Digestive and Liver Disease xxx (xxxx) xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Review Article

Efficacy of immunotherapy in hepatocellular carcinoma: Does liver disease etiology have a role?

Elisa Pinto[1], Paola Meneghel[1], Fabio Farinati, Francesco Paolo Russo*, Filippo Pelizzaro, Martina Gambato*

Gastroenterology and Multivisceral Transplant Unit, Padua University Hospital, Padua, Italy

ARTICLE INFO

Article history:
Received 2 July 2023
Accepted 30 August 2023
Available online xxx

Keywords:
Immune checkpoint inhibitors
Liver cancer
NASH
Non-alcoholic fatty liver disease
Systemic therapy

ABSTRACT

The systemic treatment of hepatocellular carcinoma (HCC) is changing rapidly. After a decade of tyrosine kinase inhibitors (TKIs), as the only therapeutic option for the treatment of advanced HCC, in the last few years several phase III trials demonstrated the efficacy of immune checkpoint inhibitors (ICIs). The combination of the anti-PD-L1 atezolizumab and the anti-vascular endothelial growth factor (VEGF) bevacizumab demonstrated the superiority over sorafenib and currently represents the standard of care treatment for advanced HCC. In addition, the combination of durvalumab (an anti-PD-L1) and tremelimumab (an anti-CTLA4) proved to be superior to sorafenib, and in the same trial durvalumab monotherapy showed non-inferiority compared to sorafenib. However, early reports suggest an influence of HCC etiology in modulating the response to these drugs. In particular, a lower effectiveness of ICIs has been suggested in patients with non-viral HCC (in particular non-alcoholic fatty liver disease). Nevertheless, randomized controlled trials available to date have not been stratified for etiology and data suggesting a possible impact of etiology in the outcome of patients managed with ICIs derive from subgroup not pre-specified analyses. In this review, we aim to examine the potential impact of HCC etiology on the response to immunotherapy regimens for HCC.

1. Introduction

The global burden of primary liver cancer is considerable and continuously growing [1]. According to 2020 estimates, liver cancer is the sixth most commonly diagnosed cancer and the third most common cause of cancer-related death [2]. Incidence and mortality rates of liver cancer have dropped in some Eastern Asian countries including Japan, China, and the Republic of Korea, but its rates have increased in many previously low-incidence countries across the world, such as the US, Australia, and several European countries [1]. Among primary liver cancers, hepatocellular carcinoma (HCC) is the most important [3], and it commonly develops in the context of chronic liver disease, driven by liver inflammation.

Worldwide, the main causes of HCC remain chronic hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection and alcohol abuse. However, over the last two decades, a growing proportion of HCCs has been associated to metabolic disorders such as obesity, diabetes and hyperlipidemia, inducing fatty liver. Indeed, non-alcoholic fatty liver disease (NAFLD) has grown over the past two decades from a relatively unknown disease (and underestimated in terms of clinical consequences) to one of the recognized most common cause of chronic liver disease worldwide. Currently, NAFLD is estimated to affect 25% of the general population. Non-alcoholic steatohepatitis (NASH), the subtype of NAFLD that can progress to cirrhosis, HCC and liver-related death, is the most rapidly increasing indication for liver transplantation in the United States (US) [4].

HCC is characterized by a poor prognosis (5-year survival rate of approximately 20%), mainly due to the fact that the majority of patients are diagnosed in advanced stage when curative treatments are no longer an option [5]. Until recently, the only available systemic therapy options in the treatment of HCC were tyrosine kinase inhibitors (TKIs). In this setting, sorafenib was the first drug that demonstrated to be effective [6,7]. For a decade, all drugs evaluated in randomized phase III trials failed to demonstrate efficacy, until the advent of lenvatinib in frontline setting [8], and regorafenib, cabozantinib and ramucirumab in the second line [9–11]. Despite the expanding treatment possibilities, the survival benefit has been modest, with a median overall survival

* Corresponding authors.
E-mail addresses: francescopaolo.russo@unipd.it (F.P. Russo), martina.gambato@gmail.com (M. Gambato).
[1] These authors contributed equally.

https://doi.org/10.1016/j.dld.2023.08.062

(OS) ranging from 11 to 14 months with first-line sorafenib or lenvatinib [12]. In the setting of systemic treatment for HCC, the demonstration of immune checkpoint inhibitors (ICIs) efficacy has been a breakthrough. In particular, in the IMbrave150 trial the combination of atezolizumab (an anti-programmed death ligand 1 [PD-L1] monoclonal antibody) and bevacizumab (an anti-VEGF monoclonal antibody) demonstrated to be significantly superior compared to sorafenib, with a median OS in the combination arm of 19.2 months [13,14]. After these positive results, the atezolizumab + bevacizumab combination became the standard of care first-line treatment in patients with HCC. Very recently, another ICIs-based combination proved to be significantly superior to sorafenib in frontline. In the HYMALAIA trial, the median survival of patients treated with durvalumab (anti-PD-L1) and tremelimumab (anti-CTLA4) was significantly longer compared to those receiving sorafenib [15]. Considered the remarkable survival benefit obtained with ICIs-based regimens, the treatment of HCC entered the era of immunotherapy.

Despite these very encouraging results, not all patients with HCC benefit from receiving these drugs. Indeed, a relevant proportion of patients do not achieve disease control with ICIs [16]. Among the variable and multiple reasons that may explain the poor response of some patients, HCC etiology has been suggested has a role. Some studies showed that patients with non-viral HCC may have a poorer response to ICIs compared to those with virus-related HCC [17]. This clinical observation could be explained by the specific immune dysfunctions associated with different liver disease etiologies [18]. Chronic viral infections can contribute to hepatocarcinogenesis both by inducing pro-inflammatory innate immune activation and by driving aberrant adaptive immune responses that fail to clear hepatotropic viruses (for example, HCV-induced T cell exhaustion) and instead promote tumorigenesis. On the other hand, emerging evidence points towards a more prominent role of adaptive immune cells in the NASH–HCC transition with a decrease in anti-tumor CD4+ T cells and aberrant CD8+ T cell activation within the tumor [18]. Several data have been recently published regarding a possible role of liver disease etiology in modulating the response to different HCC immunotherapy regimens and, in this review, we aimed to report the data available so far.

2. Landscape of immunotherapy for HCC

Our immune system plays a fundamental anti-tumor activity, recognizing and destroying cancer cells. The activation of antitumor immunity is a complex process, in which several cells are involved. The uncontrolled proliferation of cancer cells causes the activation of innate immunity, namely natural killer (NK) cells, that targets cancer cells causing their apoptosis and the release of tumor-associated antigens (TAAs). These TAAs released in the tumor microenvironment (TME) are captured by antigen presenting cells (APCs), which then migrated to lymph nodes where neoantigens are presented through major histocompatibility complex (MHC) to T-cell receptor (TCR) on immature T lymphocytes. The recognition of TAAs presented by the APCs as non-self is not sufficient to activate naïve T lymphocytes and an additional co-stimulatory signal is required. This co-stimulatory signal, that makes the T cell fully activated, is usually provided by the interaction between CD28 on T cells and B7-1 (or B7-2) on APCs (*priming phase*). Once activated, T lymphocytes return to the tumor through the bloodstream, recognize tumor antigens presented by tumor cells MHC and triggers an attack with the release of perforin and granzyme that destroy cancer cells (*effector phase*) [19].

This mechanism is at the basis of antitumor immune surveillance, but on the other hand cancer cells are able to develop strategies aimed at evading the host's immune control. In particular, cancer cells can express molecules that inhibit immune response reducing MHC expression in APCs, inhibiting co-stimulatory signals or promoting co-inhibitory signals [20,21]. These molecules, that are fundamental in counterbalancing lymphocyte activation in physiological condition in order to avoid overactivation of immune system, are known as immune checkpoint inhibitors (ICIs). The most important of these molecules are cytotoxic T lymphocytes antigen 4 (CTLA4), programmed cell death protein-1 (PD-1) and its ligand (PD-L1). In detail, CTLA4 exerts its activity binding to B7-1 and B7-2 with an affinity 10-times higher compared to CD28. As a consequence, B7 (1 and 2) preferentially bind to CTLA4 over CD28 and the co-stimulatory signal necessary to T lymphocytes activation does not occur. PD-1 is a co-inhibitory receptor expressed on T cells (as well as in other immune cells), that prevents their antigen-specific activation through the interaction with its ligand (PD-L1). As a results of this interaction, T lymphocytes are inhibited in their activation and the immune response is weakened, resulting in immune escape or immune tolerance. Tumors can use these mechanisms in order to avoid immune-mediated destruction, not only by expressing ligands activating the immune checkpoints themselves, but also favoring the development of a tolerant TME through the recruitment of non-neoplastic cells expressing these molecules. ICIs are monoclonal antibodies specifically designed to disrupt these ligand/receptor interactions, removing T cells inhibition and promoting their antitumoral cytotoxic activity.

Several ICIs have been investigated as systemic therapies for HCC. In Table 1, the results of the most important clinical trials investigating immunotherapies in this setting are reported. Several other trials are currently ongoing, also in adjuvant/neoadjuvant setting for patients at earlier tumor stage.

2.1. ICIs monotherapies

The era of immunotherapy for HCC started with trials investigating ICIs monotherapies. Based on the very promising results on tumor objective response obtained in phase II trials (Checkmate040 and KEYNOTE-224), the Food and Drug Administration (FDA) accelerated the approval to nivolumab (anti-PD1) and pembrolizumab (anti-PD1) as second-line treatment for sorafenib-experienced advanced HCC patients [22,23]. Unfortunately, the encouraging results with these anti-PD-1 molecules were not confirmed in the phase III randomized controlled trials, as OS was not superior in ICIs arm. Indeed, in the Checkmate459 trial, Nivolumab failed to demonstrate a superiority in OS over sorafenib in first-line since it did not meet the prespecified statistical significance (HR = 0.85, 95% CI 0.72–1.02; $p = 0.075$) [24]. Similarly, in the KEYNOTE-240 trial comparing pembrolizumab vs. placebo in second-line after sorafenib, OS (HR = 0.781, 95% CI 0.611–0.998; $p = 0.0238$) and progression free survival (PFS) (HR = 0.775, 95% CI 0.609–0.987; $p = 0.0186$) did not reach statistical significance for the specific endpoints [25]. Recently, pembrolizumab was tested versus placebo in Asian patients with advanced HCC progressed after the first-line (KEYNOTE-394 trial), demonstrating a significant improvement of OS, PFS and ORR [26]. These results were consistent with that previously observed in K EYNOTE-224 and KEYNOTE-240 trials.

Despite unsuccessful, these trials with ICI monotherapies provided valuable insights. Firstly, these drugs demonstrated to be safe and well-tolerated even in compensated cirrhotic patients [24,25]. Secondly, the objective response rate achievable with ICIs was 15–18%, significantly higher compared to TKIs [22]. Lastly, patients with an objective response rate showed long survival (17 months, 95% CI 6–24).

To address the limitations of single-agent immunotherapy in terms of survival benefit, combination strategies involving different drugs have been explored, as following explained.

Table 1
Results of the most important clinical trials investigating immunotherapies in HCC.

Trial	Phase	Investigational drug(s)	Comparator	Median OS (HR, 95% CI)	Median PFS (HR, 95% CI)	ORR
First-line setting						
IMbrave150 [13,14]	III	Atezolizumab + Bevacizumab (n = 336)	Sorafenib (n = 165)	19.2 vs. 13.4 months (0.66, 0.52–0.85; p < 0.001)	6.9 vs. 4.3 months (0.65, 0.53–0.81; p < 0.001)	30% vs. 11% (p < 0.001)
ORIENT-32 [29]	III	Sintilimab + IBI305 (bevacizumab biosimilar) (n = 380)	Sorafenib (n = 191)	NE vs. 10.4 months (0.57, 0.43–0.75; p < 0.0001)	4.6 vs. 2.8 months (0.56, 0.46–0.70; p < 0.0001)	21% vs. 4% (p < 0.0001)
CheckMate 459 [24]	III	Nivolumab (n = 371)	Sorafenib (n = 372)	16.4 vs. 14.7 months (0.85, 0.72–1.02; p = 0.075)	3.7 vs. 3.8 months (0.93, 0.79–1.10; p = ns)	15% vs. 7% (p = NR)
Cosmic 312 [a] [33]	III	Atezolizumab + Cabozantinib (n = 432)	Sorafenib (n = 217)	15.4 vs. 15.5 months (0.90, 0.69–1.18; p = 0.44)	6.8 vs. 4.2 months (0.63, 0.44–0.91; p = 0.0012)	11% vs. 4% (p = NR)
HIMALAYA[b] [15]	III	Tremelimumab + Durvalumab (STRIDE) (n = 393)	Sorafenib(n = 389)	16.4 vs. 13.8 months (0.78, 0.65–0.93; p = 0.0035)	3.8 vs. 4.1 months (0.90, 0.75–1.05; p = NR)	20.1% vs. 5.1% (p = NR)
		Durvalumab (n = 389)	Sorafenib(n = 389)	16.4 vs. 16.6 months (0.86, 0.73–1.03; noninferiority margin 1.08)	3.7 vs. 4.1 months (1.02, 0.88–1.19; p = NR)	17.0% vs. 5.1% (p = NR)
LEAP-002[c] [34]	III	Lenvatinib + Pembrolizumab (n = 395)	Lenvatinib (n = 399)	21.2 vs. 19.0 months (0.840, 0.708–0.997; p = 0.0227)	8.2 vs. 8.0 months (0.867, 0.734–1.024; p = 0.0466)	26.1% vs. 17.5% (p = NR)
RATIONALE-301[c] [99]	III	Tislelizumab (n = 342)	Sorafenib (n = 332)	15.9 vs. 14.1 months (0.85, 0.71–1.02; p = NR) [d]	2.2 vs. 3.5 months (1.10, 0.92–1.33; p = NR)	14.3% vs. 5.4% (p = NR)
NCT03764293[c] [35]	III	Camrelizumab + Rivoceranib (Apatinib) (n = 272)	Sorafenib (n = 271)	22.1 vs. 15.2 months (0.62, 0.49–0.80; p < 0.0001)	5.6 vs. 3.7 months (0.52, 0.41–0.65; p < 0.0001)	25.4% vs. 5.9% (p < 0.0001)
Second-line setting						
KEYNOTE-224 [23]	II	Pembrolizumab (n = 104)	–	12.9 months	4.9 months	17%
KEYNOTE-240 [25]	III	Pembrolizumab (n = 278)	Placebo (n = 135)	13.9 vs. 10.6 months (0.781, 0.611–0.998; p = 0.0238)	3.0 vs. 2.8 months (0.718, 0.570–0.904; p = 0.0022)	18.3% vs. 4.4% (p = 0.00007)
KEYNOTE-394[c,e] [26]	III	Pembrolizumab (n = 300)	Placebo (n = 153)	14.6 vs. 13.0 months (0.79, 0.63–0.99; p = 0.018)	2.6 vs. 2.3 months (0.74, 0.60–0.92; p = 0.0032)	12.7% vs. 1.3% (p = 0.00004)
CheckMate 040 [31]	I/II	Nivolumab (n = 214 [f])	–	15.6 months [g]	4.0 months [h]	14% [g]
CheckMate 040 [31]	I/II	Nivolumab + ipilimumab (n = 50 in arm A [i])	–	22.8 months	NR	32%
RESCUE [100]	II	Camrelizumab + Apatinib (n = 120)	-	NR	5.5 months	22.5%
NCT02519348	I/II	Durvalumab + Tremelimumab (n = 75[l])	–	18.7 months	2.2 months	24%
NCT01008358	II	Tremelimumab (n = 21)	–	8.2 months	6.5 months	17.6%
NCT02989922	II	Camrelizumab (n = 217)	–	13.8 months	2.1 months	14.7%
RATIONALE-208 [101]	II	Tislelizumab (n = 249)	–	13.2 months	2.7 months	13%

2.2. Anti-PD1/PD-L1 in association with intravenous anti-VEGF agents

The results of the IMbrave150 trial represented a breakthrough in the field of systemic treatment for HCC, changing the paradigm of TKIs-based therapy that dominated the previous decade. In this trial, patients were randomized in a 2:1 ratio to receive the anti-PD-L1 monoclonal antibody atezolizumab plus the anti- VEGF bevacizumab or sorafenib [13]. This combination is rationale from a scientific point of view considering that bevacizumab not only targets the angiogenetic pathway, which is one of the most important in the progression of HCC, but also is able to convert an immunosuppressive TME in an immunostimulatory milieu through the normalization of tumor vasculature and an immunomodulator effect [27,28]. In the IMbrave150 trial, atezolizumab + bevacizumab demonstrated to be significantly superior compared to sorafenib both in OS and in PFS (co-primary endpoints), and the median survival of patients treated with the combination was 19.2 months (95% CI 17.0–23.7), the longest OS achieved in HCC patients treated with systemic therapies [13,14]. In addition, atezolizumab and bevacizumab combination were superior for all secondary endpoints (objective response rate, duration of response, time to deterioration of quality of life) compared to TKI. As a consequence, atezolizumab + bevacizumab is currently recommended as standard of care first-line treatment in HCC.

The efficacy of this combination has been recently confirmed in another phase III trial (ORIENT-32) in which the combination of sintilimab (an anti-PD-1 monoclonal antibody) and the anti-VEGF IBI305 (a bevacizumab biosimilar) was compared to sorafenib in Chinese patients with HBV-related HCC [29]. Also, in this trial the combination of ICIs with antiangiogenic therapy was able to provide a statistically significant survival benefit compared to TKI therapy.

2.3. Combination of PD-1 and CTLA4 inhibitors (dual checkpoint blockade)

In order to enhance immune response against tumor, the dual blockade of CTLA4 and PD-1/PD-L1 was investigated. The rationale was that cancer cells are able to evade immune surveillance by exploiting different checkpoints inhibitors.

In the phase III HYMALAIA trial, the combination of the anti-PD-L1 durvalumab and of the anti-CTLA4 tremelimumab (STRIDE, single-tremelimumab regular-interval durvalumab) was compared to sorafenib in first-line [30]. The trial met its primary endpoint of superiority of the combination over sorafenib, with a median OS of 16.4 months (95% CI, 14.2–19.6) for the STRIDE group vs 13.8 months (95% CI, 12.3–16.1) for the sorafenib group (HR=0.78, 96% CI, 0.65–0.93). Grade 3/4 treatment-adverse events (AEs) occurred in 25.8% of patients treated with STRIDE and in 36.9% patients receiving sorafenib [30]. In the same trial durvalumab monotherapy demonstrated its non-inferiority compared to sorafenib, with a me-

dian OS of 16.6 months (95% CI, 14.1–19.1; HR 0.90; 96% CI, 0.75–1.03; non-inferiority margin, 1.08).

In the nivolumab + ipilimumab (an anti-CTLA4 monoclonal antibody) cohort of the phase 1/2 Checkmate040 trial, this treatment combination demonstrated manageable safety, promising objective response rate, and durable responses [31]. These results granted FDA accelerated approval for the combination therapy in second-line setting. The phase III trial investigating nivolumab + ipilimumab combination against sorafenib (Checkmate 9DW, NCT04039607) is currently ongoing.

2.4. Anti-PD1/PD-L1 in association with TKIs

Another strategy developed to overcome the resistance to ICIs monotherapy is the combination of immunotherapy with TKIs. A synergistic effect has been proposed based on the mechanism of action of TKIs [32], because these drugs are known to block signaling from multiple growth factors and also impact immune effectors, leading to a potentially enhanced therapeutic effect of ICIs. However, despite these encouraging premises, data from the available phase III clinical trial seem not to confirm a statistically significant advantage of ICIs + TKIs combination compared to TKIs monotherapy.

In the COSMIC-312 trial, patients were randomized to receive sorafenib monotherapy compared to the combination cabozantinib + atezolizumab. This trial was designed to demonstrate the superiority of the combination in OS and PFS as co-primary endpoints [33]. While cabozantinib + atezolizumab was able to provide a PFS superiority compared to sorafenib (6.8 vs. 4.2 months, respectively; HR 0.63, 99% CI 0.44–0.91), the two treatment arms were not different in terms of OS (15.4 vs. 15.5 months; HR 0.90, 96% CI 0.69–1.18).

Another TKI + ICI combination was tested in the LEAP-002 study. This trial compared the combination lenvatinib + pembrolizumab vs. lenvatinib monotherapy in previously untreated patients with HCC [34]. This trial also failed to demonstrate a superiority of the combination therapy, since for both OS (HR = 0.840, 95% CI0.708–0.997, $p = 0.0227$) and PFS (HR = 0.867, 95% CI 0.734–1.024, $p = 0.0466$) the pre-specified statistical significance was not met. In the explanation for the negative results of this study, probably the long survival showed in the lenvatinib monotherapy arm (19.0 months [95% CI 17.2–21.7] the longest ever observed with lenvatinib monotherapy) played an important role.

The first ICI + TKI therapy that demonstrated a statistically significant benefit compared to the TKI monotherapy comparator was recently presented [35,36]. The combination of camrelizumab (an anti-PD-1 monoclonal antibody) and rivoceranib (a TKI targeting VEGFR-2) was statistically significant superior to sorafenib for both OS and PFS (HR = 0.62, 95% CI 0.49–0.80, and HR 0.52, 95% CI 0.41–0.65, respectively). Although this combination is associated with a relatively high rate of treatment-related AEs compared to sorafenib (80.9% vs. 52.4%), it may represent a useful first-line treatment option in patients with HCC.

3. Etiological role in the immune microenvironment

3.1. The immune microenvironment in viral cirrhosis

HBV infection induces several changes in the hepatic immune system by inducing the production of the immunosuppressive cytokine IL-10. This cytokine suppresses the activity of T cells that are specific to HBV, making them more vulnerable to apoptosis and deletion by TRAIL+NKG2D+ NK cells. These cells utilize BIM-mediated mechanisms to eliminate the T cells [37]. Chronic HBV infection also results in increased expression of inhibitory checkpoint proteins on both global and virus-specific T cells, especially in the liver, which impairs the ability of T cells to target HCC cells. Interestingly, there is evidence that highly suppressive PD-1hi Treg cells are present in HBV-related HCCs, and their presence is associated with a poor prognosis. On the other hand, CD8+ tissue-resident memory T cells in patients with HBV-related HCC are linked to a better outcome. These findings were based on multidimensional analyses that revealed distinct immune microenvironments in HBV-related HCC [38]. These observations suggest that therapeutic strategies targeting these specific T cell populations may potentially improve outcomes in patients with HBV-related HCC [39].

On the other hand, in HCV infection the process of hepatocarcinogenesis seems to be related to IFNγ and IL-12 depletion which lead to CD8+ and CD4+ T cells dysfunction [40].

HCV is known to evade the immune system through the induction of exhausted and dysfunctional CD8+ T cells. These cells are characterized by low levels of interferon-gamma (IFNγ) production and CD127 expression, a lack of proliferation, and upregulation of PD-1 and T cell immunoglobulin and mucin domain 3 (TIM3) [41]. Moreover, HCV-infected cells can further perpetuate this dysfunctional state by secreting exosomes that promote galectin 9 secretion by monocytes. Galectin 9, in turn, upregulates TIM3 expression in CD8+ T cells, contributing to the impaired immune response against HCV-infected cells. Additionally, during chronic HCV infection, there is a depletion of interleukin-2 (IL-2)-producing CD4+ T cells and an upregulation of suppressive CD4+CD25+ regulatory T (Treg) cells [42]. Virus-specific, IL-10-producing CD8+ T cells are also upregulated during chronic HCV infection, which may contribute to hepatocarcinogenesis. These factors suggest that chronic HCV infection may lead to a suppression of the immune response, allowing the virus to persist and potentially leading to the development of HCC. Furthermore, viral escape mutations and HCV core proteins, which act as immunoevasins and interfere with MHC I-dependent antigen presentation, may also contribute to the immune evasion of HCV-related HCC [43]. These factors may reduce the recognition of HCV-infected cells by CD8+ T cells, allowing for the survival and proliferation of these cells, ultimately leading to the development of HCC. These mechanisms collectively contribute to the development of HCV-related HCC by impairing the immune system's ability to recognize and eliminate HCV-infected cells.

Finally, the role of hepatic macrophages in viral hepatitis progression and hepatocarcinogenesis is controversial. During chronic HBV/HCV infection, activated Kupffer cells (KCs) with upregulated CD33 and CD163 accumulate, producing IL-1β, TNF-α, and IL-6 with strong antiviral activity [44,45]. KCs may eliminate infected hepatocytes via cytotoxic molecules like granzyme B, perforin, ROS, TRAIL, and Fas ligand [46] and can also contribute to fibrosis development by producing TGF-β1 and CCL5 in response to HBV/HCV stimulation [47,48]. Moreover, the phenotype of hepatic macrophages may shift during infection, with chronic hepatitis suppressing the pro-inflammatory phenotype and promoting an immunoregulatory one, favoring viral persistence [49].

3.2. The immune microenvironment in NAFLD/NASH

Several features of the hepatic microenvironment have been hypothesized to promote hepatocarcinogenesis in NAFLD. A recent review summarized current evidence of the procarcinogenic processes that lead from NASH to HCC [50]. Firstly, metabolite overload, oxidative stress, endoplasmic reticulum (ER) stress leads to chronic inflammation in the liver with subsequent activation of innate and adaptive immune-cells; this phenomenon, via an enhanced expression of cytokines, causes a metabolic reprogramming that, in conjunction with enhanced hepatocyte damage, leads to a cycle of cell death and compensatory proliferation that facilitates HCC development.

Focusing on the immune response aberration, much effort has been put into depicting the role that effector T cells play in the tumor microenvironment and in the pathogenesis of HCC. Most importantly, effector T cells harbor the inhibitory immune checkpoint molecules PD-1 that nurtures different functions depending on the cell that lodges its ligand, PD-L1, particularly in the setting of HCC [17,51,52] broadly explained the altered immune-cell composition in the tumoral microenvironment; in the livers of murine models of NASH, a progressive accumulation of unconventionally activated CD8+PD1+ T cells occurs, with an aberrant differentiation with gene expression profiles related to cytotoxicity, effector-function and inflammation markers with elevated exhaustion traits. Then the effect of T-cell immunity depends on the type of cells with which PD-1 CD8+ T cells interact. In a preclinical mouse model of NASH, it was demonstrated that IL-15 induced FOXO1 downregulation and CXCR6 upregulation, which rendered liver-resident CXCR6+ CD8 T cells auto-aggressive; these cells showed effector (granzyme) and exhaustion (PD1) patterns. The auto-aggressive killing of hepatocytes was due to MHC-class-I-independent citoxicity, contributing to liver damage [53]. Shalapour et al. demonstrated that the enhanced expression of liver-resident regulatory B cells in NAFLD has been shown to inhibit the cytotoxic activation of CD8+ cells in NASH related HCC, by expressing PD-L1 and producing IL-10, hampering tumor cell clearance; at the same time, genetic or pharmacological interference with IgA+ cell generation attenuates liver carcinogenesis and induces cytotoxic T-lymphocyte-mediated regression of established hepatocellular carcinoma [54].

Other cells may be involved in the impaired anti-tumor surveillance in NAFLD-related HCC in addition to Treg cells. The selective ROS-dependent loss of CD4+ T cells was demonstrated to occur in mice models of NAFLD causing impaired antitumor surveillance, since this relies on an intact CD4+ T-cell-mediated adaptive immune response [55,56] NK T cells have been shown to be strongly contributing to the development of NASH and HCC in mice models of hypercaloric-induced NASH, being present in consisting amounts in the affected livers; here their activation, dependent on LIGHT factor expression in hepatocytes, promotes lipid uptake in hepatocytes and favors liver damage by CD8+ lymphocytes.

We should also underline that a high-fat diet promotes the recruitment of bone marrow-derived monocytes to the liver in mice [57]. These monocytes differentiate into anti-inflammatory macrophages, which protect against diet-induced insulin resistance through the PPARδ pathway [57]. In contrast, the NASH niche favors pro-inflammatory macrophage/monocyte infiltration, leading to liver damage and inflammation [58]. The fate of monocyte-derived macrophages depends on the type of fatty acids they are exposed to, with saturated fatty acids promoting pro-inflammatory differentiation and unsaturated fatty acids enhancing anti-inflammatory differentiation in NASH. Therefore, the balance between these macrophage subsets may determine the role of hepatic macrophages in NASH pathogenesis but its impact is still largely unknown.

4. Etiological role in the microbiome composition

The microbiome composition can vary significantly among different etiologies of HCC.

The intestinal microbiota of patients with chronic hepatitis B and cirrhosis showed specific features compared to healthy individuals. Specifically, Bifidobacteria and Lactobacillus levels are dramatically decreased, while Enterococcus and Enterobacteriaceae levels are significantly increased in these patients, contributing to the progression of liver diseases, particularly liver cirrhosis [59,60].

Indeed, an imbalance in the intestinal microbiota leads to increased mucosal permeability, allowing harmful bacteria to enter the liver through the portal vein, activating the liver's innate immune system leading to the transformation process of CHB to liver fibrosis [61,62].

In chronic HBV infection, hepatocyte injury is not only caused by the cellular immune response to HBV invasion but also by the natural immune response triggered by pathogen-associated molecular patterns (PAMPs) produced by intestinal microbes with structural disorders. Intestinal PAMPs associated with chronic HBV infection consist mainly of lipopolysaccharide (LPS), unmethylated CpG DNA, bacterial cell wall components, and bacterial DNA/RNA. These factors contribute to the immune mechanisms related to the liver disease.

HCV infection negatively impacts the gut microenvironment by reducing beneficial bacterial families, such as Ruminococcaceae and Lachnospiraceae, which produce essential short-chain fatty acids (SCFAs) crucial for metabolic balance, maintaining intestinal barrier integrity, and promoting the differentiation of Treg cells [63,64].

Conversely, HCV affects gut B-lymphocytes, leading to decreased IgA levels and increased intestinal permeability, allowing for bacterial translocation [65]. This heightened intestinal permeability facilitates the transition of lipopolysaccharide (LPS)-induced liver inflammatory reactions via TLR4, promoting HCC progression, especially in individuals with chronic alcohol consumption [66].

Furthermore, during chronic HCV infection, elevated levels of cytokines, IgA, and T cells play a role in controlling the diversity of the gut microbial community. Particularly, the abundance of Prevotella seems to be associated with the inflammatory mediator IL-17 [67]. Treatment of HCV could impact gut microbiota but regarding this topic there are still contrasting results [68–71].

NAFLD and NASH in humans often co-occur with obesity and poor dietary habits, making it challenging to distinguish the effects of diet and metabolic changes from those mediated by the altered microbiome under these conditions. Nevertheless, certain bacterial species in humans have been associated with NAFLD and NASH. For instance, Proteobacteria, Enterobacteria, Escherichia, and Bacteroides were found to be more abundant in patients with NASH compared to healthy individuals [72,73]. Stool microbiome profiling of children with NAFLD revealed a higher abundance of Gammaproteobacteria and Prevotella compared to obese children without NAFLD [74,75]. Interestingly, during the progression of NAFLD, there were changes in the abundance of Proteobacteria and Firmicutes, indicating that the gut microbiome may not be consistently dysbiotic throughout the disease [75].

Dietary intervention studies have also shown that changes in the microbiome can impact NAFLD. For example, a low-choline diet in NAFLD patients led to alterations in the microbiome, with certain bacterial groups correlating positively or negatively with hepatic lipid content [76]. Additionally, nonabsorbable antibiotic treatment in NAFLD and NASH patients has shown improvements in liver function, suggesting a potential role of the microbiome in the pathogenesis of these conditions [77].

However, these association studies have some limitations, including the lack of reproducibility between different study cohorts, the absence of a clear mechanistic explanation for dysbiosis, and the final effects on NAFLD and NASH evolution and prognosis.

Research has shown that the gut microbiota can play a critical role in modulating systemic immunity and influencing the response to immunotherapy in cancer patients, including those with HCC [78–82]. In particular, the gut microbiome's diversity and specific bacterial populations have been linked to the efficacy of immunotherapy treatments.

Some studies have indicated that certain microbial species or patterns may be associated with improved responses to immunotherapy, while others may be linked to treatment resistance or adverse events. However, the precise impact of microbiome composition on the response to ICIs in HCC pa-

Table 2
Different responses to ICIs in relation to HCC etiology.

Study	Results
Checkmate 459 [24]	-Survival benefit from ICI in viral patients (HBV: HR = 0.77, 95% CI 0.56–1.05; HCV: HR = 0.71, 95% CI 0.49–1.01) -No survival benefit from ICI in non-viral patients (HR = 0.95, 95% CI 0.74–1.22)
IMbrave150 [13,14]	-Survival benefit from ICI in viral patients (HBV:HR = 0.58, 95% CI 0.40–0.83; HCV: HR = 0.43, 95% CI 0.25–0.73). -No survival benefit from ICI in non-viral patients (HR = 1.05, 95% CI 0.68–1.63)
KEYNOTE-240 [25]	-Survival benefit from ICI in HBV patients (HR = 0.57, 95% CI 0.35–0.94) -No survival benefit from ICI in HCV patients (HR = 0.96, 95% CI 0.48–1.92) and non-viral patients (HR = 0.88, 95% CI 0.64–1.20)
HIMALAYA [15,85]	-Survival benefit from ICI in HBV patients (HR = 0.64, 95% CI 0.48–0.86) and non-viral patients (HR = 0.74, 95% CI 0.57–0.95). -No survival benefit from ICI in HCV patients (HR = 1.06, 95% CI 0.76–1.49)
Camrelizumab plus rivoceranib [35]	-Survival benefit from ICI in HBV patients (HR = 0.66, 95% CI 0.50–0.87) -No survival benefit from ICI in HCV patients (HR = 0.45, 95% CI 0.18–1.16) and in non-viral patients (HR = 0.71, 95% CI 0.37–1.36
Metanalysis by Haber et al. [80]	-Survival benefit from ICI in viral patients (HR = 0.64, 95% CI 0.50–0.83). -No survival benefit from ICI in non-viral patients (HR = 0.92, 95% CI 0.77–1.11)
Metanalysis by Vogel et al. [87]	-Survival benefit from ICI in non-viral and viral patients (HR = 0.79, 95%CI: 0.72 to 0.86, $p < 0.001$)
Retrospective study by Casadei-Gardini [84]	-Lenvatinib is more effective treatment for HCC compared to atezolizumab plus bevacizumab, especially in patients with NAFLD/NASH

tients with different etiologies remains an active area of investigation.

5. Response to immune checkpoint inhibitors: data from clinical trials

5.1. Response to immune checkpoint inhibitors in viral vs. non-viral hepatocellular carcinoma – data from clinical trials (Table 2)

Whether the efficacy of ICIs may vary across different etiology of liver disease in HCC patients is needed to clarify. From pathophysiological studies, the immunological microenvironment in viral cirrhosis has different features compared to NAFLD/NASH as well as the activation of innate immune system leading to chronic liver inflammation virus and non-virus related, as described above.

The impact of liver disease etiology on ICIs-treatment outcome was firstly evaluated in a subgroup analysis of Checkmate 459 trial [24]. The statistical significance for the superiority of nivolumab was not reached in none of the etiology subgroups. However, the benefit from immunotherapy tended to be higher in patients with HBV- (HR = 0.77, 95% CI 0.56–1.05) and HCV-related HCC (HR = 0.71, 95% CI 0.49–1.01) compared to patients with non-viral HCC (HR = 0.95, 95% CI 0.74–1.22) [23]. In the IMbrave150 trial, subgroup analyses were performed in three populations according to HCC etiology: HBV, HCV and non-viral HCCs. The combination atezolizumab + bevacizumab was demonstrated to be superior as compared to sorafenib in patients with HBV-HCCs (HR = 0.58, 95% CI 0.40–0.83) and HCV-HCCs (HR = 0.43, 95% CI 0.25–0.73). By contrast, patients with non-viral HCC did not demonstrate a survival benefit from atezolizumab + bevacizumab compared to sorafenib (HR = 1.05, 95% CI 0.68–1.63). Importantly, regarding patients defined as non-viral HCCs, we acknowledge that in this trial there was no differentiation between alcoholic liver disease and NAFLD or NASH [14].

A recent metanalysis of IMbrave150, KEYNOTE-240 and Checkmate 459 trials (for a total of 1656 patients) showed that patients with virus-related HCC treated with ICIs had a significantly greater OS benefit compared to the control group, treated with sorafenib (HR = 0.64, 95% CI 0.50–0.83). On the other hand, in patients with non-viral HCC the survival of those treated with ICIs was not significantly superior to that of the control group (HR = 0.92, 95% CI 0.77–1.11) [83] . Remarkably, the clinical benefit provided by ICIs was similar in HBV- and HCV-related HCC. However, it is important to notice that this metanalysis included studies with the use of different agents in first- and second-line setting, comparing ICIs alone or in combination. Moreover, it is important to emphasize that these results may be susceptible to a confounding effect associated with the absence of stratification by etiology in the different trials. This makes difficult to interpret these data and derive useful information that can be applied to all patients with advanced HCC treated with ICIs. Still, although trials included in this meta-analysis did not differentiate between alcoholic liver disease and NAFLD or NASH, these results confirmed the need of stratification of patients according to the etiology of their liver damage.

In two additional cohorts, patients with NASH-related HCC who received anti-PD1 or anti-PDL1 treatment showed reduced overall survival in comparison to patients with other causes of liver disease [52].

In a retrospective study by Casadei-Gardini et al. [84], including patients who received different regimens (atezolizumab plus bevacizumab $n = 190$, Lenvatinib $n = 569$, sorafenib $n = 210$), patients treated with lenvatinib had longer OS and PFS compared to those treated with atezolizumab plus bevacizumab. These findings were confirmed only in the subgroup of patients with NAFLD/NASH. Overall, the study suggests that lenvatinib may be a more effective treatment for HCC compared to atezolizumab plus bevacizumab, especially in patients with NAFLD/NASH. We should highlight that, due to the retrospective nature of this study, the diagnostic criteria for NAFLD/NASH were not homogeneous defined and propensity score analyses account only for known confounders, unlike randomized controlled trials.

Also in viral population the efficacy may be different, as reported in the phase III trial KEYNOTE-240 [25] where the OS benefit of immunotherapy over placebo was confirmed in HBV-infected patients (HR = 0.57, 95% CI 0.35–0.94), and not confirmed for HCV-infected patients (HR = 0.96, 95% CI 0.48–1.92) and uninfected patients (HR = 0.88, 95% CI 0.64–1.20) [25].

Recently, in the phase III HIMALAYA trial, where patients have been stratified according to etiology, subgroup analyses demonstrated that STRIDE provided a significantly longer OS in patients with HBV-related HCC (HR = 0.64, 95% CI 0.48–0.86) and non-viral HCC (HR = 0.74, 95% CI 0.57–0.95), but not in those with HCV-related HCC (HR = 1.06, 95% CI 0.76–1.49) [15,85].These results may suggest that there could be differences between HBV and HCV- related HCC but more data are needed [3].

In the subgroup analysis of the phase III trial investigating the combination of camrelizumab plus rivoceranib, the OS benefit over sorafenib was confirmed for patients with HBV-related HCC (HR = 0.66, 95% CI 0.50–0.87), while no significant difference was shown in patients with HCV-related HCC (HR = 0.45, 95% CI 0.18–

1.16) and in those with non-viral HCC (HR = 0.71, 95% CI 0.37–1.36) [35]. The results of these subgroup analyses should be interpreted with caution, since in this study the large majority of patients included had an HBV-related HCC (76.5% in the camrelizumab + rivoceranib group and 72.7% in the sorafenib group).

The different results in term of efficacy of ICIs across liver etiologies may be explained by the heterogeneous definition of "non-viral etiologies", including patients with NASH, alcohol or other liver diseases with different pathological mechanisms of carcinogenesis. This is confirmed by a recent analysis from Espinoza et al. who categorized the IMbrave150 NAFLD patients based on investigator assignment of nonalcoholic liver damage, or a non-viral cause in report forms and no alcohol history in the patient's lifetime. In this pre-proof analysis, NAFLD was not associated with significant differences in ORR, PFS or OS [86].

More recently, Vogel et al. [87], performed a metanalysis including IMbrave 150, COSMIC-312, HIMALAYA, LEAP-002, RATIONALE-301 and camrelizumab and rivoceranib trials. The survival advantage was significant both in non-viral and viral aetiologies (HR = 0.79, 95%CI: 0.72 to 0.86, $p < 0.001$), with more benefit for those with hepatitis B (Hepatitis B, HR = 0.70, $p < 0.001$; Hepatitis C, HR = 0.78, $p = 0.04$; Non-viral, HR = 0.87, $p = 0.02$). For the non-viral subgroup, the tremelimumab plus durvalumab seemed to provide the most significant benefit for ICIs. Based on this analysis, it is premature to conclude that patients with non-viral liver disease do not benefit from ICI-based therapy.

Even though an etiology-based choice of treatment is not evidence-based to date, in the next future specific criteria to stratify patients by etiology should be used in clinical trials. On the other hand, we should also take in account that many patients have multiple contributing factors of liver disease (e.g. metabolic plus viral or metabolic plus alcohol) and subgroup analyses could be challenging to create. The interplay of multiple factors may introduce complexities and confounding variables that warrant careful consideration in research design and data interpretation.

5.2. Response to immunotherapy in non-alcoholic fatty liver disease hepatocellular carcinoma

When treating with immunotherapy a patient with NAFLD-related HCC, the possibility of achieving a poor response should be considered. Indeed, in mouse models, NASH-induced HCC revealed to be less responsive to anti-PD-1 immunotherapy [52]. This lack of efficacy of immunotherapy is related to changes in tumor microenvironment, with a decrease in anti-tumor CD4+ T cells and aberrant CD8+ T cell activation within the tumor. These CD8+ T cells exert cytotoxic activity against hepatocytes, resulting in necroinflammation, and their auto-aggressive behavior results in a loss of tumor surveillance function and in the development of a pro- tumorigenic microenvironment [52,88]. Although in mouse models ICIs revealed to be less effective, caution is warranted when extrapolating these results to patients with NAFLD, and further investigation are necessary. In order to characterize the clinical effect of anti-PD-1 immunotherapy with respect to underlying NAFLD, a cohort of 130 patients with HCC (13 patients with NAFLD and 117 with other etiologies) was investigated by Pfister et al. [52]. NAFLD was associated with a shorter median OS after immunotherapy (5.4 vs. 11.0 months; $p = 0.023$), even though patients with NAFLD had less frequent macrovascular invasion (23% vs. 49%) and immunotherapy was more frequently used in first-line in these patients (46% vs. 23%). After correction for confounders, NAFLD remained an independent negative prognostic predictor in patients with HCC after anti-PD-1 treatment (HR = 2.6, 95% CI 1.2–5.6). In a further validation cohort of 118 patients treated with anti-PD-1 immunotherapy (11 patients with NAFLD and 107 patients with other etiologies), NAFLD was again associated with poorer survival compared to other etiologies of liver damage (8.8 vs. 17.7 months; $p = 0.034$). These results may suggest that immunotherapy is less effective in patients with NAFLD than in those with other etiologies, however, they are based on retrospective studies, including small and unbalanced numbers of patients and a prospective validation is required. It is noteworthy that obesity has been regarded as a predictive factor for a more favorable response to ICIs in certain types of cancer [89,90] but this does not seem to apply to HCC probably because of the liver's central role in fat metabolism.

In addition, further data suggested that anti-angiogenic therapies (such as bevacizumab) might have reduced efficacy in obese patients [88,91,92]. Pre-clinical data in breast-cancer models, showed that obesity induces the production of pro-inflammatory and pro-angiogenic cytokines, such as interleukin-6 (IL-6) and fibroblast growth-factor-2 (FGF-2), resulting in a decrease efficacy of anti-VEGF agents [93]. Obese patients may also not derive benefit from bevacizumab because of an increased level of circulating VEGF caused by its secretion by the adipose tissue [94,95]. Even though there is no data specifically for HCC, these findings may contribute to explain the observed decreased efficacy of immunotherapy, and mainly atezolizumab + bevacizumab, in NAFLD-HCC patients.

6. Conclusions

In conclusion, several factors may influence the efficacy of ICIs in patients with HCC, including the cause of underlying liver disease, as different etiologies contribute differently in modulating immune tumor microenvironment immune surveillance [18].

Some data suggested that non-viral HCC seems to respond lower than viral-HCC to different ICIs regimens. However, for patient-selection bias and retrospective nature of analysis, we are not able to define the real role of etiology in the ICIs response. Therefore, a different therapeutic approach of HCC according to etiology should not be recommended [96]. Furthermore, it should be taken into account that liver function significantly affects the prognosis of patients with HCC [94] and it might depend on treatment of the underlying etiology. For instance, the use of direct-acting antivirals (DAAs) for HCV in patients with early HCC showed positive effect on OS, improving liver function [95]. Still, patients with HCC and HBV infection have often chronic hepatitis rather than decompensated cirrhosis (especially in randomized Asian controlled trials), which might significantly impact on patient survival. Additional research will be needed to understand the role of liver disease severity across different etiologies in HCC patients outcomes and the underlying mechanisms to identify useful biomarkers to guide tailored treatment decisions in order to ultimately improve patient survival [97,98].

Financial disclosure

The authors declare no financial support for this study.

Conflict of interest

The authors declare no potential conflict of interest.

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