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Breakthrough and Boundaries in Management of Hepatocellular Carcinoma by Immunotherapy

(Advanced Treatments for Hepatocellular Carcinoma)

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Abstract: Recognizing the immune system's anti-tumor activities is an important new method to address the shortcoming of systemic approach to treat hepatocellular carcinoma. To pursue this line of treatment, it is imperative that immune cells should differentiate between normal and cancer cells to specifically attack the cancer cells. Recently, many types of immunotherapies have been developed, and checkpoint inhibitors emerges as central point because of positive outcomes from different types of cancer. Normally, hepatocellular carcinoma has been treated with standard cytotoxic chemotherapy and in advanced stage, antiangiogenic tyrosine kinase inhibitors (TKIs) were used as systemic therapeutic approach. These treatments were not very beneficial in metastatic malignancies. Checkpoint inhibitor therapy provided better hopes as these agents enable immune cells to eradicate cancer cells precisely and effectively. Currently, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 and its ligand (PD-1 and PD-L1) are the most popular choice of checkpoint inhibitors in management of advanced hepatocellular carcinoma. In this mini review, we provide the breakthroughs coming from currently available immune checkpoint inhibitors in HCC and their boundaries in management of these malignancies.

Keywords: *Hepatocellular Carcinoma (HCC), Tyrosine Kinase Inhibitors (TKIs), Immune Checkpoint Inhibitors (ICIs).*

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I. INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most lethal and widespread type of cancer among men and women worldwide (1, 2). It makes up for 80%-90% of all type of primary liver cancers (3, 4). HCC has been accounted for 5th most common cancer among men, and the 9th most common among women, which makes it 2.3 times more frequent among men in comparison to women (5). Almost 90% of the HCC cases are arising from chronic inflammation along with subsequent fibrosis and cirrhosis (5,6). Among other contributing factors towards HCC occurrence are the infection and inflammation caused by hepatitis B viruses (HBV), hepatitis C viruses (HCV), alcohol abuse, and metabolism associated liver disease (6). It has been reported that at diagnostic phase, liver cirrhosis is pretty dominant with its presence among 70-90% of HCC patients (7). Other factors making patients more prone toward developing HCC include heavy alcohol use (8), aflatoxin B1 exposure (9), nonalcoholic steatohepatitis (NASH) (10), and cigarette smoking (11).

Because of its diagnosis at advanced stage, rapid progression, and high metastatic rate, management of HCC treatment is challenging (12, 13). Surgery, liver transplantation, percutaneous ablation, transcatheter arterial chemoembolization, and systemic treatments are possible treatment options. These therapeutic options are possible only for some selected candidates (14, 15). Because of their efficacy and minimum toxicity, TKIs (tyrosine kinase inhibitors) have been approved as systematic treatment for HCC patients (16). TKIs exert their anti-tumorigenic effects by binding to tyrosine kinase receptors (17). This process activates intracellular signaling, resulting in autophosphorylation of cytoplasmic domains(18), which ultimately inactivates downstream signaling pathways (Figure 1) to prevent tumor growth and metastasis (19, 20). The first FDA –approved TKI for treating advanced primary

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HCC was Sorafenib, which was primarily recommended for treatment of renal cell carcinoma (22,23).

Lenvatinib, was approved in 2018 by FDA as first line treatment option for HCC (21). In addition to inhibiting broad range of receptors like sorafenib, Lenvatinib control cell proliferation by inhibiting proto-oncogenes KIT and RET (22). Due to more pharmacologically potent and with broad spectrum targets, FDA approved regorafenib (23), and carbozantinib (24) as second-line drugs for treating HCC patients. Despise delayed HCC progression and prolonged overall survival (OS) with use of TKIs to treat HCC patients from last 16 years, drug resistance(25), side effects (26), and low solubility (27) impose serious challenges to overcome.

Immunotherapy fundamentally changed the landscape of management of cancer patients treatment by reactivating patient's own immune system with combination of some drugs, which ultimately recognize and destroy the cancer cells (1). However, it is simultaneously imperative that the immune system does not attack normal cells. To manifest this goal, body system reorganizes checkpoints to switch one the immune system (31,32). Depending on the need to maintain normal homeostasis, checkpoint proteins in immune cells get switched on/off (28, 29). By activating cancer immune surveillance, immune system recognizes and destroy cancer cells effectively (33). During tumor progression, some tumor cells acquired higher level of surface proteins, which attach to and activate "brakes" on T cells (30). Immune checkpoint proteins are exactly these surface proteins brakes, stopping T cells from attacking cancer cells, allowing tumor progression to proliferate. Immune checkpoint inhibitors (ICIs) counteract these brakes, triggering T cells to target and eliminate cancer cells (31). As such, these immune checkpoint inhibitors are a staple of immunotherapy, holding a lot of promise to the management of variety of cancers (28, 32). These ICIs are monoclonal antibodies, which avoid the inactivation of T cells through blocking the interaction of checkpoints with their ligands (Figure 2). For last 6 years, 2 classes of checkpoint inhibitors: programed cell death protein1 (PD-1) and cytotoxic T lymphocyte associated antigen 4 (CTLA4) have been studied extensively in their use of treating HCC patients (33). In this review, the authors aim to provide the benefits of using immune checkpoint inhibitors (ICIs) for treating HCC patients and the restraints to overcome in future to have better management of these patients.

II. THERAPEUTIC ROLE OF IMMUNE CHECKPOINT INHIBITORS IN TREATMENT OF HEPATOCELLULAR CARCINOMA

Genetic mutations, epigenetic factors, immunosuppressive microenvironment, and prolonged inflammation from variety of toxic substances give rise to hepatocellular damage (37-39). Among main contributors of immunosuppressive microenvironment include Kupffer cells (34), monocyte derived macrophages, regulatory T (T_{reg}) cells, and myeloid-derived suppressor cells (MDSCs) (35). By evading the host's immune surveillance protocols, this microenvironment supports tumor cell growth (36). These liver cell types in cooperation with dysfunctional dendritic cells (DCs) promote tumorigenesis through the prevention of effective immune responses against foreign tumor cells (37, 38). Kupffer cells and other tumor-associated macrophages are associated with hepatocarcinogenesis and immune invasion through various channels (39, 40). B and T cells, tumor-associated macrophages, dendritic cells, natural killer cells, monocytes, and myeloid derived suppressor cells express immune checkpoints and their ligands on their surface (41). These checkpoints prevent overactivation of T-cell, a physiological mechanism, exploited by tumor cells not to get destroyed by anti-tumor immune responses (42). Cytotoxic T lymphocyte associated antigen 4 (CTLA4), programmed cell death protein1 (PD-1), T cell immunoglobulin and mucin domain containing-3 (TIM3), and lymphocyte-activation gene 3 (LAG3) are the most prominent immune checkpoint proteins, which have strong evidence of enhancing T cell expansion (43). Among these, the primary therapeutic agents in immunotherapy targeted at solid tumors are CTLA-4 and PD-1 (44). PD-1 is primarily expressed by activated T cells, natural killer (NK) cells, Treg cells, monocytes and dendritic cells and its ligand PD-L1 is expressed by stromal and tumor cells and myeloid cells (45). The interaction between PD-1 and its ligand PD-L1 stimulates the dephosphorylation of T cell-activating kinases, which ultimately results in T-cell inactivation (46).Thus, when cancer cells that expressPD-1 or PD-L1 (Figure 2) obstruct an immune attack, the drugs that target either PD-1 or PD-L1 can undo this barrier and trigger the proper immune response against cancer cells to eradicate them (47). CTLA-4, which is mainly expressed by activated T cells, binds to B7-1 (CD80) and B7-2 (CD86) competing with CD28 to block the activation of T-cells. Immune checkpoint inhibitors that target CTLA-4 prevent the inactivation of T cells, thereby reactivating the anticancer immune response (48). Immune checkpoint inhibitors generate effective immune responses, resulting in the elimination of tumor cells across the tumor types (49).

Chronic inflammation from different toxic substances induces hepatocellular damage, genetic and epigenetic mutations along with immunosuppressive tumor microenvironment (50-52). Kupffer cells (34), monocyte derived macrophages, regulatory T (T_{reg}) cells, and myeloid-derived suppressor cells (MDSCs) (35) are the main contributors of immunosuppressive microenvironment. This microenvironment supports the growth of tumor cells by evading the host immune surveillance system (53). These liver cell types in cooperation with dysfunctional dendritic cells (DCs) prevent effective innate and adaptive immune response against tumor cells and promote tumorigenesis (37, 38). Kupffer cells and other tumor-associated macrophages are involved in hepatocarcinogenesis and in immune invasion through many mechanisms (39, 40). Immune checkpoints and their ligands are expressed by B and T cells, dendritic cells, tumor-associated macrophages, natural killer cells, monocytes, and myeloid derived suppressor cells on their surface. These checkpoints prevent overactivation of T-cell, a physiological mechanism, exploited by tumor cells not to get destroyed by anti-tumor immune responses (42). Cytotoxic T lymphocyte associated antigen 4 (CTLA4),

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programmed cell death protein1 (PD-1), T cell immunoglobulin and mucin domain containing-3 (TIM3), and lymphocyte-activation gene 3 (LAG3) are main immune checkpoint proteins, which have been reported to enhance T cell expansion (43). Among these, CTLA-4 and PD-1 are considered as main therapeutic targets for immunotherapy of solid tumors (44). PD-1 is primarily expressed by activated T cells, natural killer (NK) cells, Treg cells, monocytes and dendritic cells and its ligand PD-L1 is expressed by stromal and tumor cells and myeloid cells (45). Interaction between PD-1 and its ligand PD-L1 stimulates dephosphorylation of T cell-activating kinases, which ultimately resulting in T-cell inactivation (46).Hence cancer cells expressing PD-1 or PD-L1 (Figure 2) hide from an immune attack and the drugs, which target either PD-1 or PD-L1 can block this interaction and stimulate the immune response against cancer cells to eradicate them (47). CTLA-4 mainly expressed by activated T cells, binds to B7-1 (CD80) and B7-2 (CD86) competing with CD28 to block the activation of T-cells (54). Immune checkpoint inhibitors targeting CTLA-4, prevents the inactivation of T cells leading to reactivation of anticancer immune response. Generation of effective immune response with use of immune checkpoint inhibitors results in elimination of tumor cells across the tumor types (49).

- *The First Immune Checkpoint Inhibitor in HCC: CTLA-4*

Clinical trials of immune checkpoint inhibitors against hepatocellular carcinoma and chronic hepatitis C began with the administration of tremelimumab, a monoclonal antibody that blocks cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) (55). Every 90 days, tremelimumab was administered at a dose of 15 mg/kg intravenously (55). Steroids were not used in this trial due to severe, adverse immune-mediated events. A partial response rate of 17.6% and a 76.4% disease control rate was associated with the treatment (55). With a strong potential safety profile associated with both antitumor and antiviral activities, future investigation with larger clinical trials is imperative for tremelimumab treatment (49, 55).

In another study with 32 patients, tremelimumab was intravenously administered at 3.5 mg/kg and 10 mg/kg, every 4 weeks for 6 doses followed by 3-monthly infusions (56) . Radiofrequency ablation or chemoablation were undergone on day 36 (56). Out of 19 patients, five demonstrated a confirmed partial response (56). The six-month tumor progression free survival rate was 57.1 % and the 12-month tumor progression free survival rate was 33.1%. The median overall survival was 12.3 months (56). This trial provides a potential novel advanced HCC treatment dose (56). However, because the sample patient sizes are limited in these trials, any concrete conclusions about the efficacy and safety of CTLA-4 immune check point inhibitors as immunotherapeutic agents are not possible. We did not find any ongoing trials investigation monotherapy with CTLA-4 immune check point inhibitors.

- *Role of PD-1/ PD-L1 Immune Checkpoint Inhibitors in Treatment of HCC*

Since the first ICI, ipilimumamb, was approved in March 2011metastatic melanoma, the U.S.FDA has continued to approve 11 more immune checkpoint inhibitors. These approved ICIs target one out of three different T-cell checkpoints: CTLA-4, PD-1/PD-L1, or LAG-3. Over 3000 clinical trials have evaluated PD-1/PD-L1 inhibitors worldwide, the majority of which focus on the analysis of the combination of these agents (57). The PD-1 inhibitor, nivolumab, was the first approved trial-approved ICI for HCC patients in 2017(58) (Table 1). The trial consisted of 262 patients with either active HBV or HCV infections, the majority of whom had already received one line of sorafenib therapy/ Roughly 18% of patients were placed in a dose-escalation phase, while the remaining 82% were in the dose-expansion phase (58) . Intravenous nivolumab was administered at a dose of 0.1-10 mg/kg every 2 weeks for those in the dose-escalation phase (58). For dose-expansion-phase, 3mg/kg dose of nivolumab was administered. Among dose-escalation patients, a 58% disease control rate was exhibited, in comparison to 64% for the dose-expansion phase. The overall objective response rate for the former was 15% for the former, and 20% for the latter (58).

In a different phase III study, the clinical safety and potency of nivolumab and sorafenib as first line therapy was studied among 742 patients with advanced HCC (59). Nivolumab was administered intravenously once every two weeks at a dose of 240 mg among 371 patients, while sorafenib was given orally twice at a dose of 400 mg among 372 patients (59) . It is important to note that this trial, with a limited follow up on 22.8 months) failed to meet the predefined threshold of statistical significance with its hazard ratio (HR=0.84, p=0.0419) (59). Subsequent therapy was pursued for 38% of nivolumab patients and 46% of sorafenib treated patients (59). For the nivolumab group, the median overall survival was 16.4 months, compared to a mere 14.7 months for sorafenib treated patients (59). Nivolumab treatment demonstrated favorable safety profile, but not many details were provided (59).

Another PD-1 inhibitor, pembrolizumab (Keytruda) was administered at a dose of 200 mg every 3 weeks for ≤ 35 cycles among 104 patients with advanced hepatocellular carcinoma who had already received sorafenib treatment (60). Among the treatment group, a disease control rate of 61.5%, a median progression-free survival of 4.9 months and median overall survival of 13.2 months were reported (60). Out of 104, 76 patients demonstrated treatment-related adverse low-grade severity. After following the patients for more than 2.5 years, treatment with pembrolizumab resulted into continued stable anti-tumor activity without any new safety concerns (60).

Using camrelizumab to block the interaction of PD-1 to its ligand PD-L1 was tried as a treatment strategy among 220 patients at 13 sites in China (61). The patients were randomly assigned to receive 3 mg/kg camrelizumab intravenously every 2 or 3 weeks (61). Out of the 220 patients, 83% had an HBV infection and 23% had already received two or more lines of systemic treatments (61). The overall survival probability at 6 months for the treatment group was 74.4 % and 22% of patients suffered grade 3 or 4-treatment-related adverse effects (61). This camrelizumab treatment regimen

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indicated antitumor activity in pretreated Chinese HCC patients, reflecting its potential as an ultimate line of defense for patients with a history of systemic treatments (61).

Eight cycles of 350 mg of cemiplimab were administered intravenously to 21 patients with resectable hepatocellular carcinoma every 3 weeks in a phase II, single-arm, open label clinical trial (62). Pre-treatment biopsies were collected, and blood sample collection was performed throughout the entire treatment regimen (62). 20% of the patients had significant tumor necrosis, while 15 % exhibited a partial response, and the remaining maintained stable disease (62). 95% of patients had treatment-emergent adverse effects ranging from increased aspartate aminotransferase, increased blood creatinine phosphokinase, constipation, and fatigue (62). These results support the design of larger clinical trials to definitively outline the clinical efficacy and benefits of preoperative PD-1 blockades for HCC treatment (62).

- *Combinatorial Effect of CTLA-4 and PD-1/PD-L1 Inhibition in the Treatment of Hepatocellular Carcinoma*

Previous studies involving monotherapy either with CTLA-4 and PD-1/PD-L1 inhibition have showcased significant improvements in treating patients with hepatocellular carcinoma (63). Further studies focused on evaluating combination of immune immunotherapeutic agents among HCC patients (63). In the checkmate 040 randomized clinical trial, 148 patients with hepatocellular cancer previously treated with sorafenib were treated with a combined treatment regimen of nivolumab and ipilimumab (63). Across 10 countries, patients were recruited at 31 centers from Asia, Europe, and North America. In this randomized clinical trial, different levels of nivolumab and ipilimumab combinations demonstrated safety, improved response rates, and predictable responses (63). Based on the findings of this trial, the USA recommended 4 doses nivolumab 1mg/kg plus ipilimumab 3 mg/kg every 3 weeks then nivolumab 240 mg every 2 weeks for accelerated approval (63).

In one recent study of 1171 patients unpresentable hepatocellular carcinoma patients (Table 1), solely one high priming dose of tremlimumab (anti-CTLA-4) plus durvalumab (anti PD-1/PD-L1) demonstrated increased safety and exciting clinical activity in a phase II trial (64). This 2022 study compared three treatment regimens of tremelimumab (300 mg, one dose) plus durvalumab (1500 mg every 4 weeks), durvalumab (1500 mg every 4 weeks), or sorafenib (400 mg twice daily) (64). The combination of the infusion regimen of tremelimumab and durvalumab was named STRIDE (Single Tremelimumab Regular Interval Durvalumab). Comparing STRIDE, durvalumab, and sorabenib, the overall survival rate for the first was 30.7% at 36 months, 24.7% for the second, and 20.2% for the third (64). There was no significant difference among all three groups for median progression-free survival (64). This study concluded that patients who were treated with STRIDE had significantly improved overall survival outcomes compared to patients who were treated with sorafenib (64).

- *Efficacy of Antiangiogenic and Chemotherapeutic Agents Along with PD-1/PD-L1 Inhibition in HCC*

Because of its particularly vascularized nature, hepatocellular cancers exploit angiogenesis to rate and disseminate (65). Vascular endothelial growth factors (VEGFs) are the measure players in angiogenesis and by targeting VEGFs in collaboration with immune checkpoint inhibitors, may lead to better treatment strategies for HCC patients (66). For example, a treatment regimen that combined atezolizumab and bevacizumab (Table 1) was studied among 501 patients in a global, open label, phase III trial (IMbrave150) (67). All the patients in this trial had unresectable hepatocellular carcinoma and were not subjected to any previous systemic treatment (67). Out of 501, 336 patients were treated with the atezolimumab-bevacizumab regimen and 165 patients were treated with sorafenib (67). At 12 months, overall survival was 67.2% among atezolimumab-bevacizumab group, compared to 54.6% for the sorafenib treated group (67). The median progression survival rate for atezolimumab-bevacizumab treated patients was 6.8 months, while for sorafenib treated patients, it was 4.3 months (67). This trial concluded that combination of atezolimumab with bevacizumab treatment is better than sorafenib in terms of both overall and progression-free survival outcomes (67).

Another clinical study was undergone to compare a different combination treatment regimen versus sorafenib at 95 study sites across 13 countries; this studied camrelizumab (anti PD-1) plus rivoceranib/apatinib (VEGFR2-tragtegte TKI) versus sorafenib as the first line treatment for unresectable hepatocellular carcinoma (68). Patients who had never been priorly exposed to systemic treatments were randomly assigned to one of two groups: receiving either camrelizumab 200 mg intravenously every 2 weeks plus rivocreanib 250 mg orally one daily or sorafenib 400 mg orally twice daily (68). For the camrelizumab-rovoceranib treated patients (n=272), their median progression-free survival rate was 5.8 months in comparison to 3.7 months among sorafenib treated patients (n=271) (68). Overall survival was significantly extended to 22.1 months among camrelizumab–rivoceranib patients, with only 15.2 months among sorafenib treated patients (68). However, while only 6% of the sorafenib group demonstrated adverse effects associated with the treatment, 24% of the ICI treatment regimen. In sum, just like the combination of atezolimumab and bevacizumab, camrelizumab–rivoceranib had a significantly higher overall and progression free survival rate compared to sorafenib (68). This study's findings' illuminate a new, effective first-line treatment for unresectable hepatocellular carcinoma (68).

A newly developed humanized anti-PD-1, penpulimab, was combined with anlotinib (VEGF inhibitor) in a study involving 31 patients (69). In this study, all enrolled patients had confirmed unresectable HCC and had not exposed to any previous systemic treatment (69). The study involved an intravenous dose of penpulimab (200 mg every 3 weeks) and an oral dose of anlotinib (8 mg/kg, 2 weeks on/1 week off) was administrated among patients (69). 31% of objective response rate, 82.8% of disease control rate, 8.8 months of

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medial progression-free survival, and 8.8 months of time to progression were observed among treated patients (69). This trial reflected important anti-tumorigenesis activity and an improved safety profile as a potential first line treatment of patients with unresected hepatocellular carcinoma (69).

In another study, the combination of avelumab (10mg/kg intravenously every 2 weeks) and axitinib (5mg orally twice daily) was studied among 22 enrolled Japanese patients (70). All eligible patients had confirmed unresected HCC with no history of previous systemic treatment (70). For this treatment combination, progression free survival was reported to be 5.5 months and the median overall survival for patients was 14.1 months (70). This trial advocates for treating unresected HCC with a combination of avelumab and axitinib with positive outcome of manageable toxicity profile along with antitumor activity (70).

Finally, the combination of immune checkpoint inhibitors (ICIs) and hepatic arterial infusion chemotherapy (HAIC) was analyzed among 130 patients with advanced HCC in a clinical trial in Taiwan (71). Doxorubicin and cisplatin were the therapeutic agents in this trial, while immune check point inhibitors included in the trial were nivolumab, pembrolizumab, nivolumab plus ipilimumab, atezolimumab plus bevacizumab, and spartlizumab (71). While there was a lack of a significant effect on overall tumor response among treated groups, a significant effect of 78.57% on vessel response was observed among patients treated with HAIC plus ICIs (71). Additionally, for patients who were treated with HAIC plus ICIs, there was a significant effect of 90% on portal vein tumor thrombus (PVTT) (71). Thus, the combination of HAIC and ICIs has a superior response on PVTT than HAIC alone (71). This response is also associated with a reduced risk of tumor progressor or death (71). Both the inhibition of CTLA-4 and PD-1/PD-L1 with monoclonal antibodies and combination treatments with multiple compounds resulted in improved outcomes for hepatocellular carcinoma patients (71). The outcome of the combinatorial treatments of systemic therapies and immune checkpoint inhibitors are considered one of the most interesting approaches to treat hepatocellular carcinoma. Especially, for unresectable hepatocellular carcinoma, many clinical trials have been going on globally (table 2). Results from these trials wills shape how hepatocellular carcinoma patients can be treated, improving cancer outcomes.

III. CONCLUSION

Over the past decade, treating hepatocellular carcinoma patients has been revolutionized through immunotherapy. In comparison to traditional systemic therapies such as chemotherapy, immunotherapy has led to more cancer survivors (72), and yet, many pitfalls of using immunotherapy needs to be addressed. For example, because traditional components like overall survival rates, progression free survival rates, and overall response rates are not well characterized for ICIs, making it hard to determine when exactly a patient should receive immunotherapy (73, 74). Clinicians use the presence of biomarkers like PD-1, PD-L1, and CTLA-4 to determine if a patient will respond to specific immunotherapy, which can be a challenge as some biomarkers are not very stable over the progression of the cancer (75). Moreover, among patients treated with ICIs, the development of immune-related side effects ranges from 13.7%-54% (76, 77). A better understanding to avoid this side effects will improve the quality of hepatocellular carcinoma patients under immunotherapy. With emerging evidence of positive outcome of immunotherapies, availability of immunotherapy to Hispanic and Black patients is limited in comparison to White HCC patients (78), even though HCC incidence is higher among Hispanic and Black populations (79). This disparity needs to be addressed so that the underserved patients can also get better treatment of HCC.

➢ *Disclosure*

The authors have no financial disclosures to report.

Table 1 USA FDA Approved ICIs (Immune Checkpoint Inhibitors) to Treat Hepatocellular Carcinoma

Target	Trade Name	Year	Indication
PD-1	Nivolumab (Opdualag)	September 2017	Sorafenib treatment did not provide expected outcome among HCC patients (58)
PD-1	Pembrolizumab (Keytruda)	November 2018	Sorafenib treatment did not provide expected outcome among HCC patients (60)
PD-1+CTLA-4	Nivolumab (Opdualag) + ipilimumab (Yervoy)	March 2020	Sorafenib treatment did not provide expected outcome among HCC patients (63)
PD-1/PD-L1 + VEGF	Atezolizumab (Tecentriq) + bevacizumab (Avastin)	May 2020	Unresectable HCC (67)
CTLA-4+PD-1/PD-L1	Tremelimumab (Imjudo) + durvalumab (Imfinzi)	October 2022	Unresectable HCC (64)

Table 2 Selected Ongoing ICIs (Immune Checkpoint Inhibitor) Clinical Trials for Unresectable Hepatocellular Carcinoma Patients

Drug/Phase	Sponsor	Design/Procedure	Size (n)	Trial (NCT Number)
Cardonilimab+ Renvatinib/Phase I and II	Guangxi Medical University	“Renvatinib (once daily) + radiotherapy+ Cardonilimab (once every 3 weeks)”	30	NCT06040177 (80)

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Drug/Phase	Sponsor	Design/Procedure	Size (n)	Trial (NCT Number)
Durvalumab/Phase II	The University of Hong Kong	"Durvalumab (750 mg intravenously once every 2 weeks for 26 cycles) + radiation (27.5 Gy-50 Gy) in 5 fractions over 5-14 days"	37	NCT04913480 (81)
HAIC+ Lenvatinib+ Tislelizumab/Phase II	Second Affiliated Hospital of Nanchang University	"Lenvatinib (12 mg/d for bodyweight ⩾ 60 kg or 8 mg/d for bodyweight <60 kg) + Tislelizumab (200 mg every3 weeks)"	60	NCT05582278 (82)
HAIC+Lenvatinib+Tislelizumab/Phase II	Genentech, Inc.	"Lenvatinib (12 mg/d for bodyweight ⩾ 60 kg or 8 mg/d for bodyweight <60 kg) +Tislelizumab (200 mg every 3 weeks)"	60	NCT05582278 (82)
Atezolizumab +Bevacizumab/ Phase II	Genentech, Inc.	"Atezolizumab (1200 mg by IV infusion on Day 1 of each 21-day cycle) + Bevacizumab (15 mg/kg by IV infusion on Day 1 of each 21-day cycle)"	120	NCT06096779 (83)
Atezolizumab + Bevacizumab/ Phase II	Chang Gung Memorial Hospital	"Atezolizumab (1200 mg) + Bevacizumab (15 mg/kg) once each 3 weeks + Proton radiotherapy"	45	NCT06133062 (84)
Atezolizumab + Bevacizumab/ Phase II	Ludwig-Maximilians - University of Munich	"Atezolizumab + Bevacizumab intravenously every three weeks for up to 24 months"	106	NCT04224636 (85)
Atezolizumab + Lenvatinib + Sorafenib9 Phase III	Hoffmann-La Roche	"Atezolizumab (1200 mg intravenously every 3 weeks) + Lenvatinib (8-12 mg) once daily orally + Sorafenib (800 mg/day orally)"	554	NCT04770896 (86)
Atezolimumab+ Bavacizumab + Ezupimtrostat/Phase II	University Hospital, Grenoble/ Genoscience Pharama	"Atezolizumab (1200 mg) + Bevacizumab (15 mg/kg) once every 3 weeks + Ezurpimtrostat"	196	NCT05448677 (87)
Atezolizumab + Bevacizumab/ Phase II	Genentech, Inc./ Rutgers Cancer Institute of New Jersey	"Atezolizumab (1200 mg) + Bevacizumab (15 mg/kg) once eevery 3 weeks"	50	NCT04829383 (88)
Atezolizumab + Bevacizumab+ NP137/ Phase I	University Hospital, Grenoble/NETRIS Pharma	"NP137 (9 or 14 mg/kg) + Atezolizumab (1200 mg) + Bevacizumab (15 mg/kg) once every 3 weeks"	52	NCT05546879 (89)
Atezolizumab + Bevacizumab+ UCPVax/ Phase II	Centre Hospitalier Universitaire de Besancon	"Atezolizumab (1200 mg) + Bevacizumab (15 mg/kg) once every 3 weeks + UCPVax vaccine (combined with Montanide ISA51 as adjuvant) at 0.5 mg subcutaneously"	105	NCT05528952 (90)
Atezolizumab + Bevacizumab+ Radiotherapy/ Phase II	Asan Medical Center, Seoul National University Hospital	"Atezolizumab (1200 mg) + Bevacizumab (15 mg/kg) once every 3 weeks + (30 Gy-45 Gy) Radiotherapy after days 2 of the first cycle of atezolimumab and bevacizumab"	138	NCT05992220 (91)

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Drug/Phase	Sponsor	Design/Procedure	Size (n)	Trial (NCT Number)
	Hanyang University Soon Chun Hyang University			
Atezolizumab + Cabozatinib + Lenvatinib/ Phase II	Academic and Community Cancer Research United/ National Cancer Institute (NCI) Genentech, Inc.	"Atezolizumab intravenously once every 3 weeks + Cabozantinib and Lenvatinib once daily orally"	122	NCT05168163
Ipilimumab + Nivolumab/ Phase II	Academic and Community Cancer Research United/ National Cancer Institute (NCI)	"4 cycles of nivolumab intravenously over 30 minutes and ipilimumab intravenously over 90 minutes on day 1 for every 3 weeks."	40	NCT05199285(92)
Durvalumab + Tremelizumab/ Phase I	City of Hope Medical Center/ National Cancer Institute (NCI)	"Radioemboilization with Ytrium-90 SIR-spheres intra-arterially+ durvalumab and tremelimumab once every 4 weeks for 12 months"	32	NCT04605731 (93)
Pembrolizumab+ Lenvatinib Phase II	Eisai, Inc./ Merck Sharp & Dohme LLC	"Pembrolizumab (200 mg intravenously once every 3 weeks) + Lenvatinib (8 mg capsule) once daily"	156	NCT05091346 (94)

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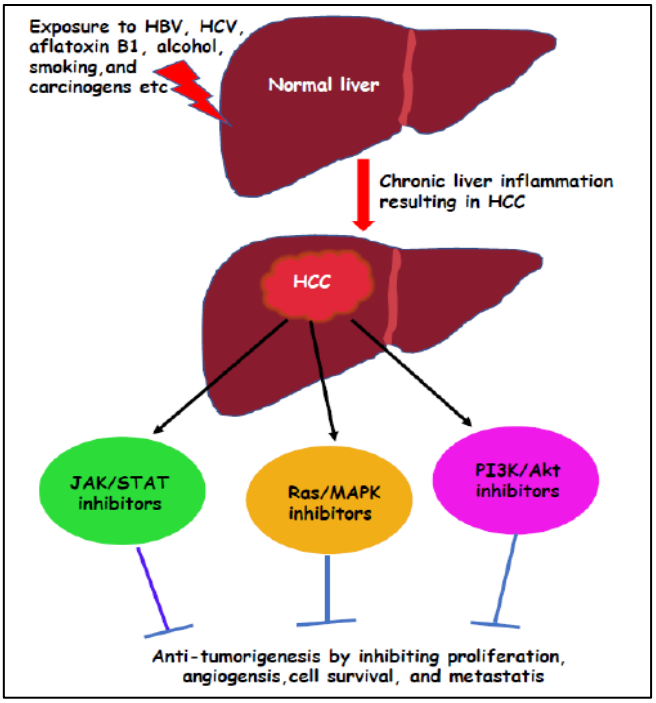

Fig 1 Graphical Presentation of Development of Hepatocellular Carcinoma in Liver from Exposure to Different Toxins. Inhibition of JAK/STAT, Ras/MAPK, and PI3K/Akt pathways by tyrosine kinase inhibitors (TKIs) prevents tumor growth, proliferation, and metastasis in hepatocellular carcinoma (HCC).

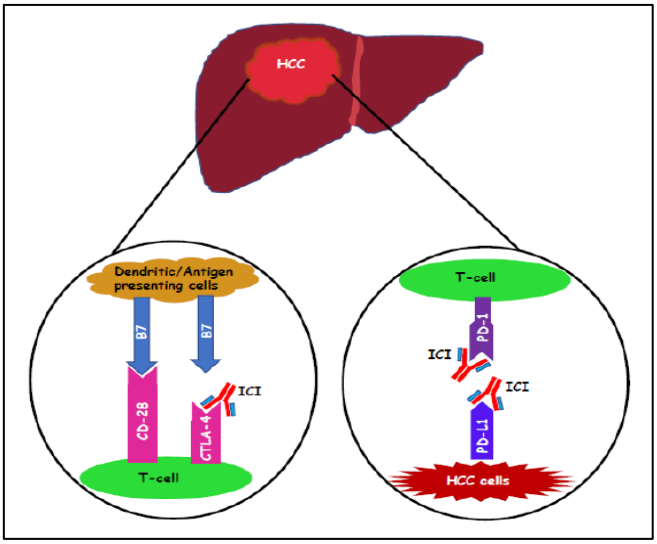

Fig 2 Immune Checkpoint Inhibitors (ICIs) Targeting PD-1, PD-L1, and CTLA-4 can Block the Binding of Checkpoint Proteins to their Ligands. Blocking of this Binding Boosts the Immune Response against Cancer Cells in Hepatocellular Carcinoma (HCC).