Review

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Immunotherapy for hepatocellular carcinoma: The next evolution in expanding access to liver transplantation

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Summary

Immunotherapy has revolutionised the treatment of advanced hepatocellular carcinoma (HCC). In addition, several phase III trials of immunotherapy in combination with surgical or locoregional therapies for early-to intermediate-stage HCC have recently reported positive results, and other phase III trials in the same patient population are currently in progress. As the application of immunotherapy is shifting to include patients with earlier stages of HCC, one looming question now emerges: What is the role of immunotherapy in the pre-liver transplant population? Liver transplantation is a potentially curative therapy for HCC and confers the additional advantage of restoring a normal, healthy liver. In pre-transplant patients, immunotherapy may improve downstaging success and tumour control at the cost of some immunologic risks. These include immune-related toxicities, which are particularly relevant in a uniquely vulnerable population with chronic liver disease, and the possibility of acute rejection after transplantation. Ultimately, the goal of immunotherapy in this population will be to effectively expand access to liver transplantation while preserving pre- and post-transplant outcomes. In this review, we discuss the mechanisms supporting combination immunotherapy, summarise key recent clinical data from major immunotherapy trials, and explore how immunotherapy can be applied in the neoadjuvant setting prior to liver transplantation in selected high-risk patients.

Introduction

Immunotherapy has revolutionised cancer treatment, including the treatment of hepatocellular carcinoma (HCC), the third leading cause of cancer death in the world.[1,2] Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that target cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed cell death protein 1 (PD-1), or programmed cell death ligand 1 (PD-L1). These proteins are involved in downregulating the host response against tumours, and ICI therapy therefore prevents tumour cells from evading T cell-mediated immune defenses.[3] Two different ICI-containing regimens are currently established as first-line therapy in advanced HCC and were shown to improve overall survival when compared to sorafenib, the previous first-line systemic therapy for HCC.

Given their efficacy in advanced HCC, there is substantial interest in expanding immunotherapy to earlier stages of HCC. In this review, we discuss the rationale and emerging evidence supporting immunotherapy in early-to intermediate-stage HCC, including potential immunological risks and toxicities related to ICI therapy in this unique cancer population for whom liver transplantation (LT) may provide a definitive cure for both their underlying liver disease and their HCC.

Tumour response drives expansion of LT selection criteria for HCC

HCC is unique in that it is one of the only indications for solid organ transplantation to treat cancer.[4] LT is the optimal strategy for management of HCC in selected individuals because it simultaneously offers a curative cancer therapy and also restores a healthy, "normal" liver.[4,5] Up to 90% of patients with HCC have cirrhosis,[6–8] which is not only a life-limiting disease but also represents a tumourigenic environment for HCC recurrence or *de novo* development even after potentially curative resection or ablation.[9,10] Most patients treated with resection or ablation develop HCC recurrence, with rates approaching 70% by 5 years.[11–14] In contrast, recurrence rates following LT are substantially lower, ranging from 10-15% in patients within Milan criteria.[15–17] The Milan criteria, either one tumour <5 cm or up to three tumours each <3 cm (plus no macrovascular invasion or extrahepatic metastasis), have been utilised for over 25 years as part of LT patient selection,[4,5,18] though some patients beyond Milan criteria due to tumour burden achieve similar post-LT outcomes to patients within them. Several proposed expanded criteria exist, including the University of California, San Francisco (UCSF) criteria,[19] the up-to-seven criteria,[20] total tumour volume,[21] the alpha-

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Keypoints

- The success of combination immunotherapy regimens in advanced HCC has led to substantial interest in incorporating immunotherapy into the treatment of earlier stages of HCC.
- New clinical data from phase III clinical trials support the efficacy of immunotherapy in combination with curative treatments in early-stage HCC and with locoregional treatments in intermediate-stage HCC.
- The efficacy of immunotherapy combinations in controlling HCC at various stages of development may justify its use in protocols of tumour downstaging to curative liver transplantation.
- Experience in liver transplantation after immune checkpoint inhibitors is limited and more research is required; in this setting, fine tuning of immunotherapy-induced pre-transplant lymphocyte activation and post-liver transplantation immunosuppression is needed to maximise post-transplant antitumour surveillance and graft tolerance.
- Future directions include investigation of clinical predictors and biomarkers associated with high-risk HCC features (downstaging failure, waitlist dropout) and with treatment toxicities.

fetoprotein (AFP)-French criteria,[22] and the Toronto criteria.[23] The independent development of various expanded criteria by different centres strongly implies that increasing access to LT in patients beyond Milan criteria is feasible while preserving excellent outcomes post-LT.

In Europe and the US, patients who are initially beyond Milan or other criteria can be LT candidates if they are successfully downstaged. Downstaging is defined as utilising treatment to bring tumour burden down to within accepted limits for LT. In addition to the logical expected benefit of reducing tumour burden, successful downstaging is also associated with factors like well-differentiated HCC histology and absence of microvascular invasion that suggest more favourable tumour biology.[24] In the US, the United Network for Organ Sharing (UNOS) has adopted the UCSF downstaging protocol cut-offs (one lesion up to 8 cm, 2-3 lesions <5 cm, or 4-5 lesions <3 cm with total tumour diameter <8 cm)[24,25] for its official downstaging criteria, and patients within these limits who are successfully downstaged to within Milan are eligible to receive model for end-stage liver disease (MELD) exception points. In Europe there are no pre-determined downstaging criteria, and patients without extrahepatic spread or macrovascular invasion who achieve a sustained reduction in tumour burden can be listed for LT. The only prospective European experience enrolled patients with a 5-year estimated post-LT survival of 50% based on the Metroticket 2.0 calculator, achieving similar outcomes to UNOS-downstaging criteria, suggesting that expanding LT to patients with profound post-downstaging tumour response is feasible without affecting post-LT survival.[26,27]

Currently, downstaging relies upon locoregional therapies (LRTs) such as transarterial chemoembolisation (TACE), transarterial radioembolisation (TARE), and ablative therapies. With downstaging being a broadly accepted clinical practice, there are three major potential implications for immunotherapy: ***improving*** downstaging success to expand access to LT in patients initially beyond LT selection criteria due to tumour burden, ***maintaining*** disease control in patients listed for LT to minimise waitlist dropout, and ***extending*** downstaging potentials by controlling possible occult extrahepatic micrometastases through systemic therapy.[28,29] In the following sections, we will discuss current downstaging strategies, evaluate the unique push-and-pull of pre-LT immunotherapy and post-LT immunosuppression, and describe the current and emerging evidence for immunotherapy across all stages of HCC.

Downstaging HCC

The benefits of LT in patients with HCC and a disease burden beyond conventional criteria are not uniform as we are currently unable to predict significant adverse biologic factors in the pre-LT setting, including microvascular invasion, microsatellites, tumour grading, cellular mutations, and the independent carcinogenic potential of the liver parenchyma and tumour microenvironment,[30,31] which explains the renewed interest in both liquid and tumour biopsies in patients with HCC.[32] In the absence of validated molecular biomarkers enabling more sophisticated predictions of HCC recurrence risk, the best surrogate of tumour biology in clinical decision-making is the tumour response to appropriate treatments, as downstaging is a specific form of successful neoadjuvant anti-cancer therapy applied in the field of transplant oncology. Evidence derived from trials and large cohort studies confirm the benefit of LT after successful and sustained downstaging compared to non-transplant care in terms of both overall and tumour-free survival.[26,33] These data support downstaging as a minimal requirement for LT in patients with tumour burden beyond conventional criteria, as well as repeated locoregional therapy (LRT) until the best response is achieved prior to LT. Society guidelines now include response to neoadjuvant therapies as a cornerstone for transplant allocation in patients beyond conventional criteria.[5,34,35]

Limits to downstaging have also been advocated since "all-comers" policies applied to any presentation of non-metastatic HCC are burdened by a higher risk of waitlist dropout and microvascular invasion in explanted livers compared to more restrictive upper limits of downstaging (*i.e.* UNOS-downstaging criteria). AFP plays a crucial role in risk stratification; AFP levels >100 ng/ml and <20 ng/ml following downstaging treatments were associated with >50% probability of waitlist dropout for tumour progression and <10% probability of post-LT recurrence, respectively, and absolute AFP response following LRT was shown to be the best surrogate of tumour biology in a multicentre US cohort.[36,37] In addition, AFP dynamics following treatment combined with morphometric tumour parameters can identify patients at risk of downstaging "failure".[27,30,38] In

the US, patients with AFP ≥1,000 ng/ml are not eligible for standard MELD exception points unless they receive treatment to achieve an AFP <500 ng/ml. Other tumour markers include AFP-L3 and DCP (des-gamma-carboxy prothrombin), which have been shown to predict high-risk explant features following LT[39] and outperform AFP in predicting waitlist dropout[40] and HCC recurrence after LT.[41]

All the progress in HCC downstaging was made prior to the inception of the current immunotherapy era. Downstaging strategies, therefore, will expand access to LT in HCC after various forms of immunotherapy alone or in combination with LRT have demonstrated efficacy in ongoing prospective studies. In this context, two additional considerations accompany the already-known advantages of downstaging. The biological mechanisms underlying the efficacy of downstaging imply that a mere reduction of tumour burden based on cross-sectional imaging is not completely sufficient. Instead, optimal downstaging should increase the probability of treating occult micrometastases, enlarge tumour-free margins, and achieve a response that reduces the risk of recurrence,[28,29] all features that should be closer at hand by employing systemic immune-driven strategies. Similarly, the concept of viable HCC tissue after downstaging with immunotherapies should be revised to consider markers of patient immunocompetence and the tumour microenvironment, as has been attempted in tumour burden scores used for outcome prediction after resection.[13,42]

The challenge of pre-transplant immunotherapy and post-transplant immunosuppression

The complexity of human cancer immune biology, not always well reflected in preclinical models, leaves the mechanisms of action of ICIs partially understood.[43] Nevertheless, dominant drivers of cancer immunity triggered by different ICIs (alone or in combination) have been established in murine models and via the *ex vivo* assessment of responding cancer lesions.[44] This justifies the difficulties in moving these treatments to the pre-LT setting where antitumour surveillance and graft tolerance are opposing forces that must be considered in patient outcomes.

In addition, ICIs have different mechanisms of action that may have important clinical implications in the post-LT setting. Some of these mechanisms are summarised in Fig. 1. Most ICIs target the PD-1/PD-L1 axis, a key regulatory system in the maintenance of immune tolerance, which is upregulated in the microenvironment of immunogenic tumours.[44] As the binding of PD-1 (expressed on activated T cells) to PD-L1 triggers a negative feedback loop which attenuates T-cell immunity at the tumour site, PD-1 blockade is believed to promote antitumour responses through activation of tumour-infiltrating effector T cells (Fig. 1A).[44–46] While anti-PD-L1 and anti-PD-1 therapies achieve similar outcomes in clinical practice,[47] preclinical studies suggest a different potential of the two strategies in harnessing antitumour immunity, with PD-L1 blockade possibly

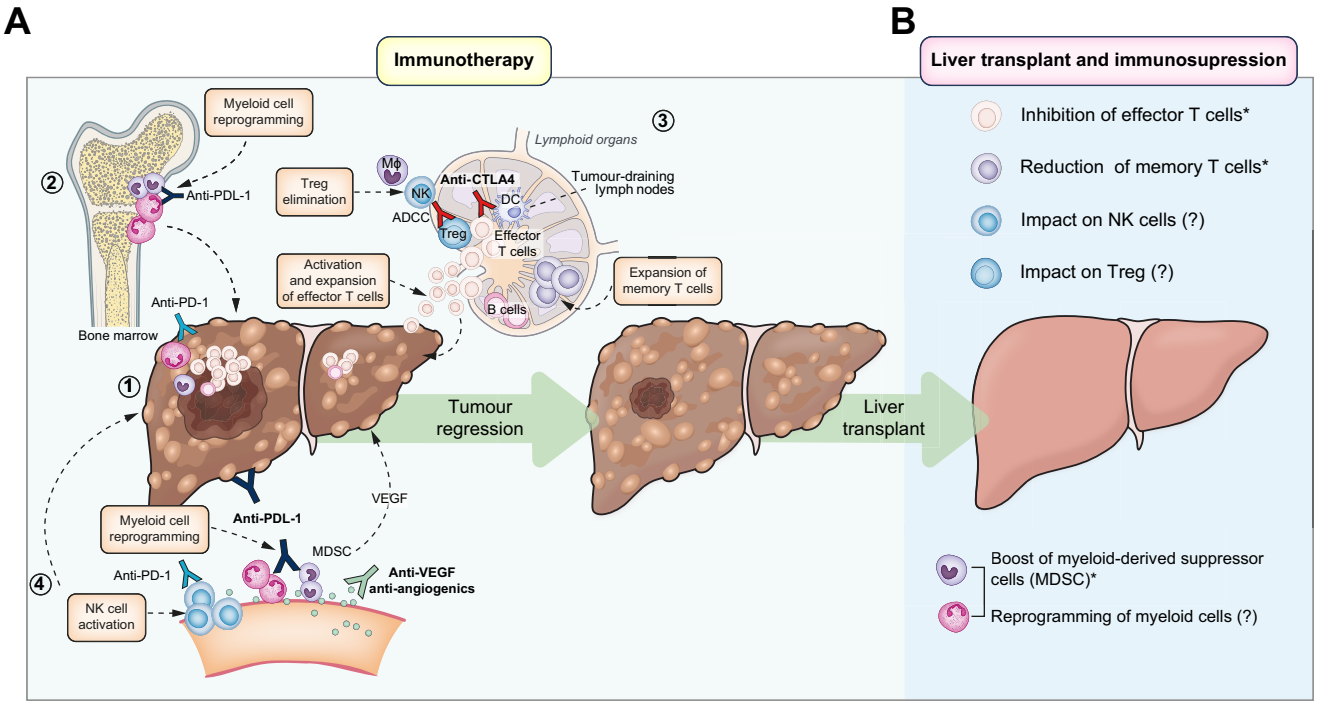

Fig. 1. Mechanisms involved in liver transplantation for hepatocellular carcinoma after tumour response to immunotherapy. (A) Potential antitumour immune effects mediated by different immune checkpoint inhibitors in: 1) liver microenvironment, 2) bone marrow, 3) lymph nodes, 4) blood vessels. (B) Immune checkpoint inhibitor-induced immune effects after liver transplantation; question mark (?) indicates unknown effects on immune-cell subgroups. ADCC, antibody-dependent cellular cytotoxicity; CTLA-4, cytotoxic T-lymphocyte antigen-4; DC, dendritic cell; MDSCs, myeloid-derived suppressor cells; NK, natural killer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; Treg, regulatory T cell; VEGF, vascular endothelial growth factor.

being superior to PD-1 blockade in reverting PD-1 signaling[48] and in activating PD-L1+ myeloid cells in the bone marrow (Fig. 1A).[49]

An additional immune checkpoint target for treatment of HCC is CTLA-4, a receptor able to regulate T-cell proliferation early in the immune response primarily in lymph nodes (distinct from PD-(L)1 which suppresses T-cell effector function primarily at tumour sites). CTLA-4 blockade is thought to mediate antitumour activity (*i.e.* tumour rejection) by enabling efficient T-cell priming by antigen-presenting cells in lymph nodes and by inducing rapid regulatory T cell (Treg) depletion through antibody-dependent cellular cytotoxicity.[50,51] This specific blockade differs from PD-1/PD-L1 inhibition in the amplitude of the immunological effects, featuring a broader expansion of effector T cells regardless of their specificity. As Tregs may be actively engaged in maintenance of graft tolerance,[52] this process could also be involved in rejection pathways (Fig. 1A). Both anti-PD-(L)1 and anti-CTLA-4 therapy can cause immune-related toxicities, and in theory these could be minimised by adequate washout strategies in patients with HCC awaiting LT.

While ICIs exert direct immunomodulating effects, other anti-cancer therapies are also used in combination with ICI treatment. Angiogenesis is a well-established mechanism of both HCC development and immune evasion,[53,54] and vascular endothelial growth factor (VEGF) is in fact a target of sorafenib and other tyrosine kinase inhibitors used in HCC (*e.g.*, lenvatinib, regorafenib, cabozantinib). Furthermore, the addition of an anti-angiogenic agent in combination with ICI therapy is hypothesised to have synergistic effects by modulating the tumour immune microenvironment; VEGF inhibition increases tumour infiltration of cytotoxic T and natural killer cells, blocks stimulation of Tregs, and inhibits the immunosuppressive phenotype of myeloid cells (Fig. 1A).[55–58] Predicting the final impact of such different immunological scenarios on successful organ engraftment represents one of the major challenges of immunotherapy in the pre-LT population.

The effect of different post-LT immunosuppressive regimens on systemic antitumour immunity and on long-term immune memory adds an additional layer of complexity. Considering that a large part of the clinical benefit of ICIs stems from their ability to trigger peripheral T-cell memory,[59,60] one could speculate that liver tolerance cannot come without a cost to protective antitumour immunosurveillance (Fig. 1B). Current post-LT immunosuppressive regimens (corticosteroids, calcineurin inhibitors, mycophenolate) predominantly target the adaptive immune response and prevent rejection by inhibiting the function of allo-reactive T and B cells either directly or through the activation of collateral immunosuppression circuits involving myeloid-derived suppressor cells.[61,62] While the Silver study was a negative trial in terms of demonstrating a protective effect of mTOR inhibitors on the overall risk of recurrence, a subgroup analysis suggested that sirolimus use in post-LT immunosuppression may reduce recurrence in patients with low tumour burden (within Milan criteria) at transplant.[63] While immunosuppressive therapy is expected to control adaptive immune responses and possibly abrogate the long-term effects exerted by pre-LT ICIs, other mechanisms may play a role independently from current immunosuppressive drugs, including activation of the innate immune system by ischaemia-reperfusion injury, which is a specific feature inherent to the procedure of solid organ transplantation (Fig. 2).[64] Decoupling anti-allogenic from antitumour immune activity in LT will be key to the development of selective drugs or regimens which allow for the survival and function of tumour-specific T-cell effectors while maintaining organ tolerance.

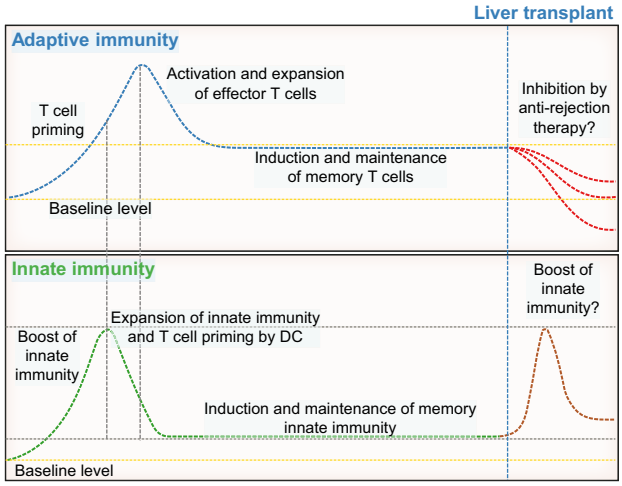

Fig. 2. Envisioned kinetics of adaptive and innate immunity in the liver transplant setting. DC, dendritic cell.

Advances in immunotherapy for advanced HCC – combination therapy

ICI-based regimens have been adopted as first-line therapy in patients with advanced HCC, and their effectiveness raises the possibility that they may also play a role in earlier-stage disease. Earlier trials mostly assessed the efficacy of ICI monotherapy, but the current standard of care is combination therapy. Two landmark trials, IMbrave150 and HIMALAYA, demonstrated significant improvement in overall and progression-free survival in ICI-treated patients with unresectable HCC when compared to those who received sorafenib, a multikinase inhibitor which was for almost a decade the only approved systemic therapy for HCC.[65–67] IMbrave150 studied the combination of atezolizumab (anti-PD-L1) with the anti-angiogenic agent bevacizumab. Combined therapy with atezolizumab and bevacizumab was superior to sorafenib in the IMbrave150 trial, with median overall survival of 19.2 *vs*. 13.4 months (hazard ratio [HR] 0.58), median progression-free survival of 6.8 *vs*. 4.3 months (HR 0.59), and objective response rates of 30% *vs*. 11%.[68] The HIMALAYA trial investigated a different form of combination therapy by combining two different ICIs: durvalumab (anti-PD-L1) and tremelimumab (anti-CTLA-4). Based on data from a phase II trial, durvalumab and tremelimumab were combined in what was termed the STRIDE regimen, which involves a single high priming dose of tremelimumab in conjunction with monthly durvalumab infusions. STRIDE led to superior overall survival when compared against sorafenib (median 16.4 *vs.* 13.8 months, HR 0.78) and was associated with a significantly higher objective response rate (20.1% *vs.* 5.1%).[66]

The CARES-310 study is the third phase III trial of an ICI-containing regimen to report positive results. Patients in the CARES-310 investigational arm received treatment with camrelizumab (anti-PD-1) in combination with rivoceranib, an oral tyrosine kinase inhibitor that is a highly selective inhibitor of

VEGFR-2. Camrelizumab and rivoceranib therapy improved overall survival (median 22.1 *vs.* 15.2 months, HR 0.62) and objective response rate (25% *vs.* 6%) compared to sorafenib therapy.[69] Camrelizumab and rivoceranib are currently under review for regulatory approval, and if approved would represent a combination therapy option with an oral anti-angiogenic component. In the meantime, current guidelines support either atezolizumab plus bevacizumab or STRIDE as the preferred first-line regimens in untreated advanced HCC. Notably, there are no head-to-head studies comparing ICI regimens, though a meta-analysis of major HCC immunotherapy trials found that the various first-line combination regimens had similar overlapping HRs for overall survival when compared to sorafenib.[70] It is also unclear whether aetiology of liver disease impacts the efficacy of immunotherapy; while early data from preclinical and clinical studies suggested that ICI treatment is less effective in patients with metabolic dysfunction-associated steatotic liver disease, data from the major ICI trials have not clearly demonstrated any difference in treatment response based on type of liver disease.

Rationale for combining immunotherapy with LRT

TACE, TARE, and ablation are types of LRT that are cornerstones of therapy for early/intermediate-stage HCC, including for downstaging or reducing the risk of waitlist dropout in pre-LT patients. All these treatments cause the release of tumour antigens and proinflammatory cytokines, leading to a "priming" effect on adaptive immunity with the activation of T cells by antigen-presenting cells promoting an immunogenic tumour microenvironment.[71] As a result, patients who exhibit T-cell responses following TACE[72–74] or TARE[75,76] have improved clinical outcomes. ICI treatment therefore may have a synergistic effect in the context of the immunogenic microenvironment promoted by TACE or TARE, and this along with robust existing evidence in advanced HCC has led to strong interest in investigating the efficacy of combining immunotherapy with LRT in intermediate-stage HCC. At the time of writing, multiple international phase III trials (EMERALD-3, LEAP-012, and REPLACE) investigating various ICI-containing regimens in combination with TACE are enrolling participants and will be assessing progression-free survival compared to TACE alone as their primary outcome. A phase II trial (ROWAN) comparing TARE plus STRIDE *vs.* TARE alone is also underway, and a phase Ib trial of TACE plus pembrolizumab (anti-PD-1) showed that combining LRT with immunotherapy is reasonably well-tolerated.[77]

EMERALD-1 is a phase III trial that recently reported positive results and is the first combined LRT-ICI trial to meet a primary endpoint of improved progression-free survival.[78] The study randomised 616 patients to three treatment arms: (1) combined durvalumab plus bevacizumab plus TACE, (2) durvalumab plus TACE, and (3) TACE alone. Patients in the TACE/durvalumab/bevacizumab arm had significantly improved progression-free survival when compared to those receiving TACE alone (median 15.0 *vs.* 8.2 months, HR 0.77), an effect that was generally consistent across key subgroups including those stratified by degree of tumour burden and liver function. Interestingly, there was no difference in progression-free survival when comparing the durvalumab plus TACE to the TACE alone arms (median 10.0 *vs.* 8.2 months, HR 0.94). One can speculate on an additional synergistic treatment effect in the bevacizumab-containing arm; in addition to the theorised synergy of anti-angiogenic therapy with ICI treatment described earlier, VEGF levels are also increased after TACE,[71] providing a plausible mechanism by which the addition of bevacizumab could promote improved outcomes. While overall survival data is not yet available and thus the data should be interpreted cautiously, improved progression-free survival is notably a primary goal of LRT in the pre-LT population, as the predominant driver of waitlist dropout in patients with HCC listed for LT is tumour progression beyond Milan or other criteria. There is also real-world data suggesting improved progression-free survival with combined TACE and nivolumab (anti-PD-1) compared to nivolumab monotherapy.[79] With regards to the objective of expanding LT access in patients with HCC, reducing waitlist dropout in selected high-risk patients by providing more durable disease control means that the adoption of immunotherapy in patients who previously would have received LRT alone is on the horizon.

Adjuvant immunotherapy after resection or ablation

Surgical resection is the treatment of choice in patients with early-stage HCC who have well-compensated cirrhosis without portal hypertension. Patients with solitary lesions who are not eligible for resection or who have very early-stage HCC (*e.g.* a single tumour less than 2 cm) can be considered for ablation. While resection and ablation are potentially curative therapies, up to 70% of patients will develop recurrence within 5 years[11–14] meaning that a substantial proportion of those treated with resection or ablation will develop indications for LT. Furthermore, ablation is often utilised as bridging therapy in patients with non-HCC indications for LT to achieve tumour control prior to transplantation.

Ablation is associated with tumour antigen and inflammatory cytokine release, just as described earlier for TACE and TARE, meaning that the same rationale for a synergism with immunotherapy via promotion of an immunogenic tumour microenvironment holds true.[71] HCC recurrence following resection is typically attributed to higher risk tumour burden (*e.g.*, microvascular invasion, satellite nodules/multiple tumours, tumour size) which increase the risk of occult micrometastases.[10,80,81] These risk factors may be exacerbated by the immunosuppressive effect of cancer surgery related to expansion of Tregs caused by trauma, blood loss, sepsis, hypothermia, and other surgical factors.[82] Although these drawbacks of resection are alleviated by minimally invasive laparoscopic-robotic resection techniques, adjuvant immunotherapy is an attractive option in post-resection patients considered to be high risk, as it can treat residual disease and reverse the immunosuppressive post-surgical environment.

Multiple phase III trials of adjuvant immunotherapy following resection or ablation are ongoing, including EMERALD-2 (durvalumab and bevacizumab), KEYNOTE-937 (pembrolizumab), and CheckMate 9DX (nivolumab; anti-PD-L1). The IMbrave050

study was the first phase III clinical trial of adjuvant immunotherapy following resection or ablation of HCC at high-risk of recurrence to report positive results. In this study, adjuvant therapy with 12 months of atezolizumab plus bevacizumab was found to be superior to surveillance alone with regards to the primary endpoint of progression-free survival (median not reached in either group, HR 0.72; 12-month recurrence event rate 20% *vs.* 34%).[81] However, the relatively short follow-up time (median of 17 months), which precluded overall survival analyses, also raises the possibility that the progression-free survival benefit seen in the study may not be durable, as the Kaplan-Meier curves appeared to be merging at their tails. As the primary goal of adjuvant immunotherapy is to prevent recurrence rather than simply delay it, data from additional follow-up will be crucial. A phase II trial of adjuvant sintilimab (anti-PD-1) in patients with HCC found to have microvascular invasion after resection reported similar results with improved progression-free survival,[83] although with similar caveats (short follow-up time, no overall survival analyses). While current oncology society guidelines have not yet made any recommendations regarding the role of adjuvant immunotherapy based on these trials, these data contribute to the growing body of evidence supporting the role of immunotherapy after surgical resection in selected patients with HCC. Of note, extrapolating post-resection/ablation data to the transplant setting may be inappropriate given the unpredictable effects of ICIs on tumour surveillance while on post-LT immunosuppressive regimens as well as the risk of rejection and other adverse events described in the next section.

Potential risks of immunotherapy in the pre-transplant population

Because ICIs work by manipulating the "brakes" of the immune system, immune-related adverse events (irAEs), which mimic autoimmune disorders and can affect almost any organ system, are common. High-grade irAEs are immune toxicities requiring systemic corticosteroid or immunomodulatory therapy and generally lead to discontinuation of ICI therapy. HCC patients develop high-grade irAEs at similar rates to patients with other cancers (10-20%, depending on the exact ICI regimen).[65,68,84–87] Notably, patients with HCC are a particularly vulnerable population with regards to irAEs due to the presence of pre-existing liver disease. Given that up to 90% of patients with HCC have underlying cirrhosis, concerns exist regarding the possibility of irAEs leading to hepatic decompensation. Hepatic decompensation may be triggered by severe inflammation of other organs or through direct liver inflammation (*e.g.*, ICI hepatitis) which can cause worsening liver function and portal hypertension. ICI hepatitis is one of the most common severe irAEs; 2-10% will experience high-grade ICI hepatitis depending on the regimen,[88–90] and ICI hepatitis is the irAE most likely to be high-grade if it occurs.[91,92] While it is difficult to distinguish the underlying aetiology of elevated liver tests in a patient population with cirrhosis and liver cancer, a real-world study of 375 patients treated with atezolizumab and bevacizumab reported an incidence of ICI hepatitis of 11.4%,[93] and 6-9% of patients in phase III clinical trials received corticosteroid therapy for ICI hepatitis.[65,66,69] Clinical trial data also support the possibility of hepatic decompensation, with ascites (6-7%), portal hypertension-related bleeding (1-4%), and encephalopathy (1-3%) being reported. While these trials did not report on suspected causation (*i.e.*, if an irAE was temporally related to a decompensating event), and at least some of the reported decompensating events were likely related to natural progression of liver disease, the fact that all three trials only included patients with excellent baseline liver function (Child-Pugh class A) suggests that irAE development precipitates hepatic decompensation in a proportion of patients and that decompensation could occur more frequently in the real-world setting when using immunotherapy in patients with more advanced liver disease. Real-world evidence,[94] a small clinical trial,[95] and a meta-analysis[96] suggested that treating patients with Child-Pugh class B disease is feasible with similar rates of irAE development as in those with Child-Pugh A cirrhosis, though the absence of decompensation data and the finding that patients with Child-Pugh B cirrhosis have worse overall survival mean that further investigation is needed.

Combination therapy, which is more effective at treating HCC than ICI monotherapy, adds another layer of complexity to toxicity concerns. It is well established in other cancers that

Table 1. Uniquely relevant risks to the pre-LT population that are associated with immunotherapy regimens.

Toxicity or adverse outcome	Anti-PD-(L)1*,#	Combined anti-PD-(L)1/CTLA-4^	Bevacizumab
Any immune-mediated toxicity requiring immunomodulatory therapy	10–16%	19–20%	–
Hepatitis requiring steroid treatment	6–7%	8–9%	–
Colitis requiring steroid treatment	1–2%	5%	–
Ascites	6–7%	6%	–
Encephalopathy	1–2%	1–3%	–
Portal hypertension-related bleeding	1%	1%	2–4%
Proteinuria	–	–	20–44%
Nephritis and/or acute kidney injury	–	–	1–5%
Gastrointestinal perforation	–	–	1%
Wound healing complications	–	–	1%
Post-LT rejection	17–33%	–	–
Post-LT graft loss successfully treated with re-transplantation	3–5%	–	–
Post-LT death from graft loss or hepatic necrosis	5%	–	–

CTLA-4, cytotoxic T-lymphocyte antigen-4; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; LT, liver transplantation.
*Includes atezolizumab (in combination with bevacizumab, IMbrave150) and durvalumab (monotherapy arm from HIMALAYA), camrelizumab (in combination with rivoceranib, CARES-310).
#For post-LT outcomes, data aggregated from currently available case reports and case series. Nivolumab was the most common ICI reported, but other anti-PD-(L)1 monotherapy included pembrolizumab, durvalumab, atezolizumab, sintilimab, and camrelizumab.
^Includes durvalumab/tremelimumab (combination arm from HIMALAYA).

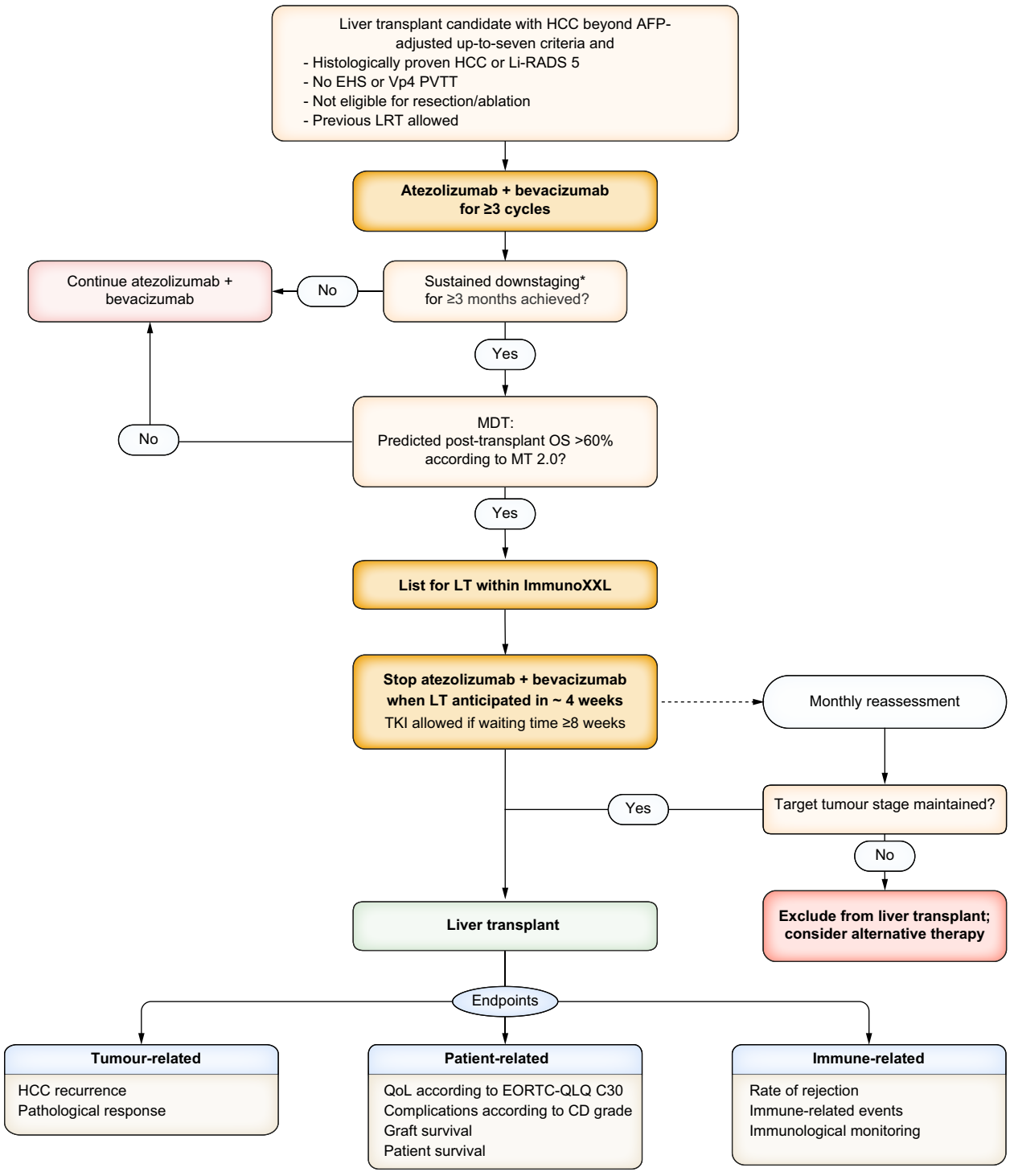

Fig. 3. ImmunoXXL study workflow. * Defined as: mRECIST partial or complete response; AFP response (<100 ng/ml if baseline >100, decrease parallel to mRECIST if baseline <100). AFP, alpha-fetoprotein; EHS, extrahepatic spread; HCC, hepatocellular carcinoma; LRT, locoregional therapy; LT, liver transplantation; MDT, multidisciplinary tumour board; MT 2.0, Metroticket 2.0; OS, overall survival; PVTT, portal vein tumour thrombus; QoL, quality of life; TKI, tyrosine kinase inhibitor.

combination anti-CTLA-4/PD-(L)1 therapy is associated with a higher risk of irAE development than ICI monotherapy due to the more potent immune activation that results from dual checkpoint blockade. This effect appears to hold true in HCC as well; 12% of patients in IMbrave150 (whose regimen contains a single ICI, atezolizumab) received corticosteroid therapy for presumed irAEs compared to 20% of patients in HIMALAYA (combination anti-CTLA-4 and anti-PD-L1). On the other hand, non-ICI agents like bevacizumab are also linked to toxicities. Importantly, bevacizumab increases the risk of gastrointestinal bleeding, and patients with HCC being considered for bevacizumab-containing regimens need to undergo variceal screening and appropriate treatment for varices prior to starting the bevacizumab component. Bevacizumab can also cause

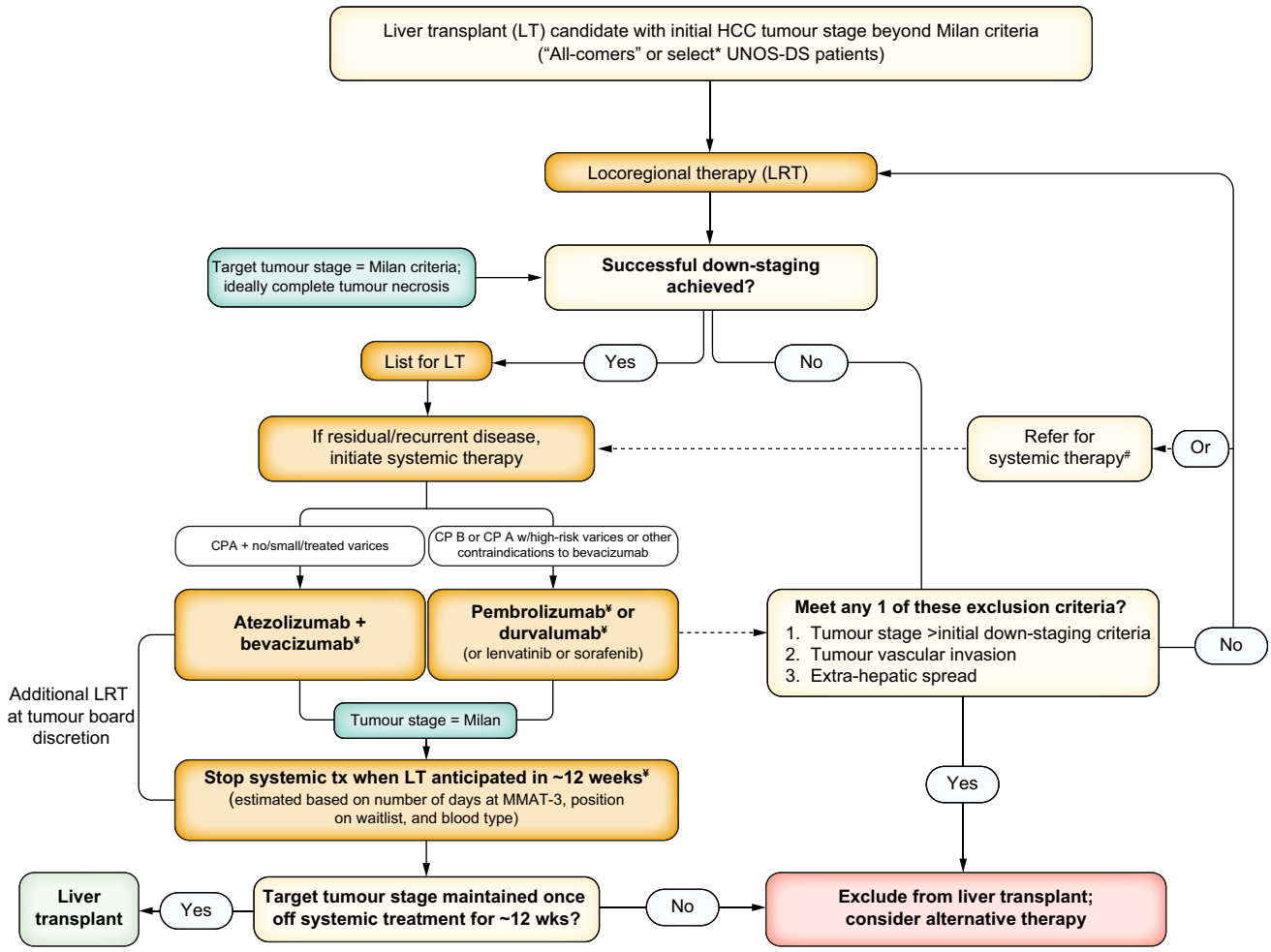

Fig. 4. MERITS-LT study workflow. CP, Child-Pugh; LRT, locoregional therapy; LT, liver transplantation; UNOS-DS, United Network for Organ Sharing-downstaging. *e.g. UNOS-DS pts with elevated AFP and/or multi-focal HCC with high risk of dropout. #Expected to be an uncommon pathway to tumor down-staging. ¥Donor age adjusted to 98-99 to ensure patients do not receive LT offer while on immunotherapy or for 12 weeks after.

proteinuria and renal toxicity, and acute kidney injury is uniquely dangerous in a cirrhotic patient population. Finally, bevacizumab impairs wound healing, and a washout period of at least 60 days is recommended in patients potentially eligible for LT based on the surgical literature.[97] Table 1 summarises toxicity data with a focus on the uniquely relevant risks in the pre-LT population.

Unlike the advanced HCC population, where toxicities may be more acceptable given the substantial superiority of immunotherapy when compared to other systemic therapies, the more incremental advantages offered by adjuvant immunotherapy or combined immunotherapy/LRT over existing treatment paradigms in the pre-LT population may warrant a more selective approach. Indeed, IMbrave050, the adjuvant sintilimab trial, and the other phase II-III adjuvant trials still in process all limited enrolment to patients at high risk of recurrence (*i.e.*, those with the most to gain) and to patients with Child-Pugh class A liver disease (*i.e.*, those with the greatest hepatic reserve who are most likely to tolerate toxicities). Combined immunotherapy plus TACE trials are slightly more lenient, allowing up to Child-Pugh class B7 liver disease which reflects the generally sicker patient population eligible for TACE while still ensuring reasonable liver function. However, the absence of biomarkers of treatment response or of irAE development in patients with HCC treated with immunotherapy remains an unmet clinical need. Future studies addressing this knowledge gap may enable more sophisticated application of immunotherapy in the pre-LT population beyond Milan criteria by relying upon measures of liver function and/or predictors of HCC recurrence.

Neoadjuvant immunotherapy prior to LT

While LT is contraindicated in patients with advanced HCC, some patients can develop robust, sustained complete response after receiving immunotherapy, and case reports have been published on successful LT in patients who experience exceptionally durable responses to ICI treatment.[98,99] The increasing incidence of HCC combined with broad adoption of immunotherapy as standard of care in advanced HCC mean that more and more ICI-treated patients may unexpectedly become LT candidates.

The concept of immunotherapy being effective as part of downstaging is strongly supported by the data from EMERALD-1. While EMERALD-1 was not intentionally designed to answer

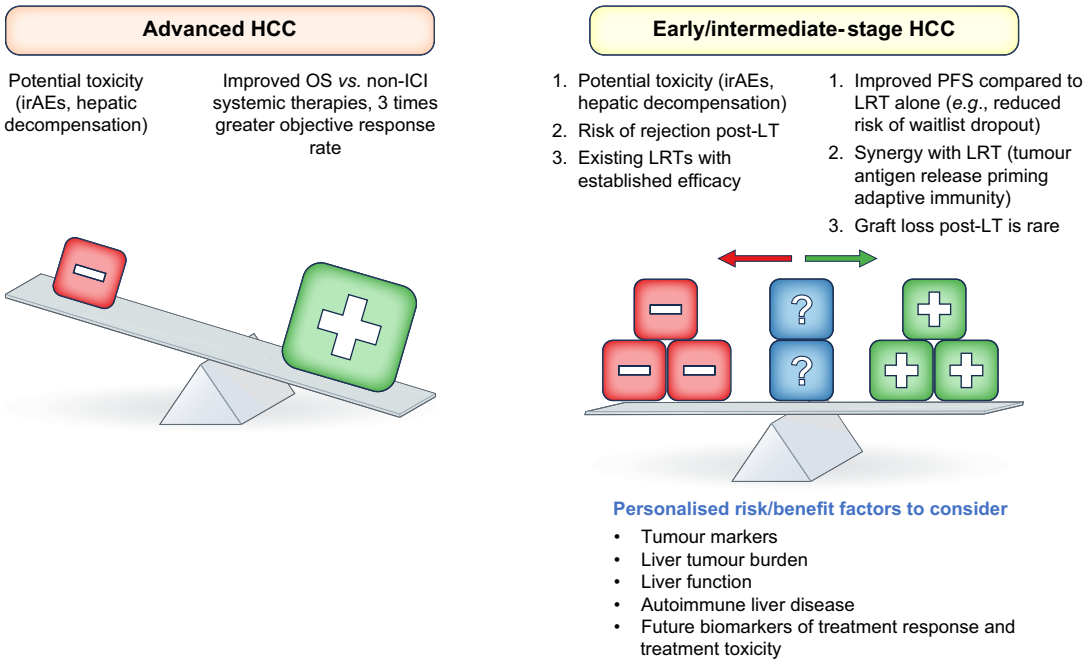

Fig. 5. Risks *vs.* benefits of immunotherapy in advanced *vs.* early/intermediate-stage HCC. HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events; LRT, locoregional therapy; LT, liver transplantation; OS, overall survival; PFS, progression-free survival.

questions about LT, the patient population (mostly intermediate-stage HCC) and the type of non-ICI therapy (TACE) mirror the pre-LT population who receive LRT either for downstaging purposes or to reduce risk of waitlist dropout. Thus, we can draw reasonable conclusions about immunotherapy boosting the effectiveness of HCC treatment in the pre-LT population. In addition, there is emerging data on pathological response (extent of non-viable tumour due to ICI treatment found in resection specimens) being associated with recurrence-free survival,[100] which is similar to data from LRT studies suggesting that setting a more aggressive treatment goal of eliminating viable disease is superior to simply remaining within Milan criteria. However, EMERALD-1 and other phase III clinical trials that are still in process do not provide insight into the *safety* of neoadjuvant immunotherapy prior to LT, particularly regarding risk of allograft rejection post-LT.

There are numerous case reports and case series which support the notion that pre-LT immunotherapy is generally safe. Tabrizian *et al.* initially described nine patients who received LT after being treated with nivolumab monotherapy, with only one episode of mild acute rejection.[101] Wang *et al.*, in the largest series published thus far, described 16 patients who received various anti-PD-1 monotherapies; while acute rejection occurred in nine patients, rejection in this study was defined by liver test elevations rather than histology and notably there were no cases of graft loss.[102] In the published literature, over 60 patients receiving immunotherapy prior to LT have been described, with three reported graft losses, all in patients who received ICI therapy within 90 days of LT.[103] Tabrizian *et al.* have also presented, in abstract form, results from a multicentre study of 80 ICI-treated patients with HCC evaluated for LT, with 30 having undergone LT at the time of abstract publication. Rejection occurred in five patients (16.7%), with only one graft loss (3.3%); similar to prior reports, the two cases of severe rejection (including the one case of graft loss) occurred in patients who received ICI treatment within 90 days of LT.[104] A 90 day "washout" period based on the current evidence and the half-life of ICIs (18-27 days) may be reasonable to reduce risk of severe post-LT rejection, though as the effects of ICIs can far surpass their pharmacokinetic half-life (given long-term durable treatment responses and the fact that irAEs can develop 6-12 months after cessation of therapy), a washout period may not guarantee safety. Notably, almost all the patients described in the literature received anti-PD-1 monotherapy, while one of the two standard of care immunotherapy regimens (STRIDE) is an anti-CTLA-4/PD-L1 combination therapy and may thus be associated with increased risk of immunologic complications. Given that all ICI trials exclude patients with autoimmune disease, we would also caution against neoadjuvant immunotherapy pre-LT in patients with autoimmune hepatitis given their presumed increased risk of disease flare and post-LT rejection.

Several ongoing studies are assessing the safety (and efficacy) of neoadjuvant immunotherapy in patients listed for LT. ESR-20-21010 is a single-arm, phase II trial evaluating the STRIDE regimen in patients listed for LT who have tumour burden within UCSF criteria, and its primary endpoint is post-LT rejection. Participants in ESR-20-21010 will receive STRIDE treatment for up to 4 months and will have a minimum washout period of 72 days prior to LT. The PLENTY trial is a single-centre study of pembrolizumab plus lenvatinib (tyrosine kinase inhibitor) in patients listed for LT with tumour burden exceeding Milan criteria. While its primary endpoint is recurrence-free survival, adverse events including rejection are a secondary endpoint, and participants have a minimum pembrolizumab washout period of 42 days. In Europe, the ImmunoXXL study (NCT05879328) is an observational prospective single-arm multicentre study investigating the efficacy

of LT in HCC with partial/complete and sustained (>3 months) response to atezolizumab and bevacizumab (*i.e.* achieving ≥60% post-transplant survival according to the Metroticket 2.0 calculator). Patients with extrahepatic spread or macrovascular invasion are excluded. A minimum washout period of 30 days prior to LT is required (Fig. 3).

Given their inclusion criteria (ImmunoXXL: beyond up-to-seven criteria; PLENTY: beyond Milan criteria; ESR-20-21010: up to UCSF criteria), the above studies can be classified as investigating neoadjuvant immunotherapy as part of or as the entire downstaging strategy. With regards to assessing the efficacy and safety of immunotherapy to *maintain* downstaging and reduce risk of dropout in high-risk patients, the Multicenter Evaluation of Reduction in Tumor Size before Liver Transplantation (MERITS-LT) is a consortium of US centres that prospectively investigates downstaging outcomes.[33,105] Given that a substantial proportion of downstaged patients either experience waitlist dropout or are "understaged" (*e.g.*, tumour burden exceeding T2/Milan criteria) based on explant pathology, MERITS-LT has implemented a workflow for high-risk patients to receive either atezolizumab plus bevacizumab or STRIDE after downstaging. Immunotherapy in the MERITS-LT workflow (Fig. 4) is offered to patients with residual or recurrent disease after downstaging. MERITS-LT additionally restricts candidates to those who initially had more substantial disease burden before LRT (*e.g.*, patients beyond UNOS-downstaging criteria or select patients within UNOS-downstaging criteria deemed to be higher risk, including those with elevated AFP or multi-focal disease). Patients are eligible to receive LT after a 12-week washout period based on the half-lives of atezolizumab, durvalumab, and tremelimumab.

With numerous studies investigating efficacy and safety of neoadjuvant immunotherapy prior to LT, there remains a major need to better understand which patients with HCC should be considered "high risk". Unless compelling data emerges suggesting that neoadjuvant immunotherapy for HCC in patients being considered for LT is clinically superior to LRT and surveillance, the application of pre-LT immunotherapy will likely remain selective.

Conclusion

The expansion of immunotherapy use from advanced HCC to earlier stages is underway. Clinical data showing improved outcomes with combined TACE and immunotherapy in intermediate-stage HCC support the idea that combined ICI treatment can enhance tumour control, which has strong implications for applying immunotherapy in the pre-LT setting to reduce waitlist dropout in high-risk patients and improve post-LT outcomes through systemic tumour control. There is emerging evidence that pre-LT immunotherapy is safe, and multiple studies assessing the safety and efficacy of immunotherapy in patients listed for LT are underway. We believe that immunotherapy is appropriate, in select high-risk patients, to enhance effectiveness of downstaging in those with more advanced tumour burden or to maintain more durable response while awaiting LT (Fig. 5). Management of post-LT immunosuppression will need to be reviewed after the results of prospective studies in this setting become available. Data from ongoing studies may be practice changing for the entire transplant oncology field due to broader adoption of immunotherapy.

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Abbreviations

AFP, alpha-fetoprotein; CTLA-4, cytotoxic T-lymphocyte antigen-4; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; LRT, locoregional therapy; LT, liver transplantation; MELD, model for end-stage liver disease; MVI, macrovascular invasion; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TACE, transarterial chemoembolisation; TARE, transarterial radioembolisation; Tregs, regulatory T cells; UCSF, University of California, San Francisco; UNOS, United Network for Organ Sharing; VEGF, vascular endothelial growth factor.

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Conflict of interest

ML, VM: None. SB: Consulting/advisory fees to self from: Genentech/Roche, Astra Zeneca, Boston Scientific, Terumo. NM: Research funding to institution from: FujiFilm WAKO, Glycotest, Genentech/Roche, and Target Pharmasolutions. Consulting/advisory fees to self from: Exact Sciences, Genentech/Roche, Fuji-Film WAKO, Merck, and Exelixis.

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

Authors' contributions

ML, SB: writing (original draft), writing (review and editing). NM, VM: conceptualization, writing (original draft), writing (review and editing).

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Supplementary data

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