Review

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Navigating the landscape of liver cancer management: Study designs in clinical trials and clinical practice

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Summary

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer death worldwide and its prognosis is highly heterogeneous, being related not only to tumour burden but also to the severity of underlying chronic liver disease. Moreover, advances in systemic therapies for HCC have increased the complexity of patient management. Randomised-controlled trials represent the gold standard for evidence generation across all areas of medicine and especially in the oncology field, as they allow for unbiased estimates of treatment effect without confounders. Observational studies have many problems that could reduce their internal and external validity. However, large prospective (well-conducted) observational real-world studies can detect rare adverse events or monitor the occurrence of long-term adverse events. How best to harness real world data, which refers to data generated from the routine care of patients, and real-world 'evidence', which is the evidence generated from real-world data, represents an open challenge. In this review article, we aim to provide an overview of the benefits and limitations of different study designs, particularly focusing on randomised-controlled trials and observational studies, to address important and not fully resolved questions in HCC research.

Introduction

Randomised-controlled trials (RCTs) represent the most powerful tool to change clinical practice and the gold standard by which new cancer treatments are assessed and through which therapeutic progress is made. Clearly, RCTs provide the highest level of evidence because of their rigorous design, the application of strict selection criteria and precise evaluation of drug efficacy in a well-defined population.

The ability of an RCT to detect a difference between groups requires strict specification of study conditions related to all aspects of its conduct, such as participant selection, treatment and control assignment arms, inclusion/exclusion criteria, randomisation method, concealment, outcome measurement, and many other considerations. These highly selective criteria are linked to the need to have well-designed and clean RCTs to generate robust efficacy information. So, in the hierarchy of research designs, the results of RCTs are considered evidence of the highest grade.

On the other side, observational studies have many limitations that could reduce their internal and external validity. The primary concern lies in the potential for an inappropriate selection of patients, which can result in inaccurate findings, spurious associations, and misleading correlations. Specifically, confounding variables may account for the disparity in reproducibility between the outcomes of an RCT and an observational study. So, when the results of RCTs are not fully reproduced in a real-world setting, it does not necessarily imply that RCTs are not valid. However, it is also important to note that if prospective observational studies are designed with rigorous methods, that mimic those of RCTs, they can partially overcome their limitations and make important potential contributions. For instance, carefully conducted observational real-world studies (RWS) can detect rare adverse events, monitor the occurrence of long-term adverse events that did not appear during the short time intervals of an RCT, or detect interactions with comorbidities. Nonetheless, when interpreting the findings of observational studies, it is crucial to acknowledge that, although inherently interconnected, real-world data (RWD) and real-world evidence (RWE) delineate discrete concepts. RWD represent raw unprocessed data related to patient health status or the delivery of healthcare that are routinely collected by different sources, including, but not limited to, registries, electronic health records, and administrative and medical claims databases. On the other side, RWE derives from the systematic analysis, evaluation, and interpretation of RWD to generate evidence on the risk-benefit ratio of medical interventions in real-world populations and to inform healthcare decision-making. It should be noted that RWD do

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Keypoints

- Hepatocellular carcinoma (HCC) is characterised by biological and clinical heterogeneity and wide variations in prognosis.
- Evidence from both well-designed and -conducted randomised-controlled trials and cohort studies can and should be used to inform clinical decision-making in the setting of HCC.
- The advent of innovative systemic treatments will radically change the therapeutic approach from the early to advanced stages of HCC.
- The presence of underlying cirrhosis makes the clinical and methodological interpretation of HCC trial results more challenging.
- In patients with HCC, hepatic decompensation, which does not always coincide with tumour progression, is part of this complex dynamically evolving system and has a strong impact on prognosis.

not automatically translate into RWE, given possible limitations related to data quality and completeness, confounding factors, lack of suitable methodologies to demonstrate causation, generalisability of results, and changes in temporal trends.

Lastly, it is crucial to emphasise that achieving statistical significance for the primary efficacy outcome is a critical criterion for deeming a trial "positive". Nevertheless, it is the assessment of its clinical applicability, in accordance with physicians' judgment, that should take precedence.[1] Before defining a new intervention or drug as a "*therapeutic innovation*", it is necessary to evaluate the internal and external validity, effectiveness, and net-health benefit in real-world patients. In fact, further safety studies (including RCTs or observational registries) are sometimes requested by regulators before approval to clarify the safety profile of a new drug. Furthermore, it is important to note that negative evidence can lead to important breakthroughs in patient management. For example, retrospective analysis of the CRYSTAL trial revolutionised the management of patients with RAS wild-type metastatic colorectal cancer, despite the results of the trial being negative for overall survival (OS).[2]

Moreover, evidence from both well-designed and -conducted RCTs and cohort studies can and should be used to inform clinical decision-making. In the setting of advanced hepatocellular carcinoma (HCC), similar RCTs have been conducted using similar inclusion criteria, as was the case for the evaluation of sorafenib in the SHARP[3] and Asia-Pacific trials[4] or pembrolizumab in KEYNOTE-240[5] and KEYNOTE-394.[6] Even if two RCTs share similar inclusion criteria and are conducted in the same setting, it does not necessarily imply identical study populations. Variations in healthcare pathways and risk factors can result in disparate outcomes or varying effects of an intervention. While the trials may appear similar, they cannot be mutually compared due to differences in populations, despite the use of the same drugs and similar inclusion criteria/settings.

This review offers a comprehensive exploration of the advantages and constraints associated with various study designs, with a specific emphasis on RCTs and observational studies. Its primary objective is to address pivotal, yet still unresolved, inquiries in HCC research.

Randomised-controlled trials *vs.* real-world evidence

Randomised-controlled trials

In oncology, RCTs seek to determine whether a new drug has superior (or non-inferior) efficacy, with improved OS being a frequent primary endpoint. In the context of intermediate-advanced HCC, some examples are the IMbrave150 trial,[7] which demonstrated the superiority of atezolizumab plus bevacizumab over sorafenib in terms of OS, progression-free survival (PFS) and objective response rate (ORR), and the HIMALAYA trial,[8] which showed the superiority in OS of durvalumab plus tremelimumab (according to the STRIDE regimen) over sorafenib. Both IMbrave150 and HIMALAYA are positive RCTs, since they met the pre-specified measure of success for the primary outcome, that was OS and PFS as co-primary endpoints in IMbrave150 and OS in HIMALAYA. When addressing results and conclusions from RCTs, it should be noted that their interpretation cannot merely rely on a simplistic dichotomy between "positive" *vs.* "negative" trials according to treatment effect on primary outcome, but it should provide a careful assessment of the overall evidence, including secondary endpoints, safety issues, and the size and quality of RCTs.[1] Both IMbrave150 and HIMALAYA were large (N = 501 and 1,171, respectively), international RCTs, designed on a clinically important primary outcome, providing a convincing magnitude of treatment benefit in their experimental arms compared to sorafenib, with hazard ratios (HRs) for death of 0.58 (95% CI 0.42-0.79, p <0.001) and 0.78 (96.02% CI 0.65 to 0.93, p = 0.0035), respectively. HRs for disease progression or death *vs.* sorafenib were 0.59 (95% CI, 0.47 to 0.76; p <0.001) for atezolizumab + bevacizumab, and 0.90 (95% CI, 0.77 to 1.05) for STRIDE (single tremelimumab regular interval durvalumab); moreover, both trials showed a manageable safety profile, with adverse events consistent with the known individual drug profiles. Finally, both the IMbrave150 and HIMALAYA trials were characterised by high-quality study designs and rigorous execution.

Impact of RCTs on clinical practice

Differences in the inclusion criteria across RCTs should also be considered and applied in clinical decision-making, when choosing one therapeutic option over another. Findings of any trial apply to the specific patients enrolled and the question of whether the results can be generalised to other patients must always be considered when facing patients in routine clinical practice.[1] The IMbrave150 trial[7] included patients with neoplastic invasion of the main portal trunk, who were instead excluded by other RCTs conducted in the first-line setting, such as REFLECT[9] and HIMALAYA,[8] likely leading to the inclusion of a positively selected population in the latter trials. It should also be considered that patients with 50% or higher liver occupation or obvious invasion of the bile duct were also

excluded by REFLECT. Therefore, caution should be taken when comparing indirectly the OS and associated results from RCTs with different inclusion criteria[10,11] or when applying evidence from RCTs to patients who would have been excluded. RCTs usually exclude some populations with special characteristics, like significant cardiovascular or kidney comorbidities,[12] solid organ transplant recipients, patients with Child-Pugh class B or C cirrhosis or, at least in past years, HIV infection. This is a relevant point in the context of HCC superimposed on cirrhosis and introduces the issue of competing risks.[13,14] A competing risk is an event whose occurrence precludes, or modifies, the probability of the occurrence of the primary event of interest. For instance, in a study in which the primary outcome was time to death attributable to HCC progression, death attributable to reasons different from HCC progression (*i.e.*, impairment of liver function) represents a competing event. Because of the knowledge gap deriving from the exclusion of these patients from RCTs, only data arising from RWS are available in these special settings.

A phase III non-inferiority RCT seeks to determine whether a new drug is not worse than the standard of care in terms of efficacy. Non-inferiority trials should be used with drugs that may offer other advantages – such as superiority in surrogate outcomes, decreased toxicity, or reduced cost – but they are statistically complex with inherent limitations.[15] The choice of the non-inferiority margin is a critical aspect, influencing the trial's interpretation and potential impact on clinical practice. The REFLECT trial[9] and the HIMALAYA trial[8] aimed to demonstrate non-inferiority in overall survival (OS) between lenvatinib and sorafenib or between durvalumab and sorafenib, respectively, both with a pre-specified margin of 1.08 for the HR. This means that lenvatinib or durvalumab would be considered non-inferior to sorafenib if the upper limit of the 95% CI for the HR did not exceed 1.08. A value of 1.08 indicates that the new treatment can be up to 8% less effective than the reference treatment without being considered clinically worse. The choice of the margin is based on clinical judgment and consensus within the scientific community and represents a trade-off between statistical precision and clinical practicality. Narrower margins necessitate larger studies to demonstrate non-inferiority, while wider margins may allow for smaller studies but could permit a clinically relevant difference.[16]

Moreover, in the REFLECT study,[9] lenvatinib was non-inferior to sorafenib for OS, but actually superior for PFS, contributing to the debate on the concordance between OS and radiology-based endpoints and on the choice of outcome to power a trial. Hence, it is important to consider that, in recent years, there has been a progressive increase in the use of intermediate endpoints in submissions to the FDA. However, the FDA often requires companies to share OS data when they become available following accelerated approval or traditional approval.[17] Nonetheless, crossover trial designs and subsequent lines of therapy may make long-term monitoring of OS difficult, requiring alternative analyses to adjust for the effect of subsequent treatments, such as time-dependent covariates Cox models, inverse probability of censoring weighting models, RPSFT (rank-preserving structural failure time) models, or two-stage methods.[18–20] Although these techniques have never been used to adjust for crossover in trials conducted in patients with HCC, a RPSFT model has been used in the setting of advanced intrahepatic cholangiocarcinoma to adjust for the effect of crossover from the placebo arm to active treatment on OS results.[18]

In the last five years, "negative" RCTs have also been published in the setting of systemic treatment for HCC[21–23]; Others have met only one of the primary co-endpoints and could be considered partially positive (only for PFS) or negative because the OS endpoint was not met.[23,24] The key findings of these RCTs are reported in Table S1. When the primary outcome is not reached, one should ask whether the trial was sufficiently powered; whether the population, treatment regimen and primary outcome were appropriate; or whether secondary outcomes showed positive results. Regarding the appropriateness of primary outcome, most of the aforementioned RCTs[7,21,23] were designed to prove superiority on a co-primary endpoint of PFS and OS, an approach associated with increased risk of type I error, that requires multiple testing corrections and that can be affected by the unsatisfactory surrogacy between the two co-primary outcomes in this setting.[25,26] Other relevant issues when interpreting "negative" RCTs are the differences in the administration of post-progression therapies between trial arms, that could affect OS estimates, and the role of the pattern of progression, that could be different according to the treatment, potentially translating into differences in OS.

When trying to apply evidence from RCTs to routine clinical practice, some relevant differences between these two settings need to be accounted for.[27] RCTs are characterised by a well-defined and regular radiological evaluation of tumour burden established by protocols that usually use RECIST criteria. Meanwhile, in clinical practice, follow-up may not be regular and radiological response may not be assessed by RECIST. Another relevant difference relates to the critical point of treatment interruption because oncology RCT protocols traditionally mandated treatment discontinuation at the time of radiological progression, while in clinical practice treatment may be maintained beyond progression if there is clinical benefit. However, in the HCC setting, the SHARP trial[3] already allowed for continuation of treatment until symptomatic progression, incorporating both the concept of perceived clinical benefit and the concept that radiological progression does not necessarily mean treatment inefficacy. In this line, more recent RCTs have allowed for treatment continuation beyond radiological progression in the presence of clinical benefit. Moreover, in the HCC setting, the pattern of progression, a well-validated predictor of survival in patients under tyrosine kinase inhibitors[28] and immune checkpoint inhibitors (ICIs),[29,30] can guide clinical decision-making. Finally, safety reporting in RCTs is usually graded according to CTCAE, while different criteria are often used by clinicians and researchers in routine clinical practice.[31]

The advent of innovative treatments may also increase the complexity of interpreting trial results, as in the case of ICIs. Oncological RCTs usually express treatment benefit through traditional effect measures, including median survival times and HRs. However, the unconventional pattern of response/progression associated with ICIs (including pseudo-progression, hyper-progression or dissociated responses), as well as the long-term benefit achieved by a subgroup of patients, could mean that traditional effect measures are not completely suitable to estimate treatment benefit and to evaluate comparative

effectiveness.[32] The reliability of these measures is related to the presence of proportional HRs[33] and only HIMALAYA[8] and COSMIC-312[23] RCTs formally provided an assessment of the proportionality of hazard. This is relevant since it has been demonstrated that non-proportionality of HRs is not rare in RCTs of systemic treatment for HCC,[10,34] especially when analysing PFS. For this reason, innovative methodologies such as milestone analysis or restricted mean survival time[35] could be more suitable to assess the benefit associated with ICI-based combinations. Particularly, the calculation of restricted mean survival times using reconstructed curves from individual patient survival data led to different results when evaluating PFS in a recently published network meta-analysis,[10] compared to previously published aggregate data network meta-analyses.[11,36]

In addition to methodological issues, the inherent limitations of RECIST criteria should also be addressed, since they focus solely on changes in the size of target lesion(s), using arbitrary boundaries, without considering relevant features related to tumour biology, heterogeneity and to non-measurable lesions. At the same time, symptomatic progression and other clinically relevant features, including the depth of response (*i.e.*, the maximum percentage change in tumour size compared with baseline), the duration of response or the area under the curve of response,[37] are neglected by RECIST criteria, as is the possibility of experiencing a response after initial progression (as sometimes observed during ICI treatment). Alternative radiological criteria based on changes in tumour vascularisation, such as EASL criteria or modified RECIST (mRECIST), can be more suitable than traditional RECIST criteria to assess the response to locoregional treatments, but they may be flawed in case of tumour progression during follow-up. All in all, RECIST criteria and other radiology-based criteria commonly used to define response and progression in RCTs need to be critically reviewed and replaced by more reliable and reproducible tools that effectively capture the true benefit of an intervention.

Real-world data

RWD, defined as information generated outside RCTs that advances our understanding, can fill knowledge gaps between RCT scenarios and real-world clinical practice. For example, in some cases new treatments are over-indicated in real-world patients with liver decompensation or deterioration of ECOG-PS (Eastern Cooperative Oncology Group-Performance Status). RWD has the potential to guide and refine research directions and RCT designs (Fig. 1).

Special populations

An international academic multicentre RWS including patients with HCC under haemodialysis treated with sorafenib has demonstrated that treatment outcomes in these patients are similar to those in the non-dialysis population.[12] Similarly, patients who received liver (or other solid organ) transplants are usually excluded from RCTs evaluating systemic treatment, though RWSs have recently been performed in this setting.[38,39]

Liver decompensation

Another special setting is represented by patients with worse liver function (*i.e.,* Child-Pugh class B and C). They have been historically excluded from RCTs of systemic therapies,[40–43] in order to minimise the possible impact of liver dysfunction on treatment outcomes and they still represent a treatment-deprived population. In this scenario, unlike special populations, real-world analysis becomes more intricate due to patients presenting with varying Barcelona Clinic Liver Cancer (BCLC) stages.[44] Furthermore, this complexity can potentially lead to over- or under-interpretations. It is not equivalent to compare a decompensated patient with a low tumour burden and ECOG-PS 0 to those experiencing HCC-related symptoms. Consequently, a multiparametric assessment, such as tumour staging, should not be confined solely to liver function. Furthermore, the reason behind decompensation and its timing are crucial factors in decision-making. If the analysis is

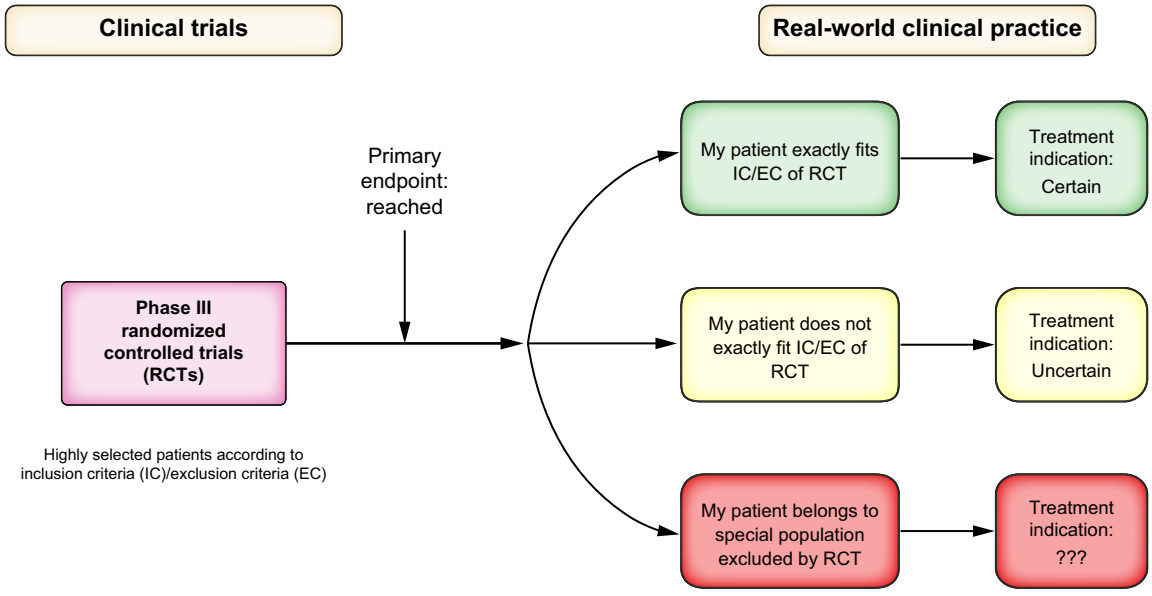

Fig. 1. Translating evidence from randomised-controlled trials to real-world clinical practice.

confined solely to Child-Pugh B or C classification, the real-world interpretation loses its significance. It should also be noted that decompensation events have a deeply different clinical significance compared to the mere treatment-related increase in aminotransferases during immunotherapy, since the latter does not negatively affect outcomes in terms of survival, response rates and treatment discontinuation.[45] A recent retrospective RWS suggested that patients with Child-Pugh class B cirrhosis and unresectable HCC treated with atezolizumab plus bevacizumab could have similar tolerability and objective response rates, but worse OS and PFS compared to those with Child-Pugh class A cirrhosis.[46] Reduced survival outcomes in patients with worse liver function were also confirmed by a recent meta-analysis including about 700 patients with Child-Pugh class B/C cirrhosis treated with immunotherapy, showing a high heterogeneity across the studies in terms of patient characterisation and line of treatment.[47] While we await RCTs or large meticulously designed prospective RWSs with adjustment of confounding by propensity score techniques, available data suggest that recommending immunotherapy for these patients should not be done universally. Instead, the decision should be approached with caution and on a case-by-case basis. In this setting, it should be noted that clinical events of decompensation (ascites, encephalopathy, variceal bleeding, jaundice) represent non-preserved liver function irrespective of traditional composite scores, such Child-Pugh score, that could be abandoned, as suggested by the latest versions of BCLC.[44,48] Alternative tools to assess liver function (*i.e.*, ALBI [albumin-bilirubin] score) have been shown to be more granular, especially in compensated cirrhosis,[49] and a refinement of prediction models for liver function is needed, especially in the setting of unresectable HCC in patients who are eligible for immunotherapy. In this line, although data on the efficacy and safety of different systemic agents have been reported in RWSs conducted in this setting,[46,50] evidence is not sufficient to support one treatment over another. When there are no RCTs available, the choice of using these drugs as "off-label" agents should be carefully evaluated – balancing their safety, efficacy and costs – and requires a careful discussion with the patient and his/her family, who should be involved in the decision-making process. While waiting for high-quality evidence from RCTs, the lower risk of severe adverse events associated with ICI monotherapy[10] compared to combination therapies should be considered.

Finally, patients with significant non-liver-related comorbidities are usually excluded from RCTs, but they represent a population commonly seen in real-world clinical practice. It is expected that comorbidities could have a relevant impact on HCC treatment outcomes, as demonstrated in a recent study on 225 patients with BCLC 0/A stage HCC treated with percutaneous ablation, showing that the risk of death was significantly higher in patients who did not receive further locoregional or systemic treatment for HCC recurrence due to comorbidities, compared to those who received treatment.[51]

Overall, data from RWSs are undoubtedly useful both for understanding the real-world management of patients with HCC, and to inform the design and outcome assumptions in RCTs. However, when faced with patients with clinical characteristics that do not fit with RCTs' inclusion/exclusion criteria, RWD should always be critically assessed according to the quality and the strength of evidence provided, keeping in mind that RWD do not always translate into RWE. When data from RCTs and high-quality RWE are lacking, the latest version of the BCLC staging system,[44] a Policy Review from the HCC Special Interest Group of the Italian Association for the Study of the Liver[52] and the recently published multisociety Italian guidelines[53,54] highlight that the multidisciplinary team are ultimately responsible for evaluating several factors as part of 'clinical decision-making'.[55]

Adjuvant treatment to reduce the risk of HCC recurrence after curative treatments: The quest for the holy grail

The interpretation of studies evaluating adjuvant treatments to reduce the risk of HCC recurrence after curative treatments represents one of the hottest topics in the field, posing several clinical and methodological challenges. HCC recurrence after curative treatments is common, reaching a rate of about 50% at 2 years, according to an aggregate data meta-analysis.[56] This finding underlines the urgent need for an effective adjuvant treatment for these patients. The clinical and methodological approach to this topic is highly complex for different reasons, starting from the lack of a universal consensus on the definition of early and late recurrence.[57–64] Differences in timing and schedule of radiological follow-up after curative treatments across studies can affect the estimate of early (meaning dissemination of first cancer) or late (meaning *de novo* cancer) recurrences and make their distinction less certain.

Conventionally, it has been proposed that early recurrences are related to pre-treatment tumour cell dissemination linked to microvascular invasion or cell dedifferentiation, or to incomplete resection/ablation.[51,60] Conversely, late recurrences represent *de novo* tumours, probably related to inflammatory and proliferative milieu associated with underlying cirrhosis.[56,63] Although most previously published studies adopted 2 years as a temporal cut-off to distinguish early from late recurrence,[57,59–61] there is no final consensus on this and some of them excluded recurrences within the first 6 months or 1-year after diagnosis.[62,63] Unsuccessful efforts have been made in the past to identify an effective adjuvant treatment for HCC recurrence after curative treatments. Particularly, in 2015, the STORM RCT[65] evaluated sorafenib in comparison with placebo following resection or ablation, showing no significant differences in either recurrence-free survival (RFS) or OS. More recently, the debate on this topic has been reignited by the results of the IMbrave050 RCT.[66] IMbrave050 is a global, open-label, phase III RCT that compared the combination of atezolizumab plus bevacizumab with active follow-up in patients at high risk of HCC recurrence after curative resection or ablation. Criteria for high risk of HCC recurrence were defined according to tumour burden (number and size of lesions), vascular invasion or Edmondson grading. Adjuvant treatment with atezolizumab plus bevacizumab led to a significant improvement in RFS (the primary endpoint of the study), with a HR of 0.72 (95% CI 0.56-0.93, $p = 0.012$). Despite the striking impact that these results could have on clinical practice, the findings from IMbrave050 deserve several clinical and methodological considerations. First, it should be considered that more than 80% of patients in this RCT were of Asian ethnicity, most of them with HBV as the aetiology of HCC, raising doubts about the generalisability of these results to the Western population, in

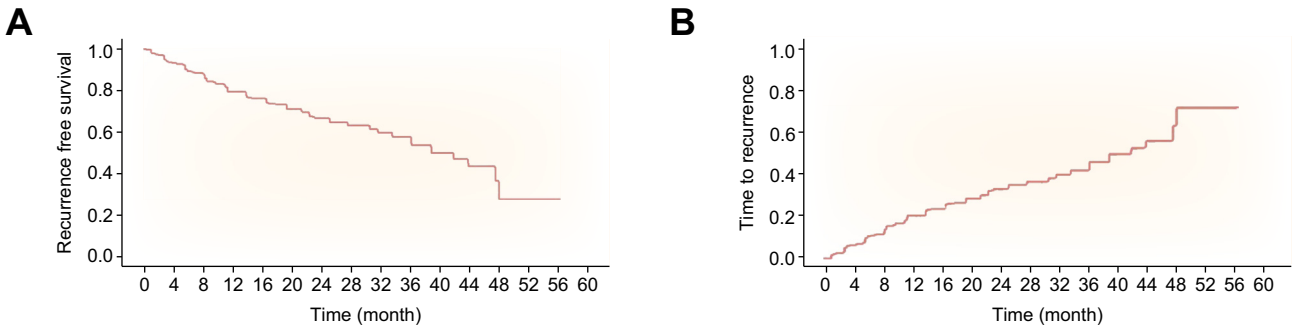

Fig. 2. Reconstructed pooled curves of recurrence-free survival and time-to-recurrence in control arms from STORM and IMbrave050 randomized-controlled trials.[65,66] (A) Recurrence-free survival; (B) Time-to-recurrence. "Recurrence-free survival and time-to-recurrence were calculated according to Kaplan-Meier method".

whom the prevalence of cirrhosis and HCV/metabolic aetiologies is higher. In fact, the geographic representation of RCTs may affect the generalisability of their results. Most major RCTs are multinational, but regional differences in healthcare practices, as well as genetic and environmental risk factors, may limit worldwide applicability when patient recruitment is dominated by one region.[1] Moreover, although patients with multifocal HCC were included in IMbrave050, about 90% of included patients had single tumours.

Although adjuvant treatment with atezolizumab plus bevacizumab is already endorsed by the latest AASLD guidance,[67] caution should be taken when interpreting the conclusions of the IMbrave050 trial,[66] given the lack of mature OS data. So, with the aim of better understanding the underlying risk of recurrence, we extracted individual survival data from Kaplan-Meier RFS and time-to-recurrence (TTR) curves of placebo arms from the STORM and IMbrave050 RCTs in order to reconstruct pooled survival curves and to provide a useful benchmark. Pooled reconstructed curves of RFS and TTR curves of placebo arms are shown in Fig. 2A,B, respectively (individual reconstructed curves from the two RCTs are reported in Figs S1-4). Median RFS was 41.1 months (95% CI 41.0-47.0) and RFS rates by Kaplan-Meier analysis were 79.6% at 1 year, 67.4% at 2 years, 56.7% at 3 years and 35.4% at 4 years. Median TTR was 41.5 months (95% CI 38.5-43.5) and TTR rates by Kaplan-Meier analysis were 20.3% at 1 year, 32.6% at 2 years, 45.6% at 3 years and 71.2% at 4 years. Subsequently, we estimated the overall hazard function for HCC recurrence by using extracted individual survival data to visually depict chronological change in the recurrence rate after curative treatments (Fig. 3). We found that the risk of HCC recurrence is characterised by a peak within the first year of follow-up, followed by a decrease in the risk and a subsequent further increase in the risk, starting from about 2 years of follow-up after curative treatment. Overall, this two-phase shape is in line with previous reports,[57,60,68–70] substantiating the suggestion to delay liver transplant until 6 months after resection to prevent an early disseminated recurrence.[70] Despite the relatively short follow-up time for RFS in the STORM and IMbrave050 trials (median follow-up times of 8.5 and 17.4 months, respectively), the forecast remains stable beyond 2 years due to the estimated hazard, employed within a generalised survival model. However, when interpreting these results, it should be considered that the indolent behaviour of HCC in some patients could be a potential unmeasured confounder.[71]

It could be speculated that the first peak in the risk of HCC recurrence is mainly related to a pre-treatment cancer "understaging", related to an underlying multifocal and more aggressive tumour or to a partially complete curative treatment. The early peak could potentially be reduced by an effective adjuvant treatment, likely atezolizumab plus bevacizumab in the near future. Conversely, the second peak in the risk of HCC recurrence could be related to underlying cirrhosis, which represents a persistent and hardly modifiable risk factor for *de novo* HCC. The presence of underlying cirrhosis makes the clinical and methodological interpretation of the effectiveness of adjuvant agents in this setting more challenging than in other oncological scenarios wherein cancer usually arises in the absence of a co-existing organ disease.

Finally, it is important to consider that preliminary data suggest that durvalumab in combination with TACE (transarterial chemoembolisation) and bevacizumab was associated with improved PFS *vs.* TACE alone in the EMERALD-1 phase III trial,[72] with HR for disease progression or death of 0.77 (95% CI 0.61–0.98, $p = 0.032$). As we await a full report of the study results, it is likely that new treatment options will become available and the complexity of HCC management will further increase in the near future.

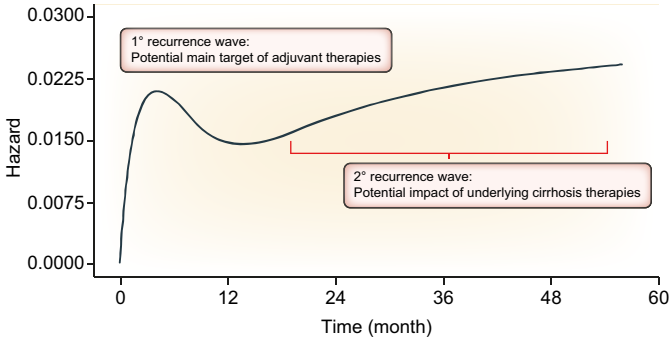

Fig. 3. Estimated hazard function of pooled hepatocellular carcinoma recurrence over time after curative treatments of control arms from STORM and IMbrave050 randomized-controlled trials.[65,66]

The role of aetiology of liver disease on response to systemic treatments

The role of aetiology as a potential effect modifier of systemic treatments has been widely debated since sorafenib monotherapy represented the standard of care. In this setting, a pooled exploratory analysis of the SHARP and Asia-Pacific trials showed that the positive effect of sorafenib on OS was consistent in both HBV- and HCV-positive patients, but with higher magnitude of effect in HCV-positive patients.[73] The debate became even hotter after the publication of a study conducted on both preclinical mouse models and human cells, demonstrating that anti-PD1 treatment led to an increase in hepatic CD8+PD1+ cells in MASH (metabolic dysfunction-associated steatohepatitis)-HCC and that this may reduce responsiveness to ICIs through an impairment of immune surveillance.[74] The same study also presented an aggregate data meta-analysis of three RCTs on ICI treatments, showing that, when grouping patients by aetiology, ICIs significantly improve OS in patients with viral HCC but not in those with "non-viral" HCC. Overall, caution should be taken when interpreting results from subgroup analyses in which patients are not stratified by aetiology or the definition of aetiology is not accurate. Subgroup analyses usually lack the required sample size to provide robust information and even if they come from RCTs they remain a tool for hypothesis generation. Ideally, subgroup analyses should be based on a clinical rationale, they should be predefined and based on a power calculation accounting for between-subgroup treatment effects, but above all, randomisation should be stratified for subgroup covariates. In the absence of proper stratification, different outcomes among different subgroups could be affected by confounding related to the loss of randomisation. Unfortunately, none of the three RCTs included in the previously mentioned meta-analysis was stratified for aetiology. Moreover, in clinical practice, different aetiologies are frequently overlapping in the same patient and "non-viral" HCC represents an umbrella term that covers a highly heterogeneous group of patients with alcohol-related, metabolic, or other less common causes of liver cancer, alongside those with previously cured HCV infection. Lumping these broad classes of different aetiologies into one big basket is highly misleading and poorly informative for daily clinical practice. Finally, subsequent exploratory analyses from IMbrave150,[7] the most recent RCTs with stratified randomisation for aetiology,[8,23] and an updated meta-analysis[75] confirmed a significant survival advantage provided by ICIs across both non-viral and viral aetiologies. In conclusion, there is no reliable data to support that aetiology impacts outcomes of patients treated with ICIs and thus the choice of treatment in daily clinical practice should not be based on disease aetiology. Nevertheless, in our opinion, large-scale international phase III RCTs should be designed with a pre-planned stratification according to geographical regions and accurately registered aetiologies of liver disease.

The issue of DAA therapies in HCV-infected patients with prior history of HCC

The clinical impact of direct-acting antivirals (DAAs) on HCC recurrence was a controversial topic because no RCT evaluated this population and the individual data meta-analysis which summarised the available data was inconclusive.[76] In addition, DAA-induced HCV eradication can result in immune-modulation that may contribute in some patients to HCC recurrence, as well as rare cases of HBV or herpetic reactivations, underlining that no therapy is free of risks.[77]

Briefly, initial studies assessing risk of HCC recurrences after DAA therapy may be affected by many weaknesses,[78] such as retrospective design, lack of control group, and differences in inception point, baseline patient and tumour characteristics, type of curative treatment, criteria to assess complete radiological response, HCC recurrence definition (early/late and local/distant), schedules of follow-up, as well as misclassification and immortal-time biases. Nevertheless, RCTs evaluating the efficacy of DAAs in patients successfully treated for HCC are no longer feasible, ethical, or timely.

The impact of DAA treatment on OS in the adjuvant setting was assessed for the first time in an Italian multicentre prospective study that compared 163 patients with diagnosis of early-stage HCC who obtained complete radiologic response after resection or ablation and were subsequently treated with DAAs *vs.* a historical control cohort who did not receive treatment for HCV (n = 328).[79] Both propensity score matching (PSM) and inverse-probability-of-treatment-weighting analyses showed that DAA treatment significantly improves OS, compared to no DAA treatment (HR 0.39; 95% CI 0.17–0.91; p = 0.03 in PSM analysis). HCC recurrence risk was not significantly different between the two groups (HR 0.70; 95% CI 0.44–1.13; p = 0.15), while a significant benefit of DAA treatment in reducing the risk of hepatic decompensation was observed (HR 0.32; 95% CI 0.13–0.84; p = 0.02). Therefore, it has been speculated that the positive impact of DAAs on OS could be mediated by a reduction in the risk of decompensation, even if it is not proven to support the indication for this aim in the context of all patients with HCC. This result is interesting in that, although DAAs did not affect the risk of HCC recurrence, they improve survival through a longer preservation of liver function. The design of this study represents an attempt to emulate an RCT using observational data and for this purpose, the authors mitigated the impact of time-related biases by performing time-dependent analyses and establishing a comparable index time for DAA-untreated patients.

Similar results were obtained by Singal *et al.*[80] in a large retrospective study conducted in North America on 793 patients. They assessed cause-specific OS between DAA-treated and untreated patients with prior HCC, showing that liver-related deaths were significantly lower in DAA-treated than untreated patients (16.3% *vs.* 34%, p = 0.03), whereas HCC-related deaths were similar between the two groups (30.2% *vs.* 29.1%, p = 0.89).

Regarding the controversial issue of the potential association between DAA therapy and HCC, an individual participant data meta-analysis[76] did not demonstrate a clear association between DAA therapy and higher HCC recurrence rates, but confirmed that DAA-mediated eradication does not eliminate HCC recurrence risk after effective therapy, which remains significant in both DAA-treated and -untreated patients. Sapena *et al.*,[76] by pooling the data of 977 consecutive patients

from 21 studies, found that the recurrence rate in DAA-treated patients was 20 per 100-patient-years (95% CI 13.9-29.8, I^2 = 74.6%). Moreover, no significant difference was observed in relative risk between DAA-exposed and DAA-unexposed groups in PSM analysis (risk ratio = 0.64, 95% CI 0.37 to 1.1; p = 0.1).

Finally, the impact of DAA therapy in patients with active HCC, particularly in the intermediate/advanced stage, should also be addressed.[13,14,78] Hepatic decompensation, which does not always coincide with tumour progression, is part of this complex dynamically evolving system, and must be promptly recognised and adequately managed to allow patients to continue in the therapeutic course. It is well-known that the risk of hepatic decompensation may affect HCC treatment and reduce the possibility of receiving subsequent systemic therapy after progression. Similarly, it is also known that tumour progression and decompensation are competing events that negatively impact OS both in intermediate/advanced HCC[13,14,81] and in early HCC,[64] although they are not yet adequately measured in RCTs.

Hence, considering the data on early improvements in liver disease severity in most HCV-positive patients treated with DAAs,[82–84] with long-term preservation of liver function, similar to observations on nucleos(t)ide analogues for HBV infection,[85,86] the decision to use DAAs should be considered on a case by case basis.[13]

Conclusions

In the setting of HCC, characterised by high clinical complexity and heterogeneity,[71,87] the delivery of precision oncology to an individual patient in clinical practice represents a challenge for clinicians. In the future, possible solutions to fill this gap could be to design innovative trials, based on translational and causation research knowledge (including omics approaches), on stratification for relevant potential treatment effect modifiers, and on novel methodologies to quantify treatment benefit. In this line, phase III RCTs should represent the final step of a route that begins from preclinical models, early phase trials and hypothesis-generating observational studies. They should be designed according to adaptive and biomarker-enriched approaches, and they should consider the non-proportionality of HRs when assessing the magnitude of treatment effect. Moreover, RCTs should also be able to quantify the true value of an innovative treatment, in terms of risk and benefit, and the management of patients with HCC should be guided by a risk-benefit analysis balancing treatment effectiveness and the risk of treatment-related adverse events, as assessed by the incremental safety-effectiveness ratio.[34] Finally, a stronger and closer cooperation between physicians with scientific background and extensive clinical practice experience, the pharmaceutical industry, and regulatory agencies, as well as greater involvement of clinicians in designing and planning new RCTs, is needed to provide solid evidence.

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Abbreviations

BCLC, Barcelona Clinic Liver Cancer; DAAs, direct-acting antivirals; HR, hazard ratios; ICIs, immune checkpoint inhibitors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PSM, propensity score matching; RCTs, randomised-controlled trials; RWD, real-world data; RWE, real-world evidence; RWS, real-world studies; TTR, time-to-recurrence.

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Conflict of interest

GC participated in advisory board and received speaker fees for Bayer, Eisai, Ipsen, and AstraZeneca, MSD, Roche, Gilead. **CiC** received speaker fees from Eisai, Ipsen, MSD and AstraZeneca and travel support from Roche. **LR** reports consulting fees from AstraZeneca, Basilea, Bayer, BMS, Eisai, Elevar Therapeutics, Exelixis, Genenta, Hengrui, Incyte, Ipsen, IQVIA, Jazz Pharmaceuticals, MSD, Nerviano Medical Sciences, Roche, Servier, Taiho Oncology, Zymeworks; lecture fees from AstraZeneca, Bayer, BMS, Eisai, Incyte, Ipsen, Merck Serono, Roche, Servier; travel expenses from AstraZeneca; research grants (to Institution) from Agios, AstraZeneca, BeiGene, Eisai, Exelixis, Fibrogen, Incyte, Ipsen, Lilly, MSD, Nerviano Medical Sciences, Roche, Servier, Zymeworks. **RK** consults and advises for Boston Scientific, Bristol-Myers Squibb, Guerbet, Roche, and SIRTEX and is on the speakers' bureau for BTG, Eisai, Guerbet, Ipsen, MSD Sharp & Dohme, and SIRTEX. But none of them are related to this project at all. **FT** received DSMB fees from Argenx BV, Archivel and Connecta, and consultancy fees from Archivel, UniversalDX LEO Pharma, Ferrer and Boehringer Ingelheim, all outside the submitted work. **JB** Consultancy: AbbVie, Adaptimmune, Arqule, Astra-Medimmune, Basilea, Bayer-Shering Pharma, Bio-Alliance, BMS, BTG-Biocompatibles, Eisai, Gilead, Incyte, Ipsen, Kowa, Lilly, MSD, Nerviano, Novartis, Polaris, Quirem, Roche, Sirtex, Sanofi, Terumo. Paid conferences: Bayer, BTG, Ipsen, Astra-Zeneca. Paid talks: Bayer, BTG- Biocompatibles, Eisai, Terumo, Sirtex, Ipsen, Roche **CaC** participated in the advisory board for Bayer, MSD/Merck, Ipsen, AstraZeneca, Roche, and Eisai. **MR** consults for, advises, is on the speakers' bureau for and received grants from AstraZeneca. She consults for, is on the speakers' bureau for and received grants from Bayer. She consults for and is on the speakers' bureau for BMS, Eli Lilly, and Roche. She consults for and received grants from Ipsen. She consults for Geneos, Merck, and Universal DX. She received educational Support (to the institution) from Astrazeneca, Bayer, Roche, Eisai, Ipsen, Lilly, Terumo.

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Authors' contributions

Interpretation of data and drafting of the manuscript (all authors); critical revision of the manuscript for important intellectual content (all authors). All authors approve final version of the manuscript.

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Supplementary data

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References

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[1] Pocock SJ, Stone GW. The primary outcome is positive - is that good enough? N Engl J Med 2016;375:971–979.
[2] Tejpar S, Stintzing S, Ciardiello F, et al. Prognostic and predictive relevance of primary tumor location in patients with RAS wild-type metastatic colorectal cancer: retrospective analyses of the CRYSTAL and FIRE-3 trials. JAMA Oncol 2017;3:194–201.
[3] Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–390.
[4] Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25–34.
[5] Finn RS, Ryoo BY, Merle P, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial. J Clin Oncol 2020;38:193–202.
[6] Qin S, Chen Z, Fang W, et al. Pembrolizumab versus placebo as second-line therapy in patients from Asia with advanced hepatocellular carcinoma: a randomized, double-blind, phase III trial. J Clin Oncol 2023;41:1434–1443.
[7] Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382:1894–1905.
[8] **Abou-Alfa GK**, **Lau G**, Kudo M, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. NEJM Evid 2022;1:EVIDoa2100070.
[9] Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163–1173.
[10] Celsa C, Cabibbo G, Pinato DJ, et al. Balancing efficacy and tolerability of first-line systemic therapies for advanced hepatocellular carcinoma: a network metanalysis. Liver Cancer; 2023.
[11] Fulgenzi CAM, Scheiner B, Korolewicz J, et al. Efficacy and safety of frontline systemic therapy for advanced HCC: a network meta-analysis of landmark phase III trials. JHEP Rep 2023;5:100702.
[12] **Diaz-Gonzalez A**, **Sanduzzi-Zamparelli M**, **da Fonseca LG**, et al. International and multicenter real-world study of sorafenib-treated patients with hepatocellular carcinoma under dialysis. Liver Int 2020;40:1467–1476.
[13] Reig M, Cabibbo G. Antiviral therapy in the palliative setting of HCC (BCLC-B and -C). J Hepatol 2021;74:1225–1233.
[14] Cabibbo G, Aghemo A, Lai Q, et al. Optimizing systemic therapy for advanced hepatocellular carcinoma: the key role of liver function. Dig Liver Dis 2022;54:452–460.
[15] Garattini S, Bertele V. Ethics in clinical research. J Hepatol 2009;51:792–797.
[16] Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: the importance of rigorous methods. BMJ 1996;313:36–39.
[17] https://www.aacr.org/professionals/policy-and-advocacy/regulatory-science-and-policy/events/fda-aacr-asa-workshop-overall-survival-in-oncology-clinical-trials. In.
[18] Zhu AX, Macarulla T, Javle MM, et al. Final overall survival efficacy results of ivosidenib for patients with advanced cholangiocarcinoma with IDH1 mutation: the phase 3 randomized clinical ClarIDHy trial. JAMA Oncol 2021;7:1669–1677.
[19] Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME, Groothuis-Oudshoorn CGM. Time-varying covariates and coefficients in Cox regression models. Ann Transl Med 2018;6:121.
[20] Latimer NR, Abrams KR. In: NICE DSU technical support document 16: adjusting survival time estimates in the presence of treatment. London: Switching; 2014.
[21] Llovet JM, Kudo M, Merle P, et al. Lenvatinib plus pembrolizumab versus lenvatinib plus placebo for advanced hepatocellular carcinoma (LEAP-002): a randomised, double-blind, phase 3 trial. Lancet Oncol 2023;24:1399–1410.
[22] Yau T, Park JW, Finn RS, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol 2022;23:77–90.
[23] **Kelley RK**, **Rimassa L**, Cheng AL, et al. Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2022;23:995–1008.
[24] Cabibbo G, Celsa C, D'Alessio A, Fulgenzi CAM, Pinato DJ. COSMIC-312: mounting immunotherapy enigmas for hepatocellular carcinoma. Lancet Oncol 2022;23:e441.
[25] https://www.fda.gov/files/drugs/published/Multiple-Endpoints-in-Clinical-Trials-Guidance-for-Industry.pdf.
[26] Cabibbo G, Bruix J. Radiological endpoints as surrogates for survival benefit in hepatocellular carcinoma trials: all that glitters is not gold. J Hepatol 2023;78:8–11.
[27] Bruix J. Endpoints in clinical trials for liver cancer and their value in evidence-based clinical decision making: an unresolved Gordian knot. J Hepatol 2021;74:1483–1488.
[28] Reig M, Rimola J, Torres F, et al. Postprogression survival of patients with advanced hepatocellular carcinoma: rationale for second-line trial design. Hepatology 2013;58:2023–2031.
[29] **Campani C**, **Vallot A**, **Ghannouchi H**, et al. Impact of radiological response and pattern of progression in patients with hepatocellular carcinoma treated by atezolizumab-bevacizumab. Hepatology 2023. Jan 1;79(1):49–60.
[30] **Rimola J**, **Da Fonseca LG**, et al. Radiological response to nivolumab in patients with hepatocellular carcinoma: a multicenter analysis of real-life practice. Eur J Radiol 2021;135:109484.
[31] Sherman M. Assessing toxicity in drug trials in liver disease. Semin Liver Dis 2021;41:277–284.
[32] Ferrara R, Pilotto S, Caccese M, et al. Do immune checkpoint inhibitors need new studies methodology? J Thorac Dis 2018;10:S1564–S1580.
[33] Hernan MA. The hazards of hazard ratios. Epidemiology 2010;21:13–15.
[34] **Cabibbo G**, **Reig M**, Celsa C, et al. First-line immune checkpoint inhibitor-based sequential therapies for advanced hepatocellular carcinoma: rationale for future trials. Liver Cancer 2022;11:75–84.
[35] **Pak K**, **Uno H**, **Kim DH**, et al. Interpretability of cancer clinical trial results using restricted mean survival time as an alternative to the hazard ratio. JAMA Oncol 2017;3:1692–1696.
[36] Sonbol MB, Riaz IB, Naqvi SAA, et al. Systemic therapy and sequencing options in advanced hepatocellular carcinoma: a systematic review and network meta-analysis. JAMA Oncol 2020;6:e204930.
[37] Bruix J, da Fonseca LG, Reig M. Insights into the success and failure of systemic therapy for hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol 2019;16:617–630.
[38] Iavarone M, Invernizzi F, Ivanics T, et al. Regorafenib efficacy after sorafenib in patients with recurrent hepatocellular carcinoma after liver transplantation: a retrospective study. Liver Transpl 2021;27:1767–1778.
[39] Rimassa L, Personeni N, Czauderna C, Foerster F, Galle P. Systemic treatment of HCC in special populations. J Hepatol 2021;74:931–943.
[40] Bruix J, Chan SL, Galle PR, Rimassa L, Sangro B. Systemic treatment of hepatocellular carcinoma: an EASL position paper. J Hepatol 2021;75:960–974.
[41] Rimassa L, Finn RS, Sangro B. Combination immunotherapy for hepatocellular carcinoma. J Hepatol 2023;79:506–515.
[42] Cabibbo G, Cucchetti A, Camma C, et al. Outcomes of hepatocellular carcinoma patients treated with sorafenib: a meta-analysis of Phase III trials. Future Oncol 2019;15:3411–3422.
[43] Llovet JM, Di Bisceglie AM, Bruix J, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst 2008;100:698–711.
[44] Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol 2022;76:681–693.
[45] **Celsa C**, **Cabibbo G**, Fulgenzi C, et al. Characteristics and outcomes of immunotherapy-related liver injury in patients with hepatocellular carcinoma versus other advanced solid tumours. J Hepatol 2024. Mar;80(3):431–442.
[46] D'Alessio A, Fulgenzi CAM, Nishida N, et al. Preliminary evidence of safety and tolerability of atezolizumab plus bevacizumab in patients with hepatocellular carcinoma and Child-Pugh A and B cirrhosis: a real-world study. Hepatology 2022;76:1000–1012.
[47] **El Hajra I**, **Sanduzzi-Zamparelli M**, Sapena V, et al. Outcome of patients with HCC and liver dysfunction under immunotherapy: a systematic review and meta-analysis. Hepatology 2023;77:1139–1149.
[48] Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;391:1301–1314.
[49] **Pinato DJ**, **Sharma R**, Allara E, et al. The ALBI grade provides objective hepatic reserve estimation across each BCLC stage of hepatocellular carcinoma. J Hepatol 2017;66:338–346.
[50] Marrero JA, Kudo M, Venook AP, et al. Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: the GIDEON study. J Hepatol 2016;65:1140–1147.
[51] Munoz-Martinez S, Sapena V, Garcia-Criado A, et al. Risk of treatment failure and death after ablation in hepatocellular carcinoma patients-A multiparametric prediction. Cancers (Basel) 2023;15.
[52] **Vitale A**, **Cabibbo G**, Iavarone M, Vigano L, Pinato DJ, Ponziani FR, Lai Q, et al. Personalised management of patients with hepatocellular carcinoma: a multiparametric therapeutic hierarchy concept. Lancet Oncol 2023;24:e312–e322.

[53] Cabibbo G, Daniele B, Borzio M, et al. Multidisciplinary treatment of hepatocellular carcinoma in 2023: Italian practice treatment guidelines of the Italian association for the study of the liver (AISF), Italian association of medical oncology (AIOM), Italian association of hepato-bilio-pancreatic surgery (AICEP), Italian association of hospital gastroenterologists (AIGO). Italian association of radiology and clinical oncology (AIRO), Italian society of pathological anatomy and diagnostic cytology (SIAPeC-IAP), Italian society of surgery (SIC), Italian society of Gastroenterology (SIGE), Italian society of medical and interventional radiology (SIRM), Italian organ transplant society (SITO), and association of patients with hepatitis and liver disease (EpaC) - Part I - surgical treatments. Dig Liver Dis 2024 Feb;56(2):223–234. https://doi.org/10.1016/j.dld.2023.10.029.
[54] Cabibbo G, Daniele B, Borzio M, et al. Multidisciplinary treatment of hepatocellular carcinoma in 2023: Italian practice treatment guidelines of the Italian association for the study of the liver (AISF), Italian association of medical oncology (AIOM), Italian association of hepato-bilio-pancreatic surgery (AICEP), Italian association of hospital gastroenterologists (AIGO). Italian association of radiology and clinical oncology (AIRO), Italian society of pathological anatomy and diagnostic cytology (SIAPeC-IAP), Italian society of surgery (SIC), Italian society of Gastroenterology (SIGE), Italian society of medical and interventional radiology (SIRM), Italian organ transplant society (SITO), and association of patients with hepatitis and liver disease (EpaC) - Part II - non-surgical treatments. Dig Liver Dis 2024. Mar;56(3):394–405.
[55] **Munoz-Martinez S**, **Iserte G**, Sanduzzi-Zamparelli M, Llarch N, Reig M. Current pharmacological treatment of hepatocellular carcinoma. Curr Opin Pharmacol 2021;60:141–148.
[56] Cabibbo G, Petta S, Barbara M, et al. A meta-analysis of single HCV-untreated arm of studies evaluating outcomes after curative treatments of HCV-related hepatocellular carcinoma. Liver Int 2017;37:1157–1166.
[57] Imamura H, Matsuyama Y, Tanaka E, et al. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. J Hepatol 2003;38:200–207.
[58] Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Intrahepatic recurrence after curative resection of hepatocellular carcinoma: long-term results of treatment and prognostic factors. Ann Surg 1999;229:216–222.
[59] Fuster J, Garcia-Valdecasas JC, Grande L, et al. Hepatocellular carcinoma and cirrhosis. Results of surgical treatment in a European series. Ann Surg 1996;223:297–302.
[60] Mazzaferro V, Romito R, Schiavo M, et al. Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. Hepatology 2006;44:1543–1554.
[61] Hoshida Y, Villanueva A, Kobayashi M, et al. Gene expression in fixed tissues and outcome in hepatocellular carcinoma. N Engl J Med 2008;359:1995–2004.
[62] Muto Y, Moriwaki H, Ninomiya M, et al. Prevention of second primary tumors by an acyclic retinoid, polyprenoic acid, in patients with hepatocellular carcinoma. Hepatoma Prevention Study Group. N Engl J Med 1996;334:1561–1567.
[63] **Nault JC**, **De Reynies A**, Villanueva A, et al. A hepatocellular carcinoma 5-gene score associated with survival of patients after liver resection. Gastroenterology 2013;145:176–187.
[64] Cabibbo G, Petta S, Barbara M, et al. Hepatic decompensation is the major driver of death in HCV-infected cirrhotic patients with successfully treated early hepatocellular carcinoma. J Hepatol 2017;67:65–71.
[65] Bruix J, Takayama T, Mazzaferro V, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol 2015;16:1344–1354.
[66] Qin S, Chen M, Cheng AL, et al. Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050): a randomised, open-label, multicentre, phase 3 trial. Lancet 2023;402:1835–1847.
[67] Singal AG, Llovet JM, Yarchoan M, et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology 2023;78:1922–1965.
[68] Sapisochin G, Goldaracena N, Astete S, et al. Benefit of treating hepatocellular carcinoma recurrence after liver transplantation and analysis of prognostic factors for survival in a large euro-American series. Ann Surg Oncol 2015;22:2286–2294.
[69] Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. Ann Surg 2002;235:373–382.
[70] **Ferrer-Fabrega J**, **Forner A**, Liccioni A, et al. Prospective validation of ab initio liver transplantation in hepatocellular carcinoma upon detection of risk factors for recurrence after resection. Hepatology 2016;63:839–849.
[71] Iavarone M, Nault JC, Cabibbo G, Torres F, Reig M. Indolent cancer and pattern of progression: two missing parameters in trial design for hepatology. Hepatology 2023. Jul 3. https://doi.org/10.1097/HEP.0000000000000527. Epub ahead of print.
[72] Lencioni R, Kudo M, Erinjeri J, et al. EMERALD-1: a phase 3, randomized, placebo-controlled study of transarterial chemoembolization combined with durvalumab with or without bevacizumab in participants with unresectable hepatocellular carcinoma eligible for embolization. In: 2024 ASCO gastrointestinal cancers symposium; 2024.
[73] Bruix J, Cheng AL, Meinhardt G, Nakajima K, De Sanctis Y, Llovet J. Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: analysis of two phase III studies. J Hepatol 2017;67:999–1008.
[74] Pfister D, Nunez NG, Pinyol R, et al. NASH limits anti-tumour surveillance in immunotherapy-treated HCC. Nature 2021;592:450–456.
[75] Meyer T, Galani S, Lopes A, Vogel A. Aetiology of liver disease and response to immune checkpoint inhibitors: an updated meta-analysis confirms benefit in those with non-viral liver disease. J Hepatol 2023;79:e73–e76.
[76] **Sapena V**, **Enea M**, Torres F, et al. Hepatocellular carcinoma recurrence after direct-acting antiviral therapy: an individual patient data meta-analysis. Gut 2022;71:593–604.
[77] Pisaturo M, Macera M, Alessio L, Calo F, Coppola N. Hepatitis B virus (HBV) reactivation following pharmacological eradication of hepatitis C virus (HCV). Viruses 2019:11.
[78] Cabibbo G, Celsa C, Camma C, Craxi A. Should we cure hepatitis C virus in patients with hepatocellular carcinoma while treating cancer? Liver Int 2018;38:2108–2116.
[79] **Cabibbo G**, **Celsa C**, Calvaruso V, et al. Direct-acting antivirals after successful treatment of early hepatocellular carcinoma improve survival in HCV-cirrhotic patients. J Hepatol 2019;71:265–273.
[80] Singal AG, Rich NE, Mehta N, et al. Direct-acting antiviral therapy for hepatitis C virus infection is associated with increased survival in patients with a history of hepatocellular carcinoma. Gastroenterology 2019;157:1253–1263 e1252.
[81] **Iavarone M**, **Cabibbo G**, Biolato M, et al. Predictors of survival in patients with advanced hepatocellular carcinoma who permanently discontinued sorafenib. Hepatology 2015;62:784–791.
[82] Belli LS, Perricone G, Adam R, et al. Impact of DAAs on liver transplantation: major effects on the evolution of indications and results. An ELITA study based on the ELTR registry. J Hepatol 2018;69:810–817.
[83] Mandorfer M, Kozbial K, Schwabl P, et al. Changes in hepatic venous pressure gradient predict hepatic decompensation in patients who achieved sustained virologic response to interferon-free therapy. Hepatology 2020;71:1023–1036.
[84] Pascasio JM, Vinaixa C, Ferrer MT, et al. Clinical outcomes of patients undergoing antiviral therapy while awaiting liver transplantation. J Hepatol 2017;67:1168–1176.
[85] Papatheodoridis GV, Sypsa V, Dalekos G, et al. Eight-year survival in chronic hepatitis B patients under long-term entecavir or tenofovir therapy is similar to the general population. J Hepatol 2018;68:1129–1136.
[86] Rizzo GEM, Cabibbo G, Craxi A. Hepatitis B virus-associated hepatocellular carcinoma. Viruses 2022:14.
[87] Cabibbo G, Enea M, Attanasio M, Bruix J, Craxi A, Camma C. A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. Hepatology 2010;51:1274–1283.