Role of immunotherapy in downsizing hepatocellular carcinoma prior to liver transplantation

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Abstract

Hepatocellular carcinoma (HCC) is an aggressive primary liver neoplasm that, according to tumor stage, can be treated with resection, transplantation, locoregional treatment options, or systemic therapy. Although interventions only in early-stage disease can offer complete tumor regression, systemic therapy in advanced disease can significantly prolong overall survival, according to published clinical trials. The emergence of immunotherapy in the field of cancer therapy has had a positive impact on patients with HCC, resulting in atezolizumab–bevacizumab currently being the first-line option for treatment of advanced HCC. In light of this, application of immunotherapy in the preoperative process could increase the number of patients fulfilling the criteria for liver transplantation (LT). Implementation of this approach is faced with challenges regarding the safety of immunotherapy and the possibly increased risk of rejection in the perioperative period. Case reports and clinical trials assessing the safety profile and effectiveness of neoadjuvant immunotherapy, highlight important aspects regarding this newly evolving approach to HCC management. More studies need to be conducted in order to reach a consensus regarding the optimal way to administer immunotherapy prior to LT. In this review, we summarize the role, safety profile and future considerations regarding the use of neoadjuvant immunotherapy prior to LT in patients with HCC.

Key Words: Hepatocellular carcinoma; Immunotherapy; Tumor downsizing; Liver transplantation; Neoadjuvant; Rejection
Core tip: Immunotherapy has been used in the treatment of advanced hepatocellular carcinoma (HCC) with promising results. Extending its use in the preoperative period prior to liver transplantation (LT), either alone or in combination with other locoregional treatment modalities, could increase the pool of potential LT candidates. Data from case reports and ongoing clinical trials assessing neoadjuvant immunotherapy prior to LT could revolutionize the current consensus regarding HCC downsizing practices and improve survival of patients with this type of malignancy.

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INTRODUCTION
Hepatocellular carcinoma (HCC), the most common primary liver malignancy, constitutes the sixth most common cancer worldwide and the fourth most common cause of cancer-related mortality[1]. Incidence of HCC has been on the rise in some parts of the world, such as Europe and the USA, where the main risk factors for HCC development include HBV and HCV infection, alcohol consumption and nonalcoholic fatty liver disease (NAFLD)[2-4]. Due to the fact that HCC has been the fastest-rising cause of cancer-related mortality[2], and that most patients present at an advanced stage at the time of diagnosis, multiple treatment approaches have been thoroughly investigated by the scientific community in an effort not only to detect the cancer at an earlier stage, when more treatment modalities are applicable, but also ensure complete eradication of the tumor.

Optimal treatment options for HCC depend on tumor morphological characteristics, liver functionality and overall physical status of the patient, as suggested by the Barcelona Clinic Liver Cancer staging system (BCLC); one of the most used staging systems. According to BCLC, very early (0) and early (A) stages are potentially curative with radiofrequency ablation (RFA), surgical resection or liver transplantation (LT), with an overall survival (OS) > 60 mo. Patients with intermediate (B), advanced (C) and terminal (D) disease, however, who are not candidates for curative resection or transplantation, are best treated with transarterial chemoembolization (TACE), systemic therapy and supportive care, respectively, and face a grim prognosis with an OS of 20 mo for stages B and C and < 3 mo for stage D[5-7].

Patients with early-stage disease who are not candidates for surgical resection can undergo liver transplantation (LT) as a curative option, given that they fulfill the respected criteria, with a 4-year survival rate of 75%. These criteria, widely known as the Milan criteria (MC), screen patients for liver transplantation eligibility based on morphological characteristics of the tumor. However, strict application of the MC can exclude many patients from receiving the potentially curative treatment of LT, solely on the basis of tumor size and number[8,9]. In an effort to include more patients within the MC and further utilize the clinical benefits of LT, the concept of downstaging has been introduced in the treatment of HCC. Downstaging refers to a decrease in the tumor burden to the point where patients meet the MC and can receive LT. Downstaging options include, but are not limited to, TACE combined or not with doxorubicin eluting beads (TACE ± DEB), RFA, microwave ablation (MWA), transarterial radioembolization (TARE), irreversible electroporation (IRE), high-intensity focused ultrasound (HIFU), stereotactic body radiotherapy (SBRT), and systemic therapy[10]. Post-transplant survival rate in patients who had undergone LT after successful downstaging to MC have been shown to be comparable to that of patients undergoing LT and initially presenting within the MC[11].

In the modern era of cancer immunotherapy, alteration of signals that modulate the interaction between cancer cells and cells of the immune system, has led to many advances in the treatment of various cancer types, including HCC[12]. Although immuno.modulating therapies are mainly used in advanced HCC, neoadjuvant immunotherapy is a promising approach as a means of downstaging the tumor prior to LT, yielding positive outcomes in the post-transplant period[13,14]. The aim of this review is to summarize the role of immunotherapy as a downstaging technique and also highlight future considerations regarding its safety and clinically beneficial endpoints in the perioperative period and beyond.

ORTHOTOPIC LT FOR HCC
The MC have been widely used as a tool for determining which patients are eligible for LT. According to these criteria, patients may undergo LT if the following requirements are met: (1) Single tumor with a diameter ≤ 5 cm; or (2) up to three tumors, each ≤ 3 cm in diameter and no extrahepatic spread or
vascular involvement. Although patients with HCC transplanted within the MC have a 4-year survival rate of 75% and a recurrence-free survival rate of 83%, there are studies suggesting that patients not fulfilling the MC may still benefit from LT[15,16]. Overdependence on the MC may mask the true number of patients that would benefit from a transplant. In light of this, several expanded criteria have been proposed in an effort to include patients in the transplant process. What makes these criteria stand out from MC, is that they take into account not only morphological characteristics of the tumor, but also integrate biological aspects of the disease and response to locoregional treatment (LRT) in their algorithm[17]. One of the most commonly used biological parameter is -fetoprotein (AFP). AFP serves as marker of HCC differentiation and can be used in the pretransplant period to identify patients at high risk for HCC recurrence after LT. AFP levels ≥ 1000 ng/mL are associated with poor outcomes following LT, although there are no established guidelines that indicate the optimal AFP threshold that accurately predicts post-LT outcomes[18,19]. Other well-studied biological parameters that can be taken into consideration include des-carboxyprothrombin (DCP) levels, neutrophil-to-lymphocyte ratio (NLR), prognostic nutritional index, aspartate aminotransferase-to-platelet ratio index, and aspartate aminotransferase-to-neutrophil ratio index[18]. Evaluation of tumor response to LRT is a newly evolving concept in optimal selection of patients for LT, that aims to downstage patients within the MC, promising comparable survival rates to patients with HCC receiving LT and already within the MC. Response to treatments that result in decreased tumor burden can be viewed as a complementary marker of the biological aggressiveness of the tumor and risk of HCC recurrence after LT[15]. All of the proposed expanded criteria that include the aforementioned parameters have 5-year survival rates that approximate that of MC, resulting in many institutions adopting them for the purpose of selecting patients with HCC for LT[18].

Application of the expanded criteria, however, requires an adequate reserve of available organs for transplantation, since more patients are included in the transplant process. And while this is not a problem for countries located in Asia, where living donor LT (LDLT) is the main organ source, western countries mainly depend on deceased donor LT (DDLT), which necessitates strict selection of eligible patients for LT[19]. Moreover, patients receiving DDLT typically have longer wait times when compared to patients receiving LDLT, raising concern for tumor progression in such circumstances. The above remarks highlight the importance of careful selection of patients for LT, in order to maximize the positive outcomes following LT. Downstaging therapy, ideally within the MC, is common practice nowadays and has a robust armamentarium of treatment approaches that serve to reduce tumor burden and make HCC amenable to transplantation. Also, bridging therapy aims to halt tumor progression and allow patients to receive curative treatment. Although there are no clear-cut indications for downstaging or bridging therapy, results from various studies suggest that patients presenting with tumor characteristics beyond the established criteria for LT, as well as patients with waiting times ≥ 6 mo until LT, should receive neoadjuvant therapy[20,21]. Outcomes following implementation of pretransplant treatment modalities have been mixed. A study from Yao et al[8] revealed post-transplant survival and recurrence-free probabilities of patients with HCC successfully downstaged within MC to be comparable to those observed in patients with HCC and already within the MC at the time of diagnosis[22]. Other studies conducted by Lao et al[23], Chapman et al[24], and Gordon-Weeks et al[25] have also reached to similar conclusions. However, several other studies examining the effect of LRT on post-LT outcomes found out that neoadjuvant therapy is not associated with improved outcomes and may even increase recurrence of HCC following downstaging protocol implementation[26-30]. The lack of consistent outcomes following LRT application prior to LT has generated an extensive discussion of whether conventional LRT should be modified or enriched with the aim of enhancing the downstaging and bridging options for HCC[31]. Immunotherapy has been on the spotlight of HCC in recent years and is mainly used for late-stage disease when curative treatment is unfeasible, resulting in improved OS and progression-free survival (PFS)[32]. Neoadjuvant immunotherapy as a form of LRT prior to LT is a promising new approach that aims to leave behind the flaws associated with conventional LRT and increase the number of patients receiving curative treatment.

**IMMUNOTHERAPY FOR ADVANCED HCC**

**Tumor microenvironment in HCC**

The liver is an immunogenically active organ. Under normal conditions, antigen-presenting cells (APCs) take up, process and present the antigens that enter the hepatic sinusoids on T cells, in an effort to elicit a robust immune response and prevent tissue damage. Kupffer cells, which are liver-specific macrophages, liver sinusoidal endothelial cells (LSECs) and hepatic stellate cells (HSCs) constitute the most important APCs in the liver parenchyma and, apart from their antigen-presenting role, complement the immunological repertoire of the liver by other means as well[33]. Kupffer cells produce anti-inflammatory molecules, mainly interleukin (IL)-10 and transforming growth factor (TGF)-β, attracting regulatory T (Tregs) cells that possess immunosuppressive properties, whereas LSECs and HSCs express high levels of programmed cell death ligand (PDL)1, contributing to attenuation of the immune response[34]. As a result, the liver can fight off antigens that could cause tissue damage and
also maintain immune tolerance, thereby avoiding autoimmunity.

HCC development is governed by alterations in the normal liver environment that promote tumoral spread via upregulation of immunosuppressive molecules that hinder the immune response against cancer cells[35]. Maintenance of this immunosuppressive tumor microenvironment (TME) is achieved not only by liver-residing immune cells, but also from migrating populations of lymphocytes, collectively referred to as tumor-infiltrating cells (TICs)[36]. According to the subpopulation being studied, TICs can elicit an antitumoral immune response or result in upregulation of immune evasion by cancer cells. Figure 1 depicts the dynamic and complex interactions of the components of the TME and their effect on tumor spread[35-38] (Figure 1).

Mechanisms of immune evasion are of special concern, since many cancer treatment modalities depend on them. Immune checkpoint molecules modulate T-cell activation and function, attenuate the immune response against cancer cells and allow for unchecked cellular proliferation[39,40]. More specifically, PDL1, expressed by cancer cells or cells of the TME, binds to PD1 on the surface of T cells, leading to T-cell exhaustion and inability to mount an effective immune response. Also, cytotoxic T-lymphocyte-associated protein (CTLA)-4 on T cells outcompetes CD28 for B7 on the surface of APCs, leading to loss of the co-stimulatory signal necessary for T-cell activation[41]. In order to halt tumorigenesis, alteration of the signals that promote immune evasion was made possible with the introduction of antibodies known as immune checkpoint inhibitors (ICIs). Such antibodies that mainly target PD1 (ceplimumab, nivolumab and pembrolizumab), PD1L (atezolizumab, durvalumab and avelumab) and CTLA-4 (ipilimumab), have been used in the treatment of various cancers, including HCC, and have been shown to correlate with improved OS in major studies assessing their efficacy[42].

**Role of immunotherapy in advanced HCC**

Although systemic therapy targeting signal conduction pathways appeared in the treatment of HCC in 2007, immunotherapy lagged for about a decade before making a debut in 2017[43-45]. Nivolumab, a PD1 immune checkpoint inhibitor, was the first monoclonal antibody to be assessed in the treatment of advanced HCC. The CheckMate 040 was a noncomparative, dose escalation and expansion trial that included 262 patients (48 in the dose escalation and 214 in the dose expansion phase) and revealed that nivolumab had an objective response rate (ORR) of 15%–20% according to the mRECIST criteria and a median OS of 13.2–15 mo; findings that were comparable to the outcomes produced by sorafenib, the first-line treatment for HCC at that time. Due to the fact that no control arm was available in that trial, subsequent analyses comparing nivolumab to sorafenib were conducted. The CheckMate 459 phase III trial, assigning 743 patients with HCC to receive either nivolumab (intervention arm) or sorafenib (control arm), however, failed to show a statistically significant improvement in median OS [hazard ratio (HR) 0.85 (95% confidence interval (CI): 0.72–1.02); P value above the protocol-defined significance level] and PFS [HR 0.93 (95% CI: 0.79–1.1); P value above the protocol-defined significance level], but revealed a clinically significant median OS of 16.4 mo versus 14.7 mo in the intervention and control arms, respectively. Even more, grade 3/4 adverse effects were reported in 22% of patients treated with nivolumab compared with 49% of patients treated with sorafenib, justifying the use of this immunomodulating therapy in patients who are not candidates for sorafenib[32,46-49]. Pembrolizumab, another PD1 immune checkpoint inhibitor, was also assessed in the KEYNOTE 224 study, yielding an ORR of 17% and median OS of 12.9 mo[49]. Phase III trials assessing the comparative efficacy of pembrolizumab to best supportive care, failed to show significance in the primary endpoints of OS and PFS; albeit a clinically significant increase in OS[32,50,51]. Several other monoclonal antibodies have been thoroughly investigated as potential first-line treatment options for advanced HCC, including tislelizumab, durvalumab, avelumab, tremelimumab and atezolizumab. Results from these studies have revealed promising outcomes regarding the effect of these immunotherapies in OS and PFS when compared to currently established first-line options for HCC. Table 1 summarizes the major trials that harness immunotherapy, either alone or in combination with other modalities (e.g., addition of a second ICI or systemic therapy), for the treatment of advanced HCC[32,33,39-42,46,47,49,52-54] (Table 1).

The IMbrave150 trial was a cornerstone in the management of advanced HCC. This global, open-label phase III randomized trial compared atezolizumab–bevacizumab with sorafenib in the treatment of advanced HCC. Atezolizumab is a PDL1 ICI and bevacizumab is a vascular endothelial growth factor inhibitor. 501 patients were randomly assigned in 2:1 ratio to receive either atezolizumab–bevacizumab or sorafenib until there was clinical benefit or emergence of unacceptable side effects. The primary endpoints were OS and PFS, whereas secondary endpoints included ORR, duration of response, deterioration of quality of life, physical functioning, and role functioning. According to the results, median OS was 19.2 mo (95% CI: 17.0–23.7) with atezolizumab–bevacizumab and 13.4 mo (95% CI: 11.4–16.9) with sorafenib [HR 0.66 (95% CI: 0.52–0.85), P < 0.001], whereas PFS was 6.9 mo (95% CI: 5.7–8.6) with atezolizumab–bevacizumab and 4.3 mo (95% CI: 4.0–5.6) with sorafenib [HR 0.65 (95% CI: 0.53–0.81), P < 0.001]. Results of secondary endpoints were also significant and favored the atezolizumab–bevacizumab group being high-grade hypertension (15.2% of patients)[55]. The overall outcome of this study resulted in atezolizumab–bevacizumab being the current first-line treatment option for managing advanced HCC[56-59].
### Table 1: Clinical trials assessing the effectiveness of immunotherapy in patients with advanced hepatocellular carcinoma

| Trial name                                           | Phase | Intervention                                                                 | Status                                      |
|------------------------------------------------------|-------|------------------------------------------------------------------------------|---------------------------------------------|
| **Single-agent immunotherapy**                       |       |                                                                              |                                             |
| NCT02576509                                         | III   | Nivolumab vs sorafenib                                                       | Completed                                  |
| NCT02702414                                         | II    | Pembrolizumab (single-arm study)                                             | Completed                                  |
| NCT02702401                                         | III   | Pembrolizumab vs BSC                                                          | Completed                                  |
| NCT03062358                                         | III   | Pembrolizumab and BSC vs BSC and placebo                                      | Not yet completed; estimated completion date: June 2023 |
| NCT03412773                                         | III   | Tislelizumab vs sorafenib                                                     | Not yet completed; estimated completion date: May 2022 |
| NCT02989922                                         | II/III| Camrelizumab (single-arm study)                                              | Not yet completed                          |
| NCT01008358                                         | II    | Tremelimumab (single-arm study)                                              | Completed                                  |
| **Combination of immunotherapy with other treatment modalities** | |                                                                              |                                             |
| NCT02423343                                         | I/II  | Galunisertib and nivolumab (dose escalation and cohort expansion study)      | Completed                                  |
| NCT03893695                                         | I/II  | Acsrinvacumab and nivolumab (single-arm study)                               | Not yet completed; estimated completion date: June 2022 |
| NCT03099147                                         | I     | PI3 kinase/BRD4 inhibitor small molecule and nivolumab (single-arm study)    | Not yet completed; estimated completion date: October 2022 |
| NCT03211416                                         | I/II  | Pembrolizumab and sorafenib                                                  | Not yet completed; estimated completion date: December 2022 |
| NCT03713593                                         | III   | Lenvatinib and pembrolizumab vs Lenvatinib and placebo                        | Not yet completed; estimated completion date: December 2022 |
| NCT03316872                                         | II    | Pembrolizumab and SBRT (single-arm study)                                    | Not yet completed; estimated completion date: December 2022 |
| NCT03099564                                         | I     | Pembrolizumab and Radioembolization (single-arm study)                        | Not yet completed; estimated completion date: June 2022 |
| NCT03939975                                         | II    | Pembrolizumab or nivolumab or toripalimab with thermal ablation, RFA or MWA | Completed                                  |
| NCT02715531                                         | I     | Ateolizumab with bevacizumab or other chemotherapy agents                     | Completed                                  |
| NCT03434379                                         | III   | Ateolizumab and bevacizumab vs Sorafenib                                     | Not yet completed; estimated completion date: June 2022 |
| NCT03755791                                         | III   | Ateolizumab and cabozantinib vs sorafenib vs cabozantinib                     | Not yet completed; estimated completion date: December 2023 |
| NCT04310709                                         | II    | Reforafenib and Nivolumab (single-arm study)                                 | Not yet completed; estimated completion date: May 2023 |
| NCT03869034                                         | II    | HAIC and sintilimab vs HAIC                                                  | Completed                                  |
| NCT03794440                                         | II/III| Anti-VEGF monoclonal antibody and sintilimab vs sorafenib                   | Not yet completed; estimated completion date: December 2022 |
| NCT03764293                                         | III   | Apatinib and PD1 monoclonal antibody vs sorafenib                            | Not yet completed; estimated completion date: June 2022 |
| NCT03755739                                         | II/III| Pembrolizumab and/or ipilimumab administered via arterial infusion or intra-tumor fine needle injection vs pembrolizumab and/or ipilimumab administered via vein infusion | Not yet completed; estimated completion date: November 2033 |
| NCT042273100                                         | II    | PD1 monoclonal antibody and TACE and lenvatinib (single-arm study)           | Not yet completed                          |
| NCT03857815                                         | II    | PD1 monoclonal antibody and SBRT (single-arm study)                          | Not yet completed                          |
| NCT01853618                                         | I/II  | Tremelimumab and/or TACE and/or RFA (sequential assignment)                  | Completed                                  |
| NCT04124991                                         | I/II  | Durvalumab and TARE (single-arm study)                                       | Not yet completed                          |
| NCT03475953                                         | I/II  | Regorafenib and avelumab (sequential assignment)                             | Not yet completed; estimated               |
Combination therapy includes using two or more ICIs, an ICI plus systemic therapy and/or ICI plus LRT. BSC: Best supportive care; TACE: Transarterial chemoembolization; TAE: Transarterial embolization; PI3 kinase: Phosphoinositide 3 kinase; BRD4 inhibitor: Bromodomain-containing protein 4 inhibitor; SBRT: Stereotactic body radiotherapy; RFA: Radiofrequency ablation; MWA: Microwave ablation; HAIC: Hepatic arterial infusion chemotherapy; VEGF: Vascular endothelial growth factor; PD1: Programmed cell death receptor; ICI: Immune checkpoint inhibitor; LRT: Locoregional therapy.

Figure 1 Schematic representation of the major components of the tumor microenvironment in patients with hepatocellular carcinoma. The main elements of the TME can affect tumor spread both positively and negatively. The migration of TAMs and TANs can enhance the antitumoral immune response (M1 and N1 subpopulations) through the production of inflammatory mediators, such as TNF-α, NO and IL-1β, whereas M2 and N2 subpopulations promote tumor spread by producing immunosuppressive molecules and modulating T-cell function. The immune upregulating effects of NK cells and CTLs are typically blunted in patients with HCC due to the presence of factors secreted by components of the TME. MDSCs mute NK responses, increase levels of galectin-9, IL-10, TGF-β, and promote PD1-PDL1 interactions, favoring tumor spread. Treg cells, LSECs and KCs all promote HCC development by inducing CTL dysfunction, immune evasion, and expression of immune-downregulating factors. CCL2: Chemokine receptor type 2; CCL5: Chemokine receptor type 5; CCL7: Chemokine receptor type 7; CX3CL: Chemokine (C-X3-C motif) ligand 1; M-CSF: Macrophage colony stimulating factor; GM-CSF: Granulocyte macrophage colony stimulating factor; VEGF: Vascular endothelial growth factor; TAMs: Tumor associated macrophages; M1: Subpopulation 1 of TAMs; M2: subpopulation 2 of TAMs; IL-10: Interleukin 10; TGF-β: Transforming growth factor beta; TNF-α: Tumor necrosis factor alpha; NO: Nitric oxide; IL-1β: Interleukin 1 beta; TANs: tumor associated neutrophils; N1: Subpopulation 1 of TANs; N2: subpopulation 2 of TANs; CD66b: Cluster of differentiation 66 type b; PDL1: Programmed cell death ligand 1; PD1: Programmed cell death receptor 1; CTL: Cytotoxic CD8+ T cells; Tregs: T regulatory cells; FasL: Fas ligand; IFN-γ: Interferon gamma; CXCL17: Chemokine (C-X-C motif) ligand 17; NK: Natural killer cells; MCP-1: Monocyte chemotactic protein-1; HIF: Hypoxia inducible factor; HSCs: Hepatic stellate cells; MDSCs: Myeloid derived suppressor cells; CAFs: Cancer associated fibroblasts; FGFR: Fibroblast growth factor; MMP2/9: Matrix metalloproteases 2 and 9; LSECs: Liver sinusoidal endothelial cells; KCs: Kupffer cells.

Recently, the HIMALAYA study assessed the efficacy of combination tremelimumab and durvalumab in advanced HCC. This phase III study involved 1234 patients that were randomly assigned to receive durvalumab and tremelimumab or sorafenib or durvalumab monotherapy. The ORR was 20.1% in the durvalumab–tremelimumab group compared with 5.1% and 17% in the sorafenib and durvalumab groups, respectively. The PFS and OS were 3.78 and 16.4 mo in the durvalumab and tremelimumab group, 4.07 and 13.8 mo in the sorafenib group, and 3.65 and 16.6 mo in the durvalumab group. Grade 3/4 adverse events occurred at a lower rate in the durvalumab–tremelimumab and durvalumab groups when compared with the sorafenib arm. Overall results of this breakthrough study open up new treatment options that could be integrated into the treatment algorithm of HCC management[60].

As suggested by the above remarks and Table 1, clinical trials assessing the combination of immunotherapy and systemic therapy or the use of two ICIs concurrently, have shown greater outcomes when compared to trials that use single-agent therapy (immunomodulating or systemic) in the intervention arm. An ambitious treatment approach is the combination of ICIs with LRT, the latter of which is traditionally used in early-stage disease or as a means of downstaging or bridging therapy prior to LT.
The idea behind this approach is that LRT can alter the TME by inducing a robust antitumoral immune response and reduce the number of immunosuppressive molecules. Although these effects could theoretically justify LRT as a single therapy to control tumor progression, evidence suggests that such responses are weak and transient and cannot completely control the tumor. The addition of immunotherapy could amplify the antitumoral responses produced by LRT, thus creating a synergistic interaction between ICIs and LRT that could effectively control tumor spread[62,63]. There are a few trials assessing the combination of LRT with ICIs, since most of them take advantage of immunotherapy in the form of adoptive cell and vaccine therapy. However, results from these studies have demonstrated favorable outcomes in terms of OS and safety, thus encouraging the implementation of this combination in case other first-line treatment modalities fail[62].

Although combination immunotherapy is a superior approach than single-agent immunotherapy for the treatment of HCC, there are a few remarks that need to be pointed out. The need of combining various immunotherapeutic drugs in specific dosages may come as a challenge for smaller hospitals that are neither readily equipped, nor familiar with the specific combination regimens used to treat HCC. The lack of availability of highly efficacious drugs in resource-limited hospitals prevents the widespread application of immunotherapy, leaving healthcare providers with a restricted panel of drug options, mainly systemic chemotherapeutic agents, that, although effective, do not demonstrate the superiority of immunotherapy in treating HCC. Unfortunately, this hurdle inevitably affects pre-transplant ICI use for the same reasons mentioned above.

**IMMUNOTHERAPY AS A DOWNSTAGING THERAPY PRIOR TO LT**

It seems evident that immunotherapy has an integral role in the management of advanced HCC. The success of ICIs use in the long-term survival of patients with HCC has brought into question whether immunotherapy could also produce significant outcomes in early-stage disease and mainly as neoadjuvant treatment modality prior to LT. Although data on this topic are scarce, valuable information can be extracted regarding the future applications of ICIs in HCC management.

**Goals of neoadjuvant immunotherapy**

Delivery of immunotherapy prior to LT serves the same goals as application of conventional LRT, and, at the same time, establishes new perspectives in terms of prediction of post-LT outcomes and survival following transplantation. Bridging and downsizing ICI therapy is a novel approach to maintaining or even increasing the pool of transplant HCC candidates able to undergo curative LT. Beyond that, ICIs may have additional benefits post-LT, since they may be able to decrease disease recurrence by treating micrometastatic disease that was not detected prior to LT[14]. The basis behind the already mentioned promising benefits of neoadjuvant immunotherapy stems from the ability of ICIs to reconstitute the immune response towards an antitumoral microenvironment that halts disease progression. More specifically, histological analysis of a specimen from a subject enrolled in a study evaluating the perioperative use of ICIs in patients with HCC revealed an increase in the number of cytotoxic CD8+ T cells and levels of interferon (IFN)-γ, which are both known to mitigate the immunosuppressive TME seen in HCC and at the same time mount an effective antitumoral, inflammatory response that controls tumor spread. Also, although the cluster of Treg cells, which are known to induce an immunosuppressive environment and promote cancer spread, was increased, there was an eventual complete pathologic response observed in the analyzed specimen. This could be due to the high CD8+ T cell/Treg cell ratio, favoring the antitumoral immune response, or to the presence of a mixed population of regulatory T cells that serve to halt disease progression[64]. Other studies have also evaluated the mechanisms responsible for producing favoring outcomes following periprocedural ICI administration and have concluded that the overwhelming infiltration of tumor-specific CD8+ T-cells, the release of inflammatory cytokines, such as IFN-γ and tumor necrosis factor (TNF)-α, the elevated number of tumor neoantigens that attract T cells and the relative decrease in the number of immunosuppressive and Treg cells, all contribute to the positive immunomodulating outcomes of neoadjuvant ICI use[65-68]. Overall, neoadjuvant immunotherapy prior to LT in HCC serves three main goals: (1) Preventing patients from waitlist dropout, when the time interval to LT is substantial (bridging therapy); (2) increasing the number of patients eligible for transplantation by including them in established LT criteria (downstaging therapy); and (3) ensuring micrometastatic spread eradication after LT, thereby increasing the chances of prolonged survival after surgery.

**Considerations regarding the safe use of neoadjuvant immunotherapy prior to LT in patients with HCC**

When contemplating ICI administration prior to LT, one has to take into account the time interval between the last dose of ICI therapy and LT, factors that predict response to ICI therapy, in order to prevent graft rejection, and the possible adverse events associated with ICI and how they could be effectively managed.
Post-LT ICI administration has been linked to donor allograft rejection[69]. Indications for using immunotherapy after transplant include recurrence of malignancy or emergence of a new tumor that is responsive to ICI therapy. When a transplant process takes place, immunosuppression typically follows to prevent the host immune response against the transplanted allograft. ICI administration, by upregulating the T-cell response and dampening the signals that create a state of relative immunosuppression that is desirable post-LT, can result in T cells attacking the graft, resulting in dysfunction, subsequent rejection, and eventual graft and/or patient loss. Despite this feared outcome, studies evaluating graft function after ICI administration in patients undergoing LT have been mixed, and no consensus has been reached regarding the safety profile of immunotherapy in the perioperative period[70]. A case series study evaluating 13 HCC patients who received ICI post-LT revealed that four patients (31%) developed graft rejection[71]. Another study identified a cohort of 14 patients who received ICIs post-LT, with four of them (29%) experiencing graft rejection[72]. Moving to the downstaging setting, it is important to consider a washout period between the last dose of immunotherapy and LT in order to downregulate the immune response that was accentuated during ICI therapy, thus allowing the allograft to be successfully transplanted. The ideal time interval until LT has not been decided, mainly due to the limited number of studies harnessing ICIs as a downstaging tool, but there are some important aspects to consider regarding this topic. The half-life of the immunomodulating agent could be used as an adjunctive parameter to calculate the time of immunotherapy discontinuation to LT. However, further understanding of the mechanism of action of ICIs may prove the above remark unreliable. Indeed, occupancy of drug-specific targets by these medications can be prolonged, resulting in a duration of effect that extends beyond the period one would calculate based on the half-life of the ICI[73]. For example, although the half-life of nivolumab is ~25 d, it has been observed that its effects may last for up to 2 mo following a single infusion of the drug, due to sustained occupancy of PD1 on the surface of T cells. Although a short washout period would theoretically correlate with increased risk of graft rejection, there are notable examples that prove this point wrong. A study by Tabrizian et al[13] assessed the outcome of nine HCC patients who were transplanted in a single center between 2017 and 2020 after receiving nivolumab 240 mg every 2 wk as downstaging therapy. Washout period did not exceed 30 d for any patient after discontinuation of treatment and, notably, two patients discontinued nivolumab 1 and 2 d prior to LT. Following transplantation, no severe graft rejection, tumor recurrence or death occurred, with one patient developing mild rejection that was appropriately managed with an increase in the dose of tacrolimus. Intraoperative blood transfusion was administered in the two patients who received LT within 2 d of nivolumab discontinuation, which could have accelerated the rate of drug washout[13]. In another study by Chen et al[74], a patient who underwent LT and discontinued preoperative toripalimab 93 d before the procedure, suffered ICI-induced acute hepatic necrosis. Results of these studies could indicate that half-life of a drug could not by itself predict the optimal time to LT after downstaging therapy implementation. Other potential parameters or markers should be investigated in order to attain a more precise estimate of the washout period.

Predicting if a liver graft is suitable for transplantation after ICI administration is a promising feat that could smooth out the perioperative process. PDL1 molecule expression on the transplanted graft could act as surrogate biomarker of the safety of ICIs in terms of inducing or not graft rejection. The idea behind this approach is that PDL1-negative grafts will have fewer rejections when compared to positive ones, since ICIs will not be able to mount an inflammatory immune response in the absence of drug-binding molecules on the cells of the transplanted parenchyma, thus maintaining the immunosuppressive environment required for LT. A study by Shi et al[75] was conducted to compare the graft rejection rate in five cancer patients who received PDL1-negative allografts when compared to controls with an unknown PDL1 status in their transplanted liver, after receiving the immunomodulating agent toripalimab. Results showed that none of the five patients who received PDL1-negative grafts experienced rejection, whereas another patient treated off-record who received PDL1-positive graft, experienced rejection after ICI administration. In another study conducted by Friend et al[76], graft rejection was detected in two HCC patients who received nivolumab after being transplanted with PDL1-positive allografts. DeLeon et al[77], conducted a retrospective evaluation of seven cancer patients undergoing LT to assess the safety of post-transplant ICI use. Five out of seven patients in the study were assessed for PDL1 expression and two of them were positive. One of the two patients who received PDL1-positive grafts also demonstrated high levels of tumor-infiltrating lymphocytes in the transplanted liver. The results of the final study indicate that apart from PDL1 status, other potential biomarkers should be assessed to predict the outcomes of ICI use in the operative period. Although no major studies have been conducted up to date that could reliably emphasize the role of miscellaneous biomarkers that predict the safety of ICI use during LT, immunohistochemical analysis of the transplanted allograft could be used as a surrogate parameter that aims to better delineate the outcome of LT following ICI administration.

Although rejection is an undesirable outcome of ICI therapy, other adverse events can also occur, collectively known as immune-related adverse effects (iRAEs). Such adversities can prolong or even terminate the transplant process, not only because iRAEs may make the patient ineligible for LT, but also because effective management of such outcomes may prolong the time interval to LT, resulting in progression of the malignancy and dropout from the transplantation criteria. Most iRAEs present within the first 2 wk of treatment initiation, although they can occur at any time. Every organ can be involved,
and severity can range from mild to life-threatening[78,79]. Results from major clinical trials have found that grade 3/4 adverse events occur at an acceptable rate that would justify their use in HCC treatment. In the IMBrave150 trial, grade 3/4 adverse effects occurred in 56.53% of patients who were treated with atezolizumab–bevacizumab when compared with 55.13% of patients in the control group who were treated with sorafenib. The percentage of high-grade adverse effects in the intervention group was not attributed solely on atezolizumab, since hypertension, the most common high-grade adverse event observed in the study, was most likely attributable to bevacizumab[47,58]. In the KEYNOTE 240 trial, grade 3/4 adverse effects occurred in 52% of patients treated with pembrolizumab compared with 46.27% in the control arm[47].

It is not yet clear which class of ICIs is safer. While CTLA4 plays an important role in the induction of graft tolerance, PD1/PDL1 interactions result in both induction and maintenance of graft tolerance. Theoretically, this could imply that immunotherapy targeting PD1 and/or PDL1 molecules is more likely to cause organ rejection than agents that target CTLA4[80]. However, there are still no published studies that assess the comparative safety profiles of various classes of immunotherapy, so no definite conclusions can be drawn[71]. Regardless of which class will be chosen, treatment of iRAEs is the same, with glucocorticoids being the most common immunosuppressant agent that can effectively ameliorate negative outcomes of ICIs[78]. Patients undergoing LT for HCC usually have compromised liver function. Nonetheless, ICI use is safe in this patient population, since these drugs are not metabolized in the liver.

As already mentioned before, the paucity of available donors for LT substantially limits this treatment approach for the management of HCC. Although currently not employed in the armamentarium of HCC management, autologous LT is a theoretically promising approach that could increase the number of patients receiving curative treatment. Data regarding autologous LT following immunotherapy are not yet available, but a hypothetical explanation of the mechanism behind this approach could include future discussions around this topic. Liver regeneration capabilities are well studied in the literature. The effects of immunotherapy in the TME have been extensively discussed above and generally promote an antitumoral immune response that aims to halt tumor progression and decrease tumor burden. As such, more liver parenchyma can be restored to its physiologic architecture. Such an occurrence can aid in the autologous LT process by increasing the available tissue for extraction and reimplantation following diseased liver removal. As ideal as this approach may sound, challenges along the way, such as remaining unidentified tumor burden, metastatic disease and recurrence of malignancy are all topics of concern that need further investigation. For the time being, autologous LT following immunotherapy requires more research in order to delineate the exact mechanisms that could result in positive outcomes.

**Clinical trials and case reports assessing the use immunotherapy as a downstaging technique prior to LT in patients with HCC**

**Case reports:** According to literature review, 20 cases involving patients with HCC receiving ICIs prior to LT have been published[13,73,74,81-83] (Table 2). The majority of the patients were male (85%) and the mean age was 58.4 years. The most common underlying liver disease was HBV-induced liver disease, while HCV infection, alcoholic liver disease and NAFLD were also observed. One patient had no underlying liver disease. The most commonly used ICI prior to LT was the PD1 inhibitor nivolumab (55% of cases). Other immunomodulating agents used were toripalimab, durvalumab, camrelizumab and pembrolizumab. The time interval between the last dose of ICI and LT varied significantly among the cases, with one patient receiving the last ICI dose 1 d prior to LT and another one almost 29 mo prior to the operation. No recurrence of the tumor occurred in patients that had a successful LT after ICI use. Nonfatal perioperative complications, excluding rejection, occurred in only one patient, who developed bile leak that was appropriately managed without further consequences. Out of the 20 cases described, two patients had fatal rejection and two others experienced mild rejection that was adequately treated. The first patient with fatal graft rejection, described by Chen et al[74], had chronic HBV infection. He underwent DDLT due to recurrent HCC that was previously treated with resection, RFA, TACE, MWA, sorafenib, lenvatinib and toripalimab. The last cycle of ICI therapy was administered 93 d prior to LT. Following the procedure, the patient’s liver function status deteriorated rapidly, and a liver biopsy performed on the second postoperative day revealed massive liver tissue necrosis that was attributed to toripalimab. The patient expired 3 d after the procedure[73]. The second patient with fatal graft rejection, described by Nordness et al[81], had chronic HCV infection. He underwent DDLT due to recurrent HCC previously treated with resection, sorafenib, RAE, TACE and nivolumab. The last dose of nivolumab was administered 8 d prior to LT. On postoperative day 5, rapid elevation of liver enzymes was noted, and the patient deteriorated clinically to the point where he was transferred to the intensive care unit. A biopsy that was performed on the next day revealed acute hepatic necrosis with a dense lymphocytic infiltration, findings that point towards a diagnosis of ICI-induced graft rejection. Reversible graft rejection that was observed in two patients was due to low levels of immunosuppressive medications and was appropriately treated with dose escalation, without inflicting any major damage to the graft recipients.
Ouranos K et al. Immunotherapy prior to liver transplantation

### Table 2 Summary of case reports assessing immune checkpoint inhibitors as a downstaging and/or bridging therapy prior to liver transplantation in patients with hepatocellular carcinoma

| Sex | Age, yr | Underlying liver disease | ICI            | Cycles (d) | Washout period | Post-LT outcome   |
|-----|---------|--------------------------|----------------|------------|----------------|------------------|
| M   | 66      | ALD                      | Nivolumab      | 34         | 105            | No rejection     |
| M   | 65      | HCV                      | Nivolumab      | 44         | 8              | Fatal rejection  |
| M   | 39      | HBV                      | Toripalimab    | 10         | 93             | Fatal rejection  |
| M   | 69      | None                     | Nivolumab      | 21         | 18             | No rejection     |
| F   | 56      | HCV                      | Nivolumab      | 8          | 22             | No rejection     |
| M   | 58      | HBV                      | Nivolumab      | 32         | 1              | No rejection     |
| M   | 63      | HCV                      | Nivolumab      | 4          | 2              | No rejection     |
| M   | 30      | HBV                      | Nivolumab      | 25         | 22             | Mild rejection²  |
| M   | 63      | HBV                      | Nivolumab      | 4          | 13             | No rejection     |
| M   | 66      | HBV                      | Nivolumab      | 9          | 253            | No rejection     |
| F   | 55      | HBV                      | Nivolumab      | 12         | 7              | No rejection     |
| F   | 53      | NASH                     | Nivolumab      | 2          | 30             | No rejection     |
| M   | 61      | HBV                      | Durvalumab     | NA         | > 90           | No rejection     |
| M   | 53 ± 12.1 | NA              | Camrelizumab and/or Pembrolizumab | 3 ± 2 | 870 on average | 1 rejection in the cohort¹ |

¹The rejection was appropriately treated and the patient suffered no major adverse outcomes. ICI: Immune checkpoint inhibitor; HCC: Hepatocellular carcinoma; M: Male; F: Female; LT: Liver transplantation; ALD: Alcoholic liver disease; HCV: Hepatitis C virus; HBV: Hepatitis B virus; NASH: Non-alcoholic steatohepatitis; NA: Not available.

**Clinical trials:** Currently, there is a limited number of clinical trials assessing the use of ICIs prior to LT in patients with HCC. However, there are multiple studies evaluating neoadjuvant administration of immunotherapy prior to liver resection in patients with HCC[39](Table 3). These are mainly phase I/II studies with no control arm that assess safety, efficacy, and tolerability of the immunomodulating agent, either alone or in combination with other therapies. Nivolumab is the most used ICI in these studies[84-88]. Other ICIs used include tislelizumab, cemiplimab, toripalimab and camrelizumab[89-92]. Most of these trials are ongoing, with most of them not having any published results. Analysis of completed studies, however, reveals satisfactory objective response rates and an acceptable rate of adverse events, setting the stage for the recommencement of phase III, randomized studies that will provide us with valuable information regarding the benefits of neoadjuvant immunotherapy before resection or LT.

To date, there are two clinical trials of neoadjuvant immunotherapy prior to LT in patients with HCC. The first trial (NCT04425226) is a randomized study that will assess the neoadjuvant use of pembrolizumab and lenvatinib as a downstaging and/or bridging therapy prior to LT in 192 patients with HCC. Participants will receive pembrolizumab 200 mg intravenously on day 1 of each 21-d cycle. Treatment will continue until unacceptable toxicity develops or until there are at least 42 d remaining to LT. Concurrently, study subjects will receive lenvatinib 8-12 mg orally at least 38 d every 6 wk and until there are at least 7 d prior to LT. The primary endpoint will be RFS, whereas secondary endpoints include objective remission rate and RFS, time to progress and rate of adverse events. Results of this study are expected in December 2024[93]. The second trial (NCT04035876) is a phase 1/II, single-arm study that evaluated the use of camrelizumab and apatinib as downstaging and/or bridging therapy prior to LT in 120 patients with HCC. Participants received camrelizumab 200 mg intravenously every 2 wk and apatinib 250 mg orally every day. Camrelizumab was discontinued 5 wk before and apatinib 1 wk before LT. Primary endpoints included objective remission rate and RFS, whereas secondary endpoints included OS, time to progress and rate of adverse events. Results of this study are not yet available[94].

**CONCLUSION**

LT is a curative treatment approach for HCC. With respect to the current transplant criteria, conventional LRT has been widely used as downstaging and/or bridging therapy to increase the pool of
potential LT candidates. Nevertheless, the benefits of immunotherapy in patients with advanced HCC have generated an extensive discussion whether ICIs could be used safely and effectively in the pretransplant process in order to yield favorable outcomes. When contemplating neoadjuvant immunotherapy, the risk of graft rejection after LT is a matter of concern. Results from a limited number of case reports, however, showed that the risk may not be as high, with fatal rejection presenting in only two out of 20 cases of LT after ICI administration. More studies need to be conducted to delineate the factors that could reliably predict outcomes after LT in patients receiving neoadjuvant immunotherapy. Determination of surface molecule expression, such as PD/PDL1, obtained via liver biopsy, is a tempting marker that could predict response to outcome, but, utilized alone, does not seem to accurately include all patients that would benefit from ICIs. More markers need to be taken into consideration, either alone or in conjunction with other aspects of disease treatment that focus on the pharmacokinetics of immunotherapy. Drug half-life could theoretically play an important role in determining the ideal time interval spanning from ICI discontinuation to LT. In practice, however, no fatal rejection was observed in patients with cessation of drug therapy even 1 d before surgery, emphasizing the fact that individualization of treatment regimen is a superior approach than strict adherence to the properties of the drug in order to allocate patients to the appropriate drug scheme. Patient comorbidities, availability of other neoadjuvant treatment options, and the ability to timely treat emerging ICI-related adverse effects are all remarks that should be explored prior to initiating immunotherapy. Clinical trials that assess neoadjuvant ICI therapy, either before liver resection or transplantation, show promising results, both in treatment safety and efficacy, with primary and secondary study endpoints being met successfully. Insights from future studies, which are currently underway, are necessary to better understand the impact of neoadjuvant immunotherapy in the perioperative period and beyond.

**FOOTNOTES**

**Author contributions:** Ouranos K drafted the article; Chatziioannou A contributed to the acquisition of analyses of data; Goulis I made critical revisions related to important intellectual content and approved the final version of the manuscript; Sinakos E designed the study, made critical revisions related to important intellectual content, approved the final version of the manuscript and supervised the project.

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REFERENCES

1. Renne SL, Sarcogno S, Sacchi D, Guido M, Roncalli M, Terracciano L, Di Tommaso L. Hepatocellular carcinoma: a clinical and pathological overview. Pathologica 2021; 113: 203-217 [PMID: 34294938 DOI: 10.32074/1591-951X.295]

2. Kulik L, El-Serag HB. Epidemiology and Management of Hepatocellular Carcinoma. Gastroenterology 2019; 156: 477-491.e1 [PMID: 30367835 DOI: 10.1010/gastro.2018.08.065]

3. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymouth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol 2019; 16: 589-604 [PMID: 31439937 DOI: 10.1038/s41575-019-0108-y]

4. Tang A, Hallouche O, Chernekov Y, Kamaya A, Sirlin CB. Epidemiology of hepatocellular carcinoma: target population for surveillance and diagnosis. Abdom Radiol (NY) 2019; 43: 13-25 [PMID: 30187256 DOI: 10.1007/100261-017-1209-1]

5. Karademir S. Staging of hepatocellular carcinoma. Hepatoma Res 2018; 4: 58 [DOI: 10.20517/2394-5079.2018.40]

6. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999; 19: 329-338 [PMID: 10518312 DOI: 10.1055/s-2007-1007122]

7. Maida M, Orlando E, Cammag C, Cabibbo G. Staging systems of hepatocellular carcinoma: a review of literature. World J Gastroenterol 2014; 20: 4141-4150 [PMID: 24764652 DOI: 10.3748/wjg.v20.i15.4141]

8. Yao FY, Mehta N, Flemming J, Dodge J, Hameed B, Fix O, Hirose R, Fidelman N, Kerlan RK Jr, Roberts JP. Downstaging of hepatocellular cancer before liver transplant: long-term outcome compared to tumors within Milan criteria. Hepatology 2015; 61: 1968-1977 [PMID: 25689798 DOI: 10.1002/hep.27572]

9. Fujiki M, Auejo F, Choi M, Kim R. Neo-adjuvant therapy for hepatocellular carcinoma before liver transplantation: where do we stand? World J Gastroenterol 2014; 20: 5308-5319 [PMID: 24833861 DOI: 10.3748/wjg.v20.i18.5308]

10. She WH, Cheung TT. Bridging and downstaging in patients suffering from hepatocellular carcinoma waiting on the list of liver transplantation. Transpl Gastroenterol Hepatol 2016; 1: 34 [PMID: 28136801 DOI: 10.21037/tgh.2016.03.04]

11. Yao FY, Kerlan RK Jr, Hirose R, Davern TJ 3rd, Bass NM, Peters M, Terrault N, Freise CE, Ascher NL, Roberts JP. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. Hepatology 2008; 48: 819-827 [PMID: 18688876 DOI: 10.1002/hep.22412]

12. Yang L, Ni a Q, Tang SS. Recent Advances and Next Breakthrough in Immunotherapy for Cancer Treatment. J Immunol Res 2022; 2022: 8052212 [PMID: 35340585 DOI: 10.1155/2022/8052212]

13. Tabrizian P, Florman SS, Schwartz ME. PD-1 inhibitor as bridge therapy to liver transplantation? Am J Transplant 2021; 21: 1979-1980 [PMID: 33316117 DOI: 10.1111/ajt.16449]

14. Pinato DJ, Fessas P, Sapisochin G, Marron TU. Perspectives on the Neoadjuvant Use of Immunotherapy in Hepatocellular Carcinoma. Hepatologia 2021; 74: 483-490 [PMID: 33369758 DOI: 10.1002/hep.31697]

15. Tonutto P, Fumolo E, Fornasieri E, Bitetto D. Liver Transplantation in Patients with Hepatocellular Carcinoma beyond the Milan Criteria: A Comprehensive Review. J Clin Med 2021; 10: 34501381 DOI: 10.3390/jcm10173932

16. Muhammad H, Tehreem A, Ting PS, Gurakar M, Li SY, Simsek C, Alqahtani SA, Kim AK, Kohli R, Gurakar A. Hepatocellular Carcinoma and the Role of Liver Transplantation: A Review. J Clin Transl Hepatol 2021; 9: 738-748 [PMID: 34722189 DOI: 10.14218/JCTH.2021.00125]

17. Rudnick SR, Rusu MW. Liver transplantation beyond or downstaging within the Milan criteria for hepatocellular carcinoma. Expert Rev Gastroenterol Hepatol 2018; 12: 265-275 [PMID: 29231769 DOI: 10.1080/17474124.2018.1417035]

18. Vilbert E, Schwartz M, Olthoff KM. Advances in resection and transplantation for hepatocellular carcinoma. J Hepatol 2020; 72: 262-276 [PMID: 31954491 DOI: 10.1016/j.jhep.2019.11.017]

19. Duvoux C, Roudot-Thoraval F, Decaens T, Pesineste F, Badran H, Piardi T, Francoz C, Compagnon P, Vanlemmens C, Dumortier J, Dharmency S, Guguenheim J, Bernard PH, Adam R, Radenne S, Muscari F, Conti F, Hardwigen J, Pageaux GP, Chazouillères O, Salame E, Hilleret MN, Lebray P, Abergel A, Debette-Gratien M, Kluger MD, Malat A, Azoulay D, Cherqui D; Liver Transplantation French Study Group. Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein improves the performance of Milan criteria. Gastroenterology 2012; 143: 986-94.e3; quiz e14 [PMID: 22750200 DOI: 10.1053/j.gastro.2012.05.052]

20. Clavien PA, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A; OLIT for HCC Consensus Group. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. Lancet Oncol. 2012; 13: 11-22 [DOI: 10.1016/S1470-2045(11)70175-9]

21. Ogawa K, Takaya Y. Role of Pretransplant Treatments for Patients with Hepatocellular Carcinoma Waiting for Liver Transplantation. Cancers (Basel) 2022; 14 [PMID: 35035358 DOI: 10.3390/cancers14020396]

22. Kim Y, Stahl CC, Makramalla A, Olowokure OO, Ristagno RL, Dhar VK, Schoech MR, Chadalavada S, Latif T, Kharofa J, Bari K, Shah SA. Downstaging therapy followed by liver transplantation for hepatocellular carcinoma beyond Milan criteria. Surgery 2017; 162: 1250-1258 [PMID: 29033224 DOI: 10.1016/j.surg.2017.08.007]
Luo OB, Weissman J, Perkins JD. Pre-transplant therapy for hepatocellular carcinoma is associated with a lower recurrence after liver transplantation. *Clin Transplant* 2009; 23: 874-881 [PMID: 19453644 DOI: 10.1111/j.1399-0012.2009.00993.x]

Chapman WC, Garcia-Aroz N, Vachhrajani N, Fowler K, Saad N, Lin Y, Wellen J, Tan B, Khan AS, Doyle MB. Liver Transplantation for Advanced Hepatocellular Carcinoma after Downstaging Without Up-Front Stage Restrictions. *J Am Coll Surg* 2017; 234: 610-621 [PMID: 28069927 DOI: 10.1016/j.jamcollsurg.2016.12.020]

Gordon-Weeks AN, Snaith A, Petrinic T, Friend PJ, Buris A, Silva MA. Systematic review of outcome of downstaging hepatocellular cancer before liver transplantation in patients outside the Milan criteria. *Br J Surg* 2011; 98: 1201-1208 [PMID: 21618496 DOI: 10.1002/bjs.7561]

Huang X, Lu S. Impact of preoperative locoregional therapy on recurrence and patient survival after liver transplantation for hepatocellular carcinoma: a meta-analysis. *Scand J Gastroenterol* 2017; 52: 143-149 [PMID: 27623157 DOI: 10.1080/00365521.2016.1236396]

Ravaioli M, Oddoli F, Cucchieta A, Trevisani F, Piscaglia F, De Pace V, Bertuzzo VR, Neri F, Golfsier R, Cappelli A, D’Errico A, Cescon M, Del Gaudio M, Fallani G, Siniscalchi A, Morelli MC, Ciccarese F, Di Marco M, Farinati F, Giannini EG, Pinna AD. Long term results of down-staging and liver transplantation for patients with hepatocellular carcinoma beyond the conventional criteria. *Sci Rep* 2019; 9: 3781 [PMID: 30846792 DOI: 10.1016/j.sciabc.2019.4043-4]

Dorcarato D, Udupa V, Hogan NM, Brophy DP, McCann JW, Maguire D, Geoghegan J, Cantwell CP, Hoit E. Does neoadjuvant doxorubicin drug-eluting bead transarterial chemoembolization improve survival in patients undergoing liver transplant for hepatocellular carcinoma? *Diagn Interv Radiol* 2017; 23: 441-447 [PMID: 29063856 DOI: 10.1512/dir.2017.171106]

Toso C, Meeberg G, Andres A, Shore C, Saunders C, Bigam DL, Shapiro AMJ, Compagnon P, Berney T, Majno P, Kneteman N. Downstaging prior to liver transplantation for hepatocellular carcinoma: advisable but at the price of an increased risk of cancer recurrence - a retrospective study. *Transpl Int* 2019; 32: 163-172 [PMID: 30152891 DOI: 10.1111/tiz.13337]

Parikh ND, Waljee AK, Singal AG. Downstaging hepatocellular carcinoma: A systematic review and pooled analysis. *Liver Transpl* 2015; 21: 1142-1152 [PMID: 25981135 DOI: 10.1002/hep.27469]

Li HL, Ji WB, Zhao R, Duan WD, Chen YW, Wang XQ, Yu Q, Luo Y, Dong JH. Poor prognosis for hepatocellular carcinoma with transarterial chemoembolization pre-transplantation: retrospective analysis. *World J Gastroenterol* 2015; 21: 3599-3606 [PMID: 25834326 DOI: 10.3748/wjg.v21.i12.3599]

Kole C, Charalampakis N, Tsakatikas S, Vailas M, Moris D, Kikatos S, Karamouzis MV, Schizas D. Immunotherapy for Hepatocellular Carcinoma: A 2021 Update. *Cancers (Basel)* 2020; 12 [PMID: 33020428 DOI: 10.3390/cancers12102859]

Sangro B, Sarobe P, Herras-Stubbis S, Melero I. Advances in immunotherapy for hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol* 2021; 18: 525-543 [PMID: 33850328 DOI: 10.1038/s41575-021-00438-0]

Krenkell O, Tacke F. Liver macrophages in tissue homeostasis and disease. *Nat Rev Immunol* 2017; 17: 306-321 [PMID: 28317925 DOI: 10.1038/nri.2017.11]

Fasano R, Shadbad MA, Brunetti O, Argentiero A, Calabrese A, Nardulli P, Calbi R, Baradaran B, Silvestris N. Immunotherapy for Hepatocellular Carcinoma: New Prospects for the Cancer Therapy. *Life (Basel)* 2021; 11 [PMID: 34947886 DOI: 10.3390/Life11111355]

Chew V, Lai L, Pan L, Lim CJ, Li J, Ong R, Chu C, Leong JY, Lin KH, Lee SY, Chan CY, Goh BKP, Chung A, Chow PKH, Albani S. Delineation of an immunosuppressive gradient in hepatocellular carcinoma using high-dimensional proteomic and transcriptomic analyses. *Proc Natl Acad Sci U S A* 2017; 114: E5900-E5909 [PMID: 28674001 DOI: 10.1073/pnas.1706559114]

Keenan BP, Fong L, Kelley RK. Immunotherapy in hepatocellular carcinoma: the complex interface between inflammation, fibrosis, and the immune response. *J Immunother Cancer* 2019; 7: 267 [PMID: 31627733 DOI: 10.1186/s40425-019-0749-z]

Patek K, Lamm R, Altsulher P, Dang H, Shah AP. Hepatocellular Carcinoma-The Influence of Immunoanatomy and the Role of Immunotherapy. *Int J Mol Sci* 2020; 21 [PMID: 32942580 DOI: 10.3390/ijms11216757]

Fulgenzi CAM, Talbot T, Murray SM, Silletta M, Vincenzi B, Cortellini A, Pinato DJ. Immunotherapy in Hepatocellular Carcinoma. *Curr Treat Options Oncol* 2021; 22: 87 [PMID: 34422442 DOI: 10.1007/s11864-021-00886-5]

Liu Z, Liu X, Liang J, Liu Y, Hou X, Zhang M, Li Y, Jiang X. Immunotherapy for Hepatocellular Carcinoma: Current Status and Future Prospects. *Front Immunol* 2021; 12: 765101 [PMID: 34675942 DOI: 10.3389/fimmu.2021.765101]

van Doorn DJ, Takkenberg RB, Klümpen HJ. Immune Checkpoint Inhibitors in Hepatocellular Carcinoma: An Overview. *Pharmaceuticals (Basel)* 2020; 14 [PMID: 33374927 DOI: 10.3390/ph14010003]

Ghavimi S, Afpel T, Azimi H, Persaud A, Pyrsopoulos NT. Management and Treatment of Hepatocellular Carcinoma with Immunotherapy: A Review of Current and Future Options. *J Clin Transl Hepatol* 2020; 8: 168-176 [PMID: 32832397 DOI: 10.14281/JCTH.2020.00001]

Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Lencioni R, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovich M, Volotsis D, Brux J. SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; 359: 359-360 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]

Zhao Y, Zhang YN, Wang KT, L. Lenvatinib for hepatocellular carcinoma: From preclinical mechanisms to anti-cancer therapy. *Biochim Biophys Acta Rev Cancer* 2020; *1874*: 188391 [PMID: 32659252 DOI: 10.1016/j.bbcan.2020.188391]

Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, Blanc JF, Vogel A, Komov D, Evans TRJ, Lopez C, Dutcuc G, Guo M, Saito K, Kraljevic S, Tamai T, Ren M, Cheng AL. Lenvatinib vs sorafenib in first-line treatment of patients with hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018; 391: 1163-1173 [PMID: 29433850 DOI: 10.1016/S0140-6736(18)30207-1]

El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, Kim TY, Choo SP, Trojan J, Welling TH RD, Meyer T, Kang YK, Yeo W, Chopra A, Anderson J, Dela Cruz C, Lang L, Neely J, Tang H, Dastani HB, Melero I. Nivolumab in
Ouranos K et al. Immunotherapy prior to liver transplantation

patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017; 389: 2492-2502 [PMID: 28434468 DOI: 10.1016/S0140-6736(17)31046-2]

Zeng L, Su J, Qui W, Jin X, Qiu Y, Yu W. Survival Outcomes and Safety of Programmed Cell Death/Programmed Cell Death Ligand 1 Inhibitors for Unresectable Hepatocellular Carcinoma: Result From Phase III Trials. Cancer Control 2022; 29: 10732748221092924 [PMID: 35418272 DOI: 10.1177/10732748221092924]

Kudo M, Matilla A, Santoro A, Melero I, Gracian AC, Acosta-Rivera M, Choo SP, El-Khoueiry AB, Kuromatsu R, El-Raysse B, Numata K, Ishi Y, Di Costanzo F, Crysler O, Reig M, Shen Y, Neely J, Tschaika M, Wisniewski T, Sangro B. CheckMate 040 cohort S: A phase I/II study of nivolumab in patients with unresectable hepatocellular carcinoma and Child-Pugh B cirrhosis. J Hepatol 2021; 75: 600-609 [PMID: 34051329 DOI: 10.1016/j.jhep.2021.04.047]

Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, Verslype C, Zagolov V, Fatouxs L, Vogel A, Sarker D, Verset G, Chan SL, Knox J, Daniele B, Webber AL, Ebbinghaus SW, Ma J, Siegel AB, Cheng AL, Kudo M; KEYNOTE-224 investigators. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol 2018; 19: 940-952 [PMID: 29875066 DOI: 10.1016/S1470-2045(18)30351-6]

Study of Pembrolizumab (MK-3475) vs Best Supportive Care in Participants with Previously Systematically Treated Advanced Hepatocellular Carcinoma (MK-3475-240/KEYNOTE-240). [accessed 2022 Apr 30]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/show/NCT02702401 ClinicalTrials.gov identifier: NCT02702401

Study of Pembrolizumab (MK-3475) or Placebo Given With Best Supportive Care in Asian Participants with Previously Treated Advanced Hepatocellular Carcinoma (MK-3475-394/KEYNOTE-394). [accessed 2022 Apr 30]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/show/NCT03062359 ClinicalTrials.gov identifier: NCT03062359

Luo Y, Teng F, Fu H, Ding GB. Immunotherapy in liver transplantation for hepatocellular carcinoma: Pros and cons. World J Gastrointest Oncol 2022; 14: 163-180 [PMID: 35116109 DOI: 10.4251/wjgo.v14.i1.163]

Ziogas IA, Evangelou AP, Giannis D, Hayat MH, Mylonas KS, Tohme S, Geller DA, Elias N, Goyal L, Tsouflas G. The Role of Immunotherapy in Hepatocellular Carcinoma: A Systematic Review and Pooled Analysis of 2,402 Patients. Oncologist 2021; 26: e1036-e1049 [PMID: 33314549 DOI: 10.1002/onco.13638]

Cheng AL, Hsu C, Chan SL, Choo SP, Kudo M. Challenges of combination therapy with immune checkpoint inhibitors for hepatocellular carcinoma. J Hepatol 2020; 72: 307-319 [PMID: 31954494 DOI: 10.1016/j.jhep.2019.09.019]

Salem R, Li D, Sommer N, Sperber S, Verret W, Ding B, Lencioni R. Characterization of response to atezolizumab + bevacizumab vs sorafenib for hepatocellular carcinoma. Results from the IMbrave150 trial. Cancer Med 2021; 10: 5437-5447 [PMID: 34180969 DOI: 10.1002/cam4.4090]

Cheng AL, Qin S, Ikekda M, Galle PR, Ducreux M, Kim TY, Lim HY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Ma N, Nicholas A, Wang Y, Li L, Zhu AX, Finn RS. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs sorafenib for unresectable hepatocellular carcinoma. J Hepatol 2022; 76: 862-873 [PMID: 34902530 DOI: 10.1016/j.jhep.2021.11.030]

C-H Hsu, M. S. Lee, K-H Lee, N. Numata, S. Stein, W. Verret, S. Hack, J. Spahn, B. Liu, C. Huang, R. He, B-Y Ryoo. Randomized efficacy and safety results for atezolizumab (Atezo) + bevacizumab (Bev) in patients (pts) with previously untreated, unresectable hepatocellular carcinoma (HCC). Annals of Oncology 2019; 30: v851-v934 [DOI: 10.1093/annonc/mdz939]

Finn RS, Qin S, Ikekda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang M, Muller S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab vs Sorafenib in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020; 382: 1894-1905 [PMID: 32402160 DOI: 10.1056/NEJMoa1915745]

Vogel A, Rimassa L, Sun HC, Abou-Alfa GK, El-Khoueiry A, Pinato DJ, Sanchez Alvarez J, Daigl M, Orfano P, Leibfried M, Blanchet Zumoos MH, Gaillard VE, Merle P. Comparative Efficacy of Atezolizumab plus Bevacizumab and Other Treatment Options for Patients with Unresectable Hepatocellular Carcinoma: A Network Meta-Analysis. Liver Cancer 2021; 10: 240-248 [PMID: 34239810 DOI: 10.1159/000515302]

Akce M, El-Rayes BF, Bekkai-Saas TS. Frontline therapy for advanced hepatocellular carcinoma: an update. Therap Adv Gastroenterol 2022; 15: 17562848221086126 [PMID: 35432597 DOI: 10.1177/17562848221086126]

Leone P, Solimando AG, Fasano R, Argentiero A, Malerba E, Buonavaglia A, Lugo LP, De Re V, Silverstris N, Raccuri V. The Evolving Role of Immune Checkpoint Inhibitors in Hepatocellular Carcinoma Treatment. Vaccines (Basel) 2021; 9 [PMID: 34065489 DOI: 10.3390/vaccines9050532]

Wang K, Wang C, Jiang H, Zhang Y, Lin W, Mo J, Jin C. Combination of Ablation and Immunotherapy for Hepatocellular Carcinoma: Where We Are and Where to Go. Front Immunol 2021; 12: 792781 [PMID: 34975896 DOI: 10.3389/fimmu.2021.792781]

Shi L, Wang J, Ding N, Zhang Y, Zhu Y, Dong S, Wang X, Peng C, Zhou C, Zhou L, Li X, Shi H, Wu W, Long X, Wu C, Liao W. Inflammation induced by incomplete radiofrequency ablation accelerates tumor progression and hinders PD-1 immunotherapy. Nat Commun 2019; 10: 5421 [PMID: 31780645 DOI: 10.1038/s41467-019-13204-3]

Kaseb AO, Vence L, Blazdo J, Yadav SS, Ikoma N, Pestana RC, Vauthay JN, Allisson JP, Sharma P. Immunologic Correlates of Pathologic Complete Response to Preoperative Immunotherapy in Hepatocellular Carcinoma. Immunol Res 2019; 7: 1390-1395 [PMID: 31280900 DOI: 10.1186/s40164-016-0605]

Krishnamoorthy M, Lenehan JG, Maleki Vareki S. Neoadjuvant Immunotherapy for High-Risk, Resectable Malignancies: Scientific Rationale and Clinical Challenges. J Natl Cancer Inst 2021; 113: 823-832 [PMID: 33432320 DOI: 10.1093/jnci/djaa216]

Peyrottes O, Ouzaid I, Califano G, Hermieu JF, Xylina E. Neoadjuvant Immunotherapy for Muscle-Invasive Bladder Cancer. Medicina (Kaunas) 2021; 57 [PMID: 34440975 DOI: 10.3390/medicina7080769]

Rouanne B, Bajorin DF, Hanann R, Galksy MD, Williams SB, Necchi A, Sharma P, Powles T. Rationale and Outcomes for Neoadjuvant Immunotherapy in Urothelial Carcinoma of the Bladder. Eur Urol Oncol 2020; 3: 728-738 [PMID: 31975066 DOI: 10.1016/j.euo.2020.01.002]
Doroshow D, Legg M, Hammad A, Magen A, Kamphorst AO, Shareef M, Gupta NT, Deering R, Wang W, Wang F, https://clinicaltrials.gov/ct2/show/NCT03630640
In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: Neoadjuvant and Adjuvant Nivolumab in HCC Patients Treated by Electroporation (NIVOLEP). [accessed 2022 May 5].

Cabozantinib and Nivolumab Converts Locally Advanced HCC into Resectable Disease with Enhanced Antitumor Response. Swiss J Surg Onkol 2018; 57: 293-300 [DOI: 10.1159/000486687].

Munker S, De Toni EN. Use of checkpoint inhibitors in liver transplant recipients. United States European Journal of Gastroenterol 2018; 6: 970-973 [PMID: 30228883 DOI: 10.1177/2050640618774631].

Gao Q, Anwar II, Abraham N, Barbas AS. Liver Transplantation for Hepatocellular Carcinoma after Downstaging or Bridging Therapy with Immune Checkpoint Inhibitors. Cancers (Basel) 2021; 13 [PMID: 34944927 DOI: 10.3390/cancers13246307].

Chen GH, Wang GB, Huang F, Qin R, Yu XJ, Wu RL, Hou LJ, Ye ZH, Zhang XH, Zhao HC. Pretransplant use of toripalimab for hepatocellular carcinoma resulting in fatal acute hepatic necrosis in the immediate postoperative period. Transpl Immunol 2021; 66: 101386 [PMID: 33744409 DOI: 10.1016/j.trn.2021.101386].

Shi GM, Wang J, Huang XW, Huang XY, He YF, Ji Y, Chen Y, Wu D, Lu JC, Sun QM, Liu WR, Wang T, Yang LX, Hou YY, Shi YH, Sun J, Xiao YS, Wang Z, Fan J, Bartagalli MM, Zhou J. Graft-Related Death After Pre-Immunotherapy: A Case Report. Transplant Proc 2021; 53: 444-449 [PMID: 32897657 DOI: 10.1016/j.transproceed.2021.02.058].

Friend BD, Venick RS, McDermid SV, Zhou X, Naini B, Wang H, Farmer DG, Busuttil RW, Federman N. Fatal orthotopic liver transplant organ rejection induced by a checkpoint inhibitor in two patients with refractory, metastatic hepatocellular carcinoma. Pediatr Blood Cancer 2017; 64: 28643391 DOI: 10.1002/pbc.26682.

DeLeon TT, Salomao MA, Agel BA, Sonbol MB, Yokoda RT, Ali AH, Mosaq AA, Mathur AK, Chascsa DM, Rakela J, Bryce AH, Borad MJ. Pilot evaluation of PD-1 inhibition in metastatic cancer patients with a history of liver transplantation: the Mayo Clinic experience. J Gastrointest Oncol 2018; 9: 1045-1062 [PMID: 30603124 DOI: 10.21037/jgo.2018.07.05].

Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med 2018; 378: 158-168 [PMID: 29320654 DOI: 10.1056/NEJMra1703481].

Abdel-Wahab N, Shah M, Suarez-Almazor ME. Adverse Events Associated with Immune Checkpoint Blockade in Patients with Cancer: A Systematic Review of Case Reports. PLoS One 2016; 11: e0160221 [PMID: 27472273 DOI: 10.1371/journal.pone.0160221].

Wanchoo R, Riella LV, Uppal NN, Lopez CA, Nair V, Devoe C, Jhasveri KD. Immune Checkpoint Inhibitors in the Liver Transplant Patient. Journal of Oncology-Neophylology 2017; 1: 42-48 [DOI: 10.5301/jo-n.500006].

Nordness MF, Hamel S, Godfrey CM, Shi C, Johnson DB, Goff LW, O'Dell H, Perri RE, Alexopoulos SP. Fatal hepatic necrosis after nivolumab as a bridge to liver transplant for HCC: Are checkpoint inhibitors safe for the pretransplant patient? Am J Transplant 2020; 20: 879-883 [PMID: 31550417 DOI: 10.1111/ajt.16517].

Schwacha-Epper B, Mincuina I, Banz V, Dufour JF. Immunotherapy as a Downstaging Therapy for Liver Transplantation. Hepatology 2020; 72: 1488-1490 [PMID: 32171041 DOI: 10.1002/hep.31334].

Qiao ZY, Zhang ZJ, Lv ZC, Tong H, Xi ZF, Wu HX, Chen XS, Xiao L, Feng H, Zhang JG, Xia Q. Neoadjuvant Programmed Cell Death 1 (PD-1) Inhibitor Treatment in Patients With Hepatocellular Carcinoma Before Liver Transplantation: A Cohort Study and Literature Review. Front Immunol 2021; 12: 653475 [DOI: 10.3389/fimmu.2021.65347].

Mehr R, Jost-Brinkmann F, Özdirik B, Lambrecht J, Hammerich L, Loosin SH, Luedde T, Demir M, Tacke F, Roderburg C. Lessons From Immune Checkpoint Inhibitor Trials in Hepatocellular Carcinoma. Front Immunol 2021; 12: 652172 [PMID: 33859646 DOI: 10.3389/fimmu.2021.652172].

Pinato DJ, Cortellini A, Sukamaran A, Cole T, Pai M, Habib N, Spalding D, Sodergren MH, Martinez M, Dhillon T, Tait DT, Thomas R, Ward C, Kocher H, Yip V, Slater S, Sharma R. PRIME-HCC: phase Ib study of neoadjuvant ipilimumab and nivolumab prior to liver resection for hepatocellular carcinoma. J Hepatol 2016; 64: 970-973 [PMID: 27472277 DOI: 10.1002/hep.31234].

Safety and Bioactivity of Ipilimumab and Nivolumab Combination Prior to Liver Resection in Hepatocellular Carcinoma (PRIME-HCC). [accessed 2022 May 4]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT03682276 ClinicalTrials.gov identifier: NCT03682276.

Ho WJ, Zhu Q, Durham J, Popovic A, Xavier S, Leatherman J, Mohan A, Mo G, Zhang S, Gross N, Charnsang T, Lin D, Dong Q, Wilt B, Kamel IR, Weiss M, Philibote B, Burkhart R, Burns WR, Shubert C, Ejaz A, Je L, Deshpande A, Danilova L, Stein-O'Brien G, Sugar EA, Laheru DA, Anders RA, Fertig EJ, Jaffe EM, Yachoo M. Neoadjuvant Cabozantinib and Nivolumab Converts Locally Advanced HCC into Resectable Disease with Enhanced Antitumor Immunity. Nat Cancer 2021; 2: 891-903 [PMID: 34796337 DOI: 10.1038/s43018-021-00234-4].

Neoadjuvant and Adjuvant Nivolumab in HCC Patients Treated by Electroporation (NI-VOLEP). [accessed 2022 May 5].
In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT03630640 ClinicalTrials.gov identifier: NCT03630640.
Thanigaimani P, Mani J, Troncoso L, Tabachnikova A, Chang C, Akturk G, Buckup M, Hamel S, Ioannou G, Hennequin C, Jamal H, Brown H, Bonaccorso A, Labow D, Sarpel U, Rosenbloom T, Sung MW, Kou B, Li S, Jankovic V, James N, Hannon SC, Cheung HK, Sims JS, Miller E, Bhardwaj N, Thurston G, Lowy I, Gnjaic S, Taouli B, Schwartz ME, Merad M. Neoadjuvant cemiplimab for resectable hepatocellular carcinoma: a single-arm, open-label, phase 2 trial. *Lancet Gastroenterol Hepatol* 2022; 7: 219-229 [PMID: 35065058 DOI: 10.1016/S2468-1253(21)00385-X]

Shangai Junshi Bioscience Co. Toripalimbib in Combination With Lenvatinib as Neoadjuvant Therapy in Resectable Hepatocellular Carcinoma. [accessed 2022 May 5]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT03867370 ClinicalTrials.gov identifier: NCT03867370

Tislelizumab or Tislelizumab Combined With Lenvatinib Neoadjuvant Treatment for Resectable RHCC (TALENT). [accessed 2022 May 4]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT04615143 Clinical Trials.gov identifier: NCT04615143

Xia Y, Tang W, Qian X, Li X, Cheng F, Wang K, Zhang F, Zhang C, Li D, Song J, Zhang H, Zhao J, Yao A, Wu X, Wu C, Ji G, Liu X, Zhu F, Qin L, Xiao X, Deng Z, Kong X, Li S, Yu Y, Xi W, Deng W, Qi C, Liu H, Pu L, Wang P, Wang X. Efficacy and safety of camrelizumab plus apatinib during the perioperative period in resectable hepatocellular carcinoma: a single-arm, open label, phase II clinical trial. *J Immunother Cancer* 2022; 10 [PMID: 35379737 DOI: 10.1136/jitc-2022-004656]

Pembrolizumab and LENvatinib in Participants With Hepatocellular Carcinoma (HCC) Before Liver Transplant (PLENTY2020001). [accessed 2022 May 5]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT04425226 ClinicalTrials.gov identifier: NCT4425226

Combination Camrelizumab (SHR-1210) and Apatinib for Downstaging/Bridging of HCC Before Liver Transplant. [accessed 2022 May 5]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT04035876 ClinicalTrials.gov identifier: NCT04035876
