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# Research Progress and Clinical Translation of Combined Targeted Therapy and Immunotherapy for Liver Cancer

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**Abstract:** Primary liver cancer is a highly prevalent malignant tumor worldwide, with hepatocellular carcinoma (HCC) being characterized by insidious onset and rapid progression. Most patients are diagnosed at advanced stages, losing the opportunity for radical surgery, making systemic therapy the core approach to prolong survival and improve quality of life. Historically, molecular targeted therapy has been the mainstay of systemic treatment for advanced liver cancer, offering some control over tumor progression but with limitations such as low objective response rates, frequent drug resistance, and limited survival benefits. The advent of immune checkpoint inhibitors has revolutionized the landscape of systemic liver cancer therapy, providing hope for long-term survival in advanced patients through their unique mechanism of reshaping the tumor immune microenvironment and activating endogenous anti-tumor immunity. However, monotherapy with immune checkpoint inhibitors is effective only in a minority of immunologically favorable patients, limiting overall benefit. In recent years, the combination of targeted therapy and immunotherapy (targeted-immunotherapy combination) has broken through the efficacy bottleneck of monotherapy through synergistic anti-tumor effects, becoming the standard first-line treatment for advanced liver cancer. This article provides a comprehensive review of the mechanisms of action, core clinical research progress, and optimization strategies for clinical translation of targeted-immunotherapy combination therapy in liver cancer, aiming to provide references for clinical practice and future research in this field.

**Keywords:** Hepatocellular carcinoma; Targeted therapy; Immunotherapy; Combination regimen; Clinical translation

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## 1. Introduction

Liver cancer is a highly prevalent malignant tumor in China, ranking among the top in terms of incidence and mortality, imposing a significant disease burden [1]. Its pathogenesis is directly associated with various factors such as chronic hepatitis virus infection, cirrhosis, long-term alcohol consumption, and metabolic-associated fatty liver

disease. The tumor microenvironment of liver cancer is highly immunosuppressive, characterized by low immune cell infiltration, high expression of immune checkpoints, and disordered angiogenesis, which are key reasons for its insensitivity to traditional chemotherapy and limited efficacy of single-agent immunotherapy [2]. Commonly used systemic therapies in clinical practice include molecular targeted drugs, which target specific molecules to disrupt tumor growth and spread, with representatives such as sorafenib and lenvatinib [3]; and immunotherapy, primarily immune checkpoint inhibitors like PD-1/PD-L1 inhibitors, which relieve immunosuppression and activate T-cell-mediated tumor killing, with common drugs including camrelizumab and sintilimab [4]. However, single-agent therapies have significant limitations: targeted drugs struggle to completely eradicate cancer cells and are prone to drug resistance with long-term use; immunotherapy has limited efficacy in patients with strong immunosuppression and high tumor burden. The targeted-immunotherapy combination can form synergistic effects, with targeted drugs improving the immune microenvironment and enhancing sensitivity to immunotherapy, while immunotherapy enhances the efficacy of targeted drugs and reverses drug resistance [5]. Currently, the targeted-immunotherapy combination has become the preferred first-line systemic treatment for advanced liver cancer, recommended by multiple domestic and international guidelines, with ongoing optimization research. This article provides a systematic review of this topic.

## 2. Mechanisms of action

### 2.1. Remodeling of the tumor immune microenvironment by targeted drugs

Liver cancer is a vascular-rich tumor, with abnormal angiogenesis being a core biological feature. The VEGF/VEGFR pathway is a key regulator of tumor angiogenesis and a core target of targeted therapy [6]. Anti-angiogenic targeted drugs can normalize abnormal tumor vasculature by inhibiting angiogenesis, improving tumor tissue hypoxia, and reducing the immunosuppressive microenvironment. Specifically, vascular normalization increases the infiltration of anti-tumor immune cells such as effector T cells and dendritic cells in tumor tissue, reduces the aggregation of immunosuppressive cells such as regulatory T cells (Tregs) and tumor-associated macrophages (M2 type), and decreases the expression of immune checkpoints like PD-L1 and CTLA-4, relieving immunosuppression and laying the foundation for the efficacy of immune checkpoint inhibitors [7]. Additionally, multi-target tyrosine kinase inhibitors (TKIs), besides their anti-angiogenic effects, can directly inhibit proliferation signaling pathways within tumor cells, induce tumor cell apoptosis, release tumor-associated antigens, and activate specific anti-tumor immune responses in the body, forming "immunogenic cell death" and further enhancing the efficacy of immunotherapy. Meanwhile, some targeted drugs can inhibit the secretion of immunosuppressive cytokines such as interleukin-6 (IL-6) and transforming growth factor-β (TGF-β), further improving the immunosuppressive microenvironment and enhancing the killing activity of immune cells.

### 2.2. Synergistic and drug resistance-reversing effects of immunotherapy on targeted therapy

Immune checkpoint inhibitors can activate long-lasting anti-tumor immune memory in the body, allowing immune cells to continue exerting anti-tumor effects even after discontinuation of targeted drugs, delaying tumor progression, and prolonging the duration of response [8]. Clinical studies have confirmed that the duration of response in targeted-immunotherapy combination therapy is significantly longer than that in single-

agent targeted therapy, closely related to the formation of immune memory [9]. Meanwhile, one of the core mechanisms of resistance to targeted therapy is the further deterioration of the tumor immune microenvironment and enhanced tumor cell immune escape. Immunotherapy can reverse tumor cell resistance to targeted drugs by reshaping the immune microenvironment, restoring sensitivity to targeted drugs, and overcoming the drug resistance bottleneck of single-agent targeted therapy [10].

### 2.3. Synergistic anti-tumor network of combination therapy

The targeted-immunotherapy combination forms a triple synergistic network of "anti-angiogenesis + immune activation + direct anti-tumor effects": anti-angiogenic targeted drugs remodel tumor vasculature and the immune microenvironment, opening pathways for immune cell infiltration [11]; immune checkpoint inhibitors activate effector T cells to precisely kill tumor cells [12]; their synergistic effects significantly improve the objective response rate of tumors, reduce tumor burden, while decreasing the dosage of single drugs, lowering the incidence of adverse reactions, and enhancing patient treatment tolerance. This synergistic mechanism provides a solid theoretical foundation for the clinical application of targeted-immunotherapy combination therapy and promotes the clinical development and translation of various combination regimens.

## 3. Clinical Research Progress

### 3.1. First-line treatment: Establishing the standard status of targeted-immunotherapy combination

In recent years, multiple clinical studies have successively established the core position of targeted-immunotherapy combination in the first-line treatment of advanced liver cancer. Different combination regimens have demonstrated varying efficacy and safety profiles, providing evidence-based support for individualized clinical selection.

The study by Bi Jingpeng [13] and colleagues confirmed that the targeted-immunotherapy combination outperformed single-agent targeted therapy. This study compared the efficacy of pembrolizumab combined with bevacizumab versus bevacizumab alone in treating advanced metastatic hepatocellular carcinoma (HCC). The results showed that the combination group had significantly lower tumor markers AFP and CA125 compared to the control group, with higher levels of CD3+ T cells and CD4+ T cells among T lymphocyte subsets. Additionally, the overall survival (OS) and progression-free survival (PFS) times were significantly prolonged in the combination group. This confirmed the significant clinical efficacy of pembrolizumab combined with bevacizumab in treating advanced metastatic liver cancer, helping to reduce tumor markers, restore T lymphocyte subsets, improve immune function, and prolong survival, with good safety.

Su Zhan [14] and colleagues compared the effects of sintilimab combined with bevacizumab versus sorafenib in treating advanced HCC. The results showed that the median PFS and OS in the monoclonal antibody group were significantly higher than those in the sorafenib group ($P < 0.05$). The objective response rate (ORR) in the monoclonal antibody group was also significantly higher than that in the sorafenib group ($P < 0.05$), with good safety, making it more suitable for clinical practice in China.

Chen Fengsui [15] compared the efficacy of tislelizumab combined with lenvatinib versus lenvatinib alone in treating advanced HCC. The results showed that the ORR in the combination group was 63.33%, higher than the 30.00% in the single-agent group. Moreover, the reduction in PIVKA-Ⅱ, AFP, ALT, AST levels, as well as

neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), was greater in the combination group than in the single-agent group. This confirmed that the combination therapy significantly improved the ORR in patients with advanced HCC, effectively reduced tumor marker levels, NLR, PLR, and liver function indicators, with relatively high safety.

## 3.2. Second-line treatment exploration: Breaking through the resistance dilemma of first-line treatment

For patients with advanced liver cancer who fail first-line targeted-immunotherapy combination treatment, second-line treatment options are extremely limited, posing a significant clinical challenge. Currently, second-line targeted-immunotherapy combination treatment mainly involves switching targeted drugs and combining them with immune checkpoint inhibitors targeting different pathways. Some studies have explored the combination of targeted therapy with dual immunotherapy or targeted therapy combined with immunotherapy and local treatment [16].

Multiple Phase II clinical studies have shown that for patients who develop resistance to first-line anti-angiogenic targeted drugs combined with PD-1 inhibitors, switching to novel targeted drugs such as FGFR inhibitors or MET inhibitors combined with PD-L1 inhibitors can yield certain clinical benefits [17]. The dual-function combination antibody, ipilimumab and toripalimab, developed in China, demonstrated excellent efficacy in the Phase II DUBHE-H-308 study for first-line treatment of advanced HCC, with a median PFS of 13.1 months, an ORR of 40.0%, and a disease control rate (DCR) of up to 90.0%. Its application in second-line treatment is also being explored, with the potential to break through the resistance dilemma [18]. Additionally, the triple combination of targeted therapy, chemotherapy, and immunotherapy has shown potential in second-line treatment, further improving disease control rates and prolonging patient survival [19].

## 3.3. Perioperative application: expanding the boundaries of curative treatment for liver cancer

In addition to systemic treatment for advanced liver cancer, targeted-immunotherapy combination treatment has also demonstrated significant value in perioperative treatment for resectable liver cancer and conversion therapy for unresectable liver cancer, becoming an important means to improve curative rates and reduce recurrence rates [20]. For patients with resectable liver cancer at high risk of recurrence, preoperative neoadjuvant targeted-immunotherapy combination treatment can shrink tumor volume, reduce tumor stage, clear micrometastases, and enhance surgical curability [21]. Postoperative adjuvant targeted-immunotherapy combination treatment can inhibit tumor recurrence and metastasis, prolonging recurrence-free survival (RFS).

Studies have confirmed that the “A+T regimen” (apatinib combined with toripalimab) used in perioperative treatment for HCC at high risk of recurrence, employing a “neoadjuvant + surgery + adjuvant” sandwich approach, significantly prolonged disease-free survival (DFS) and reduced recurrence risk compared to surgery alone, with the median RFS doubling. This provides high-level evidence-based support for perioperative treatment of resectable liver cancer [22]. For unresectable locally advanced liver cancer, targeted immunotherapy combined with local treatments such as transarterial chemoembolization (TACE) can achieve tumor downstaging, enabling some patients to undergo curative surgery. Studies such as LEAP-012 have confirmed that TACE combined with targeted-immunotherapy significantly improves conversion success rates and prolongs patient survival, reshaping the treatment landscape for unresectable liver cancer [23].

## 4. Optimization strategies

### 4.1. Identifying precise predictive biomarkers for individualized stratified treatment

In the future, it is necessary to rely on multi-omics technologies to integrate genomic, transcriptomic, proteomic, immune, and gut microbiome data to identify predictive biomarkers with high specificity and strong predictive value. For example, exploring the correlation between VEGFR expression levels, immune cell infiltration profiles, serum cytokine profiles, gut microbiome abundance, and the efficacy of targeted-immunotherapy combination treatment to construct a multidimensional predictive model. This will enable precise stratification of patients, screening of advantageous populations, and avoidance of ineffective treatments. Simultaneously, conducting biomarker-guided clinical studies to validate the clinical value of these biomarkers and promote their translation from basic research to clinical practice.

### 4.2. Standardizing adverse reaction management to improve treatment safety

Develop unified guidelines and consensus on adverse reaction management for targeted-immunotherapy combination treatment in liver cancer, clarifying the identification, grading, and treatment protocols for various adverse reactions. Strengthen training for primary care clinicians to improve their ability for early diagnosis and treatment [24]. Comprehensively evaluate patients' underlying diseases, liver function, and immune function before treatment to screen for high-risk populations for adverse reactions. Closely monitor vital signs and laboratory indicators during treatment, promptly intervene in mild adverse reactions to prevent progression to severe ones, and conduct long-term follow-up after treatment to ensure patient safety. Simultaneously, optimize drug dosages and administration regimens, exploring low-dose combinations and intermittent administration to reduce the incidence of adverse reactions while ensuring efficacy.

### 4.3. Deepening exploration of resistance mechanisms and developing novel combination regimens

Focus on the resistance mechanisms of targeted-immunotherapy combination treatment, conducting basic and translational research to identify key resistance targets and develop novel targeted drugs, bispecific antibodies, and immunomodulators [25]. Explore novel combination models, such as targeted therapy combined with dual immunotherapy, targeted therapy combined with immunotherapy and local treatment, targeted therapy combined with immunotherapy and oncolytic virus therapy, and targeted therapy combined with immunotherapy and gut microbiome modulation, to break through the resistance bottleneck. Simultaneously, conduct dynamic biopsy studies to monitor changes in the tumor microenvironment and gene expression during treatment, adjusting treatment plans in a timely manner to achieve individualized precision treatment.

## 5. Conclusion

The combination of targeted therapy and immunotherapy for liver cancer has revolutionized the systemic treatment landscape for advanced liver cancer through its synergistic anti-tumor mechanisms. From first-line treatment for advanced stages to perioperative treatment and conversion therapy, it has demonstrated excellent clinical efficacy, becoming the core direction for individualized and precision treatment of liver cancer. In

the future, targeted-immunotherapy combination treatment for liver cancer will move towards precision, individualization, and diversification. Relying on multi-omics technologies to achieve precise screening of advantageous populations, novel combination regimens continuously breaking through the resistance bottleneck, and comprehensive models combining local and systemic treatments further improving efficacy, while drug accessibility continues to improve, benefiting more liver cancer patients.

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