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Tumour Review

The present and the future of immunotherapy in hepatocellular carcinoma and biliary tract cancers

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ABSTRACT

Hepatobiliary malignancies encompass a spectrum of invasive carcinomas arising in the liver [hepatocellular carcinoma (HCC), bile ducts [intrahepatic cholangiocarcinoma (ICC), and extrahepatic cholangiocarcinoma (EHC)] and the gallbladder. These malignancies represent a growing global health burden, with rising incidence and mortality rates and their overall prognosis remains poor because many patients present with advanced unresectable disease at diagnosis. In recent years, significant advancements in understanding HCC immunogenicity have reshaped the therapeutic scenario of advanced HCC with the immunotherapy revolutionizing the current HCC treatment landscape and patients' prognosis. Moreover, the addition of immunotherapy to chemotherapy has recently established a new standard of care first-line treatment for patients with biliary tract cancers (BTCs) who had historically few therapeutic options. Currently, immunotherapy and immune checkpoint inhibitor (ICI)-based regimens stand as a valuable and practice-changing options in both HCC and BTC management. The mounting recent evidence supporting immunotherapy's survival benefit demands clinicians to stay updated with a rapidly evolving treatment landscape as well as gain knowledge about patient selection, response rate compared with other systemic treatments and immune-mediated adverse events (imAEs) management. A panel of international Experts, comprising hepatologists and oncologists, gathered to explore the challenges in effectively integrating immunotherapy in routine clinical practice. The aim of this review is to present the Experts' insights to inform treatment choice in HCC and BTC with a special emphasis on the role of currently available ICI-based therapies in shifting treatment paradigms and potentially reversing the natural course of these two deadly malignancies.

Introduction

Hepatobiliary malignancies represent a growing global health burden, with rising incidence rates worldwide [1–3]; however, recent years have witnessed remarkable therapeutic breakthroughs that are reshaping the treatment landscape for these challenging cancers. The term hepatobiliary cancer refers to primary malignancies, which develop in the liver, either hepatocellular carcinoma (HCC), or the intra-

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and extra-hepatic biliary ductal system giving rise to biliary tract carcinomas (BTC) [1].

Liver cancer is the sixth cancer worldwide and the third most frequent cause of cancer death with 865,269 new cases and accounting for 757,948 deaths in 2022 [3,4]. Current estimates predict that by next year more than 1 million individuals will be living with liver cancer [5]. About 8 in 10 liver cancer cases are hepatocellular carcinoma (HCC) with the remaining being intrahepatic cholangiocarcinoma (iCCA). Biliary tract cancers encompass a spectrum of mostly adenocarcinomas, arising from the gallbladder or the biliary tree (CCA). Most HCC cases occur in the setting of chronic liver disease with cirrhosis from any etiology being the strongest risk factor for HCC [6,7]. From an anatomical standpoint, cholangiocarcinoma (CCA) is distinguished into intrahepatic CCA (iCCA), perihilar CCA (pCCA), and distal CCA [8,9]. In most CCA cases, the biliary epithelium is chronically inflamed while cirrhosis and hepatotropic viruses stand as main risk factors for iCCA [10] along with autoimmune diseases (*e.g.,* primary sclerosis cholangitis, PSC), diabetes, obesity, and, in Asia, liver fluke [11]. Of note, cholelithiasis stands as risk factor for extrahepatic CCA (eCCA).

Both HCC and BTCs are associated with an alarming mortality rate [2,5] and are mostly diagnosed at advanced unresectable stage. However, even when diagnosed at earlier resectable stage, the 5-year overall survival (OS) rate among patients with HCC is less than 50 % [12]. Similarly, the 5-year survival rate for patients with resectable BTCs is approximately 20 % [8,9]. In most patients, cirrhosis underlies HCC, and the deterioration of the underlying liver severely impacts HCC prognosis, irrespective of tumor stage [13,14]. Importantly, liver function conditions the clinical decision making, and its improvement may influence the response to therapies with potential deleterious effects on the liver [15,16]. Moreover, it is well known that hepatic decompensation is the main driver of death at early-stage HCC [17,18], as well as in advanced stages treated with systemic therapies [19,20]. Unfortunately, either relevant risk factors (beyond PSC) nor prognostic biomarkers have been identified for BTC, thus no screening programs are in place and early diagnosis remains a challenge [21,22]. Overall, a fully successful management of HCC and BTCs has been often precluded owing to their silent presentation, clinical and biological heterogeneity, aggressive nature, resistance to treatment and occurrence of relapses and metastases [6,23].

In recent years, significant advancements in understanding HCC immunogenicity have transformed the therapeutic scenario of advanced HCC. Immune checkpoint inhibitor (ICI) −based combination regimens were granted both US Food and Drug Administration (FDA) and European Medicine Agency (EMA) approval and provided durable survival benefit compared to tyrosine kinase inhibitors (TKIs) with favorable adverse event profiles. Finally, with the approval of antiangiogenic/ICI and dual ICI combinations [24], there are now unprecedented opportunities to treat HCC.

Owing their rarity, patients with advanced BTCs have historically had few options. The combination of gemcitabine and cisplatin provides a median OS of 11 months and an estimated 24-month survival rate of less than 20 % [25]. Importantly, over the last two decades, survival trends among BTC patients did not change considerably as documented in a retrospective analysis [26]. Recently, immune-based therapies provided improved outcomes with the addition of durvalumab [27,28] or pembrolizumab to gemcitabine and cisplatin [29,30] which currently stand as standard of care; of note, the clinically meaningful improvement in OS was maintained with a median follow-up of 36 months [28,30].

The aim of this review is to provide insights to inform treatment choice in HCC and BTC with a special emphasis on the role of currently available ICI-based therapies in shifting treatment paradigms and potentially reversing the natural course of these two deadly malignancies. For the purpose of this work, a panel of Experts, encompassing hepatologists and oncologists, reviewed evidence in the published literature and clinical trial data and, based on their own practical experience, explored the challenges in effectively integrating immunotherapy in routine clinical practice.

ICI-based regimens: The way forward to shift treatment paradigm and modify the natural course of HCC and BTCs

ICI-based regimens: the clinical rationale

The liver is a frontline immune tissue and is home for the largest pool of macrophages in the body. The immune unresponsiveness of hepatic T cell to antigens mostly absorbed from the intestine is central to the immune-tolerant profile of the liver. HCC tumor microenvironment (TME) is characterized by the presence of tumor-infiltrating lymphocytes (TILs), tumor-associated macrophages and fibroblasts, dysregulated extracellular matrix (ECM) remodeling and abnormal angiogenesis. The HCC TME is the result of the immune evasion occurring through the recruitment of regulatory T cells (Treg) and the upregulation of immune checkpoints such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1). The features of the HCC TME and the finding that TILs' levels correlated with survival [31] and with lower tumor recurrence following resection in HCC [32] laid the foundation for the earlier investigation of the use of ICI in HCC. In addition, in HCC the vascular endothelial growth factor (VEGF) can upregulate IC molecules expression thereby providing the rationale for exploring the effect of a dual PD-L1 or PD-1/VEGF inhibition.

The immune-resistant desmoplastic TME of BTCs encompasses carcinoma cells, TILs, tumor-associated macrophages along with blood vessels and ECM components [7]. Of note, PD-L1 expression has been reported in up to 70 % of BTCs and when its expression was found high, BTC patients exhibited a dismal prognosis. Overall, the HCC and BTC TME features (Fig. 1) provided the clinical rationale for exploiting ICI-based regimens to confer survival benefit in liver cancers, as consistently reported in other solid cancers including melanoma and lung cancer.

ICI-based regimens: shifting treatment paradigms in advanced unresectable HCC management

In advanced HCC, sorafenib dominated the therapeutic scenario for over a decade along with other TKIs investigated as first and second line therapies, namely lenvatinib, regorafenib and cabozantinib [33] (Fig. 2).

First evidence of the survival benefit with PD-1 inhibitors was first explored in previously treated patients with HCC (second-line and beyond). Nivolumab and pembrolizumab monotherapy efficacy stemmed from the landmark trials CheckMate 040 [34,35] and KEYNOTE-224 [36] in second line setting, respectively. Although later phase 3 studies, including the CheckMate 459 and the KEYNOTE-240 trial, failed to support the superiority of ICI monotherapy over sorafenib or placebo [37,38]. Of note, durvalumab monotherapy was also found non-inferior compared to sorafenib for OS in the recent HIMALAYA trial in naïve patients with HCC [39]. Similar data were also reported with tislelizumab in the RATIONALE 301 trial [40]. Given the limited activity of single-agent anti-PD-1/anti-PD-L1 inhibitors in an immunosuppressive microenvironment like HCC, a combinational approach was explored and the 5-year follow-up of CheckMate 040 suggested that nivolumab plus ipilimumab can provide long-term survival with no new safety signals in patients previously treated with sorafenib [41].

Moving into studies in the first-line setting, the IMbrave150 was the first phase 3 trial to demonstrate survival benefit compared to sorafenib with the combination of atezolizumab, PD-L1 inhibitor, and bevacizumab, anti-VEGF antibody, lowering by 34 % the risk of death [HR death: 0.66, P = 0.0009] [42,43]. Therefore, atezolizumab plus bevacizumab was the first ICI-based regimen to be considered a standard-of-care in HCC treatment [7,43–47].

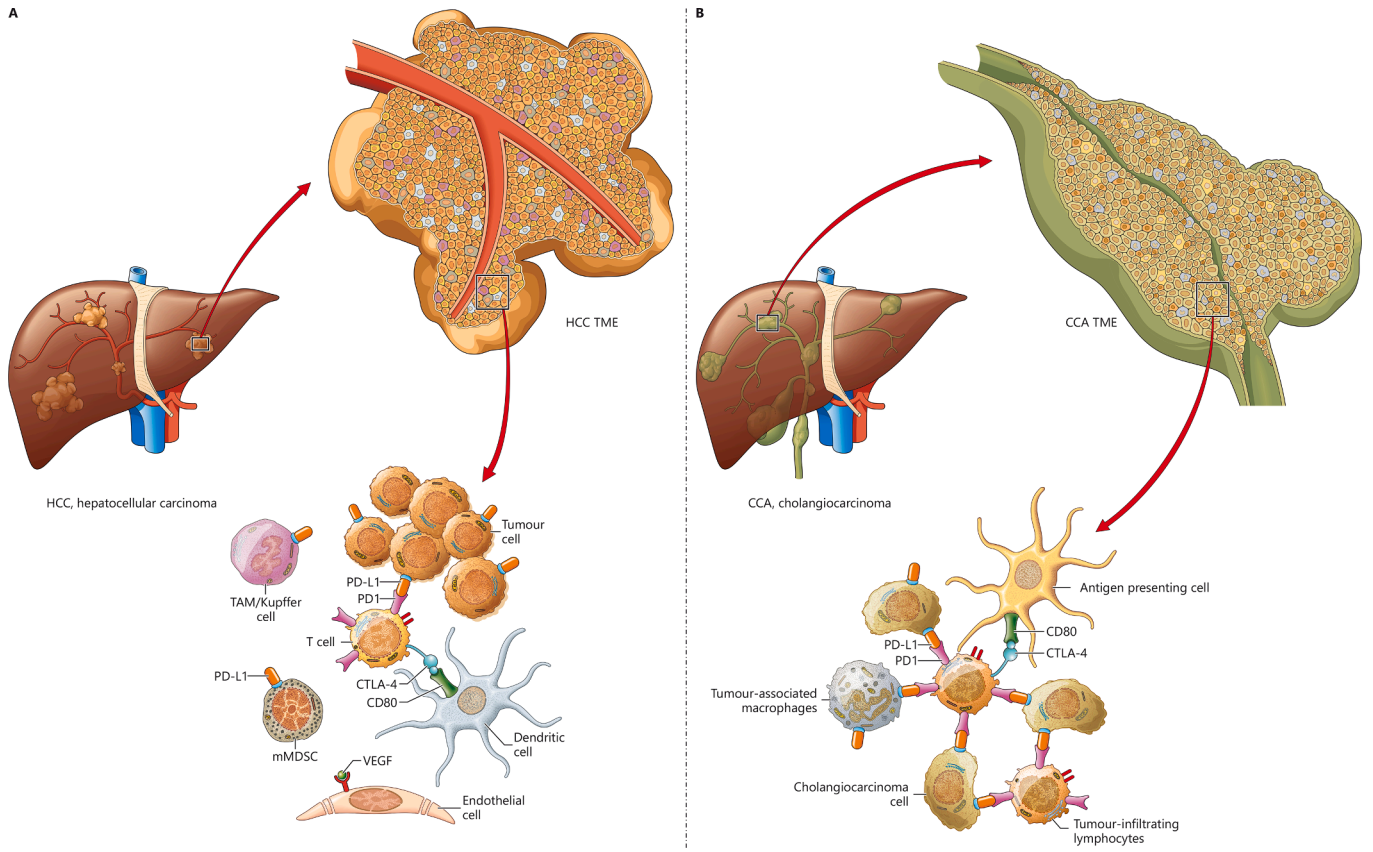

Fig. 1. Molecular targets of immune-checkpoint inhibition in HCC and CCA TME. CCA, cholangiocarcinoma; CTLA-4, Cytotoxic T-Lymphocyte Antigen 4; HCC, hepatocellular carcinoma; PD-L1; Programmed Cell Death Ligand 1; TAM; tumour-associated macrophage; TME, tumor microenvironment.

A single priming dose of tremelimumab, a CTLA-4 inhibitor, in combination with durvalumab, a PD-L1 inhibitor (STRIDE regimen), was investigated in the phase 3 HIMALAYA trial and provided significant life extension compared to sorafenib with no significant difference in median progression free survival (PFS) [39,48,49]. Accordingly, the latest international guidelines [6,44,50,51], recommend STRIDE as another first-line treatment option. In the CheckMate 9DW trial the combination of nivolumab and ipilimumab (nivolumab 1 mg/kg IV + ipilimumab 3 mg/kg IV Q3W (up to 4 cycles) then nivolumab 480 mg Q4W) vs lenvatinib (8 or 12 mg PO QD) or sorafenib (400 mg PO BID) provided clinically meaningful OS [23.7 vs. 20.6 months, (HR: 0.79), P = 0.018)] and ORR (36 % vs. 13 %, P < 0.0001) benefit vs lenvatinib or sorafenib [52]. No difference was shown in median PFS, but high response rate and durable responses (median DOR: 30.4 [95 % CI 21.2–not estimable] vs. 12.9 [95 % CI 10.2–31.2] mo) were observed [53]. Based on the results of the CheckMate 9DW trial, the combination of nivolumab with ipilimumab has been approved by EMA and recommended as a further first-line option by the latest ESMO guidelines [44]. In the CARES-310 trial the combination of camrelizumab with rivoceranib provided survival benefit [OS: 22.1 vs. 15.2 months (HR:0.62) vs. sorafenib with greater proportion of patients with ORR (25 % vs. 6 %) [54,55]. Other ICI-based combinations investigated in the first-line setting are described in Table 1 [54,56,57,58,59]. Contraindications for immunotherapy are rare [*e.g.,* prior liver transplant, severe autoimmune diseases]. In these cases, the first-line option remains unchanged with lenvatinib or sorafenib although the long survival documented in the lenvatinib arm from the LEAP-002 [56] and in CheckMate 9DW [52] trials supports the use of lenvatinib in the presence of a contraindication to an immunotherapy-based treatment.

Because of their underlying liver disease and high likelihood of portal hypertension, patients with unresectable HCC are at particular risk of gastrointestinal bleeding, and this risk may be exacerbated by treatments that include antiangiogenic agents. For this reason, risk of variceal bleeding following treatment with VEGF inhibitor bevacizumab could be considered a possible criterion to select first line treatment [6,7]. Similarly, the risk of immuno-related toxicities with anti CTLA4 + anti PD1 combinations should be taken into account when choosing between the two combination therapy options.

As direct comparisons across first-line regimens are currently unavailable, recent network *meta*-analyses (NMAs) can provide practice-informing comparisons across therapies. Two recent NMAs did not find clear differences in terms of life extension across combination regimens [60,61]. Overall, from a clinical standpoint, the survival benefit of atezolizumab in combination with bevacizumab [42,43] and tremelimumab in combination with durvalumab [39,48,49] over sorafenib not only marked a treatment paradigm shift but also expanded the armamentarium to tackle the HCC heterogeneity and overcome the shortcomings associated with sorafenib-based therapy. Importantly, in clinical practice, clinicians must consider individual patient factors such as comorbidities, concomitant medications, and risk profiles, basing their treatment decisions on clinical characteristics and data from relevant trials.

ICI-based regimens: reshaping the first-line standard-of-care in BTC management

Since 2009, gemcitabine plus cisplatin has been the first line standard-of-care regimen [25] and since then, no significant improvements in advancing BTC therapeutic management were reported (Fig. 3). In the phase 3 TOPAZ-1 trial, the addition of durvalumab to gemcitabine plus cisplatin significantly improved OS compared with placebo in chemotherapy-naïve patients with advanced BTCs with improvements also observed in PFS and objective response rate (ORR) thus setting a new course for patients with BTCs [27,28]. The phase

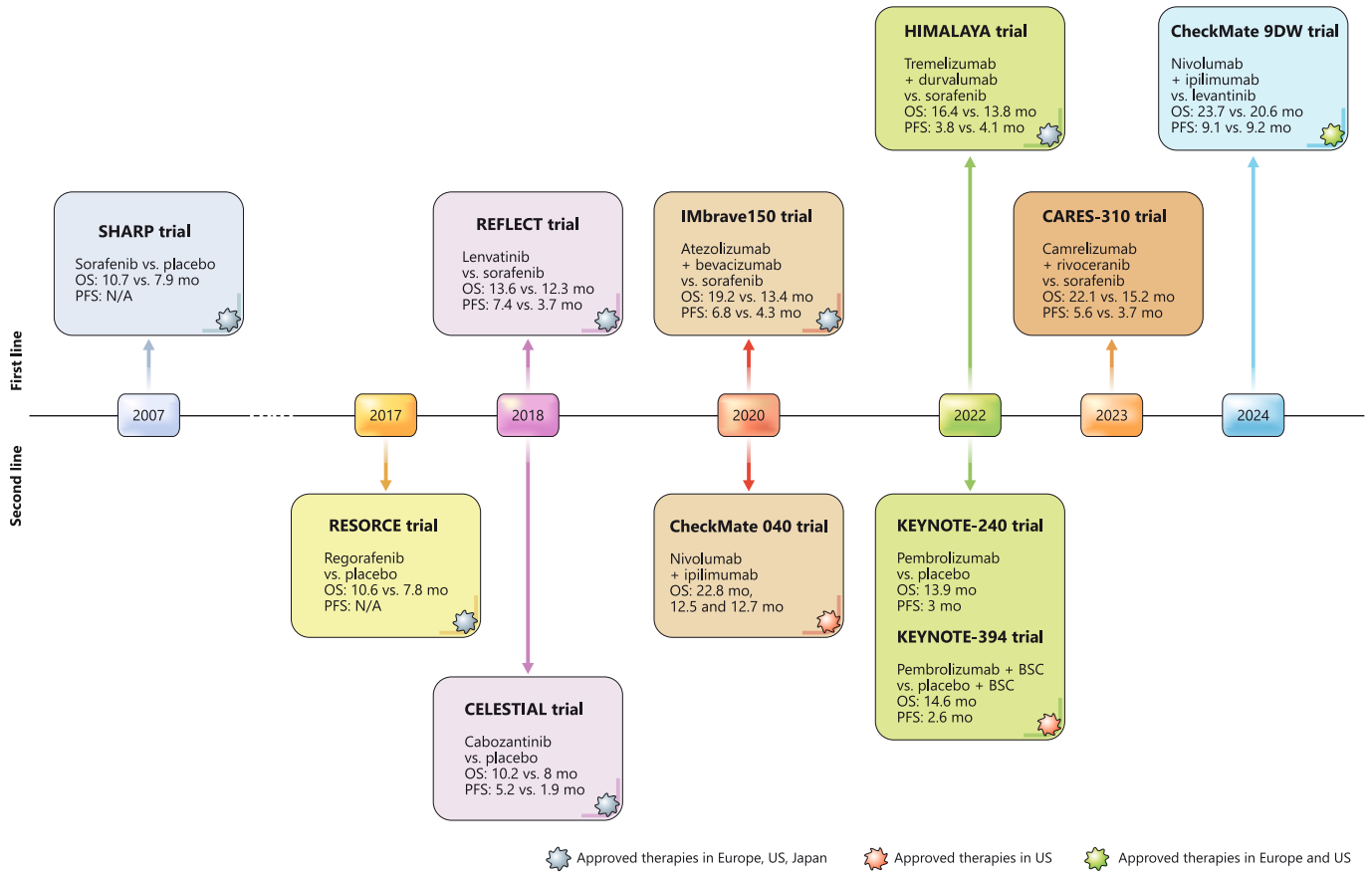

Fig. 2. Evolving treatment landscape for advanced HCC (first and second line): timeline of approval of systemic therapies. BSC, best supportive care; MO, months; N/A, not available; OS, overall survival; PFS, progression free survival.

KEYNOTE-966 study (gemcitabine plus cisplatin with pembrolizumab) showed very similar outcomes with the addition of pembrolizumab providing longer OS than chemotherapy alone. However, no difference in PFS and ORR were reported [29,30]. Durvalumab and pembrolizumab are both approved in combination with gemcitabine plus cisplatin as first-line option in BTCs. In line with this, the latest international guidelines recommend durvalumab or pembrolizumab in combination with gemcitabine plus cisplatin as the new first-line standard of care for patients with advanced BTCs [8,9,23] thus reshaping the treatment paradigm.

ICI-based regimens: potential role in tumor downsizing and conversion therapy

Patients with early-stage HCC and fulfilling the Milan criteria (MC) or alternative transplantation eligibility criteria including up-to-seven, University of California, San Francisco (UCSF) or Toronto criteria [62] may undergo liver transplantation (LT) which is associated with a 5-year OS rates of 60–85 %. However, in routine practice, few patients have tumors that fully satisfy standard MC to receive LT. Thus, with more extended criteria patients could experience comparable post-transplant OS and recurrence rate (RR). The Italian multisociety guidelines for the treatment of HCC recently proposed that it is of relevance adopting the principle of "transplant benefit" as a selection criterion for LT. Of note, the feasibility of a transplant should consider patients' global health and nutritional status, comorbidities, and age [63]. In line with this, several consensus documents [64–66] strongly advocated the need for a personalized treatment to achieve a down-staging prior LT. Patients with stage B BCLC who meet the "extended liver transplantation criteria", and successfully down-staged patients (initially beyond the MC) treated with locoregional therapies (LRT), like transcatheter arterial chemoembolization (TACE), transarterial radioembolization (TARE), ablation and radiotherapy can become eligible for the upfront LT [64].

The survival benefit of ICI-based regimens in advanced-stage HCC prompted clinicians to investigate their use at earlier stages. Pending well-designed prospective studies confirming immunotherapy's efficacy and safety in early-stage HCC or patients with HCC waitlisted for LT [67], it may stand as a potential promising approach to downstage the tumor before LT. In certain patients with early-stage HCC, TACE stands as a downstaging intervention for patients beyond MC and the resulting effective downstaging correlated with promising post-LT outcomes [68,69]. Administering immunotherapy before LT has the same objectives as conventional LRT; thus, bridging and downstaging ICI therapy could expand the number of transplant HCC candidates eligible for curative LT. Beyond that, ICIs may also minimize disease recurrence by treating micro-metastatic disease that was not previously detected. In patients with HCC, the advantage of combining LRT with immunotherapy can be two-fold. First, immunotherapy could expand the extent of LRT's antitumoral immune response, improving patients' outcomes and decreasing recurrence rates. Second, LRTs may influence the TME, thus enhancing the efficacy of immunotherapy.

ICI-based regimens: moving systemic therapies into earlier stages

The morbidity and mortality associated with HCC are significant in all BCLC stages despite the wide range of treatments available. In the intermediate stage, there is a subgroup of initially unresectable HCC that are not initially deemed eligible or failed to downstaging with locoregional treatment. In patients with intermediate-stage HCC, unsuitable or

Table 1
ICI-based combinations investigated in randomized phase III studies in the first-line setting. CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; HR, hazard ratio; ITT, intention-to-treat; LRT, locoregional therapies; NDA, new drug application; ORR, overall response ratio; OS, overall survival; PFS, progression free survival. Elaborated from data in ref. 54,56,57,59.

ICIs-based combinations in first line setting	Landmark trial	Study population	Primary Endpoint	Median OS	Median PFS	Proportion of patients with ORR	Proportion of patients with disease control	Regulatory status
Camrelizumab + rivoceranib	CARES-310 Open label, randomized (vs. sorafenib)	Advanced HCC patients not amenable to curative or LRT and previously untreated with systemic therapy	The primary endpoints were PFS, as assessed by the blinded independent review committee per RECISTs version 1.1, and OS in the intention-to-treat (ITT) population	22.1 vs 15. 2 months (HR: 0.62)	5.6 months vs. 3.7 months (HR: 0.52)	25 % vs. 6 %	78 % vs. 54 %	Feb 2023: approved by China's National Medical Products Administration as a first-line treatment for patients with liver cancer July 2023: NDA submitted to FDA
Sintilimab + bevacizumab biosimilar	Positive trial ORIENT-32 (vs. sorafenib)	Unresectable or metastatic HCC, no previous systemic treatment, and a baseline ECOG PS of 0 or 1	Co-primary endpoints: OS and PFS as assessed by the IRRC per RECIST version 1.1	median not reached [95 % CI not reached–not reached] vs 10·4 months [8·5–not reached] (HR: 0.57)	4.6 months vs 2.8 months (HR: 0.56)	21 % vs. 4 %	72 % vs. 64 %	This combination is currently approved in China.
Cabozantinib + atezolizumab	Positive trial COSMIC-312 (vs. sorafenib)	Advanced HCC not amenable to curative or LRT and previously untreated with systemic anticancer therapy (n = 837)	The dual primary endpoints were PFS in the first 372 patients randomly assigned to cabozantinib plus atezolizumab or sorafenib (the PFS ITT population), and OS in all patients randomly assigned to the combination treatment of cabozantinib plus atezolizumab or sorafenib	15.4 vs 15.5 months	6.8 vs 4.2 months (HR:0.63)	11 % vs. 4 %	78 % vs 65 %	As no significant survival benefit has been documented, no regulatory assessment procedures are currently ongoing.
Levantinib + pembrolizumab	Negative trial LEAP-002 (vs. levantinib)	Unresectable HCC, Child Pugh class A liver disease, an ECOG-PS of 0 or 1, and no previous systemic treatment (n = 794)	Dual primary endpoints were OS (superiority threshold at final overall survival analysis, one-sided p = 0·019; final analysis to occur after 532 events) and PFS (superiority threshold one-sided p = 0·002; final analysis to occur after 571 events) in the ITT population	21.2 vs 19 months (HR: 0.84)	8.2 vs 8.0 (HR:0.87)	26.1 % vs. 17.5 %	81.3 % vs. 78.4 %	

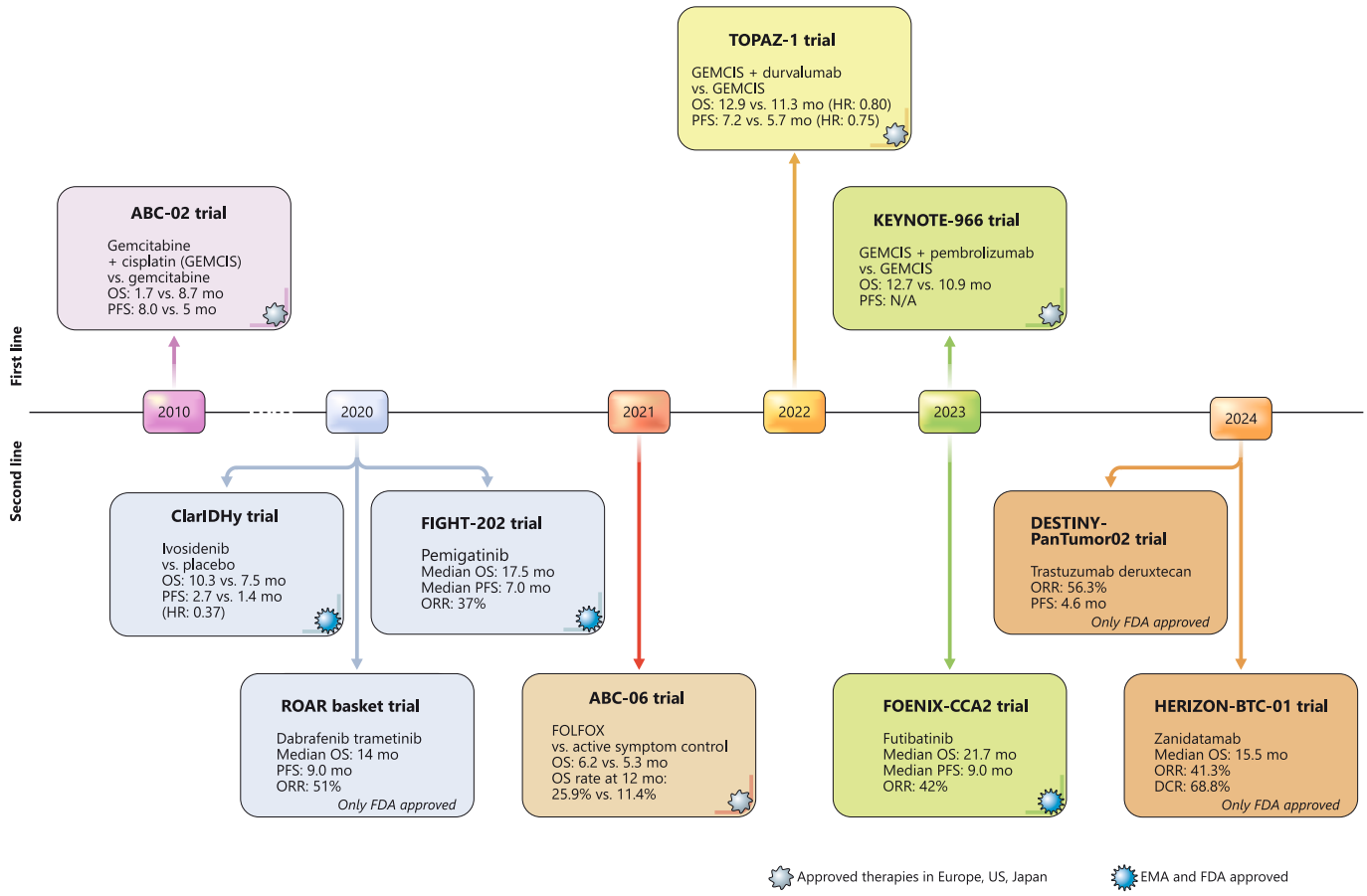

Fig. 3. Evolving treatment landscape for advanced BTC (first line): timeline of approval of systemic therapies. DCR, disease control rate; HR, hazard ratio; MO, months; ORR, overall response rate; OS, overall survival; PFS, progression free survival.

refractory to TACE, who are then eligible to be treated with systemic therapies, ICI-based regimens may stand as useful option [70]. The recent phase III EMERALD-1 and LEAP-012 trials showed that combining ICI-based regimens with TACE could be an effective mean to improve PFS [71,72]. However, when considering adding durvalumab–bevacizumab or pembrolizumab–lenvatinib to TACE in patients with intermediate-stage HCC, the latest ESMO guidelines [44] recommended shared decision making due to the immature OS data and

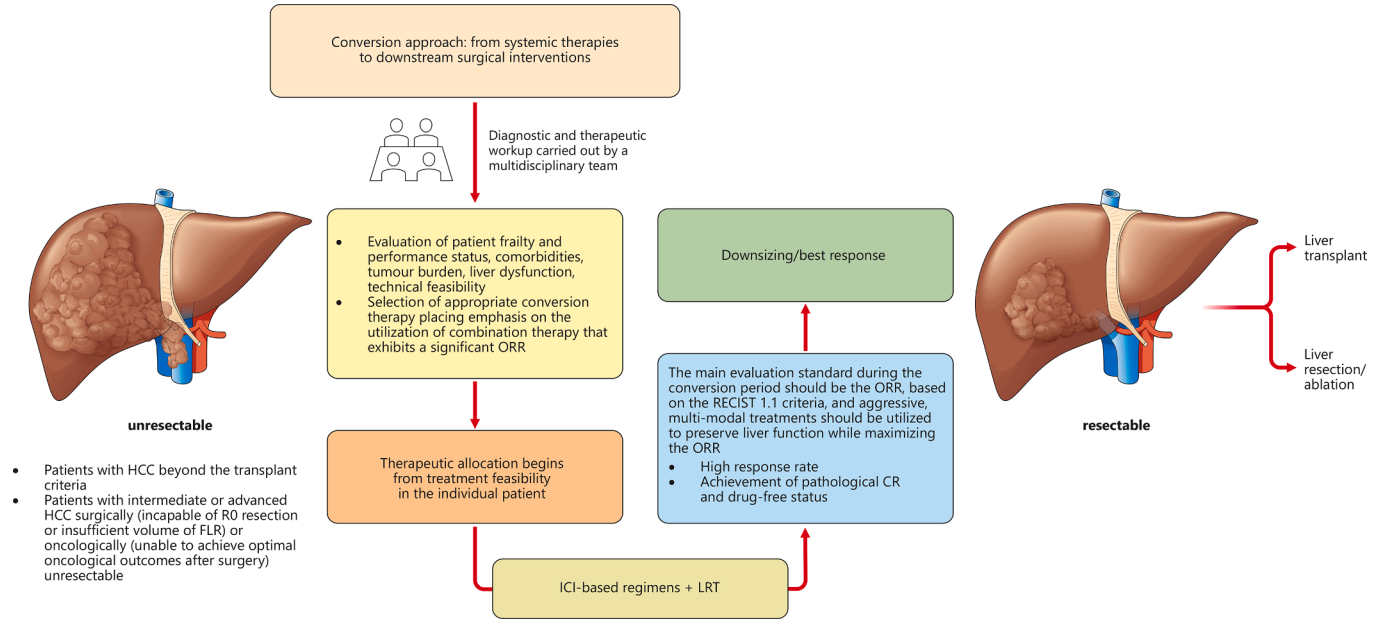

Fig. 4. ICI-based regimens and conversion approach: improving feasibility and effectiveness of radical treatments. CR, complete response; FLR, future liver remnants; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; LRT, locoregional therapies; ORR, objective response rate.

increased risk of toxicity (namely increase rate of grade ≥ 3 AEs) [44]. Of note, studies testing the combination of ICI-based regimens with LRT or resection found a complete response rate in no more than 30 % of patients with TACE-unsuitable intermediate-stage HCC [73]. The available evidence suggests that at early- and intermediate-stage systemic therapies, aimed at reducing post-surgical recurrence in resectable patients as well as increasing the downstaging rate in initially unresectable patients, can stand as valuable options with the aim of increasing OS and recurrence free survival (RFS). The potential of combining systemic drugs with LRTs to maximize the feasibility and effectiveness of radical therapies is best represented in the multiparametric therapeutic hierarchy concept recently proposed by Vitale et al. [65]. This concept questions the traditional treatment hierarchy and recognizes the possibility that systemic drugs, including ICI-based regimens, may expand the indications for radical therapies and their subsequent effectiveness (Fig. 4).

Overall, ICI-based regimens hold a great potential in HCC management as they may promote tumor downsizing in patients with initially unresectable tumors by synergistically enhancing LRT's effect and contributing to reducing tumour burden so that it becomes amenable to surgical resection or meeting criteria for LT. In contrast, the evidence supporting the role of immunotherapy in BTC downsizing, thus improving surgical resection rate, is in its infancy.

Use of ICI-based regimens in HCC: From survival benefit to improved patient outcomes

Atezolizumab plus bevacizumab

In the IMbrave150 trial, treatment with atezolizumab plus bevacizumab was associated with significantly better life extension than sorafenib along with a response rate of 27.3 %, with 88 % of responding patients continuing to have a response at 6 months. To date, a greater disease control rate (DCR) with atezolizumab plus bevacizumab vs. sorafenib (73.6 vs. 55.3 %) was also observed along with a longer time to deterioration (TTD) of patient reported QoL and functioning than sorafenib (11.2 vs. 3.6 months, HR: 0.63) [42]. The updated analysis with 12 months of additional follow-up showed a longer median OS (19.2 vs. 13.4 months) and greater survival at 18 months (52 % vs. 40 %) and ORR (29.8 vs. 11.3 %) with atezolizumab plus bevacizumab vs. sorafenib [43] and such survival benefit was consistent across subgroups, including patients with a baseline albumin-bilirubin (ALBI) grade equal to 1 [74]. Finally, a lower risk of deterioration in patient-reported cancer symptom scales, including appetite loss, diarrhea, fatigue, and pain was also reported [75]. Consistently with the known safety profile of bevacizumab, the most common grade 3 or 4 event observed with the combination was hypertension (15.2 %). Administration of atezolizumab could be immunogenic and may induce undesirable antidrug antibody (ADA) responses. In the IMbrave150 study, almost one in three patients with advanced HCC developed atezolizumab ADAs following atezolizumab plus bevacizumab treatment although following adjustment for imbalances in baseline characteristics no differences in OS were found. Importantly, the clinical implementation of this combination therapy can be impeded by the bleeding events with potential compromisation of vascular integrity and heightened risk of hemorrhage; although well documented, clinicians should take into account such risks in therapy selection and are advised to be cautious in patient selection and monitoring.

Following IMbrave150 study, there was great interest in investigating whether its positive findings could have confirmed in real life [76–78]. The earlier AB-real studies demonstrated the reproducibility and wider generalizability of outcomes of atezolizumab plus bevacizumab in HCC in real-life setting [79] and clarified that hepatic decompensation is the main driver of death in patients with HCC treated with atezolizumab plus bevacizumab [20]. The decisive prognostic role of hepatic decompensation was recently confirmed by a post-hoc analysis of the IMbrave150 study [80].

Finally, similar results in terms of OS and safety have been reported in an ongoing prospective phase IIIb study, the AMETHISTA trial [81], which however leaves unanswered the question regarding the safety and efficacy of atezolizumab plus bevacizumab in patients with CP- B. A recent retrospective analysis suggested that the treatment with atezolizumab plus bevacizumab as a first-line therapy could confer a prognosis advantage compared to lenvatinib, although in a large real-world population such survival advantage of atezolizumab plus bevacizumab over lenvatinib was not confirmed [82].

Durvalumab + tremelimumab

In the HIMALAYA trial, the STRIDE regimen was superior to sorafenib with longer median OS (16.4 vs. 13.8 months; OS HR, 0.78; 96.02 % CI, 0.65 to 0.93; P = 0.0035). In contrast, the study did not show any PFS benefit (HR for PFS were 0.90 (95 % CI, 0.77 to 1.05) for STRIDE vs. sorafenib and 1.02 (95 % CI, 0.88 to 1.19) for durvalumab vs. sorafenib). To date, a greater proportion of patients receiving STRIDE remained progression free compared to those treated with sorafenib (12.5 vs. 4.9 %). A recent post-hoc analysis of the HIMALAYA trial assessed the use of subsequent anticancer therapy and the time to first subsequent treatment (TFST) and showed that TFST was longer with STRIDE than sorafenib [8.4 vs. 7.13 months; HR, 0.77]. Thus, the delayed TFST with STRIDE provides an additional measure of effectiveness for STRIDE in addition to its effect on patient survival [83]. Finally, the median TTD of patient-reported GHS or QoL was longer for STRIDE than for sorafenib (7.5 vs. 5.7 months) [39]. The OS benefit (*e.g.*, reduction of risk of death by 22 %) with STRIDE regimen was confirmed on long-term being sustained and clinically meaningful at four [48] (OS rate: 25.2 % vs 15.1 %) and five years (the longest follow-up in a phase III study in HCC to date) [49]. About one in five patients treated with the STRIDE regimen were alive at five years (OS rate: 19.6 % vs 9.4 %; rate ratio, 2.09), representing an unprecedented survival rate in this disease setting. Importantly, the sustained long-term survival benefits are further improved in patients achieving disease control (OS rate at 5 years: 28.7 % vs 12.7 %; rate ratio, 2.26) thus emphasizing the notion that achieving disease control with STRIDE may stand as a meaningful measure of clinical benefit [49]. Finally, the survival benefit of the STRIDE regimen vs. sorafenib was consistent regardless of the underlying disease cause (HBV, HCV or nonviral) or other baseline demographics including comorbidities [48,84–86]. Importantly, the STRIDE regimen provides a manageable safety profile with a relatively low steroid requirement and a convenient dosing schedule. Real-world experience with STRIDE as first line treatment in unresectable HCC is still limited. Preliminary observational data from DT-real confirm uptake of STRIDE and durvalumab across various lines of therapy with encouraging efficacy and safety outcomes in routine practice [87] but further studies are needed.

Intermediate stage setting

Limited treatment options are available for patients with intermediate-stage HCC. In this setting, patients responding to the early use of immunotherapy may undergo a reduced number and extent of TACE cycles needed to achieve tumor control and can maintain liver function while preserving hepatic parenchyma from TACE-related collateral damage. To this end, an ongoing multi-center, randomized, open-label phase II trial (NCT04224636, DEMAND study) is investigating the efficacy and ideal sequence of TACE and immunotherapy in intermediate stage HCC (Table 1**S**). The phase III EMERALD-1 trial showed that durvalumab in combination with TACE and bevacizumab can improve PFS vs. TACE alone. In the trial, median PFS increased from 8.2 months with placebo plus TACE to 15.0 months with durvalumab plus bevacizumab + TACE, thus providing almost a 25 % reduction in disease progression or death risk (HR: 0.77; P = 0.032). Treatment with durvalumab plus bevacizumab + TACE was associated with greater ORR

(43.6 vs. 29.6 %) and longer median time to progression vs. TACE alone [22 months vs. 10 months, HR:0.63, (95 % CI 4.48–0.82)] [71]. Of note, PFS for durvalumab + TACE vs TACE alone was not statistically significantly different [10 vs. 8.2 months, (HR:0.94), P = 0.638]. The phase III LEAP-012 trial showed that adding lenvatinib and pembrolizumab to TACE improves median PFS compared to TACE alone [14.6 vs 10 months, (HR: 0.66)] with an early trend in OS. However, OS data are not mature, and the significance threshold was not met [72]. Therefore, ongoing trials in intermediate stage setting (Table 1**S**) are expected to provide further evidence for the effectiveness of combining immunotherapy with LRT and may offer insights on the optimal treatment combination or sequence as well as may identify predictive factors for treatment response. Fig. 1**S** illustrates the place in role of ICI-based regimens across HCC stages.

Adjuvant setting

In HCC the rates of recurrence associated with liver resection (LR) and ablation at 5 years are 25–50 % and 70 %, respectively. The risk of HCC recurrence appears bimodal with an early peak within the first year of follow-up and a later peak occurring about 2 years of follow-up after curative treatment. The early peak can serve as a potential target for an effective adjuvant treatment [88]. To date, no approved therapy used in combination with potentially curative treatment is available for patients with HCC in the adjuvant setting [88]. It can be hypothesized that adjuvant therapy with ICIs may potentially provide a two-fold advantage. First, by facilitating the systemic removal of hidden residual disease, it may prevent the occurrence of an early recurrence. Second, it may potentially reduce the incidence of *de novo* HCC by activating immune surveillance processes which in turn will decrease the late recurrence rate. Therefore, patients at high risk of recurrence may experience the greatest benefit from such approach. However, clinical evidence of ICI-based regimens use in HCC adjuvant setting is still lacking. Although the IMbrave050 trial initially showed that atezolizumab plus bevacizumab achieved a statistically significant recurrence free survival (RFS) compared to active surveillance alone (HR: 0.72; P = 0.012) [89], in a recent follow up analysis the initial RFS benefit was not sustained, and OS remained immature [90]. In line with this, the latest ESMO guidelines did not recommend adjuvant systemic treatment with ICI-based combinations after resection or ablation [44]. Results from other studies in this setting are awaited (i.e., EMERALD-2). In the meantime, neoadjuvant strategies are also being investigated in patients with surgically resectable HCC as in the MORPHEUS NEO trial (NCT05908786).

Use of ICI-based regimens in BTCs: Harnessing synergy with chemotherapy to prolong survival

The TOPAZ-1 trial was the first phase III study that demonstrated an OS benefit when durvalumab is added to chemotherapy for up to eight cycles as first-line treatment [27]. The HR for PFS was 0.75 (P = 0.001) with longer median PFS with durvalumab (7.2 months vs. 5.7 months) and greater ORR (26.7 % vs. 18.7 %) than with placebo. Of note, response to treatment for 12 months or more was observed at greater extent in the durvalumab arm compared to placebo arm (26.1 % vs. 15.0 %). A recent updated analysis showed that more than twice as many patients were estimated to be alive at 24 months with durvalumab addition to gemcitabine plus cisplatin vs. placebo addition to gemcitabine plus cisplatin [OS rates: 23.6 % (18.7–28.9) vs. 11.5 % (7.6–16.2)]. Importantly, more patients in the durvalumab plus gemcitabine–cisplatin group were long-term survivors than in the chemotherapy group and survival benefit extended to patients with disease control [28]. To date, patients who received durvalumab and chemotherapy experienced a survival benefit which was incremental over time (OS rates: 54.3 % vs. 47.2 % at 12 months; 22.9 % vs. 13.1 % at 24 months; 14.6 % vs. 6.9 % at 36 months). Notably, the addition of durvalumab to chemotherapy was shown not negatively to influence the patients' QoL [91]. In addition, durvalumab could be administered without interruption because of AEs as maintenance therapy until disease progression. Of note, the survival benefit reported in the TOPAZ-1 trial was confirmed in the real-world setting [92]. Finally, a recent single-center retrospective analysis confirmed the safety of durvalumab addition to gemcitabine plus cisplatin even beyond the TOPAZ-1 inclusion criteria [93].

More recently, the addition of pembrolizumab to gemcitabine plus cisplatin was evaluated in the KEYNOTE-966 trial which confirmed the OS benefit of pembrolizumab addition to gemcitabine plus cisplatin [HR 0.83 (95 % CI 0·72–0·95) primary analysis; HR 0.86, (95 % CI 0.75–0.98) at three year follow-up] while suggesting a similar PFS between treatment arms [6.5 vs. 5.6 months, HR 0.85, 95 % CI (0.75–0.97)]. Response rate was similar in both arms but with longer duration of response in the intervention arm. Importantly, the addition of pembrolizumab did not impact the HRQoL [29,30,94].

It has been hypothesized that the dual blockade of PD-L1 and VEGF pathways coupled with gemcitabine plus cisplatin could effectively target relevant immune mechanisms within the TME. The phase II IMbrave151 trial (NCT04677504) showed similar PFS adding atezolizumab plus/minus bevacizumab to gemcitabine plus cisplatin in patients with newly diagnosed, advanced BTC [95] (8.3 months vs. 7.9 months; HR: 0.76) thus not providing conclusive evidence regarding the potential efficacy of combining dual blockade of PD-L1 and VEGF pathways with gemcitabine plus cisplatin.

Ongoing clinical trials are currently examining the efficacy of other ICIs in the treatment of BTCs, such as the REGOMUNE trial (NCT03475953) and the LEAP-005 study (NCT03797326). Following the results of the TOPAZ-1 study, the efficacy of tremelimumab (two dosing regimens) in combination with durvalumab + gemcitabine plus cisplatin is currently evaluated in the phase II IMMUCHEC study (NCT03473574). The use of immunotherapy combination in the neoadjuvant and adjuvant setting is also under investigation in several clinical trials such as the DEBATE and ADJUBIL studies and the ongoing phase III ARTEMIDE-Biliary01 trial (NCT06109779).

Expert opinion

The landscape of systemic therapy and the place in role of ICI in managing HCC and BTCs are ever-changing and clinical studies are expected to further advance current practice (Table 1**S**). In routine clinical practice, several questions emerge for all treating oncologists and hepatologists regarding patient selection, treatment response, optimal timing, and sequencing and imAE management.

Despite advances in HCC and BTC therapy, only a small proportion of patients respond to immune-based treatments and several unmet needs still hinder the clinical practice (Fig. 5). A major challenge is identifying biomarkers to predict which patients will benefit from these therapies. Inter/intra-tumoral heterogeneity and the lack of predictive biomarkers complicate the selection of responders to ICI-based regimens. While many biomarkers are found in the tumor microenvironment (TME), invasive biopsies are needed. Peripheral blood offers easier sampling but may not reflect the local immune context. Research focuses on potential biomarkers like tumor mutational burden (TMB), infiltrating lymphocytes, ctDNA, and circulating tumor cells (CTCs) [96,97].

Knowledge gaps on how to sequence drugs after the establishment of immunotherapy–based combinations are still hindering routine practice. In patients with HCC not previously treated with sorafenib, clinicians are still lacking evidence-based information on how to best manage them. Small studies have suggested some responses with combinations of CTLA-4 with anti–PD-1 after prior ICI [98,99]. Recent clinical data reported that regorafenib has similar activity regardless of the first-line regimen that was used, including after prior ICI [100]. Similarly, a prospective study supported cabozantinib efficacy in patients who had received prior ICI regimens [101]. In BTC, we should

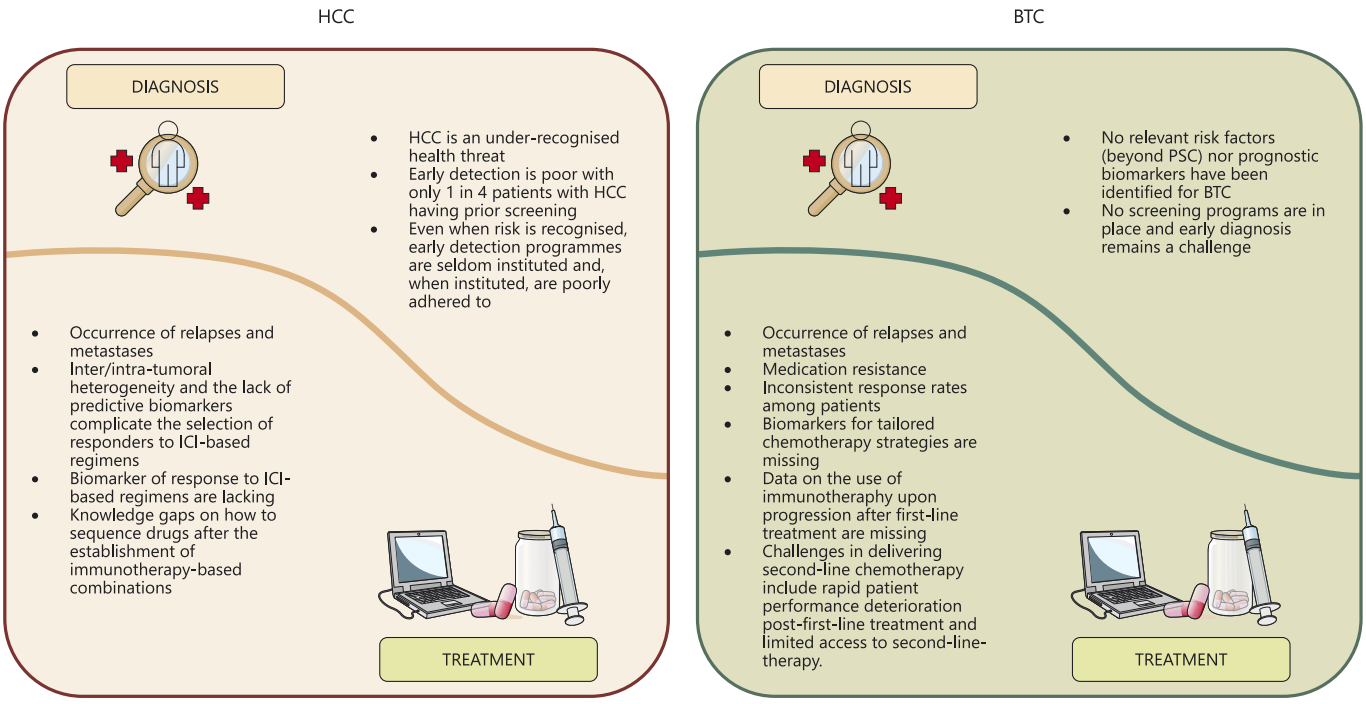

Fig. 5. Unmet needs in HCC and BTC management. BTC, biliary tract cancer; ICI,immune-checkpoint inhibitor; HCC, hepatocellular carcinoma; PSC, primary sclerosing cholangitis.

consider that most of studies investigating the second line setting were conducted when chemotherapy alone was still considered a standard first-line therapy. Currently, second-line therapy is based on the presence of therapeutic targets with approved drugs. In the absence of such targets, only chemo-based regimes remain available for our patients. Future studies should assess whether progression following a first-line treatment with chemo-immunotherapy yields the same outcomes as in the past, when immunotherapy was not used in the first line. At present, we do not have data on the use of immunotherapy upon progression after first-line treatment.

ICI-based combinations have varying toxicity profiles. Atezolizumab plus bevacizumab commonly causes hypertension, proteinuria, elevated aspartate aminotransferase, and fatigue. In the IMbrave150 trial, 70 % of patients had atezolizumab-related AEs, but immune mediated AEs (imAEs) were not mentioned. ImAEs can affect the skin, gastrointestinal system, and thyroid glands, often requiring steroids. The HIMALAYA study reported hepatic events, diarrhea/colitis, and rash as common imAEs. Only 20 % of patients needed high-dose steroids [102]. The STRIDE regimen's toxicity profile is favorable compared to TKI or atezolizumab plus bevacizumab. Liver injury related to ICI occurs more often in HCC but typically resolves without impacting outcomes. Finally, future studies investigating the use of ICI-based regimens in the early and intermediate stages are expected to provide practice-informing insights to expand the pool of patients with HCC who most likely benefit from immunotherapy.

The landscape of BTC management has changed in recent years, moving from traditional chemotherapy towards personalized medicine as the heterogeneous genetic complexity of BTC impact significantly patient's clinical outcome. While molecularly targeted therapeutics are currently being used in the second line, there are trials underway that have the potential to move actionable mutations to first-line settings.

Overall, in recent years, new medications and techniques have implemented the already complex therapeutic landscape of HCC and BTC thus demanding a multidisciplinary approach. In HCC, the complexity of the disease, the underlying cirrhosis, which affects the feasibility of many therapies, as well as the wide range of available therapeutic options, calls on collective decision-making. In BTC, clinical management is complex and close cooperation between hepatobiliary and surgeons, interventional radiology, endoscopists, and oncologists is mandatory in the treatment of each patient with BTC. As international guidelines advocate, both HCC and BTC patients should be managed by multidisciplinary teams [23,44]. In the absence of RCTs directly comparing the available ICI-based combination regimens, there is a pressing need for large real-world studies to inform treatment decisions in real practice. Pending such evidence, clinicians may rely on a multidisciplinary holistic approach to HCC and BTC care which may offer significant benefits in patient diagnosis, treatment planning, and OS outcomes.

In conclusion, immunotherapy and ICI-based regimens stand as a valuable and practice-changing option in both HCC and BTC management. With advances in immunotherapy-based combinations coming at a rapid pace, recalcitrant and deadly cancers like BTC and HCC are foreseen to be more successfully managed soon.

CRediT authorship contribution statement

Giuseppe Cabibbo: Conceptualization, Writing – original draft, Methodology, Visualization, Formal analysis, Data curation. **Lorenza Rimassa:** Conceptualization, Writing – original draft, Methodology, Visualization, Formal analysis, Data curation. **Angela Lamarca:** Writing – review & editing. **Gianluca Masi:** Writing – review & editing. **Bruno Daniele:** Writing – review & editing. **David James Pinato:** Writing – review & editing. **Andrea Casadei-Gardini:** Conceptualization, Writing – original draft, Methodology, Visualization, Formal analysis, Data curation.

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