Beyond rejection risk: Identifying ideal candidates for pretransplant immune checkpoint inhibitors for HCC

VISUAL ABSTRACT

Beyond rejection risk: Identifying ideal candidates for pretransplant immune checkpoint inhibitors for HCC

Current published literature
- Case reports
- Case series
- Retrospective cohorts
- Prospective studies

N=39 studies = 261 cases

237 patients with available data on HCC recurrence

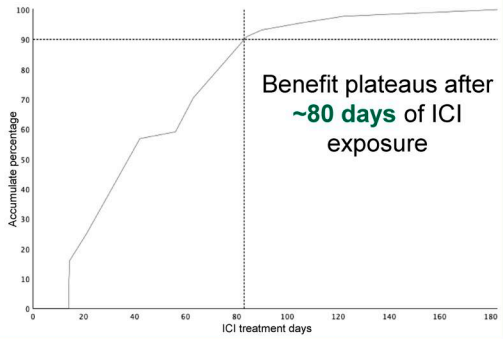
- 78% multifocal HCC
- Median largest tumor 3.7 cm
- 24.6% within Milan
- 15.7% macrovascular invasion
- 77% received prior LRT
- Median ICI duration: 63 days (4 cycles)

HCC RECURRENCE

Recurrence happened in 18.6% (44/237)

Shorter ICI exposure linked to higher recurrence: 42 vs. 63 days ($p < 0.001$).

Multivariate analysis:
- Longer ICI duration ↓ recurrence (OR 0.98 per day; $p < 0.001$).
- BCLC A ↑ recurrence risk (OR 5.23; $p = 0.005$).



Rejection: 23%

Rejection risk ↑ : Short washout (<50 days) & Younger age (<50 years)

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ORIGINAL ARTICLE

OPEN

Beyond rejection risk: Identifying ideal candidates for pretransplant immune checkpoint inhibitors for HCC

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Abstract

The role of immune checkpoint inhibitors (ICIs) before liver transplantation (LT) for HCC remains uncertain. In particular, the optimal treatment duration and the potential long-term oncologic benefits remain unclear. Thus, we conducted a systematic review to evaluate outcomes of ICI as bridging or downstaging therapy before LT. Following PRISMA guidelines (PROSPERO CRD1082620), 5 databases were systematically searched up to March 2025. All published studies reporting ICI before LT in HCC were included. Data were synthesized descriptively, and exploratory regression models, including restricted cubic splines, were performed. Thirty-nine studies comprising 261 patients were included. Most were male (87.3%), over 50 years old, and had viral hepatitis as the predominant etiology of their liver disease. ICIs were mainly used for downstaging (84.2%), most frequently using nivolumab (24.5%). The median ICI duration was 63 days

Abbreviations: BCLC, Barcelona Clinic Liver Cancer (staging system); CENTRAL, Cochrane Central Register of Controlled Trials; ICI, immune checkpoint inhibitor; LRT, locoregional treatment; LT, liver transplantation; MeSH, Medical Subject Headings; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International Prospective Register of Systematic Reviews; Q1–Q3, first to third quartiles (interquartile range bounds).

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(42–105), with a median washout period of 57 days (29–116). Most patients presented with multifocal disease (77.9%) and tumors beyond Milan criteria, with a median largest lesion size of 37.5 mm (9.4–78.5). Macrovascular invasion was present in 15.7%. Posttransplant recurrence occurred in 18.6%. Shorter ICI exposure was significantly associated with a higher risk of recurrence (OR: 0.9; $p < 0.001$). Spline models demonstrated that the benefit of ICI treatment was achieved at 80 days. Paradoxically, patients with BCLC A exhibited higher recurrence risk (OR: 5.2; $p = 0.01$), perhaps underscoring the limitations of conventional staging in candidate selection. Allograft rejection occurred in 23.0% of patients and led to graft failure in 14.7%. Younger age (< 50 y) and a shorter washout period (< 50 d) were independently associated with an increased risk of recurrence and rejection, respectively. The duration of ICI treatment before LT is a critical factor influencing HCC recurrence risk, with an optimal treatment duration of more than 80 days. Furthermore, a confirmatory washout period of at least 50 days appears to be important to mitigate the risk of rejection.

Keywords: graft rejection, immunotherapy, liver cancer, liver transplantation

INTRODUCTION

Liver transplantation (LT) for HCC remains the best curative approach for selected patients.[1] It addresses both the tumor and the underlying liver disease, thereby reducing the risk of recurrence.[2]

HCC treatment decisions are primarily guided by tumor burden and liver function, with the Barcelona Clinic Liver Cancer (BCLC) staging system being the most widely adopted algorithm.[3] Immune checkpoint inhibitors (ICIs) are a therapeutic option for HCC, demonstrating efficacy in both early and advanced stages of the disease.[4–8]

The optimal length for a washout period before LT remains uncertain. While some experts recommend over 30 days,[9] an earlier meta-analysis of individual cases found a 90-day period to be safe,[10] while a more recent case review suggested ~50 days.[11] The only available guideline suggests a washout period of 2–3 half-lives of the ICI drug,[12] which range from 12 to 24 days and may not be adequate to fully reduce the risk of rejection.

Despite the challenges, such as rejection risk, uncertainties surrounding optimal washout intervals, treatment durations, and a lack of standardized post-transplant management, ICIs continue to be explored as a potential option for selected patients awaiting LT.[10] However, the current evidence is largely limited to case reports, case series, and small prospective studies. Most studies to date have concentrated on the risk of rejection and its management. However, a critical unanswered question is which candidates are most suitable for ICI use before transplantation, and whether ICIs can be actively considered as a bridging or downstaging strategy before LT. Alternatively, ICI treatment may be viewed as not constituting a contraindication in patients who have achieved a significant tumor response in more advanced stages.

The aim of this study was to conduct a systematic review of the existing literature to evaluate not only the rejection rates and clinical outcomes, but, more importantly, to identify patient characteristics and pretransplant factors that may determine which patients are most likely to benefit from, or to be harmed by, ICI therapy as downstage/bridge to transplantation.

METHODS

Study design

This systematic review was designed to identify patient characteristics and pretransplant factors that may be associated with optimal oncological benefit and reduced HCC recurrence in those who receive ICI before transplantation. This objective is pursued while explicitly acknowledging and evaluating the associated inherent risk of allograft rejection from ICI treatment, particularly challenging and potentially lethal rejection episodes that may be more difficult to control with conventional immunosuppression.

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review protocol was prospectively registered with PROSPERO (International Prospective Register of Systematic Reviews) under Registration ID: CRD1082620.

This study was conducted in accordance with the principles of the Declaration of Helsinki and the Declaration of Istanbul.

Search strategy and information sources

A comprehensive systematic literature search was conducted across the following electronic medical databases:

- PubMed/MEDLINE
- Embase
- Scopus
- Cochrane Library (Cochrane Central Register of Controlled Trials—CENTRAL)
- Web of Science

The search encompassed all studies published until March 1, 2025. The search strategy was developed in consultation with an experienced medical librarian and included a combination of Medical Subject Headings (MeSH) terms and free-text keywords to maximize sensitivity. Key terms included, but were not limited to:

- Hepatocellular carcinoma: "hepatocellular carcinoma," "HCC," "liver cancer"
- Immune checkpoint inhibitors: "immune checkpoint inhibitors," "ICI," "PD-1," "PD-L1," "CTLA-4," "nivolumab," "pembrolizumab," "ipilimumab," "atezolizumab," "durvalumab," "tremelimumab"
- Liver transplantation: "liver transplantation," "LT," "hepatic transplantation," "transplant"
- Related concepts: "transplant rejection," "allograft rejection," "downstaging," "bridging therapy," "recurrence," "oncological outcome"

The full search strategy, including all MeSH terms and Boolean operators, for each database is provided in Supplemental Appendix 1, http://links.lww.com/LVT/B92. The search was restricted to studies published in English. No limitations were applied regarding publication date. A PRISMA flow diagram outlining the study selection process is presented in Supplemental Figure S1, http://links.lww.com/LVT/B93.

Eligibility criteria

All the studies published that include patients who received ICI for an HCC before transplantation (including case reports, case series, and prospective studies) were included. The cases with fibrolamellar HCC and cholangiocarcinoma were excluded. Patients who received ICI after transplant were excluded. Find the details of the inclusion-exclusion criteria in Supplemental Table S1, http://links.lww.com/LVT/B93

Study selection and data collection

Following the comprehensive database searches, all identified citations were imported into a reference management software (Mendeley) to remove duplicates. Two independent reviewers then independently screened all titles and abstracts against the predefined eligibility criteria. Full-text articles of potentially relevant studies were retrieved and independently reviewed by the same 2 reviewers. Any disagreements regarding study eligibility were resolved through discussion and consensus.

Data extraction was performed independently by the 2 reviewers using a standardized, pre-piloted data extraction form. Discrepancies were resolved by discussion (see the data extracted in Supplemental Table S2, http://links.lww.com/LVT/B93).

Outcome measures

The primary outcome of this systematic review is the description and identification of patient characteristics (eg, tumor burden and pathological response to ICI) and pretransplant factors (eg, type and duration of ICI therapy and washout period) potentially associated with HCC recurrence following LT in patients who received ICI before transplant.

Secondary outcomes include:

- The rates, time to onset, and severity of allograft rejection after transplantation.
- Response to standard and rescue rejection treatments.
- Graft survival and patient survival rates.

For each included study, HCC recurrence and mortality attributable to these events were extracted and evaluated based on the definitions and reporting available from the original studies.

Data synthesis and statistical analysis

Due to the anticipated significant heterogeneity in study design, patient characteristics, ICI regimens, and outcome reporting across the included literature (predominantly case reports and small case series), a formal meta-analysis was not performed. Instead, a descriptive synthesis of the findings was conducted.

Given the exploratory nature of this individual patient-level systematic review, and acknowledging the heterogeneity and variable reporting across studies, we established an a priori approach to missing data. Variables with missing data in < 20% of the overall cohort were considered for inclusion in univariable analyses. The variables included in the logistic regression aligned with clinical relevance, prior literature, and complete data. If any other significant association with the outcome of interest was observed, and if the number of events permitted, those variables were further evaluated and included in the multivariate models. This strategy aimed to balance the need for hypothesis generation with the limitations inherent to aggregated case reports and series.

A comprehensive list of all included articles with detailed characteristics of the included studies can be found in the Supplemental Table S3, http://links.lww.com/LVT/B93.

Data from individual patient records (from case reports and detailed case series) were included. For studies reporting aggregated data or summary statistics (from larger cohorts), the individual patient count underlying these summary statistics was considered, and each contributing patient case was proportionally weighted based on the total number of contributing patients to ensure balanced representation in descriptive analyses.

For continuous variables, descriptive statistics (median and Q1–Q3) were reported. Differences in distributions (eg, age, washout period) across groups (eg, rejection vs. no-rejection, recurrence vs. no recurrence) were described qualitatively, or if suitable, simple comparative statistics (eg, independent *t* tests) were used for illustrative purposes on weighted cases, but without formal hypothesis testing or pooling across studies due to heterogeneity. To ensure the stability and interpretability of the regression coefficients, multicollinearity among the independent variables was assessed using a preliminary linear regression model, preceding the primary univariate and multivariate analyses. Univariable and multivariable associations with the outcome were assessed using binary logistic regression models. To capture potential nonlinear relationships in the data, natural cubic splines were employed. Analyses were performed using SPSS v.XX (IBM Corp.).

RESULTS

Study characteristics and patient demographics

A total of 39 studies comprising 261 unique patients were included in this systematic review. These studies originated from North America (n = 18; 108 patients), Asia (n = 13; 145 patients), Europe (n = 7; 7 patients), and South America (n = 1; 1 patient). Most studies were published between 2021 and 2024. A detailed description of all included studies is provided in Supplemental Table S3, http://links.lww.com/LVT/B93.

The majority of patients were male (206/261, 87.3%) and > 50 years old (181/261, 76.4%). The most common etiology of underlying liver disease was viral hepatitis (146/261, 77.2%), 111 of 261 patients had hepatitis B, and 35 had hepatitis C. Among the patients infected with HCV, most studies either did not report whether antiviral therapy had been administered or, when mentioned, did not specify whether treatment was effective. In the cases with available information, 3 patients received HCV therapy after transplantation (none had rejection), 1 due to lack of response pre-LT, and the other two were treated after LT. With regards to tumor burden, 77.9% (173/261) had multifocal disease with a median size of the largest lesion at the time of diagnosis of 37.5 mm (9.4–78.5). Milan criteria were met by 43/261 patients (24.6%) at the diagnosis, while most patients had tumors beyond the Milan criteria. Macrovascular invasion was identified in 37 of 261 patients (15.7%). Among patients for whom BCLC staging was available at diagnosis (207/261; 79.3%), 31 (15.0%) were classified as BCLC A, 137 (66.2%) as BCLC B, and 39 (18.8%) as BCLC C. Only 1 patient had evidence of pretransplant extrahepatic spread (this was a patient with previous oligometastatic disease in the lungs).

The goal of ICI treatment was downstaging in 139 patients (84.2%). 77.4% of the patients received at least 1 locoregional treatment (LRT) before the ICI. The most common ICI used was nivolumab (64, 24.5%), followed by pembrolizumab (49, 18.8%) and camrelizumab (45, 17.2%). There were 7 reported cases of combination therapy, 4 including ipilimumab/nivolumab and 3 not defined. The median duration of ICI therapy before transplantation was 4.0 cycles (2.0–7.0), with a median of 63 days (42–105) of ICI treatment. The median washout period was 57 days (29–116) (detailed data are described in Table 1).

Impact of ICIs on HCC recurrence after transplant

Out of the 261 patients, data on HCC recurrence after transplant were available in 237 (90.8%), with 44 (18.6%) patients with posttransplant HCC recurrence. Patients with recurrence had shorter treatment durations (median 42.0 d vs. 63.0 d, $p < 0.001$). Tumor size at diagnosis was significantly smaller among patients who developed recurrence (median 35.0 mm) compared with those without recurrence (median 40.0 mm; $p = 0.01$). Recurrence was more common in patients with BCLC A than BCLC B/C (23.1% vs. 6.5%,

TABLE 1 Detailed demographics, tumor burden, and cohort comparison between no-rejection and rejection

	All (N = 261)	Missing data	No-rejection (n = 201)	Rejection (n = 60)	p[a]
Age ≥ 50 y old, n (%)	181 (76.4)	24 (9.2)	149 (81.0)	32 (60.4)	< 0.001
Sex, male, n (%)	206 (87.3)	25 (9.6)	158 (86.8)	48 (88.9)	0.7
Underlying liver disease, viral, n (%)	146 (77.2)	72 (27.6)	106 (74.6)	40 (85.1)	0.16
Largest lesion at transplant time (mm)	37.5 (9.4-78.5)	63 (24.1)	36.0 (6.6-68.75)	43.5 (20.0-94.5)	0.34
Milan criteria, n (%)	43 (24.6)	86 (33.0)	30 (22.7)	13 (30.2)	0.32
BCLC		54 (20.7)			
A, n (%)	31 (15.0)		21 (13.3)	10 (20.4)	0.22
B, n (%)	137 (66.2)		106 (67.1)	31 (63.3)	0.62
C, n (%)	39 (18.8)		31 (19.6)	8 (16.3)	0.60
Multifocal, n (%)	173 (77.9)	39 (14.9)	135 (78.9)	38 (74.5)	0.50
Number of lesions	2.0 (1.0-3.0)	173 (66.3)	2.0 (1.0-3.0)	1.5 (1-2.8)	0.32
Macrovascular invasion, n (%)	37 (15.7)	25 (9.6)	28 (15.6)	9 (15.9)	0.98
Locoregional treatment, n (%)	202 (77.4)	35 (13.4)	162 (92.0)	40 (80)	0.02
Number of locoregional treatments	2.0 (1.0-2.0)	35 (13.4)	2.0 (1.0–2.0)	2.0 (1.0-2.0)	0.49
Histology					
Well differentiated, n (%)	50 (43.9)	147 (56.3)	36 (43.4)	14 (45.2)	0.86
Moderate differentiated, n (%)	53 (46.5)		38 (45.8)	15 (48.4)	0.80
Poorly differentiated, n (%)	10 (8.8)		8 (9.6)	2 (6.5)	0.73
Microvascular invasion, n (%)	47 (33.1)	118 (45.2)	30 (27.5)	17 (51.5)	0.01
Type of ICI					
PD-1, n (%)	204 (78.2)		149 (76.8)	55 (91.7)	0.01
PD-L1, n (%)	50 (19.2)		45 (23.2)	5 (8.3)	
Combination, n (%)	7 (2.7)		7 (3.5)	0 (0)	0.36
PD-1 (programmed death-1 inhibitors)					
Nivolumab, n (%)	64 (24.5)		46 (22.9)	18 (30.0)	0.26
Toripalimab, n (%)	1 (0.4)		0 (0)	1 (1.7)	0.23
Pembrolizumab, n (%)	49 (18.8)		33 (16.4)	16 (26.7)	0.07
Sintilimab, n (%)	18 (6.9)		11 (5.5)	7 (11.7)	0.14
Camrelizumab, n (%)	45 (17.2)		37 (18.4)	8 (13.3)	0.36
Tislelizumab, n (%)	16 (6.1)		13 (6.5)	3 (5.0)	> 0.99
None defined PD-1 inhibitor	11 (4.2)		9 (4.5)	2 (3.3)	> 0.99
PD-L1 (programmed death-ligand 1 inhibitors)					
Durvalumab, n (%)	1 (0.4)		1 (0.5)	0 (0)	> 0.99
Atezolizumab, n (%)	4 (1.5)		2 (1.0)	2 (3.3)	0.23
Atezolizumab/bevacizumab, n (%)	45 (17.2)		42 (20.9)	3 (5.0)	< 0.01
Combination					
Ipilimumab/nivolumab, n (%)	4 (1.5)		4 (2.0)	0 (0)	0.58
Other combinations, n (%)	3 (1.1)		3 (1.5)	0 (0)	> 0.99
Number of cycles	4.0 (2.0-7.0)	13 (5.0)		4.0 (1.0-6.0)	0.49
Days of ICI treatment	63.0 (42.0-105.0)	13 (5.0)		84.0 (42.0-126.0)	0.25
Washout (d)	57.0 (29.0-116.5)	3 (1.1)		35.0 (18.5-95.5)	0.17
Washout range					
< 50 d, n (%)	108 (41.9)		74 (37.4)	34 (56.7)	0.01
50–100 d, n (%)	71 (27.5)		57 (28.8)	14 (23.3)	0.41
100–150 d, n (%)	61 (23.6)		53 (26.8)	8 (13.3)	0.03
150–200 d, n (%)	9 (3.5)		7 (3.5)	2 (3.3)	> 0.99
200–250 d, n (%)	2 (0.8)		2 (1.0)	0 (0)	> 0.99

TABLE 1. (*continued*)

	All (N = 261)	Missing data	No-rejection (n = 201)	Rejection (n = 60)	p[a]
250–300 d, n (%)	1 (0.4)		1 (0.5)	0 (0)	> 0.99
> 300 d, n (%)	7 (2.7)		5 (2.5)	2 (3.3)	0.67
Histopathological response to ICI					
Nonresponse, n (%)	30 (27.3)	151 (57.9)	26 (27.1)	4 (28.6)	> 0.99
Partial, n (%)	31 (28.2)		28 (29.2)	3 (21.4)	0.75
Complete, n (%)	46 (41.8)		39 (40.6)	7 (50.0)	0.51
Time from ICI to rejection (mo)	9.0 (7.0–14.3)	5 (9.1)			
ICI treatment objective-downstaging, n (%)	139 (84.2)	96 (36.8)	106 (82.8)	33 (89.2)	0.45
PRBC transfusions during the surgery	1.0 (0.0-3.6)	220 (84.3)	1.0 (0.0-5.2)	1.0 (0.0-1.8)	0.05
Graft failure, n (%)	11 (4.2)		2 (1.0)	9 (15.0)	< 0.001
Retransplant, n (%)	5/7 (71.4)		1 (0.5)	4 (6.7)	0.01
HCC recurrence, n (%)	44 (18.6)	24 (9.2)	36 (19.5)	6 (15.4)	0.50
Death, n (%)	27 (10.3)		18 (9.0)	9 (15.0)	0.18

Continuous variables are expressed as median (P_{25}–P_{75}).
[a]Comparisons between cohorts for continuous variables were performed using the Student *t* test and for categorical variables using the chi-square test or Fisher test, when appropriate (if expected frequencies in any cell were < 5).
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ICI, immune checkpoint inhibitor; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1. PRBC, packed red blood cells.

$p < 0.001$). No statistically significant differences in recurrence were observed between patients within or beyond Milan criteria ($p = 0.76$). In addition, there were no significant differences between those who received LRT and those who did not ($p = 0.18$). However, patients with smaller tumors (< 30.0 mm) at diagnosis appeared to be more frequently managed without LRT, although this trend did not quite reach statistical significance (37.5% vs. 52.9%; $p = 0.07$).

In patients with recurrence, the number of LRTs received was correlated with the size of the largest tumor at the time of transplantation, with larger tumors requiring more treatments ($r = 0.2$, $p < 0.001$). Furthermore, the purpose of the treatment, treatment versus bridging, differed between the recurrence and nonrecurrence groups. Specifically, 100% of the recurrence group received ICI as a downstaging strategy, while in the nonrecurrence group, only 80% of the patients received downstaging therapy ($p = 0.01$).

Regarding pathological response, nonresponse was more frequent in the recurrence group (63.6% vs. 23.4%, $p = 0.01$), and partial response was observed only in the nonrecurrence group (0.0% vs. 33.0%, $p = 0.03$). These data were not included in the univariate or multivariate analysis due to a high proportion of missing data (detailed description can be found in Table 2).

To determine the optimal ICI treatment duration before LT, models utilizing restricted cubic splines were employed. These models, with knots placed at 50, 60, 70, 80, 90, and 100 days, demonstrated a progressive attenuation in the association between treatment duration and the risk of recurrence (Figure 1). The slope at day 0 was steepest in the model with a 50-day knot (+0.0030), and gradually diminished in models with knots at 60 (+0.0025), 70 (+0.0021), 80 (+0.0013), 90 (+0.0010), and 100 days (+0.0002).

In the multivariate analysis (Table 3), longer ICI treatment duration was associated with a lower risk of HCC recurrence ($p < 0.001$; OR: 0.9 per day, 95% CI: 0.97–0.99). Patients with BCLC stage A had a higher risk of recurrence compared to those with more advanced stages ($p = 0.01$; OR: 5.2, 95% CI: 1.66–16.45). Pathological response was excluded from this analysis due to > 20% missing data.

Risk of rejection in patients treated with ICI before transplant

The overall allograft rejection rate was 23.0% (60/261 patients). The median time to rejection after transplantation was 9.0 months (7.0–14.3). The rate of rejection was significantly lower in patients over 50 years (60.4% vs. 81.0%, $p < 0.001$). Patients with microvascular invasion in the explant were more likely to have rejection (51.5% vs. 27.5%, $p = 0.01$).

Graft failure occurred in 14.7% of patients with rejection compared to 1.0% in the nonrejection group ($p < 0.001$). None of the graft failures was attributed to hepatitis B or hepatitis C reactivation. The graft failures related to ICI occurred early after transplantation, with a median of 7 days (3.0–10.0). Out of the 9 graft failures due to ICI, 4 patients underwent retransplantation and 5 died.

A shorter washout period (< 50 d) was associated with a higher risk of rejection (56.7% vs. 37.4%,

TABLE 2 Comparison between HCC recurrence and no recurrence (N = 237; 90.8%)

	Missing data	No recurrence (n = 193)	HCC recurrence (n = 44)	p^a
Age ≥ 50 y old, n (%)	15 (6.3)	140 (76.1)	29 (76.3)	0.98
Sex, male, n (%)	17 (7.2)	158 (86.3)	34 (91.4)	0.43
Underlying liver disease, viral, n (%)	64 (27.0)	110 (76.9)	27 (90.0)	0.14
Largest lesion at transplant time (mm)	41 (17.3)	40.0 (6.9-82.2)	35.0 (20.0-57.0)	0.01
Tumor size range				
< 30 mm, n (%)		61 (37.2)	10 (31.3)	0.55
30–60 mm, n (%)		51 (31.1)	16 (60.0)	0.04
60–90 mm, n (%)		19 (11.6)	4 (12.5)	> 0.99
90–120 mm, n (%)		16 (9.8)	4 (12.5)	0.75
> 120 mm, n (%)		23 (14.0)	0 (0)	0.01
Number of lesions, n (%)	150 (63.3)	2.0 (1.0-3.0)	3.0 (1.5-3.0)	0.45
Outside Milan criteria, n (%)	65 (27.4)	105 (76.1)	25 (73.5)	0.76
BCLC	44 (18.6)			
A, n (%)		10 (6.5)	9 (23.1)	< 0.001
B, n (%)		114 (74.0)	22 (56.4)	0.03
C, n (%)		30 (19.5)	8 (20.5)	0.88
Multifocal, n (%)	23 (9.7)	139 (77.7)	29 (82.9)	0.49
Macrovascular invasion, n (%)	24 (10.1)	31 (17.9)	5 (12.5)	0.41
Locoregional treatment, n (%)	21 (8.9)	252 (87.3)	41 (95.3)	0.18
Number of locoregional treatments	21 (8.9)	2.0 (1.0-2.0)	3.0 (1.5-3.0)	0.88
Added any LRT during ICI treatment/ posttreatment?	173 (73.0)	37 (66.1)	4 (50.0)	0.44
Histology	129 (54.4)			
Well differentiated, n (%)		33 (38.4)	11 (50.0)	0.32
Moderate differentiated, n (%)		43 (50.0)	10 (45.5)	0.70
Poorly differentiated, n (%)		9 (10.5)	1 (4.5)	0.68
Microvascular invasion, n (%)	142 (59.9)	38 (32.8)	9 (34.6)	0.86
Pathological response, n (%)	132 (55.7)			
Nonresponse, n (%)		22 (23.4)	7 (63.6)	0.01
Partial, n (%)		31 (33.0)	0 (0.0)	0.03
Complete, n (%)		40 (42.6)	2 (18.6)	0.19
Washout		60.0 (28.5-120.0)	57.0 (28.2-101.0)	0.29
ICI treatment objective, downstaging, n (%)	83 (35.0)	100 (80.0)	29 (100%)	0.01
PD-1 (programmed death-1 inhibitors)		141 (75.4)	40 (93.0)	0.01
Nivolumab, n (%)		45 (23.3)	8 (18.2)	0.46
Toripalimab, n (%)		1 (0.5)	0 (0)	> 0.99
Pembrolizumab, n (%)		37 (19.2)	11 (25.0)	0.39
Sintilimab, n (%)		13 (6.7)	5 (11.4)	0.30
Camrelizumab, n (%)		31 (16.1)	14 (31.8)	0.01
Tislelizumab, n (%)		14 (7.3)	2 (4.5)	0.74
PD-L1 (programmed death-ligand 1 inhibitors)		46 (24.6)	3 (7.0)	0.01
Atezolizumab, n (%)		4 (2.1)	0 (0)	0.34
Atezolizumab/bevacizumab, n (%)		42 (21.8)	3 (6.8)	0.02
Combination				
Ipilimumab/nivolumab, n (%)		3 (1.6)	1 (2.3)	0.74
Other combinations, n (%)		3 (1.6)	0 (0)	> 0.99
Cycles	5 (2.1)	4.0 (2.0-7.4)	3.0 (2.0-4.0)	< 0.001
Days of treatment		63.0 (42.0-126.0)	42.0 (26.2 -84.0)	< 0.001
Days of treatment range				

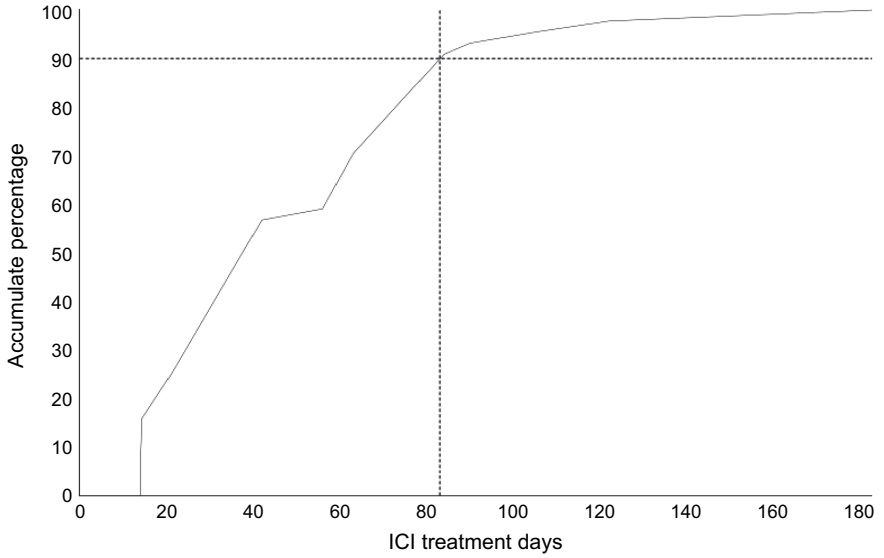
TABLE 2. (*continued*)

	Missing data	No recurrence (n = 193)	HCC recurrence (n = 44)	p^a
< 30 d, n (%)		45 (23.9)	11 (25.0)	0.88
30–60 d, n (%)		40 (21.3)	15 (34.1)	0.07
60–90 d, n (%)		35 (18.6)	15 (34.1)	0.03
90–120 d, n (%)		20 (10.6)	2 (4.5)	0.21
> 120 d, n (%)		48 (25.5)	2 (4.5)	< 0.001
Death, n (%)		17 (8.8)	6 (13.6)	0.33

Continuous variables are expressed as median (P_{25}–P_{75}).
[a]Comparisons between cohorts for continuous variables were performed using the Student *t* test and for categorical variables using the chi-square test or Fisher test, when appropriate (if expected frequencies in any cell were < 5).
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ICI, immune checkpoint inhibitor; LRT, locoregional treatment; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

$p = 0.01$), while longer intervals (100–150 d) were less common in the rejection group (13.3% vs. 26.8%, $p = 0.03$). As shown in Figure 2, ~50% of rejection events occurred in patients with a washout shorter than 30 days, highlighting this period as a high-risk window. To better characterize the nonlinear relationship between washout duration and rejection risk, spline logistic models were generated with knots placed at 30, 50, and 60 days. The spline models showed a consistent decrease in rejection risk with increasing washout duration. The model with a 30-day knot exhibited the steepest slope (–0.012), indicating the most pronounced early decline in predicted risk. The 50-day knot model showed a more gradual slope (–0.008), reflecting a smoother reduction in risk over time. The 60-day knot had the gentlest slope (–0.006), suggesting a stabilization. While all models showed decreasing risk as washout increased, the less abrupt slope beyond 50 days suggests a stabilization in the risk curve, supporting the consideration of a 50-day knot as a potentially more clinically robust threshold.

In the multivariate analysis, risk factors identified associated with rejection were: age < 50 years ($p < 0.001$; OR: 5.8; 95% CI: 2.41–13.75) and washout period < 50 days ($p = 0.01$; OR: 3.1; 95% CI: 1.36–7.14). In contrast, a washout period of 100–150 days ($p = 0.04$, OR: 0.3, 95% CI: 0.11–0.93) was associated with a lower risk of rejection (Table 4).



Days	<30d	30-60	60-90	90-120	>120
Accumulate cases	11	26	41	42	44

FIGURE 1 Days of treatment and the accumulated proportion of recurrence. Cumulative incidence of HCC recurrence following liver transplantation in patients previously exposed to ICIs. Note the inflection point at which the recurrence curve begins to flatten. Abbreviation: ICI, immune checkpoint inhibitor.

TABLE 3 Univariate and multivariate analyses associated with HCC recurrence

	Univariate		Multivariate	
	p	OR (95% CI)	*p*	OR (95% CI)
Tumor size at transplant time (mm)	0.13	0.9 (0.99-1.00)		
Treatment duration (d)	0.01	0.9 (0.99-0.99)	< 0.001	0.9 (0.97-0.99)
PD-1 treatment	0.01	0.2 (0.07-0.78)	0.60	
BCLC A	< 0.001	4.3 (1.62-11.54)	0.01	5.2 (1.66-16.45)
BCLC B	0.03	0.5 (0.22-0.94)	0.88	

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; PD-1, programmed cell death protein 1.

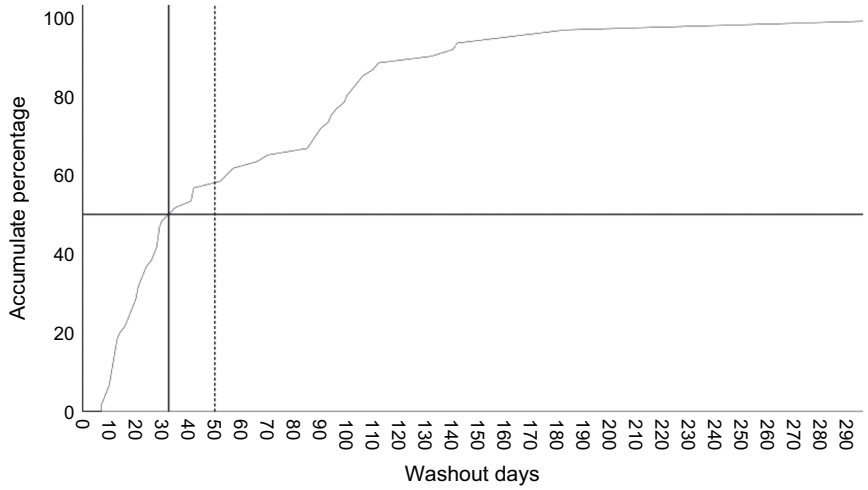
Given collinearity between treatments, only treatment category was included in the multivariable model (Supplemental Table S4, http://links.lww.com/LVT/B93)

DISCUSSION

This study highlights several critical findings regarding ICI therapy in the pretransplant setting for HCC. First, a key observation is the association between longer duration of pretransplant ICI therapy and a reduced risk of recurrence. Despite the inclusion of patients with locally advanced tumors (eg, multifocal disease, larger lesions, BCLC B and C stages), the overall posttransplant HCC recurrence rate remained acceptable at 18.6%. In addition, this study confirms that there is a significant correlation between a shorter washout period of < 50 days and an increased risk of allograft rejection.

Our findings show an overall HCC recurrence rate of 18.6%, consistent with previously reported ranges.[13–15] However, these patients present with higher tumor burden (more BCLC C, tumors outside Milan criteria and macrovascular invasion among others) which makes it challenging to compare our findings to those of previously known cohorts.[1] As the recurrent rate is similar to cohorts where patients were transplanted with tumors beyond Milan criteria, our data suggest that immunotherapy may offer a valid strategy for downstaging without significantly increasing the risk of recurrence if a washout period of at least 50 days is maintained.[2,16] This, however, will need to be demonstrated in randomized trials.

Notably, a shorter treatment duration was associated with a significantly increased risk of HCC recurrence. Given the retrospective design of this analysis, this observation should be regarded as hypothesis-generating. It is plausible that brief or suboptimal treatment courses are insufficient to establish durable tumor



Days	<50d	50-100	100-150	150-200	200-250	250-300	>300
Accumulate cases	34	48	57	59	59	59	60

FIGURE 2 Washout period (days) and accumulated proportion of rejection. Cumulative incidence of acute rejection following liver transplantation in patients previously exposed to ICIs. A similar inflection point is observed where the curve flattens. The solid line represents the 50% rejection rate, while the dotted line represents patients with a 50-day washout period. Abbreviation: ICI, immune checkpoint inhibitor.

TABLE 4 Univariate and multivariate analyses associated with rejection

	Univariate		Multivariate	
	p	OR (95% CI)	*p*	OR (95% CI)
Age < 50 y	< 0.001	2.8 (1.44-5.42)	< 0.001	5.8 (2.41-13.75)
PD-1 inhibitor use	0.01	3.3 (1.25-8.80)	0.07	
PD-L1 inhibitor use		0.3 (0.11-0.79)		
Washout period < 50 d	< 0.001	2.2 (1.21-3.93)	0.01	3.1 (1.36-7.14)
Washout period 100–150 d	0.03	0.4 (0.19-0.94)	0.04	0.3 (0.11-0.93)

Abbreviations: PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

control before transplantation. Consistent with our modeling, a treatment duration of at least 80 days appeared to confer the greatest benefit from pretransplant immunotherapy. Prospective studies are needed to define not only optimal baseline tumor characteristics of patients selected for ICI before transplant, but also to determine the optimal duration of such treatment.

A perhaps critically important finding of this study is that BCLC A status at the time of diagnosis was identified as a risk factor for HCC recurrence. This is a counterintuitive finding, as BCLC A represents a lower tumor burden compared to patients with BCLC B and C.[3] In this cohort, patients with BCLC A tumors received less locoregional therapy and had shorter exposure to ICI compared with those with more advanced disease. Thus, the association between smaller tumor size and higher recurrence risk may indicate that tumor volume alone does not adequately reflect underlying tumor aggressiveness or potential for immune escape.[17] Given the retrospective nature of these findings and the relatively small sample size, these should be considered hypothesis-generating and thus require validation in larger prospective cohorts.

As the next step, prospective studies will be essential to clarify the true oncologic benefit and risk of ICI therapy in this population. It would also be valuable to assess the predictive role of biomarkers such as alpha-fetoprotein, lens culinaris agglutinin–reactive alpha-fetoprotein, des-γ-carboxy prothrombin (also known as PIVKA-II), and circulating tumor DNA in future studies,[18] which may help stratify recurrence risk in patients exposed to immunotherapy before transplantation.

Initial case reports and small case series have described a seemingly high incidence of severe rejection after ICI exposure, which likely reflected the early experience where there were no clear washout protocols. Our data reinforce the importance of washout duration. Shorter washout periods (< 50 d) were independently associated with increased rejection risk. This is consistent with previous reports,[10,11] and our spline analysis further supports a 50-day washout as a meaningful inflection point where rejection risk begins to decline. Selecting a 50-day interval may therefore offer a balanced approach between maximizing oncologic response and minimizing graft injury in patients exposed to ICIs.

Our cohort had few patients receiving combination treatments, making it difficult to fully describe the role of cytotoxic T-lymphocyte–associated protein 4 in the rejection setting in this paper. However, our findings support the hypothesis that programmed cell death protein 1 blockade may provoke more sustained or intense immune activation,[19,20] thereby increasing the risk of graft-directed immune responses in transplant workflows.

Our findings are consistent with previous observations in the broader transplant population:[21] patients under 50 years of age were significantly more likely to experience rejection. This may reflect more robust immune reconstitution or lower immunosenescence in younger individuals.[22,23] Interestingly, as suggested before,[23] packed red blood cell transfusions appeared to be protective against rejection, although this could not be formally included in the univariate model due to a high proportion of missing data. This needs to be further explored.

Unfortunately, management strategies for posttransplant rejection varied widely across studies, precluding meaningful conclusions about treatment efficacy. Nevertheless, the incidence of graft failure in the rejection group was considerable (15%). In limited cases with available virologic information, HCV or HBV recurrence did not appear to contribute to graft failure, and biopsy findings were instead consistent with acute rejection. Particularly, several of the graft failures that resulted in patient deaths occurred among the earliest ICI-treated cases, a period during which patients were often not considered candidates for retransplantation due to high tumor burden. This likely contributed to the higher mortality observed in this subgroup. Future research should focus not only on prevention but also on standardized and idealized approaches to rejection management in the context of prior ICI exposure.

This study has several strengths. Most importantly, the present study focused on HCC recurrence as a primary oncological outcome in the setting of pretransplant ICI therapy. By systematically aggregating data from multiple reports, we aimed to move beyond isolated case experiences and identify clinical variables associated with favorable transplant outcomes, including both

graft survival and long-term HCC remission. In addition, our cohort included patients with a high tumor burden, supporting the notion that modifying the immune microenvironment may improve transplant eligibility and posttransplant control of HCC in carefully selected cases of patients with high tumor burden.

Despite these strengths, several limitations should be acknowledged. The most critical is the limited availability of comprehensive, high-quality data across the included studies. Substantial missing data contributed to heterogeneity and restricted the robustness of some analyses. In addition, the scarcity of long-term follow-up in many reports impeded the assessment of late recurrence and long-term graft outcomes. There is also a marked geographical imbalance, with most studies originating from Asia (55.5%) and North America (41.3%). This uneven distribution is associated with demographic differences, including sex and underlying liver disease, which may somewhat limit the overall representativeness of this study. These limitations underscore the urgent need for larger, multicentric, prospective studies with standardized reporting protocols to better define the role of ICIs in the pretransplant management of HCC.

In summary, our study highlights a complex interplay between pretransplant ICI therapy, tumor recurrence, graft rejection, and survival. While shorter treatment durations may be associated with increased HCC recurrence, factors such as younger recipient age appear to be linked to a higher risk of rejection. These findings underscore the need for careful patient selection, optimized treatment duration, and consideration of adequate washout periods to balance oncological benefit with graft safety.

CONFLICTS OF INTEREST

Grainne M. O'Kane consults for BMS. She advises Zymeworks and Regeneron. She received grants from Roche and AstraZeneca. She has other interests in MSD. Parissa Tabrizian consults for AstraZeneca, Boston Scientific, and Bayer. She received grants from Genentech. Beatriz Mínguez consults for, is on the speakers' bureau for, and received grants from Roche and AstraZeneca. She consults for and received grants from Eisai-MSD. Arndt Vogel consults for Roche, AstraZeneca, Boehringer Ingelheim, Ipsen, Incyte, Cogent, EISAI, Zymeworks, Biologix, BMS, Terumo, Elevar, Servier, MSD Tahio, Jazzpharma, Medivir, AbbVie, and Tyra. Gonzalo Sapisochin consults for and received grants from AstraZeneca, Roche, Integra, Natera, Stryker, and HeparegeniX. The remaining authors have no conflicts to report.

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