

Advancing Adjuvant Immunotherapy in Hepatocellular Carcinoma: A Comprehensive Review

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Abstract: Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality globally, with high rates of recurrence even after curative-intent treatments such as hepatectomy and liver transplantation (LT). In recent years, immune checkpoint inhibitors (ICIs) have transformed the therapeutic landscape for HCC, demonstrating significant efficacy among advanced-stage tumors through combination regimens, such as anti-programmed cell death ligand-1 (PD-L1)/PD-1 inhibitors with anti-vascular endothelial growth factor agents. Recent advances have highlighted the potential of ICIs as adjuvant therapy to improve recurrence-free survival among high-risk patients post-resection. However, challenges such as low immunogenicity, the immunosuppressive tumor microenvironment, and immune resistance remain substantial barriers to the broader success of ICIs. In the context of LT, the use of ICIs is further complicated by the concurrent need for immunosuppressive agents, which can exacerbate the risk of recurrence. Emerging strategies focusing on the optimization of the timing of ICI therapy and the utilization of novel biomarkers are being explored to mitigate graft rejection while maintaining antitumor efficacy. Additionally, immune-cell-based therapies based on chimeric antigen receptor-T and natural killer (NK) cells, adoptive cell transfer, and liver-resident NK cell approaches are also being investigated for their potential to reduce recurrence and improve survival outcomes. This review focuses on the current landscape of adjuvant immunotherapy and immune-cell therapy in the postoperative management of HCC, highlighting ongoing clinical trials, therapeutic potential, and associated risks. With continued advancements in immunotherapeutic strategies and personalized approaches, these therapies hold the promise of transforming outcomes for patients undergoing curative resection or LT.

Keywords: hepatocellular carcinoma, hepatectomy, liver transplantation, immune checkpoint inhibitors, adjuvant immunotherapy, immune-cell therapy

Introduction

Hepatocellular carcinoma (HCC) is one of the fastest-growing causes of cancer-related mortality worldwide.^{1,2} Curative treatments such as hepatectomy and liver transplantation (LT) are viable options for patients in the early stages of the disease. However, approximately 50–60% of patients with HCC eventually require systemic therapy due to disease progression.³ Radical surgical resection is not a feasible option for many patients with advanced HCC, thus leaving systemic therapies as first-line treatment. Despite achieving a median overall survival (OS) of 11–14 months,^{3–5} these therapies often fail to effectively control tumor progression or prevent recurrence. Recent advancements in immunoncology have introduced immune checkpoint inhibitors (ICIs), which have transformed the management of many malignancies, including HCC.^{6–8} Remarkable efficacy has been demonstrated by combination regimens, such as anti-programmed cell death ligand-1 (PD-L1) or PD-1 inhibitors with anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) monoclonal antibodies and anti-vascular endothelial growth factor (VEGF) agents like bevacizumab. This approach has extended median survival to approximately 19 months in some cases, offering new hope to patients with advanced HCC.^{9–12} Clinical trials have consistently demonstrated the superior efficacy of combination ICI therapies compared to

tyrosine kinase inhibitors alone.¹³ In HCC management, neoadjuvant downstaging therapies, including immunotherapy, have shown potential in converting previously unresectable diseases into resectable. Similarly, the use of ICIs as bridging therapy during LT waitlisting has been proposed to reduce waitlist mortality. Moreover, adjuvant immunotherapy has been gaining recognition for its potential to prevent both postoperative recurrence and de novo malignancies following resection or LT. Clinical trials investigating neoadjuvant and adjuvant immunotherapies for HCC have been reporting encouraging outcomes. Of note, the IMbrave050 trial initially suggested that adjuvant therapy with atezolizumab and bevacizumab might improve recurrence-free survival (RFS) over active surveillance among patients at high risk of HCC recurrence.^{14,15} However, updated data presented at ESMO 2024 showed that this difference in RFS was not statistically significant, prompting a re-evaluation of the clinical utility of this regimen in the adjuvant setting. These findings underscore the need for further studies to identify which patient subsets may benefit most from adjuvant immunotherapy.^{14,15} In this context, a recent study published in *Nature Communications*¹⁶ demonstrated that perioperative administration of immunotherapy—specifically combining neoadjuvant and adjuvant approaches—can significantly enhance anti-tumor immune responses in early-stage HCC, further supporting the rationale for immunotherapy in the curative setting.

Importantly, the prevalence and incidence of HCC vary significantly according to the etiology of chronic liver disease. Viral hepatitis B and C are the most common underlying causes of HCC, particularly in cirrhotic livers, whereas autoimmune liver diseases such as autoimmune hepatitis and primary biliary cholangitis are associated with a much lower incidence of HCC, even in the presence of cirrhosis.¹⁷ This epidemiological distinction underscores the relevance of immune microenvironment differences and may impact response to immunotherapy.¹⁷

Despite the progress, several challenges limit the efficacy of ICIs in the management of HCC. The response rate to ICI monotherapy is under 20%, primarily due to the complex immunosuppressive tumor microenvironment (TME) and the heterogeneous pathogenesis of HCC.¹⁸ Although combination therapies have demonstrated better response rates of 30–36%, the development of immune resistance is common and presents a significant hurdle.^{19,20} Factors contributing to resistance include impaired antigen presentation, abnormal activation of immunosuppressive cells, and dysfunctional anti-tumor immune cells within the TME.²⁰ Moreover, tumor heterogeneity, lack of tumor antigen expression, and gut microbiota dysregulation further exacerbate immune resistance.²⁰ Importantly, ICIs carry a risk of severe immune-related adverse events (irAEs) leading to life-threatening complications in up to 10% of patients.²¹ This concern is particularly relevant among LT recipients, since the use of immunosuppressive agents is required to prevent graft rejection, but simultaneously increases susceptibility to infections, tumor recurrence, and de novo malignancies.^{22–24} Even though ICIs are largely excluded from clinical trials involving immunocompromised or transplanted patients due to concerns about graft rejection, emerging reports have started to explore their feasibility and safety in pre- and post-LT settings; however, evidence remains sparse and controversial.

Beyond ICIs, alternative immunotherapies, including T-cell and natural killer (NK) cell therapies, have also been under investigation. These therapies aim to enhance anti-tumor immunity, potentially reducing postoperative recurrence and preventing de novo malignancies.²⁵ If proven safe and effective, these strategies could significantly improve outcomes for patients with HCC undergoing resection or LT. This review focuses on the current landscape of adjuvant immunotherapy and immuno-cell therapy during the postoperative management of HCC, highlighting ongoing clinical trials, therapeutic potential, and associated risks (Figure 1).

Overview of Immunotherapy for HCC

Cancer immunosurveillance is a complex and dynamic process wherein malignant cells are detected and eliminated through the coordinated activity of innate and adaptive immune responses. This process is profoundly influenced by the TME, which plays a pivotal role in shaping immune interactions. In the liver, the immunological landscape is predominantly characterized by immunosuppressive cells and signals, creating a tolerogenic microenvironment that facilitates immune evasion.^{26,27} Key cellular players moderating immune suppression within the TME of HCC include regulatory T cells (Tregs), Kupffer cells (liver-resident macrophages), monocyte-derived macrophages, and myeloid-derived suppressor cells (MDSCs).²⁶ These cells collectively impair effective antitumor immunity by suppressing innate and adaptive immune responses. Dysfunctional dendritic cells and regulatory B cells further contribute to this immunosuppressive milieu, impeding robust immune activation.^{28,29}

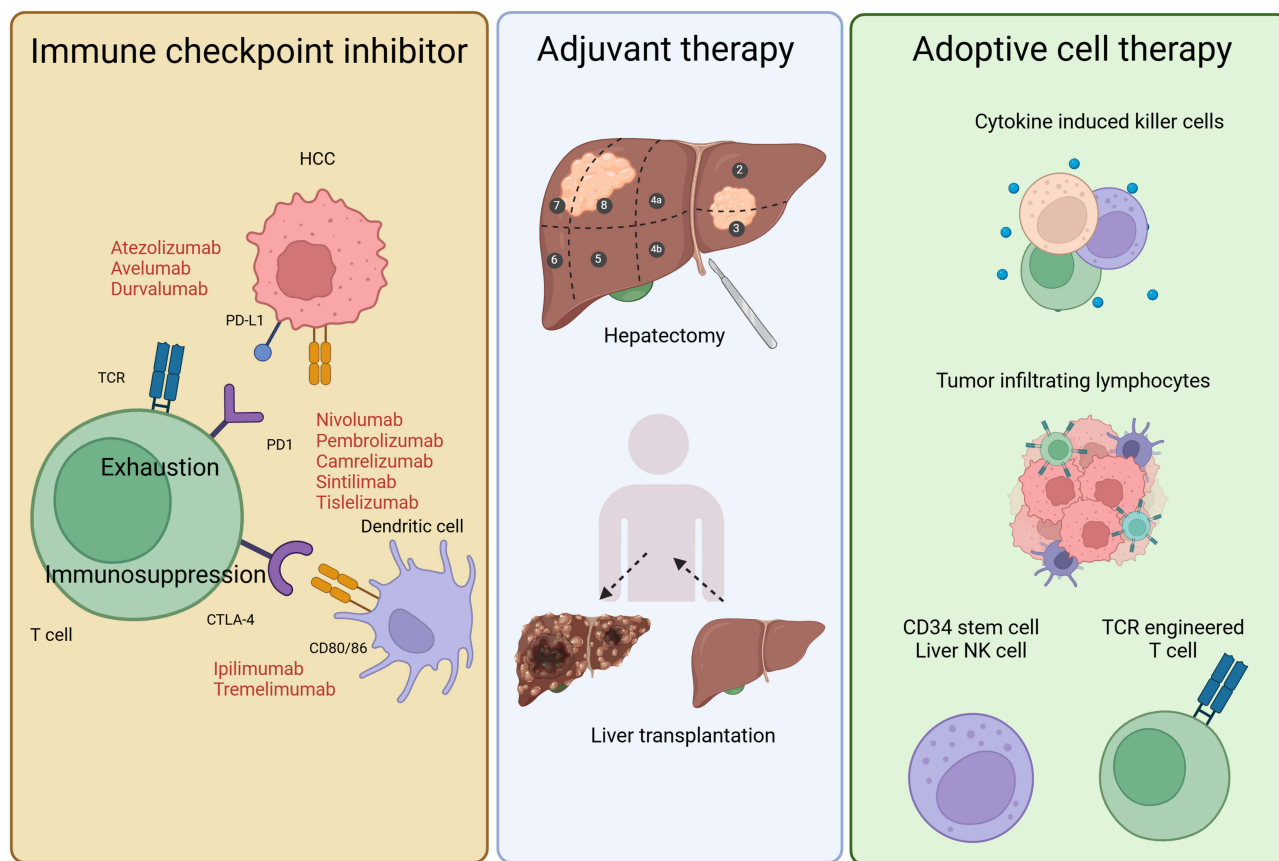


Figure 1 Schematic overview of adjuvant immunotherapy and adoptive immune-cell therapy in the postoperative management of hepatocellular carcinoma (HCC). This illustration summarizes the major immunotherapeutic strategies following hepatectomy or liver transplantation for HCC. Left panel (Immune checkpoint inhibitors): Immune checkpoint blockade restores T cell antitumor function by targeting PD-1/PD-L1 and CTLA-4 pathways. Agents shown include PD-1 inhibitors (nivolumab, pembrolizumab, camrelizumab, sintilimab, tislelizumab), PD-L1 inhibitors (atezolizumab, avelumab, durvalumab), and CTLA-4 inhibitors (ipilimumab, tremelimumab). These therapies aim to overcome T cell exhaustion and immunosuppression within the tumor microenvironment. Middle panel (Adjuvant therapy): Curative treatments such as hepatic resection and liver transplantation are represented. Adjuvant immunotherapies, including ICI, are being explored to reduce recurrence after these interventions. Right panel (Adoptive cell therapy): Various immune-cell-based strategies are depicted, including cytokine-induced killer cells, tumor-infiltrating lymphocytes, CD34 stem cell-derived liver NK cells, and genetically engineered TCR T cells. These approaches aim to enhance antitumor immunity and prevent recurrence following surgery or transplantation.

Tumor-associated macrophages (TAMs), which comprise a significant portion of macrophages in the HCC TME, are central to immune evasion and tumor progression. These cells exert their effects through multiple mechanisms, including the secretion of immunosuppressive cytokines, expression of PD-L1, recruitment of Tregs and Th17 cells, promotion of angiogenesis, and downregulation of pro-inflammatory cytokines.³⁰ High TAM density has been correlated with poor prognosis among patients with HCC.³¹ Neutrophils also play a role in tumor progression, likely by fostering an immunosuppressive environment, enhancing tumor cell survival, remodeling the extracellular matrix, and promoting angiogenesis.³² Additionally, the liver harbors a significant population of MDSCs producing factors that inhibit T-cell activation. Patients with HCC often exhibit elevated levels of circulating MDSCs and Tregs compared to healthy individuals, further contributing to systemic immune suppression.³³ Regulatory dendritic cells, through the production of IL-10, exacerbate this immunosuppressive state.²⁸ Interestingly, B cells have a dual role in HCC immunobiology by promoting tumor development under certain conditions, while also supporting antitumor immunity via the production of tumor-targeting antibodies and activating T cells that potentially enhance response to immunotherapy.²⁹

Importantly, angiogenesis is now recognized as a key element not only in supporting tumor vascularization but also in promoting immune evasion through modulation of the TME. Pro-angiogenic factors such as VEGF contribute to T cell dysfunction, exclusion from the tumor bed, and impaired dendritic cell maturation. These insights provide a strong mechanistic rationale for combining anti-angiogenic agents, such as tyrosine kinase inhibitors, with ICIs, as demonstrated

by the clinical success of regimens like atezolizumab plus bevacizumab. This combination enhances antitumor efficacy by concurrently inhibiting angiogenesis and restoring antitumor immune responses.³⁴ Moreover, some tyrosine kinase inhibitors, such as regorafenib, exert direct immunomodulatory effects. Regorafenib has been shown to reduce the infiltration of TAMs, suppress angiogenesis, and shift macrophage polarization from the pro-tumor M2 phenotype to the antitumor M1 phenotype, thereby further remodeling the TME to enhance immune-mediated tumor control.³⁵ Recent profiling studies indicate that the neo-angiogenic vasculature in HCC is closely linked to an immunosuppressive milieu; regorafenib can normalize aberrant vessels, dampen macrophage-mediated suppression, and recruit effector T cells, thereby providing a clear rationale for combining this TKI with PD-1/PD-L1 blockade.

Although the liver's TME is predominantly immunosuppressive, the presence of specific immune cells capable of eliminating cancer cells may counterbalance this effect.^{32,36} Key players in antitumor immunity include CD8+ T cells and both liver-resident and infiltrating NK cells.²⁶ These cells facilitate adaptive immune responses by targeting a broad spectrum of tumor antigens, such as tumor-associated antigens (TAA) and neoantigens, which are tumor-specific antigens (TSA) that arise from genomic alterations, abnormal RNA splicing, post-translational modifications, or integrated viral elements.

Among certain malignancies, a high tumor mutational burden (TMB) has been correlated with improved responses to ICIs.³⁷ However, this association appears less clear in HCC. Specifically, in the IMbrave 150 trial, which demonstrated a survival benefit of atezolizumab combined with bevacizumab over sorafenib as a first-line treatment for unresectable HCC, TMB showed no significant correlation with overall response rate or survival.³⁸ The TMB distribution in HCC was narrow, with a low median of 4.4 mutations per megabase (mut/Mb). Although a small subset of HCCs with high TMB (>10 mut/Mb) might derive greater benefit from ICIs, this has not yet been definitively established.^{39,40} Unlike other malignancies, HCCs typically exhibit low TMB, while even high TMB does not necessarily translate to increased immune cell infiltration,^{39,40} potentially due to deficiencies in antigen-presentation pathways within HCC.^{40,41} Copy number alterations, which frequently occur in HCC, lead to the loss of genes critical for effective antigen presentation, thereby shaping the immunosuppressive nature of the TME.⁴⁰ Additionally, cancer cell-intrinsic signaling pathways have demonstrated a significant role in modulating the immune microenvironment. For instance, activation of WNT- β -catenin signaling in murine models of HCC suppressed dendritic cell recruitment and impaired NK cell recognition, thus facilitating immune evasion.⁴² Transforming growth factor- β (TGF- β) signaling contributed to an immunosuppressive "cancer field effect" by further inhibiting antitumor immunity.⁴³ Moreover, MYC overexpression enhanced PD-L1 expression, while TP53 mutations drove the recruitment of immunosuppressive cell populations.⁴⁴ Interestingly, mutations in epigenetic regulators, which increased TMB, were paradoxically associated with reduced interferon- γ (IFN- γ) signaling, underscoring the complex interplay between genetic alterations and immune suppression in HCC.^{45,46}

HCCs can be broadly classified as inflamed or non-inflamed based on the characteristics of their immune microenvironment. Inflamed tumors, accounting for approximately 30% of cases, are defined by robust immune cell infiltration and immune activity. These tumors exhibit increased expression of immune checkpoints, such as PD-1 and PD-L1, activation of IFN signaling pathways, and relatively low levels of large chromosomal alterations.^{39,40,47} On the basis of mRNA-based gene expression profiles, inflamed HCCs can be further categorized into immune-active, immune-like, and immune-exhausted subtypes.^{39,47} Immune-active HCCs are characterized by heightened cytolytic activity and strong activation of IFN signaling, reflecting an active immune response. Immune-like tumors also demonstrate IFN signaling but are frequently associated with CTNNB1 mutations, suggesting a unique interplay between immune activation and oncogenic signaling. Conversely, immune-exhausted tumors display features of T cell exhaustion and are marked by the activation of TGF- β signaling pathways.^{39,47} Patients with inflamed HCCs generally have better prognoses and are more likely to benefit from ICIs due to the presence of responsive immune cells.^{39,41,47} Several gene expression signatures capturing the inflamed components of the TME have been linked to favorable responses to ICIs.^{38,41,47-49} On the other hand, non-inflamed HCCs are associated with minimal immune cell infiltration and low immune activity in the TME.^{39,47} These tumors exhibit T cell exclusion and are classified into two subtypes: immune-intermediate tumors, which often harbor TP53 mutations and exhibit high chromosomal instability, and immune-excluded tumors, characterized by CTNNB1 mutations and activation of the canonical WNT signaling pathway.^{39,47} Patients with non-inflamed HCCs typically have limited responses to immunotherapy, demonstrating the challenges that immune evasion poses for these tumors.^{41,50}

Immune cells express ligand-receptor checkpoints that regulate their activity, either enhancing or inhibiting effector functions. These checkpoints play a crucial role in modulating the duration and intensity of immune responses while minimizing collateral tissue damage. Stimulatory immune checkpoints, such as CD28, GITR, and OX40, promote T cell activation and proliferation, whereas inhibitory checkpoints, including PD-1, CTLA-4, LAG3, TIGIT, and TIM3, suppress immune activity to prevent overactivation.²⁶ In the context of HCC, immunotherapy predominantly focuses on restoring antitumor immunity through ICIs, which are monoclonal antibodies targeting inhibitory checkpoints or their ligands.²⁶ As such, the adjuvant combination of atezolizumab and bevacizumab has demonstrated efficacy in improving RFS in patients at high risk of recurrence following curative resection or local ablation.¹⁴

In HCC, immunotherapy is categorized into neoadjuvant and adjuvant approaches.⁵¹ Neoadjuvant therapies, such as bridging and downstaging strategies, have distinct objectives. In LT, bridging therapy aims to stabilize disease and reduce the risk of dropout among patients that have already met the Milan criteria, while downstaging therapies seek to decrease tumor burden, enabling patients initially outside the Milan criteria to become eligible for LT. Within this framework, neoadjuvant ICIs have emerged as a promising option, offering the potential to improve patient outcomes.⁵² On the other hand, adjuvant therapies focus on preventing disease recurrence following curative treatments such as hepatic resection or local ablation. Despite advancements in HCC management, the majority of patients experience recurrence or metastasis within five years of curative intervention, underscoring the critical need for effective systemic therapies in the adjuvant setting.^{53,54} Towards addressing this unmet need, ICIs have shown increasing promise in preventing or delaying HCC recurrence, with a growing body of evidence supporting their efficacy.²⁶ In addition to ICIs, immune-cell-based therapies have garnered significant interest in recent years. These therapies, which include adoptive T-cell transfer and NK cell-based approaches, hold potential for clinical application. Building on these developments, the subsequent sections of this review will examine the current status of adjuvant immunotherapy and immune-cell therapy in HCC, focusing on their applications in resection and LT, with a particular emphasis on recent clinical trials.

The Role of ICIs in Adjuvant Immunotherapy After Resection for HCC

Surgical resection is widely recognized as the treatment of choice among patients with early-stage HCC who qualify as suitable candidates. For patients with early-stage disease who are not eligible for resection, LT serves as an alternative option.^{1,15} Despite its curative intent, surgical resection is associated with a high risk of disease recurrence, ranging from 50% to 70% within five years. The first 12 months post-resection represent the period of highest recurrence risk.⁵⁵ Early recurrence often manifests as either extrahepatic or intrahepatic metastases located far from the resection margin, believed to originate from occult micrometastases that were present at the time of surgery.^{56,57} Tumor characteristics such as size, number, vascular invasion, grade of differentiation, and α -fetoprotein have been associated with early recurrence.⁵⁸ On the contrary, late recurrence occurring more than 12 months after resection has been typically attributed to new primary tumors (de novo HCCs), potentially influenced by the underlying liver disease. Risk factors for late recurrence include patient demographics, the etiology of the underlying liver disease, and the presence of cirrhosis.⁵⁹ The substantial risk of recurrence underscores the critical need for effective perioperative adjuvant therapies to reduce tumor recurrence and metastasis while improving long-term survival.

Adjuvant therapies offer several advantages compared to neoadjuvant approaches. The utilization of postoperative pathology and molecular classification can facilitate more precise patient selection and individualized treatment plans without delaying surgery. The primary candidates for adjuvant therapy are patients who have undergone surgical resection but remain at high risk for recurrence and metastasis based on tumor pathology and clinical factors. Of note, adjuvant ICIs have emerged as a promising approach to address this unmet need, based on their ability to restore and enhance antitumor immunity, thus offering potential benefits towards targeting residual microscopic disease and preventing early recurrence. In the near future, the utilization of ICIs in the postoperative setting is expected to play a pivotal role in reshaping HCC management and establishing a pathway toward improved outcomes for patients following surgical resection.

In recent years, ICIs such as anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies have revolutionized the treatment landscape for various cancers, including HCC.^{11,60–62} These biologic agents enhance antitumor immunity by promoting T cell activation and enabling the immune system to effectively target and eliminate tumor cells. Ongoing clinical trials evaluating adjuvant ICIs in this population are summarized in [Table 1](#). Importantly, early-phase studies are underway to explore novel perioperative

Table 1 Summary of Clinical Trials on Adjuvant Immunotherapy for Liver Resection Among Patients with Hepatocellular Carcinoma

NCT Number	Country	Phase	Case Number	Year	Status
NCT06581315	China	PHASE3	204	2024	RECRUITING
NCT02436902	China	PHASE3	240	2019	UNKNOWN
NCT04947371	China	PHASE2	0	2018	WITHDRAWN
NCT01760616	China	PHASE4	790	2011	TERMINATED
NCT04981665	China	PHASE2	50	2021	UNKNOWN
NCT05221398	China	Observational	517	2019	COMPLETED
NCT02738697	China	PHASE3	290	2016	UNKNOWN
NCT05111366	China	PHASE2	37	2022	UNKNOWN
NCT01418729	Spain	PHASE2	216	2011	COMPLETED
NCT05113186	France	PHASE2	32	2022	ACTIVE NOT RECRUITING
NCT03630640	France	PHASE2	43	2018	COMPLETED
NCT00908752	Thailand	PHASE3	734	2009	COMPLETED
NCT03261791	China	PHASE2	30	2017	UNKNOWN
NCT05516628	Singapore	PHASE2	30	2023	RECRUITING
NCT04930315	China	PHASE2	78	2021	RECRUITING
NCT01033578	China	Unknown	260	199	UNKNOWN
NCT05307926	China	Observational	573	2019	COMPLETED
NCT02125396	China	PHASE3	150	2019	RECRUITING
NCT05161143	China	PHASE2	30	2021	UNKNOWN
NCT00921531	China	PHASE3	200	2009	UNKNOWN
NCT05546619	China	Unknown	30	2022	ACTIVE NOT RECRUITING
NCT00819650	China	PHASE2	200	2022	COMPLETED
NCT00692770	United Kingdom	PHASE3	1,114	2008	COMPLETED
NCT02129322	China	PHASE2	0	2015	WITHDRAWN
NCT01966133	China	PHASE3	280	2011	UNKNOWN
NCT00149565	Taiwan	PHASE3	268	1997	COMPLETED
NCT06454578	China	PHASE2	30	2024	RECRUITING
NCT04891874	China	Unknown	76	2015	COMPLETED
NCT03971201	China	PHASE2	200	2019	UNKNOWN
NCT03859128	China	PHASE2 3	402	2019	ACTIVE NOT RECRUITING
NCT06218511	Italy	PHASE1	10	2022	RECRUITING
NCT02650271	China	PHASE3	240	2021	COMPLETED
NCT04727307	France	PHASE2	202	2021	RECRUITING
NCT04521491	China	Unknown	184	2020	UNKNOWN
NCT00247728	Taiwan	PHASE2	172	2004	COMPLETED
NCT01924624	China	Unknown	140	2013	UNKNOWN
NCT04227808	China	PHASE2	50	2019	UNKNOWN
NCT00234182	Hong Kong	PHASE1 2	84	2000	COMPLETED
NCT04653389	China	PHASE2	10	2020	TERMINATED
NCT06089369	China	PHASE3	360	2024	NOT YET RECRUITING
NCT04102098	Turkey	PHASE3	668	2019	ACTIVE NOT RECRUITING
NCT01512407	China	Unknown	58	2011	COMPLETED
NCT02537158	China	Unknown	90	2015	UNKNOWN
NCT03203005	United Kingdom	PHASE1 2	22	2017	COMPLETED
NCT04297202	China	PHASE2	20	2019	UNKNOWN
NCT05545124	China	PHASE2	32	2022	UNKNOWN
NCT05489289	China	PHASE3	405	2022	NOT YET RECRUITING
NCT04178642	France	PHASE2	0	2020	WITHDRAWN
NCT04224480	Singapore	PHASE1	8	2019	ACTIVE NOT RECRUITING
NCT02867280	China	PHASE3	154	2016	TERMINATED

(Continued)

Table 1 (Continued).

NCT Number	Country	Phase	Case Number	Year	Status
NCT03511703	China	PHASE2	40	2018	UNKNOWN
NCT06089382	China	PHASE3	104	2023	NOT YET RECRUITING
NCT06546280	China	PHASE2	38	2024	NOT YET RECRUITING
NCT03867084	United Kingdom	PHASE3	950	2019	ACTIVE NOT RECRUITING
NCT04418401	China	PHASE1	30	2020	RECRUITING
NCT04143191	China	PHASE3	158	2019	UNKNOWN
NCT05389527	China	PHASE2	43	2022	ACTIVE NOT_RECRUITING
NCT06311929	China	PHASE4	300	2024	RECRUITING
NCT06193733	Taiwan	PHASE2	74	2024	NOT YET RECRUITING
NCT06498622	China	PHASE2	45	2024	RECRUITING
NCT05910970	China	PHASE3	200	2024	NOT YET RECRUITING
NCT02631499	China	PHASE4	256	2015	UNKNOWN
NCT06644937	China	PHASE2 3	30	2024	NOT YET RECRUITING
NCT03515369	China	PHASE4	459	2015	UNKNOWN
NCT05407519	China	PHASE2	40	2022	RECRUITING
NCT00455091	Taiwan	PHASE3	117	2007	TERMINATED
NCT04053972	China	PHASE3	377	2018	UNKNOWN
NCT05576909	China	PHASE2	20	2023	RECRUITING
NCT04658147	United States	PHASE1	20	2021	RECRUITING
NCT05564338	Unknown	PHASE3	0	2023	WITHDRAWN
NCT06205472	China	PHASE2	100	2024	RECRUITING
NCT00116454	France	PHASE3	73	2024	COMPLETED
NCT02309788	China	Observational	100	2016	UNKNOWN
NCT03192618	China	PHASE3	290	2017	RECRUITING
NCT02767375	China	PHASE2 3	192	2015	UNKNOWN
NCT05862337	China	PHASE3	480	2023	RECRUITING
NCT02253511	China	PHASE4	400	2014	UNKNOWN
NCT01681446	China	PHASE3	296	2012	UNKNOWN
NCT02724332	China	PHASE1	300	2012	COMPLETED
NCT00561522	China	PHASE2 3	290	2007	UNKNOWN
NCT04639180	China	PHASE3	687	2021	ACTIVE NOT RECRUITING
NCT04233840	Taiwan	PHASE1 2	72	2019	UNKNOWN
NCT03722875	China	Unknown	45	2018	UNKNOWN
NCT04682210	China	PHASE3	246	2020	UNKNOWN
NCT03732105	China	Unknown	148	2018	RECRUITING
NCT03847428	Vietnam	PHASE3	908	2019	ACTIVE NOT RECRUITING
NCT05602974	China	PHASE3	140	2023	NOT YET RECRUITING
NCT03267641	Thailand	Observational	86	2016	COMPLETED
NCT00568308	Thailand	PHASE3	600	2007	TERMINATED
NCT06664996	China	PHASE2	33	2024	RECRUITING
NCT01402908	Taiwan	PHASE3	520	2011	TERMINATED
NCT04213118	China	PHASE2	30	2020	UNKNOWN
NCT00282100	Singapore	PHASE2	40	2005	UNKNOWN
NCT02109146	China	PHASE3	332	2014	COMPLETED
NCT00051545	United Kingdom	PHASE3	608	1999	TERMINATED
NCT02281266	China	PHASE4	360	2015	UNKNOWN
NCT04147078	China	PHASE1	80	2019	RECRUITING
NCT00273247	Italy	PHASE3	150	1998	COMPLETED
NCT04962958	China	PHASE2	30	2023	NOT YET RECRUITING
NCT05367687	China	PHASE2	251	2022	ACTIVE NOT RECRUITING
NCT03184493	China	PHASE3	200	2017	UNKNOWN

strategies. The PRIME-HCC Phase Ib trial (NCT03682276) is evaluating the safety and tolerability of nivolumab/ipilimumab in the perioperative setting, whereas a Phase II trial (NCT03222076) is assessing the efficacy of combined perioperative nivolumab/ipilimumab versus nivolumab monotherapy.^{63,64} The NIVOLVE trial, a phase II multicenter study, assessed the safety and efficacy of adjuvant nivolumab in patients undergoing surgical resection or radiofrequency ablation.⁶⁵ The trial reported a 1-year RFS rate of 78.6% and a median RFS of 26.3 months. Additionally, exploratory analyses identified factors such as copy number gains in WNT/ β -catenin-related genes, activation of the WNT/ β -catenin pathway, increased Foxp3⁺ cells, and low CD8⁺ tumor-infiltrating lymphocytes as potential markers of recurrence after adjuvant nivolumab. Several Phase III trials are investigating other ICI regimens in the adjuvant setting. These include CheckMate 9DX (adjuvant nivolumab; NCT03383458), IMbrave050 (atezolizumab plus bevacizumab; NCT04102098), KEYNOTE-937 (pembrolizumab; NCT03867084), and EMERALD-2 (durvalumab with or without bevacizumab; NCT03847428).^{66,67}

Notably, the global, open-label phase III IMbrave050 trial evaluated whether adjuvant therapy with atezolizumab plus bevacizumab could improve RFS compared with active surveillance in patients at high risk of recurrence after resection or local ablation.¹⁴ While initial analyses suggested a potential benefit, updated results presented at ESMO 2024 indicated that the combination did not achieve a statistically significant improvement in RFS. The trial enrolled 668 patients randomized 1:1 to either the intervention or surveillance arm. Although a previously reported hazard ratio (HR) for RFS favored the intervention group (HR 0.72, 95% CI 0.56–0.93), the updated analysis failed to confirm statistical significance, prompting a reassessment of the clinical utility of this adjuvant regimen. Treatment-related AEs occurred in 41% of patients in the intervention group compared with 13% in the surveillance group, with most events being manageable. The most common immune-related AEs included hepatitis (32% vs 15%), rash (20% vs 2%), and hypothyroidism (20% vs <1%), primarily of grade 1–2 severity.¹⁴ These findings highlight the need for refined patient selection and biomarker-based stratification to enhance the effectiveness of adjuvant immunotherapy in HCC.

Despite advancements in immunotherapy, the response rate of HCC to ICIs remains below 20%, largely due to the low immunogenicity of HCC tumors.⁶⁸ The limited efficacy of ICIs is often attributed to the scarcity of tumor-infiltrating lymphocytes (TILs) in HCC, as tumors with fewer TILs—often referred to as “cold tumors”—are less responsive to immunotherapy. Although global efforts have been made to convert immunologically cold tumors into hot tumors with enhanced immune infiltration, effective strategies for HCC remain elusive.⁶⁹ Peptide vaccination therapy, which aims to induce tumor antigen-specific T cells, represents one promising avenue.⁷⁰ Recent studies have demonstrated the efficacy of combining hLAG-3-Ig, a fusion protein of human lymphocyte activation gene 3 (LAG-3) and immunoglobulin G1 (IgG1) Fc, with poly-ICLC, a synthetic double-stranded RNA adjuvant.⁷¹ This combination enhances immune activation by blocking inhibitory LAG-3 signaling in T cells, while simultaneously stimulating dendritic cells and monocytes via interaction with major histocompatibility complex class II molecules.^{72–74} Poly-ICLC further amplifies immune responses by binding to Toll-like receptor 3 and other pattern recognition receptors, inducing type I interferons and IL-12 production, and enhancing dendritic cell cross-priming.^{75–77} Building on these principles, a novel therapeutic vaccine was developed by combining heat shock protein 70 (HSP70) and glypican-3 (GPC3)-derived peptides with multi-human leukocyte antigen (HLA)-binding capabilities and adjuvants like poly-ICLC.⁷⁸ A Phase I trial (YNP01, jRCTs061180058) involving patients with advanced gastrointestinal cancers demonstrated its safety and robust induction of peptide-specific T-cell production.⁷⁹ Immunohistochemical analysis in the trial revealed HSP70 and GPC3 expression in 71% of 112 HCC cases, with at least one of these antigens expressed in 87% of tumors. Notably, three out of four enrollees with stage IVB HCC survived for over two years, qualifying as the only long-term survivors. These promising data have prompted a phase I trial (YCP02) to evaluate the vaccine’s safety as perioperative immunotherapy for resectable HCC.

Moreover, certain clinical trials have explored PD-L1 expression as a predictive marker for immunotherapy response. Elevated PD-L1 levels have been associated with poor prognosis among patients with advanced HCC.^{19,80,81} The ORIENT-32 trial demonstrated that sintilimab combined with IBI305 significantly improved OS and RFS compared with sorafenib in patients with unresectable, HBV-related HCC.⁸² Similarly, early studies on tislelizumab reported non-inferior OS compared with sorafenib, a higher objective response rate, and a more durable response, despite sorafenib showing slightly longer RFS.⁸³ However, inter-institutional variability in PD-L1 assessment methods has led to inconsistent findings, highlighting the need for standardized techniques to measure PD-L1 expression. Additionally,

understanding the temporal dynamics of PD-L1 expression and determining whether it should be measured in tumor or stromal tissues present ongoing critical challenges.⁸⁴

Given the heterogeneity of HCC, tailored combination therapies are becoming essential. A meta-analysis by Li et al demonstrated that external beam radiotherapy (EBRT) combined with sorafenib improved outcomes in unresectable HCC.⁸⁵ Another multicenter study by Su et al suggested that EBRT outperforms transcatheter arterial chemoembolization for HCC tumors ≥ 5 cm.⁸⁶ Li et al also reported significant benefits when combining PD-1 inhibitors with transcatheter arterial chemoembolization.⁸⁷ These findings highlight the evolving role of combination therapies in extending patient survival. Biomarkers such as alkaline phosphatase, albumin-bilirubin score, and aspartate-aminotransferase-to-platelet ratio index are emerging as useful tools for predicting prognosis and assessing treatment response.^{88–90} Future research is likely to focus on refining immunotherapy combinations and identifying reliable biomarkers to guide personalized treatment strategies.^{91,92}

The Role of ICIs in Adjuvant Immunotherapy After Liver Transplantation for HCC

LT is a cornerstone treatment for HCC among patients who meet stringent selection criteria, such as the Milan Criteria. However, its widespread application is limited by donor scarcity and the significant risk of post-LT tumor recurrence, which occurs in approximately 8% to 20% of cases despite careful candidate selection.^{93–95} Post-LT recurrence is associated with a poor prognosis, and therapeutic options for these patients remain limited.^{96,97} To optimize the use of scarce donor resources, minimizing post-LT recurrence and mortality is critical. Achieving this goal necessitates precise donor-recipient matching and ongoing refinement of LT selection criteria, a topic that has been actively debated for over a decade.^{96,98,99}

The use of ICIs in the LT setting presents unique challenges compared to ICI use in HCC resection. Unlike resection, LT patients are immunocompromised due to the use of immunosuppressive agents, especially in the critical early post-LT period. This immunosuppressive state is thought to contribute significantly to HCC recurrence, with two primary mechanisms proposed to explain how immunosuppression drives recurrence.²² The first mechanism suggests that undetectable micrometastases, present outside the liver at the time of LT, may proliferate under the influence of immunosuppressive therapy. The second posits that circulating tumor cells (CTCs) from the primary tumor can engraft in various tissues, including the allograft liver, lymph nodes, lungs, or bones.^{100–102} During the early post-LT period, when immunosuppression is at its peak, these cancer cells are more likely to evade immune surveillance and establish metastases. Efforts to reduce HCC recurrence post-LT have included strategies to minimize the use of immunosuppressive agents.^{103–106} Tacrolimus (FK506), one of the most commonly used immunosuppressive agents, has been implicated in promoting HCC cell migration and proliferation through pathways such as Rho/ROCK and Ras signaling.^{107–110} Additionally, CTCs may escape immune detection by expressing molecules like PD-L1, CD44, and CD47, which facilitate immune evasion.^{111–113} These findings suggest that modifications to immunosuppressive regimens could reduce recurrence risk to levels observed in non-transplant patients with HCC. Despite these insights, the optimal immunosuppressive protocol post-LT remains uncertain. While some centers have explored reducing exposure to calcineurin inhibitors or incorporating mammalian targets of rapamycin inhibitors to balance graft protection and tumor recurrence prevention, no consensus has been reached.²⁴ Further translational and clinical studies are needed to develop evidence-based regimens that balance graft protection with recurrence prevention.

Emerging evidence highlights the potential of ICIs for managing HCC recurrence after LT. Patterns of recurrence indicate that approximately 11% and 56% of patients experience intrahepatic and extrahepatic recurrence, respectively, while 33% present with both.^{114–130} Standard immunosuppression protocols vary across centers but typically include high-dose corticosteroids immediately after liver reperfusion to broadly suppress the immune response. These steroids induce T-cell apoptosis and halt T-cell proliferation, serving as the primary treatment for severe irAEs associated with ICIs. Calcineurin inhibitors suppress T-cell activation and cytokine production, while mycophenolate inhibits T and B lymphocyte proliferation by depleting guanosine nucleotides. In recent years, there has been a growing trend towards minimizing or even eliminating steroid use following LT, a shift that has been generally associated with improved patient outcomes. Variability in early steroid use may partially explain differences in the incidence of early graft rejection reported among patients receiving ICIs prior to LT. In addition to steroids, T-cell-depleting agents, such as anti-

thymocyte globulin, have been employed as part of immunosuppressive induction protocols to significantly reduce T-cell counts. While this strategy may lower the risk of ICI-related rejection, it comes with potential drawbacks. The depletion of T cells can trigger the homeostatic proliferation of surviving lymphocytes, which may generate memory T cells and complicate long-term graft tolerance.¹³¹

The timing of ICI therapy post-LT has emerged as a crucial factor influencing both rejection risk and therapeutic outcomes. Recent studies have shed light on the relationship between the interval from LT to ICI initiation and patient response.¹³ Shorter intervals between LT and the start of ICI therapy have been associated with a heightened risk of rejection.¹³ Conversely, a longer LT-to-ICI interval has been linked to improved therapeutic responses, as reflected in higher disease control rates. One study reported that the median interval from LT to ICI initiation was six years in patients who responded to ICIs, compared to three years in non-responders.¹³ As the post-LT period progresses, immunosuppression is typically tapered to reduce the risk of long-term complications. This reduction allows for the development of a more immune-tolerant graft environment. In patients with older grafts, the immune system may become less focused on rejecting the transplanted organ and more capable of mounting an effective antitumor response.¹³ These findings highlight the importance of individualized timing when considering ICI therapy in LT recipients to maximize efficacy while minimizing rejection risk.

The integration of molecularly targeted therapies with immunotherapy has become a cornerstone in the management of advanced HCC. Regulatory bodies, including the FDA, have approved the combination of the PD-L1 inhibitor atezolizumab with the VEGF inhibitor bevacizumab as a first-line systemic therapy for advanced HCC. This regimen, now recommended by the National Comprehensive Cancer Network guidelines, has replaced previous standards such as sorafenib and lenvatinib.¹³² Emerging evidence suggests that other combinations of targeted and immune-based therapies may further enhance treatment outcomes. The pairing of lenvatinib with pembrolizumab has shown significantly higher response rates compared to pembrolizumab monotherapy, although this benefit is accompanied by an increased incidence of toxicities.¹⁸ Tyrosine kinase inhibitors such as sorafenib, regorafenib, and lenvatinib not only target VEGFR signaling but also exhibit immune-modulating properties that complement immunotherapy.¹³³ Sorafenib has been shown to enhance antitumor immune responses by promoting CD4+ and CD8+ T-cell activation and infiltration while suppressing Tregs.^{134,135} These immune-enhancing effects position tyrosine kinase inhibitors as valuable partners in combination therapies. The potential for synergistic effects between tyrosine kinase inhibitors and ICIs has been highlighted in specific clinical scenarios. A case study described the treatment of a patient with HCC who developed metastatic lung lesions following LT. Initially treated with sorafenib monotherapy, the patient's disease progressed after one year. However, the subsequent addition of pembrolizumab resulted in a complete response, with no evidence of allograft rejection.¹²¹ This case underscores the potential of combining tyrosine kinase inhibitors with PD-1 inhibitors to achieve superior antitumor effects, even in complex post-LT settings where monotherapy has limited efficacy.

While maintaining immunological tolerance is essential to prevent allograft rejection, ICIs activate cellular immunity, potentially disrupting this delicate balance. This activation can lead to T-cell-mediated rejection, making ICIs traditionally contraindicated among LT recipients.¹³⁶ Preclinical models have highlighted the risks associated with ICIs in LT. In animal studies, blockade of the PD-1/PD-L1 pathway or the use of PD-L1 knockout liver allografts resulted in acute rejection characterized by increased T-cell infiltration, hemorrhage, and necrosis.¹³⁷ Similarly, inhibition of CTLA-4 exacerbated lymphocyte infiltration and enhanced cytotoxic T lymphocyte and NK cell activity, thereby increasing the likelihood of rejection.¹³⁸ As such, the role of ICIs in the setting of managing de novo or recurrent tumors in LT recipients is an area of active investigation.^{139,140}

Specifically, the development of de novo malignancies following LT represents a significant long-term concern for recipients. Data from the United States Scientific Registry of Transplant Recipients, encompassing over 108,000 LT recipients between 1987 and 2015, estimated the cumulative incidence of de novo extrahepatic cancers to be approximately 1.3% within the first year and up to 18.8% at 20 years post-LT.¹⁴¹ Of note, compared to HCC recurrence, de novo cancers typically have a longer latency period before onset.¹⁴² Common de novo malignancies in LT recipients include non-Hodgkin's lymphoma, keratinocyte skin cancers (basal cell carcinoma and squamous cell carcinoma), cervical cancer, and head and neck cancers. Preventative strategies such as careful immunosuppression management, regular cancer screenings (eg, dermatologic evaluations and Pap smears), and minimizing sun exposure are recommended to

facilitate early detection and intervention.^{143,144} Emerging evidence suggests differential responses to ICIs between de novo malignancies and recurrent HCC in LT recipients. A systematic review reported better disease control rates for de novo malignancies treated with ICIs compared to recurrent HCC.¹³ However, graft rejection rates in the de novo cancer group (21.4%) were similar to those observed in patients with post-LT HCC recurrence. These findings highlight that further studies are needed to refine the use of ICIs in this population and manage the associated risks effectively.¹⁴²

Off-label use of ICIs in LT recipients has yielded insights into their safety and efficacy. Histological analysis of PD-L1 expression has been proposed as a potential biomarker for rejection risk, with some studies reporting higher rejection rates in PD-L1-positive cases. However, PD-L1 staining alone is not yet a reliable predictor of rejection or therapeutic response.^{13,125,145} For example, one case study detailed a patient with recurrent HCC post-LT who was treated with atezolizumab and bevacizumab. Despite negative PD-L1 staining on a pre-treatment biopsy, the patient tolerated two cycles of therapy before experiencing tumor progression.¹²⁵ Such examples underscore the need for further research to clarify the role of ICIs in LT recipients, including the timing of therapy, the utility of biopsy-based biomarkers, and the most effective methods for assessing treatment response.

Numerous clinical trials are currently investigating the role of ICIs in managing HCC recurrence following LT. A summary of these ongoing studies is presented in Table 2. Trials such as NCT03966209 and NCT04564313 are evaluating the safety and efficacy of ICIs in this challenging clinical setting. ICIs, particularly in combination with other treatments, have shown superior OS compared to tyrosine kinase inhibitors, solidifying their status as first-line therapeutic options for advanced HCC. Tyrosine kinase inhibitors exert their antitumor effects by inhibiting tyrosine kinase receptors, thereby blocking downstream signaling pathways, promoting apoptosis, and exerting anti-angiogenic effects within the TME.¹⁴⁶ Sorafenib, a small molecule tyrosine kinase receptor, was the first treatment for advanced HCC to gain FDA approval, following the results of the landmark SHARP trial in 2008.¹⁴⁷ Cabozantinib, another tyrosine kinase receptor, has since been approved as a second-line therapy for advanced HCC.¹⁴⁸ Emerging combination therapies are also showing promise in intermediate-stage HCC. The phase III Emerald-1 trial demonstrated that combining durvalumab, bevacizumab, and transarterial chemoembolization significantly improved objective response rates and RFS compared to transarterial chemoembolization alone.¹⁴⁹ These findings suggest that integrating ICIs with locoregional treatments may offer a superior strategy for managing intermediate-stage HCC. Additionally, small-scale clinical trials have reported positive outcomes for ICI-based therapies in early-stage resectable HCC.^{64,150,151} These studies reflect the expanding application of ICIs across the HCC treatment spectrum, from early-stage surgical candidates to advanced and post-transplant cases.

Recommendations for addressing graft rejection in LT recipients treated with ICIs are largely derived from protocols developed for managing ICI-induced liver toxicity in native livers.¹⁵² Recent studies emphasize the importance of liver biopsy in patients presenting with grade 2 or higher liver toxicity—defined by alanine aminotransferase or aspartate aminotransferase

Table 2 Summary of Clinical Trials on Adjuvant Immunotherapy for Liver Transplantation Among Patients with Hepatocellular Carcinoma

NCT Number	Country	Phase	Case Number	Year	Status
NCT06041490	China	PHASE2	88	2023	NOT YET RECRUITING
NCT04415567	China	Observational	23	2018	COMPLETED
NCT02202564	China	PHASE2	81	2006	COMPLETED
NCT02580253	China	PHASE2	0	2017	WITHDRAWN
NCT05576909	China	PHASE2	20	2023	RECRUITING
NCT06409637	China	PHASE1 2	62	2025	NOT YET RECRUITING
NCT02129322	China	PHASE2	0	2015	WITHDRAWN
NCT03313596	China	PHASE3	180	2013	UNKNOWN
NCT00300521	China	PHASE2	40	2000	COMPLETED
NCT06564103	China	Observational	1	2024	COMPLETED
NCT01125020	China	PHASE3	150	2008	UNKNOWN
NCT06327269	Taiwan	PHASE1	40	2021	RECRUITING

levels exceeding three times the upper limit of normal, or bilirubin levels exceeding 1.5 times the upper limit of normal.¹⁵³ Biopsy not only confirms and grades histological rejection but also excludes alternative causes of liver injury. For cases of mild rejection, oral prednisone at 0.5–1.0 mg/kg/day is typically recommended. In moderate to severe rejection, intravenous methylprednisolone at 1–2 mg/kg/day is the preferred treatment. Corticosteroid therapy resolves liver toxicity within 5–9 weeks, correlating with the terminal half-life of most ICIs, which ranges from 15 to 27 days.^{154,155} Patients who do not respond to corticosteroids may require additional immunosuppressive therapies, including mycophenolate mofetil, cyclosporine, tacrolimus, anti-thymocyte globulin, or targeted agents such as tocilizumab (an IL-6 receptor antagonist) and infliximab, while plasmapheresis may also be considered in refractory cases.¹⁵² Of note, salvage re-LT may be an option in situations of irreversible allograft failure, provided the underlying malignancy does not contraindicate LT.

Emerging data indicate that anti-PD-1 therapies may elicit stronger rejection responses compared to other ICIs.^{156,157} This observation has led some experts to suggest anti-CTLA-4 therapies as a safer alternative for patients where preserving graft function is paramount. Preliminary studies suggest that anti-PD-1 and anti-CTLA-4 therapies may exhibit synergistic effects, with combination treatments occasionally demonstrating superior efficacy compared to monotherapy.^{158–160} However, combining these therapies did not appear to confer a significant survival benefit over monotherapy in other reports and was associated with increased risks of toxic side effects, making concurrent or sequential use less favorable.^{161,162} While anti-PD-1/PD-L1 agents have demonstrated slightly better efficacy in some studies compared to anti-CTLA-4 therapies, the difference was not statistically significant.¹⁶³ Thus, the increased toxicity associated with combination regimens necessitates careful consideration, and conflicting results regarding overall survival benefits underscore the need for further investigation. The mechanisms underlying the PD-1 and CTLA-4 pathways exhibit both similarities and differences.^{164,165} The PD-1 pathway primarily regulates effector T cell activity in peripheral tissues and tumors by inhibiting the interaction between PD-1 and PD-L1, thereby enhancing antitumor immune responses.^{166–168} In contrast, the CTLA-4 pathway acts during the initial T cell activation phase, where CTLA-4 competes with CD28 for binding to CD80/CD86, dampening T cell activation. Anti-CTLA-4 therapies block this inhibitory interaction, thereby facilitating CD28-mediated activation.^{169,170} Both pathways are also highly expressed in Tregs, which enhance their immunosuppressive functions via increased Foxp3 expression.^{60,171–173} There are notable intersections between the PD-1 and CTLA-4 pathways. Both therapies elevate IL-2 levels, thus activating donor-specific T cells, enhancing cytotoxic activity, and reducing apoptosis from allogeneic reactivity.¹⁶⁴ Additionally, these agents induce phosphorylation within the T cell receptor signaling pathway, which suppresses downstream activation signals and prevents excessive T cell activation.¹⁷⁴ Both pathways also modulate immune responses through Tregs, contributing to their overlapping mechanisms of action. Further research is needed to elucidate the interplay between these pathways, optimize graft rejection management, and balance tumor immunity with graft tolerance in LT recipients, particularly in light of these sometimes conflicting findings regarding combination therapy.

The relationship between irAEs and post-LT outcomes is a crucial consideration in patient management.^{175–193} The efficacy of ICIs is tempered by irAEs, which affect up to 70% of patients and result from the restoration of antitumor immunity, often disrupting self-tolerance.¹⁹⁴ Of note, liver injury is among the most common irAEs, occurring in approximately one out of four patients. This condition is typically managed with corticosteroids as first-line therapy, and additional immunosuppressive drugs are used for more severe or refractory cases.¹⁹⁵ Recently, ICI-induced cholangitis has emerged as a notable irAE. While most irAEs occur within the initial months of therapy, late-onset toxicities—sometimes arising after discontinuation of ICIs—have also been documented. Management strategies for irAEs generally involve pausing or permanently stopping ICI therapy and administering steroids for grade 2 or higher toxicities. Prompt recognition and treatment of irAEs are essential for the optimization of outcomes among LT recipients receiving ICIs.

Determining which LT recipients can safely receive ICIs is an area of growing interest, with efforts focused on balancing immunological risks and oncological benefits. One potential approach involves using PD-L1 expression levels in transplanted livers as a biomarker for safety, as suggested by retrospective analyses and small prospective studies. While promising, the clinical utility of PD-L1 as a predictive tool remains inconclusive and requires further validation. Recent work has introduced a comprehensive framework for guiding ICI administration in LT recipients.¹⁵³ This model incorporates a detailed evaluation of immunological risk factors, including the time elapsed since LT, patient demographics such as age and sex, the underlying etiology of liver disease, the presence of donor-specific antigens, prior

episodes of graft rejection, baseline transaminase levels, and the extent of liver fibrosis. Oncological benefits are assessed by considering tumor stage, survival improvements, and quality-of-life enhancements demonstrated in randomized controlled trials, alongside the patient's overall performance status and comorbidities. Based on these parameters, patients are stratified into categories to recommend the optimal course of treatment. While ICIs may be cautiously prescribed in some cases with rigorous monitoring, they may be strongly discouraged or replaced with alternative therapies in others, depending on the risk-benefit profile.¹⁵³ The therapeutic potential of ICIs in this population is supported by pooled analyses, which report a disease control rate of 44.2% among LT recipients treated with these therapies. Patients who responded to ICIs exhibited significantly longer OS, with a median of 26.4 months compared to 3.4 months for non-responders.¹³ Despite these encouraging outcomes, the evidence remains insufficient to draw definitive conclusions due to limitations such as small sample sizes and heterogeneity in study designs. To establish ICIs as a viable therapeutic option for LT recipients, further research is essential. Large, well-controlled studies are needed to confirm safety and efficacy, as well as to refine and standardize clinical guidelines.

Adjuvant Immuno-Cell Therapy After Resection for HCC

Adoptive cell therapy (ACT) represents an innovative and potent approach to cancer treatment, aiming to enhance the antitumor capabilities of immune cells. This therapeutic modality involves the *ex vivo* process of sensitizing and expanding lymphocytes, either autologous or allogeneic, before reinfusing them into the patient.¹⁹⁶ This represents a highly personalized cancer therapy, since the effector cells in ACT predominantly originate from the patient's immune system. The primary strategies employed in ACT include T cells expressing chimeric antigen receptors (CAR), T cells engineered with tumor-specific T cell receptors (TCR), cytokine-induced killer (CIK) cells, TILs, lymphokine-activated killer (LAK) cells, and NK cells.^{196,197} Although ACT has primarily been applied to hematologic malignancies, its success has encouraged researchers to explore its applicability in solid tumors, including HCC.¹⁹⁸ In the context of HCC, ACT is predominantly used for advanced or unresectable cases, while its use as an adjuvant therapy to prevent postoperative recurrence remains limited. Table 3 summarizes clinical trials, as reported on clinicaltrials.gov, investigating the role of ACT as an adjuvant therapy for HCC, and highlights these developments.

Among ACT modalities that do not involve genetic modification, CIK cells, TILs, and NK cells are noteworthy. CIK cells, which are CD3⁺CD56⁺ NK-like T cells, exhibit non-MHC-restricted cytotoxicity and proliferation capabilities. TILs, on the other hand, consist of polyclonal tumor-targeting T cells expanded *ex vivo* for use as autologous therapy. NK cell therapies are divided into several groups based on whether they were derived from peripheral blood, tissue-resident cells, apheresis-derived products, or umbilical cord blood. Recent advances in genetic engineering technologies have enabled the modification of immune cells with synthetic receptors, such as CAR-T and TCR-T, thereby enhancing the visibility of TAAs and TSAs. The antigens targeted by ACT for HCC are categorized into three main groups: TAAs (eg, AFP and GPC-3), virus-derived cancer antigens (eg, HBV and HCV), and cancer-testis antigens (eg, NY-ESO-1 and MAGE).¹⁹⁷

For the generation of CIK cells, IL-2, IFN- α , and anti-CD3 monoclonal antibodies are utilized to stimulate peripheral blood mononuclear cells (PBMCs) under laboratory conditions.¹⁹⁹ CIK cells predominantly comprise NK cells, NKT cells, and cytotoxic T lymphocytes (CTLs). Through adhesion molecules, CIK cells can recognize tumor cells independently of MHC and lyse them. Takayama et al conducted a clinical trial involving 150 postoperative HCC patients and reported an 18% reduction in recurrence rates in the treatment group compared to the control group, with no significant AEs observed.²⁰⁰ A multicenter, randomized, non-blinded phase III trial assessed the efficacy and safety of adjuvant immunotherapy with activated CIK cells among 230 patients who underwent curative therapies for HCC, such as surgical resection, radiofrequency ablation, or percutaneous ethanol injection. While the incidence of severe AEs did not significantly differ between groups (7.8% vs 3.5%; $P=0.15$), adjuvant therapy with activated CIK cells improved RFS and OS rates.²⁰¹ On the contrary, a single-institution, randomized, non-blinded phase III trial involving 200 patients who underwent curative resection failed to demonstrate improvements in disease-free survival or OS.²⁰² While the utility of CIK therapy continues to be investigated across various HCC treatment settings, its potential remains promising.^{203–210}

TILs represent a component of the host immune response against tumors and comprise T cells, Tregs, NK cells, and B cells.²¹¹ TILs are harvested from surgically resected tumor tissues and demonstrate superior antitumor efficacy compared to drugs targeting specific antigens or mutations, as they can detect multiple antigens. A phase I clinical trial involving 17 patients

Table 3 Summary of Clinical Trials on Adjuvant Immuno-Cell Therapy for Liver Resection Among Patients with Hepatocellular Carcinoma

NCT Number	Location	Phase	Cell Product	Case Number	Year	Status
NCT00699816	Korea	PHASE3	CIK cells	230	2008	COMPLETED
NCT03592706	Taiwan	PHASE2/3	Ex vivo expanded autologous immune killer cells	60	2009	UNKNOWN
NCT01749865	China	PHASE3	CIK cells	200	2012	COMPLETED
NCT01828762	China	PHASE1/2	Autologous dendritic cells	8	2013	COMPLETED
NCT01914263	China	PHASE1	Cord Blood-derived CIK Cells	40	2013	UNKNOWN
NCT02008929	Korea	PHASE2	Ex Vivo Expanded Allogeneic NK Cell	5	2013	COMPLETED
NCT02026362	China	PHASE1/2	Multiple Antigen-Specific Cell	100	2013	SUSPENDED
NCT02725996	China	PHASE2	Autologous NK Cells	140	2016	UNKNOWN
NCT03067493	China	PHASE2	Neoantigen-loaded dendritic cell vaccine and neoantigen-activated T-cell therapy	98	2017	UNKNOWN
NCT03575806	China	PHASE2	TACE plus autologous Tcm immunotherapy	52	2017	COMPLETED
NCT05213637	China	PHASE2	Expanded Activated Lymphocytes	430	2018	UNKNOWN
NCT05352646	China	PHASE1	Autologous memory lymphocyte	26	2018	RECRUITING

who underwent hepatectomy for primary HCC confirmed the safety of TIL therapy.²¹² Similar to other solid tumors, immune infiltration significantly impacts postoperative survival in HCC, warranting further clinical trials to validate its potential.²¹³

CAR-T therapy, a focus of current ACT research, involves genetically engineering T cells to recognize specific TAAs, representing a novel immunotherapeutic approach against cancer.²¹⁴ Although CAR-T therapy as an adjuvant treatment for postoperative HCC has not yet progressed to clinical trials, preclinical studies and clinical trials have identified potential target antigens, such as mucin-1, GPC-3, AFP, NKG2D ligands, and c-MET.²¹⁴ However, the migration of CAR-T cells to tumor sites is critical for achieving cytolytic effects.²¹⁵ This remains a challenge as T cells lack chemokine receptors,²¹⁶ and the dense fibrotic structure of HCC tissues reduces chemokine expression, significantly impairing the ability of CAR-T cells to infiltrate tumors.^{217,218} The technology used to produce CAR-T cells can also generate CAR-NK cells. Compared to CAR-T cells, CAR-NK cells have a shorter lifespan, potentially reducing the risks of autoimmunity and tumorigenicity.²¹⁹ While CAR-NK cells have been investigated in clinical trials for leukemia, lymphoma, and some solid tumors, no trials have yet evaluated their efficacy in treating HCC.

A phase I trial is currently underway investigating the infusion of peripheral blood CD34⁺ stem cell-derived NK cells in patients with high-risk recurrent HCC following curative hepatectomy.²²⁰ NK cell-based therapies can be categorized into approaches utilizing primary peripheral blood NK cells, apheresis-derived products, or umbilical cord blood. Peripheral blood NK cells are readily accessible and widely used but are less amenable to functional enhancement due to their mature state and short lifespan. Furthermore, NK cell activity in patients with cirrhosis or HCC is already depleted, making them less favorable for therapeutic use.^{221–223} In contrast, methods producing NK cells from hematopoietic stem cells via apheresis are unaffected by the underlying disease and yield NK cells with promising activity. In cases where alternative sources are used, graft-versus-host disease poses a significant risk, necessitating the removal of T cells to prevent rapid elimination of infused NK cells.²²⁴

In summary, ACT has demonstrated significant potential in cancer therapy, and ongoing advancements continue to broaden its applicability, particularly in solid tumors such as HCC. Future research efforts should aim to overcome existing challenges and establish safer, more effective treatment modalities.

Adjuvant Immuno-Cell Therapy After Liver Transplantation for HCC

ACT among LT recipients requires careful consideration due to the unique immunological environment post-transplantation. Of note, the immunosuppression necessary to prevent graft rejection by suppressing adaptive immunity paradoxically increases the risk of tumor recurrence. To address this issue, studies have investigated the potential use of CAR T-cell immunotherapy targeting TAAs, demonstrating potent antitumor effects. Nevertheless, the occurrence of severe AEs, such as neurotoxicity and cytokine release syndrome (CRS), has limited its application in LT settings.^{225,226} On the other hand, the feasibility of hepatitis B virus-specific T-cell receptor (HBV-TCR) engineered T-cell therapy for recurrent HCC post-transplantation has been reported, with Phase I clinical trials confirming its safety.^{114,227} Notably, no participants in these trials exhibited CRS or neurotoxicity. Unlike CAR-T cell therapy, CAR-NK cell therapy has been associated with a minimal risk of neurotoxicity and CRS, making it a more viable option for LT patients.²²⁸ However, clinical trials for CAR-NK therapy in this context have not yet been conducted.

Autologous CIK cell therapy has demonstrated significant improvements in RFS and OS among HCC patients following curative treatment.^{201,229} The main advantage of CIK cells is that they can be administered multiple times after surgery. Based on this approach, a phase I/II trial is currently underway to evaluate the application of these techniques as adjuvant therapy after LT for HCC (NCT03983967). At present, this group's research is the most advanced and is closest to clinical application. A search of the ClinicalTrials.gov clinical trial registry revealed that there are currently seven clinical trials underway or completed in the United States and East Asia related to cell therapy for HCC after LT. (Table 4)

Importantly, in organ transplantation, immunosuppressive therapy primarily targets the adaptive immune system, specifically T and B lymphocytes, while relatively sparing the innate immune system, including NK cells. Consequently, NK cells serve as a crucial defense mechanism after LT, protecting recipients from infections and potential malignancies.^{230,231} Researchers in Japan and the United States have been conducting clinical trials to evaluate the potential of NK cell-based therapies in preventing HCC recurrence post-LT.^{25,232} Notably, these trials have reported no severe AEs such as acute rejection or graft-versus-host disease

Table 4 Summary of Clinical Trials on Adjuvant Immuno-Cell Therapy for Liver Transplantation Among Patients with Hepatocellular Carcinoma

NCT Number	Location	Phase	Cell Product	Case Number	Year	Status
NCT01147380	United States	PHASE I	Liver NK cells	18	2010	COMPLETED
NCT02399735	Korea	PHASE I	Peripheral NK cells	18	2015	UNKNOWN
NCT02719782	China	PHASE I	TCR-Redirected T cell	10	2015	COMPLETED
NCT02849015	China	PHASE I/2	Peripheral NK cells	20	2016	COMPLETED
NCT03634683	Singapore	PHASE I/2	TCR-Redirected T cell	60	2018	UNKNOWN
NCT03983967	Korea	PHASE I/2	CIK cells	19	2019	COMPLETED
NCT04677088	China	PHASE I	TCR-Redirected T Cell	7	2020	UNKNOWN

(GVHD), which were initially concerns associated with cell-based therapies. Furthermore, complication rates were comparable between high-dose and low-dose groups, demonstrating the safety of adoptive liver NK cell therapy.

These research groups have employed a distinctive approach, focusing on liver-resident NK cells rather than peripheral blood-derived NK cells. The greatest advantage lies in the fact that liver perfusate, which was previously discarded at LT, contains an abundant source of liver-derived lymphocytes. This eliminates concerns regarding material supply shortages, making it a highly sustainable resource for therapeutic applications. Liver-resident NK cells exhibit superior antitumor activity against HCC cells, primarily through the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptor pathway, conferring higher antitumor efficacy compared to peripheral NK cells.^{233–235} The expression of TRAIL and the NK activation receptor NK group 2 member D (NKG2D) has been correlated with the cytotoxicity of liver NK cells against tumor cell lines.²³⁶ Interestingly, an exploratory study involving 77 Japanese patients with HCC post-LT evaluated the impact of donor-derived NK cells on recurrence prevention. The findings revealed significantly improved outcomes in patients with mismatched NK cell genotypes, particularly those involving specific interactions between killer immunoglobulin-like receptors (KIR) and human leukocyte antigens. These results highlight the potential of donor liver-derived NK cell-based immunotherapy for achieving favorable outcomes in such patients.²³⁷

Globally, early-phase clinical trials utilizing donor-derived liver NK cells, HBV-TCR-engineered T-cells, and CIK cells have shown promising results regarding safety and efficacy in preventing recurrence. Advances in molecular engineering are expected to further drive the development of TCR-T, CAR-T, and CAR-NK therapies, particularly in addressing the unique immunological challenges of HCC patients post-LT. These advancements aim to reduce toxicity and enhance the antitumor cytotoxicity while expanding clinical applicability in this LT patient population for HCC.

Conclusion

In conclusion, advances in immunotherapy have ushered in a new era of potential breakthroughs in the postoperative management of HCC. Both ICIs and immune-cell therapies have demonstrated promising roles in reducing recurrence and improving survival among patients undergoing resection or LT. However, significant challenges remain, including the low immunogenicity of HCC, the immunosuppressive TME, and the complexities of balancing graft tolerance with antitumor immunity in LT recipients. Emerging strategies, such as tailored combination therapies, ACT, and innovative approaches like liver-resident NK cell-based therapies, are expanding the horizon of clinical applicability. Continued efforts to refine immunotherapeutic regimens, identify predictive biomarkers, and enhance safety profiles are critical for translating these advancements into durable clinical benefits. Equally important will be future studies focused on the characterization and validation of prognostic biomarkers that can guide risk stratification and enable truly personalized immunotherapeutic strategies tailored to the heterogeneity of HCC. As ongoing and future clinical trials address these challenges, the integration of immunotherapy into standard treatment paradigms holds immense promise for transforming outcomes in HCC.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

All authors declared that there are no conflicts of interest.

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