules, discrete versus infiltrative appearance, propensity for microvascular or macrovascular invasion, propensity for distant metastasis, and association with elevation of AFP, AFP-L3, DCP and other biomarkers. Apart from the limitations that multifocal, invasive or metastatic disease have placed on application of potentially curative treatments such as surgical resection, liver transplantation, and local ablation, we have only recently began to incorporate markers of tumor biology into therapeutic decision making. Applications of tumor

biologic characteristics into therapeutic approaches have been scarce in HCC and mostly focused on using AFP levels for selection policy for transplantation, as an stratification factor in most of trials and finally for selecting candidates to ramucirumab in the management of advanced HCCs in second line.

With the advent of next generation DNA, RNA and non-coding RNA sequencing and similar genome wide methodologies for copy number variation, methylation and proteomic characterization, we now stand ready to translate information from these technologies to the care of HCC patients, transforming the selection of systemic therapy and the selection of optimal candidates for loco-regional therapies. Results suggesting that *CTNNB1*-mutated HCCs are immune excluded and potentially resistant to immune checkpoint inhibitors(198–200) but potentially susceptible to mTOR inhibitors are an early indication of the potential value of genomics in personalizing HCC therapy. These studies may also provide us with tools for better understanding the recent borderline negative results of phase 3 trials with single agent immune checkpoint inhibitors. Personalization of therapy using molecular and genomic signatures will require integration of molecular subclasses into clinical staging systems, to better guide treatment selection. Optimal treatment selection will depend on the ability to target oncogenic signaling pathways that drive tumorigenesis, tumor progression and metastasis. The development of new preclinical tumor models, including organoids, patient derived xenografts, and syngeneic models that preserve aspects of the immune response will be critical for the testing of novel agents and combinations. Ideally, integration of molecular profiling into the HCC treatment paradigm will require genomic data derived in real time from patients, either by tissue biopsy or through liquid biopsy-based access to circulating tumor DNA or other analytes. This will require a cultural change in the care of HCC patients, shifting from a state in which the diagnosis and evaluation of patients is performed non-invasively, to regular use of tissue biopsy and highly sensitive liquid biopsy assays. Development of robust, reproducible predictive biomarkers of high reliability is a key priority to facilitate this transition (**Table 6**). The first implementations of the biomarker-based approaches should be within RCT, which should now routinely require tissue biopsy and liquid biopsy collection as a condition of trial enrollment. Tumor biopsy at screening for trial entry and liquid biopsy at different time points should be mandatory in clinical trials for advanced HCC to allow identification of prognostic and predictive biomarkers, guide clinical decision-making and improve patient outcomes.

Novel endpoints might be adopted

The revolution in drug development in HCC has created the need to revisit established conventions in trial design. OS is regarded as a core endpoint. Nonetheless, the realization that more than 60% of patients progressing after TACE and 50% of patients progressing after first-line systemic therapies receive effective next line therapies may compel the adoption of PFS as an acceptable primary endpoint for major trials (**Table 1)**. In this position paper, we already are recommending PFS as co-primary endpoint for intermediate HCC trials, and for phase II-III trials assessing systemic therapies, with restrictive cut-points. Similarly, patient reported outcomes (PRO) should be pursued as a relevant endpoint in HCC trials, particularly as we enter an era of potent, but seemingly toxic, dual or triple combination therapies possibly associated with serious adverse events. It is important to recognize that currently many HCC patients reach a point in their therapeutic journey when they elect to forgo potentially life extending therapy in favor of approaches that optimize their quality of life. It is therefore critical to extend decisions about HCC trial design and endpoints to incorporate elements that reflect the importance of patient well-being.

FIGURE LEGENDS

Figure 1. Modified BCLC staging system considering new effective therapies in advanced stages [modified and up-dated from EASL Guidelines(3)] Management of patients with HCC is guided by the Barcelona Clinic Liver Cancer (BCLC) staging system, which takes into account both tumor extent and the severity of the underlying liver disease, and defines five prognostic subgroups with respective treatments. Treatment for early stage tumors is with curative intent and options include radiofrequency ablation, hepatic resection, and liver transplantation. Patients with intermediate or advanced HCC are candidates for chemoembolization or systemic therapies, respectively. *Patients with end-stage liver disease if Child-Pugh class C should first be considered for liver transplantation. **Patients with preserved hepatic function Child-Pugh class A with normal bilirubin and no portal hypertension are optimal candidates for hepatic resection. ‡The combination of atezolizumab plus bevacizumab is not yet approved but is set to become the new first-line treatment for advanced HCC(134)- DDLT, deceased donor liver transplantation; ECOG, Eastern Cooperative Oncology Group; LDLT, living donor liver transplantation; M1, distant metastasis; N1, lymph node metastasis; OS, overall survival.

Figure 2. Overall survival outcomes (HR, 95% CI) of phase III clinical trials testing molecular targeted therapies, checkpoint inhibitors and radioembolization in patients with advanced-stage hepatocellular carcinoma. Blue=positive trials for superiority. Orange=positive trials for non-inferiority. Black=negative trials for the primary end-point, Red=tested drug was significantly worse than the standard of care. Vertical red line at HR=1.08 defines the upper boundary of 95% confidence interval accepted by FDA for a positive non-inferior study.

Figure 3. Correlation between progression-free survival and overall survival in 27 phase III trials of advanced HCC (modified from Llovet, J Hep 2019(20)**) .** Trial-level correlation between endpoints using criteria from the Institute for Quality and Efficiency in Health Care (IQWIG). R and R2 refers to the weighted Pearson coefficient between the HR of OS and the HR of the surrogate endpoint. Each dot represents one of the phase III clinical trials conducted on advanced HCC. Size of the dot is proportional to the total number of patients enrolled in the trial. First 21 phase III trials defined a cut-off of 0.6 for PFS to correlate with a significant OS (colored in grey)(20). Afterwards, six additional phase III trials have been reported afterwards: two positive for survival show a HR for PFS <0.6 (green color) and four negative for OS show a PFS HR> 0.6 (red color). X- and Y-axis depict the value of the HR for the surrogate and the hard endpoint, respectively. Gray shaded areas represent the upper and lower limits of the 95% confidence intervals for the regression. HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival.

TABLES

Table 1. Recommendations for Trial design and endpoints in patients with HCC by AASLD panel of experts.

Aim	Factor	Considerations and recommendations
Select the target population	BCLC stage	Include patients according to specific BCLC stage (0–C)
	Child-Pugh classification	Include patients in Child–Pugh class A. Consider ALBI grade and MELD score for refinements on Child A class
	Biomarker-based enrichment	Define rationale for using biomarker and tool
Selection of endpoints	Overall survival (OS)	Primary endpoint for phase II and III studies assessing treatments in intermediate and advanced HCC.
	Progression-free survival (PFS)	Primary endpoint for Phase II studies assessing primary treatments in intermediate and advanced HCC. Consider co-primary in phase III studies in intermediate and advanced HCC, with strict rules for calling superiority Independent centralized blinded review*
	Time to Progression (TTP)	Secondary (or co-primary) endpoint for Phase II studies assessing primary treatments in intermediate and advanced HCC. Independent centralized blinded review*

	Recurrence-free survival (RFS)	Primary endpoint in phase II/III studies assessing adjuvant treatments
	Time to recurrence (TTR)	Primary endpoint (2nd choice) in phase II/III studies assessing adjuvant treatments
	Objective response rate	Phase II co-primary endpoint, Phase III secondary end-point Surrogate endpoint for accelerated approval Independent blinded review assessing mRECIST for interventions at early/ intermediate HCC. Both RECIST 1.1 and mRECIST for interventions at advanced stages
	Patient reported outcomes (PRO)	Recommended as secondary endpoint in all phase III investigations, particularly when testing loco-regional or systemic therapies
	Composite endpoints	OS plus PFS might be considered
Select control arm	Surveillance	Ultrasound with or without AFP
	Adjuvant therapy after resection or local ablation for early stage HCC	Placebo
	Early stage-non surgical	Radiofrequency ablation. Special consideration for single large (>4cm tumoral diameter) when standard of care is TACE as per the stage migration principle.
	Intermediate stage disease	Chemoembolization**
	First line treatment for advanced stage disease	Atezolizumab plus bevacizumab will be considered when

		approved. Sorafenib or lenvatinib plus supportive care Other treatments in Asia**
	Second-line treatment for advanced stage disease	Regorafenib (only in patients tolerant to sorafenib) or cabozantinib. Ramucirumab only in patients with AFP> 400 ng/ml
	Third-line treatment for advanced stage disease	Placebo
To stratify factors before randomization	Adjuvant	A) Geographical region B) Tumor size and number C) Type of curative treatment D) Pathological factors of high risk (size >3cm, microvascular invasion, poor differentiation degree and tumor satellites)
	Intermediate-stage	Child-Pugh class, AFP >400 ng/ ml and geographical region. ALBI score might be considered. Selection of large tumoral burden as per above 7-up-to-7 has been proposed (adopting criteria for extended indications in liver transplantation), but requires validation
	First-line advanced stage	ECOG status, MVI-EHS, AFP >400 ng/ ml and geographical region, Etiology (HCV vs others when testing sorafenib)
	Second-line advanced stage	ECOG status, MVI, EHS, geographical region, AFP >400 ng/ ml. Type of progression might be considered

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HCC; hepatocellular carcinoma; EHS=extrahepatic spread; MVI=macrovascular invasion; RECIST, Response Evaluation Criteria In Solid Tumours.

*= not always recommended

**= Asian guidelines recommend additional treatments for

Intermediate HCC: Japan: HAIC; China: Resection; Taiwan: Resection/Y90

Advanced HCC: Japan : HAIC/Resection/TACE; China: FOLFOX4, resection/TACE; Korea: TACE

Table 2. Expected outcomes reported in phase III trials in HCC research.

Expected outcomes	Early	Intermediate	Advanced (1st line) ***	Advanced (2nd line)
Overall survival		TACE: 21 mo(93), 26mo (95)-33 mo(96)	Sorafenib: ~11-14(7,11,24) mo Lenvatinib: ~13 mo(7) Atezolizumab+bevacizumab *** (134)	Regorafenib: ~11 mo(8) Cabozantinib: ~10 mo(9) Ramucirumab (only AFP> 400 ng/ml): ~8 mo(10)
PFS	RFS*adjuvant resection /ablation: 33mo	TACE: 7mo (93,95)	Sorafenib: ~4(7) months Lenvatinib: ~7 months(7)	Regorafenib: ~3 mo(8) Cabozantinib: ~5 mo(9) Ramucirumab (only AFP> 400 ng/ml): ~3 mo(10)
ORR*		TACE: ~45-54% (93)	Sorafenib: ~10%(7) Lenvatinib: ~24%(7) Atezolizumab+bevacizumab : 33%; RECIST: 27%(134)	Regorafenib: ~10%(8) Cabozantinib: ~4%(9) Ramucirumab (only AFP> 400 ng/ml): ~5%(10)

*RFS: Recurrence free survival

** ORR as per mRECIST

***Atezolizumab+bevacizumab is expected to be fist line, while sorafenib and lenvatinib will be second line therapies, see **Fig 1**

Table 3. Phases of Surveillance Test Validation in Hepatocellular Carcinoma [(adopted from Pepe et al(57))]**.**

Phases	Type of Study	Design	Aims	Comments
1	Preclinical exploratory	Case-control from biobanked samples	Promising HCC biomarkers identified	Avoid multiple freeze-thaw for blood and tissue samples
2	Clinical Assay and Validation	Large case-controlled accounting for confounders	Biomarker detects clinically established early stage HCC	Appropriate sample size and power essential
3	Retrospective longitudinal	PRoBE	Biomarker detects pre-clinical HCC	Assess benefits and harms of surveillance
4	Prospective screening	Prospective cirrhosis cohort	Confirms the ability of the novel biomarker to detect early stage disease	Assess benefits and harms
5	Cancer control	Randomized study of new biomarker compared to US and AFP	Impact of screening on reducing mortality in patients with cirrhosis (or high-risk populations)	Survival primary endpoint; secondary endpoint early stage detection, assess harms

Table 4. Guidelines recommendations for treatment according to levels of evidence* and strength of recommendation.** *Treatments accepted in guidelines (EASL(3) and AASLD(4)) and level of evidence* (modified from Llovet et al(119))

Category	Treatment	Eligibility criteria or alternative approaches	Evidence level	Recommendation strength
Surgical treatment	Resection	Patient with solitary tumors and well-preserved liver function	2A	Strong
	Liver transplantation	Patients with single tumors of ≤ 5cm or ≤ 3 nodules of ≥ 3cm (Milan criteria) not suitable for resection. Down staging to Milan *.	2A	Strong; Moderate: down staging (US), not recommended in Europe
Loco-regional treatment	Local-ablation	Radiofrequency, BCLC 0-A not suitable for surgery, upper limit 4-5cm Radiofrequency ablation (and alternatively percutaneous ethanol) injection for patients with BCLC 0-A tumours that are not suitable for surgery.	2A 2B	Strong
	Chemoembolization	BCLC B (multinodular asymptomatic tumours without vascular invasion or extra-hepatic spread)	1A	Strong
Systemic treatment	Atezolizumab+ bevacizumab	Child-Pugh A Advanced HCC tumours (BCLC C) or BCLC B progressing upon loco-regional therapies	1A	Strong (not yet included in guidelines)
	Sorafenib	Child-Pugh A	1A	Strong

		Advanced HCC tumours (BCLC C) or BCLC B progressing upon loco-regional therapies		
	Lenvatinib	Child-Pugh A Advanced HCC tumours (BCLC C) or BCLC B progressing upon loco-regional therapies. No Main portal vein invasion	1A	Strong
	Regorafenib	Child-Pugh A Tolerant to sorafenib. Advanced HCC progressing on sorafenib	1A	Strong
	Ramucirumab	Child-Pugh A Advanced HCC progressing on sorafenib AFP> 400 ng/dL	1A	Strong
	Cabozantinib	Child-Pugh A Advanced HCC progressing on sorafenib	1A	Strong
Palliative care	Palliative support	Patients with BCLC D tumours should receive management of pain, nutrition and psychological support	2B	
Treatments under investigation or with further evidence required to be adopted in guidelines				
Surgical treatment	Resection	Patients with multifocal small tumors (≤ 3 nodules ≤ 3cm) or mild portal hypertension)	3A	Moderate
		Adjuvant treatments after resection/local ablation	1D	Strongly not recommended

	Liver transplantation	Up-to-seven criteria in patients without microvascular invasion	2B	Moderate
		Neo-adjuvant loco-regional therapies if the waiting list exceeds 6 months	2D	Moderate
		Living donor liver transplantation in patients with a waiting list exceeding 6-7 months	2A	Moderate
Loco-regional treatment	Other ablative therapies, such cryoablation, laser, irreversible electroporation or high-intensity focused ultrasound	Patients with BCLC 0-A tumours that are not suitable for surgery	N/A	Not recommended
	Chemoembolization	Use of drug-eluting beads, which has shown similar response rates as gelfoam-lipiodol particles associated with less systemic adverse events	1D	Moderate
	Chemoembolization combined with systemic TKis	Multiple RCT failed to show improved outcomes	1A	Not recommended
	Y90-Radioembolization-	In patients at stage BCLC B and in patients BCLC A with a single nodule larger than 4 cm as an alternative to resection	1D	No recommendation
	External 3D conformal radiotherapy (SBRT)	Single tumors at early stages (BCLC A)	3A	No recommendation

Systemic treatment	Molecular targeted therapies and immune-based therapies	- Patients BCLC A as neo-adjuvant therapies. - Patients BCLC B in combination with TACE, Child Pugh A class, ECOG 0-1	1A	No recommendation
Palliative care	Radiotherapy to alleviate pain	Patients with bone metastasis	3A	Moderate

AASLD, American Association for the Study of Liver Diseases; BCLC, Barcelona Clinic Liver Cancer Group; EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma.

*National Cancer Institute classification: **Strength of evidence:** Level #1 (RCT or meta-analysis); #2 non-randomized controlled studies; #3 case series; **Strength of end-point**: A: survival B: cancer-specific survival; C Quality of life, and D: others.**

Table modified from EASL-EORTC guidelines(5)

Table 5. Basic concepts and key points for standard RECIST 1.1 and mRECIST assessment in HCC(27)

Evaluation		RECIST 1.1	mRECIST
Baseline Assessment	Target lesions	• Identify up to 2 intrahepatic tumor lesions ≥ 1 cm, that appear suitable for accurate and repeat assessments; measure their longest viable tumor diameter. • Identify extrahepatic tumor lesions that are ≥ 1 cm in longest diameter and appear suitable for accurate and repeat assessments; measure their longest overall tumor diameter. • When selecting lymph nodes as extrahepatic target lesions, the short axis must be measured and it must be ≥ 1.5 cm. • Overall, include a maximum of 2 target lesions per organ and 5 target lesions in total.	• Identify up to 2 intrahepatic tumor lesions ≥ 1 cm, that show typical intratumoral arterial enhancement and appear suitable for accurate and repeat assessments; measure their longest viable tumor diameter. • Identify extrahepatic tumor lesions (and intrahepatic lesions with atypical enhancement in patients without typical intrahepatic lesions) that are ≥ 1 cm in longest diameter and appear suitable for accurate and repeat assessments; measure their longest overall tumor diameter. • When selecting lymph nodes as extrahepatic target lesions, the short axis must be measured: it must be ≥ 1.5 cm for all lymph nodes except for porta hepatis lymph nodes where it is required that it is ≥ 2 cm. • Overall, include a maximum of 2 target lesions per organ and 5 target lesions in total.
	Non-target lesions	• Tumor lesions or sites of disease that have not been selected as target lesions should be recorded at baseline as non-target lesions.	• Tumor lesions or sites of disease that have not been selected as target lesions should be recorded at baseline as non-target lesions. • Malignant portal vein thrombosis should be considered as a non-target lesions. • Ascites and pleural effusions should not be considered as tumor lesions, unless associated with unequivocal neoplastic peritoneal or pleural nodules.
		• Measure the longest overall tumor diameter for intrahepatic	• Measure the longest viable tumor diameter of typical intrahepatic

Post-Baseline Assessments	**Target lesions**	and non-nodal extrahepatic target lesions, and the short axis diameter for nodal target lesions.	target lesions avoiding the inclusion of any major intervening areas of necrosis. ● Pay attention in distinguishing areas of tumor necrosis from areas of reduced arterial perfusion caused by changes in local hemodynamics. A change from hypervascularity to hypovascularity does not represent tumor necrosis. Only tumors or tumor areas that show complete absence of contrast enhancement can be assumed to represent necrotic tissue. ● Measure the longest overall tumor diameter for atypical intrahepatic target lesions and non-nodal extrahepatic target lesions, and the short axis diameter for nodal target lesions
	Non-target lesions	● Qualitative assessment of response.	● Qualitative assessment of response, taking into account tumor necrosis for typical intrahepatic non-target lesions. ● Complete disappearance of enhancement inside malignant portal vein thrombus should be considered equivalent to complete regression
	New lesions	· Any new lesion that has no corresponding lesion on baseline imaging and is unequivocally malignant is considered as evidence of PD.	● By definition, a new lesion has no corresponding lesion on the baseline imaging. ● A new liver lesion ≥ 1 cm that shows nonrim-like hypervascularization in the arterial phase with nonperipheral washout in the portal venous or the delayed phase meets the criteria for unequivocal new lesion and declares PD. ● Any new liver lesion <1 cm or any new liver lesion of any size that fails to show the enhancement pattern described above should be considered as equivocal and can only be diagnosed as HCC by evidence of either a change in enhancement pattern (when ≥ 1 cm) or an interval growth ≥ 1 cm in subsequent scans. ● If an equivocal new lesion is later determined to be unequivocal, the timepoint of progression will be the

			timepoint that the lesion was first noted as equivocal. ● Ascites or pleural effusion that appear during treatment should not be assumed to represent PD, unless associated with the emergence of unequivocal neoplastic peritoneal or pleural nodules.

Overall assessment of tumor response by RECIST 1.1 or mRECIST

Target lesions	Non-target lesions	New lesions	**Overall response**
CR	CR	No	CR
CR	Non-CR-NonPD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 6. Unmet needs in trial design in HCC.

1. Clinical trials:
    - Evidence-based data from RCT to provide standard of care in
        a) Adjuvant setting after resection/local ablation
        b) Neo-adjuvant setting prior resection/liver transplantation
        c) Define role of loco-regional therapies or SBRT in large single non-surgical tumors
    - Evidence-based data from RCT to improve the standard of care in
        a) Combination or systemic therapies to improve chemoembolization in intermediate HCC
        b) Combination (or triple) therapies for 1st line advanced HCC
        c) Molecular and immune-based therapies for patients with HCC and impaired liver function (Child-Pugh B).
    - Pivotal proof-of-concept phase II trials and trial enrichment for oncogenic drivers or signaling pathways
    - Systematic inclusion of cost-benefit analyses
2. Identification and validation of biomarkers:
    - Develop biomarkers for early detection in surveillance programs
    - Identify biomarkers predicting treatment response and primary resistance (tissue or liquid biopsy)
3. Quality of life & patient reported outcomes:
    - Incorporate tools for measuring quality of life into clinical trial design as an endpoint
    - Systematic inclusion of patient reported outcomes
4. Molecular pathogenesis and drug development:
    - Integrate molecular subclasses to the clinical staging system in order to better guide treatment allocation
    - Target oncogene addiction loops that result from DNA amplifications and gene mutations or overexpression
    - Improve models for pre-clinical testing of novel drugs

Table 7. Variables to be included in clinical trials assessing treatments for HCC patients

Demographic	Age, sex, ethnicity
	Underlying liver disease (cirrhosis, chronic hepatitis)
	Etiology : define based upon HCV, HBV, alcohol, NASH-NAFLD and others.
Tumor description	Radiological characteristics: size, number of nodules, macroscopic vascular invasion, extrahepatic spread
	Alpha-fetoprotein
	Pathological characteristics in adjuvant trials: size, number, differentiation degree, satellites, micro and macroscopic vascular invasion, pTNM
Staging system	BCLC staging classification
Liver function	Bilirubin, aminotransferases, albumin, alkaline phosphatase, gamma-glutamyl transpeptidase, serum creatinine, serum sodium, prothrombin time, INR, platelet count
	Presence of ascites or encephalopathy
	Child – Pugh score
	ALBI and MELD score
General health	ECOG status, pain, constitutional syndrome

* Modified from Llovet et al, JNCI 2008(12) HCV = hepatitis C virus; HBV = hepatitis B virus; pTNM = pathological tumor–node–metastasis;

BCLC = Barcelona Clinic Liver Cancer; BUN = serum urea nitrogen; MELD: Model of End-Stage Liver Disease; ECOG = Eastern Cooperative

Oncology Group.

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Figure 1

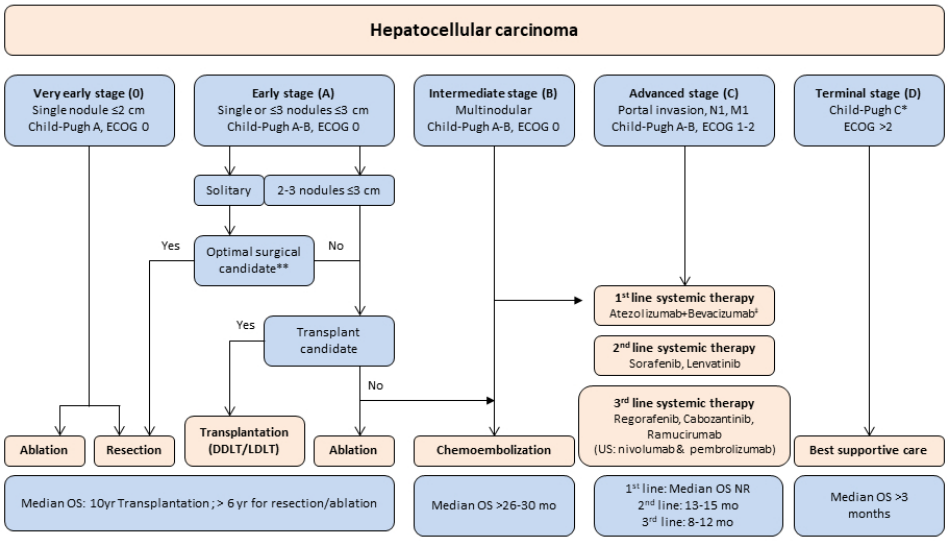

Figure 1

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Figure 2A

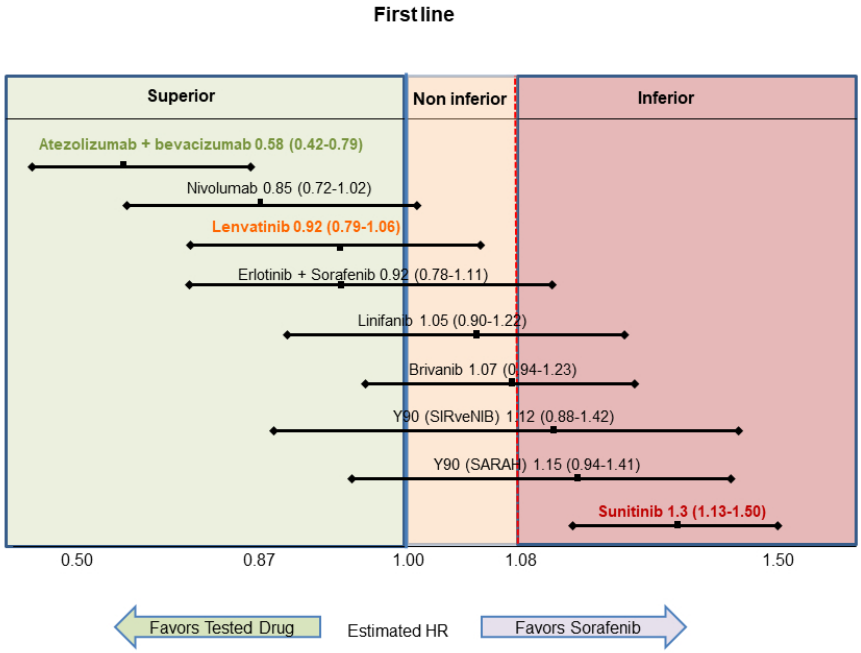

Figure 2A

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Figure 2B

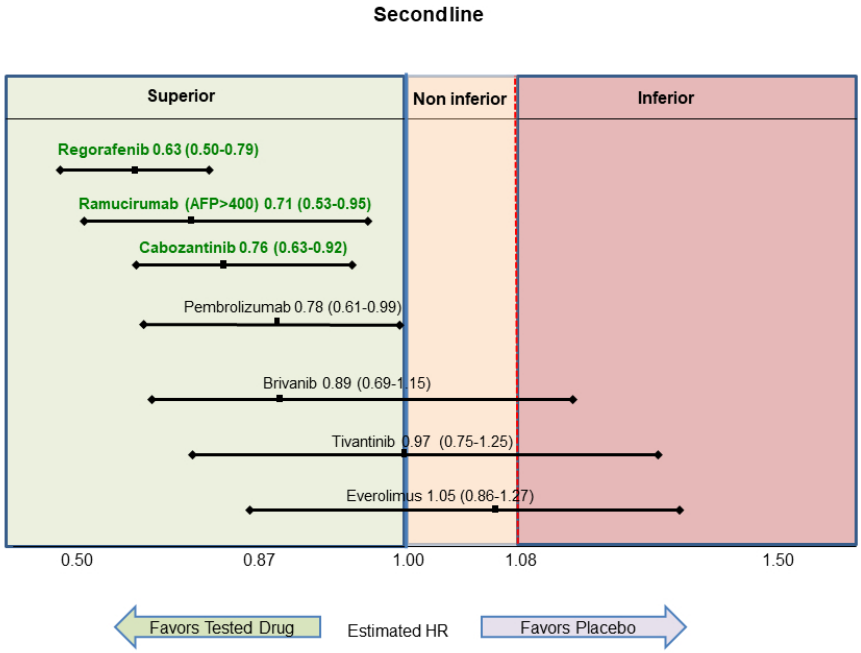

Figure 2B

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Figure 3

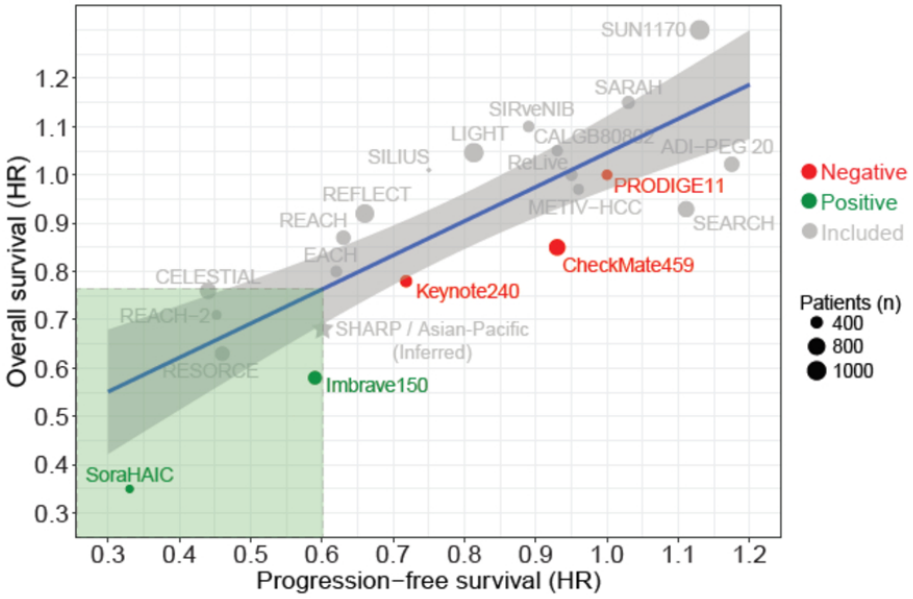

Figure 3

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