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Original Article

Expert consensus on the use of immune checkpoint inhibitors in the liver transplant setting: Guidance from the Liver Transplant Committee of the Italian Association for the Study of the Liver (AISF)☆

Francesca Romana Ponziani [1,2,*], Valerio Giannelli [3], Giuseppe Marrone [1], Silvia Martini [4], Maria Cristina Morelli [5], Duilio Pagano [6,7], Gianluca Svegliati Baroni [8], Giacomo Germani [9], Patrizia Burra [9], Pierluigi Toniutto [10]

[1] *Liver Unit, CEMAD Centro Malattie dell'Apparato Digerente, Medicina Interna e Gastroenterologia, Fondazione Policlinico Universitario Gemelli IRCCS, Rome, Italy*
[2] *Dipartimento di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome, Italy*
[3] *Hepatology Unit, San Camillo Hospital, Rome, Italy*
[4] *SSD Insufficienza Epatica e Trapianto, Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Torino, Italy*
[5] *IRCCS Azienda Ospedaliero Universitaria Sant'Orsola Malpighi, Bologna, Italy*
[6] *Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione ISMETT IRCCS, 90127 Palermo, Italy*
[7] *University of Pittsburgh Medical Center UPMC Italy, 90127 Palermo, Italy*
[8] *Liver Injury and Transplant Unit, Polytechnic University of Marche, Ancona, Italy*
[9] *Gastroenterology, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, Padua, Italy*
[10] *Hepatology and Liver Transplantation Unit, Azienda Sanitaria Universitaria Friuli Centrale, University of Udine, Udine, Italy*

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ABSTRACT

Immune checkpoint inhibitors (ICIs) have transformed the treatment landscape for advanced hepatocellular carcinoma, increasing opportunities for downstaging and conversion to liver transplantation (LT) eligibility. However, the use of ICIs in the LT setting raises challenges regarding the optimal timing and duration of treatment, safety, and assessment of tumor response. Moreover, the use of ICIs for hepatocellular carcinoma recurrence after LT is associated with an increased risk of acute cellular rejection and potential graft failure. This article presents expert consensus guidance developed by a

Abbreviations: ACR, acute cellular rejection; AFP, α-fetoprotein; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; LT, liver transplantation; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; RELAPSE, Recurrent Liver Cancer Prediction Score; RETREAT, Risk Estimation of Tumor Recurrence After Transplant score; TKI, tyrosine kinase inhibitor.

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* Corresponding author. Liver Unit, CEMAD Centro Malattie dell'Apparato Digerente, Medicina Interna e Gastroenterologia Dipartimento di Medicina e Chirurgia Traslazionale, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy.
E-mail address: francesca.ponziani@gmail.com (F.R. Ponziani).

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panel of 9 LT experts from the Permanent Transplant Commission of the Italian Association for the Study of the Liver (AISF) and conducted based on the modified Delphi method. Fifteen clinically relevant questions were developed through an iterative process involving structured literature review, clinical experience, and identification of practice gaps. Each question was assigned to 1 to 2 panel members with topic-specific expertise, who were responsible for performing a targeted literature review, drafting the evidence summary, and proposing a recommendation. Statements receiving >75% agreement in 2 rounds of voting were considered approved and presented in this article. Until prospective data become available, this guidance aims to assist clinical decision making within the evolving field of LT oncology.

1. Introduction

Systemic therapies, initially based on tyrosine kinase inhibitors (TKIs)[1-4] and more recently on immune checkpoint inhibitors (ICIs),[5-7] have revolutionized the treatment landscape for advanced hepatocellular carcinoma (HCC) and established a new standard of care.[8-12] The efficacy of ICIs has prompted investigation of their potential role, either as monotherapy or in combination with locoregional treatments to downstage HCCs initially beyond standard liver transplantation (LT) criteria (eg, Milan-out) into expanded acceptable thresholds, as documented in several case series and reports.[8-14] This strategy, referred to as conversion therapy, broadly encompasses the transformation of initially nonresectable or nontransplantable HCCs into candidates eligible for potentially curative approaches.[15-17]

Successful downstaging through conversion therapies has yielded post-LT survival rates comparable with those observed in patients initially meeting conventional LT criteria,[8-14] reflecting a growing emphasis on tumor biology and treatment response.[18] However, the use of ICIs in LT candidates, limited to those with compensated liver disease,[19] raises concerns due to their immunostimulatory effects, which conceptually conflict with the need for long-term immunosuppression to ensure graft tolerance. This issue is underscored by serious adverse events reported in early case series,[20-22] including immune-mediated hepatic toxicity, thereby fueling an ongoing debate regarding the feasibility, timing, and safety of integrating ICIs in the pretransplant setting.

To date, there is no clear guidance on the use of ICIs in LT candidates. This expert consensus, developed by members of the Permanent Transplant Commission of the Italian Association for the Study of the Liver (AISF), seeks to address this unmet need by providing evidence-based responses to key clinical questions surrounding the use of ICIs in the context of LT, with a focus on controversial areas and practical clinical implications.

2. Methods

This expert consensus guidance was developed by a multidisciplinary panel of Italian LT experts with recognized experience in HCC and ICI management from academic and transplant centers throughout Italy. Fifteen clinically relevant questions were developed through an iterative process involving a structured literature review, clinical experience, and identification of practice gaps. The coordinating authors (F.R.P. and P.T.) generated the initial draft based on a preliminary scoping review and clinical input. Questions were refined through structured group discussions during 2 virtual meetings and several rounds of written feedback. Each question was assigned to 1 or 2 topic-specific experts responsible for performing a targeted literature review, drafting the evidence summary, and proposing a recommendation (Supplementary Table S1).

The consensus process was based on the modified Delphi method.[23,24] The first round of voting was conducted online. Clinicians were asked to rate their agreement with each of the 15 proposed statements; voting was anonymous, and results were collected in aggregate form.

Following the initial round, results were presented, and each statement was discussed considering the initial voting data. Any agreed modifications were made to the statements in real time. A second round of blinded voting was then carried out; statements receiving >75% agreement during voting rounds were considered approved. Those failing to reach this threshold, despite discussion and amendments, were deemed rejected. The quality of evidence and strength of recommendations were assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology. For each answer, the certainty of evidence, strength of recommendation, and strength of agreement are provided. The detailed methodology of the consensus process is provided in Supplementary Material 1. An extended version of the narrative text supporting each answer is available in Supplementary Material 2.

3. Expert opinions

Question 1: In patients achieving a complete response (CR) or successful downstaging/conversion to the within-accepted LT criteria during ICI therapy, is it preferable to continue immunotherapy or to prioritize curative strategies such as LT?

Answer: The expert panel suggests that LT, as the most effective curative option for HCC, should be considered in patients achieving a CR or successful HCC downstaging/conversion following noncurative, ICI-based systemic treatments.

Certainty of evidence: low

Strength of recommendation: strong

Strength of agreement: strong

A subset of patients with advanced HCC achieves CR to ICI-based treatments.[25] However, it remains unclear whether the modified Response Evaluation Criteria in Solid Tumors (mRECIST) accurately identify complete tumor necrosis during immunotherapy or whether only the complete disappearance of lesions according to RECIST v1.1 reflects a true CR.[26] A large international, multicenter retrospective study published in 2025 evaluated the clinical outcomes and management strategies of patients achieving CR following ICI-based therapies.[27] Among 3933 patients treated with ICIs, CR was reported in <5% according to mRECIST and in 2.5% according to RECIST v1.1. Seven patients who achieved CR according to mRECIST underwent conversion therapy with surgical resection or LT, with 6 achieving complete pathologic response. The optimal duration of ICI treatment after successful downstaging remains undefined. Once LT eligibility is achieved, a comprehensive LT workup should be initiated promptly, given that the overarching therapeutic goal is curative intent.[28]

Question 2: What is the optimal timing for ICI withdrawal in patients achieving partial response or CR before or after LT listing?

Answer: The expert panel suggests that the optimal timing for ICI discontinuation before LT should be individualized. A minimum washout period of 30 to 50 days should be considered, whereas an interval of approximately 90 days represents a preferable approach to reduce the risk of acute cellular rejection (ACR).

Certainty of evidence: moderate

Strength of recommendation: strong

Strength of agreement: consensus

Li et al[29] suggested that a 90-day washout period, based on published data and ICI pharmacokinetics (half-life: 18-27 days), may be a reasonable strategy to reduce the risk of severe post-LT rejection.[14] Additional insights are derived from case series,[30-34] retrospective cohorts, and small prospective studies (Table 1).[35–44] A recent individual patient data meta-analysis,[36] including 91 patients with a median follow-up of 690 days, reported an ACR incidence of 26.4%. The overall median washout period was 41 days. Notably, patients with an estimated ACR probability of ≤20% had a median washout of 94 days, while those with >30% risk had a shorter median washout of 72 days. A washout period of <30 days was associated with a higher risk of rejection, including severe episodes and graft loss. A similar correlation between shorter washout period and occurrence of ACR was reported in the ImmunoXXL trial.[100] The class of ICI used also influenced this risk: programmed cell death protein-1 (PD-1) inhibitors appeared to induce ACR more frequently than anti–programmed death-ligand 1 (PD-L1) or anti–cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) agents, possibly due to more direct activation of graft-targeting T cells.[45] The Italian I-BELT consortium recommends prolonged ICI washout (≥3 months) before LT.[46] Similarly, the ILTS-ILCA consensus suggests at least 2 to 3 ICI half-lives to mitigate rejection risk.[45] However, data quality is currently limited by study designs and the absence of standardized protocol biopsies to define robust end points.

Question 3: Should TKIs be considered as a bridging treatment during the waiting list period following ICI discontinuation?

Answer: The expert panel does not suggest the use of TKIs as a bridge to LT during the ICI washout period in patients on the waiting list.

Certainty of evidence: very low

Strength of recommendation: strong

Strength of agreement: strong

TKIs, which do not require a washout period before LT, may theoretically be considered as a bridging strategy to prevent tumor progression during ICI washout. However, none of these agents is currently approved for neoadjuvant use in LT candidates, and data on their use following ICI therapy remain limited.[31,47] Further concerns arise from prescribing restrictions in certain health care systems: in some jurisdictions, lenvatinib or sorafenib may be limited to first-line therapy only, and subsequent ICI use following TKI treatment may not be permitted.[48] Moreover, introducing a TKI during the ICI washout phase could preclude ICI reintroduction if transplantation becomes unfeasible, potentially depriving patients of more effective therapeutic options.

Question 4: How long should downstaging response to ICIs be maintained before considering LT eligibility?

Answer: The expert panel suggests that patients should demonstrate radiological disease stability for at least 3 months under ICI therapy following downstaging before being considered for LT.

Certainty of evidence: low

Strength of recommendation: strong

Strength of agreement: strong

Downstaging protocols require a minimum observation period of 3 months to confirm sustained disease stability, thereby identifying patients with favorable tumor biology and a durable response who are more likely to benefit from LT.[49-51] The duration of ICI therapy prior to LT has been highly variable. In the VITALITY study,[37] the median treatment duration was 7.6 months. Similarly, Tabrizian et al[34] reported a median duration of 7 months of atezolizumab plus bevacizumab therapy before LT. Another multicenter study suggested that continuing immunotherapy for ≥6 months after achieving a first mRECIST-defined CR is associated with improved recurrence-free survival.[27] Nonetheless, standardized strategies are needed to reduce interradiologist variability in assessing the extent of downstaging when using mRECIST[52] compared with that using RECIST 1.1 criteria.[53]

Question 5: Should patients achieving successful HCC downstaging/conversion with ICIs be prioritized for LT?

Answer: The expert panel suggests that LT should be considered with priority for selected patients achieving a successful HCC downstaging following ICI-based therapy.

Certainty of evidence: very low

Strength of recommendation: strong

Strength of agreement: strong

A retrospective analysis by the Cleveland group[54] showed that patients who respond well to downstaging may achieve

Table 1
Postliver transplant ACR rates and clinical outcomes in patients previously treated with immune checkpoints inhibitors.

Author, year	Design	Patients receiving ICIs pre-LT (n)	Type of ICIs	Washout period	Rejection rate (%)/ biopsy proven (%)	Outcome
Tabrizian et al,[35] 2021	Retrospective	9	Nivolumab	Last dose within 4 wk of transplant	89	All resolved with treatment
Qiao et al,[32] 2021	Retrospective	7	PD-1 (camrelizumab or pembrolizumab)	42 d (fixed)	14.3/100	1 mild cellular rejection, liver function recovered 71% partial response
Chen et al,[31] 2021	Retrospective	5	PD-1 (nivolumab)	Mean, 63.8 ± 18.26 d	0	2 patients had recurrence; all had normal liver function at follow-up
Dave et al,[30] 2022	Retrospective	5	PD-1 (nivolumab)	Median, 105 d (IQR, 11-354 d)	40/100	2 graft losses: 1 immune-mediated rejection and 1 sudden circulatory death
Wang et al,[33] 2023	Retrospective	16	PD-1 (nivolumab, pembrolizumab, sintilimab, and camrelizumab)	Median, 21 d (IQR, 15.5-27.5 d) for the rejection group; 60 d (IQR, 34-167 d) otherwise	56.3/44.4	No immune-related graft loss or death; all rejections reversed with immunosuppression
Rezaee-Zavareh et al,[36] 2025	Individual patient data meta-analysis	91	Various (PD-1, PD-L1, and CTLA-4 inhibitors)	Median, 42 d (IQR, 71 d); 94 d (IQR, 196 d) for <20% rejection risk	26.4/100	83% resolved with treatment; 2 graft losses; 2 deaths due to rejection 9.9% mortality
Tabrizian et al,[34] 2025	Prospective	17	Atezolizumab + bevacizumab	Median, 78 d (IQR, 41-123 d)	11.8/100	No graft losses 88% pathologic response 94.2% and 88.2% 1- and 3-y post-LT survival, respectively
Tabrizian et al,[37] 2025	Prospective	43	Nivolumab, atezolizumab/ bevacizumab, durvalumab/ tremelimumab, and pembrolizumab	Median, 43 mo (IQR, 13-120 mo); 67.4% <3 mo	16.3/100	1 graft loss; no deaths due to rejection 85% 3-y post-LT survival
Moeckli et al,[38] 2025	2025	119	Various (PD-1, PD-L1, and CTLA-4 inhibitors)	Median, 56 d (IQR, 30-122 d)	20.2/70.8	Rejection risk ↓ with washout >50 d 7.5% mortality, 21.8% recurrence

(*continued on next page*)

Guo et al,[39] 2024	2024	83	Various (PD-1, PD-L1, and CTLA-4 inhibitors)	Median, 58 (IQR, 29-110)	27.7/8.4	56.5% resolved with treatment, 34.8% graft loss, 8.7% death due to rejection 71.4% rejection if washout < 30 d compared with 13% 9.6% mortality at 8.1 mo
Pang et al,[40] 2025	Retrospective, controlled	35	Various (PD-1, PD-L1, and CTLA-4 inhibitors)	ACR: median, 15 (IQR, 6-28) No rejection: median, 50 (IQR, 25-100)	22.9	4 deaths due to rejection Higher 90-d post-LT mortality rate in the ICI group (14.3% vs 2.3%) -21 d was the optimal washout period for predicting 90-d rejection-free survival
Xu et al,[41] 2024	Retrospective	25	Various (PD-1, PD-L1, and CTLA-4 inhibitors)	Median, 64 (IQR, 40-150.75)	12/100	1 resolved with treatment; 2 deaths due to rejection
Lu et al,[42] 2024	Retrospective	39	Various (PD-1, PD-L1, and CTLA-4 inhibitors)	Median, 50 (IQR, 3-840)	23.1/12.8	7 resolved with treatment, 3 graft losses, and 1 death due to rejection No difference in survival/RFS
Fang et al,[43] 2025	Retrospective	209	Various (PD-1, PD-L1, and CTLA-4 inhibitors)	Median, 66 (IQR, 35-128)	17.2	1-y survival rate ↓ in the rejection group; however, this significant difference was not observed at 3 y irAEs predict rejection
Lv et al,[44] 2024	RCT	11	Pembrolizumab + lenvatinib (PLENTY arm) vs LRT	Median, 60.5 (range, 25-193)	0	No difference in survival 70% RFS in PLENTY group vs 30%
Bhoori S et al,[100] 2026	Prospective	16	Atexolixumab + bevacizumab	Median 57.5 d (29-87)	25/100	All resolved with treatment

ACR, acute cellular rejection; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ICI, immune checkpoint inhibitor; IQR, interquartile range; irAE, immune-related adverse event; LT, liver transplantation; LRT, locoregional therapy; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PR, partial response; RFS, recurrence-free survival.

recurrence and survival outcomes comparable with those initially within standard criteria. However, prioritization for LT should not be unconditional. High-risk features (eg, α-fetoprotein [AFP] > 203.3 ng/mL, poor tumor differentiation, or multiple prior local therapies) are associated with significantly higher recurrence rates and poorer survival, suggesting that not all downstaged patients are equally suitable candidates for LT.[55] Tools such as the Recurrent Liver Cancer Prediction Score (RELAPSE)[56] and the Risk Estimation of Tumor Recurrence After Transplant (RETREAT)[57] score help stratify the risk of HCC recurrence by combining histopathological features with pre-LT AFP levels and neutrophil-to-lymphocyte ratio. However, since these scores can only be calculated after histologic evaluation of the explanted liver, they are not useful for assessing the risk of HCC recurrence prior to LT. Integrating mRECIST response with AFP or PIVKA-II dynamics may improve the prediction of major pathologic response, thus supporting more accurate curative-intent treatment decisions.

Question 6: Can patients with advanced HCC without extrahepatic spread but with macrovascular invasion be considered for LT after a CR to ICIs?

Answer: The expert panel suggests that patients with advanced HCC presenting with baseline macrovascular invasion but without extrahepatic spread may be considered for LT if a complete and sustained response to ICI-based therapy is achieved, following a rigorous multimodal risk assessment confirming low recurrence risk and favorable long-term prognosis.

Certainty of evidence: very low

Strength of recommendation: weak

Strength of agreement: strong

Emerging evidence suggests that ICIs can induce complete radiologic and biologic responses in patients initially deemed ineligible for LT due to macrovascular invasion.[58] If these responses are sustained, they may significantly modify tumor biology, lower the risk of recurrence, and support reconsideration of candidacy for LT.[47] The RELAPSE score[56] provides a validated framework for selecting such high-risk patients, particularly when dynamic pre-LT markers (eg, AFP decline and neutrophil-to-lymphocyte ratio) indicate a low residual risk. Given the scarcity of donor organs and the ethical implications of allocation, these cases should be managed preferentially within structured prospective protocols and performed in high-volume centers with expertise in post-LT surveillance and recurrence management.

Question 7: Should dual (or future triple) ICI-based regimens be considered as safe as single-agent therapies for HCC in LT-eligible patients?

Answer: The expert panel suggests that, although not formally contraindicated, dual or triple ICI combinations may be used with caution in LT candidates due to the potentially higher risk of ACR after LT compared with single-agent ICI regimens.

Certainty of evidence: very low

Strength of recommendation: strong

Strength of agreement: strong

In the context of LT, combining ICIs is expected to further enhance alloimmune activation, thereby increasing the risk of ACR beyond that associated with single-agent ICIs. Dual regimens targeting both CTLA-4 and PD-1 pathways may trigger an even more fulminant alloreactive response, while any hypothetical triple ICI-based therapy would likely amplify this effect even further.[59] To date, no studies have directly compared ICI combinations with single agents in LT candidates. Multicenter registries and prospective studies are urgently needed to better define the actual ACR risk associated with ICI combinations and to identify potential strategies for their safer use.

Question 8: Should ACR in LT recipients previously treated with ICIs be managed differently compared to ICI-naïve recipients?

Answer: The expert panel suggests that histologically documented ACR in LT recipients previously treated with ICIs should be managed according to standard protocols used for ICI-naïve patients.

Certainty of evidence: low

Strength of recommendation: strong

Strength of agreement: strong

No studies have specifically addressed the management of ACR in LT recipients previously treated with ICIs. A recent systematic review and individual patient data meta-analysis[36] reported 24 cases of ACR in such patients, with data available for 17. ACR was classified as mild in 9 cases, moderate in 4, and severe in 4. Twenty of the 24 cases were successfully managed with medical therapy, including thymoglobulin, plasmapheresis, intravenous immunoglobulin, rituximab, intensified immunosuppression (eg, tacrolimus), and corticosteroids. Four cases resulted in graft loss.

Question 9: Should early and long-term immunosuppression strategies be modified in LT recipients previously treated with ICIs?

Answer: The expert panel suggests that no specific modifications to maintenance immunosuppression regimens are currently indicated for LT recipients previously treated with ICIs.

Certainty of evidence: low

Strength of recommendation: strong

Strength of agreement: consensus

Although ACR risk appears to be higher in patients previously exposed to ICIs, the optimal post-LT immunosuppressive strategy remains undefined. Wang et al[33] reported median tacrolimus trough levels of 7.1 μg/L in previously ICI-exposed patients who developed post-LT rejection, which was subsequently managed by increasing levels to 15 μg/L. A cautious approach may avoid early aggressive minimization of calcineurin inhibitors, as rejection frequently occurs shortly after LT (median, 9-14 days). However, in studies with comparative groups, the timing of rejection did not significantly differ from that observed in ICI-naïve patients.[33,42] No data are currently available on the use of mTOR inhibitors in patients who underwent successful HCC downstaging followed by LT. A potential rationale for using sirolimus or everolimus may be extrapolated from the SILVER study, in which patients receiving mTOR inhibitors (mainly sirolimus) experienced improved post-LT survival and lower HCC recurrence rates, particularly in the context of hepatitis C virus–related liver disease.[60]

Question 10: Should post-LT surveillance be individualized in patients previously treated with ICIs, given their potentially increased risk of HCC recurrence?

Answer: The expert panel recommends that patients who received ICIs prior to LT should be considered at high risk for HCC recurrence. Accordingly, post-LT surveillance should be personalized and guided by the RETREAT and RELAPSE scores.

Certainty of evidence: moderate

Strength of recommendation: strong

Strength of agreement: strong

Patients undergoing downstaging with ICI therapy prior to LT should be considered at high risk of recurrence.[35,42,61,62] Given their history of tumor downstaging, multifocal disease, or biologically aggressive features, imaging surveillance is recommended for at least 2 years, with possible extension up to 5 years based on individual disease dynamics.[63] Besides common recommendations, a risk-adapted strategy could promote a more efficient and personalized post-LT surveillance strategy for HCC recurrence. The RETREAT score[57] is a validated tool that guides post-LT surveillance by estimating the risk of HCC recurrence based on explant tumor burden, pre-LT AFP levels, and the presence of microvascular invasion. Patients with a RETREAT score of 0 (no viable nodules, no AFP expression, and absence of microvascular invasion) do not require specific oncologic follow-up. Patients with scores between 1 and 3 should undergo moderate surveillance, including AFP measurement and abdominal/chest imaging every 6 months for at least 2 years. Those with scores $\geq$4 warrant intensive follow-up, with imaging every 3 to 4 months and AFP monitoring continued for up to 5 years. The RELAPSE score[53] estimates post-LT HCC recurrence risk by integrating explant-based tumor characteristics, including tumor burden and adverse histopathological features, such as macrovascular or microvascular invasion and poor tumor differentiation. Because specific evidence supporting the adoption of a fully personalized post-LT surveillance for HCC recurrence is still lacking, a proposed approach for post-LT surveillance in patients previously treated with ICIs is outlined in Table 2.[53,57,64-66]

Question 11: In noncirrhotic patients achieving successful HCC downstaging after ICIs, is LT a feasible and appropriate curative option?

Answer: The expert panel suggests that LT may be considered in carefully selected noncirrhotic patients achieving a successful HCC downstaging within-accepted LT criteria after ICI therapy.

Certainty of evidence: low

Strength of recommendation: weak

Strength of agreement: strong

In both cirrhotic and noncirrhotic patients, successful downstaging within-accepted criteria,[51,67-70] characterized by the absence of macrovascular or biliary invasion and extrahepatic spread[71-73] and low serum AFP levels,[74] is associated with excellent post-LT outcomes. Patients downstaged to within Milan criteria achieve 5-year posttransplant survival rates of 70% to 90%, while those beyond Milan but within the up-to-7 criteria can reach survival rates as high as 71% at 5 years.[75] In contrast, liver resection is associated with higher recurrence rates, particularly in the presence of microvascular invasion, satellite nodules, or poor differentiation. These findings support LT as the preferred curative strategy in selected high-risk patients, including those without cirrhosis.[76-78]

Table 2
Proposed scheme of postliver transplant surveillance in patients exposed to ICIs–based regimen for HCC treatment prior to liver transplant.

Time from LT	Conventional post-LT HCC surveillance	Previous ICI treatment post-LT HCC surveillance	Core imaging and biochemical tests	Optional investigations
RETREAT 0	None	Every 6 mo for 2 y	Abdominal contrast-enhanced CT/MRI + chest CT + AFP	Brain CT, bone scintigraphy, FDG/choline/dual tracer PET-CT, DCP, and ctDNA
RETREAT 0-3 or RELAPSE low	Every 6 mo for 2 y	Every 6 mo for 5 y	Abdominal contrast-enhanced CT/MRI + chest CT + AFP	Brain CT, bone scintigraphy, FDG/choline/dual tracer PET-CT, DCP, and ctDNA
RETREAT 4 or RELAPSE intermediate	Every 6 mo for 5 y	Every 4 mo for 2 y, then every 6 mo for year 2-5	Abdominal contrast-enhanced CT/MRI + chest CT + AFP	Brain CT, bone scintigraphy, FDG/choline/dual tracer PET-CT, DCP, and ctDNA
RETREAT $\geq$5 or RELAPSE high	Every 3-4 mo for 2 y then every 6 mo for year 2-5	Every 3 mo for 2 y, then every 4 mo for year 2-5	Abdominal contrast-enhanced CT/MRI + chest CT + AFP	Brain CT, bone scintigraphy, FDG/choline/dual tracer PET-CT, DCP, and ctDNA

AFP, α-fetoprotein; CT, computed tomography; ctDNA, circulating tumor DNA; DCP, des-γ-carbossiprothrombin; FDG, fluorodeoxyglucose; LT, liver transplantation; MRI, magnetic resonance imaging; RELAPSE, Recurrent Liver Cancer Prediction Score; RETREAT, Risk Estimation of Tumor Recurrence After Transplant score; PET, positron emission tomography.

Question 12: How should ICI-related toxicity be managed in patients awaiting LT?

Answer: The expert panel recommends that ICI-related toxicity in patients awaiting LT should be managed through early recognition, careful assessment of severity, and prompt initiation of appropriate immunosuppressive therapy.

Certainty of evidence: moderate

Strength of recommendation: strong

Strength of agreement: strong

The incidence of immune-related adverse events (irAEs) induced by ICIs in patients awaiting LT ranges from 20% to 35%.[43] Most irAEs are of mild to moderate severity and lead to treatment discontinuation in approximately 9% of cases.[79,80] The management of ICI-induced irAEs in LT candidates presents unique clinical challenges.[62,81-83] These patients frequently exhibit complex comorbidities and underlying hepatic dysfunction, which may complicate both the diagnosis and management of irAEs.[84,85] Therefore, prompt recognition and tailored immunosuppressive strategies are essential, ideally managed by an experienced multidisciplinary team.[86-88]

Question 13: Is there a role for ICIs in the management of HCC recurrence after LT?

Answer: The expert panel suggests that patients with HCC recurrence after LT who are not amenable to surgery or locoregional therapies, as well as those with disease progression despite sequential TKI treatments, may be considered for ICI therapy.

Certainty of evidence: very low

Strength of recommendation: weak

Strength of agreement: strong

The use of ICIs in LT recipients remains highly debated, with current evidence limited to case reports and small retrospective series. Kayali et al[89] analyzed 52 LT recipients treated with ICIs (28 with HCC), reporting a disease control rate of 44.2%. Responders had significantly longer overall survival (26.4 months) than nonresponders (3.4 months). However, ACR occurred in 28.8% of patients, and 13.4% of the entire cohort died from graft loss. In a systematic review, Kahramangil et al[90] evaluated 39 post-LT patients treated with ICIs, reporting a disease control rate of 25.6%. ACR occurred in approximately 20.5% of patients, with half of those cases resulting in graft loss. Another study assessing atezolizumab in 8 LT recipients reported objective response and ACR rates of 28.5% and 25%, respectively.[91] A recent review proposed a risk stratification model for ICI use in LT recipients, identifying patients at high immunologic risk as those transplanted within 12 months prior, young women, patients with autoimmune diseases, preformed or de novo donor-specific antibodies, prior rejection episodes, elevated baseline transaminases, increased liver stiffness, or evidence of subclinical rejection on liver biopsy.[92]

Question 14: Is there an ICI-based treatment regimen that should be preferred for managing HCC recurrence after LT?

Answer: The expert panel suggests that anti–PD-L1–based therapy may be considered as a first-line option in LT candidates, as it may be associated with a lower risk of ACR.

Certainty of evidence: very low

Strength of recommendation: weak

Strength of agreement: strong

The main concern regarding ICI use in LT recipients is the high risk of severe ACR, occurring in more than 25% of cases,[93] due to T cell activation triggered by ICIs. Lower ACR incidence has been reported with anti–PD-L1 agents than that with anti–PD-1 or anti–CTLA-4 therapies.[94,95] Moreover, initiating ICI treatment after a longer interval from LT and administering lower drug doses appear to further mitigate this risk.[96]

Question 15: Is there a preferred immunosuppressive regimen during ICI therapy for HCC recurrence after LT?

Answer 15: The expert panel suggests that there is insufficient evidence to support a specific immunosuppressive regimen to be used in combination with ICIs in treating HCC recurrence after LT.

Certainty of evidence: very low

Strength of recommendation: strong

Strength of agreement: strong

The replacement of calcineurin inhibitors with mTOR inhibitors could represent a potential strategy to enhance the efficacy of ICIs in treating HCC recurrence. An Italian study involving 50 patients reported that the combination of TKIs and mTOR inhibitors was associated with significantly improved overall survival compared with TKIs alone.[97] Similarly, a French study[98] showed that sorafenib combined with everolimus resulted in better overall survival rates than sorafenib monotherapy. However, these findings should be interpreted with caution. Both studies enrolled a limited number of patients, and additional interventions, such as surgical resection or locoregional therapies, were frequently used, making it difficult to isolate the true effect of the systemic regimen. Currently, no data are available on the potential anticancer benefit of adding mTOR inhibitors to ICIs in the treatment of post-LT HCC recurrence.

4. Conclusions

The use of ICIs in LT candidates and recipients with HCC represents one of the most striking paradoxes in modern oncology. ICIs have transformed the treatment landscape of advanced HCC; yet, their integration into transplant settings remains constrained by a fundamental immunologic conflict: the immune activation that drives tumor regression may also jeopardize the allograft.

The principal barrier is the risk of ACR, often severe and occasionally fatal, with rejection rates reported as high as 30% to 40% despite intensified immunosuppression.[96,99] This risk persists across time points but is especially pronounced in early post-LT recurrence, when immunosuppression is at its peak and graft vulnerability is maximal. In contrast, late recurrence, when immunosuppressive regimens are tapered and immunologic tolerance may be more established, offers a theoretical window of opportunity, yet rejection remains a real and unpredictable threat.

Navigating this narrow therapeutic window demands a delicate balance. Reducing immunosuppression to potentiate ICI

activity may unmask life-threatening graft rejection, while maintaining high immunosuppression risks blunting the antitumor responses ICIs are meant to unleash. No validated algorithms currently guide clinicians through this immunologic tightrope.

Clinical evidence is sparse, fragmented, and largely retrospective, with small patient cohorts and heterogeneous treatment strategies. We lack prospective trials, optimal dosing schemes, validated biomarkers, and standardized management protocols, leaving clinicians to operate in a space of clinical uncertainty.

In this complex and high-stakes scenario, multidisciplinary collaboration is not optional but essential. Tailored, patient-specific risk-benefit analyses must drive decision making, supported by structured protocols and rigorous surveillance. Prospective studies and international registries are urgently needed to illuminate this frontier.

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Declaration of competing interest

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Data availability

Data are available from the corresponding author upon reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajt.2026.02.024.

ORCiD

Francesca Romana Ponziani https://orcid.org/0000-0002-5924-6238
Valerio Giannelli https://orcid.org/0009-0003-4079-7974
Giuseppe Marrone https://orcid.org/0000-0002-9475-3948
Silvia Martini https://orcid.org/0000-0002-9738-5538
Maria Cristina Morelli https://orcid.org/0000-0002-9742-1981
Duilio Pagano https://orcid.org/0000-0003-3987-9262
Gianluca Svegliati Baroni https://orcid.org/0000-0003-4399-3359
Giacomo Germani https://orcid.org/0000-0002-4332-2072
Patrizia Burra https://orcid.org/0000-0002-8791-191X
Pierluigi Toniutto https://orcid.org/0000-0002-2566-3041

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