JHEP|Reports

Liver resection and transplantation in the era of checkpoint inhibitors

Parissa Tabrizian[1], Rebecca Marino[1], Pierce K.H. Chow[2,3,*]

Summary

Immune checkpoint inhibitors (ICIs) have revolutionised the treatment landscape for advanced hepatocellular carcinoma (HCC). The combination of atezolizumab and bevacizumab has demonstrated efficacy, establishing a new standard of care for advanced HCC. Neoadjuvant studies have shown promising results with high response rates, increasing research into ICIs' role. In the perioperative setting, in addition to adjuvant and neo-adjuvant therapies, strategies for "downstaging" and "bridging" patients to liver transplantation (LT) are being investigated, broadening the eligible candidate pool. Furthermore, therapeutic advances have reshaped conversion strategies for hepatic resection, with emerging evidence indicating a role for adjuvant immunotherapy in patients at high risk of postoperative recurrence. In LT, concerns have arisen over the potential conflict between immunosuppression needs and the immune-enhancing effects of ICIs, with reports of severe rejection. However, liver-specific factors may lessen rejection risks, prompting exploration into the safety of pre-transplant ICI administration. Moreover, ongoing trials must prioritise patient selection and vigilant management protocols. Despite the remarkable progress in immunotherapy, the intricate molecular interactions within the tumour microenvironment and their implications on oncogenic pathways remain incompletely understood. This highlights the need for specialised expertise to effectively integrate immunotherapy into the surgical management of HCC. Key challenges include ensuring safety, optimising oncological outcomes, managing the risk of graft rejection in transplant recipients, and refining patient selection criteria. In this review, we aim to provide a comprehensive overview of the evolving role of immunotherapy in the surgical management of HCC, discussing the rationale for its application in both pre- and post-surgical contexts, leveraging current clinical experience, identifying potential limitations, and envisioning future applications. By integrating existing knowledge and highlighting areas for further investigation, this review seeks to inform clinical practice and guide future research endeavours.

Introduction

The management of hepatocellular carcinoma (HCC) faces persistent challenges. The advent of effective systemic therapies, particularly immune checkpoint inhibitors (ICIs), has improved outcomes for patients in the advanced stages. Curative therapies, including ablation, resection, and transplantation, are offered to approximately 30% of patients and result in a median overall survival (OS) of more than 5 years for those with early HCC within the Milan criteria.[1–4] Despite the curative intent, 30–50% of patients experience disease recurrence at 3 years.[4,5] While the SHARP study established sorafenib, a tyrosine kinase inhibitor (TKI), as the first effective systemic therapy for advanced HCC in 2008,[6] the efficacy of sorafenib remains modest and debated owing to the absence of a predictive biomarker. Importantly, the large SPACE phase III trial failed to establish a role for sorafenib, even when combined with effective loco-regional therapy (LRT, *e.g.* doxorubicin-eluting beads transarterial chemoembolisation [TACE]), for intermediate-stage HCC. The trial demonstrated the feasibility of the technique but showed no clinical benefit in terms of time to tumour progression or survival.[7]

Recent advances in immunotherapeutic and targeted approaches have transformed therapeutic protocols. ICIs targeting PD-1 and PD-L1 have shown promise, particularly in patients with advanced HCC in whom first-line TKIs fail.[8–10] In this regard, the CheckMate 040 randomised trial demonstrated that the combination of nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) further improved survival rates, with a good safety profile, in patients who were either refractory or intolerant to previous treatment attempts with sorafenib.[11] In 2018, the combination therapy of atezolizumab plus bevacizumab replaced sorafenib as first-line systemic therapy in advanced HCC as a result of the IMbrave150 trial. IMbrave150 was a significant milestone, with atezolizumab plus bevacizumab achieving a 19.2 month median OS for patients with advanced HCC, surpassing sorafenib as first-line therapy.[12] In 2022, the STRIDE regimen (durvalumab plus tremelimumab) was also shown to be superior to sorafenib for advanced HCC in the HIMALAYA trial and delivered a median OS of 16.4 months.[13] Among the recent phase III trials, CARES-310 provided further evidence supporting immunotherapy combinations, including anti-PD-1 agents, for advanced and unresectable

* Corresponding author. Address: Duke-NUS Medical School Singapore, 30 Hospital Boulevard, 168583, Singapore; Tel.: +65 63065424.
E-mail address: pierce.chow@duke-nus.edu.sg (P.K.H. Chow).
https://doi.org/10.1016/j.jhepr.2024.101181

Keypoints

- Neoadjuvant immunotherapy in early-stage HCC shows promise in safely expanding resection indications and potentially reducing post-surgery recurrence, with early clinical trials indicating significant pathological responses without compromising the feasibility of surgery.
- Immunotherapy in the pre-transplant setting has shown initial oncologic success as both a "downstaging" and "bridging" strategy. The controversial theme of hepatotoxicity and graft rejection, coupled with limited knowledge of the interplay between immunosuppression and immunotherapy, has challenged its systematic application. An 8-week interval between immunotherapy and transplantation is advised.
- The IMbrave050 trial revealed the groundbreaking efficacy of adjuvant atezolizumab and bevacizumab combination therapy in improving recurrence-free survival after curative resection or ablation for HCC, marking the first evidence of combination immunotherapy's effectiveness in reducing postoperative recurrence.
- Immune checkpoint inhibitors for recurrent HCC after transplantation have been burdened by high acute rejection rates and graft losses. Recent experiences with combination schemes, involving bevacizumab and anti-PD-1/PD-L1, demonstrated sustained disease control and tolerance, providing hope for future advances in patient selection and understanding of immunological interactions.
- The potential role of immunotherapy (either alone or in combination, and as either a neoadjuvant or adjuvant option) in the surgical management of HCC is currently being explored by over 30 clinical trials. These trials are likely to further transform and improve current management protocols.

HCC. The combination of camrelizumab and rivoceranib (a VEGFR2-targeted TKI) demonstrated impressive survival outcomes, with a striking median OS of 22.1 months compared to 15.2 months with sorafenib monotherapy.[14]

In addition to the absence of predictive molecular biomarkers, the mechanisms dictating the response and resistance to ICIs remain incompletely understood. The relationship between chronic liver inflammation, changes in the hepatic immune microenvironment, and post-surgical tumour recurrence or new lesion development requires further exploration.[3] While ICIs and combination immunotherapy show promise for advanced HCC, their efficacy in early/intermediate stages is uncertain.[15–17]

Efforts have shifted toward extending immunotherapy to patients with lower tumour burden. Recent FDA approvals for perioperative immunotherapeutic strategies in other resectable early-stage malignancies have spurred interest in expanding immunotherapy's role.[18–20] The goal is to facilitate curative surgery by identifying effective immunotherapeutic and combination strategies to reduce historically high recurrence rates and to serve as a downstaging therapy.

In this review, we aim to elucidate the evolving landscape of novel systemic immunotherapy approaches in the perioperative management of HCC. We seek to provide insights into their adjunctive role in liver resection and transplantation settings, exploring their potential to improve outcomes and reshape therapeutic paradigms for patients with HCC across disease stages.

The immune landscape beyond immunotherapy for HCC

Immunogenomic profile

Adaptive and innate immunity are pivotal in cancer immunosurveillance, where the activation of effector T cells controls cancer progression, while exhaustion and the influx of regulatory cells promote disease advancement. The liver's immune landscape, marked by immunosuppressive cells and signals, fosters a tolerogenic microenvironment.[3] Resident cells respond to tumorigenic cues by activating evasion mechanisms, including immunosuppressive cytokine secretion (*e.g.*, IL-10), upregulation of PD-1 and PD-L1, CTLA-4 expression, neoangiogenesis, recruitment of regulatory T helper 17 cells and oncofoetal regression.[21,22]

Immunotherapy encompasses a wide spectrum of therapeutics, ranging from CAR (chimeric antigen receptor) T-cell therapies to ICIs. ICIs target PD-1, PD-L1 and CTLA-4 in solid tumours. PD-1 and PD-L1 inhibition restores CD8+ T-cell function by disrupting the PD-1-PD-L1 synapse, while CTLA-4 blockage enhances T-cell activation by promoting CD28-B7 interactions, altering effector and regulatory dynamics.[23–26]

Hepatocarcinogenesis's primary immune escape mechanisms explain the efficacy of novel ICI regimens. The liver environment naturally bears an anti-inflammatory imprint to achieve immune tolerance toward harmless foreign molecules. Kupffer cells and stellate cells are key actors in maintaining an effective tolerogenic environment. They function as antigen-presenting cells, producing inhibitory cytokines such as IL-10 and promoting the activation of regulatory T cells, which leads to the upregulation of PD-L1 expression and T-cell apoptosis.[27–29] These mechanisms create a permissive tumour microenvironment, which serves as the primary substrate mediating immune evasion.[3] However, the heterogeneous HCC microenvironment, influenced by liver damage aetiology, yields varied immunological profiles, explaining variable ICI outcomes.[3,30] "Inflamed" HCC subtypes, constituting about 35% of cases, exhibit robust immune responses akin to successfully treated malignancies such as melanoma, suggesting potential ICI efficacy across disease stages. Conversely, "non-inflamed" tumours feature immune exclusion mechanisms, including M2 macrophages, regulatory T cells, chromosomal instability, and TP53 mutations, underpinning resistance to ICIs.[31,32]

Understanding these immune profiles informs personalized ICI approaches. "Inflamed" signatures predict favourable ICI responses, indicating therapeutic benefits across HCC stages.

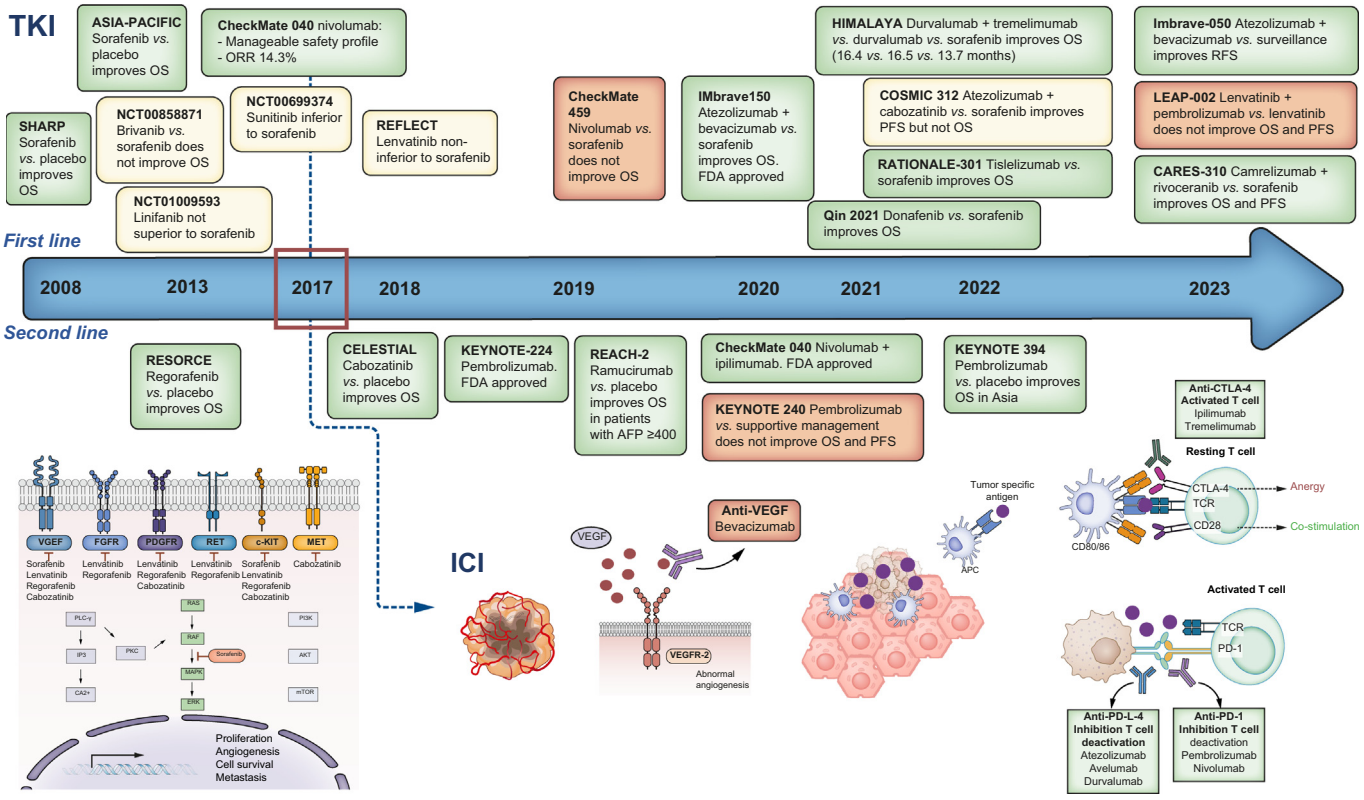

Fig. 1. Chronological overview of all clinical trials investigating immunotherapy and immune checkpoint inhibitors in the treatment of HCC. Each trial is represented on a timeline, color-coded to reflect outcomes: green squares denote trials with a statistically significant benefit in overall survival and/or recurrence-free survival due to immunotherapy/ICI regimens; yellow squares represent trials with inconclusive benefits; and red squares indicate trials where immunotherapy did not result in survival improvements. HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor.

Conversely, "non-inflamed" phenotypes suggest resistance to conventional ICIs, necessitating alternative strategies.[3,32]

A chronological overview of all clinical trials investigating TKIs and ICIs in the treatment of HCC is provided in Fig. 1.

Rationale

Recent technological advances and strategic screening protocols have increased the diagnosis of early-to-intermediate-stage HCC, suitable for surgical intervention. However, despite curative intent, recurrence rates can reach up to 70% after resection, with 50% recurring within 2 years.[1,5,33] Recurrence following surgical resection for HCC follows a bimodal distribution, with the first peak at around 12 months linked to micro-metastases arising from the index resected tumour, and a lower peak at 4–5 years linked to *de novo* HCC arising from the underlying diseased liver.[34,35] While liver transplantation (LT) may demonstrate superior long-term survival outcomes, stringent selection criteria and organ shortages limit its widespread application.[36,37] However, in recent years, with advances in bridging therapies and a deeper understanding of tumour biology, the boundaries of transplantation have been continuously pushed, prompting exploration and expansion of eligibility criteria and treatment modalities.[38]

While no adjuvant therapy has yet been approved for HCC after curative intent therapy, there has been a growing interest in strategies to deliver systemic or loco-regional therapy before curative intent therapy.[3,39] Neoadjuvant therapy refers to therapy delivered to tumours that are already amenable to surgical resection (or transplantation in HCC) but the term is sometimes also loosely used to include conversion/down-staging therapy and bridging therapy.[40] In short, the rationale behind the use of systemic or loco-regional treatment protocols prior to curative intent therapy is grounded in four main oncologic pillars: 1) to address micro-metastatic disease, thereby reducing postoperative recurrence rates in patients already meeting surgical criteria; 2) to induce effective regression of tumour burden in cases that do not meet surgical criteria, as a "downstaging" strategy for transplantation or as a "conversion" strategy for resection; 3) to halt tumour growth and potential progression in patients already listed for transplantation, as a "bridging strategy", to prevent waitlist dropouts; and 4) to provide prognostic insights into tumoural pathologic responses that could guide subsequent adjuvant decisions.

Neoadjuvant immunotherapies, especially in patients with immunocompetent systems and less heterogeneous tumour microenvironments, have shown success in melanoma and lung cancer.[20,41] Not all patients share the same risk of recurrence, with distinct underlying immune molecular bases for early and late recurrence. The risk-benefit ratio may also be problematic, as ICIs are associated with high rates of hepatotoxicity and graft failure after transplantation.[3]

Nevertheless, comprehensive analysis of survival outcomes from landmark phase III trials showed an overall improvement in OS when specifically combining ICIs with anti-VEGF agents, with data suggesting a remarkable reduction of death by up to

43%, and further confirmed the reduced risk of death with ICI monotherapies compared to sorafenib.[17] The survival benefit justifies the widespread use of ICIs in previously stagnant HCC management protocols.

The rationale behind the implementation of immunotherapeutic schemes as neoadjuvant or adjuvant strategies is illustrated in Figs 2 and 3, respectively.

Liver resection: The role of preoperative immunotherapy

Neoadjuvant immunotherapy for resectable HCC

In patients with well-compensated liver function and early-stage HCC, surgical resection is the primary treatment option. Numerous Eastern and certain Western guidelines advocate for surgical resection beyond the recommendations provided by AASLD and EASL.[42–45] Their objective is to attain negative surgical margins and broaden the scope of indications for resection.

Despite this, only four early-phase clinical trials (phase Ib/II) have investigated the use of neoadjuvant ICIs in cases of upfront resectable HCC.[46–49] The primary objectives focused on ensuring safety, assessing feasibility, and evaluating pathologic responses. The rationale was to optimise the risk-benefit ratio, considering the high risk of post-surgery recurrence by targeting existing micro-metastatic spread.

A randomised, phase II trial by Kaseb *et al.* investigated the safety and efficacy of a 6-week neoadjuvant regiment with nivolumab compared to the combination of nivolumab and ipilimumab.[46] The combination arm showed a significantly higher incidence of treatment-related adverse events (TRAEs) compared to the other arm (43% *vs*. 23%), as previously observed in more advanced settings. However, no TRAEs compromised the feasibility of resection and no surgical delays were recorded in either arm. Of 27 patients, 20 underwent surgical resection. Notably, eight had tumours exceeding 10 cm, and nine presented with multifocal tumours. Major pathologic response (MPR), defined as necrosis ≥70%, was documented in six patients (three in each arm); however, no responses according to RECIST 1.1 were reported, suggesting inconsistencies between radiological and pathological assessments. During follow-up (median 2 years), none of the six MPR achievers showed signs of recurrence, while almost half of the non-responders experienced tumour relapse. Specimens with MPR displayed increased expression of effector T cells, emphasising the impact of "inflamed" HCC subtypes on responses to ICI regimens.[46]

Similarly, D'Alessio *et al.* investigated the neoadjuvant combination of nivolumab and ipilimumab for early-stage HCC.[47] No delays in surgery were reported; however, despite the non-availability of precise tumour necrosis rates, pathological responses were achieved in seven of nine pathologic evaluations, including two complete responses. This contrasted with the radiological evaluation, which indicated two partial responses and an objective response rate of 23%.

While no standardised pathologic response has been validated as a clinical endpoint for HCC, the results mentioned

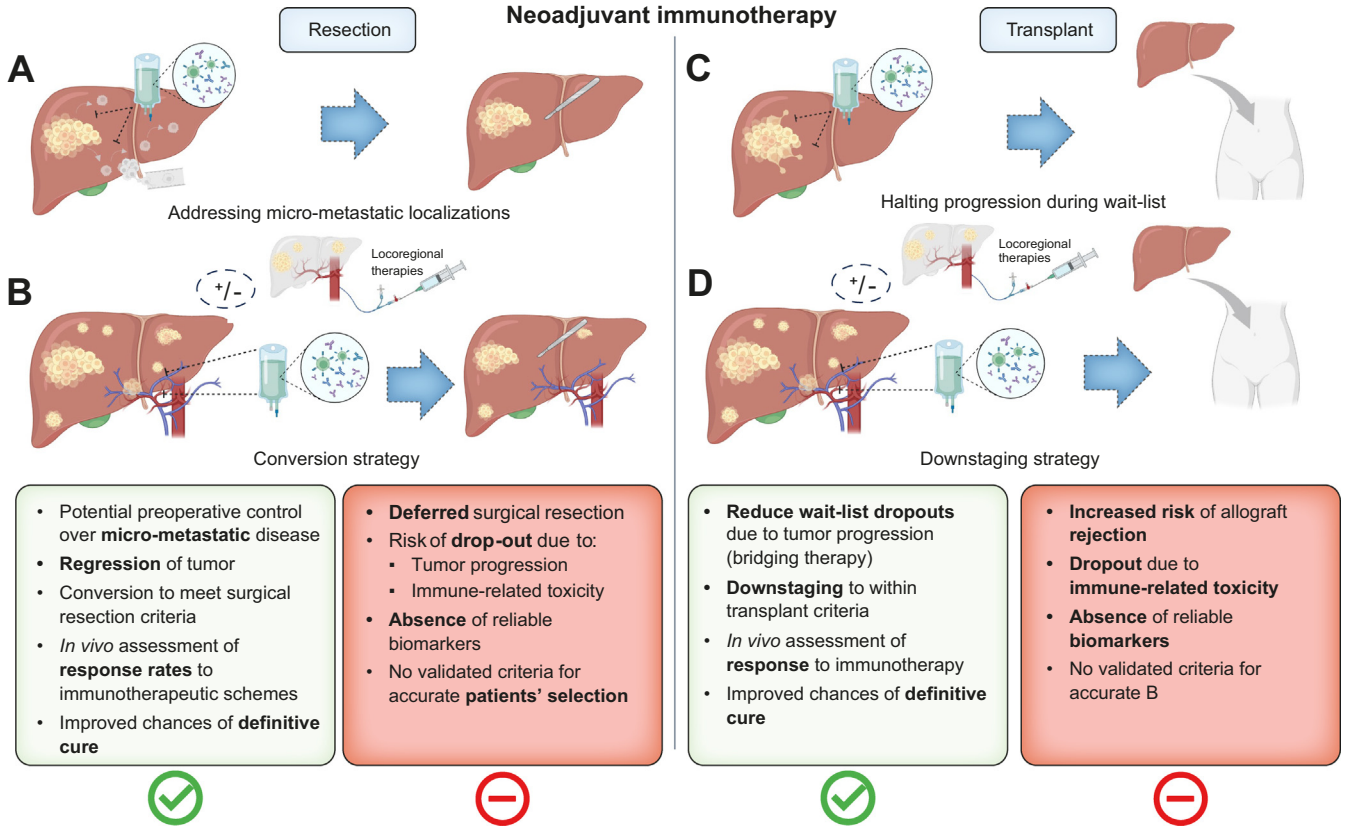

Fig. 2. Rationale for implementing neoadjuvant immunotherapy regimens before liver resection and before liver transplantation. (A, B) Rationale for implementing neoadjuvant immunotherapy regimens before liver resection. (C, D) Rationale for implementing neoadjuvant immunotherapy regimens before liver transplantation.

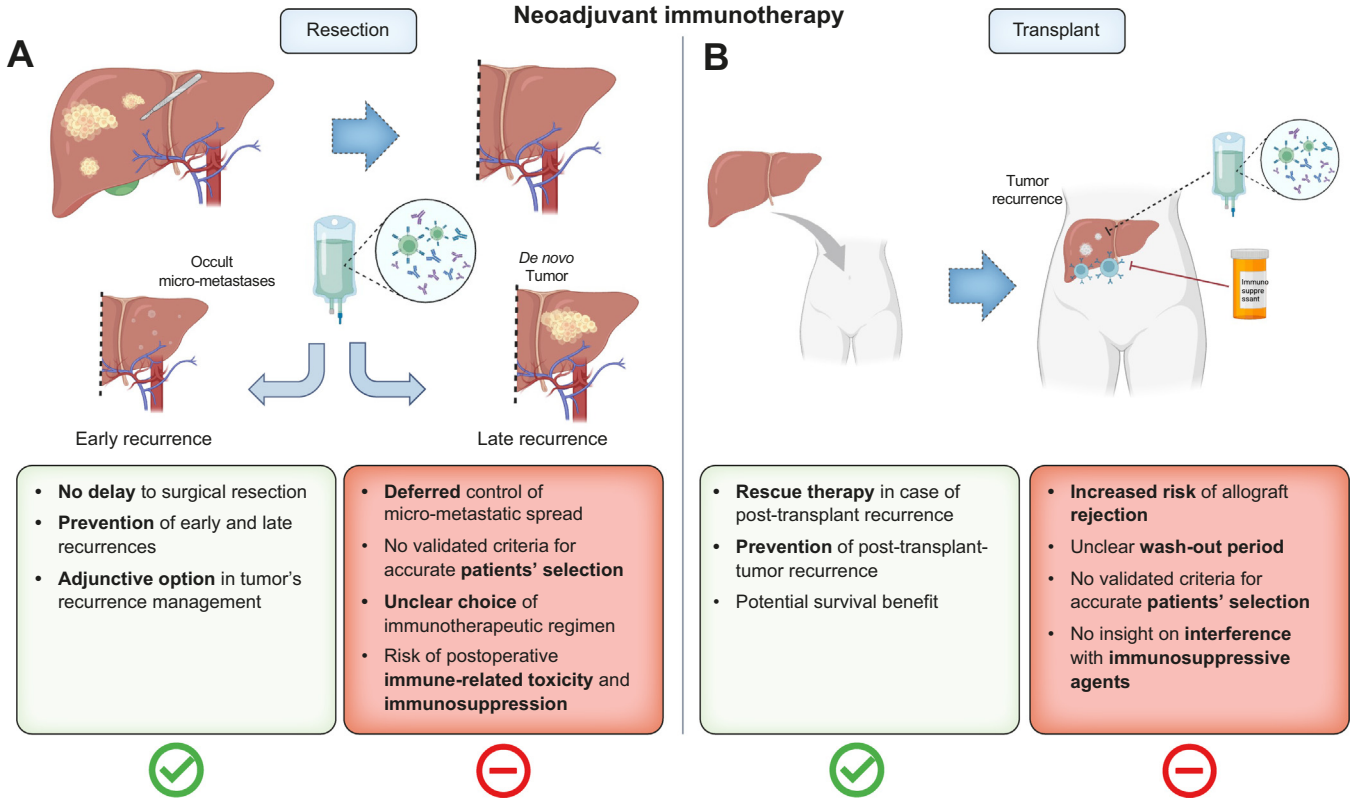

Fig. 3. Rationale for implementing adjuvant immunotherapy regimens after liver resection and after liver transplantation. (A) Rationale for implementing adjuvant immunotherapy regimens after liver resection. (B) Rationale for implementing neoadjuvant immunotherapy regimens after liver transplantation.

above align with the phase II trial by Marron *et al.* In this trial, neoadjuvant cemiplimab led to successful surgical resection in 20 of 21 patients without delays. Notably, 35% of treated patients reported a significant pathological response.[48] Once again, the extent of the pathological response achieved was not adequately captured by radiological assessment (RECIST1.1), while tumours exhibiting a robust baseline "inflammatory" phenotype demonstrated favourable correlations with the tumour's response to neoadjuvant therapy.

Finally, although the predominant proposal for TKI/ICI combinations has been in advanced HCC, the use of camrelizumab with apatinib as a neoadjuvant strategy has yielded satisfactory results. This approach was associated with low rates of grade 3 TRAEs and led to MPR in 4 of 17 patients who underwent surgical resection.[49]

Table 1 presents a comprehensive review of the available literature regarding the application of neoadjuvant immunotherapy for resectable HCC and as downstaging or conversion therapy for unresectable HCC.

Immunotherapy for unresectable HCC: The concept of "conversion"

Despite poor survival outcomes, surgical resection in the absence of effective alternatives may offer a prognostic advantage for advanced HCC. Over the last decade, the concept of conversion therapy, leveraging new systemic therapies, has emerged as a central theme.[50] Initially applied through LRTs, such as TACE, hepatic arterial infusion pump, and transarterial radioembolisation and systemic TKIs, these interventions aimed to reduce tumour burden and enhance resection rates. However, their application has yielded unclear prognostic outcomes and lacks discernible benefits.[51–66] With reference to the role of preoperative LRT, mixed results have been reported with preoperative TACE, with some studies suggesting inferior outcomes. However, differences in definitions of resectability worldwide hamper a univocal interpretation of such perioperative studies. A potential role for LRT combined with resection has been highlighted in patients with vascular encasement, a cohort considered unresectable by BCLC guidelines.[2,15] Randomised trials are ongoing to explore the potential application of combining LRT with ICIs, as new hopes to enhance their efficacy are based on the hypothesised synergistic effect of LRT and ICIs. LRT, particularly when inducing a partial response, can stimulate a systemic immune response by releasing neoantigens. This immunogenic role can complement ICI's modulation, positively upregulating the tumour microenvironment (TME) by boosting immune cell activation.[39]

Here, we review conversion immunotherapy. Conversion strategies with ICIs, and combinations like atezolizumab and bevacizumab, have shown promising results.[67–76] The introduction of ICIs marked a significant advance in the conversion space for initially unresectable HCC. A phase Ib clinical study investigated the combination of neoadjuvant cabozatinib and nivolumab, and reported an 80% success rate in enabling R0 surgery, with associated molecular profiling confirming the role of an "inflammatory" phenotype in determining the pathological response to ICIs.[77]

Despite variations in patient selection and treatment protocols, studies have suggested the feasibility, safety, and oncologic benefits of ICIs as a conversion strategy for

Table 1. Immunotherapy as a neoadjuvant strategy before liver resection.

Author	Year	Patients, n	Study type	Aetiology	Neoadjuvant immunotherapy	Neoadjuvant duration	Other pre-resection treatments	Neoadjuvant TRAEs ≥ Grade 3	Surgical resection	Adjuvant immunotherapy	Tumour necrosis ≥ 50%	Recurrence
Resectable HCC at diagnosis												
Kaseb *et al.*[46]	2022	30	Randomised clinical trial	HBV (7), HCV (7), Other (13)	Nivolumab (13) Nivolumab + Ipilimumab (14)	3 cycles 3 cycles	No	3 6	20	Yes; nivolumab *vs.* nivolumab + ipilimumab	6	Yes (7)
D'Alessio *et al.*[47]	2022	17	Single-arm clinical trial (phase Ib)	Viral hepatitis (7), Other (10)	Nivolumab (day 1) + Ipilimumab (day 22)	2 cycles	No	1	10	No	7	Yes (1)
Marron *et al.*[48]	2022	21	Single-arm clinical trial (phase II)	HBV (8), HCV (5), NASH (5), alcohol related (1)	Cemiplimab	2 cycles	No	2	20	Yes; cemiplimab (8 cycles)	14	NR
Xia *et al.*[49]	2022	20	Single-arm clinical trial (phase II)	HBV (15), HCV (1), Other (2)	Camrelizumab + Apatinib	3 cycles 21 days	No	3	17	Yes: camrelizumab + apatinib (8 cycles)	4	Yes (6)
Unresectable HCC at diagnosis												
Williet *et al.*[51]	2011	1	Case report	HCV	Sorafenib	NR	Yes: gemcitabine + oxaliplatin	No	1	Yes: sorafenib + gemcitabine	NR	NR
Barbier *et al.*[52]	2011	2	Case report	Alcohol related	Sorafenib	9 months	No	No	2	No	1	Yes (1/2)
Irtan *et al.*[53]	2011	2	Case report	Haemochromatosis HBV	Sorafenib	6 months 1 year	No	No	2	No	2	No
Curtit *et al.*[54]	2011	1	Case report	HCV	Sorafenib	6 months	No	1	1	No	1	No
Kermiche-Rahali *et al.*[55]	2013	1	Case report	Alcohol related	Sorafenib	9 months	No	1	1	No	1	No
Nakamura *et al.*[56]	2015	1	Case report	HBV	Sorafenib	3 months	Yes: TACE	NR	1	Yes: sorafenib	NR	No
Kitajima *et al.*[57]	2015	1	Case report	HCV	Sorafenib	5 months	Yes: EBRT	1	1	NR	1	No
Kim *et al.*[58]	2017	1	Case report	HCV	Sorafenib	12 months	No	No	1	NR	1	No
Yoshimoto *et al.*[59]	2018	38	Case series	NR	Sorafenib	NR	Yes	NR	8	No	NR	Yes (2/8)
Chen *et al.*[78]	2019	1	Case report	HBV	Lenvatinib + nivolumab	4 months	No	1	1	NR	NR	No
He *et al.*[60]	2019	247	Randomised clinical trial	HBV (199), HCV (13), other (35)	Sorafenib (day 1 to 21) Sorafenib + HAIC (every 3 weeks)	3 weeks cycles	No	51 66	1 16	NA	NR	Yes
Tomonari *et al.*[61]	2020	3	Case Series	NASH (2), alcohol related (1)	Lenvatinib	6 months	Yes: TAE	No	2	Yes in 1: lenvatinib	NR	No
Ohya *et al.*[62]	2020	1	Case report	HBV	Lenvatinib	4 months	No	No	1	Yes: lenvatinib	NR	No
Takeda *et al.*[63]	2020	1	Case report	HBV	Sorafenib/ regorafenib	12 months	No	1	1	NR	1	No
Takahashi *et al.*[64]	2021	1	Case report	HCV	Lenvatinib	3 months	No	No	1	NR	NR	No
He *et al.*[65]	2021	157	Retrospective	NR	Lenvatinib Lenvatinib + toripalimab + HAIC (every 3 weeks)	Until tumour shrinkage/ progression	NA	 22 61	0 9	NA	NR	Yes
Shindoh *et al.*[66]	2021	107	Retrospective	HBV (16), HCV (54), HBV+HCV (1), other (36)	Lenvatinib	Until tumour shrinkage/ progression	Yes: TACE	29	16	No	NR	NR

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Table 1. (*continued*)

Zhu *et al.*[79]	2021	63	Retrospective	HBV (61), HCV (0), other (2)	Lenvatinib/apatinib (TKI) + nivolumab/ pembrolizumab/sinti-limab/camrelizumab (anti-PD1)	3.2 months range (2.4- 8.3)	No	2/10	10	No	6/10	Yes (1/10)
Ho *et al.*[77]	2021	15	Single-arm clinical trial (phase Ib)	HBV (3), HCV (4), non-viral (8), other (3)	Nivolumab + cabozatinib	8 weeks	No	2/15	12	Yes; nivolumab + cabozatinib (4-6 weeks post-surgery)	5/12	Yes (5/12)
Zhang *et al.*[80]	2021	10	Retrospective	HBV (8), HCV (1), other (2)	Lenvatinib/apatinib (TKI) + pem-brolizumab/sintili-mab/torialimab (anti-PD1)	4-10 cycles	Yes: TACE	0	8	No	NR	Yes (2/10)
Huang *et al.*[81]	2021	60	Retrospective	NR	Lenvatinib + nivolu-mab/camrelizumab/ pembrolizumab/sinti-limab/toripalimab	7.5 months range (2-22)	No	23/60	6	No	NR	NR
Yi *et al.*[82]	2022	107	Retrospective	HBV (24/30), other (6/30)	Lenvatinib + camreli-zumab/sintilimab/ toripalimab/pem-brolizumab/tislelizu-mab (anti-PD1)	4 cycles range (3-21)	No	25/107	30	No	10/30 complete pathological response	11/28
Matsuki *et al.*[67]	2022	1	Case report	Other	Atezolizumab + bevacizumab	4 cycles	No	1 (colitis)	1	No	1	No
Fukunaga *et al.*[68]	2023	1	Case report	Alcohol related	Atezolizumab + bevacizumab	7 cycles	No	1 (hepatitis/ intra-tumoural haemorrhage)	1	No	1	No
Uchida *et al.*[69]	2023	1	Case report	NR	Atezolizumab + bevacizumab	3 cycles	No	NR	1	NR	1	NR
Takamoto *et al.*[70]	2023	2	Case report	NR	Atezolizumab + bevacizumab	8 cycles 5 cycles	Yes in 1: HAIC	NR	2	No	2	NR
Tsunemitsu *et al.*[71]	2023	2	Case report	Alcohol related (1), other (1)	Atezolizumab + bevacizumab	10 cycles 7 cycles	No	NR	2	NR	2	NR
Miyata *et al.*[72]	2023	1	Case report	NR	Atezolizumab + bevacizumab	15 cycles	Yes: TAE (rupture)	0	1	No	NR	No
Kurisaki *et al.*[73]	2023	1	Case report	HBV	Atezolizumab + bevacizumab	4 cycles fol-lowed by 1 cy-cle of atezolizumab monotherapy	No	0	1	No	1	No
Sato *et al.*[74]	2023	1	Case report	HCV	Atezolizumab + bevacizumab	4 cycles fol-lowed by 1 cy-cle of atezolizumab monotherapy	No	0	1	No	1	No
Chiang *et al.*[85]	2023	33	Single-arm clinical trial "STAR-FIT" (phase II)	HBV (24), HCV (4), alcohol abuse (2), other (3)	TACE + SBRT (5 fractions 40Gy) + avelumab	No minimum treatment duration	No	11	2*	No	2	NR
Zhang *et al.*[84]	2023	56	Single-arm clinical trial (phase II)	HBV (49), HCV (5), other (2)	Lenvatinib + anti-PD1	Up to 48 weeks	No	24	21 (31 conversions, 10 refused surgery)	Yes: anti-PD1 for 6 months	17/21	47.6% 12-months RFS

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Table 1. (*continued*)

Author	Year	Patients, n	Study type	Aetiology	Neoadjuvant immunotherapy	Neoadjuvant duration	Other pre-resection treatments	Neoadjuvant TRAEs ≥ Grade 3	Surgical resection	Adjuvant immunotherapy	Tumour necrosis ≥ 50%	Recurrence
Zhu *et al.*[83]	2023	101	Retrospective	HBV (97), HCV (4)	Lenvatinib/apatinib/sorafenib (TKI) + pembrolizumab/nivolumab/camrelizumab/toripalimab/sintilimab (anti-PD1)	3.9 months IQR (2.5 - 5.9)	No	0	24	Yes (TKI + anti-PD1)	33	7/24
Tomonari *et al.*[75]	2023	244	Retrospective	HBV (32), HCV (94), other (118)	Lenvatinib (131) Atezolizumab + bevacizumab (113)	211 days IQR (162-310)	Yes: immunotherapy	NR	6 (atezolizumab + bevacizumab) 6 (lenvatinib)	Yes (4/12)	NR	9/12
Kudo *et al.*[76]	2023	110	Retrospective	HBV (16), HCV (41), non-viral (47), other (6)	Atezolizumab + bevacizumab	6 cycles	Yes: TACE, lenvatinib	NR	7**	NR	3/7 complete response	No

EBRT, external beam radiotherapy; HAIC, hepatic arterial infusion chemotherapy; NA, not applicable; NASH, non-acoholic steatohepatitis; NR, not reported; RFS, recurrence-free survival; SBRT, stereotactic body radiotherapy; TAE, transarterial embolisation; TACE, transarterial chemoembolisation; TKI, tyrosine kinase inhibitor; TRAE, treatment-related adverse events.
*Curative conversion achieved in 18 patients overall, with 14 complete responses.
**Curative conversion achieved in 35 patients overall.

advanced HCC. Multiple retrospective reports have shown R0 resection rates surpassing 20%, particularly in cases with significant tumour response, according to RECIST v1.1.[78–83] While the R0 rates were modest, these were in the context of initially unresectable cases.

There have been few prospective clinical trials in this space. Two trials have recently combined perioperative ICIs with either lenvatinib or sequential LRTs in a conversion setting and demonstrated encouraging results. These trials have reported conversion success rates ranging from 32.1% to 55.4%, along with meaningful OS rates.[84,85]

A phase II single-arm clinical trial conducted by Zhang *et al.* demonstrated favourable oncological outcomes with a combination of TKIs and ICIs (anti-PD-1 agents) in patients with macroscopic vascular invasion. The study achieved high rates of conversion surgery with curative intent and recurrence-free survival at 12 months. The therapy utilised four different drug regimens: lenvatinib combined with sintilimab (n = 42), lenvatinib with pembrolizumab (n = 8), lenvatinib with toripalimab (n = 4), and lenvatinib with tislelizumab (n = 2). Among the 51 patients who underwent clinical evaluation, 31 met the criteria for successful conversion, including four patients who achieved a complete response. The resulting conversion success rate stood at 55.4% (31 of 56).[84]

The STAR-FIT trial, a phase II study with a single arm, provided insights into successfully combining LRTs with ICIs, resulting in a significant proportion of patients with unresectable HCC becoming eligible for curative treatment.[85] The focus of the study was on investigating the sequential integration of TACE, stereotactic body radiotherapy, and avelumab (anti-PD-L1 agent) in patients diagnosed with locally advanced unresectable HCC. Notably, more than 60% of the total cohort was classified as BCLC stage C, which is a group with a poor baseline prognosis.

The primary goal was to determine the proportion of patients eligible for potentially curative treatment following conversion therapy. Of the 33 patients evaluated, 4 (12%) achieved curative treatment – two through resection and two through radiofrequency ablation. Additionally, 14 patients (42%) experienced complete radiological responses, showing an impressive OS rate of 92% at 2 years.[85]

The assessment of HCC recurrence in patients who have undergone resection following successful conversion immunotherapy remains limited. The primary focus is on identifying the optimal immunotherapeutic combination capable of enabling surgical resection for patients initially deemed ineligible for curative options. Zhang *et al.* documented a postoperative median recurrence-free survival of 11.6 months, while the STAR-FIT trial reported an overall median progression-free survival of 20.7 months.[84,85] Notably, in the former, 42% of patients achieved a complete radiological response, and no post-treatment resection was attempted. Despite the scarcity of available data, meticulous preoperative patient selection emerges as pivotal for optimising postoperative outcomes. This is underscored by the association between a longer time to recurrence and sustained radiological responses, which is further supported by the attainment of major or complete responses upon final pathology evaluation.[77,81,83] Consequently, the true oncological efficacy of sequential resection depends on accurately assessing preoperative responses, as proceeding with resection following an inadequate radiologic response may prove futile.

Table 2. Review of ongoing clinical trials assessing the role of ICIs (either as a neoadjuvant, combined neoadjuvant/adjuvant or adjuvant strategy) in the resection setting.

Trial number	Year	Status	Type	Neoadjuvant immunotherapy	Adjuvant immunotherapy	Primary outcome	Enrolment	Region	Estimated study completion
Neoadjuvant									
NCT03510871	2019	Completed	Interventional, phase II	Nivolumab + ipilimumab (2 to 4 cycles)	No	>10% of decrease of the sum of the target lesions according to RECIST 1.1	40	Taiwan	2022 Preliminary results available
NCT04174781	2019	Active	Interventional, phase II	DEB-TACE + sintilimab	No	3-year progression-free survival	61	China	2022
NCT05471674	2020	Completed	Interventional, phase II	Nivolumab (3 doses)	No	Patients with resected tumours having ≥30% necrosis	20	Hong Kong	2022
NCT04888546	2021	Recruiting	Interventional, phase II	Anlotinib hydrochloride capsules + TQB2450 injection (anti-PD-L1)	No	Pathological complete response; overall response rate	20	China	2024
NCT04857684	2021	Recruiting	Interventional, phase I	SBRT + atezolizumab + bevacizumab	No	Safety (grade 3-4 adverse events); objective response rate	20	USA	2025
NCT04721132	2021	Recruiting	Interventional, phase II	Atezolizumab + bevacizumab (3 cycles)	No	Pathological complete response; safety	30	USA	2027
NCT04850040	2021	Not yet recruiting	Interventional, phase II	Camrelizumab + apatinib mesylate + oxaliplatin	No	Major pathologic response	15	China	2024
NCT05137899	2022	Recruiting	Interventional, phase II	Atezolizumab + bevacizumab (4 cycles)	No	Proportion of patients proceeding to resection	70	Canada	2026
PRIMER-I/ NCT05185739	2022	Recruiting	Interventional, phase II	A: Pembrolizumab (2 cycles) B: Lenvatinib (6 weeks) C: Pembrolizumab + lenvatinib	No	Major pathologic response	60	UK	2026
NCT05908786	2023	Recruiting	Interventional, phase II	A: Atezolizumab + bevacizumab (3 cycles) B: Atezolizumab +bevacizumab + tiragolumab (3 cycles) C: Bevacizumab + tobemstoming (3 cycles)	No	Major pathologic response	150	USA	2027
NCT05194293	2023	Recruiting	Interventional, phase II	Regorafenib + durvalumab	No	Objective response rate (complete response or partial response)	30	USA	2028
Neoadjuvant + adjuvant									
AURORA/ NCT03337841	2010	Active	Interventional, phase II	Pembrolizumab	Pembrolizumab	1-year recurrence-free survival	50	Japan	2031
NCT03299946	2018	Completed	Interventional, phase I	Cabozantinib + nivolumab	Cabozantinib + nivolumab	Safety	15	USA	2021
N03630640	2018	Completed	Interventional, phase II	Nivolumab	Nivolumab (up to 1 year)	1-year local recurrence-free survival	43	France	2023 Preliminary results available
NCT04224480	2019	Not yet recruiting	Interventional, phase I	Pembrolizumab (4 weeks prior to resection)	Pembrolizumab (4 weeks post-resection)	Recurrence within 2 years; tumour microenvironment immunophenotype	20	Singapore	2025

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Table 2. (*continued*)

Trial number	Year	Status	Type	Neoadjuvant immunotherapy	Adjuvant immunotherapy	Primary outcome	Enrolment	Region	Estimated study completion
NCT03867370	2019	Completed	Interventional, phase II	A: Toripalimab (single dose) B: Toripalimab + lenvatinib (single dose) C: Toripalimab + lenvatinib (single dose)	A:Toripalimab (up to 48 weeks) B: Toripalimab + lenvatinib (up to 48 weeks) C: Toripalimab (up to 48 weeks)	Complete pathologic response; major pathologic response	40	China	2023 Preliminary results available
NCT04615143	2020	Recruiting	Interventional, phase II	A: Tislelizumab (4 cycles) B: Tislelizumab + lenvatinib (6 weeks)	A: Tislelizumab (1 year) B: Tislelizumab + lenvatinib (1 year)	1-year disease-free survival	80	China	2025
NCT04123379	2020	Recruiting	Interventional, phase II	A: Nivolumab (2 cycles) B: Additional BMS-813160 (CCR2/5 inhibitor) C: Additional BMS-986253 (anti-IL8)	Nivolumab (3 cycles)	Major pathologic response; significant tumour necrosis	36	USA	2024
AB-LATE02/ NCT04727307	2021	Recruiting	Interventional, phase II	A: Atezolizumab + RFA B: Atezolizumab	A: Atezolizumab + bevacizumab B: Atezolizumab + bevacizumab + RFA	2-year recurrence-free survival	202	France	2027
DYNAMIC/ NCT04954339	2021	Recruiting	Interventional, phase II	Atezolizumab + bevacizumab (2 cycles)	Atezolizumab + bevacizumab (4 cycles)	Complete pathologic response	45	South Korea	2025
NCT04930315	2021	Recruiting	Interventional, phase II	A: Camrelizumab + apatinib	B: Camrelizumab	1-year recurrence-free survival	78	China	2024
NCT04521153	2021	Recruiting	Interventional, phase II	Camrelizumab + apatinib mesylate (2 cycles)	Camrelizumab + apatinib mesylate (6 cycles) + TACE	3-year event-free survival; major pathologic response	290	China	2026
NCT04658147	2021	Recruiting	Interventional, phase I	A: Nivolumab (10 months) B: Nivolumab + relatlimab (10 months/up to 1 year)	Yes	Number of patients who complete pre-op treatment and proceed to surgery	20	USA	2026
NCT05389527	2022	Active, not recruiting	Interventional, phase II	Pembrolizumab + lenvatinib (9 weeks)	Pembrolizumab + lenvatinib (1 year)	Major pathologic response	43	China	2025
NEOTOMA/ NCT05440864	2023	Recruiting	Interventional, phase II	Tremelimumab + durvalumab (2 cycles)	Durvalumab (11 cycles)	Safety (grade 3 adverse events)	28	Canada, Spain, Italy	2026
Adjuvant									
CheckMate 9DX/ NCT03383458	2018	Active, not recruiting	Interventional, phase III	No	Nivolumab	Recurrence-free survival (49 months)	545	USA	2025
KEYNOTE 93/ NCT03867084	2019	Active, not recruiting	Interventional, phase III	No	Pembrolizumab (up to 17 cycles)	Recurrence-free survival; overall survival	950	USA	2029
EMERALD2/ NCT03847428	2019	Active, not recruiting	Interventional, phase III	No	Durvalumab + bevacizumab	Recurrence-free survival (49 months)	908	USA	2025
NCT04682210	2020	Not yet recruiting	Interventional, phase III	No	Sintilimab + bevacizumab	Recurrence-free survival	246	China	2024
NCT04418401	2020	Recruiting	Interventional, phase I	No	Donafenib + anti-PD1 (up to 6 months)	1-year recurrence-free survival	30	China	2024

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Table 2. (*continued*)

NCT05545124	2022	Not yet recruiting	Interventional, phase II	No	Donafenib + tislelizumab	1-year recurrence-free survival	32	NR	2024
NCT05111366	2022	Recruiting	Interventional, phase II	No	Anlotinib + TQB-2450 (anti-PD-L1)	1-year recurrence-free survival	37	China	2024
EMPHASIS/ NCT05516628	2023	Not yet recruiting	Interventional, phase II	No	Atezolizumab + bevacizumab (up to 1 year)	Recurrence-free survival; biomarkers predictive of recurrence	30	Singapore	2027
NCT06089382	2023	Not yet recruiting	Interventional, phase III	No	Sintilimab + lenvatinib (up to 1 year)	Recurrence-free survival	104	China	2026

DEB-TACE, drug-eluting bead-transarterial chemoembolisation; ICIs, immune checkpoint inhibitors; RFA, radiofrequency ablation.

Table 2 provides an overview of ongoing clinical trials involving candidates eligible for surgical resection of HCC. The table is organised into three distinct sections based on the administration of the immunotherapeutic regimen: as a neoadjuvant, as a combined neoadjuvant and adjuvant, or solely as an adjuvant option.

Ongoing challenges

Analysing how immunotherapy regimens have shaped the concept of conversion strategies reveals several challenges: 1) standardised pathological endpoints are essential for regulatory approval, but early trials for immunotherapy in the conversion setting in HCC lack consistency in defining pathologic complete response and MPR; 2) criteria for defining clinically significant radiographic response lack standardisation; 3) defining "successful conversion" is subjective due to varied definitions of resectability; 4) optimal duration of neoadjuvant immunotherapy and correlation with pathological response and toxicity reduction remain unclear; and 5) biomarkers guiding allocation of neoadjuvant immunotherapy require further assessment.

Liver transplantation: The role of preoperative immunotherapy

Preoperative immunotherapy: The concepts of "bridging" and "downstaging"

The increasing interest in implementing immunotherapy schemes in the pre-transplant setting, either alone or in combination, is focused on two primary goals: successfully "bridging" patients to transplant and implementing an effective conversion/downstaging strategy to broaden the pool of patients eligible for transplantation.[3,40,86] Despite the theoretical advantages of immunotherapy prior to LT, no prospective randomised-controlled trials have been published, so the available evidence is primarily anecdotal, deriving from case series and reports.[87–103]

The limited literature on this topic stems from hesitancy in adopting immunotherapeutic agents, given their inherent antitumoural mechanism involving the activation of the suppressed adaptive immune synapses and the potential, yet uncovered, interference with innate immunity pathways. This approach contradicts the conventional use of immunosuppressants after transplantation, substantiating initial concerns about their widespread adoption.[3] Nevertheless, successful series have shown encouraging results, justifying the integration of immunotherapy in the context of LT.[88,90,92,94–99,101–103]

The largest series to date presented the outcomes of 16 patients who underwent donation after brain death LT following preoperative anti-PD-1 blockade.[101] The study documented 15 successful downstagings, with four cases that were beyond the UCSF criteria returning to within UCSF criteria following treatment. Complete remission was observed in two cases. Post-transplant rejection occurred in nine cases (56.3%), but all experienced mild to moderate rejection, successfully managed by adjusting the immunosuppressive regimen, with no instances of graft loss or fatal rejection reported at follow-up. Similarly, Tabrizian *et al.* reported successful downstaging and LT in nine patients who received pre-transplant nivolumab, encountering only one case of mild acute rejection attributed to suboptimal tacrolimus levels. Furthermore, more than 33% of

the cases reported an excellent pathological response, with >90% tumour necrosis observed on explant pathology.[95]

Other successful downstaging cases following pre-transplant PD-1 blockade have been reported, with nivolumab being the most commonly used agent, even in paediatric recipients.[88,90,92,96,99,101,102]

Table 3 presents a comprehensive review of the available literature on neoadjuvant immunotherapy, both as a bridge and as a downstaging option for LT candidates.

Graft rejection

Primary safety data for ICIs mainly derive from phase III clinical trials in advanced HCC, indicating acceptable TRAEs, with grade 3 or higher events reported in 18% and 20% of patients using pembrolizumab and nivolumab monotherapies, respectively.[9,104] However, combination schemes like nivolumab and ipilimumab or atezolizumab and bevacizumab show significantly higher percentages, reaching peaks of up to 56.6%.[11,13]

While there has been limited experience in combining atezolizumab and bevacizumab in the transplant setting,[98,103] the effects of double immunomodulation by blocking both the CTLA-4 inhibitory co-receptor and PD-L1 could be detrimental and are yet to be explored. Both pathways are extensively activated in allograft tolerance, potentially leading to acute rejection and graft loss.[3,25,29] To date, definitive data on the risk of graft rejection following pre-transplant ICIs, as well as the molecular mechanisms behind ICI-induced graft rejection, remain unclear.[3,86] A recent theory, drawn from pathological evaluations of allograft PD-1/PD-L1 staining in patients who received post-LT ICI, suggests that PD-1/PD-L1 expression may play a crucial role in determining the risk of donor graft failure. The PD-1/PD-L1 immune checkpoint is vital for inducing and maintaining immune tolerance, particularly in patients with a positive PD-L1 signature. However, for those with negative PD-L1, maintaining immune tolerance seems to involve other factors, such as B- and T-lymphocyte attenuators. Graft PD-L1 expression could serve as a key biomarker for the safe use of anti-PD-1 agents.[105,106] Nevertheless, the precise mechanisms preventing graft rejection in PD-L1-negative patients after anti-PD-1 therapy remain elusive, primarily due to the lack of reported PD-1/PD-L1 status in liver grafts, warranting further exploration.

Washout period

Another crucial aspect to clarify is the timing between the last dose of an ICI and LT. The existing literature recommends a washout period of 4 to 8 weeks. Many anti-PD-1/PD-L1 regimens have extended half-lives of >20 days.[86] The timing between the last ICI dose and LT has been directly linked to graft rejection, indicating that an insufficient washout period, compared to the ICI's half-life, in the pre-transplant setting could compromise graft function.[86,107]

However, the suggested 8-12-week washout period is primarily precautionary, as there is no evidence confirming a direct correlation between ICI half-lives and their clinical effectiveness. Additionally, the precise role of receptor occupancy rate remains unclear.

Two case series have revealed higher rates of severe postoperative complications, including hepatic necrosis, graft loss, and rejection, when the interval between the last ICI dose and LT was less than 3 months.[87,97] In a recent series from China, the rejection group had a significantly shorter interval between the last PD-1 inhibitor dose and LT (median 21 days) than the non-rejection group (median 60 days).[101] A single study reported successful LT with no severe allograft rejection, despite the last ICI dose being administered just 4 weeks before LT.[95] However, all cases required substantial transfusion support, potentially leading to quicker clearance of serum nivolumab. This suggests that alternative strategies should be considered, such as plasmapheresis, to expedite clearance. In centres where living donation is available, living donor liver transplantation (LDLT) may allow for the safe coordination and optimisation of drug administration and LT.

Immunosuppression

The preoperative administration of ICIs, whether alone or in combination with LRT, has raised questions regarding the approach to post-LT immunosuppression, which is a debated theme for which consensus is lacking. While essential for safeguarding the graft, immunosuppression's role extends to potentially compromising the positive antitumor effects of immunotherapy, thereby raising additional concerns about the long-term efficacy of ICIs. Nevertheless, preclinical data postulated a boost in effector memory T cells and naïve T-cell subsets during the post-LT period, despite immunosuppressive regimens, indicating a possible resurgence of anti-tumoural immunity.[3,106]

A recent review, in an attempt to assess the recipient's immunological risk profile, defined high-immunological-risk patients as follows: LT performed less than 12 months ago, diagnosed autoimmune disease, young female, baseline altered transaminases, subclinical rejection observed in liver biopsy, preformed or *de novo* donor-specific antibodies, and elevated transient elastography. For this category of patients, depending on whether the predicted oncologic benefit was high or low, the administration of ICIs was either advised with extreme caution (*e.g.*, strict surveillance of liver function tests and early withdrawal if mild alterations were detected, coupled with liver biopsy and steroid administration) or strongly discouraged.[107] Striking a balance remains crucial, as immunosuppressive measures are vital for protecting the allograft, but their impact on the anticancer benefits of immunotherapy requires careful consideration.

Combining ICI with LRT: An advantage?

LRT appears to benefit from combination with immunotherapy in HCC. The recently published STAR-FIT trial provided encouraging insights into the potential for enhancing conversion strategies for cases deemed unresectable at diagnosis.[85] While upcoming trials are further investigating the potential of combination schemes as an additional preoperative optimisation strategy before surgical resection, the application of this concept to the transplant setting is still in its infancy due to unresolved concerns regarding the safety of ICIs in an immunosuppressive environment.[86,105] Nevertheless, while the real effects of combination schemes are yet to be demonstrated in surgical planning, the synergistic effects of combining local therapy with immune-enhancing agents have been proven effective in advanced HCC.[108–111]

Table 3. ICIs as neoadjuvant strategy in the pre-liver transplant setting.

Author	Year	Patients, n	Aetiology	Milan Criteria	Pre-ICI tumour size	Macrovascular involvement	ICI	ICI duration	ICI as bridge to transplant?	ICI as first downstaging option?	Downstaged?	Other pre-transplant treatments	Time interval between last ICI and LT	Rejection	Recurrence	Death within 12 months
Nordness *et al.*[87]	2020	1	HCV	Yes	NR	No	Nivolumab	2 years	Yes	No	Yes	Resection, radio-embolisation, TACE, sorafenib	8 days	Acute rejection, 6 POD	N/A	Yes
Schwacha-Eipper *et al.*[88]	2020	1	Alcohol-related cirrhosis	No	1 (2.5 cm) 3 (<2 cm)	No	Nivolumab	34 cycles	No	No	Yes	Resection, sorafenib, regorafenib, microwave ablation	21 weeks	No	No	No
Chen G. *et al.*[89]	2021	1	HBV	Yes	N/A	No	Toripalimab + lenvatinib	10 cycles, unknown	No	No	No	Resection, TACE, sorafenib, MWA, RFA	93 days	Acute hepatic necrosis, 1 POD	N/A	Yes
Chen Z. *et al.*[90]	2021	5	Cirrhosis of unknown aetiology	No	NR	No	Nivolumab	1 cycle (3), 6 cycles (2)	No	No	NR	TACE, resection, 3 RFA	59 - 122 days	No	2 Recurrences (metastatic disease)	Unknown
Dehghan *et al.*[91]	2021	1	HCV	Yes	2 (2.5 cm; 1.0 cm)	No	Nivolumab	16 cycles	No	No	Yes	TACE, MWA, sorafenib	5 weeks	Subacute hepatic necrosis (10 POD), graft loss, retransplant successful	Unknown	Unknown
Lizaola-Mayo *et al.*[92]	2021	1	NASH	Yes	1 (2.8 cm)	No	Nivolumab + ipilimumab	6 months	No	No	Yes	Radio-embolisation, sorafenib	8 weeks	No	No	No
Qiao *et al.*[93]	2021	7	Unknown	NR	NR	NR	Pembrolizumab or camrelizumab + lenvatinib	1 - 5 cycles	Yes	NR	Yes	No	40 days	Acute cellular rejection (10 POD)	Unknown	Unknown
Sogbe *et al.*[94]	2021	1	HBV	No	13 (largest 47 mm)	No	Durvalumab	15 months	No	No	Yes	Resection, sorafenib	90 days	No	No	No
Tabrizian *et al.*[95]	2021	9	5 HBV; 2 HCV; 1 NASH; 1 None	6 Yes 3 No	NR	NR	Nivolumab	2 - 32 cycles	Yes	No	NR	Chemo- and radio-embolisation, ablation, radiation	4 weeks	1 mild rejection due to low tacrolimus levels	No	No
Schnickel *et al.*[96]	2022	5	4 HCV; 1 HBV	Unknown	NR	No	Nivolumab	8 - 18 months	NR	NR	NR	No	10 days - 83 months	1 acute hepatic necrosis (14 POD), graft loss, retransplant successful	No	No
Aby *et al.*[97]	2022	1	HCV	No	3 (2.0 cm, 2.4 cm 2.4 cm)	Yes; PVT	Nivolumab	23 cycles	No (intended as destination therapy)	No	Yes	Chemo- and radio-embolisation, MWA, sorafenib	16 days	Acute cellular rejection (9 POD)	Unknown	No
Abdelrahim *et al.*[98]	2022	1	HCV	Yes	1 (5 cm)	No	Atezolizumab + bevacizumab	6 cycles 5 cycles	No	Yes	No (new 8 mm lesion but shrink of main lesion 3.3 cm)	No	2 months	No	No	No
Kang *et al.*[99]	2022	1	NR	Yes	NR	No	Pembrolizumab	3 cycles	Yes	No	No	Cisplatin, doxorubicin, dexrazoxane, TACE, resection	138 days	No	No	No
Dave *et al.*[100]	2022	8	4 HCV; 1 HBV; 1 NASH; 2 Other	Yes (7)	NR	NR	Nivolumab	Unknown	Yes	NR	NR	Mean of 2 loco-regional treatments	105 days	2 rejections; graft loss, retransplant successful	Unknown	1 Yes
Wang *et al.*[101]	2023	16	14 HBV; 2 ALD	No	range 1.5 cm - 10 cm	3	2 nivolumab 7 pembrolizumab. 4 sintilimab 2 camrelizumab1 multiple	1 - 27 Cycles	Yes	NR	Yes	Yes	1 - 184 days	9 acute liver rejection	5 Yes	Unknown
Rudolph *et al.*[102]	2023	1	Unknown	Unknown	NR	No	Nivolumab	7 cycles	NR	No	NR	Resection, bland embolisation, SIRT, MWA	55 days	GVHD (35 POD)	No	No

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Table 3. (*continued*)

Author	Year	Patients, n	Aetiology	Milan Criteria	Pre-ICI tumour size	Macrovascular involvement	ICI	ICI duration	ICI as bridge to transplant?	ICI as first downstaging option?	Downstaged?	Other pre-transplant treatments	Time interval between last ICI and LT	Rejection	Recurrence	Death within 12 months
Choulk *et al.*[103]	2023	1	Alcohol-related cirrhosis	No	6 cm	No	Atezolizumab, bevacizumab	18 cycles	No (intended as destination therapy)	NA	Yes	No	1 week	No	No	No

GVHD, graft *vs.* host disease; MWA, microwave ablation; NA, not applicable; NASH, non-alcoholic steatohepatitis; NR, not reported; POD, postoperative day; PVT, portal vein thrombosis; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolisation.

Data from two single-arm, phase II studies and real world data from the US National Cancer Database suggest benefits of immunotherapy for patients who have undergone prior radioembolisation (RE).[108–110] In the two single-arm phase II trials of RE from Spain and Singapore both with SirSphere® Yttrium-90 followed by nivolumab 21 days later and every 2 weeks thereafter, de la Torre-Aláez and Tai reported ORRs of 40% and 43.5%, respectively, for locally advanced HCC without extrahepatic metastases.[108,109] Yeo reported real world data from the US National Cancer Database of 142 patients with advanced HCC who received combined RE and immunotherapy and 1,522 patients with advanced HCC who received immunotherapy alone and showed median OS of 19.8 *vs.* 9.5 months favouring combination therapy.[110] Results from the EMERALD-1 study were recently reported at ASCO GI 2024. This was a phase III, randomised, placebo-controlled study of TACE combined with durvalumab with or without bevacizumab in participants with unresectable HCC eligible for embolisation and showed superior median progression-free survival of 15.0 (11.1-18.9) *vs*. 8.2 (6.9-11.1) months for durvalumab plus bevacizumab plus TACE *vs.* placebo and TACE. However, OS data was still immature.[111]

Although LRT remains the primary choice for initial treatment, ICIs become a consideration when responses are inadequate, or LRT options are not feasible.[1,112]

Patient selection

No guidelines offer recommendations on optimal candidates for immunotherapy, necessitating a multidisciplinary assessment of each case's unique characteristics. Whether immunotherapeutic regimens confer an advantage in patients who have been downstaged or those with high-risk features such as elevated alpha-fetoprotein (AFP) levels, or high tumour burden remains unknown.[86]

Despite the challenges in profiling candidates who would benefit most from preoperative immunotherapy, the primary goal remains to expand the pool of patients eligible for LT and/or resection while maintaining an acceptable safety profile. Achieving optimal patient selection relies on early detection of tumour response, which has been complicated by the complete lack of predictive biomarkers.[3,112] Additionally, pre-treatment and on-treatment biopsies are rarely performed due to heterogeneity in the HCC microenvironment and the risk of tumour spread.

Moreover, the assessment of radiologic response to ICI has proven unreliable, with significant discrepancies between final pathological reports and on-treatment radiologic evaluations. In light of recent data recognising MPR as a predictor of relapse-free survival, the preoperative evaluation of treatment response has gained renewed significance.[113] Efforts aimed at accurately assessing the impact of ICIs on tumour burden, specifically through enhanced radiologic protocols offering better sensitivity to detect changes in tumour burden and inflammatory/necrotic modifications, are crucial for developing updated management algorithms and for the appropriate selection of patients who may derive the greatest benefit from ICIs.

How far is too far?

The success of immunotherapy as a preoperative strategy for the downstaging or conversion of patients initially deemed

Table 4. Review of ongoing clinical trials assessing the role of ICIs (either as a neoadjuvant, combined neoadjuvant/adjuvant or adjuvant strategy) in the liver transplant setting.

Trial number	Year	Status	Type	Outside Milan?	Pre-transplant immunotherapy	Post-transplant immunotherapy	Primary outcome	Enrolment	Region	Estimated study completion
Pre-transplant										
NCT05027425	2021	Recruiting	Interventional, phase II	Yes	Durvalumab + tremelimumab (4 months)	No	Safety (cellular rejection rates)	30	USA	2030
Dulect2020-1 NCT04443322	2020	Recruiting	Interventional	Yes	Durvalumab + lenvatinib	No	PFS/RFS	20	China	2025
NCT04425226	2020	Recruiting	Interventional	Yes	Pembrolizumab + lenvatinib	No	RFS	192	China	2024
NCT05339581	2022	Not yet recruiting	Interventional	Yes	IMRT + anti-PD1 + lenvatinib	No	PVTT-related response and necrosis rate	78	China	2024
NCT05879328 (ImmunoXXL Study)	2023	Recruiting	Interventional	Yes	Atezolizumab + bevacizumab	No	RFS	12	Italy	2031
NCT05185505	2023	Recruiting	Interventional, phase IV	Yes	Atezolizumab + bevacizumab (up to 8 cycles) + TACE	No	1-year graft rejection	24	USA	2027
NCT05475613	2023	Recruiting	Interventional, phase II	Yes	Anti-PD1 (tislelizumab, pembrolizumab, nivolumab) up to 12 cycles	No	Downstaging 2-years event-free survival	59	China	2028
Post-transplant										
NCT06041490	2023	Not yet recruiting	Interventional, phase II	Yes	No	TKI + bevacizumab (up to 12 months)	1-year RFS	88	China	2027

IMRT, intensity-modulated radiotherapy; NR, not reported; NA, not applicable; PFS, progression-free survival; PVTT, portal vein tumour thrombosis; RFS, recurrence-free survival; TACE, transarterial chemoembolisation; TKI, tyrosine kinase inhibitor.

unresectable or untransplantable has led to an expansion of the criteria for potentially curative surgery. While the presence of extrahepatic disease remains an exclusion criterion, the presence of macrovascular invasion and portal vein tumour thrombosis without extrahepatic disease is no longer an absolute contraindication for surgical intervention.[42–45,114] Selected retrospective studies have indicated improved survival after upfront resection of HCC with portal vein tumour thrombosis.[115,116] However, recent technological advances and remarkable results with immunotherapy suggest that curative surgery following a successful radiologically and biologically proven downstaging combination (*e.g.* immunotherapeutic scheme with or without LRT) could yield better and more efficient intention-to-treat outcomes.[65,67–72,79–85] The principles guiding successful surgical outcomes in patients with advanced disease and macrovascular invasion are linked to favourable tumour biology and patient selection.[3,86] Not every patient may benefit from a downstaging approach. Furthermore, in donation after circulatory death cases and LDLT, adherence to equitable distribution and double equipoise principles is mandatory. Thus, in light of proven downstaging alternatives, offering an upfront approach in such advanced cases may not be ethical. However, adequate pre-LT downstaging may represent a viable and sustainable alternative.[112,117]

The complexity of such cases mandates a multidisciplinary approach. Adequate and effective tumour responses must be documented through serial radiological and biological assessments, including structured evaluation of AFP level trends.[86,117] Additionally, an appropriate timeframe should be established to ensure the absence of disease progression. However, to date, no standardised response parameter or permissive tumour biology has been identified. Even for AFP values, no significant threshold has been established. Therefore, a multidisciplinary discussion for each case is mandatory to determine the final indication for surgical intervention. Results from the TALENTop trial will elucidate the feasibility and safety of potentially curative resection for HCC with macrovascular involvement after successful downstaging with the combination of atezolizumab and bevacizumab.[118] However, applying such a concept in a transplant setting requires specific attention, given the complexities associated with ethical considerations, organ allocation, and LDLT cases, making the road ahead challenging.

Liver resection: The role of adjuvant immunotherapy

A significant limitation of curative resection for HCC is the high postoperative recurrence rate, manifesting in a bimodal distribution. Early recurrence, within 2 years, is driven by occult micro-metastases, while late recurrence, typically between 4 and 5 years, stems from *de novo* tumours in a dysfunctional liver microenvironment.[34,35] Despite aggressive biological features indicating a higher risk of recurrence, even small HCCs (<2 cm) carry a 10% risk of occult micro-metastatic disease linked to microvascular invasion.[4] Therefore, post-resection, patients often face repeated recurrences necessitating adjunctive treatments, such as radiofrequency ablation, re-resection, or TACE, which may ultimately lead to liver failure or prove insufficient for disease control.

Various adjuvant strategies have been explored, including antiviral agents for HBV- and HCV-related HCC.[119] Interferon-α

has shown effectiveness in reducing recurrences in HCV-related HCC and nucleotide analogues are associated with reduced recurrence rates and improved survival rates in HBV-related HCC.[120,121] However, studies focusing on anti-angiogenic agents, such as heparinase inhibitors and sorafenib, have yielded disappointing results.[3]

In light of successful immunotherapeutic schemes in other malignancies, several trials have emerged to assess the impact of adjuvant immunotherapy after curative resection. The IMbrave050 trial, a phase III randomised clinical trial, demonstrated groundbreaking efficacy in improving recurrence-free survival with adjuvant atezolizumab and bevacizumab combination therapy.[12] Subgroup analyses highlighted enhanced outcomes, especially in high-risk patients undergoing ablation. This trial signifies the first evidence of combined immunotherapy's effectiveness post-resection or ablation.

Preceding trials, notably the NIVOLVE trial, revealed some limitations of nivolumab monotherapy in addressing HCC recurrence.[122] While NIVOLVE showed a halving of recurrence rates compared to the STORM trial, biomarker analyses indicated an immunosuppressive tumour microenvironment correlated with heightened recurrence frequencies, suggesting potential targets for therapy.[123] Notably, tumours expressing PD-L1 and demonstrating CD8 T-cell infiltration may respond better to immunotherapy.

Accurate classification of HCC's immune signature through molecular analysis is pivotal in establishing precise allocation policies for immunotherapy.[31,32] The aim of combining bevacizumab with anti-PD-L1 agents is to transform the immune microenvironment from suppressive to permissive by enhancing immune priming and improving T-cell infiltration.[3] This approach holds promise in the adjuvant setting.

Liver transplant: The role of adjuvant immunotherapy

Curative resection of HCC is associated with high recurrence rates, although the rates after LT are comparatively lower. Recurrence mechanisms involve the immunosuppressive environment post-LT, promoting tumour proliferation.[36,37] Extrahepatic recurrence post-LT precludes surgical options, necessitating systemic therapies for disease control. TKIs have been shown to confer survival benefits post-LT recurrence. However, concerns surround standardised immunotherapy post-LT due to potential complications, including acute graft rejection and hepatotoxicity.[124,125]

Immunosuppressive drugs such as tacrolimus and cyclosporine are pivotal for graft viability, inhibiting the calcineurin-nuclear factor of the activated T cell pathway. Conversely, ICIs reactivate immune targets, increasing the risk of graft rejection and hepatotoxicity post-LT. ICIs, notably anti-PD-1 and anti-CTLA-4 agents, are associated with hepatotoxicity in up to 29% of cases, ranging from mild elevations in liver function tests to fatal organ failure.[86,124,125]

ICIs' role in the post-LT setting has yet to be established and validated due to ongoing concerns regarding the delicate immunological interplay between immunosuppression and the immune modulation induced by ICIs, which could jeopardise transplant outcomes. Additionally, current guidelines do not support the standardised application of adjuvant chemotherapy or TKIs as effective strategies to reduce disease recurrence risk after LT.[1,3,107] In particular, the role of TKIs post-LT remains uncertain, as they have not been consistently shown to improve survival outcomes.

ICIs for HCC recurrence after LT

While the systematic application of adjuvant ICI remains limited owing to concerns regarding the safety of combining immunotherapy with immunosuppression, ICIs have been increasingly proposed as a salvage therapy, after conventional treatments fail, to address post-LT disease recurrence.[124–134] Initial experiences with ICIs, primarily deriving from case reports and series, have yielded unsatisfactory outcomes, with low ORRs and significant rates of acute rejection. Recent cases, particularly from 2020 onwards, demonstrate more promising results, especially with the combination of nivolumab and bevacizumab, showing improved OS and manageable toxicity profiles.[133] Graft rejection, as observed in some cases, has been effectively managed with corticosteroids.[129,134]

Despite encouraging reports of sustained disease control and adequate safety, the available literature is derived from selected case series where ICIs were used as a last resort for post-LT disease recurrence. The immunologic interactions regulating the complex post-LT microenvironment are not yet fully understood. The lack of larger studies limits the applicability to clinical practice, and a careful risk-benefit evaluation is mandatory when considering a post-LT regimen with ICIs. Additionally, allograft PD-L1 expression assessment is crucial, as it remains the only potentially promising tissue biomarker related to allograft rejection.[127]

Further research is needed to elucidate the optimal timing and patient selection criteria for immunotherapy post-LT, considering risk factors such as previous rejection and autoimmune diseases.[127,134]

A comprehensive summary of ongoing clinical trials for the application of immunotherapy as a neoadjuvant or adjuvant option in the LT setting is provided in Table 4.

Future perspectives

The application of immunotherapy in advanced HCC as a definitive treatment has yielded remarkable results, prompting its expansion as an adjunctive option for early-to-intermediate-stage HCC candidates eligible for curative treatments. Moving forward, the targeted application of immunotherapy to individual patients, considering the unique features of each TME, including resistance and response profiles, marks a significant step.[3,27]

Emerging immunotherapy targets, such as bispecific antibodies, engineered cytokines, adoptive cell transfer, and cancer vaccines, are poised to complement current regimens, offering a tailored approach to target tumours' biological phenotypes. Adoptive cell transfer, particularly CAR T-cell therapy against GP3 (glypican-3), shows promise in targeting circulating tumour cells and treating tumour recurrence.[135]

Recent advances in DNA sequencing technology hold potential for identifying selective immunogenic antigens, revitalising an interest in HCC vaccines. Identifying an immunosuppressive TME could enhance immune-enhancing techniques, reinvigorating conventional immunotherapy.[136]

Technological advances, including liquid biopsies utilising circulating tumour DNA and circulating tumour cells, offer nonintrusive methods to evaluate recurrence risk and treatment

effectiveness. Integrating liquid biopsies with fusion imaging like 18FDG/MRI enables prompt identification of therapeutic inefficacy or high-risk recurrence candidates, replacing traditional tumour biopsies and postoperative AFP measurements.[137,138]

Conclusion

The landscape of immunotherapy in HCC has been shaped by milestone trials like IMBrave150 and IMbrave050, which demonstrated the efficacy of bevacizumab and atezolizumab in advanced and recurrent HCC, respectively. Ongoing trials aim to integrate immunotherapy into resection strategies to reduce recurrence risk and extend resectability criteria. Immunotherapy also shows promise in LT, with concerns about compatibility effectively managed through optimised protocols. Ongoing perioperative trials will clarify optimal immunotherapy usage in resection, while LT trials face challenges due to patient complexity and organ shortages. Advances in organ allocation and patient selection are crucial for harnessing the full potential of immunotherapy in LT. These developments promise to enhance treatment outcomes and expand therapeutic options for patients with HCC undergoing curative resection or transplantation.

Affiliations

[1]*Liver Transplant and Hepatobiliary Surgery, Recanati/Miller Transplantation Institute, Icahn School of Medicine at Mount Sinai, USA;* [2]*Department of Hepato-pancreato-Biliary and Transplant Surgery, National Cancer Center Singapore and Singapore General Hospital, Singapore;* [3]*Surgery Academic-Clinical Program, Duke-NUS Medical School Singapore, Singapore*

Abbreviations

DBD, donation after brain death; HCC, hepatocellular carcinoma; ICIs, immune checkpoint inhibitors; LDLT, living donor liver transplantation; LRTs, loco-regional therapies; LT, liver transplantation; MPR, major pathologic response; ORR, objective response rate; OS, overall survival; RE, radioembolisation; TACE, transarterial chemoembolisation; TARE, transarterial radioembolisation; TKI, tyrosine kinase inhibitors; TME, tumour microenvironment; TRAEs, treatment-related adverse events.

Financial support

The authors did not receive any financial support to produce this manuscript.

Conflict of interest

Parissa Tabrizian: Boston Scientific, AstraZeneca, Bayer (consultation).

Pierce Chow: Sirtex Medical, Ipsen, BMS, Oncosil, Bayer, New B Innovation, MSD, BTG Plc, Guerbet, Roche, AUM Bioscience, L.E.K. Consulting, AstraZeneca, Eisai, Genentech, IQVIA, Abbott, AvataMed.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All authors contributed equally.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101181.

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Keywords: Immunotherapy; Hepatocellular Carcinoma; Liver Transplant; Liver Resection; Liver Surgery; Review; Outcomes.
Received 21 March 2024; received in revised form 24 June 2024; accepted 26 July 2024; Available online 6 August 2024