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·特邀述评·

Advances in immunotherapy for hepatocellular carcinoma

LI Min[1,2], LIU Xin[2,3], YUAN Dandan[2,4], WANG Jianguo[2,5], CHEN Jiang[2,6], Dan Gabriel DUDA[2,7]

(1. Department of Oncology, the First Affiliated Hospital of Anhui Medical University, Hefei 230022, China; 2. Edwin. L. Steele Laboratories for Tumor Biology, Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA; 3. Center of Hepato-Pancreato-Biliary Surgery, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China; 4. Department of Gastroenterology Oncology, Shandong Cancer Hospital and Institute/Shandong First Medical University and Shandong Academy of Medical Sciences, Ji'nan 250117, China; 5. Department of Hepatobiliary Pancreatic Surgery and Minimally Invasive Surgery, Zhejiang Provincial People's Hospital/Affiliated People's Hospital, Hangzhou Medical College, Hangzhou 310014, China; 6. Department of General Surgery, Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou 310009, China; 7. Transplant Oncology and Therapeutics Program, Department of Surgery, Houston Methodist Academic Institute, Houston, TX 77030 USA)


Dan Gabriel DUDA

Abstract Primary liver cancer (PLC) is a prevalent malignancy with high incidence and mortality rates globally. Hepatocellular carcinoma (HCC), primarily resulting from hepatitis B virus infections in Asia, constitutes most PLC cases. Despite advancements in targeted therapies and localized treatments, the 5-year survival rate remains low, indicating limited efficacy of current approaches. The advent of immunotherapy, particularly immune checkpoint inhibitors (ICIs), has brought new hope for patients with PLC. However, the liver's unique immune microenvironment presents significant challenges to the effectiveness of immunotherapy in HCC. This article reviews recent research developments in liver cancer immunotherapy, focusing on ICIs, combination therapies, emerging treatments, and prospective future directions.

Key words Carcinoma, Hepatocellular; Immunotherapy; Immune Checkpoint Inhibitors; Tumor Microenvironment

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肝细胞癌的免疫治疗进展

李敏[1,2]，刘信[2,3]，袁丹丹[2,4]，王建国[2,5]，陈江[2,6]，Dan Gabriel DUDA[2,7]

(1.安徽医科大学第一附属医院 肿瘤内科，安徽 合肥 230022；2.哈佛大学医学院附属麻省总医院 Edwin. L. Steele 肿瘤生物学实验室/放射肿瘤科，美国 波士顿 02114；3.中山大学附属第一医院 肝胆胰外科中心，广东 广州 510080；4.山东省肿瘤医院/山东第一医科大学附属肿瘤医院 消化肿瘤科，山东 济南 250117；5.浙江省人民医院/杭州医学院附属人民医院 肝胆胰外科及微创外科，浙江 杭州 310014；6.浙江大学医学院附属邵逸夫医院 普外科，浙江 杭州 310009；7.休斯敦卫理

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Author information: Dan Gabriel Duda, DMD, PhD, is a professor of Radiation Oncology at Harvard Medical School and Director of Translational Research in Gastrointestinal Radiation Oncology at Massachusetts General Hospital, Boston, USA. His research focuses on tumor-microenvironment interactions.

Correspondence: Dan Gabriel Duda, **Email:** duda@steele.mgh.harvard.edu, **ORCID:** 0000-0001-7065-8797.

公会学术研究所 移植肿瘤学与治疗学中心/外科学系，美国 休斯敦 77030）

摘　要　原发性肝癌（PLC）是全球发病率和病死率均较高的常见恶性肿瘤。肝细胞癌（HCC）是PLC的主要类型，在亚洲多由乙型肝炎病毒感染引起。尽管近年来在靶向治疗和局部治疗方面取得了进展，但其5年生存率依然较低，提示现有治疗手段疗效有限。免疫治疗的出现，特别是免疫检查点抑制剂（ICI），为PLC患者带来了新的希望。然而，由于肝脏独特的免疫微环境，免疫治疗在HCC中的疗效仍面临严峻挑战。本文综述了近年来肝癌免疫治疗的研究进展，重点讨论ICI、联合治疗、新兴疗法以及未来的发展方向。

关键词　癌，肝细胞；免疫疗法；免疫检查点抑制剂；肿瘤微环境

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According to Global Cancer Statistics 2022, approximately 866 136 new cases of primary liver cancer (PLC) were reported, representing 4.3% of all new cancer cases and ranking sixth in global cancer incidence[1]. Liver cancer accounted for about 7.8% of all cancer deaths, ranking fourth in mortality. The predominant pathological type of PLC is hepatocellular carcinoma (HCC), constituting approximately 75%−85% of PLC cases[2]. For patients with early-stage HCC, potentially curative treatments such as surgical resection, radiofrequency ablation, or transarterial chemoembolization are available. However, the rate of disease recurrence after these treatments remains high[3]. The absence of significant clinical symptoms in early PLC leads to most patients being diagnosed at advanced stages, rendering them ineligible for curative surgical resection. Anti-angiogenic tyrosine kinase inhibitor (TKI) drugs, such as sorafenib and lenvatinib, have limited efficacy for HCC, with patients often experiencing rapid disease progression and short survival[4–5].

Immune checkpoint inhibitors (ICIs), particularly programmed cell death protein 1 (PD-1)/PD ligand 1 (PD-L1) inhibitors, have revolutionized the treatment landscape for advanced HCC over the past decade. Due to their significant efficacy, these agents have become a standard therapeutic option for some patients with advanced HCC. PD-1 inhibitors function by specifically blocking the interaction between PD-1 receptors on T cells and their ligands, PD-L1 and PD-L2, on tumor cells. This blockade inhibits T cell exhaustion, thereby restoring their antitumor activity and enhancing the immune system's ability to target and destroy cancer cells effectively[6–7].

In this review, we first examine the molecular foundations of the immune response in HCC, detailing the principal cells involved and their interactions. Subsequently, we systematically assess the molecular mechanisms and sensitizing effects of combining ICIs with anti-angiogenic antibodies or TKIs. Finally, we critically evaluate ongoing clinical trials and offer recommendations for future trial designs.

1　Immunobiology of HCC

The development of HCC is closely associated with chronic liver disease (e. g., hepatitis B, alcoholic liver disease), especially cirrhosis, in most patients. In patients with chronic liver disease, the DNA of hepatocytes may be irreversibly damaged during the inflammatory response, leading to an endoplasmic reticulum stress response, which in turn triggers the formation of regenerative nodules and abnormal proliferation of hepatocytes. As these changes accumulate, normal hepatocytes may become cancerous[8].

Hepatitis B virus (HBV) and Hepatitis C virus (HCV) stimulate immune-mediated inflammation, promoting malignant transformation leading to HCC. HBV also directly affects the oncogenic properties of host cells through its encoded X protein (HBx) [9]. Once malignant transformation occurs, the tumor microenvironment (TME) forms with various degrees of immune cell infiltration. While the immune system typically acts to eliminate malignant cells and suppress tumor development, large numbers of immunosuppressive cells can promote tumor progression in the context of chronic inflammation. Studies have indicated that

approximately 25% of liver cancer patients exhibit high levels of lymphocyte infiltration and elevated inflammatory expression within their tumors[10].

In patients with HCC, the immune system mounts an antitumor response, with tumor-infiltrating lymphocytes (TILs) playing a crucial role in solid tumors[11]. However, elevated levels of $CD8^+$ and $CD4^+$ T cells can lead to immune dysfunction, potentially accelerating disease progression[12]. Furthermore, a decline in natural killer (NK) cell function in HCC patients further compromises the innate immune system[13].

In the cirrhotic microenvironment, while the organism recognizes a population of TILs, their presence is insufficient to control tumor development[14]. In addition, tumors can evade immune surveillance by producing myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) [15]. Consequently, the immune TME presents a formidable barrier to anti-cancer immunity in HCC. Therefore, immune-based combination therapies should target these immunosuppressive elements to enhance the efficacy of HCC treatment.

2 Immunotherapy strategies for HCC: progress and challenges

Contemporary immunotherapeutic approaches for HCC stimulate the body to generate novel or enhanced immune reactions. ICIs, representing a rapidly advancing field in immunotherapy, can achieve tumor cell eradication by reversing immunosuppression and amplifying the immune response. However, such responses are seen in a minority of HCC patients. Elucidating the mechanisms underlying immune responses and ICI resistance remains a major area of research. HCC cells are known to express antigens, such as alpha-fetoprotein (AFP), which can be targeted by immunotherapy to activate effector cells, including T lymphocytes and NK cells, to destroy tumor cells. Furthermore, local therapeutic interventions, such as tumor ablation, can induce the release of tumor-associated antigens, thereby enhancing the activity of cytotoxic T lymphocytes (CTLs) and promoting robust antitumor immune responses[16–19]. Immunosuppressive cytokines, such as transforming growth factor beta (TGF-β), may play a crucial role in the immune evasion mechanisms of HCC. Studies have demonstrated that TGF-β1 facilitates tumor immune escape by upregulating the expression of immune checkpoint molecules, including PD-1 and CTLA-4, on the surface of T lymphocytes, thereby diminishing their cytotoxic activity. The currently used strategies targeting these suppressive pathways in HCC patients are discussed below.

3 ICIs

3.1 PD-1/PD-L1 inhibitors

3.1.1 Nivolumab Nivolumab, a PD-1 fully human IgG4 antibody, was first provisionally approved by the FDA as a second-line treatment for patients with advanced HCC based on phase II results However, the CheckMate 459 randomized phase III clinical trial, which compared nivolumab to sorafenib as a first-line treatment for advanced HCC, demonstrated a median overall survival (mOS) of 16.4 months in the nivolumab arm *vs.* 14.7 months in the sorafenib arm, which did not reach statistical significance (P=0.075). The most frequently observed grade 3 or higher treatment-related adverse events (AEs) in the nivolumab cohort included immune-related events such as elevated liver enzymes, rash, and hepatitis. In contrast, sorafenib was mainly associated with palmar-plantar erythrodysesthesia. Serious treatment-related AEs were reported in 12% of patients treated with nivolumab, compared with 11% of patients treated with sorafenib[20].

3.1.2 Pembrolizumab Pembrolizumab is an IgG subtype antibody that blocks the binding of PD-1 to its ligands, PD-L1 and PD-L2. Due to the partial structural homology of PD-L1 and PD-L2, pembrolizumab antagonizes the interaction of PD-1 with both ligands simultaneously. In the phase II clinical trial KEYNOTE-224, the study evaluated the efficacy of pembrolizumab in previously treated patients with advanced HCC. Results showed that subjects had an objective remission rate (ORR) of 17%, a disease control rate (DCR) of 44%, a median progression-free survival (mPFS) of 4.9 months, and a mOS of 12.9 months. Based on this study, the FDA approved pembrolizumab for the second-line treatment of HCC in November 2018[21–22]. The phase III study KEYNOTE-240 evaluated the efficacy and safety of

pembrolizumab in the same setting. Trial data showed a mOS of 13.9 months for pembrolizumab *vs.* 10.6 months for placebo (P=0.023 8), which did not reach statistical significance according to the specified criteria[23].

3.1.3 Atezolizumab in combination with bevacizumab Atezolizumab is a humanized monoclonal antibody that mainly acts on the immune checkpoint PD-L1, competitively inhibiting the interaction of PD-L1 with T cells while reducing the binding of PD-1 to antigen-presenting cells, thus attenuating the PD-1/PD-L1-dominated immuno-suppressive effect and enhancing the attack of T cells on cancer cells. The Phase Ib clinical trial GO30140 evaluated the efficacy and safety of atezolizumab combined with bevacizumab in patients with unresectable HCC (uHCC). This study enrolled 104 patients, with 36% achieving a confirmed objective response. The mPFS for the combination therapy group was 6.6 months. Common grade 3 or higher AEs included hypertension (13%) and proteinuria (7%). Serious AEs occurred in 24% of patients, with three treatment-related deaths due to abnormal liver function, cirrhosis, and pneumonia. In comparison to monotherapy, the combination therapy improved mPFS from 5.6 months to 6.6 months in patients with uHCC. This suggests that atezolizumab, combined with the anti-VEGF antibody bevacizumab, offers a more effective treatment option than atezolizumab alone[24]. The Phase III IMbrave150 trial further compared atezolizumab plus bevacizumab to sorafenib monotherapy in patients with uHCC[25]. The hazard ratio for death in the combination therapy group was 0.58, indicating a significant reduction in mortality risk. The 12-month OS rate was 67.2% in the combination group, compared to 54.6% in the sorafenib group. mPFS was 6.8 months for the combination therapy, compared to 4.3 months for sorafenib, demonstrating that the combination therapy slowed disease progression and improved mOS. Grade 3 and higher AEs were reported in 56.5% of subjects in the atezolizumab plus bevacizumab group and 55.1% in the sorafenib group, indicating comparable incidence rates and probabilities of occurrence in the subject population treated with sorafenib monotherapy. The results of this pivotal Phase III clinical study led to the FDA approval for atezolizumab in combination with bevacizumab as first-line treatment for patients with uHCC, and the worldwide adoption of this regimen.

3.1.4 Camrelizumab with rivoceranib Camrelizumab is a humanized blocking antibody for PD-1, thus blocking the PD-1/PD-L1 pathway and thereby restoring the body's antitumor immunity[26–27]. The phase III clinical trial, CARES-310, demonstrated that camrelizumab combined with the anti-VEGFR TKI rivoceranib (also known as apatinib) significantly outperformed sorafenib monotherapy in treating patients with uHCC. The combination therapy achieved an mPFS of 5.6 months compared to 3.7 months with sorafenib. Furthermore, the median OS was notably extended to 23.8 months with the combination therapy, whereas sorafenib achieved 15.2 months. Regarding safety, the most common grade 3 or 4 treatment-related AEs in the combination therapy group included hypertension, palmar-plantar erythrodysesthesia syndrome, and elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Specifically, hypertension was observed in 38% of patients receiving the combination therapy, compared to 15% in the sorafenib group. The incidence of treatment-related serious AEs was higher in the combination therapy group at 24%, compared to 6% in the monotherapy group. The results showed that this ICI/TKI combination is feasible and efficacious as a first-line treatment option in patients with uHCC.

3.2 Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors

CTLA-4 is a pivotal immune checkpoint molecule expressed on the surface of T cells. It inhibits T cell activation and proliferation by binding to B7 molecules (CD80 and CD86) on antigen-presenting cells (APCs). This interaction is crucial for maintaining immune self-tolerance and preventing excessive immune responses. CTLA-4 competes with CD28 for binding to the B7 ligands, and due to its higher binding affinity, CTLA-4 effectively blocks the co-stimulatory signals provided by CD28, resulting in immunosuppression. By inhibiting the interaction between CTLA-4 and B7 molecules, CTLA-4 inhibitors alleviate T cell suppression, thereby enhancing the anti-tumor immune response. In treating HCC, CTLA-4 inhibitors (ipilimumab, tremelimumab) demonstrated significant therapeutic potential, particularly when combined with PD-1/PD-L1 inhibitors. CTLA-4

predominantly regulates the early stages of T cell activation, whereas PD-1/PD-L1 operates at the effector stage of T cell activation. Combining these inhibitors allows for a synergistic enhancement of the anti-tumor immune response at multiple stages of the immune process, ultimately improving therapeutic outcomes in HCC.

3.2.1 Ipilimumab In patients with advanced HCC previously treated with sorafenib, the CheckMate 040 randomized clinical trial assessed the efficacy of nivolumab combined with ipilimumab[28]. In group A, patients received nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg every three weeks for four doses, followed by nivolumab at 240 mg every two weeks. This regimen achieved an ORR of 32% and a DCR of 27%. These findings indicate that the combination of nivolumab and ipilimumab not only provides significant clinical efficacy but also maintains a manageable safety profile. The most common treatment-related AEs were dermatologic, occurring in 35% of patients. Gastrointestinal and hepatic treatment-related AEs were observed in approximately 14% of patients. Notably, 68% of treatment-related AEs were resolved with appropriate management. Early intervention in safety events can facilitate easier management. Emphasizing patient education, particularly regarding the importance of monitoring and reporting symptoms, along with prompt counseling, is crucial[29]. Based on these results, the FDA approved the combination therapy in March 2020 for patients with HCC that has progressed after prior treatment with sorafenib. Dual immunotherapy offers a novel treatment option for patients with advanced HCC who have progressed on sorafenib, by activating distinct immune response pathways.

In addition, in the phase III open-label, randomized CheckMate 9DW clinical trial[30], nivolumab in combination with ipilimumab was tested as a first-line treatment for patients with uHCC. The overall survival (OS) Kaplan-Meier curves crossed early, reflecting a higher number of deaths within the first 6 months in the nivolumab-ipilimumab arm (*HR*=1.65, 95% *CI*=1.12−2.43), but were followed by a sustained survival benefit favoring the immunotherapy combination (*HR*=0.61, 95% *CI*=0.48−0.77). After a median follow-up of 35.2 months (IQR: 31.1−39.9), median OS was significantly longer with nivolumab plus ipilimumab (23.7 months; 95% *CI*=18.8−29.4) compared with lenvatinib or sorafenib (20.6 months; 95% *CI*=17.5−22.5; *HR*=0.79, 95% *CI*=0.65−0.96, *P*=0.018). The 24-month and 36-month OS rates were 49% and 38%, respectively, compared to 39% and 24%. Importantly, regardless of baseline ALBI grade, the nivolumab + ipilimumab group achieved a clinically meaningful improvement in OS and higher 24-month and 36-month OS rates compared with lenvatinib or sorafenib. Rates of grade 3−4 treatment-related AEs were similar between the two arms (41% *vs.* 42%), though there were more treatment-related deaths with nivolumab plus ipilimumab (*n*=12) than with lenvatinib or sorafenib (*n*=3). Based on the above results, both China and the United States have approved nivolumab (Opdivo) combined with ipilimumab (Yervoy) as a first-line treatment for advanced HCC.

3.2.2 Tremelimumab with durvalumab In the global phase III HIMALAYA trial[31], the STRIDE regimen (single 300 mg tremelimumab plus durvalumab 1 500 mg every four weeks) demonstrated superior survival outcomes compared to sorafenib (400 mg twice daily) in patients with uHCC. Median (95% *CI*) follow-up durations were 62.49 (59.47−64.79) months (STRIDE) and 59.86 (58.32−61.54) months (sorafenib). The OS *HR* (95% *CI*) for STRIDE *vs*. sorafenib was 0.76 (0.65−0.89). OS rates at 60 months for STRIDE *vs.* sorafenib were 19.6% *vs.* 9.4% overall, 28.7% *vs.* 12.7% in participants achieving disease control per RECIST 1.1, and 50.7% *vs.* 26.3% in participants achieving greater than 25% tumor shrinkage.

These results showed that CTLA-4 inhibitors, particularly when combined with PD-1/PD-L1 inhibitors, offer substantial clinical benefits in HCC treatment. However, combination therapy may elevate the risk of immune-related adverse effects, necessitating a careful balance between efficacy and safety in clinical applications.

4 Other combination therapy approaches

4.1 Combined anti-VEGF and immunotherapy treatment

HCC progression involves multiple mechanisms, notably the overexpression of VEGF, which is pivotal in

tumor angiogenesis and immune evasion. VEGF facilitates abnormal tumor angiogenesis and enables tumor cells to evade immune surveillance by suppressing anti-tumor immune responses. Building on the success of bevacizumab in combination with atezolizumab for the treatment of advanced HCC, multiple other combinatorial strategies are being tested.

The MORPHEUS-liver phase I b/II randomized study assessed the efficacy of combining tiragolumab with atezolizumab and bevacizumab in patients diagnosed with unresectable, locally advanced, or metastatic HCC. In this trial, 58 participants were assigned to two cohorts: 40 patients received the triple regimen, while 18 were treated with atezolizumab/bevacizumab. Data showed that the combination of tiragolumab with atezolizumab and bevacizumab improved ORR (42.5% compared to 11.1% in the control group), and prolonged PFS (12.3 months *vs.* 4.2 months), without the emergence of new safety concerns. These findings supported testing this combination in phase III clinical trials [32].

SKYSCRAPER-14 study (IMbrave152) is a pivotal global phase III randomized, double-blind, placebo-controlled clinical trial designed to evaluate the efficacy and safety of tiragolumab (a novel anti-TIGIT antibody) in combination with atezolizumab and bevacizumab, compared to atezolizumab plus bevacizumab alone, in patients with previously untreated, unresectable or metastatic HCC. This trial enrolled approximately 650 patients, who were randomized 1∶1 to receive either the triplet regimen or the standard immunotherapy combination. The primary endpoints were progression-free survival (PFS) and OS. However, based on a corporate update from Roche in Q2 2025, SKYSCRAPER-14 did not meet its primary endpoint of improving PFS, and no improvement in OS was observed at the time of analysis. As a result, the trial did not meet its primary endpoints of PFS and OS. Further development of tiragolumab in HCC is currently limited, and detailed efficacy results are expected to be presented at upcoming medical meetings[33].

4.2 Combination therapeutic strategies of multi-targeted TKIs with ICIs

TKIs played an important role in HCC therapy. Sorafenib was the first multi-targeted TKI approved for HCC treatment, marking the advent of targeted therapies in this disease. Following multiple failures of other TKIs, the multi-targeted TKI lenvatinib showed an equivalent efficacy to sorafenib, becoming another first-line option for advanced cases. Additionally, the multi-targeted TKIs regorafenib and cabozantinib demonstrated efficacy in the second-line setting. These drugs impede tumor progression and target the vasculature by blocking the functions of several tyrosine kinases. Despite these advancements, the use of TKIs as monotherapy has shown limited efficacy, prompting investigations of combination strategies with other treatments. However, so far, the combination of TKIs with ICIs has shown inconsistent results in HCC patients.

4.2.1 Lenvatinib Lenvatinib, a multi-target TKI, has demonstrated the ability to decrease tumor PD-L1 expression in preclinical models, thereby enhancing the effectiveness of anti-PD-1 therapies. Clinical studies have investigated the combination of lenvatinib with PD-1 inhibitors in the treatment of advanced HCC[34]. In the KEYNOTE-524/Study 116 phase I/II clinical study[35], the combination of lenvatinib and pembrolizumab achieved an ORR of 43%. Patients exhibited an mPFS of 9.3 months and an OS of 20.4 months, indicating significant antitumor activity in advanced HCC. However, the subsequent LEAP-002 phase III trial revealed that combining lenvatinib with pembrolizumab did not result in a statistically significant improvement in OS compared to lenvatinib monotherapy (20.2 months *vs.* 19.0 months). This outcome suggests that the benefits of combination therapy require further investigation in specific patient populations[36]. The results of this study underscore the need to identify more effective biomarkers to distinguish patients who would genuinely benefit from combination therapy.

4.2.2 Sorafenib The combination of sorafenib with PD-1 inhibitors, such as tislelizumab, is currently under clinical investigation. A Phase II clinical study evaluated the efficacy of sorafenib combined with tislelizumab as a first-line treatment for uHCC and examined the predictive value of circulating tumor cells (CTCs)[37]. In this study, 32 patients received the combination therapy, resulting in an ORR of 17% and a DCR of 65%. When assessed using modified RECIST (mRECIST) criteria, the ORR improved to 24.2% and the DCR to 75%. Treatment-related AEs were observed in 75% of patients, with 35%

experiencing events of grade 3 or higher. Additionally, PD-L1-positive CTCs were detected in 78.1% of patients. After a median follow-up of six months, correlation analysis revealed that the one-year PFS rate was 54.1% in patients with PD-L1-positive CTCs, compared to 28.6% in those without detectable PD-L1-positive CTCs (*P*=0.036). The combination of tislelizumab and sorafenib represents a promising strategy in the first-line treatment of HCC. However, further clinical trials and real-world studies are necessary to fully understand its impact on long-term survival and establish optimal treatment protocols.

4.2.3 Rivoceranib Rivoceranib, also known as apatinib, is an orally administered TKI that selectively targets VEGF receptor 2 (VEGFR-2), a pivotal mediator in tumor angiogenesis. By inhibiting the VEGFR-2 pathway, apatinib disrupts the formation of new blood vessels, which are essential for tumor growth and metastasis. The CARES-310 study was an international, multicenter, randomized, open-label, phase III clinical trial designed to assess the efficacy of combining camrelizumab, an anti-PD-1 antibody, with rivoceranib (also known as apatinib) in patients with previously untreated uHCC[38]. A total of 543 patients participated, with 272 assigned to the camrelizumab plus rivoceranib group and 271 to the sorafenib group. The mPFS for the camrelizumab plus rivoceranib cohort was 5.6 months compared to 3.7 months in the sorafenib group. The final analysis of CARES-310 demonstrated a mOS of 23.8 months with camrelizumab plus rivoceranib, significantly higher than the 15.2 months observed with sorafenib (*HR*=0.64, 95% *CI*=0.52−0.79, *P*<0.000 1). The most frequently reported grade 3 or 4 treatment-related AEs in the camrelizumab plus rivoceranib group included hypertension, palmar-plantar erythrodysaesthesia syndrome (hand-foot skin reactions), and elevated levels of aspartate aminotransferase and alanine aminotransferase. Overall, the combination of camrelizumab and rivoceranib demonstrated statistically significant and clinically meaningful improvements in both PFS and OS, offering another first-line treatment option for patients with uHCC.

4.2.4 Cabozantinib Cabozantinib is a TKI that targets multiple signaling pathways, including MET, VEGFR, and AXL. In the CheckMate 040 extension cohort study[39], patients with advanced HCC received a combination therapy of cabozantinib, nivolumab, and ipilimumab, resulting in an objective response rate (ORR) of 29% and a mOS that had not yet been reached at the time of analysis.

In the phase III, open-label, randomized COSMIC-312 trial[4], cabozantinib plus the PD-L1 monoclonal antibody atezolizumab was compared with sorafenib as first-line systemic therapy for advanced HCC. The combination regimen significantly prolonged independent review facility-assessed PFS (stratified *HR*=0.63, 95% *CI*=0.44−0.91, *P*=0.001 2) but failed to confer a statistically significant OS benefit (stratified *HR*=0.90, 95% *CI*=0.69−1.18, *P*=0.44). The safety profile was clinically manageable, though treatment-emergent AEs (TEAEs) were more frequent in the combination arm. Grade ≥3 ALT elevation was the most common laboratory abnormality (cabozantinib + atezolizumab 9% *vs*. sorafenib 3%).

In summary, TKIs can enhance the immune system's ability to attack tumors by inhibiting angiogenesis-related pathways, such as VEGFR, thereby normalizing tumor vasculature and reducing the immunosuppressive microenvironment. PD-1/PD-L1 inhibitors, like nivolumab, can further alleviate immunosuppression and activate effector T cells. Therefore, combining TKIs with ICIs not only inhibits tumor growth through multiple pathways but also enhances the tumor immune response, leading to improved anti-tumor effects. Despite the promise of TKIs and ICIs combination therapies, challenges remain, including balancing efficacy and toxicity, optimizing dosage and administration timing, and identifying patient groups most likely to benefit. Future research will focus on discovering effective biomarkers, refining patient selection, and improving the safety and tolerability of combination therapies to provide better treatment options for patients with advanced HCC. The clinical trials discussed above are summarized in Table 1.

Table 1 Clinical trials reported in this article

NCT NO.	Name of study	Phase	Investigating arm	Comparative arm	Target nrollment	Primary endpoint
NCT02576509	CheckMate 459	III	Nivolumab	Sorafenib	743	OS
NCT02702414	KEYNOTE-224	II	HCC-prior systemic therapy with sorafenib: pembrolizumab	HCC-systemic therapy naïve: pembrolizumab	156	ORR
NCT02715531	GO30140	Ib	Atezolizumab	Bevacizumab	104	AEs
NCT03434379	IMbrave150	III	Atezolizumab + bevacizumab	Sorafenib	558	OS, PFS
NCT03764293	CARES-310	III	SHR-1210 + apatinib	Sorafenib	543	OS, PFS
NCT01658878	CheckMate 040	I/II	Nivolumab/nivolumab + ipilimumab	None	659	Safety, tolerability, ORR
NCT04039607	CheckMate 9DW	III	Nivolumab + ipilimumab	Sorafenib/lenvatinib	730	OS
NCT03298451	HIMALAYA	III	Durvalumab + tremelimumab-durvalumab	Sorafenib	1 324	OS
NCT04524871	MORPHEUS-LIV-ER	Ib/II	multiple immunotherapy-based treatments	None	518	ORR
NCT03006926	KEYNOTE-524/ Study 116	Ib	Lenvatinib + pembrolizumab	None	104	TEAEs, ORR, duration of response
NCT03713593	LEAP-002	III	Lenvatinib + pembrolizumab	Lenvatinib + placebo	794	PFS, OS
NCT03764293	CARES-310	III	Camrelizumab + apatinib	Sorafenib	543	OS, PFS
NCT03755791	COSMIC-312	III	Cabozantinib l + atezolizumab	Sorafenib	837	PFS, OS
NCT04246177	LEAP-012	III	Lenvatinib+ pembrolizumab + TACE	Oral placebo + IV Placebo plus TACE	480	PFS, OS
NCT01730937	RTOG 1112	III	SBRT followed by sorafenib	Sorafenib alone	193	OS
NCT00554372	JX594	II	1e8 pfu total dose of JX-594	le9 pfu total dose of JX-594	30	DCR
NCT02395250	RJ-20150313	I	Anti-GPC3 CAR-T	None	13	AEs
NCT03146234	None	Not applicable	Anti-GPC3 CAR-T	None	7	Safety, tolerability
NCT02541370	None	I/II	Anti-CD133 CAR-T	None	20	AEs
NCT05155189	0921-028	I	C-CAR031/C-CAR031+Lenvatinb/ C-CAR031 combined + PD-1 (L1) antibody	None	44	Safey, tolerability
NCT01462903	SenU-200902002-2	I	Autologous tumor-infiltrating lymphocytes	None	15	Safety, tolerability
NCT03067493	HCC008	II	6 courses of Neo-MASCT treatment	None	98	DFS, immune response rate
NCT03916627	REGN2810	II	Cohort B: cemiplimab prior to surgery; cemiplimab post surgery (HCC)	None	21	Significant tumor necrosis
NCT03222076	MDACC2017-0097	II	Nivolumab	Ipilimumab + nivolumab	30	Safety, tolerability

5 Neoadjuvant therapy

Surgical resection remains the first-line curative modality for resectable HCC; however, postoperative recurrence within five years can reach 70%. In a prospective, single-center, open-label phase II trial, perioperative immune-checkpoint blockade was systematically evaluated for safety, feasibility, and preliminary efficacy in patients with resectable HCC. Twenty-seven treatment-naïve individuals with preserved hepatic function were randomized 1∶1 to receive either monotherapy (n=13) with Nivolumab alone, or combination therapy (n=14) with nivolumab plus low-dose ipilimumab. Nivolumab plus ipilimumab overcame primary resistance conferred by low baseline TIL density and elicited major pathological responses (MPRs). Notably, even low-immune tumors achieved significant pathological regression, indicating that this regimen may shift the therapeutic paradigm from palliative to curative-intent immunotherapy in early-stage HCC[40]. In the phase

II trial, 21 treatment-naïve patients were enrolled[41]. All participants received two cycles of neoadjuvant cemiplimab monotherapy (350 mg intravenously every 3 weeks). Among the 20 evaluable tumors, four (20%) exhibited substantial necrosis (≥50%), including three (15%) that had complete tumor necrosis. Multiplex immunohistochemistry (mIHC) quantification of paired pre- and post-treatment specimens revealed that a higher baseline immune infiltrate density (as measured by CD3, CD8, FOXP3, CD68, and CD20) correlated with an enhanced pathological response. In patients achieving ≥50% tumor necrosis, post-treatment immune infiltrate density significantly exceeded baseline values, establishing an immunologic substrate for overcoming acquired resistance and potentiating antitumor efficacy in subsequent therapeutic phases.

6 Combinations with localized treatments

Combining immunotherapy with local therapies such as ablation (radiofrequency ablation, microwave ablation), transarterial chemoembolization (TACE), and radiation therapy aims to enhance the immune response by decreasing the local tumor load and promoting the release of tumor antigens. This "local tumor reduction + systemic immunity" strategy has demonstrated the potential to significantly improve outcomes in the treatment of various solid tumors in several recent clinical trials.

6.1 TACE

The LEAP-012 study, a prospective, double-blind, randomized phase III trial, is currently investigating whether the combination of lenvatinib and pembrolizumab with TACE enhances clinical outcomes in patients with intermediate-stage HCC who are not candidates for radical therapy[42]. The trial enrolled 480 participants, who were randomized into either the lenvatinib and pembrolizumab group (*n*=237) or the placebo group (*n*=243), with both groups receiving TACE. As of the first interim analysis, conducted in January 2024, the median time from randomization to data cutoff was 25.6 months (range: 12.6−43.5 months). PFS was significantly improved in the lenvatinib and pembrolizumab group compared to the placebo group, with a mPFS of 14.6 months *vs.* 10.0 months, respectively[43]. Although OS data were not yet mature, a favorable trend was observed: the 24-month OS rate was 75% with lenvatinib/pembrolizumab plus TACE and 69% with placebo. ORR by RECIST 1.1 was 46.8% *vs.* 33.3% (*P*=0.000 5), and by mRECIST were 71.3% *vs.* 49.8%, both favoring the combination treatment. Grade ≥3 treatment-related AEs occurred in 71% of patients receiving lenvatinib/pembrolizumab plus TACE *vs.* 32% in the placebo arm, with hypertension and thrombocytopenia among the most common; and there were four *vs.* one treatment-related deaths.

In the global, randomized, double-blind, placebo-controlled Phase III EMERALD-1 trial, the addition of durvalumab plus bevacizumab (D + B) to TACE was assessed in adults with uHCC amenable to embolization[44]. Patients were randomized in a 1∶1∶1 ratio to receive D + B + TACE, durvalumab + TACE, or placebo + TACE. The primary endpoint−PFS by anonymous independent central review (BICR) per RECIST 1.1−was met: median PFS was 15.0 months (95% *CI*=11.1−18.9) with D + B + TACE *vs.* 8.2 months (95% *CI*=6.9−11.1) with placebo + TACE (*HR*=0.77, 95% *CI*=0.61−0.98, *P*=0.032). The durvalumab + TACE arm did not demonstrate a significant improvement in PFS (median 10.0 months; *HR*=0.94, *P*=0.64). These findings underscore the potential of combining regional tumor reduction with systemic immunization to improve control over residual lesions in HCC and extend long-term survival, providing a novel approach to clinical treatment.

6.2 Liver transplantation (LTx)

Immunotherapy before or after LTx is complex and challenging. Recipients require continuous immunosuppressive therapy to prevent graft rejection, while ICIs function by activating the immune system to target tumor cells. This potential antagonism between immunosuppressive and immunotherapeutic mechanisms poses challenges in managing tumor recurrence post-transplant. Nonetheless, achieving a balance between these opposing effects could potentially enhance therapeutic outcomes[45]. A comprehensive analysis by Zhang et al.[46] evaluated the impact of ICI treatment on allograft rejection, mortality, and tumor response in LTx recipients. The results showed that allograft rejection occurred in 31.7% of patients and was accompanied by a

high mortality rate. In terms of tumor response to immunotherapy, the ORR was 24.4% in 41 recipients, while 51.2% of patients experienced tumor progression after ICI treatment. Although ICI therapy may offer survival benefits for certain post-LTx patients [47], these advantages are currently limited. Further validation of its efficacy and safety through large-scale clinical trials is essential. Additionally, the choice of specific ICIs and their associated rejection rates should be carefully considered, as different agents may present varying risks.

6.3 Stereotactic body radiation therapy (SBRT)

Compared with conventional radiotherapy, SBRT utilizes high-resolution CT and MRI for real-time three-dimensional reconstruction of the tumor, enabling sub-millimeter target delineation and delivering ablative, "laser-like" doses while preserving the maximum extent of normal hepatic parenchyma. Preclinical studies demonstrate that radiation-induced immunogenic cell death synergizes with ICIs to enhance antitumor immunity[48]. The phase III NRG/RTOG 1112 trial has now prospectively validated this strategy in patients with uHCC: SBRT followed by sorafenib significantly prolonged mOS (15.8 months *vs.* 12.3 months; *HR*= 0.77) and PFS (9.2 months *vs.* 5.5 months; *HR*= 0.55) compared with sorafenib alone, without increasing grade ≥3 toxicities and with meaningful improvements in patient-reported quality of life[49].

7 Novel therapies

7.1 Lysosomal virus therapy

Viral therapies encompass both non-replicating viruses, which serve as delivery vectors, and replicating lysogenic viruses capable of directly lysing tumor cells. These therapies have garnered significant attention due to their potent tumor-lysing activity, precise targeting, and reduced likelihood of inducing drug resistance[50]. Heo et al[51]. injected the Jx-594 virus vaccine into HCC tissues, and the study demonstrated that it could kill tumor cells and effectively treat HCC. Furthermore, clinical trials combining Pexa-Vec with sorafenib, a standard treatment for advanced HCC, have demonstrated that this combination therapy showed antitumor activity in early-phase studies. However, the phase III PHOCUS trial failed to establish an OS benefit, and subsequent development was discontinued in HCC patients[52].

7.2 Adoptive cell therapy

Adoptive cell therapy (ACT) is a therapeutic strategy that involves the infusion of ex vivo expanded or genetically modified immune cells into a patient to enhance the anti-tumor immune response[53]. In HCC, tumor-associated antigens (TAAs) or neoantigens, which are present on the surface of cancer cells, can be recognized by the immune system. ACT leverages these specific antigens by culturing and expanding immune cells capable of identifying them in vitro. Immune cells with antitumor activity, such as TILs or circulating T cells, are isolated from HCC patients. The antitumor capacity of these immune cells is enhanced through activation by stimuli such as antigen-presenting cells (e. g., dendritic cells), cytokines (e. g., IL-2), and tumor-specific antigens[54]. In certain cases, T cells are genetically engineered to express specific T cell receptors (TCRs) or chimeric antigen receptors (CARs) that enable them to recognize and eliminate HCC cells more effectively.

7.2.1 CAR-T cell therapy CAR-T therapy has emerged as a promising immunotherapeutic approach for HCC. Glypican-3 (GPC3), a cell membrane protein overexpressed in HCC, serves as an ideal target for this treatment due to its minimal expression in normal adult tissues[55]. Shi et al. [56] treated HCC patients with CAR-GPC3 T-cell therapy, which showed that, in a small phase I exploratory study, the 6-, 12-, and 36-month OS rates were 50.3%, 42.0%, and 10.5%, respectively, providing a new pathway for attacking HCC.

In a prospective phase I study[56], adult patients with advanced GPC3-positive HCC (Child-Pugh class A) received autologous CAR-GPC3 T-cell therapy after lymphodepletion with cyclophosphamide and fludarabine. A total of 13 patients received a median of 19.9×10^8 CAR-GPC3 T cells. AEs included fever (in 13 patients), lymphopenia (in 12 patients), and cytokine release syndrome (CRS; in 9 patients). CRS (grade 1/2) was reversible in 8 patients; 1 patient experienced grade 5 CRS, while no cases of grade 3/4 neurotoxicity occurred. OS rates were 50.3% at 6 months, 42.0% at 1 year, and 10.5% at 3 years.

Dai et al. [57] conducted a single-arm, open-label phase II trial evaluating the efficacy and biomarker

analysis of CD133-directed CAR-T cell therapy in 21 patients with CD133-positive advanced HCC. This study reported a mOS of 12 months and a mPFS of 6.8 months. Hyperbilirubinemia was the most frequent severe AE. These findings suggest that CD133 is a promising therapeutic target for CAR-T cell therapy in advanced HCC.

Another phase I trial, NCT05155189, investigated C-CAR031, a GPC3-specific CAR-T cell equipped with a dominant-negative transforming growth factor-beta receptor II (dnTGF-βR II), in patients with advanced GPC3-positive HCC who had failed at least one prior systemic therapy[58]. The study employed an accelerated titration followed by a 3+3 dose-escalation design. Preliminary results demonstrated a manageable safety profile and encouraging antitumor activity in this heavily pretreated population.

These studies demonstrate the potential therapeutic promise of GPC3-targeted CAR-T cell therapy in patients with advanced HCC, which not only has a manageable safety profile but also shows early signs of anti-tumor activity. These studies provide a strong scientific basis for the future application of GPC3-targeted CAR-T cell therapy in the treatment of HCC, laying the foundation for further clinical studies.

7.2.2 TIL therapy TIL therapy, which involves expanding a patient's tumor-specific lymphocytes in vitro followed by reinfusion, has demonstrated significant efficacy across various malignancies, notably melanoma. A phase I clinical trial evaluated the safety and feasibility of autologous TIL therapy in primary liver cancer patients[59]. The study included 15 participants, all of whom were alive after a median follow-up of 14 months; 12 (80%) exhibited no evidence of disease, while 3 experienced tumor recurrence. Moreover, mOS was higher in HCC patients receiving TIL therapy compared to those undergoing conventional treatments during the same period. The TIL infusions were well-tolerated, with only grade 1 and 2 toxicities, such as flu-like symptoms, malaise, leukopenia, and neutropenia; no grade 3 or 4 AEs were reported across 18 cell infusions.

7.2.3 Tumor vaccines and dendritic cell vaccines Dendritic cells are the most potent antigen-presenting cells in the human body, playing a crucial role in activating innate immunity and inducing CTL-mediated adaptive immunity[54]. In their immature state, dendritic cells are widely distributed in the blood and peripheral tissues, where they collect antigens from pathogens or tumor cells. Upon antigen uptake, dendritic cells undergo phenotypic and functional maturation, migrate to secondary lymphoid tissues (e. g., lymph nodes), present processed antigens to T cells, activate CTLs, and initiate antigen-specific immune responses to eliminate target cells expressing the antigen. Additionally, mature dendritic cells enhance the cytotoxic activity of NK cells, which serve as innate immune effectors to destroy pathogen-infected or tumor cells. Dendritic cell vaccines represent an emerging form of cancer immunotherapy designed to recognize and attack tumor cells by activating the patient's immune system. Leveraging these properties, dendritic cell vaccines have shown promise as immunotherapies for various cancers, including HCC.

A phase II trial (NCT03067493) investigated a personalized neoantigen-loaded DC vaccine combined with neoantigen-activated T-cell therapy as adjuvant treatment for 10 HCC patients who had undergone curative resection or radiofrequency ablation. All patients successfully received the immunotherapy, with 70% generating new, circulating, polyclonal, neoantigen-specific T-cell responses. Responders exhibited longer disease-free survival compared to non-responders, suggesting that neoantigen-based combination immunotherapy is feasible, safe, and may reduce HCC recurrence after radical treatment [60].

8 Limitations of current immunotherapy approaches

Unique clinical characteristics can significantly influence the outcomes of immunotherapy in patients with HCC. A meta-analysis of three ICI-based treatment trials, encompassing data from 1 656 patients, revealed that those with viral-associated HCC experienced a markedly greater OS benefit compared to individuals with non-viral etiologies (*HR*=0.64, 95% *CI*=0.50−0.83 *vs.* *HR*=0.92, 95% *CI*=0.77−1.11, *P*=0.026). In contrast, this etiological disparity was not observed in a separate meta-analysis involving five trials that assessed TKIs or anti-VEGF therapies in 2 083 patients (*P*=0.88) [61]. The clinical application of ICIs, either alone or in combination, has ushered in a new era for systemic

therapy in advanced uHCC patients; however, only a minority of patients achieve an improved OS or PFS with ICIs.

First, patient enrollment criteria are often based on TNM staging or BCLC staging, liver functional reserve scores, and the intended treatment regimen. None of these criteria is predictive for response or resistance to PD-1/PD-L1-targeted therapies, with some patients experiencing rapid tumor progression[62]. Second, the emergence of immune-related AEs (irAEs) necessitates close monitoring for irAEs, occurring in 15%−90% of patients, commonly manifesting as rash, pruritus, diarrhea, hepatitis, or pneumonia, while rare but severe complications such as myocarditis or cardiac arrest can be life-threatening[19,63−64]. To mitigate these risks, clinicians must closely monitor for irAEs both during treatment and for at least one month following its conclusion.

9 Conclusion

Over the past decade, immunotherapy for HCC has advanced significantly, particularly with the development of ICIs alone and in combination therapies. These treatments have shown promise in enhancing patient outcomes. However, challenges persist in addressing patient stratification using biomarkers, drug resistance, managing toxicity, and providing individualized treatment strategies. Ongoing research is essential to overcome these obstacles. Advancements in precision medicine and the emergence of novel therapies are expected to improve liver cancer immunotherapy further, offering new hope for improving outcomes in HCC patients.

Conflict of interest: *The authors declare that they have no conflicts of interest to disclose.*

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