

PERSPECTIVE

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Benefit-risk considerations of immunotherapy in chronic hepatitis B

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Abstract

Efforts are underway to develop treatments for chronic hepatitis B virus (HBV) infection that achieve a functional cure after a finite course of therapy. Immune checkpoint inhibitor (ICI) treatments targeting PD-1/PD-L1 have entered clinical development given their potential to restore HBV-specific T & B cell magnitude and function in chronic hepatitis B (CHB) patients. However, their risk–benefit profile in CHB is not fully understood. The HBV Forum of the Forum for Collaborative Research at the University of California, Berkeley established an ICI Working Group comprising experts in academia, clinical practice, pharmaceutical companies, patient representatives, and regulatory authorities, to analyze the occurrence of immune-related adverse events (irAEs) in cancer patients treated with ICIs as first-line therapy based on published literature as a proxy to help inform potential risks of ICIs in non-cancer CHB patients. Understanding that the patient populations affect the risk–benefit profile in clinical decisions, the working group also assessed potential benefits by reviewing publicly available data on clinical trials evaluating ICIs targeting PD-1/PD-L1 in CHB patients to understand overall utility and clinical value of ICIs. This Perspective outlines lessons learned from reviewing these risk–benefit data and provides considerations for the use of other immunotherapy drug classes in CHB treatment paradigms.

1 Introduction

Chronic hepatitis B virus (HBV) infection accounts for a significant global burden of disease, with an estimated 254 million individuals affected and over 800,000 deaths attributed to its complications each year [1]. Chronic HBV infection is characterized by persistent and progressive impairment of HBV-specific T and B cells through exposure to viral antigens and liver inflammation, leading to dysregulation of immune function and clinical outcomes including cirrhosis, hepatocellular carcinoma (HCC), and liver-related death [2, 3]. Chronic hepatitis B (CHB) remains incurable; current treatments aimed at lifelong viral suppression require continuous, lifelong treatment. Functional cure, defined as sustained off-treatment hepatitis B surface antigen (HBsAg) loss and HBV DNA suppression is rarely achieved in the natural history of infection or with current treatment options [3], representing an unmet medical need. The HBV therapeutic



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development pipeline is strong, with over 40 novel agents in clinical development, including various immunotherapies and immunomodulators that aim to directly, or indirectly, modulate host immunity [4]. The success of future CHB treatment paradigms will likely rely on combination therapies that synergize the effects of antiviral and immunomodulatory mechanisms of action. [5]

Immune checkpoint inhibitors (ICIs) block immunosuppressive interactions between inhibitory receptors expressed on lymphocytes and their ligands expressed on tumor cells, releasing the brakes on the immune system to fight the cancer cells. ICI treatments targeting programmed death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) have entered clinical development for the treatment of people with CHB given their potential to restore HBV-specific T & B cell magnitude and function [6–9]. However, ICIs carry the risk of long term immune-related adverse events (irAEs), causing damage to normal tissues. This presents a potential barrier to the use of anti-PD-1/PD-L1 therapies for treatment of chronic HBV infection given that the risk–benefit profile of ICIs in a CHB patient population is not fully understood.

Early studies (pre-2019) of PD-1/PD-L1 drugs to treat cancers suggested high rates of irAEs, but these studies included patients with advanced cancers, multiple lines of treatments, and add-on therapies that may have enhanced irAEs [10]. Furthermore, the risk of irAEs that are specifically of interest to a CHB patient population, including hepatic and thyroid-related issues, may not be a priority for patients when considering cancer therapy, but could dramatically impact the quality of life of a CHB patient that could otherwise remain on long-term therapy to control viral replication [11]. Whether the immunomodulatory effects of ICIs could have broad beneficial effects on HBV virological control, clearance of hepatitis B surface antigen (HBsAg), or suppression of HBV DNA remains under investigation.

The HBV Forum of the Forum for Collaborative Research (the Forum) at the University of California, Berkeley, convened a working group to facilitate a better understanding of the risk–benefit profile of ICIs for the treatment of people with CHB. The Forum addresses issues in drug development for unmet medical needs, including HBV, by providing an independent and neutral platform for multi-stakeholder engagement and dialogue [12]. Discussions were convened at four independent Forum-organized conferences (June 2023, November 2023, June 2024, and November 2024), along with a series of virtual conference calls held between June 2023 and March 2025. These meetings engaged scientists, clinicians, regulatory authorities, pharmaceutical and diagnostic companies, advocacy groups, and people with lived CHB experience. A subset of the working group conducted a literature review examining irAEs among cancer patients treated with PD-1/PD-L1 monotherapy as first-line therapy. The goal was to understand the potential risks of irAEs in a non-cancer, CHB patient population, an essential step for evaluating overall utility and clinical value of these drugs from a risk–benefit perspective and to establish a potential framework for the incidence, type, and severity of irAEs to expect in CHB patients. The group assessed potential benefits by reviewing publicly available data on clinical trials evaluating PD-1/PD-L1 targeting ICIs in patients with CHB. This Perspective outlines the lessons learned from reviewing these data and provides considerations for the use of other immunotherapy drug classes in CHB treatment paradigms.

1.1 Landscape of ICIs for HBV

ICIs are the mainstay of immunotherapies for many cancers and are attractive therapeutic candidates for the treatment of CHB given their potential to restore HBV-specific T and B cell magnitude and function. Targeting the PD-1/PD-L1 interaction in CHB patient peripheral blood mononuclear cells has repeatedly been shown to improve HBV-specific T and B cell function using in vitro assays [7–9, 13] and is used as systemic therapy for the treatment of viral hepatitis-associated HCC, including HBV [14, 15]. These data provide the rationale for the several clinical trials evaluating PD-1/PD-L1 therapies either in combination or as monotherapy to advance the HBV functional cure agenda (Table 1) [16].

Assessing benefit-risk for PD-1/PD-L1 therapies in CHB is difficult because of paucity of clinical trial data. Extrapolating from cancer trials may provide useful information, but is limited because there are fundamental clinical differences between oncology and CHB patient populations, particularly in cancer patients who have received multiple lines of treatment and/or treatment with ICIs at higher and more frequent doses than that for a CHB patients. For example, durvalumab was administered at 20 mg/kg every four weeks until disease progression in a clinical trial of metastatic non-small cell lung cancer [17], while HBV patients typically receive lower doses at around 0.3 mg/kg for generally 1–3 doses [6]. The practical consideration for lower and less frequent dosing was to reduce the risk of irAEs, which are a well-established safety consideration for the use of ICIs in oncology patients. Furthermore, irAEs of interest to a CHB patient population, including hepatic and thyroid toxicities, are significant concerns because, if they do not accompany cure, they will degrade the quality of life by adding a potential lifelong morbidity, and its subsequent management, such as hormone therapy.

Beyond these clinical differences, the immunological context of CHB and oncology diverge in important ways that limit direct extrapolation of safety data. In cancer, PD-1/PD-L1 blockade is intended to restore exhausted tumor-reactive T cells, and irAEs arise from collateral systemic immune activation in tissues expressing self-antigens. In CHB,

Table 1 Immune checkpoint inhibitors in clinical development for CHB Phase I and Beyond

Code	Phase	Drug	Sponsor	Status
NCT05275023	II	Anti-PD1	Janssen	Completed
NCT05343481	II	Nivolumab in combination	Barinthus Biotherapeutics	Active- Not Recruiting
NCT04778904	I & II	Nivolumab in combination	Barinthus Biotherapeutics	Completed
NCT04638439	I	Anti-PD-1	PharmaEssentia	Unknown
NCT04891770	II	Nivolumab in combination	Gilead Sciences	Completed
ACTRN12615001133527	I	Nivolumab in combination	Gilead Sciences	Completed
ACTRN12618001843246p	I	Nivolumab in combination	Gilead Sciences	Completed
NCT04180072	N/A	Atezolizumab	National Health Research Institutes, Taiwan	Active–Not Recruiting
NCT04225715	II	Anti-PD-L1 in combination	Roche	Completed
NCT04465890	II	Anti-PD-L1 Envafoimab	Ascleptic Pharmaceuticals	Completed
NCT06245291	II	Anti-PD-L1 in combination	Arbutus Biopharma	Withdrawn
NCT05769816	IV	Anti-PD-L1	The Second Affiliated Hospital of Chongqing Medical University	Not Yet Recruiting
NCT06357806	N/A	Sintilimab	Beijing 302 Hospital	Recruiting
NCT04133259	II	Anti-PD-1 HLX10	Henlix, Inc	Unknown

Clinical trials status was last updated May 7, 2025

PD-1 pathway upregulation contributes to the functional exhaustion of HBV-specific T cells [7]. Restoring these responses with ICIs carries the additional risk of exacerbating hepatic inflammation through immune-mediated flares. The immune activation threshold at the low doses used in CHB trials may also differ substantially from oncology dosing [7]. These immunological differences should be considered when interpreting the oncology-derived irAE data presented here as a safety proxy.

The rate of HBsAg seroclearance and suppression of HBV DNA with ICI therapy remains unknown. Moreover, a partial response to ICI therapy in cancer patients can extend patients' survival time but a partial response in patients with chronic HBV infection, such as a modest decline in HBsAg levels, may not be clinically significant because the patient remains chronically infected. Some data, however, suggest that a partial response with respect to virological decline may be associated with reduced liver transplant and mortality [18, 19].

A clear framework for evaluating clinically meaningful treatment responses in CHB is currently lacking, and this gap significantly complicates benefit assessment for ICI therapies. In oncology, established endpoints such as objective response rate, progression-free survival, and overall survival provide standardized benchmarks. No equivalent consensus exists for CHB. This is a key limitation of this analysis. In the absence of a consensus framework for evaluating clinically meaningful treatment responses in CHB, it is difficult to determine whether the virological and serological outcomes reported across CHB trials, ranging from HBV DNA suppression to quantitative HBsAg decline represent clinically meaningful benefit. The benefit side of the risk–benefit equation for ICI therapies in CHB cannot be evaluated with the same rigor as the safety side, and conclusions about therapeutic utility must therefore remain appropriately cautious.

2 Methodology

To provide a proxy for potential safety concerns for the use of ICIs in a CHB patient population, we conducted a structured literature review of irAEs in oncology patients treated with first-line PD-1/PD-L1 monotherapy. The objectives were to assess the incidence, type, and severity of irAEs in less advanced oncology patients to better understand the risk–benefit profile of anti-PD-1/anti-PD-L1 treatments in patients with CHB.

The literature search was conducted in PubMed in two stages. The initial search employed the terms "melanoma" OR "non-small cell lung cancer" AND "immune checkpoint inhibitors" to capture early-approval cancer indications for anti-PD-1/PD-L1 therapies. The search strategy was subsequently refined to "PD-1" OR "PD-L1" AND "first-line treatment," with results limited to publications from 2019 to 2024 to reflect advancements in irAE surveillance and standardized reporting practices. Alternative data sources, including registries and repositories from the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the Society for Immunotherapy for Cancer (SITC), were initially considered but deprioritized due to difficulties in navigation and limited accessibility.

Studies were included if they reported original data on irAEs associated with PD-1 or PD-L1 inhibitors administered as first-line monotherapy. Exclusion criteria were: (1) absence of irAE data relevant to the outcomes of interest; (2) publication date prior to 2019; (3) prior or concurrent chemotherapy use; and (4) combination ICI regimens, to minimize confounding irAE attribution. The search yielded 11 original research studies,

Table 2 Oncology review tables

Authors	Trial	Cancer	ICI	Drug Target	Dose	Frequency
Herbst et al	NCT02409342	Non-small cell lung cancer; non-squamous and squamous	Atezolizumab	PD-L1	1200 mg IV	Every 3 weeks
Burtneess et al	NCT02358031	Squamous cell carcinoma of the head and neck	Pembrolizumab	PD-1	200 mg	Every 3 weeks
Rizvi et al	NCT02453282	Non-small cell lung cancer	Durvalumab	PD-L1	20 mg/kg	Every 4 weeks
Tawbi et al	NCT03470922	Melanoma	Nivolumab	PD-1	480 mg	Every 4 weeks
Özgüroğlu et al	NCT03088540	Non-small cell lung cancer	Cemiplimab	PD-L1	350 mg	Every 3 weeks
McDermott et al	NCT02853344	Advanced non-clear cell renal cell carcinoma	Pembrolizumab	PD-1	200 mg	Every 3 weeks
Powles et al	NCT02516241	Urothelial carcinoma	Durvalumab	PD-L1	1500 mg	Every 4 weeks
Wu et al	NCT03850444	Non-small cell lung cancer	Pembrolizumab	PD-1	200 mg	Every 3 weeks
Vaishampayan et al	NCT01772004	Renal cell carcinoma	Avelumab	PD-L1	10 mg/kg IV	Every 2 weeks
Adams et al	NCT02447003	Triple negative breast cancer	Pembrolizumab	PD-1	200 mg	Every 3 weeks

ICI immune checkpoint inhibitor, PD-1 programmed death protein 1, PD-L1 programmed death-ligand 1

Table 3 Immune-related adverse events (irAEs) among first-line cancer patients treated with anti-PD-1 or anti-PD-L1 monotherapy, n = 2,378 (2019–2024 from 10 studies)

Immune-related adverse event (irAE), No. (%)	Grade 1 - 2	Grade ≥ 3	Any Grade
Any irAE	622 (26.2)	143 (6.0)	765 (32.2)
irAE leading to discontinuation ^a	NA	NA	191 (8.0)
irAE by category			
Thyroidism ^a	336 (14.1)	4 (0.2)	340 (14.3)
Rash/Skin involvement ^b	105 (4.4)	29 (1.2)	134 (5.6)
Pneumonitis	51 (2.1)	26 (1.1)	77 (3.2)
Diarrhea/Gut involvement ^c	51 (2.1)	21 (0.9)	72 (3.0)
Hepatitis	45 (1.9)	33 (1.4)	78 (3.3)
Infusion reaction	8 (0.3)	3 (0.1)	11 (0.5)
Nephritis	7 (0.3)	10 (0.4)	17 (0.7)
Adrenal insufficiency	5 (0.2)	4 (0.2)	9 (0.4)
Anaphylactic reaction	5 (0.2)	0	5 (0.2)
Pancreatitis	3 (0.1)	2 (0.1)	5 (0.2)
Hypophysitis	3 (0.1)	2 (0.1)	5 (0.2)
Myositis	2 (0.1)	1 (0.04)	3 (0.1)
Uveitis	1 (0.04)	0	1 (0.04)
Myocarditis	0	2 (0.1)	2 (0.1)
Encephalitis	0	1 (0.04)	1 (0.04)
Peripheral neuropathy	0	1 (0.04)	1 (0.04)
Myasthenia gravis	0	1 (0.04)	1 (0.04)
Autoimmune arthritis	0	1 (0.04)	1 (0.04)
Guillain-Barre Syndrome	0	1 (0.04)	1 (0.04)
Stevens-Johnson Syndrome	0	1 (0.04)	1 (0.04)

^a NA values are given because irAEs leading to discontinuation were not stratified by grade across all studies

^b Thyroidism is a composite category including hypothyroidism, hyperthyroidism, or increased blood TSH

^c Rash/Skin involvement is a composite category including rash and pruritus unrelated to an infusion reaction

^d Diarrhea/Gut involvement is a composite category including diarrhea, colitis, nausea, vomiting, and constipation

of which 10 were included in the final analysis (Table 2); one study was excluded due to absence of relevant data.

2.1 Assessing benefit-risk in oncology studies

Safety outcomes on irAEs from the individual studies were manually extracted and combined to yield pooled data (Table 3). The included studies are heterogeneous with respect

to patient populations, tumor types, dosing regimens, and clinical contexts. This heterogeneity precluded formal quantitative synthesis, and the pooled data presented here should therefore be interpreted as a descriptive aggregation rather than a meta-analytic estimate. No statistical weighting or adjustment for between-study variation was performed, and the aggregated irAE figures are intended to provide broad contextual estimates of irAE frequency rather than definitive incidence rates. The lack of standardized adverse event reporting across studies including inconsistent use of grading criteria and variable definitions of irAE categories further limits the comparability of safety data and underscores the need for harmonized reporting standards in future oncology and CHB clinical trials.

irAEs were graded into one of three categories using the Common Terminology Criteria for Adverse Events (CTCAE) system: Any Grade, Grade 1–2, or Grade ≥ 3 . We created composite categories of irAEs to account for heterogeneity of adverse event reporting across studies: “Thyroidism”, which includes hypothyroidism, hyperthyroidism, and increased blood TSH; “Rash/Skin involvement”, which includes rash and pruritus unrelated to an infusion reaction; and “Diarrhea/Gut involvement”, which includes diarrhea, colitis, nausea, vomiting, and constipation.

Pooling data from the 10 studies (Table 2) yielded a total of 5540 patients, of which 2378 patients were treated with anti-PD-1/anti-PDL1 monotherapy as first-line therapy. Table 3 summarizes IrAEs. The majority of patients (67.8%, $n = 1613$), did not experience an irAE. Any Grade irAEs were reported in 765 patients (32.2%), with 191 patients (8.0%) discontinuing treatment due to experiencing an irAE. Among those treated with PD-1/PDL1 monotherapy, Grade 1–2 irAEs were reported in 622 patients (26.2%) and Grade ≥ 3 irAEs were reported in 143 patients (6.0%). The most frequent irAE was the composite category “Thyroidism”: 340 cases Any Grade (14.3%), 336 cases Grade 1–2 (14.1%), and 4 cases Grade ≥ 3 (0.2%).

Of the 10 studies included in our review, the average median overall survival with ICIs was 15.7 months, while the average median progression-free survival was 5 months. Pooling data from the 10 studies, the objective response rate (ORR), or the percentage of people who experienced either a decrease in tumor size or a disappearance of all signs of cancer in the body, in the ICI arms of these studies averaged 28.41%. Some patients achieved both full and partial responses, outcomes that, in the context of cancer, contribute to improvement in disease progression and prolonged survival.

2.2 Weighing the benefit-risk in HBV studies

We then aimed to explore the potential risk–benefit profile of anti-PD-1/PD-L1 therapies in a CHB patient population. We identified 14 clinical trials utilizing PD-1/PD-L1 inhibitors as monotherapy or in combination with other drugs to treat CHB (summarized in Table 1) [20–22]. We extracted and collated clinical trial information and outcomes data, including dosage, treatment schedules, inclusion/exclusion criteria, clinical outcomes, and adverse event (AE) data for eight clinical trials with publicly available data. Data were sourced primarily from conference posters and abstracts given that these studies are ongoing and/or have limited data published in peer-reviewed articles.

Reliance on conference abstracts and preliminary reports introduces important limitations that must be acknowledged when interpreting these data. Data presented at conferences may be superseded or revised in subsequent peer-reviewed publications.

Accordingly, the benefit and safety data from CHB clinical trials presented here should be considered preliminary and interpreted with caution. Firm conclusions about the risk–benefit profile of ICIs in CHB cannot be drawn until full peer-reviewed results are available.

Unlike oncology studies, where AE grading and reporting guidelines are standardized, only one CHB study adhered to these protocols [20]. This inconsistency complicated cross-study comparisons and precluded definitive conclusions on safety outcomes within this population. Regarding the risk of irAEs, 7 of the 8 studies reported endocrine disruptions, particularly thyroid disorders, which have been identified as a major concern with anti-PD-1/PD-L1 therapies [23, 24]. Two of the studies reported that thyroiditis was transient, resolving prior to end of treatment, suggesting potential reversibility. Additionally, one study reported a case of Bell's Palsy that necessitated treatment discontinuation, but further details on the course or resolution of this AE were unavailable [20]. In the CheckMate040 trial, nivolumab showed an objective cancer response rate of 14% and disease control in 55% of HBV infected patients, with a 6-month overall survival rate of 84%. While antiviral activity was limited, no HBV reactivation or anti-HBs seroconversion were observed [25]. However, a 2023 ASCO abstract from this study reported cases of HBV reactivation, most notably with pembrolizumab, highlighting that, although rare, reactivation remains a relevant safety consideration when using anti-PD-1/PD-L1 ICIs in HBV infected individuals [26].

Gilead reported data on three clinical trials investigating the use of low-dose nivolumab for CHB patients. Two of the studies were phase 1 studies in virally suppressed HBV patients. One investigated the use of nivolumab at 0.1 mg/kg, 0.3 mg/kg, and 0.3 mg/kg with a therapeutic HBV vaccine [27]. The second study explored 0.3 mg/mL nivolumab as a monotherapy, or in combination with selgantolimod, (TLR8 agonist) or, sofosbuvir/ledipasvir(nucleos(t)ide analog) [27]. The third study was a phase 2 study exploring 0.3 mg/mL nivolumab + selgantolimod ± with elebsiran (siRNA for HBV) [27]. Of the 163 patients with CHB who received ≥ 1 dose of nivolumab in these three studies, 4.3% experienced irAEs. Two patients experienced irAEs of Grade 3 severity: one case of type 1 diabetes mellitus, which has not resolved and requires long-term management with insulin, and one case of immune-mediated hepatitis, which has since resolved after the use of corticosteroids [27].

The Piranga phase 2 platform trial (NCT04225715) evaluated the efficacy and safety of finite duration therapies to achieve functional cure in virologically suppressed CHB patients, including xalnesiran, a GalNAc-conjugated small interfering ribonucleic acid (siRNA) targeting HBsAg transcripts, in combination with PD-L1 locked nucleic acid (RO7191863), a GalNAc-conjugated locked nucleic acid delivered by subcutaneous injection that degrades PD-L1 mRNA preferentially in hepatocytes [28]. Participants were randomized to one of two arms: concurrent or sequential, in which PD-L1 was administered concurrently or sequentially after xalnesiran every four weeks. Two (6%) participants in the concurrent and 4 (13%) in the sequential arm lost HBsAg. However, 53 out of 64 participants (83%) experienced > 1 treatment related AEs, for a total of 295 events. Most AEs were Grade 1 or 2 (88%) with 22/64 and 3/64 patients with Grade 2 or 3 ALT elevation, respectively. There were no cases of AEs Grade 4 or 5 or serious AEs. There was 1 case of Grade 2 hyperthyroidism 42 weeks after EOT in the concurrent arm,

but this was determined to be non-drug related. AEs in this study were classified using the DAIDS system.

In a phase 2b of Enfavolimab, an infusion delivered PD-L1 targeting monoclonal antibody, 40 patients with an HBsAg level of 28.9 ± 28.3 were treated with 1.0 mg/kg AC22 + NAs or placebo + NAs every 2 weeks for 24 weeks. There was an elevated rate of adverse events in the Enfavolimab group, 76% of patients experienced an AE attributed to ASC22, ~91% of these AEs were grades 1–2, and ~9% of the AEs were grade 3. The AEs experienced by patients in the Enfavolimab group included ALT elevation (30%), AST elevation (23%), rash (17%), allergic dermatitis (12%), and endocrine system diseases (12%) [22, 29]. Six patients withdrew from the study in the Enfavolimab treatment group due to an adverse event. Six patients (17.6%) with a HBsAg level < 100 IU/mL achieved HBsAg loss at week 24, and 19 patients (55.9%) experienced a 0.5 log reduction in HBsAg levels.

The OCTOPUS-1 (NCT05275023) study evaluated a combination treatment of nucleos(t)ide analogues (NA), low-dose nivolumab (LDN; 0.3 mg/kg), and siRNA JNJ-3989. The trial included two arms: Arm One (n = 18), in which participants received a single dose of LDN, and Arm Two (n = 19), in which participants received three doses of LDN. By the 24-week follow-up, no participants in either arm achieved HBsAg sero-clearance. The mean HBsAg decline was -1.26 log IU/mL in Arm One and -1.52 log IU/mL in Arm Two. In Arm One, 14 treatment-emergent adverse events (TEAEs) were reported, of which 12 were Grade 1 and 2 were Grade 2. In Arm Two, 20 TEAEs were reported, with 13 classified as Grade 1 and 7 as Grade 2. Adverse events were graded according to the DAIDS scale [30]. One immune-related TEAE was reported in the follow up phase of Arm Two. Investigators defined immune-related AEs as ALT/AST elevations; gastrointestinal, neurological, pulmonary, or renal events; endocrinopathies; skin and eye manifestations; lipase/amylase elevations; and infections. Additionally, one case of hyperthyroidism was reported in Arm One, although outcome details were not provided.

The Ocean Cure study utilized 400 mg of a PD-L1 inhibitor (TQ-B2450) every 3 weeks in conjunction with a TLR 7 agonist (TQ-A3334) and Entecavir. Nine patients (37.5%) were in this treatment arm, which was associated with greater HBsAg reduction at end of treatment (0.455 ± 0.55 log₁₀IU/mL) than TQ-A3334 with Entecavir (0.03 ± 0.16 log₁₀ IU/ml) and Entecavir alone (0.04 ± 0.08 log₁₀ IU/ml). No patient lost HBsAg. Of the nine patients in the triple therapy arm, six received 1.2 mg of TQ-A3334, and three received 1.5 mg of TQ-A3334. From the 1.2 mg triple therapy group, 83.3% (5) of patients experienced at least one treatment emergent adverse event. In this group, irAEs of interest were frequent, with 50% of patients experiencing hyperthyroidism, 50% experiencing hypothyroidism, and 50% of patients experiencing ALT elevations. In the 1.5 mg triple therapy group 100% (3) of patients experienced at least one treatment emergent adverse event. In this group, rates of irAEs of interest were higher than the 1.2 mg group, with 66.6% of patients experiencing hypothyroidism, 66.6% of patients experiencing hyperthyroidism, and 66.6% of patients experiencing ALT elevation [31].

A Phase Ib/IIa trial evaluated an HBV therapeutic vaccine (VTP-300) as monotherapy or in combination with low-dose nivolumab (LDN) in virally-suppressed patients with CHB [32]. The treatment arm with VTP-300 plus LDN was the only arm that achieved a significant change in HBsAg levels, with mean log₁₀ IU/ml declines of 0.76, 0.77, and

0.80 at 3, 6, and 9 months, respectively. Two of 17(11.7%) patients treated with VTP-300 plus LDN lost HBsAg at month 3 and remained undetectable at the end of month 9. There were two cases of Grade 2 or above elevated liver enzymes, with one Grade 3 ALT elevation and another Grade 2. Both TEAEs were temporally related to nivolumab, but VTP-300 could not be definitively ruled out. No irAEs associated with LDN were observed in the two arms with LDN, although routine thyroid function tests were not performed.

We encountered challenges in extracting and interpreting benefit outcomes across the CHB clinical trials. There are no standardized measures for partial responses in a CHB patient population. One issue was that studies often reported results of a subset of their study population, specifically reporting only in patient sub-groups with lower HBV antigen loads. While this approach may highlight promising outcomes, it can also be misleading, as it limits the generalizability of the findings and reduces the overall data available for analysis. Furthermore, reporting benefit outcomes is not standardized in the way that reporting for safety outcomes is standardized according to CTCAE protocols. While data were reported on HBsAg decline and HBV DNA levels, other measures varied in their reporting, including other HBV biomarkers and T cell responses. A key takeaway from this analysis is the need for a standardized framework for irAE reporting and more consistent terminology when describing the potential clinical benefits of these therapies. These improvements could facilitate a better understanding of the potential risk–benefit of ICIs in a CHB patient population.

3 Conclusions

Pooled irAE data from first-line ICI monotherapy in oncology are broadly consistent with, though not directly comparable to, emerging safety data from CHB trials, with thyroid-related events most frequently reported. Given substantial study heterogeneity and the descriptive nature of this synthesis, these findings should be interpreted as hypothesis-generating rather than definitive.

Benefit assessment was equally constrained by inconsistent AE reporting, unstandardized efficacy endpoints, and frequent co-administration of investigational agents, which together precluded firm conclusions about the therapeutic potential of ICIs in CHB. Functional cure rates appeared low across the studies reviewed, and irAE risk including thyroid dysfunction may be a meaningful concern in a non-oncology population, though the preliminary nature of available data limits interpretation. The apparent concentration of virological benefit in patients with lower baseline HBsAg (< 100 IU/mL) warrants further investigation in appropriately designed trials.

Current evidence is insufficient to draw definitive conclusions about the role of anti-PD-1/PD-L1 therapies in CHB. Realizing their potential will require standardized AE reporting, consensus efficacy endpoints, and rigorous trial design with adequate follow-up.

4 Future directions

Future research on ICIs in CHB should prioritize several interconnected needs. More granular data on irAEs of specific relevance to a CHB population are needed, particularly on hepatic toxicities including ICI-mediated hepatitis and thyroid dysfunction. Expanding irAE reporting in oncology trials to systematically capture these endpoints

would improve the utility of cancer data as a safety proxy for CHB. Standardization and harmonization of irAE reporting in CHB trials, consistent with established oncology frameworks such as CTCAE, are essential to enable cross-study comparisons and support reliable pooling of safety data. Consensus definitions of clinically meaningful treatment responses distinguishing virological response, HBsAg loss, and intermediate endpoints such as quantitative HBsAg decline are needed to enable rigorous benefit assessment. There is need for continued and systematic assessment of the risk–benefit profile of anti-PD-1/PD-L1 therapies in CHB, through adequately powered randomized controlled trials with pre-specified virological and safety endpoints.

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AC and ML wrote the original draft of the article. AC, ML, CO, VM, SC, and AG assisted with project administration, including facilitation of working group meetings. VM, SC, and AG supervised the project team. All authors contributed equally to conceptualization, discussion of content, review, and editing.

Data availability

No datasets were generated or analysed during the current study.

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Not applicable.

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Competing interests

The authors declare no competing interests.

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