Research Status and Future Directions of PD-1/CTLA-4 Bispecific Antibodies in the Treatment of Advanced Hepatocellular Carcinoma

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Abstract. Hepatocellular carcinoma (HCC) ranks among the most prevalent malignant tumours globally. Due to its lack of pronounced early symptoms, most patients are diagnosed at an advanced stage, having lost the opportunity for timely treatment. Although immune checkpoint inhibitors, exemplified by PD-1/PD-L1 inhibitors, have achieved some progress in treating advanced HCC, they are prone to inducing drug resistance. Currently, popular combination therapies such as 'nivolumab plus ipilimumab' have demonstrated significant efficacy in clinical studies, yet they are accompanied by severe toxicity. PD-1/CTLA-4 bispecific antibodies can simultaneously target both immune checkpoints. By concurrently blocking the PD-1 and CTLA-4 pathways, they enhance T-cell activity, reshape the tumour immune microenvironment, improve efficacy, and reduce toxicity. This systematic review examines the mechanisms of action of PD-1/CTLA-4 bispecific antibodies in advanced HCC, outlines the latest clinical research progress represented by cadonimab, addresses challenges including dose optimization, resistance mechanisms, and managing heterogeneity, and explores future directions encompassing combination therapy strategies and personalized precision medicine.

Keywords: PD-1/CTLA-4, Bispecific Antibodies, Advanced Hepatocellular Carcinoma, Immunotherapy.

1. Introduction

Hepatocellular carcinoma (HCC), originating from liver cells, ranks among the world's most prevalent malignant tumours. As most patients exhibit no significant symptoms in the early stages, by the time severe discomfort arises, the disease has typically progressed to an advanced phase. This progression means most patients have already missed the optimal window for treatment upon diagnosis. Currently, immunotherapy for advanced HCC primarily relies on antibody drugs or small-molecule targeted therapies. However, the efficacy of targeted treatments remains limited, with median overall survival falling below one year. Patients inevitably face challenges such as drug resistance and slow treatment progression [1]. Consequently, developing more effective and durable therapeutic strategies represents a significant unmet medical need in the field of advanced HCC treatment.

In recent years, tumour immunotherapy, particularly immune checkpoint inhibitors (ICIs) targeting programmed cell death protein-1 (PD-1) and its ligand (PD-L1), has emerged as a therapeutic research focus for advanced hepatocellular carcinoma (HCC). The PD-1 pathway plays a pivotal role in the immunosuppressive tumour microenvironment (TME) of HCC. Tumour cells frequently evade immune surveillance by upregulating PD-L1 expression, which binds to PD-1 on T-cell surfaces. This interaction impairs immune responses by suppressing T-cell activity, proliferation, and cytokine secretion. Inhibitors of this pathway enhance TCR signaling, thereby reactivating T-cell function, lifting suppression, and re-igniting anti-tumour immune responses [2]. Based on studies such as KEYNOTE-224, PD-1 monoclonal antibodies have demonstrated favorable outcomes in patients with advanced HCC who have undergone prior treatments, leading to their approval for second-line therapy [3].

Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4) is another critical immune checkpoint molecule present on the cell surface. Its primary function is to suppress T cell activation within lymph nodes during the early stages of the immune response.

Research demonstrates that the inhibitory mechanisms of the PD-1 and CTLA-4 pathways are complementary and synergistic. The CheckMate-040 study indicated that in patients with advanced HCC previously treated with sorafenib, the combination therapy of nivolumab and ipilimumab (the 'O+Y' regimen) achieved an objective response rate (ORR) exceeding 30%, with a subset of patients demonstrating long-term survival [4]. Despite the significant efficacy demonstrated by the 'O+Y' combination therapy, its clinical application faces substantial challenges. These primarily stem from the incidence and severity of immune-related adverse events (irAEs) caused by synergistic toxicity. Although the combination regimen is effective, the currently prevalent protocol results in a high incidence (>40%) of severe adverse events such as hepatitis, colitis, and rash, alongside a high discontinuation rate (~28%). This represents a major clinical bottleneck for this treatment approach [5]. Such events frequently lead to treatment interruption or discontinuation, compromising patients' quality of life and therapeutic benefit, while also limiting its application in patients with poorer performance status, such as those with hepatic impairment [6]. Whilst adjusting the dosing ratio of the two monoclonal antibodies in combination therapy may mitigate adverse reactions, no standard regime with reliable efficacy and safety has yet been established. To enhance safety and optimise drug characteristics whilst maintaining synergistic efficacy, bispecific antibodies (BsAbs) have been developed.

PD-1/CTLA-4 bispecific antibodies, capable of simultaneously targeting PD-1 and CTLA-4, may offer a breakthrough in the treatment of advanced HCC. This paper aims to provide a systematic review of the current research landscape regarding PD-1/CTLA-4 bispecific antibody therapy for advanced HCC. It delves into their mechanisms of action, clinical efficacy, optimisation strategies, and existing challenges, while also outlining prospects for future development.

2. Mechanism of Action of PD-1/CTLA-4 Bispecific Antibodies and Their Characteristics in the HCC Tumor Microenvironment

PD-1 and CTLA-4 are both immune checkpoints on T cells, but they function at different stages through distinct mechanisms. The PD-1 pathway primarily acts during the effector phase of immune responses in peripheral tissues. The binding ofPD-L1 expressed on tumour cell membranes to PD-1 on T cell surfaces induces T cell exhaustion, resulting in the loss of cytotoxic activity and cytokine production capacity. In contrast, CTLA-4 primarily functions during the initial activation phase of immune responses within lymphoid organs. It mediates inhibitory signaling by competitively binding to B7 molecules on antigen-presenting cells, thereby inhibiting CD28 and suppressing the activation and clonal expansion of naïve T cells.

PD-1/CTLA-4 bispecific antibodies simultaneously bind to both targets and concurrently block both pathways, thereby overcoming resistance to single-pathway inhibition and activating a broader immune response. This approach not only promotes early T-cell activation and proliferation but also ensures their effector function within tumour tissue during later stages, achieving synergistic immune activation.

The tumour microenvironment of hepatocellular carcinoma exhibits a highly immunosuppressive character, marked by effector T-cell exhaustion, the enrichment of regulatory T cells and myeloid-derived suppressor cells, and the upregulation of inhibitory immune checkpoint molecules. Infiltration of immunosuppressive cells: Regulatory T cells accumulate within the TME. Myeloid-derived suppressor cells produce immunosuppressive cytokines that inhibit T cell activity and promote Treg expansion. Tumour-associated macrophages secrete immunosuppressive cytokines such as IL-10 and TGF-β, contributing to the immunosuppressive environment. Inhibitory checkpoint molecules, including PD-1 and CTLA-4, are upregulated [7].

Within the specific TME of HCC, the PD-1/CTLA-4 bispecific antibody remodels the immune landscape through multiple mechanisms. It can reverse the exhausting state of T cells. The strong co-stimulatory signals provided by dual blockade, coupled with the removal of inhibitory signals, act synergistically. The anti-PD-1 component primarily expands exhausted-like CD8+ T cells, while the anti-CTLA-4 component induces the expansion of ICOS+ Th1-like CD4+ T cells. These exhausted T cells retain proliferative capacity, and certain subsets exhibit a precursor exhausted T cell phenotype, which subsequent studies have identified as stem-like precursor T cells possessing enhanced proliferative potential and sustained cytotoxic capability [8]. The bispecific antibody effectively modulates immunosuppressive cell populations. CTLA-4 signaling is critical for the suppressive function of regulatory T cells (Tregs). Blocking CTLA-4 directly inhibits Treg function and may reduce their infiltration within the tumor microenvironment (TME), thereby alleviating their suppression of effector T cells.

Furthermore, the bispecific antibody exerts a "bridging" effect—simultaneously binding to PD-1-expressing T cells and CTLA-4-expressing cells. Compared to combination therapy, this approach more efficiently reverses T cell inhibition and/or more effectively delivers activating signals. It also enables the localized enrichment of specific functional molecules around target cells [9].

Compared to normal tissues and peripheral blood cells, tumor-infiltrating lymphocytes (TILs) exhibit significantly higher co-expression levels of both PD-1 and CTLA-4. Consequently, the anti-PD-1/CTLA-4 bispecific antibody demonstrates superior enrichment in tumor tissue over normal tissues, which is expected to enhance both efficacy and safety. Furthermore, studies have shown that cadonilimab, a PD-1/CTLA-4 bispecific antibody, possesses higher binding affinity in environments with high PD-1 and CTLA-4 density compared to environments with low PD-1 density. This characteristic may confer higher antibody activity within the PD-1-high tumor microenvironment while resulting in lower binding activity in normal tissues, thereby potentially contributing to a reduced toxicity profile for PD-1/CTLA-4 bispecific antibodies [10].

Compared to the combination therapy of nivolumab and ipilimumab, BsAbs exhibit fundamental mechanistic differences. The combination therapy involves the additive effect of two independent antibody molecules, whereas a BsAb is a single molecular entity with optimized pharmacokinetic properties, ensuring stable synergy of both targeting arms at the site of action. Its "bridging" and enrichment effects may favor localized action within the tumor, leading to higher effective drug concentrations in the TME and enabling precise immune activation while reducing non-specific immune activation in peripheral normal tissues. In contrast, combination therapy is more prone to inducing systemic, nonspecific immune overactivation. Preclinical studies have confirmed that cadonilimab demonstrates promising tumor response rates and a manageable safety profile, indicating significant potential in treating advanced solid tumors [11].

3. Clinical Research Progress

Multiple clinical trials have been conducted for PD-1/CTLA-4 bispecific antibodies, and their application in the field of advanced hepatocellular carcinoma has been studied to a certain extent.

Currently, the most rapidly advancing candidate in clinical development is Cadonilimab (AK104). It is a humanized bispecific antibody designed to simultaneously target PD-1 and CTLA-4. It incorporates an Fc-null design to eliminate Fc-mediated effector functions such as antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and antibody-dependent cytokine release (ADCR), thereby enhancing its safety profile in cancer treatment. Compared to low-density expression of a single antigen, Cadonilimab exhibits higher binding affinity in environments with high co-expression density of both PD-1 and CTLA-4. This characteristic promotes the retention of Cadonilimab within the tumor microenvironment compared to peripheral tissues [12].

A pivotal Phase II clinical trial (NCT03852251) conducted in Chinese patients with advanced solid tumors demonstrated the therapeutic potential of this drug. The study enrolled patients with advanced

HCC who had failed prior standard therapies. Results showed that cadonilimab achieved an objective response rate (ORR) of 16.7% (4 out of 24 patients; 95% CI 4.7–37.4) and a disease control rate (DCR) of 62.5% [13]. A pivotal Phase II clinical trial (NCT03852251) conducted in Chinese patients with advanced solid tumors demonstrated the therapeutic potential of this drug. The study enrolled patients with advanced HCC who had failed prior standard therapies. Results showed that cadonilimab achieved an objective response rate (ORR) of 16.7% (4 out of 24 patients; 95% CI 4.7–37.4) and a disease control rate (DCR) of 62.5%.

These data compare with previous drug therapies: PD-1 Monotherapy (Pembrolizumab): In the KEYNOTE-224 trial for second-line treatment, the ORR was 18.3%, and the disease control rate (DCR) was 61.5% [14]. "O+Y" Combination Therapy: In the CheckMate 9DW study, the ORR was 36% (121 out of 334 patients; 95% CI 31–42) [15]. This demonstrates that cadonilimab, as a monotherapy, remains effective even in the most challenging patient population who have failed prior frontline treatments. This provides proof-of-concept for its further development and has driven subsequent exploration into first-line combination therapies, such as cadonilimab plus lenvatinib.

Regarding safety, cadonilimab also demonstrates a relatively clear advantage. The incidence of grade ≥3 treatment-related adverse events (TRAEs) was 28%. Although patients still require close monitoring after administration, this figure is lower than the approximately 40% incidence of grade ≥3 TRAEs associated with the "O+Y" combination therapy. The incidence of specific irAEs, such as severe colitis and pneumonitis, also shows a decreasing trend.

4. Challenges and Future Directions for Optimization

Although PD-1/CTLA-4 bispecific antibodies have demonstrated promising efficacy and an improved safety profile in clinical trials for advanced HCC, several challenges remain in translating these findings from clinical research to widespread application.

Firstly, the dual-specificity antibody's characteristic of ‘enhancing efficacy while reducing toxicity’ offers insights for treatment optimisation, though no unified standard currently exists. As a single molecular entity, the optimal biological dose (OBD) for a dual-specificity antibody may not correspond to its maximum tolerated dose (MTD). Like exploring different dose combinations in combination therapies to balance efficacy and toxicity, determining its optimal dose requires testing across diverse patient populations. For instance, in cadonimab studies, 6mg/kg Q2W was established as the recommended dose, subsequently demonstrating favorable benefit-risk profiles. Dose optimisation can maximise safety without compromising efficacy. Future research must integrate PK/PD modelling to more clearly define optimal doses and dosing frequencies across distinct patient subgroups.

Secondly, drug resistance remains a challenge for all targeted and immunotherapies. The mechanisms of resistance to PD-1/CTLA-4 bispecific antibodies may inherit those observed with prove, even more complex. These primarily include: (1) Intrinsic tumour mechanisms, such as defects in antigen presentation pathways or mutations in the IFN-γ signalling pathway, rendering tumour cells ‘invisible’ or ‘insensitive’ to T-cell attack; (2) Tumour microenvironment-related mechanisms, including compensatory upregulation of other inhibitory checkpoints such as TIGIT and LAG-3, enrichment of immunosuppressive cells like Tregs and MDSCs, and metabolic dysregulation. Even with more potent dual blockade, these mechanisms may lead to ineffective activation or maintenance of the anti-tumour immune response. Theoretically, due to their enhanced T-cell activation and TME remodeling capabilities, bispecific antibodies may reverse certain forms of monotherapy resistance induced by inhibitory TME factors, such as high Treg infiltration. Beyond these common mechanisms, the unique structure and mode of action of bispecific antibodies may generate novel resistance pathways, such as failure of the ‘bridging’ effect due to downregulation of target expression. Further follow-up studies are therefore warranted.

In future treatment and research, the high heterogeneity of HCC, encompassing multiple molecular subtypes, must be considered. The performance of bispecific antibodies across different patient populations is key to assessing their clinical utility.

Hepatitis B virus-associated hepatocellular carcinoma: HBV infection rates reach as high as 75.09% among Chinese patients with primary liver cancer. HBV establishes a persistent immune tolerance environment. Bispecific antibodies may reshape this immune landscape by potently activating T cells and depleting regulatory T cells, thereby more effectively disrupting this virus-induced immune tolerance and exerting robust antitumor effects.

Non-viral (NASH/metabolism-related) HCC: Unlike viral HCC, NASH-related HCC often presents an immune-excluded or immune-desert tumor microenvironment, characterized by scarce T cell infiltration. Therapeutic PD-1 immunotherapy expands into intratumoral activated CD8+ PD-1+ T cells but does not lead to tumor regression. Non-viral HCC, particularly NASH-HCC, may respond poorly to immunotherapy, potentially due to aberrant T cell activation associated with NASH leading to tissue damage and consequently impaired immune surveillance [16]. The "O+Y combination therapy" is used as a second-line treatment after failure of first-line therapy [17]. While there are currently no specific studies on PD-1/CTLA-4 bispecific antibodies for this context, bispecific antibody therapy may emerge as a superior alternative to address the toxicity issues associated with combination therapy.

Building on the outstanding results from second-line monotherapy trials, the clinical exploration of PD-1/CTLA-4 bispecific antibodies is rapidly advancing.

The current standard first-line treatment regimen for advanced HCC is the combination therapy of ‘anti-PD-1/L1 monoclonal antibodies + anti-angiogenic agents (TKIs or bevacizumab).’ Combining bispecific antibodies with drugs possessing other mechanisms of action is also a key area of current research. For instance, investigations are underway into its combination with anti-angiogenic agents, such as Lenvatinib—a drug that not only inhibits tumor blood supply but also improves the immune microenvironment by promoting vascular normalization and reducing myeloid-derived suppressor cells. Theoretically, this approach could synergise with the potent immune activation induced by bispecific antibodies.

Given the issues, a clear future development direction could be establishing combination therapy pathways based on bispecific antibodies. For instance, combination with multi-targeted TKIs: Clinical trials of cadonimab combined with Lenvatinib as first-line therapy for advanced HCC demonstrated an ORR of 35.6%. This combination leverages the anti-angiogenic effects of the TME alongside immune activation induced by bispecific antibodies. Integration with local therapies: Combining bispecific antibodies with local treatments such as trans arterial chemoembolization, hyperthermic intra-arterial chemotherapy, or radiotherapy. Local therapies can induce immunogenic cell death and release tumour antigens, synergizing with bispecific antibodies to trigger systemic antitumor immune responses; Advancements in personalized medicine: Developing tailored treatment strategies based on each patient's tumour genomic profile and immune microenvironment subtype.

5. Conclusion

PD-1/CTLA-4 bispecific antibodies, as innovative engineered molecules, represent a significant direction for advancement in immunotherapy.

Current research indicates that this bispecific antibody, through its unique synergistic mechanism of simultaneously blocking the PD-1 and CTLA-4 pathways operating at different stages of the immune response, not only effectively reverses T-cell exhaustion and promotes their activation also remodels the tumour microenvironment by modulating immunosuppressive cells. Due to its molecular design advantages, it theoretically offers superior safety compared to combination therapies such as ‘O+Y’ without compromising efficacy.

PD-1/CTLA-4 bispecific antibodies remain under clinical investigation, with formulations such as cadunimab having preliminarily validated the broad potential of this therapeutic approach. Clinical trial data that their combination with anti-angiogenic agents like Lenvatinib also reveals favorable efficacy, indicating substantial therapeutic promise. Concurrently, a reduction in treatment-related adverse events has been observed, further improving clinical patient management. Nevertheless, the transition from proof-of-concept to widespread clinical application remains fraught with multiple challenges. Key among these is determining optimal administration strategies for bispecific antibodies, elucidating mechanisms of resistance, and developing differentiated therapeutic approaches to address the high heterogeneity of HCC.

In conclusion, PD-1/CTLA-4 bispecific antibodies hold promise as a pivotal step in overcoming the therapeutic challenges of advanced hepatocellular carcinoma. Future research efforts should focus on combination therapies and precision medicine to address existing obstacles, ultimately delivering more effective and safer novel treatment options for patients with advanced hepatocellular carcinoma.

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