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MINIREVIEWS

Systemic treatment of hepatocellular carcinoma secondary to non-alcoholic fatty liver disease

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Abstract

Hepatocellular carcinoma (HCC) is the third leading cause of cancer death globally, with 15% of cases arising on a background of non-alcoholic fatty liver disease (NAFLD). NAFLD is a heterogenous condition ranging from fatty liver to cirrhosis and is itself a growing global problem, with estimated worldwide prevalence of 50% in 2040. Pathophysiology of NAFLD-HCC is not well understood, there are no dedicated screening programs, and there have been no clinical studies of anti-cancer treatments in this population specifically. However, the NAFLD-HCC population appears different than other aetiologies - patients tend to be older, diagnosed at more advanced stages, have more comorbidities, and overall worse prognosis. Understanding of best treatment options for this group of patients is an urgent unmet clinical need. This narrative review discusses NAFLD-HCC pathophysiology and systemic treatment, and offers suggestions for future directions in this therapy area.

Key Words: Hepatocellular carcinoma; Non-alcoholic fatty liver disease; Systemic anti-cancer therapy; Immunotherapy; Targeted therapy; Pathophysiology

Core Tip: Hepatocellular carcinoma (HCC) arising on a background of non-alcoholic fatty liver disease (NAFLD) is not well understood but patients tend to have poorer prognosis *vs* those with other HCC aetiologies. Currently all HCC patients are treated the same regardless of aetiology, and understanding of best treatment options for the NAFLD-HCC population is an urgent clinical need. This narrative review discusses NAFLD-HCC screening, pathophysiology, systemic treatment, and offers suggestions for future directions in this therapy area.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer death globally, with both incidence and mortality on the rise[1-3]. In the United Kingdom alone, mortality rates are projected to increase 10% between 2023-2025 and 2038-2040[4]. HCC typically occurs on the background of liver cirrhosis with the main aetiologies being hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, alcoholic liver disease and non-alcoholic fatty liver disease (NAFLD)[5]. However, a recent meta-analysis found significantly higher proportion of NAFLD-related HCC arises in non-cirrhotic livers compared with other aetiologies[6].

NAFLD incidence is increasing at an alarming level, with over half of the global adult population predicted to have the condition by 2040[7]. NAFLD is a heterogenous disease comprising non-alcoholic steatosis (or fatty liver) and non-alcoholic steatohepatitis (NASH); the latter ranges in severity from fibrosis to cirrhosis[8-10]. NAFLD is associated with type 2 diabetes mellitus, insulin resistance, cardiovascular disease and obesity, and is considered a hepatic manifestation of the metabolic syndrome[8-10]. NAFLD-HCC is much less understood than HCC arising on the background of alcoholic liver disease or viral hepatitis, and the population affected appears different: Patients tend to be older, have additional co-morbidities, and are diagnosed at more advanced stage disease[6,11,12]. This often means patients are unsuitable for some of the treatments and have worse prognosis.

The systemic treatment landscape for advanced HCC has undergone a major change in the recent years. Initially, introduction of single agent tyrosine kinase inhibitor (TKI) sorafenib conferred significant survival benefit *vs* placebo, and more recently, the combination of immune checkpoint inhibitor (ICI) + anti-vascular endothelial growth factor (VEGF) bevacizumab showed further benefits *vs* sorafenib, and have become standard of care[13]. However, although data of systemic agents from trials are limited specifically for the NAFLD-HCC aetiology, some evidence suggest that immunotherapy[14] may be less effective in this population[15].

HCC in the setting of NAFLD is more likely to be diagnosed at later stages, given non-cirrhotic patients are not routinely screened[16,17]. Further, NAFLD-HCC patients are typically older, and have high prevalence of type 2 diabetes mellitus, obesity, and cardiovascular and cerebrovascular disease[6,11,12]. This raises a number of treatment considerations for this population. Firstly, co-morbidities, especially cardiovascular, may preclude surgery. Secondly, obesity may have a negative effect on angiogenesis-targeting drugs such as bevacizumab[18]. On the other hand, obesity appears to be associated with better progression free survival and overall survival (OS) with ICIs in solid tumours[19-21]. Of note, a retrospective study found comparable efficacy of ICI atezolizumab + anti-VEGF bevacizumab in overweight and non-overweight HCC patients, including those with NAFLD[22]. Finally, although older age alone is unlikely to affect systemic treatment outcomes in NAFLD-HCC[23-25], there is an association between age and frailty in both non-cirrhotic [26] and cirrhotic NAFLD[27], and thus older age may negatively influence treatment options in NAFLD-HCC. Furthermore, immune senescence may work additively with immune deregulation seen in NAFLD-HCC to impact ICI outcomes.

Overall, NAFLD-HCC has worse prognosis *vs* other aetiologies and its treatment represents an urgent unmet clinical need. In addition, based on emerging data on pathogenesis as described below, there may be inherent differences in HCC biology in those patients *vs* those with other aetiologies. This narrative review briefly considers NAFLD-HCC pathophysiology, before focusing on summarising the current knowledge on its systemic treatment, and offering a view on future trial design points that address NAFLD-HCC specifically.

PATHOPHYSIOLOGY AND THE IMMUNE MICROENVIROMENT

The underlying pathophysiology of NAFLD-HCC is not well understood, with substantial proportion of HCC developing on the background of fibrotic rather than cirrhotic changes, highlighting complexity of the process. Accumulation of free fatty acids and resulting hepatic lipotoxicity is an important process driving endoplasmic reticulum and oxidative stress, inflammation, local tissue damage and fibrosis, all of which work together to advance progression of NAFLD *via* mechanisms effecting multiple metabolic pathways, autophagy and the immune system[16,28]. Importantly, hepatic oxidative stress drives carcinogenesis *via* DNA damage[16], but has also been implicated in activation of the tumour promoting interleukin (IL)-6 and/or Janus-activated kinase-signal transducer and activator of transcription (STAT) pathways, offering potential explanation for the uncoupling of fibrosis and HCC in the setting of NAFLD. Namely, it was shown in murine models that the obesity-driven oxidative hepatic environment was associated with development of inflammation, NASH and fibrosis *via* STAT-1, and - independently of NASH - with HCC *via* STAT-3[29].

Immune system plays an important role in the pathogenesis, with initial local inflammation driven by Kupffer cells, followed by hepatocyte damage, influx of platelets, neutrophils, and inflammatory monocytes[30]. The immune milieu changes over time with arrival of dysfunctional CD8+programmed cell death protein 1 (PD-1)+ T cells, which further drives increased lipid accumulation, lipid toxicity, and fibrotic response[30,31]. In murine models, mice with NASH were shown to have increased hepatic presence of CD8+PD1+ T cells with features of exhaustion and effector functions[31].

This would appear a prerequisite for successful immunotherapy with anti-PD-1 agents, however, although anti-PD-1 treatment expanded activated CD8+PD1+ T cells within tumours of mice with NASH-HCC, this did not lead to tumour regression[31]. Further, CD8+ T cell depletion significantly decreased liver damage and the incidence of HCC in mice with NASH[31]. Of note, scRNA-seq analysis demonstrated a resident-like liver CD8+PD1+ T cell population in patients with NAFLD/NASH that shared gene expression patterns with the detrimental hepatic CD8+PD1+ T cells from NASH mice[31]. Overall, preclinical and clinical studies on adaptive immunity thus far illustrate CD8+ T cells promote HCC in NASH, likely *via* impaired tumour surveillance and enhanced T cell-mediated tissue damage[31], and CD4+ T-cells to be protective in this setting[32,33]. This is likely an important finding given that it was previously found that increased numbers of tumour infiltrating CD8+ T cells correlated with improved survival and disease progression in human HCC [34], but this was not examined based on aetiology. Further, a subset of activated CD8+ T-cells was identified in viral HCC that correlated with better patient survival[35].

TREATMENT

Currently, there are no specific guidelines for NAFLD-HCC treatment - all HCC are managed the same, regardless of aetiology.

CURRENT TREATMENT LANDSCAPE

Treatment of HCC is guided by Barcelona Clinic Liver Cancer (BCLC) staging[36]. Broadly, BCLC stages 0-A are treated with curative intent with surgery, radiotherapy, ablation and liver transplantation. Transarterial chemoembolization (TACE) and radioembolization are limited to BCLC stage B disease and systemic therapy is used for BCLC stage C where the aim is palliation[37]. Data mainly from retrospective studies suggest similar outcomes with resection, liver transplantation, ablation and TACE between NALFD and non-NAFLD-HCC, however, these treatment modalities are outside of scope of this review (reviewed in 2022 by Foerster *et al*[38], 2022 by Tan *et al*[6], 2023 by Llovet *et al*[39]).

SYSTEMIC TREATMENT

Systemic treatment in HCC is used in unresectable/advanced disease with preserved liver function (Child-Pugh A) and Eastern Cooperative Oncology Group Performance Status 0-2[37]. Approved options are either combination atezolizumab + bevacizumab or single-agent TKIs[37]. A number of clinical trials testing various combination regimens have been completed/are ongoing, with a recent meta-analysis of available results finding combinations of ICI + anti-VEGF and ICI + ICI achieving greatest OS benefit *vs* the TKI sorafenib[14]. Whilst combination immunotherapy improves clinical outcomes, evidence from initial studies suggests that underlying aetiology of liver disease determines clinical benefit, and that treatment allocation should be stratified accordingly. This concept stemmed from the initial IMbrave150 trial, which illustrated a significant survival benefit *vs* sorafenib, establishing combination immunotherapy as the first line for advanced HCC [OS hazard ratio (HR) *vs* sorafenib 0.58 (95% confidence interval: 0.42-0.79; $P < 0.001$)][40]. However, in a subgroup analysis, the non-viral population did not benefit from combination therapy[40] (Table 1).

No prospective, randomised controlled studies evaluated the efficacy and safety of systemic treatment options in NAFLD-HCC specifically. Available data are mainly from subgroup analysis of pivotal studies, where aetiologies were grouped broadly into viral *vs* non-viral; completed Phase 3 studies are shown in Table 1. Patients with known non-viral aetiology comprised between 15% and 59% of the population across those studies, with NAFLD/NASH accounting for around one-fourth of this subgroup (when reported)[40-53] (Table 1). Below we present a review of current aetiology-based evidence for NAFLD/NASH-HCC treatment.

ICI MONOTHERAPY AND COMBINATIONS

As mentioned above, the pivotal IMbrave150 study sparked concern as to benefit of ICI in patients with HCC of non-viral aetiology40 (Table 1). Looking at evidence for ICI monotherapy, Checkmate-459 (nivolumab)[52] and Keynote-240 (pembrolizumab)[46] were both negative studies with OS HR of 0.85 (95%CI: 0.72-1.02) and 0.781 (0.611-0.998), respectively. The non-viral subgroup had numerically worse survival outcome compared with HBV and HCV in Checkmate-459, and placed in-between HBV and HCV in Keynote-240[46,52] (Table 1). In the recently reported RATIONALE, tislelizumab was shown non-inferior to sorafenib with higher overall response rate and more durable responses [superiority was not met; OS HR of 0.85 (95%CI: 0.71-1.02)][51]. Here, too, the HR for OS for the non-viral subgroup placed between the two viral aetiologies[51] (Table 1), suggesting that aeitology did not determine outcome.

A meta-analysis of CheckMate-459, IMbrave150 and KEYNOTE-240 showed that although ICI improved survival in the overall population (HR = 0.77; 95%CI: 0.63-0.94), survival benefit was observed in patients with HBV-HCC ($n = 574$; $P = 0.0008$) and HCV-HCC ($n = 345$; $P = 0.04$), but not in patients with non-viral HCC ($n = 737$; $P = 0.39$)[31]. This was confirmed by another aetiology-based analysis of those three studies[54]. A number of trials studied combinations of ICI

Table 1 Phase 3 studies of systemic treatment of hepatocellular carcinoma

Trial	Line	Treatment arm	HCC aetiology[1]	*N* (%)[2]	OS HR (95%CI)
ICI monotherapy					
Checkmate-459[52]	1	Nivolumab (*vs* sorafenib)	Non-viral	168 (45)	0.95 (0.74-1.22)
			NAFLD/NASH	N/A	
			HBV		0.77 (0.56-1.05)
			HCV		0.71 (0.49-1.01)
Keynote 240[46]	2	Pembrolizumab (*vs* placebo)	Non-viral	163 (59)	0.88 (0.64-1.20)
			NAFLD/NASH	N/A	
			HBV		0.57 (0.35-0.94)
			HCV		0.96 (0.48-1.92)
RATIONALE-301[51]	1	Tislelizumab (*vs* sorafenib)	Non-viral	82 (24)	0.78 (0.55-1.12)
			NAFLD/NASH	N/A	
			HBV		0.91 (0.73-1.14)
			HCV		0.64 (0.38-1.08)
Combination ICI + anti-VEGF					
IMbrave150[40,44]	1	Atezolizumab + bevacizumab (*vs* sorafenib)	Non-viral	100 (30)	1.05 (0.68-1.63)
			NAFLD/NASH	N/A	
			HBV		0.51 (0.32.081)
			HCV		0.43 (0.22-0.87)
Combination ICI + TKI					
COSMIC-312[47]	1	Atezolizumab + cabozantinib (*vs* sorafinib)	Non-viral	169 (39)	1.18 (0.78-1.79)[3]
			NAFLD/NASH	38 (15)	Not reported
			HBV	74 (30)	0.53 (0.33-0.87)[3]
			HCV	34 (28)	1.1 (0.72-1.68)[3]
CARES-310[50]	1	Camrelizumab + rivoceranib (*vs* sorafenib) P3, 1L	Non-viral	42 (15)	0.71 (0.37-1.36)
			NAFLD/NASH	N/A	
			HBV	208 (76)	0.66 (0.50-0.87)
			HCV	22 (8)	0.45 (0.18-1.16)
LEAP-002[45]	1	Pembrolizumab + lenvatinib (*vs* lenvatinib) P3, 1L	Not reported	N/A	N/A
Combination ICI + ICI					
Himalaya[41]	1	Durvalumab + tremelimumab (*vs* sorafenib) P3, 1L	Non-viral	161 (41)	0.74 (0.57-0.95)
			NAFLD/NASH	N/A	
			HBV	122 (31)	0.64 (0.48-0.86)
			HCV	110 (28)	1.06 (0.76-1.49)
TKI monotherapy					
SHARP[49]	1	Sorafenib (*vs* placebo)	Non-viral	107 (35)	Not reported
			NAFLD/NASH	N/A	
REFLECT[48]	1	Lenvantinib (*vs* sorafenib)	Non-viral	74 (16)	Reported only for alcohol
			NAFLD/NASH	N/A	
RESORCE[43]	2	Regorafenib (*vs* placebo)	Non-viral	143 (38)	Reported only for alcohol
			NAFLD/NASH	N/A	Not reported

CELESTIAL[42]	2	Cabozantinib (*vs* placebo)	Non-viral	179 (38)	0.72 (54-0.96)
			NAFLD/NASH	43 (9)	Not reported
			HBV		0.69 (0.51-0.94)
			HCV		1.11 (0.72-1.71)
Anti-VEGF monotherapy					
REACH-2[53]	2	Ramucirumab (*vs* placebo)	Non-viral	72 (37)	0.63 (0.38-1.06)
			NAFLD/NASH	19 (10)	Not reported
			HBV		0.84 (0.52-1.35)
			HCV		0.76 (0.44-1.33)

[1]SHARP, REFLECT - alcohol, other; RESORCE, CELESTIAL - alcohol, other, non-alcoholic steatohepatitis (NASH); REACH-2 - alcohol, NASH, primary biliary cirrhosis, hereditary hemochromatosis, hepatitis non-A, non-B, non-C virus; Checkmate-459, Keynote 240, RATIONALE-301 - uninfected; IMbrave150 - alcohol, other, non-hepatitis B and C causes; COSMIC-312 - alcohol, non-alcoholic fatty liver, NASH, other; CARES-301 - NAFLD, alcohol cirrhosis, aflatoxin exposure, other unknown non-hepatitis B virus and non-hepatitis C virus causes; Himalaya - No active viral hepatitis identified.
[2]Number of patients in treatment arms; those with unknown aetiology were excluded where possible.
[3]Interim analysis.
HCC: Hepatocellular carcinoma; OS: Overall survival; HR: Hazard ratio; 95%CI: 95% confidence interval; ICI: Immune checkpoint inhibitor; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; HBV: Hepatitis B virus; HCV: Hepatitis C virus; N/A: Not applicable; VEGF: Vascular endothelial growth factor; TKI: Tyrosine kinase inhibitor.

+ TKI/ICI (Table 1). In COSMIC-312, the interim analysis of OS showed no clear benefit of atezolizumab + cabozantinib *vs* sorafenib for the non-viral population[47]. Of note, in this study, whilst there was OS benefit for the HBV-HCC group, no benefit was also observed for the HCV-HCC group[47]. Authors of another combination study, CARES-310, concluded that camrelizumab + rivoceranib *vs* sorafenib offered similar benefits in terms of progression-free survival (PFS) and OS in viral and non-viral populations[50], however, the vast majority of patients (76%) had HBV, and confidence intervals for OS crossed 1 for both HCV-HCC and non-viral HCC. Finally, in Himalaya, the survival benefit with durvalumab + tremelimumab *vs* sorafenib (overall population HR = 0.78, 95%CI: 0.65-0.93; $P = 0.0035$) was maintained in the non-viral and HBV subgroups, but not in the HCV subgroup[41].

The most recent aetiology-based meta-analysis of eight randomised trials of ICI-based systemic therapy found significant survival advantage across both non-viral and viral aetiologies (HR = 0.79, 95%CI: 0.72-0.86, $P < 0.001$), with the largest estimated benefit for those with HBV (HBV: HR = 0.70, $P < 0.001$; HCV: HR = 0.78, $P = 0.04$; non-viral: HR = 0.87, $P = 0.02$)[55]. Overall, the authors were of opinion that it is premature to conclude that patients with non-viral liver disease do not benefit from ICI-based therapy[55].

However, a recent retrospective, propensity score matched study of patients with non-viral advanced HCC who were treated with atezolizumab + bevacizumab, or lenvatinib, or sorafenib showed that treatment with lenvatinib is associated with a significant survival benefit *vs* atezolizumab + bevacizumab, in particular in patients with NAFLD/NASH-related HCC (OS HR = 0.46; 95%CI: 0.26-0.84; $P = 0.0110$; and PFS HR = 0.55; 95%CI: 0.38-0.82; $P = 0.031$); of note, no difference in OS and PFS was found in comparison of sorafenib vs atezolizumab + bevacizumab[56].

Thus, although the majority of the above studies report no survival benefit with ICI in the non-viral subgroups, this is certainly not uniform. The heterogeneity of study populations, lines of treatment, and the exploratory nature of subgroup analysis make data difficult to interpret. In addition, the control arm performed a lot better in some studies. Furthermore, mixed results among the two viral subgroups suggest that the issue of ICI efficacy is more complex and likely influenced by multiple factors related to the individual patient. Finally, the non-viral subgroup is itself a heterogeneous group, most often comprising alcoholic liver disease, NAFLD/NASH, and other aetiologies, and thus this population cannot be taken to simply represent those with NAFLD/NASH-HCC. Only COSMIC 312 reported data on 38 patients with NAFLD/NASH again illustrating the limitations of the published studies in drawing firm conclusions with regards to the efficacy of ICI in this patient group[47].

TKI OR ANTI-VEGF MONOTHERAPY

First line options in HCC are single-agent sorafenib or lenvatinib, with cabozantinib and regorafenib in second line[37]. No data on non-viral aetiology were reported in the registration trials of sorafenib (SHARP)[49], lenvatinib (REFLECT)[48], and regorafenib[43] (Table 1). In the phase 3 study of cabozantinib (CELESTIAL), the HR for OS in the non-viral group was 0.72 (95%CI: 0.54-0.96), which was similar to overall population (0.76, 95%CI: 0.63-0.92) and HBV, and numerically better than HCV[42] (Table 1). Further, in an international cohort study of 5201 HCC patients treated with sorafenib, those with NAFLD ($n = 183$) had the same OS *vs* those without (HR = 0.99, 95%CI: 0.84-1.18, $P = 0.98$), and safety profile was similar[57].

Single-agent ramucirumab is a standard of care option beyond first-line for those patients with an alpha-fetoprotein greater than 400 ng/mL[37]. In REACH-2 study, OS HR with this agent was 0.63 (95%CI: 0.38-1.06) in the non-viral population, which, again - although CIs were crossing 1 - was similar to the overall population [0.74 (95%CI: 0.56-0.99)], and numerically better than for HCV and HBV subgroups[53] (Table 1).

Finally, an aetiology based meta-analysis of five randomised controlled studies of systemic treatment with TKI/anti-VEGF (n = 2083) showed that OS benefit was unaffected by the underlying driver of HCC [HR for viral was 0.81 (95%CI: 0.71-0.92) and for non-viral was 0.82 (95%CI: 0.67-1.01); P = 0.8828][54]. Thus, based on the available data, it would appear outcomes with single-agent TKI and ramucirumab may be similar in the NAFLD and overall HCC population, however samples in individual studies are small and the same caveats regarding non-viral group composition apply as in the ICI studies.

FUTURE DIRECTIONS

NAFLD-HCC is a relatively uncharacterised yet growing clinical problem and there are several key questions future efforts should endeavour to answer. The current treatment gaps centre around pathophysiology of HCC in the setting of NAFLD and the clinical safety and efficacy of systemic treatments specifically in the NAFLD-HCC population. Further understanding of the pathophysiology is essential to develop treatment strategies. Emerging data are mainly preclinical and suggest HCC in NASH may be driven by impaired immunological surveillance and dysfunctional CD8+T-cells[31] as well as aberrant STAT-1 signalling, whilst in the absence of NASH, STAT-3 signalling has been suggested to promote NAFLD-HCC[29]. Delineating immunological milieu as well as contribution of any alterations to commonly implicated signalling pathways across natural progression from fatty liver to HCC, with or without fibrosis and cirrhosis, would likely offer some answers. This will likely involve preclinical studies involving mice studies, as well as translational studies with a bench-to-bedside approach and the use of multiomics.

Prospective clinical trials specifically of patients with NAFLD/NASH-HCC are urgently needed given paucity of evidence in this space. Currently available data seem to point towards similar efficacy with TKI/anti-VEGF and potentially poor efficacy with ICI, however, this is based on results for non-viral subgroups, where NAFLD/NASH was the aetiology in approximately 25% of patients only, a subgroup of a subgroup. In addition, those subgroups were not pre-planned and analyses were not powered. Thus, generalisation of non-viral subgroup to mean ICI does not offer benefit in NAFLD/NASH-HCC is not substantiated by robust evidence currently. Moving forward, how best to select patients for such trials is a pertinent question. Ideally, patients should include full spectrum of NAFLD, from simple fatty liver to cirrhosis, to allow assessment of any differences in treatment response and identify any relevant variables. However, this may prove difficult in practice given there are no widely-accepted uniform diagnostic criteria for NAFLD, whilst diagnosis of NASH requires liver biopsy. In addition, the term NAFLD is contended by some experts as potentially stigmatising and not sufficiently reflective of the metabolic component[58]. A recent multi-society Delphi consensus from the NAFLD Nomenclature Consensus Group suggested replacement of the term NAFLD with metabolic dysfunction-associated steatotic liver disease (MASLD), and use cryptogenic steatotic liver disease in those with no metabolic parameters and no known cause; in addition, a new category, outside pure MASLD, termed MetALD was proposed to describe those with MASLD who consume greater amounts of alcohol per week[58]. This underscores another difficulty in obtaining evidence for aetiology-based approach, namely co-existence of multiple aetiologies in one patient. In a recent comprehensive review on global epidemiology of cirrhosis, it has been highlighted that many of the included studies did not account for multiple aetiologies, and the authors speculated that more than one cause of cirrhosis is present in a substantial proportion of patients, especially considering the growing prevalence of obesity and increasing alcohol consumption[59]. By extension, the prevalence and composition of mixed aetiology as underlying cause of HCC is not known, neither is its significance for tumorigenesis and treatment response. Despite these issues, there is an increasing interest in the role of aetiology on treatment outcomes, and as our understanding improves it is likely that in the next 5 years we will see the introduction of management tailored according to disease aetiology.

Further, aside from one retrospective study of sorafenib that found similar safety profile in NAFLD- and non-NAFLD-HCC, no studies or analyses examined the nature, frequency or severity of adverse events according to HCC aetiology. For example, is hypertension with TKIs or bevacizumab more common/severe in those with metabolic syndrome, and if so if this is clinically relevant. Finally, ICI use in those with prior liver (or any solid organ) transplantation carries a risk of organ rejection, and so best possible evidence on the benefits of treatment with ICI is needed to guide informed decision making in such situations.

CONCLUSION

NAFLD-HCC is an increasing patient group that urgently requires attention both in terms of investigating pathophysiology and therapy. Whilst IMbrave150 sparked a discussion regarding aetiology based treatment stratification, this is not borne out by meta-analysis and currently there is no evidence for this approach. Prospective studies that accurately define the NAFLD population are needed to further evaluate if a different approach is needed but currently NAFLD-HCC should be treated as other aeitologies.

FOOTNOTES

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