

# World Journal of *Clinical Oncology*

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**OPINION REVIEW**

- 423 Implementation of a virtual multicenter gastrointestinal tumor board to reduce cancer disparities in Argentina

*Esteso F, Tissiera NS, O'Connor JM, Luca R, Huertas E, Sánchez Loria F, Pedraza I, Pairola A, Brancato F, Paganini L, Kucharczyk M, Amat M, Pombo MT, Galli M, Bruno L, Caro L, Rodriguez A, Enrico D, Waisberg F, Chacón M*

**REVIEW**

- 429 New perspectives in the management of small cell lung cancer

*Pangua C, Rogado J, Serrano-Montero G, Belda-Sanchis J, Álvarez Rodríguez B, Torrado L, Rodríguez De Dios N, Mielgo-Rubio X, Trujillo JC, Couñago F*

- 448 Immunotherapy for advanced hepatocellular carcinoma: From clinical trials to real-world data and future advances

*Rallis KS, Makrakis D, Ziogas IA, Tsoulfas G*

**MINIREVIEWS**

- 473 Circulating tumor DNA for diagnosis, prognosis and treatment of gastrointestinal malignancies

*Kirchweger P, Wundsam HV, Rumpold H*

- 485 Current treatment landscape for oligometastatic non-small cell lung cancer

*Garde-Noguera J, Martín-Martín M, Obeso A, López-Mata M, Crespo IR, Pelari-Mici L, Juan Vidal O, Mielgo-Rubio X, Trujillo-Reyes JC, Couñago F*

**ORIGINAL ARTICLE****Basic Study**

- 496 Molecular docking of DS-3032B, a mouse double minute 2 enzyme antagonist with potential for oncology treatment development

*da Mota VHS, Freire de Melo F, de Brito BB, Silva FAFD, Teixeira KN*

- 505 Nicotinic receptors modulate antitumor therapy response in triple negative breast cancer cells

*Español A, Sanchez Y, Salem A, Obregon J, Sales ME*

**Retrospective Study**

- 520 Risk factors for lymph node metastasis in patients with pancreatic neuroendocrine neoplasms

*Nakao Y, Hayashi H, Yamashita YI, Takashi O, Matsumura K, Uemura N, Kitamura F, Itoyama R, Yusa T, Taki K, Miyata T, Higashi T, Nakagawa S, Okabe H, Imai K, Baba H*

**Prospective Study**

- 529 Significance of serum carcinoembryonic antigen in metastatic breast cancer patients: A prospective study

*Anoop TM, Joseph P R, Soman S, Chacko S, Mathew M*

**CASE REPORT**

- 540** Epstein-Barr virus-associated smooth muscle tumors in immunocompromised patients: Six case reports  
*Khan AA, Estfan BN, Yalamanchali A, Niang D, Savage EC, Fulmer CG, Gosnell HL, Modaresi Esfeh J*

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## Immunotherapy for advanced hepatocellular carcinoma: From clinical trials to real-world data and future advances

Kathrine S Rallis, Dimitrios Makrakis, Ioannis A Ziogas, Georgios Tsoulfas

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### Abstract

Hepatocellular carcinoma (HCC) is a leading cause of cancer-associated mortality worldwide. HCC is an inflammation-associated immunogenic cancer that frequently arises in chronically inflamed livers. Advanced HCC is managed with systemic therapies; the tyrosine kinase inhibitor (TKI) sorafenib has been used in 1<sup>st</sup>-line setting since 2007. Immunotherapies have emerged as promising treatments across solid tumors including HCC for which immune checkpoint inhibitors (ICIs) are licensed in 1<sup>st</sup>- and 2<sup>nd</sup>-line treatment setting. The treatment field of advanced HCC is continuously evolving. Several clinical trials are investigating novel ICI candidates as well as new ICI regimens in combination with other therapeutic modalities including systemic agents, such as other ICIs, TKIs, and anti-angiogenics. Novel immunotherapies including adoptive cell transfer, vaccine-based approaches, and virotherapy are also being brought to the fore. Yet, despite advances, several challenges persist. Lack of real-world data on the use of immunotherapy for advanced HCC in patients outside of clinical trials constitutes a main limitation hindering the breadth of application and generalizability of data to this larger and more diverse patient cohort. Consequently, issues encountered in real-world practice include patient ineligibility for immunotherapy because of contraindications, comorbidities, or poor performance status; lack of response,

efficacy, and safety data; and cost-effectiveness. Further real-world data from high-quality large prospective cohort studies of immunotherapy in patients with advanced HCC is mandated to aid evidence-based clinical decision-making. This review provides a critical and comprehensive overview of clinical trials and real-world data of immunotherapy for HCC, with a focus on ICIs, as well as novel immunotherapy strategies underway.

**Key Words:** Hepatocellular carcinoma; Liver cancer; Immunotherapy; Immune checkpoint inhibitors; Clinical trials; Real-world data

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**Core Tip:** In the last five years, immune checkpoint inhibitors (ICIs) have entered the treatment landscape of hepatocellular carcinoma (HCC) in the 1st and 2nd line setting. However, due to restrictions in clinical trial inclusion and exclusion criteria, there remains a need for further real-world data on the efficacy, toxicity, and cost-effectiveness of ICIs in a broader cohort of HCC patients. New trials are underway investigating further ICI regimens, including combination therapy strategies, while novel immunotherapies are also being brought to the fore. This review discusses key clinical trials, real-world data, and future advances of immunotherapy for HCC, with a focus on ICIs.

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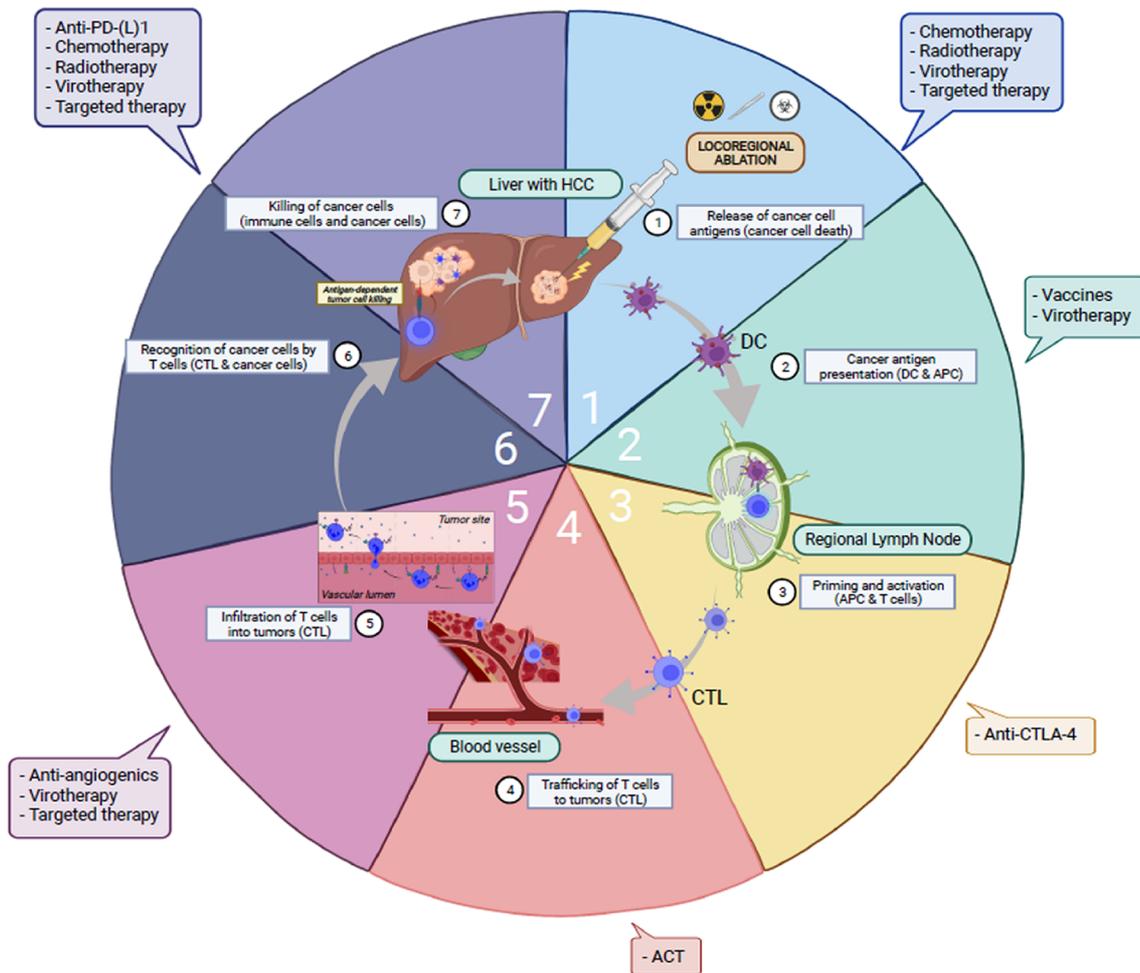
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## INTRODUCTION

Liver cancer is the third leading cause of cancer-related mortality worldwide and sixth in terms of incidence accounting for 830180 deaths and 905677 cases in 2020[1]. Hepatocellular carcinoma (HCC) is the leading type of primary liver cancer representing 85%-90% of cases[2]. The incidence of HCC is expected to continue to increase in countries, including the United States, until 2030. Asia and Africa feature the highest incidence of disease due to the endemic prevalence of hepatitis B or C virus (HBV or HCV) which, when untreated, lead to chronic liver disease and subsequent development of HCC. Global vaccination efforts against HBV and HCV are expected to lower the incidence of HCC, with effects becoming apparent after a latency period of 20-30 years correlating to the time required from liver damage to cancer development[3]. Second to viral hepatitis, alcohol abuse is another main cause of HCC development[4]. Diabetes, aflatoxin-B1 exposure, obesity, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease, and metabolic syndrome represent other leading contributors to HCC development[5]. NASH typically develops in patients with obesity, type 2 diabetes, dyslipidemia, and hypertension, therefore being a leading risk factor for HCC in rich developed countries such as the United States[3]. Both incidence and mortality of liver cancer are expected to double in the next two decades[6]. With a 5-year survival rate of less than 20%, liver cancer carries one of the worst cancer prognoses after pancreatic cancer[7]. Although this figure represents a significant improvement compared to the 3% 5-year survival observed in the 1970s[7], further research is warranted to improve treatments, especially for individuals with distant and regional metastatic disease which feature a 3% and 12% 5-year survival, respectively[8].

The current treatment landscape of HCC depends on disease stage (Figure 1). Surgical resection, liver transplantation (LT), and locoregional ablation therapies (2<sup>nd</sup>-line) are used with curative intent in early and intermediate disease. Yet, recurrence rates are high, while only 30%-40% of patients qualify for the above treatments[9,10]. Advanced HCC (aHCC) is managed with systemic therapies. Historically, systemic chemotherapies have largely been ineffective in HCC due to high rates of chemoresistance and liver impairment with associated susceptibility to toxicities[9]. Starting with the Food and Drug Administration (FDA) approval of sorafenib, a multiple tyrosine kinase inhibitor (TKI) with antian-igenic and antiproliferative action, as a frontline systemic therapy for HCC in 2007, systemic therapies for HCC have evolved remarkably[11]. In 2018, following several randomized controlled trials exploring systemic therapies, which failed to surpass sorafenib, the multikinase inhibitor, lenvatinib, gained FDA approval as another 1<sup>st</sup>-line therapy in HCC following results of a phase III non-inferiority trial[12]. Subsequently, the TKIs regorafenib[13], cabozantinib[14], and ramucirumab[15] received approval in refractory HCC.



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**Figure 1 Schematic of the cancer-immunity cycle and strategies to overcome mechanisms of resistance in each step by enhancing necessary immune stages via different anti-cancer therapeutic modalities in advanced hepatocellular carcinoma.** ACT: Adoptive cell transfer; APC: Antigen presenting cell; CTL: Cytotoxic T lymphocyte; DC: Dendritic cell.

In the last decade, the field of cancer immunotherapy has evolved tremendously, largely owing to the success of monoclonal antibodies (mAbs) directed against negative regulator molecules of T-cell activation, namely cytotoxic T-lymphocyte protein-4 (CTLA-4), programmed cell death protein 1 (PD-1), and its ligand, PD-L1. Immune checkpoint inhibitors (ICIs) reverse the immunosuppressive cancer phenotype by binding to and blocking co-inhibitory immune signalling molecules that are upregulated in cancer providing a means of systemic immune recognition and targeting of malignant cells. Following the approval of ipilimumab (anti-CTLA-4) for metastatic melanoma in 2011, ICIs have gradually been trialled and expanded across solid tumors. To date, four ICI regimens have been approved for HCC: nivolumab (anti-PD-1), approved as 2<sup>nd</sup>-line in 2017[16]; pembrolizumab (anti-PD-1), approved as 2<sup>nd</sup>-line in 2018[17]; nivolumab plus ipilimumab, approved as 2<sup>nd</sup>-line in 2020[18]; and atezolizumab (anti-PD-L1) plus bevacizumab (anti-vascular endothelial growth factor [VEGF] mAb), approved as 1<sup>st</sup>-line in 2020[19].

The complex interdependent relationship between chronic inflammation and anticancer immunity in HCC represents a possible opportunity and challenge for immunotherapy. Intelligent therapeutic strategy design that balances enhancing anti-tumor immunity whilst minimizing pro-tumorigenic inflammation and immunosuppressive adaptations lies at the center of successful immunotherapeutic regimens for HCC. Furthermore, effective anti-cancer immunity to overcome cancer immune escape involves multiple steps. Hence, new immunotherapies continue to be investigated for HCC, with novel adoptive cell transfer (ACT), therapeutic cancer vaccines, and virotherapy being developed as monotherapies or in combination strategies. This review summarizes updates and future directions for immunotherapies and their combinations in HCC.

## IMMUNOGENICITY IN HCC

Immunotherapies are potentially promising therapeutic strategies in HCC. A complex interdependent relationship exists between chronic inflammation and anticancer immunity in the normal liver and in HCC, representing an opportunity and challenge for immunotherapy in HCC.

The liver itself is an immune organ with rich and unique immune cell populations (*e.g.*, Kupffer cells), functional anatomy, and immune functions. Under normal conditions, the liver finetunes immune tolerance, systemic inflammation and immunity, and anti-tumor immunity (*reviewed in*[20]). The tolerogenic potential of the liver – required for the modulation of host response to gut flora – underlies its capacity to generate potent immune tolerance to tumors when liver metastases occur from other primary cancers[21]. This same tolerogenic potential of the liver also underlies its ability to fully accept allograft LT and safely discontinue immunosuppressants in some LT patients[22]. Immune tolerance within the liver develops through complex interactions between liver-resident cells and peripheral leukocytes involving poor or incomplete activation of CD4+ and CD8+ T cells, elevated expression of immune checkpoints, and an immunosuppressive environment mediated by IL-10 and TGFβ[23,24]. Indeed, through new technologies and machine learning algorithms tumor immune microenvironment features have been correlated with patient prognostication to classify patients into separate groups based on response to immunotherapy and other treatments[25-28].

HCC represents a typical inflammation-associated immunogenic cancer as it often arises in chronically inflamed livers (necroinflammation)[29]. It is well known that chronic inflammation causes local and systemic immunosuppression of innate and adaptive immunity due to chronically elevated pro-inflammatory stimuli[20], while scar tissue itself impedes immunosurveillance[30]. Chronic antigen stimulation results in T-cell exhaustion, immune inhibitory receptor upregulation (*e.g.*, PD-1), and progressive loss of polyfunctional cytokine production[20]. Moreover, cirrhotic patients are systemically immunocompromised, due to loss of synthetic liver functions, and are susceptible to life-threatening infections[31]. Locally, both tumor cells and surrounding stroma orchestrate tissue remodeling with concurrent functional and phenotypical immunobiology adaptations resulting in a dysfunctional and immunosuppressive tumor milieu[32]. Simultaneously, successive chronic inflammatory stresses cause hepatocellular DNA damage, whereby genetic and epigenetic mutations give rise to immunogenic pathogen-associated proteins (abnormal amino acid sequences) through transcription and translation of mutated genetic sequences. In turn, tumor associated antigens (TAA) and neo-antigens may result that act as recognizable epitope targets to facilitate effector T-cell recognition of a non-self antigen against which to mount an immune response, so long as strong human leukocyte antigen binding and immunological synapse is possible against the new abnormal peptide sequence[32].

ICIs and other emerging forms of immunotherapy display high efficacy in cancers expressing targetable TAAs and neo-antigens. Indeed, some forms of immunotherapy incorporate molecular recognition of specific TAAs and neo-antigens in their mechanistic design[33]. Tumor mutational burden (TMB) is regarded as a surrogate marker for the expression of TAA and neo-antigens, and hence immunotherapy efficacy, as seen in the case of melanoma[34]. HCC has been shown to feature a low-to-moderate TMB compared to other tumors[35]. Although this theoretically corresponds to lower probability of immunotherapy efficacy, the antigenicity and immunogenicity of any resultant TAAs and neo-antigens in HCC is not well characterized and these may still be sufficiently potent targets for immunotherapies[36].

Intelligent therapeutic strategies that achieve an acceptable balance between enhancing anti-tumor immune surveillance and destruction whilst minimizing pro-tumorigenic inflammation and immunosuppression lie at the center of successful immunotherapy regimen design for HCC.

## IMMUNE CHECKPOINT INHIBITORS IN HCC

### ICI monotherapy in aHCC

The first study to investigate the efficacy of ICIs in HCC was CheckMate 040, a phase I/II clinical trial of nivolumab with or without ipilimumab in aHCC. Patients treated in the nivolumab monotherapy arm demonstrated an objective response rate (ORR) of 20% [95% confidence interval (CI): 15-26%] and a manageable toxicity profile; 25% of patients experienced grade 3-4 treatment-related adverse events (AEs). Of interest, 68% ( $n = 145$  of 216) of patients in the expansion phase had previously received sorafenib in the 1<sup>st</sup>-line setting. Analysis was stratified by PD-L1 expression but not by receipt of previous treatment[16]. Nivolumab received accelerated approval in the 2<sup>nd</sup>-line setting for the treatment of aHCC following results from this trial.

Another phase I/II study of ICI therapy for aHCC was NCT01693562, a trial assessing the efficacy of durvalumab in advanced solid tumors, including aHCC. In this trial, 93% of patients had been previously treated with sorafenib. ORR for the whole cohort was 10% (95%CI: 2.9%-24.2%) with a median overall survival (mOS) of 13.2 mo (95%CI: 6.3-21.1). Grade 3-4 AEs were noted in 20% of patients, with elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) among the most common (7.5% and 5.0%, respectively). Overall, durvalumab was shown to exert promising

activity over aHCC with an acceptable toxicity profile. The above studies established ICIs as tolerable and effective alternative (2<sup>nd</sup>-line) options to sorafenib in patients with aHCC. ICIs were subsequently trialed in 1<sup>st</sup>-line setting against sorafenib.

CheckMate 459 was a phase III study of nivolumab *vs* sorafenib as a 1<sup>st</sup>-line therapy in patients with aHCC. No statistically significant difference in mOS was found between treatment arms (nivolumab: 15.2 mo *vs* sorafenib: 14.7 mo); however, treatment-related AEs were more favorable with nivolumab [37]. Although results from CheckMate 495 have not yet been strong enough to justify approval of nivolumab as a 1<sup>st</sup>-line therapy for aHCC over sorafenib – due to the prespecified significance boundary for superior OS compared to sorafenib not being met – conclusions from this trial are significant as they indicate nivolumab as an alternative treatment option that should be offered to patients who cannot receive anti-angiogenics and TKIs because of contraindications or AE severity. This is reflected in the National Comprehensive Cancer Network Clinical Practice Guidelines in the USA. However, it has not been adopted in the European or Asian guidelines to date. Following this trial, the accelerated FDA approval of nivolumab monotherapy was withdrawn as it did not meet the post-marketing requirements. Importantly, to date this is the only phase III clinical trial completed to investigate single-agent anti-PD-1 or anti-PD-L1 monotherapy against single agent TKI monotherapy in the 1<sup>st</sup>-line setting for aHCC.

In the 2<sup>nd</sup>-line setting for the treatment of aHCC, the use of ICIs has been investigated with more success leading to clinical approvals. Keynote 224 was a phase II study of 2<sup>nd</sup>-line pembrolizumab in patients with aHCC that had previously been treated with, or were intolerant to, sorafenib. ORR for pembrolizumab was 17% (95%CI: 11%-26%) while treatment-related AEs were noted in 73% of patients, with 25% experiencing grade 3 AEs. Of note, most common AEs were increased AST and AL in 7% and 4% of patients, respectively. Based on these results, pembrolizumab has been granted FDA approval in the 2<sup>nd</sup>-line setting for patients with aHCC who previously received treatment with sorafenib.

In another study investigating the anti-PD1 agent camrelizumab as 2<sup>nd</sup>-line therapy in patients with aHCC previously treated with sorafenib ORR was 14.7% (95%CI: 10.3%-20.2%). Grade 3-4 AEs were encountered in 22% of patients, with increased AST being the most common AE (5%). This study demonstrated that camrelizumab also had a manageable toxicity profile[38].

Following the successful results of Keynote 224, Keynote 240, a randomized phase III study of 2<sup>nd</sup>-line pembrolizumab *vs* placebo in patients treated with 1<sup>st</sup>-line sorafenib, was initiated. The study showed a benefit in both mOS [13.9 *vs* 10.6 mo, hazard ratio (HR): 0.78, 95%CI: 0.61-0.99] and median progression-free survival (mPFS) (3.0 *vs* 2.8 mo, HR: 0.71, 95%CI: 0.57-0.90) in favor of pembrolizumab. The trial did not meet the prespecified criteria for mOS and mPFS despite the superior results observed with pembrolizumab. However, pembrolizumab had a favorable risk-to-benefit ratio and received accelerated FDA approval as a 2<sup>nd</sup>-line treatment for aHCC[39]. These results were similar to those of Keynote 224, suggesting that ICIs could become the preferred treatment of choice for patients who are at high risk for AEs.

More recently, the anti-PD-L1 agent avelumab showed moderate efficacy in a phase II trial in 30 patients previously treated with sorafenib (NCT03389126)[40]. The mOS and mPFS were 14.2 mo (95%CI: 9.5-18.9) and 3.5 mo (95%CI, 2.0-5.1), respectively. Treatment was well-tolerated, with 23% of patients exhibiting grade 3 AEs – commonest being increased AST/ALT (13%) – and none experiencing grade 4 AEs.

Clinical trials of ICI monotherapy in HCC attest to their efficacy and tolerability; however, these failed to demonstrate clear superiority over sorafenib, prompting investigators towards combination strategies to increase efficacy.

### **ICI combination therapies**

**ICI duplet therapy:** The use of ICI combinations has gained attention in the last few years across a wide spectrum of solid tumors. Combinations of ICIs usually include an anti-PD-L1/PD-1 and an anti-CTLA-4 agent and demonstrate better responses compared to single-agent therapy, but also higher rates of AEs, especially serious and life-threatening ones[41]. Several clinical trials have assessed the efficacy and safety of anti-CTLA-4 and anti-PD-L1 combination regimens for aHCC.

A phase II trial (NCT02519348) assessed the efficacy of 2<sup>nd</sup>-line tremelimumab, an anti-CTLA-4 antibody, combined with durvalumab in patients with aHCC that were intolerant to, progressed to, or refused sorafenib. Patients were randomized into 4 different arms (tremelimumab 300 mg with durvalumab for the 1<sup>st</sup> cycle followed by durvalumab; durvalumab monotherapy; tremelimumab monotherapy; and tremelimumab 75mg with durvalumab for 4 cycles followed by durvalumab alone). Grade 3-4 AEs were observed in 35.1%, 17.8%, 42.0% and 24.4% of patients, respectively. ORRs were 22.7%, 9.6%, 7.2% and 9.5%, respectively, while mOS was 18.7 [95%CI: 10.8-not reached (NR)], 11.7 (95%CI: 8.5-16.9), 17.1 (95%CI: 10.9-NR) and 11.3 (95%CI: 8.4-14.6) months, respectively. Between treatment arms, tremelimumab 300 mg with durvalumab demonstrated the best benefit-to-risk profile [42]. After these results, the combination of tremelimumab-durvalumab was subsequently investigated in 1<sup>st</sup>-line setting in HIMALAYA (NCT03298451), a phase III trial that showed better outcomes with tremelimumab-durvalumab compared to sorafenib; mOS was 16.4 *vs* 3.8 mo, respectively (HR: 0.78%, 95%CI: 0.65-0.92), and ORR was 20.1% *vs* 17.0%, respectively[43].

In the nivolumab-ipilimumab combination part of the Checkmate 040 trial of patients with aHCC pre-treated with sorafenib, participants were randomized 1:1:1 into 3 different groups: Group A patients received nivolumab 1 mg/Kg every 2 wk & ipilimumab 3 mg/Kg every 3 wk for the first 3 mo, followed by nivolumab 1 mg/Kg every 2 wk; those in group B received nivolumab 3 mg/Kg every 2 wk and ipilimumab 1 mg/Kg every 3 wk for the first 3 mo, followed by nivolumab 3 mg/Kg every 2 wk; and those in group C were treated with nivolumab 1 mg/kg every 2 wk and ipilimumab 3 mg/Kg every 6 wk. ORR was 32% (95%CI, 20%-47%) for group A, 27% (95%CI: 15%-41%) for group B, and 29% (95%CI: 17%-43%) for group C. Median duration of response was not reached for patients in group A and was 15.2 and 21.7 mo for groups B and C, respectively. Although the total number of patients that experienced AEs of any grade was high (94% for group A, 71% for B, and 76% for C), serious AEs were not very common; in group A, 10% of patients reported grade 3-4 AEs, compared to 4% for group B, and 2% for group C. Overall, the study showed promising results on the efficacy and tolerability of ICI combinations for advanced HCC[18]. Following results from this trial, the combination of nivolumab-ipilimumab received FDA approval for aHCC becoming the new standard of care in the 2<sup>nd</sup>-line setting for patients who progress on prior TKI therapy and who do not have a contraindication to ICIs and are fit and able tolerate the higher toxicity observed in double ICI combination. Consequently ICI monotherapy with pembrolizumab (or nivolumab off-license) in the 2<sup>nd</sup>-line setting was reserved for less fit patients. The success of Checkmate 040 in establishing the efficacy of nivolumab-ipilimumab combination therapy for aHCC lead to Checkmate 9DW, another ongoing phase III trial comparing nivolumab-ipilimumab combination *vs* sorafenib or lenvatinib monotherapy.

**ICI+TKI:** The combination of ICIs with other factors with proven efficacy for aHCC has been investigated extensively through several trials subsequent to the negative results reported from Checkmate 459. TKIs have been among the most commonly tested agents. A recent phase Ib study investigated the use of pembrolizumab-levatinib combination therapy for patients with unresectable HCC. ORR was 36% (95%CI: 26.6%-46.2%), with a 12.6-mo duration of response, a mOS of 22 mo, and a mPFS of 8.6 mo. Grade  $\geq 3$  AEs were observed in 67% of patients[44].

The RESCUE trial was a phase II study of patients with aHCC treated with camrelizumab, a PD-1 inhibitor, combined with apatinib – another VEGFR-2 TKI that has demonstrated activity as 1<sup>st</sup>- and 2<sup>nd</sup>-line therapy for aHCC[45,46]. Patients were enrolled into the study irrespective of previous treatment status and analyses were stratified by line of therapy. For patients treated with 1<sup>st</sup>-line camrelizumab-apatinib combination, ORR was 34% (95%CI: 23.3%-46.6%) and mPFS was 5.7 mo. For 2<sup>nd</sup>-line therapy patients, ORR was 23% (95%CI: 15.4%-31.0%) and mPFS was 5.5 mo. Interestingly, grade  $\geq 3$  AEs were experienced by 77% of patients, while serious AEs were witnessed in 28.9%[47].

Another trial, COSMIC-132, is a randomized phase III trial comparing atezolizumab-cabozantinib combination *vs* cabozantinib *vs* sorafenib as a 1<sup>st</sup>-line therapy for patients with aHCC. mPFS for the combination therapy group was significantly improved over sorafenib monotherapy (6.8 *vs* 4.2 mo, HR: 0.63, 95%CI: 0.44-0.91). As expected, reported grade  $\geq 3$  AEs were much higher in the combination group (54%) as opposed to the sorafenib monotherapy group (32%)[48].

Results of ICI and TKI combination therapies have been promising; however, combination regimens have also been associated with much higher rates of AEs – especially grade  $\geq 3$  AEs – compared to ICI monotherapy or double ICI combinations. Several ongoing clinical trials are investigating combinations of ICIs, such as nivolumab, with TKIs; such studies will provide more information on the efficacy and tolerability of ICI-TKI combinations (Table 1). In the 2<sup>nd</sup>-line treatment setting of aHCC, clinicians may reserve TKI-ICI combinations for patients who are fitter, and offer double ICI combinations and ICI monotherapy options for patients who are less fit and least fit, respectively.

**ICI+VEGF:** Anti-VEGF agents are another popular category of therapeutic factors used in combination with ICIs. Existing evidence points towards a synergistic effect of anti-VEGF factors and ICIs through reversal of VEGF-mediated immunosuppression, and promotion of T-cell tumor infiltration[49,50]. IMbrave150, a phase III clinical trial of atezolizumab-bevacizumab combination *vs* sorafenib in treatment-naïve patients with aHCC, was the first study to demonstrate a benefit with such a combination. Six- and 12-mo OS was significantly better for the combination arm (85% and 67% respectively) compared to sorafenib (72% and 55% respectively), while mOS was not reached in the combination arm after 17 mo compared to a mOS of 13.2 mo for sorafenib. mPFS was also longer with atezolizumab-bevacizumab combination (6.8 *vs* 4.3 mo for sorafenib, HR: 0.59, 95%CI: 0.47-076), while ORR was also better in the combination arm (27%, 95%CI: 22.5-32.5 *vs* 12%, 95%CI: 7.4-18.0 for sorafenib). The toxicity profile of the combination therapy was manageable. As expected, rates of serious AEs were slightly higher[19]. Following results from this trial, atezolizumab-bevacizumab combination received FDA approval for aHCC becoming the new standard of care in the 1<sup>st</sup>-line setting for patients without contraindication to ICIs or anti-angiogenics; TKIs sorafenib or lenvatinib may be reserved as 1<sup>st</sup>-line treatment for patients who: (1) are less fit, and thus unlikely to tolerate atezolizumab-bevacizumab combination; and (2) those with contraindications to ICIs or anti-angiogenics[51].

NCT04393220 is another phase II clinical trial comparing nivolumab-bevacizumab combination as 1<sup>st</sup>-line therapy in aHCC. This trial was recently completed with results pending. Several other trials at various stages of completion are currently investigating combinations of ICIs with anti-VEGF agents

**Table 1** Ongoing clinical trials investigating immune checkpoint inhibitor - oral tyrosine kinase inhibitor combinations

NCT	Phase	Study drugs	Treatment line	Endpoint	Estimated End of Trial
NCT04194775	3	CS1003 +LENVATINIB <i>vs</i> LENVATINIB	1	OS, PFS	June 2023
NCT04344158	3	PENPULIMAB + ANLOTINIB <i>vs</i> SORAFENIB	1	OS	December 2024
NCT03713593	3	PEMBROLIZUMAB + LENVATINIB <i>vs</i> LENVATINIB	1	OS, PFS	May 2022
NCT04411706	2	SINTILIMAB + APATINIB + CAPECITABINE	1	ORR	June 2022
NCT04042805	2	SINTILIMAB + LENVATINIB	1	ORR	August 2024
NCT04444167	2	BISPECIFIC AK104 + LENVATINIB	1	ORR	March 2022
NCT04183088	2	TISLELIZUMAB + REGORAFENIB	1	ORR, PFS, Safety	March 2025
NCT04310709	2	NIVOLUMAB + REGORAFENIB	1	ORR	May 2023
NCT04442581	2	PEMBROLIZUMAB + CABOZANTINIB	1	ORR	September 2024
NCT03439891	2	NIVOLUMAB + SORAFENIB	1	MTD, ORR	May 2022
NCT04170556	2	NIVOLUMAB + REGORAFENIB	2	Safety	December 2022
NCT04401800	1b/2	TISLELIZUMAB + LENVATINIB	1	ORR	December 2022
NCT04443309	1b/2	CAMRELIZUMAB + LENVATINIB	1	ORR	August 2024
NCT03347292	1	PEMBROLIZUMAB + REGORAFENIB	1	DLT, Safety	October 2022

NCT: Number of the clinical trial (Clinicaltrials.gov); OS: Overall survival; PFS: Progression-free survival; ORR: Overall response rate; MTD: Maximum tolerated dose; DLT: Dose-limiting toxicities.

(Table 2).

**Immunotherapy with locoregional ablation:** Another means of enhancing the immune response is through stress-induced tissue damage which stimulates inflammation and immunogenicity. Chemotherapy and radiotherapy cause immunogenic cell death, enhance T-cell activation and priming, induce tumor T-cell trafficking and infiltration, and enhance effector T-cell function whilst depleting tolerogenic T-cells[52-54]. Early and intermediate HCC is routinely treated with percutaneous and intraarterial locoregional therapies, including radiofrequency, thermal, and non-thermal ablation, and TACE[55,56]. These approaches may be ideal candidates in sequential or simultaneous combination therapy with immune-based treatments to enhance efficacy through immune modulation[57]. Aside from local immune effects, locoregional ablation methods produce systemic immune effects in innate and adaptive immune cells stimulating immunological tumor regression in tumor sites distant to the primary site of ablation through the abscopal effect. Upregulation of local and systemic immune checkpoint expression and cytokine production are also observed (*reviewed in*[58]).

Trials have investigated the combination of ablation with immunotherapy. In a proof-of-concept study (NCT03939975), radiofrequency or microwave ablation successfully increased response rates from 10% to 24% in patients undergoing therapy with nivolumab or pembrolizumab who exhibited stable disease or atypical progressive disease; toxicity was tolerated and there was a relative improvement in median survival[59]. Vice versa, immunotherapy may also be used as an adjunct to radiofrequency ablation, with one study demonstrating superior survival from anti-PD-1 (camrelizumab) immunotherapy and radiofrequency ablation compared to radiofrequency ablation monotherapy[60]. Evidence from a phase II trial (NCT01853618) in patients receiving anti-CTLA-4 immunotherapy with tremelimumab supports the added benefit from combination with radiofrequency ablation or TACE [61]. Partial response rate was 26% (95%CI: 9.1%-51.2%) and mOS was 12.3 mo (95%CI: 9.3-15.4 mo). Tumor biopsies taken at 6 wk exhibited a clear increase in CD8+ T cells in the patients who observed a clinical benefit, and 86% of patients with active HCV infection experienced a marked reduction in viral load demonstrating positive clinical activity. Additionally, phase I and II studies (NCT02837029, NCT03380130) demonstrated the safety and tolerability of nivolumab in combination or sequential therapy with selective internal radiation therapy containing yttrium-90 resin in patients who were ineligible for TACE, offering good disease control without increasing the adverse event rate in patients with advanced Child-Pugh scores[62]. Promising results from these trials have encouraged further clinical trials to evaluate ICI combinations with ablation methods (Table 3).

### ICIs in the adjuvant/neoadjuvant setting

The use of ICIs may not be exclusive only for advanced stage disease as per BLBC criteria; they have also been investigated in adjuvant and neoadjuvant setting. In the neoadjuvant setting, preliminary

**Table 2 Ongoing clinical trials investigating combinations of immune checkpoint inhibitors and anti-vascular endothelial growth factors**

NCT	Phase	Study drugs	Treatment line	Endpoint	Estimated End of Trial
NCT03794440	2/3	SINTILIMAB + BEVACIZUMABBIO SIMILAR	1	OS, ORR	December 2022
NCT03970616	1b/2	DURVALUMAB + TIVOZANIB	1	Safety	August 2022
NCT03973112	2	HLX-10+BEVACIZUMAB BIOSIMILAR	1	ORR	June 2022

NCT: Number of the clinical trial (Clinicaltrials.gov); OS: Overall survival; ORR: Overall response rate.

results from a phase II study of camrelizumab-apatinib combination for systemic treatment-naïve, resectable HCC, showed a major pathologic response rate of 29% and a pathologic complete response rate of 6%, while demonstrating a manageable toxicity profile with 30% of patients experiencing grade 3 treatment-related AEs. No grade 4-5 AEs were observed[63]. Plenty of ongoing trials are investigating the use of ICIs with or without other agents in the perioperative setting for HCC (Table 4).

### Safety of ICIs and HCC

In recent years, ICIs have demonstrated efficacy across a broad spectrum of tumors including HCC, prompting significant interest into their therapeutic value. Due to their involvement in the immune response, ICIs have been linked to immune-related AEs (IRAEs) of varying significance, from mild to life-threatening conditions such as myocarditis, colitis, pneumonitis and hepatitis[64]. Although the precise mechanisms by which ICIs exert these AEs is not known, evidence suggests that ICI administration leads to changes in T-cell population with emergence of autoreactive T-cells, along with increased B-cell clonality and germinal center activation, and display of autoantibodies against thyroid antigens[65,66] and pancreatic islet cells[67,68]. Expression or upregulation of target molecules such as CTLA-4 or PD-1/PD-L1 in normal tissues has also been associated with risk of IRAEs targeting the respective cells[69,70]. The composition of gut microbiota is implicated in the risk for IRAEs development[71]; the former is known to be associated with response to ICIs[72] and active modification through probiotic supplementation has been shown to enhance ICI activity and responses[73]. Systemic administration of antibiotics is known to affect gut microbiota composition[74] and has been associated with worse responses to ICIs[75,76]. The risk for IRAEs also includes reactivation of pre-existing autoimmune conditions, and other complications in patient populations where IRAEs have not been extensively studied, such as transplant patients and those with chronic viral infections[77].

In patients with HCC, the most common IRAEs observed with single-agent therapy include rash (up to 23% of patients), pruritus (up to 19% of patients), and diarrhea (up to 17%). For anti-CTLA-4 and anti-PD-L1 combination treatment, incidence rates are up to 29%, 45%, and 24%, respectively. These results align with the evidence of higher risk of IRAEs with double ICI therapy[78]. Higher rates of AEs observed with combination therapy regimens are a limiting factor that should be considered in clinicians' therapeutic decision-making. Patient eligibility for combination regimens must be considered on a case-by-case basis. Hepatic-related IRAEs such as AST/ALT elevation, defined as an increase of either AST or ALT 1-2.5 times the Upper Normal Limit (UNL)[79] are more common in patients with HCC compared to other tumors. Transaminitis of any grade has been observed in up to 14% of patients with HCC compared to 3% among patients with other tumor types[78], while there are reports that estimate incidence as high as 30%[80]. The association of IRAEs and viral infections is particularly important in HCC as 50%-60% of patients with HCC in the United States are infected with HCV, while 10%-15% are infected with HBV[81]. Recent evidence suggests that ICI therapy for advanced cancer in HBV/HCV positive patients is associated with an increased risk for reactivation of hepatitis. Interestingly, the risk for hepatitis was not significantly different for patients with HCC compared to other malignancies[82]. Although IRAEs can complicate treatment with ICIs, evidence suggests that IRAE incidence positively correlates with better response to ICIs. In a study of patients with HCC treated with ICIs, patients with history of IRAEs had longer PFS, OS and higher Disease Control Rate compared to those who did not experience IRAEs[83].

Treatment of immune-related hepatitis/transaminitis is dependent upon AST/ALT levels. Temporary hold of treatment is indicated for enzyme level elevations between 2 to 5 times the UNL, while permanent discontinuation of the associated checkpoint inhibitor is indicated for elevations greater than 5 times the UNL[84-86]. For patients with an elevation 5- to 10-times the UNL, a course of 1-2 mg/kg/d prednisone is indicated with possible escalation to IV methylprednisolone if no improvement is seen in 3-5 d. Further treatment escalation to mycophenolate mofetil (1000 mg twice daily) should be considered in patients that do not improve after maximum steroid treatment[87].

**Table 3 Ongoing clinical trials investigating combinations of locoregional therapy and immune checkpoint inhibitors**

NCT	Phase	Locoregional Therapy	Systemic Therapy	Endpoint	Estimated End of Trial
NCT03817736	2	TACE + SBRT	ICI	Sequential	February 2024
NCT03638141	2	DEB-TACE	DURVALUMAB + TREMELIMUMAB	Sequential	November 2023
NCT03143270	1	TACE	NIVOLUMAB	Combination	April 2022
NCT03572582	2	TACE	NIVOLUMAB	Combination	June 2023
NCT03397654	1/2	TACE	PEMBROLIZUMAB	Sequential	December 2021 ( <i>results awaited</i> )
NCT03383458	3	Curative resection or ablation	NIVOLUMAB	Adjuvant	June 2025
NCT02821754	2	TACE, RFA, Cryo	DURVALUMAB, TREMELIMUMAB	Combination	December 2022
NCT03033446	2	Y90-Radioembolization	NIVOLUMAB	Combination	December 2021 ( <i>results awaited</i> )
NCT03099564	1	Y90-Radioembolization	PEMBROLIZUMAB	Combination	July 2022
NCT03259867	2	TATE	NIVOLUMAB OR PEMBROLIZUMAB	Combination	December 2022
NCT03937830	2	TACE	DURVALUMAB + TREMELIMUMAB + BEVACIZUMAB	Combination	December 2023
NCT03778957	3	TACE	DURVALUMAB or DURVALUMAB + BEVACIZUMAB	Combination	August 2024
NCT04340193	3	TACE	NIVOLUMAB + IPILIMUMAB or NIVOLUMAB MONOTHERAPY or DOUBLE PLACEBO	Combination	January 2024
NCT04246177	3	TACE	PEMBROLIZUMAB + LENVATINIB	Combination	December 2029
NCT04268888	2/3	TACE/TAE	NIVOLUMAB	Combination	June 2026
NCT05162898	N/A	RFA	TORIPALIMAB + LENVATINIB	Combination	December 2025
NCT05057845	2	Cryo	TISLELIZUMAB + LENVATINIB	Combination	September 2024
NCT04988945	2	TACE + SBRT	DURVALUMAB + TREMELIMUMAB	Sequential (for downstaging)	December 2026
NCT04727307	2	RFA	ATEZOLIZUMAB (neoadjuvant) + ATEZOLIZUMAB-BEVACIZUMAB (adjuvant)	Combination	July 2027
NCT04663035	2	Ablation	TISLELIZUMAB	Combination	December 2025
NCT04652440	1/2	RFA	TISLELIZUMAB	Combination	November 2023
NCT04639180	3	Curative resection or ablation	CAMRELIZUMAB + APATINIB	Adjuvant	July 2024
NCT04220944	1	MWA+TACE	SINTILIMAB	Combination	September 2022
NCT04102098	3	Surgical resection or ablation	ATEZOLIZUMAB+ BEVACIZUMAB	Adjuvant	July 2027
NCT03867084	3	Surgical resection or local ablation	PEMBROLIZUMAB	Adjuvant	June 2025
NCT03864211	1/2	Thermal ablation (MWA or RFA)	TORIPALIMAB	Combination	June 2023
NCT03753659	2	MWA or RFA or Brachytherapy or TACE	PEMBROLIZUMAB	Combination	June 2024
NCT03630640	2	Electroporation	NIVOLUMAB (neoadjuvant & adjuvant)	Combination	November 2023

NCT: Number of the clinical trial (Clinicaltrials.gov); TACE: Transarterial chemoembolization; SBRT: Stereotactic body radiotherapy; DEB: Drug eluting bead; RFA: Radiofrequency ablation; Cryo: Cryoablation; TATE: Transarterial tirapazamine embolization; TAE: Transarterial embolization; MWA: Microwave ablation.

## REAL-WORLD DATA FOR IMMUNOTHERAPY IN HCC

Despite the advances in ICI therapies for HCC in recent years, phase II/III studies are generally limited by strict inclusion and exclusion criteria, thus lacking ecological validity and generalizability to real-life clinical practice outside of clinical trial setting[88]. Real-world data describe health-related information gathered outside of clinical trials. Gathering and reporting real-world data through cohort and observational studies is important for clinicians who aim to apply approved clinical trial regimens to a broader patient group.

### **Immunotherapy ineligibility**

In clinical trials of systemic therapies in HCC, patients who have aHCC or intermediate disease and are not suitable for locoregional therapies are enrolled; however, in real-world clinical practice, a large proportion of such patients are ineligible to receive immunotherapy due to contraindications.

In unselected HCC patients in the general population, no more than a third are amenable to ICIs as a 1<sup>st</sup>-line approach and this figure decreases considerably in combination therapy with anti-VEGF or TKI agents according to an analysis of the Italian Liver Cancer (ITA.LI.CA) database involving 2483 patients across liver dysfunction stages[55,89]. When considering only aHCC and intermediate HCC that was unresponsive to locoregional ablation ( $n = 1514$ ), eligibility increased from 21% with nivolumab and 11% with pembrolizumab to 35% and 18%, respectively. Overall, the main contraindications to frontline ICI were Child-Pugh class > A (24%,  $n = 601$ ), uncontrolled ascites (15%,  $n = 380$ ), performance status > 1 (13%,  $n = 343$ ), active alcohol intake (13%,  $n = 323$ ), thrombocytopenia (12%,  $n = 299$ ), hepatic encephalopathy (6%,  $n = 155$ ), aminotransferase levels > 5 times the UNL (5%,  $n = 123$ ), and concurrent autoimmune diseases (2%,  $n = 57$ )[89]. In the 2<sup>nd</sup>-line, ICI eligibility was substantially lower with 5% and 8% of patients amenable to nivolumab and pembrolizumab, respectively[89]. When repeating this analysis to take into account anti-VEGF and TKI combination therapy with ICIs, atezolizumab-bevacizumab eligibility drops to 18% in the whole HCC population and 29% in aHCC or intermediate HCC patients who are not eligible for surgery or locoregional procedures[55]. Reasons for the exclusion of these additional patients were clinically significant heart disease ( $n = 52$ ), chronic non-healing skin ulcerations ( $n = 15$ ), uncontrolled hypertension ( $n = 10$ ), and non-liver-related coagulative abnormalities increasing the risk of bleeding ( $n = 1$ ).

The expert opinion panel of ASCO has acknowledged the role of ICIs in the treatment of patients with aHCC and especially patients with contraindications, or intolerance to, TKIs who may derive immense benefit from immune therapies[51]. However, they also highlight that patients and clinicians should be aware of life-threatening toxicities that may occur with ICIs. Future research may provide additional information on specific patient subpopulations within this subgroup that may have a favorable risk to benefit ratio.

### **Immunotherapy in patients with liver dysfunction (Child-Pugh class B and above, hepatitis, NASH)**

Due to the lack of Child-Pugh class B and above patients in HCC trials, which often specify Child-Pugh class A in the inclusion criteria, there is a large unmet need for data to support treatment efficacy and toxicity profiles in this cohort[51]. As a result, published recommendations and guidelines for systemic therapy in HCC are often limited to patients with Child-Pugh class A[51]. Experts recommend cautious consideration of systemic therapies for Child-Pugh class B HCC patients with good performance status, taking into account their liver function, bleeding risk, presence of portal hypertension, extent of extrahepatic spread, tumor burden, and major vascular invasion[51]. A handful of studies have compared explorative primary outcomes in Child-Pugh class B patients treated with immunotherapy with different outcomes. Use of the Barcelona Clinic Liver Cancer (BCLC) staging criteria helps avoid the unselect exclusion of all Child-Pugh class B and above patients by allowing for holistic patient scoring and selection based on other performance status criteria.

One retrospective case series of 18 Child-Pugh class B HCC patients treated with nivolumab monotherapy reported a higher rate of AEs compared to those observed in Child-Pugh A patients in CheckMate 040; however, the majority of serious AEs and other AEs were associated with complications of comorbid liver dysfunction and advanced tumor burden, including 11% *vs* 4% of serious treatment-related AEs, and 28% *vs* 19% treatment-related AEs grade  $\geq 3$ . The ORR was comparable in both studies (17% *vs* 20%)[90]. Notably, the mOS in this case series was 5.9 mo, which is lower compared to the 7.6-mo mOS reported in the analogous CheckMate 040 cohort, though higher compared to the limited mOS data reported for analogous patients treated with sorafenib (3-5 mo). Comparable safety and efficacy of nivolumab and pembrolizumab across Child-Pugh class and line of therapy has been confirmed in other real-world data studies with no significant difference observed in ORR and toxicity in terms of AEs; however, mOS and OS tends to be shorter in Child-Pugh B and above patients[91-93].

In a study of 34 HCC patients (5/29 BLBC B/C; 19/14/1 Child-Pugh A/B/C) including sorafenib pre-treated individuals, nivolumab was safe and efficacious with reported 6% ( $n = 2$ ) grade 3 toxicity, 12% ( $n = 4$ ) partial response, and 24% ( $n = 8$ ) stable disease[94]. However, mOS was only 7.5 wk as 59% ( $n = 20$ ) of patients had died on assessment due to tumor progression (80%,  $n = 16$ ), acute liver failure (15%,  $n = 3$ ), and variceal bleeding (5%,  $n = 1$ )[94]. On analysis, 24% of patients ( $n = 8$ ) were still on

**Table 4 Ongoing clinical trials investigating immune checkpoint inhibitor - based clinical trials in the adjuvant and neoadjuvant setting**

NCT	Phase	Study drugs	Treatment setting	Endpoint	Estimated End of Trial
NCT03383458	3	NIVOLUMAB <i>vs</i> PLACEBO	Adjuvant	RFS	June 2025
NCT03867084	3	PEMBROLIZUMAB <i>vs</i> PLACEBO	Adjuvant	RFS, OS	June 2025
NCT03847428	3	DURVALUMAB + BEVACIZUMAB <i>vs</i> PLACEBO	Adjuvant	RFS	September 2023
NCT04102098	3	ATEZOLIZUMAB + BEVACIZUMAB <i>vs</i> PLACEBO	Adjuvant	RFS	July 2027
NCT03859128	2/3	TORIPALIMAB <i>vs</i> PLACEBO	Adjuvant	RFS	April 2024
NCT03839550	2	CAMRELIZUMAB + APATINIB	Adjuvant	RFS	February 2023
NCT04418401	2	ANTI-PD1 + DONAFINIB	Adjuvant	RFS	June 2023
NCT03510871	2	NIVOLUMAB + IPILIMUMAB	Neoadjuvant	ORR, downstaging rate	December 2022
NCT04123379	2	NIVOLUMAB + CCR2/5-inhibitor <i>vs</i> NIVOLUMAB + ANTI-IL8	Neoadjuvant	Safety	October 2024
NCT03222076	2	NIVOLUMAB	Neoadjuvant	Safety	September 2022
NCT03682276	1/2	NIVOLUMAB + IPILIMUMAB	Neoadjuvant	Safety, Delay to surgery	September 2022
NCT03383458	1	NIVOLUMAB <i>vs</i> PLACEBO	Adjuvant	RFS	June 2025
NCT04425226	N/A	PEMBROLIZUMAB + LENVATINIB	Neoadjuvant	RFS, ORR	December 2025

NCT: Number of the clinical trial (Clinicaltrials.gov); RFS: Recurrence-free survival; OS: Overall survival; RFS: Recurrence-free survival; ORR: Overall response rate.

nivolumab treatment and 18% ( $n = 6$ ) had stopped treatment for other reasons [patients wish ( $n = 5$ ), toxicity ( $n = 1$ )]. On multivariate analysis, Child-Pugh stage was the only significant independent risk factor for survival (HR 7.72, 95%CI: 2.62-22.78,  $P < 0.001$ ). Although safe and efficacious, the study concluded that patients with advanced liver disease require further prospective evaluation due to probable limited efficacy of nivolumab. Overall, efficacy was approximately half of that observed in Checkmate 040. Results from this study are in agreement with latest evidence indicating that the survival of patients with aHCC treated with nivolumab is correlated to the Child-Pugh liver function score at baseline[95], as reported in aforementioned studies as well[92-94]. Equally, the finding that unselected Child-Pugh B and above patients exhibit an unsatisfactory response to and survival with nivolumab has been echoed in another retrospective study of 203 HCC patients; (ORR 3% *vs* 16% in Child-Pugh class B/A,  $P = 0.01$ ; mOS 11.3 *vs* 42.9 wk in Child-Pugh class B/A, adjusted HR, 2.10,  $P < 0.001$ )[96].

Aside from Child-Pugh class, other liver dysfunction causes have also been examined in real-world studies. Safety and antitumor activity had been demonstrated in hepatitis-induced cirrhosis and in patients with active hepatitis viral load, even those on anti-viral treatment, while viral hepatitis status has been suggested as a possible predictive biomarker for response since it is clearly not a contradiction against the use of ICIs, yet further prospective studies are mandated[93,97,98]. Conversely, the same cannot be said for patients with underlying NASH and those with HCCs with activated Wnt/ $\beta$ -catenin signaling which observe reduced efficacy from ICI therapy according to pre-clinical and clinical data (reviewed in[99]).

Given that the level of liver dysfunction in this cohort may have significant implications on guidelines regarding the optimal selection of drugs in each line of therapy, further data is needed to guide the evidence-based use of systemic immune therapies in Child-Pugh class B HCC, as supported by the above limited data.

### Macrovascular invasion

Another indicator of poor performance status is macrovascular invasion (MVI). Approximately 10%-40% of HCC patients present with MVI at diagnosis[100], and as such are not amenable to curative treatment and exhibit very poor prognosis[101]. Despite MVI being common, patients are often excluded from clinical trials. Thus, real-world data are needed to demonstrate the relative efficacy of ICIs in this cohort.

Tsai *et al*[102] retrospectively compared the efficacy of PD-1 inhibitors in 34 HCC patients with vascular metastases in the portal vein and inferior vena cava *vs* 34 patients without tumor thrombi; ORR and survival were comparable between both cohorts. The response rate of vascular tumor thrombosis

was 52.9%, and responders exhibited a superior survival benefit than non-responders. MVI responsiveness closely correlated with the maintenance of optimal liver function and a lower occurrence of distal metastases. These findings are in agreement with those from an earlier study showing that the magnitude of treatment response is significantly more intense in vascular invasion compared to hepatic tumors, and vascular response is also an independent prognostic factor that is significantly associated with PFS, while ECOG (Eastern Cooperative Oncology Group) performance status was a significant independent predictor of OS[103]. Moreover, similar findings have been observed in renal cell carcinoma displaying inferior vena cava thrombus treated with ICIs that proposed the response of vascular thrombi to ICIs is stronger in a high T-cell inflamed tumor microenvironment[104]. ICIs markedly decrease or stabilize tumor thrombus volume, and this response may be affected by the diversity of tumor microenvironments[102,103,105,106]. Vascular metastasis regression helps preserve organ function while the use of ICIs in these patients also delays distant metastases[102]. Therefore, ICIs should be prioritized in patients with MVI in an attempt to prevent further progression as well as mediate vascular tumor response, to hopefully improve outcomes.

### **Autoimmune disease**

The incidence of autoimmune diseases in cancer patients has been reported at 13%-30% with hypothyroidism, rheumatoid arthritis, type 1 diabetes and psoriasis representing the most common conditions[107,108]. Hepatobiliary autoimmune diseases, such as autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are known risk factors for HCC[109, 110]. The risk of HCC is lower with PSC compared to AIH[110], especially when the latter co-exists with cirrhosis[111]. Yet, patients with underlying autoimmune disease are typically excluded from immunotherapy trials because of the risk of immune-mediated flares of their underlying autoimmune disease [99].

In an observational, retrospective study including 15 patients with pre-existing autoimmune diseases, including 4 HCC patients treated with nivolumab, only 4 (27%) patients experienced an autoimmune disease exacerbation with ICIs, including 1 of the HCC patients[112]. Moreover, the most frequent cause of treatment discontinuation was disease progression rather than toxicity. Studies in other cancers (mostly melanoma and non-small cell lung cancer) report a wide range of incidence of flare-ups and IRAEs in patients with underlying autoimmune disease that receive ICI treatment[113-117]. One systematic review of 123 cancer patients from 49 publications reported incidences of 41% exacerbation of previous autoimmune disease, 25% de novo IRAEs, and 11% of both; no difference was observed between those with active *vs* inactive disease[118]. Patients receiving immunosuppressive therapy at initiation of ICI therapy appeared to experience fewer AEs than those not receiving treatment. AEs improved in over half of patients without ICI discontinuation while 3 patients died. The incidence of IRAEs is higher in patients with autoimmune disease treated with ICIs compared to incidences quoted in studies and trials of patients without autoimmune conditions. In terms of efficacy, studies show no difference in ORR, PFS, and OS in patients with underlying autoimmunity compared to those without [113,116]. However, the evidence is conflicting regarding the response rate depending on concomitant immunosuppressive therapy at the time of ICI initiation with some studies quoting lower response rates [114] and others quoting no association[117]. Recently, the use of selective immunosuppressive drugs over non-selective immunosuppressants in patients with underlying autoimmune disease for ICI therapy has been recommended, as the former may be less likely to adversely affect ICI efficacy[119].

Overall, although limited, these data support the administration of immunotherapy in cancer patients with a pre-existing (controlled) autoimmune disease with adequate follow-up and early management if flare ups or IRAEs occur; immune exacerbations can usually be managed with steroids or other immunosuppressants without treatment discontinuation. Therefore, every cancer patient with underlying autoimmune disease should be considered for ICI therapy with a decision on management achieved through multidisciplinary team discussion that weighs up the risks and benefits[120]. Recommendations state that ICIs should be avoided: (1) whenever autoimmune disease reactivation may be life threatening, (2) in patients with neurological or neuromuscular disorders, and (3) in patients with poorly controlled autoimmune disease or on high doses of immunosuppression[120]; TKIs should be considered 1<sup>st</sup>-line in these cases[101].

In the case of HCC particularly, there is a lack of data. Further large prospective studies are needed to establish the incidence of IRAEs and autoimmune disease exacerbations in patients with pre-existing autoimmune conditions treated with immunotherapy to evaluate the overall risk-to-benefit ratio and generate practical evidence-based management guidelines for this subpopulation.

### **Therapeutic decisions: Radiological progression**

The concurrent availability of several systemic therapy regimens in the 1<sup>st</sup>- and 2<sup>nd</sup>-line settings offers clinicians and patients a wider selection of drugs to choose from. Decisions regarding the selection of a specific agent over another is not only determined by the availability and accessibility to a specific drug, but also, more importantly, by the efficacy and tolerability that is expected or indeed observed in a patient. Thus, the decision of which agent to choose, or switch to, is largely dependent on individual patient characteristics. As previously mentioned, there are inherent difficulties regarding the lack of wide representation of patients of poor performance status in immunotherapy clinical trials that affect a

clinician's ability to triage toxicity risk in these patients. Additionally, assessing tumor progression and response to immunotherapy, which also governs treatment selection and switching, is challenging for several reasons both inside and outside of clinical trials.

Immunotherapies are known to produce an atypical response pattern featuring pseudo-progression (PP) and hyper-progressive disease (HPD). Therefore, multiple variations of Response Evaluation Criteria in Solid Tumors (RECIST) have been proposed, with RECIST 1.1 recommended for primary endpoints and immune RECIST (iRECIST) for exploratory analyses. Importantly, patients in clinical trials undergo thorough radiological assessment from specialized radiologists to a more robust standard than what is available outside of trial setting. Decisions about switching or continuing past progression (assumed PP) are usually made based on the trial radiologist report in conjunction with the opinion of experienced oncologists involved in the trial; usually, treatment is stopped in trials when patients progress on immunotherapy whereas in real life a decision may be made to continue treatment if the patient reports benefits and if the drug is well-tolerated. A retrospective multicenter analysis of 31 HCC patients treated with nivolumab in real-life practice assessed radiological response to treatment using both RECIST 1.1 and iRECIST and found that response rates were similar to those reported in prospective clinical trials[122]. However, authors highlight the heterogeneity in response and progression patterns, and emphasize the risk of misinterpretation of results in terms of endpoints as well as the difficulty of deciding when to stop treatment past progression. Additional real-life studies such as the above are warranted to support these findings.

In terms of HPD – which remains a controversial concept that is doubted by some clinicians due to lack of robust data to differentiate it from natural cancer progression in non-responders – the above study reported an occurrence of this phenomenon in four cases (13%). All of these patients presented at baseline with massive tumor burden involving different anatomical regions (burden 76-159 mm; 6-15 measurable lesions per patient) before nivolumab initiation[121]. These findings are consistent with those reported in a separate case series of 47 patients in which 3 exhibited HPD (including 1 aHCC patient) when treated with nivolumab; the main characteristics in the hyper-progressors were age < 75 years,  $\geq 2$  metastatic sites, PD-L1 < 50%, neutrophil-to-lymphocyte ratio > 3, and elevated lactate dehydrogenase[122]. This and other studies support the notion that high metastatic burden at baseline may be a clinical predictor of HPD during ICI therapy. Other predictors of HPD have been proposed with contradictory data (*reviewed in*[122]).

### Cost-effectiveness

In 1<sup>st</sup>-line setting, the combination of atezolizumab-bevacizumab *vs* sorafenib for aHCC has been shown to lack cost-effectiveness from a US payer perspective despite offering a significant clinical survival benefit, according to data from the IMBRAVE150 clinical trial; an incremental cost-effectiveness ratio of \$322500 per quality-adjusted life-year (QALY) gained was observed[123]. In a threshold analysis, prices for atezolizumab and bevacizumab would have to be reduced by 37% and 47%, respectively, to be considered a cost-effective alternative at common willingness-to-pay thresholds of \$150000 or \$100000 compared to sorafenib[123]. However, it should be noted that patients in the IMBRAVE150 disproportionately represented patients with well-preserved liver function (Child-Pugh class A) and good performance status (ECOG score 0-1), meaning that it is unclear how generalizable the benefits and/or risks, and therefore the cost-effectiveness, of these drugs are in clinical practice, where patients present with more severe disease[124]. IMBRAVE150 also disproportionately included fewer patients of Black and Hispanic ethnicity. Higher age specified mortality and incidence of aHCC are observed in Asian, Black, and Hispanics compared to non-Hispanic White individuals, while Black and Hispanic patients also tend to present with more advanced tumor burden and have worse survival compared with non-Hispanic White patients[125]. Lack of such ethnic representation in IMBRAVE150 means that the above cost-effectiveness analysis model does not accurately represent disease demographics across ethnicity and is thus likely to lack in generalizability[124]. Moreover, racial and ethnic disparities are known to occur in immunotherapy receipt; atezolizumab-bevacizumab regimens are likely to widen existing disparities in HCC mortality, especially given lack of ethnic representation in the aforementioned cost-effectiveness analysis model[124]. Aforementioned results are echoed in a separate study which indicated that 1<sup>st</sup>-line TKI followed by 2<sup>nd</sup>-line immunotherapy was the most cost-effective strategy for aHCC[125].

Lack of ICI cost-effectiveness for aHCC also stands true in the 2<sup>nd</sup>-line setting in the US, where results from a separate cost-effectiveness analysis of pembrolizumab for aHCC based on data from the KEYNOTE-240 trial reported an incremental cost-effectiveness ratio of \$340409 per QALY gained[126]. The price of pembrolizumab would need to be reduced by 58% to achieve cost-effectiveness, with a willingness-to-pay threshold of \$150000 per QALY. These results are likely to be very similar for nivolumab monotherapy as an alternative anti-PD-1 agent for aHCC in 2<sup>nd</sup>-line setting; however, further cost-effectiveness analyses are warranted especially for the combination of nivolumab-ipilimumab in the 2<sup>nd</sup>-line setting for aHCC[126]. It should be noted that other 2<sup>nd</sup>-line non-immunotherapy alternatives for aHCC including regorafenib, cabozantinib, and ramucirumab have also been shown to have an incremental cost-effectiveness ratio with \$224362 and over \$1 million per QALY for regorafenib and cabozantinib, respectively, while no cost-effectiveness data has been published for ramucirumab which is also unlikely to be cost-effective[126]. The lack of robust head-to-head trials comparing different 2<sup>nd</sup>-

line therapies means that it is difficult to undertake a robust cost-effectiveness comparison of agents in this setting[126].

From a patients' perspective, sadly, differences in drug costs are often an important factor that impact patient decision as some cancer therapies pose a more significant financial burden than others. Additionally, potential burdens—financial or otherwise—associated with regular travel to a treatment center for IV infusion therapy may render a patient more likely to opt for a treatment regimen composed of oral medications which they can take at home. In the case of the latter, the importance of medication compliance, even in the presence of adverse events, as well as patient safety-netting must be stressed. Occasionally, providers themselves may have financial biases for supporting some regimens over others when there is no significant difference in treatment effectiveness.

### **Immunotherapy in LT**

One of the questions yet to be answered is the role of immunotherapy in LT. Immunotherapy post-LT may prevent or be useful in the management of recurrent HCC as well as other post-transplant secondary malignancies. Current guidelines state that immunotherapy approaches should be avoided in patients who recur following LT because of the high rates (40%) of allograft rejection and mortality, owing to stimulation of the host immune response by these agents; however, aside from rejection, anti-tumor efficacy and tolerability are promising[127,128]. A review of 25 patients receiving immunotherapy post-transplant identified immunotherapy initiation after short duration from transplant and graft PD-L1 positivity as potential risk factors for rejection[129]. Despite the limited amount of data, in the current era it is not safe to advise for the use of immunotherapy to prevent or treat disease recurrence after transplant. Elucidating better predictors of patients that are at higher risk of experiencing transplant rejection may help identify a subset of patients who are more likely to observe a favorable benefit-to-risk ratio from immunotherapy after transplant, and may thus be eligible for this approach.

In the pre-LT setting, the role of neoadjuvant immunotherapy is even less clear. Immunotherapy pre-LT may facilitate downstaging of unresectable HCC bridging to subsequent surgical eligibility, thus offering these patients their only chance of disease cure; however, this potentially comes at a higher risk of donor graft rejection[127]. The latest study published on this topic identified seven patients from their center and three from the literature who received anti-PD-1 ICIs pre-LT[130]. Eight patients (80%) observed partial response, and the disease control rate was 100%. Acute rejection occurred in 30% of patients with two patients dying as a result, despite treatment with immunosuppressive medications. Despite this growing body of evidence, further research is warranted. Currently, a phase II multicenter clinical trial is underway to investigate the role of durvalumab and tremelimumab for patients with HCC listed for LT (NCT05027425). Such trials are needed to determine the safety and efficacy of immunotherapy as a potential bridging strategy to LT.

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## **FUTURE DIRECTIONS**

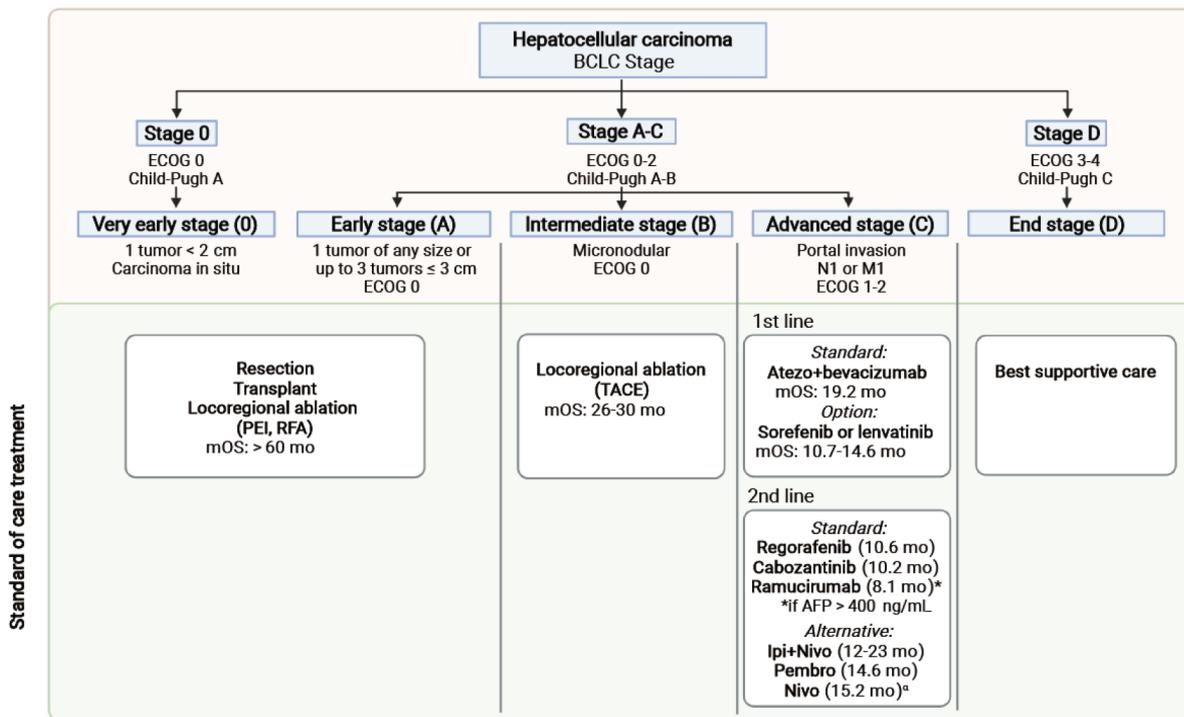
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### **Immunotherapy beyond ICIs: ACT, vaccination, and virotherapy**

Other promising forms of immunotherapy for HCC aside from ICIs include ACT strategies, anti-tumor cancer vaccines, and transgenic therapy applied through viral vectors. These strategies have begun to be investigated clinically as monotherapy options in HCC and as combination therapies, to enhance the efficacy of other treatments. The potential of such immunotherapies as combination treatments is highly promising, particularly in the context of combination with other immunotherapies, such as ICIs, as they improve immunogenicity. Combining immunotherapeutics with different mechanisms of action and primary immune effects is a well-recognized approach to counteract the multiplicity of tumor immune evasion mechanisms and ensure all necessary steps for the successful mounting of an anti-tumor immune response are met, as described in the *cancer immunity cycle* theory[31,131,132]. The same principle stands true as the underlying biological rationale to justify combination therapy of ICIs with different mechanisms of action – an example being combination with anti-PD-1 and anti-CTLA-4 agents which has been shown to significantly improve ORR, at the expense of increased but tolerable toxicity (Figure 2).

**ACT:** Following the success and approval of a plethora of ACT strategies in hematologic cancers[133], researchers have explored various forms of ACT in solid tumors. ACT involves the autologous or allogeneic transplant of tumor-infiltrating lymphocytes (TILs), or genetically modified T-cells engineered to express novel T-cell receptors (TCR) or chimeric antigen receptors (CAR)[134]. Cytokine-induced killer (CIK) cells represent another form of ACT wherein T-cells are co-cultured *in vitro* under cytokine manipulation to express natural killer (NK) cell-surface markers in addition to TCR. Cytotoxic cells with this double T/NK phenotype are capable of lysing a broad array of tumor cell targets in a non-MHC-restricted manner[135].

The primary immune effects of ACT result in supplementation of immune effector cells[31]. Compared to other immunotherapies, one of the advantages of ACT is that it is considered a “living”



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**Figure 2 Treatment algorithm for immunotherapy in hepatocellular carcinoma according to American Society of Clinical Oncology guidelines.** Atezo: Atezolizumab; Ipi: Ipilimumab; Nivo: Nivolumab; Pembro: Pembrolizumab; mOS: Median overall survival; mo: Months; PEI: Percutaneous ethanol injection; RFA: Radiofrequency ablation; TACE: Transarterial chemoembolization; ECOG: Eastern Cooperative Oncology Group; BCLC: Barcelona Clinic Liver Cancer; AFP: Alpha fetoprotein; cm: centimeter; N1: Regional nodal spread; M1: Metastatic spread.

treatment method as it exhibits the capability to become active and replicate *in vivo* for long lasting anti-tumor effect[136]. In theory, this grants the possibility of disease cure due to the accrual of long-term immunological memory; however, in practice this is often not achieved due to multifactorial lack of cell persistence[137]. Currently, most novel ACT strategies, such as CARs, are bespoke to each patient and are manufactured specifically for them. Off-the-shelf ACT strategies are being investigated as a means to improve costs, time and ease of manufacturing, and allow for universal applicability across patients [133]. Due to the presence of TAAs with an acceptable specificity, HCC in one of the most promising organs for ACT in solid tumors, as TAA specificity decreases chances of on-target off-tumor recognition and subsequent toxicity due to target antigen expression on normal cells which are then destroyed[138].

Combinations of ACT with ICIs have not yet been trialed in HCC, while in other solid malignancies such combinations have been shown to be feasible and safe[139]. Conversely, ACT in combination with ablative therapies in HCC is undergoing investigation in phase I/II setting[58]. Regarding ACT monotherapy for HCC, early phase I/II studies have shown feasibility and tolerability with TILs, TCR, and CAR cell variants while several other phase I/II trials are ongoing (reviewed in[35,138,140]). CIK is the only ACT that has been investigated for HCC in a phase III setting (NCT00699816). This multicenter trial involved 230 HCC patients who had undergone curative surgical resection, radiofrequency ablation, or percutaneous ethanol injection that were randomized to receive adjuvant CIK immunotherapy (injection of  $6.4 \times 10^9$  autologous CIK cells, 16 times over 60 wk) or no adjuvant therapy (controls)[141]. mPFS was significantly prolonged in the CIK arm *vs* control (44 mo *vs* 30 mo; HR: 0.63, 95%CI: 0.06-0.75). All-cause death and cancer-related death were also significantly reduced in the experimental arm. AE occurrence was higher in the experimental arm but SAEs did not differ significantly. In combination with transarterial chemoembolization (TACE), an international registry analysis of 106 clinical trials including 10225 patients of which 4889 patients in over 30 distinct tumor entities were treated with CIK cells alone or in combination with conventional or novel therapies, CIK has been shown to significantly improve mPFS and mOS (27 trials), and 5-year survival rate (9 trials) with mild AEs and graft-versus-host diseases[142]. Additionally, a systematic review and meta-analysis of 6 randomized controlled trials including 844 HCC patients concluded that adjuvant autologous CIK after curative resection significantly improved 1-year, 2-year, and 3-year disease-free survival and OS but did not significantly extend these at 4 and 5 years; AEs were comparable in CIK and control patients [143]. Furthermore, combination of CIK with ICIs has been trialed in solid and hematologic cancer with promising results and potential to be trialed in HCC in the future[142]. Despite these positive results, ACT including CIK is still not used in most centers as an adjuvant therapy, probably due to the limitations of in-house cell therapy facilities[35].

**Vaccination and virotherapy:** Following results of several early phase trials involving relatively small numbers of HCC patients in the past decade, vaccines and virotherapy are currently being investigated as enhancer strategies in combination with other forms of therapy as opposed to a viable monotherapy option[31,35].

**Vaccines:** The underlying primary immune effect of vaccines lies in their ability to enhance T-cell priming and expansion[31]. Cancer vaccines are being constructed to enhance presentation of tumor-associated epitopes to host immunity to overcome tumor-specific tolerance in the context of immune stimulation by activating and selectively expanding tumor-specific lymphocytes within the native effector cell repertoire while maintaining immune-regulatory protection against autoimmunity[144]. Vaccine-mediated stimulation of tumor-specific immunity provides a physiologic stimulus for T-cell activation, fostering a potentially more-sustained native immune response with greater durability for long-term antitumor surveillance. Alike engineered ACT, cancer vaccines may be designed to target TAAs or neoantigens, of which HCC exhibits many with high specificity[10]. Classical cancer vaccines rely on exogenous administration of antigens or antigen-pulsed dendritic cells (DCs). The only cancer therapy vaccine to be approved by the FDA to date is Sipuleucel-T, a DC-like anticancer vaccine for prostate cancer[145]. In HCC, vaccine constructs are mainly based on RNA, peptides, proteins, or DCs [31,140].

Early investigations in cancer patients and pre-clinical models have demonstrated the synergistic capacity of cancer vaccines in combination with anti-PD-1 and anti-CTLA-4 checkpoint blockade, with evidence also reported for HCC[146-148]. Vaccines can reverse immune tolerance and exhaustion seen in patients treated with ICIs by providing a stimulus to prime and expand tumor-specific T-cells that preserve their effector functions through the effect of ICIs[31]. Moreover, phase I/II studies have shown that vaccines are tolerable and can reduce recurrence rate[149] and prolong recurrence-free survival[150, 151] in patients treated with ablative therapy. However, trials with tumor lysate vaccines have failed to show promising results in terms of efficacy[31,151]. Today, combination of vaccines with ICIs are being investigated clinically in phase I/II trials in HCC (NCT04912765, NCT04248569, NCT04251117), as are combinations with ablative therapies (NCT03674073, NCT03942328), and other treatments.

**Virotherapy:** Cancer virotherapy represents the most common type of cancer gene therapy and involves the transfer of genetic material (transgenes) into cells to modify their gene-expression profiles *via* viral vectors[31]. Oncolytic viruses (OVs) are a type of cancer virotherapy incorporating modified viral agents that selectively replicate in cancerous cells resulting in tumor cell lysis[152]. By contrast to classical vaccines, OVs represent an *in situ* cancer vaccine[35]. The primary immune effect aimed with virotherapy is to reduce tumor burden and broaden TCR repertoire[31]. Yet, scientists have increasingly realized that most anti-cancer efficacy observed with OVs is attributable to enhanced immune response activation triggered by immunogenic cell death caused by the destruction of cancer cells and uptake of tumor antigens by antigen presenting cells – often enhanced by the arming of OVs with cytokine encoding genes, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) – rather than their oncolytic properties[153]. Additionally, OVs display short-lived efficacy and are not effective on repeated doses, due to brief vector replication and transgene expression as well as neutralizing antibody development after first vector administration, respectively. However, long-term vectors may broaden applications[31]. Hence, OVs are better candidates as an adjunct therapy to trigger adaptive antitumor responses which require maintenance and expansion with additional immunotherapies[154]. To date, three OVs have been approved for cancer therapy: RIGVIR for melanoma[155], Oncorine for head and neck cancer[156], and T-Vec for melanoma[157], though only the latter has been granted FDA approval.

In HCC, several OVs have been investigated clinically with some featuring promising results. JX-594 (Pexa-Vec), an oncolytic poxvirus carrying human GM-CSF genes, is the only OV to have successfully reached phase III investigation. Unfortunately, phase IIb/III trials showed that Pexa-Vec failed to improve treatment efficacy in patients previously treated with sorafenib[158], in combination with sorafenib[159], and in sorafenib-naïve patients[160]. Investigation of Pexa-Vec combination with nivolumab was also terminated early due to futility in other pivotal trials[161]. Still, phase I/II trials are ongoing to investigate different virotherapy agents as monotherapy (NCT00028496, NCT04246671), and in combination with pembrolizumab (NCT02509507, NCT02432963) for HCC.

## CONCLUSION

The progress achieved within the landscape of immunotherapy for HCC is remarkable. In the last five years, ICIs have become a cornerstone systemic treatment approach in the routine clinical management of aHCC. The year 2020 saw ICIs become frontline treatments for aHCC in combination with bavacizumab, rendering sorafenib frontline only for patients who are ineligible for or contraindicated to receive immunotherapy or anti-angiogenics. In 2<sup>nd</sup>-line setting, several ICIs continue to be standard of care, with more agents emerging in the horizon. Still, much progress is yet to be made, especially concerning the lack of real-world data to support the generalizability and applicability of clinical trial

findings to a broader cohort of aHCC patients who are not subjectable to stringent clinical trial inclusion and exclusion criteria. The main obstacles to immunotherapy frequently encountered in real-world practice surround patient ineligibility for immunotherapy because of contraindications, comorbidities, or poor performance status; lack of response, efficacy, and safety data; and cost-effectiveness. Hence, the reality of immunotherapy treatment for HCC outside of trial setting is far from ideal. Further real-world data from high-quality large prospective cohort studies as well as evidence from institutional experiences of immunotherapy in patients with aHCC outside of clinical trials is mandated to aid evidence-based clinical decision-making for this cohort of individuals who indeed represent the vast majority of patients encountered. At the same time, ongoing trials investigating novel approaches to optimize systemic regimens and enhance ICI efficacy through combination with locoregional ablation, other systemic agents, and novel immune-based approaches are necessary to break new grounds. With multiple ICI agents undergoing investigation, more ICIs are likely to enter the treatment landscape for aHCC. The development of new models such the *cancer immune cycle* theory to better understand and reverse limiting steps in cancer immune evasion; the characterization and subgrouping of different tumor immune microenvironment phenotypes in aHCC; and novel means of employing machine learning algorithms to predict patient response to select targeted therapies further advance the field of precision medicine in HCC into a new era. In the years to come, ACT including CAR T cells and CIK cells are likely to become part of the treatment armamentarium against aHCC. We eagerly await to monitor the field as it advances.

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## FOOTNOTES

**Author contributions:** Rallis KS and Makrakis D contributed equally to the writing, reviewing, and designing of the manuscript and are equal joint first authors; Ziogas IA and Tsoulfas G lead the initial conceptualization, designing, reviewing, and supervision of the work in this manuscript; all authors have read and approved the final manuscript.

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