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REVIEW

Preoperative Immunotherapy in Hepatocellular Carcinoma: Current State of the Art

Alena Laschtowitz[1], Christoph Roderburg[2], Frank Tacke[1], Raphael Mohr[1]

[1]Department of Hepatology and Gastroenterology, Charité – Universitätsmedizin Berlin, Campus Virchow Klinikum (CVK) and Campus Charité Mitte (CCM), Berlin, Germany; [2]Clinic for Gastroenterology, Hepatology and Infectious Diseases, University Hospital Düsseldorf, Düsseldorf, Germany

Correspondence: Raphael Mohr, Department of Hepatology and Gastroenterology, Charité – Universitätsmedizin Berlin, Augustenburger Platz 1, Berlin, 13353, Germany, Email raphael.mohr@charite.de

Abstract: Hepatocellular carcinoma (HCC) is a malignancy that requires multidisciplinary evaluation to develop individualized and tailored treatment concepts. While liver resection and transplantation represent the mainstay of curative treatment in patients with early-stage HCC, disease recurrence remains an important burden. Immune checkpoint inhibitors (ICI) have become standard of care in the palliative setting, achieving promising response rates with overall good tolerability. Accordingly, ICIs are being evaluated in (neo)adjuvant concepts in order to improve survival. Nevertheless, neoadjuvant therapies are not recommended by current guidelines as they have not been proven to improve the outcome in large Phase III trials yet. Especially in the context of liver transplantation (LT), perioperative ICI usage is in need of a particularly critical risk–benefit assessment, as the immunotherapy may significantly increase the risk of rejection. In this review, we summarize available data on ICI-based perioperative treatment strategies in HCC. We discuss current drawbacks and challenges of this treatment concept and specifically highlight the risk of allograft rejection when ICI are given in patients (subsequently) considered for liver transplantation.

Keywords: hepatocellular carcinoma, immune oncology, checkpoint inhibitor, neoadjuvant

Introduction

The development of immune checkpoint inhibitors (ICI) has fundamentally changed the clinical management of hepatocellular carcinoma (HCC). While conventional chemotherapy had minimal effect on HCC, tyrosine-kinase inhibitors (TKI) have been the standard of care in HCC patients without curative treatment options during the past decades.[1] The inhibition of programmed death receptor 1 (PD-1) or its ligand (PD-L1) in patients with advanced HCC showed clinical meaningful activity in several Phase I and II studies.[2,3] The combination of the PD-L1 antibody atezolizumab with the vascular endothelial growth factor (VEGF) inhibitor bevacizumab improved overall survival (OS) and progression-free survival (PFS) when compared with the TKI sorafenib and was approved by the international guidelines as first-line therapy for advanced HCC.[2,3] Most recently, phase III studies showed that the combination of PD-L1 inhibitor durvalumab with the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor tremelimumab, as well as the combination of PD-1 inhibitor camrelizumab with the TKI apatinib performed better than sorafenib in the setting of advanced HCC.[4,5]

For selected patients with early-stage HCC, surgical and ablative treatments are available in a (potentially) curative scenario while liver transplantation (LT) leads to improved long-term survival data in patients with cirrhosis compared to resected patients at the same tumor stage.[6] Nevertheless, both de novo tumors and recurrence of HCC after LT may occur in 9–16% of cases.[7] Thus, prevention of relapse remains an important goal in the management of HCC. TKI administration failed to show benefit in neoadjuvant randomized trials, and neither neoadjuvant nor adjuvant therapies are currently recommended by international guidelines as they have not been unequivocally demonstrated to improve the outcome. The excellent results of ICI trials in advanced HCC, on the one hand, and the high rates of recurrence after surgical treatment, on the other, support the evaluation of ICI usage in the intention of neoadjuvant or peri-interventional

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therapy concepts. Indeed, the clinical efficacy of preoperative ICI in other tumor entities has already led to FDA approvals.[8–13] Nevertheless, only limited evidence is available on the usage of ICI as preoperative treatment, especially in the context of transplantation, and only small case series or individual case reports of transplanted patients have been published so far. Particularly in the context of LT, consideration of effectiveness and safety aspects must be taken into account regarding the possible risk of rejection.

In this review, we will briefly summarize, critically discuss and classify the current available evidence on the use of checkpoint inhibitors in neoadjuvant settings and give an outlook on future directions of immunotherapy in HCC.

Rationale and Biological Aspects of Neoadjuvant Immunotherapy

HCC is a malignancy that requires interdisciplinary evaluation to develop individualized and tailored treatment concepts. The reasonable combination of appropriate surgical approaches, interventional/locoregional treatment strategies and various lines of systemic therapy are required to achieve the best possible patient survival. Although surgery and LT will remain the mainstay of HCC therapy in patients at early disease stages, recent studies have identified major challenges. Many patients are not suitable for liver surgery and/or transplantation due to tumor macrovascular invasion, multifocal disease, large tumor mass, or impaired liver function. However, while in most patients surgical resection and transplantation are performed with curative intent, the recurrence rates peak up to 70% after HCC resection and about 50% of patients show early recurrence within the first two years which is associated with large tumor size or microvascular invasion.[14,15] Neoadjuvant use of ICIs may therefore be intended as a downsizing strategy, making patients eligible for surgical treatment, but even more importantly to prevent relapses by eradication of micrometastasis.

"Immune checkpoints" are surface receptors. Under physiological conditions, their activation by the respective ligand regulates the balance between immune cell activation and immune cell quiescence, preventing normal tissues from being "attacked" by the immune system. Malignant tumors have the ability to upregulate those proteins, stimulating anti-inflammatory mechanisms, allowing the tumor to escape from being recognized by the patient's immune system. In line, a high expression of the programmed death-ligand 1 by tumor cells or cells of the tumor microenvironment predict tumor recurrence after surgery.[16] ICI block the inhibitory immune checkpoints, leading to a defense response toward the tumor tissue.

Mechanistically, ICI treatment is supposed to induce an improved priming of T cells that are directed against tumor neoantigens. In adjuvant settings, the priming is only induced by remaining micrometastasis, while in neoadjuvant settings more tumor mass is available for a stronger T cell response, underlining the benefit of ICI when used preoperatively. In line, data from melanoma and lung cancer showed the superiority of peri- versus postoperative immunotherapy.[10,17] This concept has also been validated in animal models, where a preoperative PD-1 blockade led to improved survival and enhanced tumor-specific CD8+ T cell activation compared to postoperative PD-1 blockade.[18] Furthermore, it seems intuitive that surgical intervention with removal of lymph nodes may negatively affect T cell expansion.

The principal concept of using ICI in a tumor mass reductive strategy making patients eligible for surgery is based on findings that liver-directed therapies are associated with sufficient local control and low LT waitlist dropout.[19,20] Long-term outcomes showed 10-year survival and recurrence after downstaging of 52% and 20.4% compared to 60.5% and 14.3% for patients after liver transplantation without downstaging.[21] In contrast to locoregional therapies, ICI harbor the risk of immune-related adverse events and severe allograft rejection in the transplant setting, as discussed further below. In this respect, the different metabolic half-lives of the several ICI agents which may lead to different prolonged T cell inductions need specific consideration.[22,23]

Available Data on Neoadjuvant Immunotherapy

For patients with preserved liver function and early-stage HCC, liver resection is the foremost curative strategy, with a 5-year overall survival (OS) of about 60%. But in spite of improving routine HCC surveillance to allow early detection of resectable HCC lesions, many patients present with tumors not eligible for primary resection. In this setting, ICI therapy may serve as a downstaging strategy to obtain secondary resectability while this practice already has relevant value in other tumor entities, such as for downstaging in advanced colon carcinoma.

Preoperative ICI in Initially Unresectable HCC

In HCC, this approach has been evaluated in one of the first published reports on preoperative ICI therapy in 15 patients primarily ineligible for curative resection due to high-risk features such as portal vein invasion, multifocality or advanced tumor size of more than 10 cm.[24] After two weeks lead-in therapy with the TKI cabozantinib (40mg oral daily), an additional 4 cycles of the anti-PD-1 agent nivolumab (240mg Q2W) were applied. Restaging was performed after 10 weeks. In 12 out of 15 patients, margin-negative resection could be performed. Of note, one patient did not pursue surgical resection due to missing clinical response and insufficient hepatic reserve. In 5 out of 12 patients who underwent surgery, a pathological response with >90% of tumor necrosis was detected.

In the following, two further observational studies with heterogenous TKI/ICI regimes were administrated as neoadjuvant conversion therapy prior to surgery, as displayed in Table 1, but with markedly heterogenous combinatorial TKI/ICI treatment schedules, making it difficult to objectively compare different agents.[25,26] Nevertheless, Zhang et al report on 10 patients with HCC and major vascular invasion that received different combinations of ICI and TKI with subsequent salvage surgery in 8 out of 10 patients and a 12-month recurrence-free survival rate of 75%.

Preoperative ICI in Initially Resectable HCC

The three aforementioned studies used preoperative immunotherapy in a downstaging attempt to convert initially non-resectable tumors eligible for surgery. Another approach of neoadjuvant ICI treatment accounts to the high risk of recurrence in HCC, highlighted by recurrence rates as high as 70% at 5 years.[14] Immunotherapy prior to resection aims to eradicate micrometastasis, that may lead to early recurrence, and thus to prolong recurrence-free survival. This concept has been evaluated in several Phase Ib/II trials for patients with up-front resectable tumors, as displayed in Table 1.

The efficacy and safety of camrelizumab, an anti-PD1-antibody, plus the TKI apatinib was recently evaluated in an open-label, single-arm Phase II trial enrolling 18 patients with up-front resectable HCC.[27] Neoadjuvant treatment with three doses of camrelizumab (200mg Q2W) in combination with apatinib (250mg oral daily) for 21 days was continued after HCC resection for a further 8 adjuvant cycles. Following neoadjuvant treatment, 3 and 6 out of 18 patients showed an overall response based on RECIST or mRECIST criteria, respectively. While one patient did not receive surgical resection due to disease progression, 3 out of 17 patients showed >90% tumor necrosis and 1 out of 17 patients achieved a pathologically complete response. Five patients were excluded from adjuvant therapy due to external reasons. The 1-year recurrence-free survival (RFS) rate amongst the remaining 13 patients was 53.9% (95% CI: 24.8–76.0), while the RFS rate was tendentially higher in patients with a tumor necrosis of >90%.

In line with these findings are the results from the most recently published Phase Ib study evaluating the combination of nivolumab (3 mg/kg, day 1 and day 22) plus ipilimumab (1 mg/kg, day 1 only) as a neoadjuvant therapy in 17 patients undergoing early-stage HCC resection.[28] Median tumor diameter was 3.4 cm (interquartile range [IQR] 2.4–4.0), and median number of lesions was 1 (range 1–3). After a median follow-up of 6.3 months (IQR 1.9–23.0), one disease relapse was recorded 20.8 months after treatment initiation. Pathological response was achieved in 78% of patients eligible for pathological evaluation (7 out of 9 patients), including 2 patients (22%) with complete response, while percentage of tumor necrosis was not available from published preliminary results. In contrast, when radiologically assessed, the ORR was only 23%. No severe immune-related adverse events were induced and neoadjuvant immunotherapy did not defer resection. These results underline the discrepancy between radiological and pathological tumor response and highlight the need for further evaluation of appropriate endpoints.

A Phase II trial including 27 patients with resectable HCC evaluated the administration of preoperative nivolumab (240mg Q2W, up to 3 cycles) +/- ipilimumab (1mg/kg, single dose), followed by an adjuvant therapy of nivolumab (480mg Q4W, up to 2 years) +/- ipilimumab (1mg/kg Q4W, up to 4 cycles).[29] Grade 3–4 adverse events (AEs) were higher in the nivolumab plus ipilimumab (n=14) group than in nivolumab monotherapy (n=13), with 43% vs 23%, respectively. Twenty out of 27 patients underwent resection. In all 7 cases, surgery was cancelled due to tumor progression but not because of treatment-related AEs. Estimated median progression-free survival (PFS) and median time to progression were each 9.4 vs 19.5 months with nivolumab and nivolumab plus ipilimumab, respectively. Significant pathological response, defined as >70% of tumor necrosis, was found in 3 out of 9 patients under nivolumab

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Table 1 Available Evidence for Preoperative Immunotherapy from Clinical Trials

Regime	Patients	Neoadjuvant	Adjuvant	Resection	(Histological) Response	Follow-Up	Safety Aspects	Authors
ICI use in initially unresectable HCC								
• Nivolumab • Cabozantinib	15 patients with high-risk features for resection	Lead-in with 2 weeks of cabozantinib, followed by 4 cycles of nivolumab	No	12/15 patients	5/12 patients (tumor necrosis >90%)	Recurrence in 5/12 patients after 1-year median follow-up	Grade 3/4 AEs in 2/15 patients	Ho et al[24]
• Lenvatinib • Apatinib/Nivolumab • Camrelizumab • Pembrolizumab • Sintilimab	63 patients with unresectable HCC	73–251 days of combinational therapy	Combination therapy resumed 4–6 weeks post-surgery	10/63 patients	6/10 patients (no residual viable tumor cells on hematoxylin and eosin staining on slide sections)	Recurrence in 1/10 patients and death in 1/10 patients after 11.2 months median follow-up	Death due to irAEs in 1/10 patients	Zhu et al[25]
• Lenvatinib • Apatinib/ Pembrolizumab • Sintilimab • Torioalimab	10 patients with unresectable HCC	4–10 cycles	No	8/10 patients	3/10 patients with CR using mRECIST	Recurrence in 2/10 patients after 19.7 months median follow-up	No AEs	Zhang et al[26]
ICI use in initially resectable HCC								
• Camrelizumab • Apatinib	18 up-front resection candidates	3 cycles of camrelizumab, 21 days of apatinib	8 cycles of camrelizumab with apatinib	17/18 patients	3/17 patients (tumor necrosis >90%)	1-year recurrence-free survival of 53.85%	Grade 3/4 AEs in 3/18 patients	Xia et al[27]
• Ipilimumab • Nivolumab	17 patients with early-stage HCC	Nivolumab/ ipilimumab on day 1, nivolumab on day 22	No	10/12 patients	7/9 patients (tumor necrosis >70%)	Relapse in 1/10 after 6.3 months median follow-up	Grade 3/4 AEs in 1/17 patients	D'Alessio et al[28]
• Ipilimumab • Nivolumab	27 up-front resection candidates	3 cycles of nivolumab, 50% of patients received additional single dose of Ipilimumab	Nivolumab up to 2 years, ipilimumab up to 4 cycles in combinational arm	20/27 patients	3/9 patients under monotherapy, 3/11 patients under combinational therapy (tumor necrosis >70%)	Median PFS 9.4 months (monotherapy) vs 19.53 months (combinational therapy)	Grade 3/4 AEs in 23% (monotherapy) vs 43% (combinational therapy)	Kaseb et al[29]
• Cemiplimab	21 up-front resection candidates	2 cycles	8 cycles	20/21 patients	4/20 patients (tumor necrosis >70%)	N/A	Grade 3/4 AEs in 7/21 patients	Marron et al[30]

monotherapy and in 3 out of 11 patients under combinational therapy with ipilimumab. Notably, after a 2-year follow up no recurrences in patients with pathological response were observed, while half of the non-responders developed recurrence.

A potential predictive role of preexisting immune infiltrates is underlined by the evidence of a Phase II trial where tumor tissue of pre- and post-ICI-treatment was evaluated.[30] Two cycles of cemiplimab (350mg Q3W) were administered as preoperative monotherapy in 21 patients with resectable HCC. One week after the last cemiplimab administration liver resection in curative intention was performed and was followed by an additional 8 postoperative cycles of cemiplimab. Twenty out of 21 patients received successful resection, whereof 20% of patients achieved a significant pathological response, defined as >70% tumor necrosis. Seven out of 20 patients were classified responders, defined as having >50% of tumor necrosis. Significant immune infiltrations were seen in responders compared to non-responders. Notably, increased immune infiltrates were also detected before treatment initiation among responders, indicating a potential predictive value for immune infiltrates as biomarker for rapid response to ICI therapy.

Immunotherapy in the Context of Liver Transplantation

While immunotherapies can lead to clinically significant antitumor immune responses by activating immune cells, such therapies may also induce alloreactions and even autoimmune processes against organ transplants that are usually well controlled by drugs. For LT, it could be shown that the PD-1/PD-L1 interaction plays an important role in the inhibition of rejection reactions.[31] Therefore, ICI treatment in the context of organ transplantation harbors the risk of graft rejection with ultimately graft loss and possibly patient death. There is broad consensus that any ICI-based therapy in patients potentially eligible for liver transplantation or in patients after liver transplantation (eg, in conditions of HCC recurrence or development of an extrahepatic malignancy such as melanoma) demands a careful and thorough risk–benefit assessment.[32] Little data are published on ICI use in the context of organ transplantation, but rejection appears to occur in 30–40% of patients.[33–38] A recent review on 25 LT cases described rejection in 36% of patients, which is associated with a rejection-related mortality rate of 20% of treated patients.[39]

In addition to the potential risk of rejection, a lower efficacy of ICI-based therapies in immunosuppressed patients after transplantation has to be considered. No biomarkers have been identified yet to predict rejection. However, there are findings of the histological evidence of PDL1- expression in the graft prior to initiation of ICI treatment being associated with a high risk of rejection.[40] On pretransplant ICI treatment, there is also currently little data, as displayed in Table 2. Safety remains a significant concern, with definite interest in timing of withdrawal of different ICI agents, while small

Table 2 Available Evidence for Immunotherapy in the Context of Liver Transplantation

Regime	Patients	Neoadjuvant	Withdrawal Before LT	Adjuvant	Follow-up	Rejection	Recurrence	Re-LT	Authors
Nivolumab	N=9	From 2 to 32 cycles	From 1 to 253 days	No	Median 16 months	No	No	None	Tabrizian et al[41]
Nivolumab	N=5	From 8 to 18 months	From 0.3 to 11 months	No	2–16 months	N=2	No	N=1	Schnickel et al[44]
Nivolumab/sorafenib/ regorafenib	N=1	Sorafenib for 14 months, then regorafenib for 11 weeks, then 34 cycles of nivolumab	15 weeks	No	1 year	No	No	No	Schwacha-Eipper et al[42]
Nivolumab/ipilimumab/ sorafenib	N=1	Sorafenib for 3 months, then nivolumab/ ipilimumab for 6 months	9 weeks	No	6 months	No	No	No	Lizaola-Mayo et al[45]

retrospective studies in which ICI therapy was continued until shortly before LT reported no increased rate of rejection.[41,42]

In clinical practice, the benefits and risks of preoperative immunotherapy need evaluation primarily as part of a multimodality therapeutic approach and subsequently in different scenarios. In patients with advanced tumors for whom liver transplantation is not a primary therapeutic option, an excellent response to immunotherapy may secondarily lead to the LT option in a downstaging approach. In those patients with an initial stage beyond transplantation criteria, studies have already shown a comparable outcome after LT in terms of overall survival and tumor-free survival when downstaging by locoregional measures compared to those with initial transplant eligibility.[19] Indeed, future studies have to evaluate whether this also holds true in the setting of ICI therapy as a downstaging agent, taking into account the potentially increased risk of rejection or liver failure in subsequent liver transplantation, as previously reported.[43]

ICI therapy might be a future "bridging" concept in patients eligible for transplantation while being on the waiting list. This concept aims to avoid loss of the waiting list position due to tumor progression by mostly using locoregional treatment. But to date, due to multiple alternative strategies, ICI, with its increased allograft rejection risk, is nowadays not recommended as a bridging concept.

In patients with excellent responses to ICI therapy, individual possibilities of LT with a transplant organ offered outside of organ allocation or living donation require individual evaluation in specialized centers.[32]

Ongoing Preoperative Clinical Trials

Checkpoint inhibitors have the potential to achieve significantly higher tumor response rates than TKI. Thus, immunotherapy may serve as a downstaging strategy to achieve secondary resectability. Case series and the first available data from Phase I/II trials showed pathological tumor response rates up to 50%, but also occurrence of tumor progression under therapy leading to patients no longer being candidates for curative surgery. Numerous clinical trials are currently investigating the role of different ICI regimes and combinations in a neoadjuvant setting. An overview of ongoing clinical trials is given in Table 3. Key questions being addressed, besides efficacy and safety, are length and insensitivity (agent selection and combinations) of preoperative treatment.

Discussion

As the majority of HCC is diagnosed at intermediate or advanced stages, there is a high clinical need for multimodal therapeutic approaches. While preoperative TKI administration failed to demonstrate benefit in HCC, the convincing efficacy of immunotherapy in the palliative setting raises new hopes to expand systemic therapy to earlier tumor stages and make downstaging and a prolongation of recurrence-free survival feasible. Nevertheless, neoadjuvant therapies are not yet recommended by current guidelines, as data from Phase III trials are lacking.

Preoperative immunotherapy is a promising approach for up-front resectable and borderline resectable HCC. Primary goal is to induce an immune response against micrometastasis and thus decrease the risk of disease recurrence. In this respect, it seems likely that substances with higher antitumoral activity (eg higher response rates) will achieve better survival than those with rather low activity. Recent data suggested higher response rates for drug combinations than for single substances.[2,28,29] In line with this hypothesis, the combination of nivolumab and opilimumab was associated with pathological response rates of up to 78% when used in a neoadjuvant setting. While head-to-head studies comparing different treatments are missing, it seems likely that future studies addressing the potential of immunotherapy in the neoadjuvant setting will focus on drug combinations harbouring the risk of increased immune-related toxicities.

A major drawback in the process of regulatory approval of preoperative agents in HCC is the lack of a validated endpoint. Whereas the nivolumab/cabozantinib and the camrelizumab/apatinib trials chose a pathological response of >90% tumor necrosis, the nivolumab/ipilimumab and the cemiplimab trials chose >70%. Conventional radiologic response assessments may be inapt to record changes within short time intervals, differentiate between tumor progress vs pseudoprogression through immune infiltration, and may underestimate the magnitude of tumor response. As in the nivolumab/ipilimumab trial, a pathological response was achieved in 78%, whereas the radiologic ORR was only 23%.

Another key question is the required duration of preoperative therapy. Longer treatment may enhance tumor response but harbors the risk of inducing immune-related adverse events. This was the case in the cemiplimab trial, where an ICI-

Table 3 Ongoing Clinical Trials for Preoperative Immunotherapy

NCT	ICI Regime	Key Inclusion Criteria	Interventions	Primary Endpoints	N	Phase
NCT03510871	• Nivolumab 3 mg/kg Q3W • Ipilimumab 1 mg/kg Q3W	Potentially eligible for resection, high risk for recurrence	Tumor assessment after 2 and 4 cycles, eligible patients undergo surgery	Tumor shrinkage according to RECIST	40	II
NCT05471674	Nivolumab 3 mg/kg Q2W	Borderline resectable tumor	Resection after 3 cycles of nivolumab	Pathological tumour response rate	20	II
NCT03299946	• Cabozantinib 40mg QD • Nivolumab 240mg Q2W	Locally advanced tumor	Combined treatment with nivolumab/cabozantinib for 8 weeks followed by resection	Safety	15	I
NCT03916627	Cemiplimab	Surgical candidate for tumor resection	Treatment prior to and post resection	Significant tumor necrosis	88	II
NCT04123379	• Nivolumab • BMS-813160 (CCR2/5-inhibitor) • BMS-986253 (anti-IL-8)	Surgical candidate for tumor resection	• Cohort A: Nivolumab Q4W 2 cycles prior to and 3 cycles after resection • Cohort B: additionally BMS-813160 BD during 28 days prior to resection • Cohort C: additionally BMS-986253 2400mg as single dose	Significant tumor necrosis	50	II
NCT03867370	• Lenvatinib • Toripalimab	Technically resectable tumor	• Cohort A: neoadjuvant toripalimab 480mg as a single dose; adjuvant toripalimab 240mg Q3W for 48 weeks • Cohort B: additionally lenvatinib 8–12mg QD neoadjuvant and adjuvant • Cohort C: additionally lenvatinib 8–12mg QD only neoadjuvant, but not adjuvant	Pathological response rate	40	Ib/II
NCT04850040	• Camrelizumab 200mg Q2W • Apatinib Mesylate 250mg QD • Oxaliplatin 85 mg/m2 Q2W	Locally advanced potentially resectable tumors, tumor ruptured, adjacent organ invasion	Neoadjuvant combination therapy followed by resection	Major pathological response	15	II
NCT04615143	• Lenvatinib 8–12mg QD • Tislelizumab 200mg Q3W	Tumor recurrence after initial curative treatment	• Cohort A: Tislelizumab 2 cycles neoadjuvant; up to 1 year adjuvant • Cohort B: additionally lenvatinib (neoadjuvant for 28 days; adjuvant up to 1 year)	Recurrence -free survival	80	II
NCT05194293	• Regorafenib QD • Durvalumab Q3W	Potentially resectable high risk tumor T1b / T2 / T3a	Regorafenib on days 1–21 and durvalumab on day 1. Cycle repeats every 28 days until surgery or for up to 2 years post-inclusion	Objective response rate at week 16	27	II

(*Continued*)

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Table 3 (Continued).

NCT	ICI Regime	Key Inclusion Criteria	Interventions	Primary Endpoints	N	Phase
NCT04888546	• TQB2450 (anti-PD-L1)1200mg Q3W • Anlotinib 10mg QD	Tumor with a high risk of recurrence or metastasis	Combination treatment prior to resection	• Pathological complete response rate • Overall response rate	20	Ib/II
NCT04224480	Pembrolizumab 200mg Q3W	Technically resectable tumor	Neoadjuvant cycle 4 weeks prior to resection, adjuvant cycles starting 4 weeks after resection up to 12 months	Recurrence rate within 2 years after resection	45	I
NCT05389527	• Lenvatinib 8–12mg QD • Pembrolizumab 200mg Q3W	Technically resectable tumor	Resection after 3 neoadjuvant cycles; adjuvant administration for up to 1 year	Major pathological response	43	II
NCT04930315	• Camrelizumab 200mg Q2W • Apatinib 250mg QD	Technically resectable tumor BCLC stage B / C or CNLC stage IIa-IIIb	Cohort A: neoadjuvant 4 cycles camrelizumab + 3 cycles apatinib; adjuvant 8 cycles camrelizumab Cohort B: adjuvant 12 cycles camrelizumab	1-year tumor recurrence-free rate	78	II
NCT05185739	• Lenvatinib 8–12mg QD • Pembrolizumab 200mg Q3W	Single tumour any size (if no cirrhosis), tumour ≤ 5cm (if cirrhotic)	6 weeks of neoadjuvant therapy, randomization 1:1:1 to one of 3 groups: - Pembrolizumab, - Lenvatinib - Pembrolizumab/Llenvatinib followed by12 months treatment with post-operative Pembrolizumab	Major pathological response rate	60	II
NCT04954339	• Atezolizumab 1200 mg Q3W • Bevacizumab 15 mg/kg Q3W	Potentially resectable tumor BCLC stage B/C	2 cycles neoadjuvant, 4 cycles adjuvant	Rate of pathological complete response	45	II
NCT04658147	• Nivolumab 480mg Q4W • Relatlimab 480 mg Q4W	Technically resectable tumor	Randomization to 12 months of neoadjuvant: - Nivolumab - Nivolumab/Rrelatlimab	Number of patients who complete neoadjuvant treatment and proceed to surgery within 4 years	20	I
NCT04721132	• Atezolizumab • Bevazizumab	Resectable tumor	3 cycles neoadjuvant, surgery during week 21	Rate of pathological complete response	30	II

related pneumonitis delayed one patient's resection significantly. Data from preclinical mouse models of metastatic malignancies reported that only a relatively short duration (in this case 4–5 days) between the first ICI administration to surgery was necessary for optimal outcome, while both shortening and delaying led to decreased efficacy (in this case 2 or 10 days, respectively).[46] But interestingly, even an additional 4 cycles to the basic 2 cycles of neoadjuvant ICI therapy did not improve tumor-free survival, underlining the need for more detailed data.

In the context of liver transplantation with the risk of allograft organ loss, not only the duration of preoperative ICI therapy but also the timing of withdrawal remain major challenges. Existing data showed a sustained mean occupancy of majority of PD-1 molecules on T cells even 2 months after ICI administration and regardless of application doses.[47] Moreover, a discrepancy in the pharmacological and biological half-lives of ICI agents has to be taken into consideration.[48] In view of the very limited data available, no definitive recommendation concerning the duration of ICI therapy prior to LT can be given.[32] Overall, a period of at least 3 months is considered advisable (3–5 half-life periods) to reduce the risk of rejection after LT. Nevertheless, in individual cases, a rejection after a 3-month ICI abstinence has also been described, indicating appropriate monitoring. More data is urgently needed on optimized withdrawal timing to prevent ICI-induced organ rejection. However, in real life, timing of withdrawal remains particularly challenging regarding the inability to anticipate and time organ offerings.

To improve the assessment of risk and benefits of ICI use, biomarkers may help to predict ICI response. Aside from the aforementioned possible role of PD-L1 expression in the transplant as a predictive biomarker for rejection, the study of Marron et al indicates a role for pre-existing immune infiltrates as being predictive for rapid ICI response. Accordingly, pretherapeutic liver biopsies could be implemented in the decision-making process.

A further possible factor for the prediction of ICI efficiency is the underlying etiology based on findings in NASH-HCC mice. Here, an accumulation of CD8+PD1+ T cells were detected, which surprisingly was associated with more severe hepatic tissue damage and HCC progression under PD-1 blockade, thus being different to non-NASH-HCC mice that showed tumor regression.[30,49,50] However, whether biomarkers and/or underlying etiology have an influence on the decision of using perioperative immunotherapy requires further investigation.

Given the high efficacy of ICI-based combination therapies, this systemic therapy for HCC will be increasingly used in the future in patients with earlier HCC stages, and thus also in patients before transplantation. While in the context of resection several trials are ongoing, there is a dire need for randomized, prospective trials for transplant candidates.

Conclusion

More and more evidence is accumulating indicating that immunotherapy is a powerful tool in the multimodal treatment approach for HCC. In early-stage tumors where resection is feasible, neoadjuvant immunotherapy may increase the chances of definitive cure by reducing the risk of micrometastases and tumor recurrence. For patients with borderline tumor burden at diagnosis, immunotherapy may provide a downstaging strategy converting these patients into candidates for resection. Recent data suggest higher response rates for drug combinations but with an increasing risk of immune-related toxicities. Taking into account the considerations outlined above, individualized concepts of preoperative ICI therapy are possible, also in the context of LT, until data from Phase III trials and corresponding recommendations are published in the guidelines. However, individualized concepts should only be performed in highly specialized centers and the risk of organ failure has to be critically discussed with the patient. In addition, the need for further biomarkers to identify patients with an increased risk of rejection is becoming clear. For a better risk assessment in future, data from randomized trials are required to identify the optimal combination of agents and duration of therapy, as well as to determine subsets of patients that benefit from neoadjuvant strategies.

Abbreviations

AE, adverse event; CPR, complete pathological response; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; FDA, US Food and Drug Administration; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor(s); irAE, immune-related adverse event; IQR, interquartile range; LT, liver transplantation; mRECIST, modified response evaluation criteria in solid tumors; ORR, objective response rate; OS, overall survival; PD-1, programmed death receptor 1; PD-L1, programmed death receptor 1 ligand; PFS, progression-free survival; RECIST, response evaluation criteria in solid

tumors; RFS, recurrence-free survival; Th 2 cell, T-helper cell 2; TKI, tyrosine-kinase inhibitors; VEGF, vascular endothelial growth factor.

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