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Trial watch: immunotherapeutic strategies on the horizon for hepatocellular carcinoma

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ABSTRACT

The use of immune checkpoint inhibitors (ICIs) targeting PD-L1/PD-1 and CTLA-4 has transformed the oncology practice of hepatocellular carcinoma. However, only 25–30% of the patients with advanced HCC treated with atezolizumab-bevacizumab or tremelimumab-durvalumab (STRIDE) respond initially, and mechanistic biomarkers and novel treatment strategies are urgently needed for patients who present with or acquire resistance to first-line ICI-based therapies. The recent approval of the STRIDE regimen has also engendered new questions, such as patient selection factors (e.g. portal hypertension and history of variceal bleed) and biomarkers, and the optimal combination and sequencing of ICI-based regimens. Triumphs in the setting of advanced HCC have also galvanized considerable interest in the broader application of ICIs to early- and intermediate-stage diseases, including clinical combination of ICIs with locoregional therapies. Among these clinical contexts, the role of ICIs in liver transplantation – which is a potentially curative strategy unique to HCC management – as a bridge to liver transplant in potential candidates or in the setting of post-transplant recurrence, warrants investigation in view of the notable theoretical risk of allograft rejection. In this review, we summarize and chart the landscape of seminal immuno-oncology trials in HCC and envision future clinical developments.

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and the third leading cause of cancer-related deaths globally[1,2]. HCC encompasses a profound collection of disease entities with substantial heterogeneity at the clinical, pathological, and molecular levels[3]. The most widely used method for classifying HCC is the Barcelona Clinic Liver Cancer (BCLC) score, which is based on the number and size of tumors, and the impact of the disease on the patient's quality of life. These guidelines have also been refined through the incorporation of liver function indicators such as the Child-Pugh score, Model for End-Stage Liver Disease, alpha-fetoprotein, and albumin–bilirubin ratio[4]. The BCLC score has seen widespread use in the prognostication and characterization of patients with HCC and frequently guides treatment options available. The treatment options available in different BCLC stages are summarized in Figure 1. The majority of patients present with advanced, inoperable HCC (aHCC)[5]. Even for patients with early HCC who received curative treatment, 60–70% relapse within 5 years[6–9]. Since the groundbreaking results of Checkmate-040 (ClinicalTrials.gov Identifier: NCT01658878) were first published, immune checkpoint inhibitors (ICIs) have gradually been established as a standard of care in managing aHCC[4,10]. In the second-line setting, FDA-approved ICI-containing regimens include nivolumab-ipilimumab, which demonstrated an objective response rate (ORR) of up to 32% and median overall survival (mOS) of up to 22.8 months in the CheckMate-040 cohort 4 trial, and pembrolizumab, which demonstrated an ORR of 18% in the KEYNOTE-224 trial (ClinicalTrials.gov Identifier: NCT02702414). In the first-line setting, the IMBrave150 trial (ClinicalTrials.gov Identifier: NCT03434379) established atezolizumab-bevacizumab as a new standard, demonstrating significant benefit over sorafenib (mOS 19.4 vs 13.4 months, $p < 0.001$). Recently, tremelimumab-durvalumab has been approved based on the results of the HIMALAYA trial (ClinicalTrials.gov Identifier: NCT03298451), which showed a mOS of up to 16.4 months for the combination,

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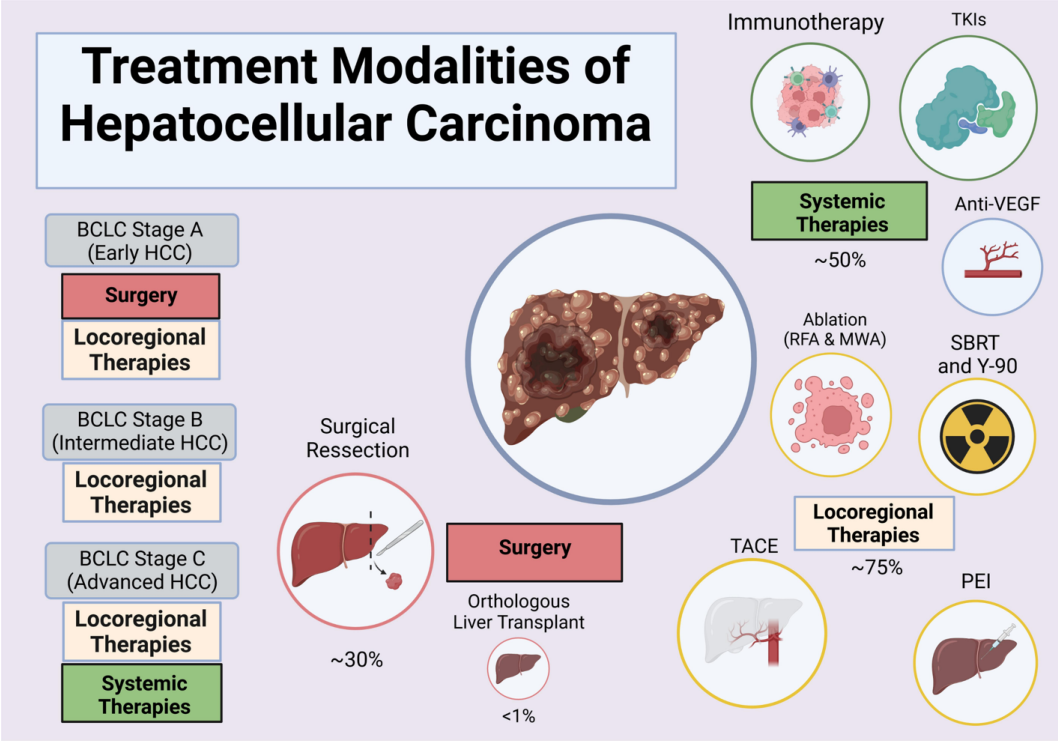

Figure 1. Overview of all commonly used treatments for Hepatocellular Carcinoma (HCC) based on the Barcelona Clinic Liver Centre (BCLC) staging system. Note: Bubble size of treatment semi-quantitatively corresponds to the frequency of treatment's use in HCC. Frequencies were obtained based on the percentage of patients eligible for the treatment based on the BCLC system and other patient data obtained from various studies [15-18]. Locoregional and systemic therapies remain the most widely used due to the limited supply of liver donors and adverse patient profiles contra-indicating surgical treatments [4]. Within systemic therapies, tyrosine kinase inhibitors (TKIs) remain the most frequently used due to their better characterized effectiveness and safety profiles. However, immunotherapies have grown in interest recently due to the successes of several clinical trials. Abbreviations: VEGF: Vascular Endothelial Growth Factor; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; MWA, microwave ablation; SBRT, stereotactic body radiation therapy; PEI, percutaneous ethanol injection; Y-90: Yttrium-90. Illustration created using Biorender

compared to 13.8 of sorafenib ($p = 0.0035$). Despite these advances, many questions remain unaddressed such as the optimal sequence of ICI treatment and the ideal dosage of various regimens. In addition, numerous trials evaluating ICIs in adjuvant and neoadjuvant settings are ongoing, and other strategies for inducing immune rejection of HCC are actively being explored. In this review, we highlight the evidence of ICIs use in HCC until August 2022 and evaluate forthcoming immunotherapeutic strategies.

Rationale for ICIs in HCC

Chronic inflammation, due to hepatitis B/C, alcoholic liver disease, or nonalcoholic steatohepatitis, is the predominant process leading to both HCC oncogenesis and the creation of a cirrhotic tumor environment[11]. In a cirrhotic liver, the combination of pro-inflammatory cytokines, neo-angiogenic signals, and immune downregulation facilitates the development and proliferation of HCC[12,13]. Immune escape is achieved through the recruitment of regulatory T cells (Treg), myeloid-derived suppressor cells (MDSCs) and the upregulation of immune checkpoints such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1)[14]. These characteristics of the HCC tumor microenvironment and the observation that tumor-infiltrating-lymphocytes in HCC were correlated to survival inspired the first attempts at using ICIs for HCC[15].

ICIs as a treatment in advanced HCC

To date, the most widespread application of ICIs in HCC is in advanced disease. Various strategies exist, from single-agent anti-PD-1 to a combination of anti-PD-1/L1 with anti-CTLA-4 or with VEGF-blocking antibodies (mAbs) or multi-kinase inhibitors. Treatment of second-line, post-sorafenib aHCC has similarly shifted toward ICIs as a single or combinatory agent. Combinatory anti-PD1 with anti-CTLA-4[16] or VEGF mAbs have been generally accepted due to superior clinical benefits and long-term outcomes compared to sorafenib[17,18]. The growing landscape of ICIs has raised discussion about the advantages and contraindications of different treatment regimens and to identify populations that would benefit the most from treatment. The conundrum of patient selection between STRIDE and atezo-beva is one such example. Due to the latter regimen's risk of bleeds[19], concerns have been raised about its application in HCC patients due to their frequent concomitant presentation with portal hypertension and esophageal varices and ongoing research is still being done to identify the optimal treatment.

The current first-line ICI therapy for advanced HCC is a combined therapeutic regimen of Atezolizumab (Tecentriq) and Bevacizumab (Avastin). IMbrave150 trial was a landmark phase 3 clinical trial that assessed the efficacy of Atezolizumab (an anti-PDL-1 mAb) and Bevacizumab (an anti-VEGF mAb) combination for the treatment of locally advanced or metastatic HCC and monitored the overall and progression-free

survival of 480 patients on treatment with the immunotherapeutic regiment against sorafenib (a tyrosine-kinase inhibitor commonly adopted in treating HCC). Overall, the results were largely optimistic, with the combined regimen providing longer overall and progression-free survival compared to sorafenib, where the median progression-free survival was 6.8 months (95% CI: 5.7–8.3 months) compared to sorafenib only (4.3 months, 95% CI: 4.0–5.6 months). Additionally, the median survival rate at 12 months was 67.2% (95% CI: 61.3–73.1%) and 54.6% (95% CI: 45.2–64%) in the atezolizumab-bevacizumab and sorafenib arms, respectively[20]. A follow-up on the trial group has reestablished median treatment effectiveness with an overall survival rate of 19.2 months with atezolizumab-bevacizumab compared to 13.4 months for sorafenib[21]. Since then, several other ICIs such as a single agent or in combination with other agents have been evaluated for their efficacy and safety.

Another such regimen was Tremelimumab and Durvalumab in the HIMALAYA trial, which aimed to determine the efficacy of a combination regimen in unresectable HCC. While similar studies of both tremelimumab and durvalumab treatment in HCC had been conducted before[22–24], the HIMALAYA trial was vital in its scale and long-term assessment of the treatment. In the randomized control trial, 1171 patients with unresectable HCC who were ineligible for locoregional therapy were treated with a regiment of Tremelimumab and Durvalumab (dubbed the Single Tremelimumab Regular Interval Durvalumab or STRIDE regiment), Durvalumab alone or a control regiment of sorafenib. The trial concluded with STRIDE significantly improving median overall survival versus sorafenib (16.42 months in STRIDE and 13.77 months in sorafenib). Overall survival at 36 months was 30.7%, 24.7%, and 20.2% in STRIDE, durvalumab and sorafenib respectively. The survival hazard ratio was 0.78 (96.02% CI, 0.65–0.93) in STRIDE and 0.86 in durvalumab (95.67% CI, 0.73–1.03) when compared to sorafenib. STRIDE and durvalumab also had a lower emergence of treatment-related adverse events (50.5% and 37.1% respectively) compared to sorafenib (52.4%) suggesting at least an identical if not favorable safety profile[25].

In the KEYNOTE-224 trial, pembrolizumab saw an overall response rate (ORR) of 17% (95% CI: 11–26) in 104 BCLC B or C patients previously treated with sorafenib[26]. A follow-up trial (KEYNOTE-240; ClinicalTrials.gov Identifier: NCT02702401) concluded with an ORR of 18.3% (95% CI, 14.0% to 23.4%) versus placebo at 4.4% (95% CI, 1.6% to 9.4%). The median progression-free survival rate at 12 months was 19.4% (95% CI, 14.6% to 24.9%) for pembrolizumab versus 6.7% (95% CI, 3.0% to 12.4%) for placebo and median overall survival using pembrolizumab was established at 13.9 months[25]. Ramucirumab (an anti-VEGF mAb) was approved in 2019 as a single-agent treatment for HCC in patients previously treated with sorafenib[27]. A double-blind phase 3 trial on 292 HCC BCLC B and C patients (REACH-2; ClinicalTrials.gov Identifier: NCT02913261) established an improved median overall survival of 8.5 months (95% CI, 7.0 to 10.6 months) compared to placebo at 7.3 months (95% CI, 5.4 to 9.1 months) and progression-free survival of 2.8 months (95% CI, 2.8 to 4.1 months) versus placebo (1.6 months, 95% CI, 1.5 to 2.7 months)[28]. A combination of nivolumab (an anti-PD-1 mAb) and ipilimumab (an anti-CTLA-4 mAb) was approved in 2020 for patients with advanced HCC who experienced radiographic progression during or after sorafenib treatment or sorafenib intolerance[29]. In the CHECKMATE-040 trial, arm A (four doses nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks followed by nivolumab 240 mg every 2 weeks) saw a response rate of 32% (95% CI, 20% to 47%), an overall survival at 12 months of 61% (95% CI, 46% to 73%), and a median survival of 22.8 months (95% CI, 9.4-not reached)[30].

Interestingly, a randomized phase 3 trial (CHECKMATE-459; Clinicaltrial.gov Identifier: NCT02576509) evaluating the use of nivolumab as a first-line treatment in advanced HCC concluded with no significant improvement in overall survival compared to sorafenib. There, 743 patients with advanced HCC refractory to surgical resection or locoregional therapies were randomly assigned a treatment of either nivolumab 240 mg intravenously for 2 weeks ($n = 371$) or sorafenib 400 mg twice daily ($n = 372$). The trial concluded with a median overall survival of 16.4 months (95% CI, 13.9 to 18.4 months) for nivolumab and 14.7 months (95% CI, 11.9 to 17.2 months) for sorafenib (hazard ratio 0.85 [95% CI, 0.72 to 1.02], $p = 0.075$). The nivolumab arm also saw fewer grade 3 or worse treatment-related adverse events such as palmar-plantar erythrodysesthesia (<1% in nivolumab vs. 14% in sorafenib) and hypertension (0% in nivolumab vs 7% in sorafenib). Conversely, the nivolumab arm reported comparable total treatment-related adverse events (12% in nivolumab and 11% in sorafenib) and a greater number of treatment-related deaths (4 in nivolumab and 1 in sorafenib). This trial highlights the alternate use of ICIs as a first-line option for patients in which tyrosine kinase inhibitors or other systemic therapies are contraindicated.

In a bid to improve responses to systemic therapy, combinatorial strategies have gained increased attention. The immunomodulatory effects of TKIs or multikinase inhibitors on HCC microenvironments could theoretically potentiate responses of ICIs in unresectable HCC. It is with that in mind that Finn et al first reported the Phase 1b study of Lenvatinib plus Pembrolizumab in 104 patients[31]. In the trial, ORRs of 46% were reported, showing the promise of such a combination. It is with this report that combination therapies are now being evaluated in not just advanced/unresectable disease but also in early and intermediate disease. These studies are shown in Table 4. Frustratingly, the much anticipated LEAP-002 trial (ClinicalTrials.gov Identifier: NCT03713593) did not meet significance in its primary endpoints of overall survival or progression-free survival compared to Lenvatinib alone[32].

As of August 2022, treatments other than the combination therapy of atezolizumab and bevacizumab are considered second-line option for the treatment of HCC, with several clinical trials ongoing to evaluate their efficacy as potential first-line treatments. These trials are shown in Table 5.

Role of ICIs in the neoadjuvant setting

Advances toward facilitating successful margin-negative resections have led to increased interest in neoadjuvant therapies for HCC[33,34]. To date, neoadjuvant therapies have failed to show a survival benefit in Phase III settings. However, smaller studies have shown promise in its use. The first significant report was

Table 1. Summary of all ongoing trials involving FDA-approved ICIs as neoadjuvant therapies as of August 2022.

NCT no. (Trial Name)	ICI	Phase	Endpoints
NCT04727307 (AB-LATE02)	Atezolizumab	2	RFS
NCT05185505		4	Transplant Rejection, AE, ORR, Transplant Bridging, OS, Biomarkers
NCT04954339		2	pCR, AE, PFS, RFS, Immunologic change
NCT05137899		2	LR, ORR, AE, PFS, OS
NCT04857684		1	AE, ORR, Transplant Bridging, pCR, OS, RFS
NCT05194293	Durvalumab	2	ORR, AE, PFS, OS, RFS, pCR
NCT04443322 (Dulect2020–1)		NA	PFS, RFS, ORR, OS, AE
NCT05440864	Durvalumab + Tremelimumab	2	AE, ORR, pCR, LR, RFS, OS, biomarkers
NCT03630640 (NIVOLEP)	Nivolumab	2	RFS, OS, AE, biomarkers
NCT05471674		2	TRR, RFS, OS, SP
NCT04912765		2	RFS, AE, OS, immunologic change
NCT03299946		1	AE, LR, pCR, MPR, ORR, OS, DFS
NCT03510871	Nivolumab + Ipilimumab	2	ORR
NCT05302921		2	ORR, AE, biomarkers
NCT04123379	Nivolumab + CCR2/5 inhibitor (BMS-813160)*/IL-8 Inhibitor (BMS-986253)*	2	MPR, ORR, AE, PFS, OS
NCT04658147	Nivolumab + Relatlimab*	1	ORR, AE, pCR, OS, DFS, R0 Resection
NCT03337841	Pembrolizumab	2	RFS, OS, ORR, biomarkers, AE
NCT05389527		2	MPR, pCR, ORR, R0 Resection
NCT05185739 (PRIMER-1)		2	MPR, ORR, RFS, AE
NCT04425226 (PLENTY202001)		NA	RFS, DCR, AE, ORR
NCT05339581	Pembrolizumab + Sintilimab/Tislelizumab/Camrelizumab	NA	ORR, PFS, ORR, TTP, DOR, biomarkers
NCT04615143 (TALENT)	Tislelizumab	2	DFS, ORR, AE, MPR
NCT04653389	Sintilimab	2	EFS, DOR, MPR, DFS, OS, AE, biomarkers
NCT05277675 (RANT)	Sintilimab/Tislelizumab	NA	RFS, AE

Abbreviations: **RFS**: Recurrence-Free Survival; **AE**: Adverse Effects; **ORR**: Overall Response Rate; **OS**: Overall Survival; **PFS**: Progression-Free Survival; **pCR**: Pathological Complete Response; **LR**: Liver Resection; **MPR**: Major Pathological Response; **DOR**: Duration of Response; **TTP**: Time-to-Progression; **DCR**: Disease Control Rate.
Search terms involved ICI AND neoadjuvant (E.g. atezolizumab AND neoadjuvant) on the clinicaltrials.gov site. Trials were included regardless of current status with the only exception of trials terminated due to poor accrual. Trials involving additional treatments (E.g. TKIs) were also included. Source: clinicaltrials.gov.

a Phase 1b trial of neoadjuvant cabozantinib and nivolumab in advanced, initially unresectable disease[35]. In this study of 15 patients, a neoadjuvant approach facilitated successful resection in 12 patients, and induced major pathologic response (>90% necrosis) in 5 patients. In another Phase II study using neoadjuvant cemiplimab (an anti-PD-1 monoclonal antibody) for patients with upfront resectable disease, 20% of the patients demonstrated significant tumor necrosis (>70% necrosis of resected tumor), with another 15% showing partial response (50–70% necrosis)[36]. The trial was a single-arm, open-label phase II trial, with 21 patients with resectable HCC (stage Ib, II, and III HCC, ECOG 0–1, and adequate liver function) receiving 2 cycles of neoadjuvant cemiplimab (350 mg) administered intravenously every 3 weeks, following which 20 patients underwent successful resection. Treatment-associated adverse reactions were observed in 95% of the patients, with 7 patients experiencing grade 3 adverse events, such as elevated blood creatine phosphokinase and hypoalbuminemia, but no grade 4 or 5 events were reported. These preliminary studies first show the utility of neoadjuvant ICIs in the conversion to resectability for locally advanced and initially unresectable tumors and secondly a very acceptable safety profile of ICIs. Long-term oncological outcomes including recurrence-free survival (RFS) and correlation of tumor necrosis with recurrence need to be further studied, especially given the high risk of recurrence with HCC resections. In both studies, an immune-rich tumor microenvironment predicted response to ICIs with both regimens, highlighting a potential biomarker in patient selection for tumor response. Recent discussion has also shifted toward identifying the sequence and dosage for optimal outcomes. Ongoing trials evaluating the use of ICIs in the neoadjuvant setting are shown in Table 1.

Role of ICIs in adjuvant treatment for HCC

Similar to its use in the neoadjuvant setting, there have been no Phase III trials showing a benefit of any agent in the adjuvant setting; the most recent negative trial being the STORM Phase III trial, which assessed adjuvant sorafenib[37]. With high rates of recurrence following curative treatments (resection, ablation etc.), the need for an adjuvant therapy is urgently needed. Recently, the NIVOLVE trial published preliminary data on the safety and efficacy of adjuvant nivolumab in patients with HCC[38]. The phase II multicenter trial included 53 patients who achieved a complete response to either surgical resection or radiofrequency ablation and were subsequently treated with nivolumab (240 mg/body every 2 weeks for 8 cycles) followed by nivolumab (480 mg/body every 4 weeks for 8 cycles) within 6 weeks after surgery. The trial reported a 1-year RFS rate of 78.6% and a median recurrence-free survival rate of 26.3 months (95% CI: 16.8 months-not reached), suggesting the potential utility of immunotherapy as an adjuvant treatment compared to historical cohorts. Additionally, the trial identified several factors associated with a shorter RFS post-adjuvant nivolumab, including activation of the WNT/β-catenin pathway (RFS = 17.0 months, $p = 0.014$), expression of Foxp3+ T-cells and low CD8+ tumor-infiltrating lymphocytes (RFS = 16.8 months, $p = 0.015$). These results indicate that further studies are needed to fully understand the role of immunotherapy as an adjuvant treatment in HCC and to identify predictive

Table 2. Summary of all ongoing trials involving FDA-approved ICIs as adjuvant therapies as of August 2022.

NCT no. (Trial Name)	ICI	Phase	Endpoints
NCT04727307 (AB-LATE02)	Atezolizumab	2	RFS
NCT04102098 (IMBRAVE150)		3	RFS, OS, TTR, AE
NCT05516628 (EMPHASIS)		2	RFS, TTR, OS
NCT03847428 (EMERALD-2)	Durvalumab	3	RFS, OS, TTR
NCT03383458 (CHECKMATE 9DX)	Nivolumab	2	RFS, OS, TTR
NCT03630640 (NIVOLEP)		2	RFS, ORR, OS, AE
NCT04912765		2	RFS, AE, OS
NCT04233840		2	DLT, RFS, DFS, Hepatitis B Ag
NCT03867084 (MK-3475-937/KEYNOTE-937)	Pembrolizumab	3	RFS, OS, AE, QoL change,
NCT04224480		1	Recurrence, CD8+ Ki67+ T cells titre
NCT04981665	Tislelizumab	2	RFS, TTR, OS, AE
NCT05545124		2	RFS, OS, AE
NCT05407519		2	RFS, TTR, OS, AE
NCT05546619		NA	RFS, OS
NCT04653389	Sintilimab	2	EFS, DOR, MPR, DFS, OS, AE, biomarkers
NCT04682210		3	RFS, OS, TTR, AE
NCT03859128 (JUPITER-04)	Toripalimab	3	RFS, TTR, OS, AE
NCT05240404		2	DFS, OS, AE, biomarkers

Abbreviation: **RFS**: Recurrence-Free Survival; **OS**: Overall Survival; **TTR**: Time-to-Response; **AE**: Adverse Effects; **DLT**: Dose-Limiting Toxicities; **QoL Change**: Quality of Life Change; **EFS**: Event-Free Survival; **DOR**: Duration of Response; **MPR**: Major Pathological Response Rate.
Search terms involved ICI AND adjuvant on the clinicaltrials.gov site. Trials were included regardless of current status except for trials terminated due to poor accrual. Trials involving additional treatments (E.g. TKIs) were also included. Source: clinicaltrials.gov.

biomarkers that may inform treatment decisions and patient selection. Ongoing trials evaluating ICIs in the adjuvant setting are shown in Table 2.

Synergistic role of local therapies with ICIs in locally advanced HCC

With current immunotherapy regimens, significant tumor responses occur in less than 50% of the patients treated with ICIs – this has been attributed to poor immune cell infiltration and an immunosuppressive tumor microenvironment. While locoregional therapies, such as transarterial chemoembolization (TACE), radiofrequency ablation (RFA), and stereotactic body radiation therapy (SBRT), have been widely used to treat HCC in patients unsuitable for resection or transplantation[39–41], the use of such directed therapies in improving ICI response rates are still being evaluated. In a mouse-model study, a T-cell mediated immune response triggered by ablative radiotherapy (and normally dampened in conventional fractional radiotherapy or chemotherapy) was shown to play a major role in primary tumor destruction[42]. In theory, the tumor immunogenic antigens released through locoregional therapies would affect synergistically with ICIs, thereby amplifying tumor-specific immune sequestration[43]. With an increasing understanding of the efficacy and safety profiles of both locoregional and immunotherapies, several combination strategies have been devised with some entering clinical development[43–45]. A retrospective study of 31 mostly BCLC Stage B or C patients evaluating the effect of concurrent TACE and nivolumab treatment on survival showed a benefit in BCLC B patients using multimodality treatment versus ICI monotherapy with a mOS of 35.1 months versus 16.6 months, respectively (HR = 0.47; 95% CI 0.19 to 1.20, $p = 0.04$). Conversely, minimal improvements were observed in BCLC C patients (mOS = 16.2 months vs 24.5 months, HR = 1.23; 95% CI 0.45 to 3.30, $p = 0.92$)[46]. Furthermore, the safety profile of the combination therapy was found to be acceptable, as evidenced by the low incidence of severe adverse drug-effects, with only three patients (10%) experiencing grade 3 or higher toxicity, demonstrating safety profiles comparable to those of sorafenib. The START-FIT trial (ClinicalTrials.gov Identifier: NCT03817736) has also recently established the synergistic benefits of ICIs and locoregional therapies. In the single-arm phase 2 trial, 33 patients with unresectable HCC and without extrahepatic or lymph node metastases were started on a combination therapy of TACE and SBRT followed by avelumab (a PD-L1 inhibitor; 10 mg/kg) to assess complete or partial response. Following treatment, 18 patients (55%) were deemed amenable to the treatment, which was defined as a complete or partial response and an eligibility for curative treatment, of which 4 (12%) successfully underwent curative resection. Significantly, 14 patients (42%) had a complete radiological response and opted for close surveillance. This study marked the first prospective trial of the combination therapy with extremely encouraging results[47]. The STRATUM trial (ClinicalTrials.gov Identifier: NCT05377034) is an ongoing multinational double-blind randomized control trial evaluating the efficacy of Yttrium-90 radioembolization with atezolizumab and bevacizumab in advanced HCC, which currently lacks large-scale prospective studies assessing its efficacy and ideal treatment protocols[48]. Similarly, the CHECKMATE-74W trial (ClinicalTrials.gov Identifier: NCT04340193), a double-blind, randomized study of nivolumab and ipilimumab in combination with TACE, is currently ongoing and anticipated to provide greater insight into the use of ICI as a combination therapy. New therapeutic regiments and sequences are also being evaluated to optimize the combination of ICIs with locoregional therapies. Other ongoing trials evaluating the combination of ICIs with liver-directed therapies are shown in Table 3.

Emerging immunotherapies

Aside from ICIs, several other immunotherapies have begun clinical evaluation for their use in HCC. The following sections will discuss two of the popular modalities seeing development, Bispecific Antibodies and Chimeric Antigen Receptor T-cell therapy (CAR-T).

Table 3. Summary of all trials involving ICIs and locoregional therapies as of August 2022.

ICI	Combinatory Locoregional Therapy	HCC Staging	Phase: Trial Number
Atezolizumab + Bevacizumab	TACE	Intermediate	Phase 4: NCT05185505[s]
			Phase 3: NCT04712643[s], NCT04803994
			Phase 2: NCT04224636 [t,s], NCT05537402
			Observational: NCT05332496
		Advanced	Observational: NCT05332821
		Not Specified	Observational: NCT04975932
Durvalumab + Bevacizumab		Not Specified	Phase 3: NCT03778957
Durvalumab + Tremelimumab + Bevacizumab		Intermediate Advanced	Phase 2: NCT03937830
Bevacizumab + Sintilimab*		Intermediate	Phase 1: NCT04592029
		Advanced	Phase 2: NCT04954794[s], NCT04796025
			Phase 1: NCT04592029
Durvalumab		Intermediate	NA: NCT04517227[t]
Durvalumab + Tremelimumab		Intermediate	Phase 2: NCT03638141[s], NCT04522544[s], NCT02821754[t]
		Advanced	Phase 2: NCT02821754[t]
		Not specified	Phase 3: NCT05301842
			Phase 2: NCT04988945[t]
Tremelimumab		Intermediate Advanced	Phase 2: NCT01853618[t]
Nivolumab		Intermediate	Phase 3: NCT04777851[s]
			Phase 2: NCT03572582[s], NCT04268888[s]
			Phase 1: NCT03143270
Nivolumab + Ipilimumab		Intermediate	Phase 2: NCT04472767[s]
			Phase 3: NCT04340193
Pembrolizumab		Intermediate	Phase 3: NCT04246177[s]
			Phase 2: NCT03397654[s], NCT03753659[t,s]
Tislelizumab*		Advanced	Phase 2: NCT04599777
Camrelizumab*/Sintilimab*/Nivolumab/Pembrolizumab/ Toripalimab*		Intermediate Advanced	Phase 2: NCT05233358
Atezolizumab + Bevacizumab	RFA	Early	Phase 2: NCT04727307, NCT04224636[t]
Bevacizumab + Sintilimab*/Tislelizumab*		Early	NA: NCT05277675
Durvalumab		Intermediate	NA: NCT04517227[t]
Durvalumab + Tremelimumab		Intermediate Advanced	Phase 2: NCT02821754[t]
Tremelimumab		Intermediate Advanced	Phase 2: NCT01853618[t]
Nivolumab		Not Specified	Phase 2: NCT03033446
Nivolumab/Pembrolizumab		Intermediate Advanced	Phase 2: NCT03939975
Pembrolizumab		Intermediate	Phase 2: NCT03753659[t]
Atezolizumab + Bevacizumab	Microwave Ablation (MWA)	Intermediate	Phase 2: NCT04224636 [t,s],
Durvalumab		Intermediate	NA: NCT04517227[t]
Pembrolizumab		Intermediate	Phase 2: NCT03753659[t, s]
Bevacizumab + Atezolizumab	SBRT	Intermediate	Phase 2: NCT05137899[s]
			Phase 1: NCT05096715, NCT04857684[s]
		Advanced	Phase 2: NCT05396937
			Phase 1: NCT05096715
		Not Specified	Phase 1: NCT05488522
Durvalumab		Advanced	Phase 2: NCT04913480[s]
Durvalumab + Tremelimumab		Intermediate	Phase 2: NCT04988945[t]
Nivolumab + BMS986218 (Anti-CTLA4 mAb)*		Advanced	Phase 2: NCT04785287
Nivolumab/Pembrolizumab		Advanced	Phase 2: NCT04193696
Pembrolizumab		Advanced	Phase 2: NCT03316872[s], NCT05286320[s]
Sintilimab*		Advanced	Phase 2: NCT04547452
Durvalumab + Tremelimumab	Cryoablation	Advanced	Phase 2: NCT02821754[t, §s]
Tremelimumab		Advanced	Phase 2: NCT01853618[t, s]
Nivolumab + Ipilimumab		Advanced	Phase 2: NCT05302921[s]

Search terms involved ICI AND locoregional therapy (E.g. atezolizumab AND TACE) on clinicaltrials.gov site. Trials were included in the list regardless of current status, with the only exception of trials terminated due to poor accrual (Example: NCT03203304). Trials involving additional treatments (E.g. TKIs or resection) were also included. ICIs included in search were atezolizumab, durvalumab, tremelimumab, ipilimumab, nivolumab, and pembrolizumab. Bevacizumab and Ramucirumab were included in search terms despite not being ICIs due to their FDA-approval together with other ICIs. Locoregional therapies included in search were TACE, SBRT, microwave ablation (MWA), RFA, percutaneous ethanol injection (PEI), cryoablation, laser interstitial thermotherapy (LITT), and irreversible electroporation. Trials were further subdivided based on their HCC-stage based on the BCLC system; BCLC Class A = 'Early', Class B = 'Intermediate', Class C = 'Advanced' and no relevant information = 'Not Specified'. Inclusion and exclusion criteria of the trials were considered for subdivision when BCLC groups were not explicitly stated. Source: clinicaltrials.gov.

*ICIs not currently FDA-approved included in trial.

[†]Trials involving multiple locoregional therapies in intervention arm that may appear under multiple categories.

[§]Trials involving a HCC stage and those above it. For example, NCT05185505s classified under intermediate indicates the trial involves patients BCLC class B or higher.

Table 4. Summary of all trials involving FDA-approved ICIs and TKIs in treating HCC as of August 2022.

ICI	TKI	BCLC Staging	Phase: Trial Number
PD-1/PD-L1 inhibitors (atezolizumab, sintilimab*, pembrolizumab, nivolumab, camrelizumab*, tislelizumab*, toripalimab*, durvalumab, penpulimab*) ± Bevacizumab	Anti-VEGF TKIs(sorafenib, lenvatinib, donafenib, apatinib, anlotinib)	Intermediate	Observational: NCT05332496, NCT04627012
		Advanced	Observational: NCT05332821, NCT04639284
		Not Specified	Observational: NCT05278195
	Lenvatinib	Intermediate	Observational: NCT05339581[s], NCT04627012
		Advanced	Observational: NCT04627012
Atezolizumab	Lenvatinib, Sorafenib	Advanced	Phase 3: NCT04770896
	Cabozantinib	Intermediate	Phase 3: NCT03755791
		Advanced	Phase 3: NCT03755791
			Phase 2: NCT05327738
			Phase 1: NCT03170960
		Not Specified	Phase 1: NCT05092373[†]
	Cabozantinib/Lenvatinib	Advanced	Phase 2: NCT05168163
Atezolizumab + Bevacizumab	Sorafenib	Advanced	Phase 3: NCT03434379[†]
		Not Specified	Phase 2: NCT05468359
HX008 (Anti-PD-1 mAb) + Bevacizumab	Lenvatinib	Advanced	Phase 2: NCT04741165[†]
Bevacizumab + Toripalimab*	Sorafenib	Advanced	Phase 3: NCT04723004[†]
	Lenvatinib	Advanced	Phase 2: NCT04605796
Durvalumab	Sorafenib/Lenvarinib, Regorafenib/Cabozantinib	Intermediate Advanced	Phase 2: NCT03899428[†]
	Lenvatinib	Intermediate	Phase 2: NCT05312216
		Advanced	Phase 2: NCT04961918, NCT05312216
			NA: NCT04443322
Durvalumab ± Tremelimumab	Cabozantinib	Advanced	Phase 3: NCT03298451[†]
			Phase 2: NCT03539822
	Lenvatinib	Intermediate	Phase 3: NCT05301842
Nivolumab	Cabozantinib	Advanced	Phase 2: NCT05039736, NCT01658878
			Phase 1: NCT03299946
		Not Specified	Phase 1: NCT04514484
	Lenvatinib	Intermediate	Phase 1: NCT03418922
		Advanced	Phase 2: NCT03841201
			Phase 1: NCT03418922
	Regorafenib	Not Specified	Phase 2: NCT04170556
	Sorafenib	Advanced	Phase 3: NCT02576509[†]
			Phase 2: NCT03439891
Nivolumab + Ipilimumab	Sorafenib/Lenvatinib	Advanced	Phase 3: NCT04039607[†]
	Cabozantinib	Advanced	Phase 2: NCT01658878, NCT04472767[s]
Pembrolizumab	Lenvatinib	Early	NA: NCT04425226, NCT05389527
		Intermediate	Phase 3: NCT04246177
			Phase 2: NCT05185739
			Phase 1: NCT03006926
		Advanced	Phase 3: NCT03713593
			Phase 2: NCT04740307, NCT05101629,
			Phase 1: NCT03006926
		Not Specified	Phase 2: NCT05286320, NCT03781934
	Q702 (Axl/Mer/CSF1R triple kinase)	Advanced	Phase 2: NCT05438420
	Regorafenib	Intermediate Advanced	Phase 2: NCT05048017
	Sorafenib	Advanced	Phase 2: NCT02702414[†], NCT03211416
Pembrolizumab + Vibostolimab*	Lenvatinib	Advanced	Phase 2: NCT05007106
Pembrolizumab + Quavonlimab*	Lenvatinib	Advanced	Phase 2: NCT04740307
Ramucirumab	Sorafenib	Not Specified	Phase 2: NCT01246986[†]
Tislelizumab*	Sorafenib	Advanced	Phase 3: NCT03412773[†]
			Phase 2: NCT04599777, NCT04992143
	Lenvatinib	Early	Phase 2: NCT04615143
		Intermediate	Phase 2: NCT04834986, NCT04401800
		Advanced	Phase 2: NCT05057845, NCT04401800, NCT05532319
			Phase 1: NCT05533892, NCT05131698
Tislelizumab*/Sintilimab*	Lenvatinib	Intermediate	Phase 2: NCT05519410[s]
			Observational: NCT05277675

(*Continued*)

Table 4. (Continued).

ICI	TKI	BCLC Staging	Phase: Trial Number
Toripalimab*	Sorafenib	Advanced	Phase 3: NCT04709380[†] Phase 2: NCT04926532, NCT04069949
		Not Specified	Phase 2: NCT04135690[†]
	Lenvatinib	Early	Phase 2: NCT03867370
		Intermediate	Phase 3: NCT05056337 NA: NCT05162898
		Advanced	Phase 3: NCT05056337, NCT04523493 Phase 2: NCT04368078, NCT03919383, NCT04044313, NCT04170179
	Anlotinib	Intermediate Advanced	Phase 2: NCT05453383
Toripalimab* + Sintilimab*	Lenvatinib	Advanced	NA: NCT04618367
Camrelizumab (SHR-1210)*	Sorafenib/Apatinib	Advanced	Phase 3: NCT03764293
	Apatanib	Advanced	Phase 2: NCT04479527
	Lenvatinib	Intermediate	Phase 3: NCT04909866 Phase 2: NCT05042336
		Advanced	Phase 3: NCT04909866 Phase 2: NCT05003700, NCT05166239 Phase 1: NCT04443309
	Lenvatinib/Regorafenib	Intermediate Advanced	Phase 2: NCT05135364
Sintilimab*	Lenvatinib	Intermediate[§]	Phase 2: NCT05519410[s], NCT05250843, NCT04618367[s]
		Advanced	Phase 2: NCT04042805, NCT04599790, NCT04814043[s] Phase 1: NCT05225116
Sintilimab + IBI305 (bevacizumab biosimilar)	Sorafenib	Advanced	Phase 3: NCT03794440[†], NCT04720716[†]

Search terms involved ICI AND "TKI" OR "tyrosine kinase inhibitor" on the clinicaltrials.gov site. Trials were included regardless of current status, with the exception of terminated trials. Trials involving additional treatments (E.g. locoregional therapies) were also included. HCC staging was based on the BCLC grading system; BCLC Class A = 'Early', Class B = 'Intermediate', Class C = 'Advanced', and no relevant information = 'Not Specified'. ICIs included in search were atezolizumab, durvalumab, tremelimumab, ipilimumab, nivolumab, and pembrolizumab. Bevacizumab and ramucirumab were included despite not being ICIs due to their FDA-approval with other ICIs. TKIs included in search were sorafenib, lenvatinib, and cabozantinib. Source: clinicaltrials.gov.

*ICIs not currently FDA-approved included in trial.

[†]Comparative study (i.e. ICI versus TKI in treating HCC).

[§]Trials involving a HCC stage and those above it. For example, NCT05185505s classified under intermediate indicates the trial involves patients BCLC class B or higher.

Unlike ICIs, Bi-specific Antibodies (BsAbs) simultaneously recognize 2 separate targets, thereby concurrently blocking 2 different tumorigenic pathways (tumor proliferation and immune evasion)[49]. Given their novel nature, aspects including their efficacy, safety, and eventual clinical utility of BsAbs remain unknown. Currently, there are no BsAbs formally approved by the FDA for use in HCC. Despite that, many BsAbs see both preclinical and clinical developments in treating various cancers including HCC[50]. Another treatment modality that has seen growing attention recently is the CAR-T. Utilizing synthetic proteins encoded within an extracellular antigen recognition domain and an intracellular immune activation domain, CAR-T therapy targets cancers by stimulating the host's adaptive immune system to recognize and eliminate malignancies[51] Currently, CAR-Ts have seen niche use in a variety of hematologic cancers such as ALL. Recently, more focus has been placed on the efficacy of CAR-Ts on solid tumors such as HCC with varying success[52]. Ongoing trials evaluating the use of such novel immunotherapies are shown in Table 6.

Clinically relevant biomarkers for immunotherapy in HCC

Despite recent advances, prediction of response to immunotherapy to guided clinical decision-making remains a challenge. While histological surrogates such as immune cell infiltrate may predict response, more robust, objective, and simple tests for treatment response/failure would significantly revolutionize patient care. Circulating tumor DNA (ctDNA) is a target of interest due to its established effectiveness in determining the response and recurrence in other malignancies[53]. After sequencing the tumor and establishing a molecular profile, CtDNA tests detect the circulation of tumor-specific DNA in the extracellular space[54]. The presence and concentration is assayed to monitor treatment and disease progression. CtDNA has already showed promising results in early clinical development in conjunction with immunotherapies. In a phase I trial (ClinicaTrials.gov Identifier: NCT02715531), 47 patients treated with atezolizumab and bevacizumab were assayed for ctDNA before, during and after treatment. Of that, ctDNA was identified in 45 out of 47 patients (96%) with a higher concentration being associated with higher tumor burden. Additionally, undetectable levels of ctDNA post-treatment were also correlated to a longer progression-free survival ($p = 0.00029$)[55]. Unfortunately, ctDNA testing is currently limited by the lack of standardization in its use. The large number of methods available for detection require high technical skills by the clinician to decide the optimal method for testing[56] and there is currently no

Table 5. Trials involving the first-line use of ICIs in advanced or metastatic HCC.

NCT no. (Trial Name)	ICI	Phase	Endpoints
NCT05448677 (ABE-LIVER)	Atezolizumab	2	PFS, ORR
NCT05134532		2	PFS, OS, TTP, ORR, DCR, SP
NCT05359861		2	PFS, ORR, TTP, DCR, OS, SP
NCT05546879 (LIVER-NET1)		1	AE, ORR
NCT05109052		1	AE
NCT02576509	Nivolumab	3	OS, ORR, PFS
NCT03071094		2	AE, ORR
NCT03841201		2	ORR, AE, TTP, PFS, OS
NCT04310709 (RENOBATE)		2	ORR, AE, PFS, OS
NCT03439891		2	Dosage, ORR, AE, DOR, PFS, OS,
NCT05337137 (RELATIVITY-106)		2	Dose-limiting Toxicities, PFS, ORR, OS, AE
NCT04039607 (CHECKMATE-9DW)	Nivolumab + Ipilimumab	3	OS, ORR, DOR, TTF
NCT05557838 (TREMENDOUS)	Tremelimumab + Durvalumab	3	AE, OS, PFS, ORR, DCR
NCT03298451 (HIMALAYA)		3	OS, TTP, PFS, ORR, DCR, DOR, AE
NCT05345678 (HIMALAYA Early Access)		NA	
NCT05312216	Durvalumab	2	ORR, DCR, DOR, PFS, OS, AE
NCT03713593 (MK-7902-002/E7080-G000-311/LEAP-002)	Pembrolizumab	3	PFS, OS, ORR, DOR, DCR, AE, TTP
NCT04740307 (MK-1308A-004)		2	DLT, AE, ORR, DOR, DCR, PFS, TTP, OS
NCT03519997		2	ORR, OS, AE
NCT03347292		1	AE, DLT, PFS, TTP, OS, ORR, DCR, DOR, dosage
NCT04720716	Sintilimab	3	OS, PFS, DOR, DCR, TTP, TTR, AE
NCT03794440		2	OS, PFS, ORR, DCR, DOR, TTP, TTR
NCT04411706		2	ORR, DCR, DOR, OS, PFS, AE
NCT04954794(TASK-02)		2	ORR, DOR, PFS, OS, DCR, AE
NCT05617430		2	PFS, AE, ORR, DCR, DOR, OS
NCT05029973		2	ORR, OS, Event Free Survival, AE
NCT04297280		2	ORR, DOR, PFS, OS, DCR, AE
NCT04547452		2	PFS, ORR, OS, DCR, DOR, AE
NCT05363722		1	ORR, DOR, DCR, TTP, PFS, OS
NCT03605706	Camerelizumab	3	OS, ORR, TTP, DCR, DOR, PFS, AE
NCT05171309		2	ORR, DCR, PFS, OS, AE
NCT04443309		1	ORR, DCR, PFS, OS, DOR, AE
NCT03412773	Tislelizumab	3	OS, AE, DLT, ORR, PFS, DOR, TTP, DCR
NCT04183088		2	AE, ORR, PFS
NCT04652492		2	TTP, PFS, ORR, DCR, DOR, OS
NCT04948697		2	ORR, DOR, TTR, DCR, PFS, AE

Abbreviations: **ORR**: Overall Response Rate; **PFS**: Progression-Free Survival; **OS**: Overall Survival; **AE**: Adverse Effect; **DCR**: Disease Control Rate; **DOR**: Duration of Response; **DLT**: Dose-Limiting Toxicity; **TTP**: Time-to-Progression; **TTF**: Time-to-Failure; **TTR**: Time-to-Response; **SP**: Safety Profile.
Search terms involved ICI AND first line on the clinicaltrials.gov site. Trials were included regardless of status with the exception of those terminated due to poor accrual. Trials involving additional treatments (E.g. TKIs) were also included. Source: clinicaltrials.gov.

framework to guide such tests for HCC. As such, while ctDNA testing may see use in the future, more developments are required to optimize its application.

Several studies have identified distinct immune subclasses of HCC through tumor immune genotyping. A study by Sia et al. identified a profile of immune signals associated ($p < 0.001$) with an active immune response against HCC, including significant enrichment of T-cell and interferon (IFN) signature. This active immunity subtype included overexpression of genes coding for an immune response (E.g. CD8A and IFN-*Y*) and IFN predictors of pembrolizumab response. Conversely, they also identified a profile of immune signals associated with immune exhaustion and immune evasion including overexpression of TGF-ß-1 and 3 ($p = 0.001$)[57]. Since then, additional genes associated with tumor behavior and immune regulation have been identified[58–60] with an increasing focus being placed on the therapeutic implications of HCC profiling. A review on the predictive implications of molecular profiling by Rizzo et al. highlighted the nuance involved in tumor genotyping[61]. For example, the CHECKMATE-459 trial[62] concluded with intra-tumoral PD-L1 expression being associated with an improved response to nivolumab (Overall response rate of 28% in PD-L1 ≥1% and 12% in PD-L1 <1%), while the CHECKMATE-040 trial contradicted that by observing no significant difference in nivolumab response between PD-L1 positive and negative HCCs (ORR of about 30% in PD-L1 ≥1% and 31% in PD-L1 <1%)[30]. This emphasizes the need for more research on the utility of genes identified through tumor genotyping.

PD-1 and PD-L1 expression in tumor-infiltrating $CD8^+$ T-cells has seen development as a prognostic biomarker and a predictor of anti-PD1/PD-L1 treatment response. In a study by Kim et al., high expression of PD-1 in HCC was associated with increased expression of other immune checkpoint receptors (such as LAG3 and TIM3) and down-regulation of CD8+ T-cell related transcription factors (TCF1, TBET, and esmodermin), suggesting increased PD-1 expression correlating with T-cell exhaustion[63]. Additionally, higher PD-1 expression was also associated with a more aggressive HCC, indicated by larger tumor burden, serum AFP, and greater correlation with microvascular invasion. Interestingly, the PD-1 expression was found to be independent of Wnt/β-catenin pathway activation (β-catenin accumulation in only 17% of the cases) and early recurrence of HCC (HR 1.25, 95% CI: 0.36 to 4.29 $p = 0.72$)[64].

Current challenges and future direction

The landscape and the role of ICIs in managing HCC are ever evolving. Despite recent advances, challenges remain,

Table 6. Summary of all trials involving bispecific antibodies and CAR-T therapies in treating HCC as of August 2022.

Immunotherapy	Trial Number
PD-1 + CTLA4	Phase 2: NCT04728321 Phase 1: NCT04444167, NCT03517488, NCT05293496
PD-1 + VEGF	Phase 2: NCT05432492
PD-1 + Inducible Co-stimulator (ICOS)	Phase 1: NCT03752398
PDL-1 + CTLA4	Phase 2: NCT04542837
CTLA4 + LAG3	Phase 1: NCT03849469
Glypican-3 (GPC-3)	Phase 1: NCT03084380, NCT02905188, NCT04121273, NCT05003895, NCT03884751, NCT05155189, NCT05103631, NCT05070156, NCT03980288, NCT02395250, NCT04951141, NCT05344664, NCT02905188, NCT03198546 NA: NCT03146234, NCT03302403
CD147	Phase 1: NCT03993743
B7H3 (CD276)	Phase 1: NCT05323201
OX40 (CD134)	Phase 1: NCT04952272
c-Met	Phase 1: NCT03672305
Natural Killer Group 2-D (NKG2D)	Phase 1: NCT05131763, NCT04550663
Epithelial Cell-Adhesion Molecule (EPCAM)	Phase 1: NCT05028933
Epidermal Growth Factor Receptor (*EGFR*) VIII	Phase 2: NCT03941626
Death Receptor 5 (DR-5)/c-Met/*EGFR* VIII	Phase 2: NCT03638206

Search terms were "bispecific OR bi-specific OR BsAB", "CART OR CAR-T" and "Hepatocellular Carcinoma" on the clinicaltrials.gov site. Trials were included regardless of current status, with the exception of trials suspended due to poor accrual. Trials were classified by immune target regardless of drug name (E.g. lorigerlimab and AK104 were both classified under PD-1 +CTLA4). Source: clinicaltrials.gov.

especially with regard to standardization in the classification of HCC, both within clinical trials and in clinical practice. The most widely used method for classifying HCC is the Barcelona Clinic Liver Cancer (BCLC) score, which is based on the number and size of tumors, and the impact of the disease on the patient's quality of life. The most recent iteration removes the classification of patients using the Childs – Pugh score, and instead dichotomizes patients into preserved or non-preserved liver function. Despite this, historically many trials of systemic therapy have excluded patients with poor liver function (the IMBrave150, for example, included only patients who were Childs A). As a significant proportion of patients with advanced HCC often have poor liver function, the treatment of such patients has been controversial and treatment options are significantly limited. As an example, in the GIDEON study evaluating the use of Sorafenib in a real-world setting, only 61% of patients in the registry were Childs-Pugh A[65]. Therefore, the examination of real-world data on the safety and clinical outcomes of systemic therapy in HCC patients with poor liver function is crucial to inform the appropriate utilization of these treatments in this patient population[66]. Recent studies, such as the CHECKMATE 040 Cohort 5 trial, have demonstrated the benefits of ICIs in this population through a higher mOS to sorafenib (7.6 months vs 2.5–5.4 months)[67]. However, further research is needed to establish the safety and efficacy of ICIs in these patients.

The utility of ICIs in advanced HCC with tumor thrombus also remains uncertain. HCC often extends into the portal vein branches and forms portal vein tumor thrombus (PVTT), which is associated with a poor prognosis. The use of ICIs as an adjuvant or neoadjuvant treatment, or as a first-line treatment, remains unclear. Preliminary data suggest that ICIs may have a role in combination with locoregional therapies in improving progression-free survival and overall survival in patients with HCC and PVTT[68]. In a retrospective analysis of 90 patients with HCC and type I/II PVTT, adjuvant TACE, and ICI compared to TACE alone exhibited longer median RFS (12.76 months vs 8.11 months respectively) and OS (24.5 months vs 19.1 months). However, larger randomized trials will be required to expand on these findings.

Finally, the increasing use of ICIs has bridged an increasing number of patients with locally advanced HCC toward an ever-expanding criterion for liver transplantation. Theoretical concerns of acute immune mediated rejection in patients receiving liver transplantation after ICI use have been tampered with in recent series showing safety in this regard. The current evidence remains sparse, with a recent series compiling 20 patients across 6 single-center series[69–75]. Despite only 2 of 18 patients reporting mild rejection that was successfully treated with adjustment of immunosuppression regimens, there were 2 cases of fatal hepatic necrosis following liver transplantation, with progressive liver failure despite the absence of obvious vascular complications[70,72]. On the further evaluation of ICIs in this setting, while most ICIs have half-lives of 12–27 days, their effects on T-cells can persist for significantly longer and hence appropriate wash-out periods need to be studied[76]. Hence, whilst data regarding the role of ICIs in liver transplantation for HCC is eagerly awaited, small case series have emerged from several centers documenting their experience in utilizing ICIs in small numbers of pre-transplantation LT candidates.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Author contributions

All authors approve the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethical Statement

The study was conducted in accordance with the Declaration of Helsinki. The study was exempt from IRB review because no confidential patient information was involved.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: gLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–249. doi:10.3322/caac.21660.
2. Balogh J, Victor D, Asham EH, Burroughs SG, Boktour M, Saharia A, Li X, Ghobrial M, Monsour H. Hepatocellular carcinoma: a review. J Hepatocell Carcinoma. 2016;3:41–53. doi:10.2147/JHC.S61146.
3. Vogel A, Meyer T, Sapisochin G, Salem R, Saborowski A. *Hepatocellular carcinoma*. the Lancet. Lancet. 2022;400 (10360):1345–1362. doi:10.1016/S0140-6736(22)01200-4.
4. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, Kelley RK, Galle PR, Mazzaferro V, Salem R, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol. 2022;76(3):681–693. doi:10.1016/j.jhep.2021.11.018.
5. Farkas S, Hackl C, Schlitt HJ. Overview of the indications and contraindications for liver transplantation. Cold Spring Harb Perspect Med. 2014;4(5):4(5. doi:10.1101/cshperspect.a015602.
6. Koh JH, Tan DJH, Ong Y, Lim WH, Ng CH, Tay PWL, Huang DQ. Liver resection versus liver transplantation for hepatocellular carcinoma within Milan criteria: a meta-analysis of 18,421 patients. Hepatobiliary Surg Nutr. 2021;11(1): 78–93. doi:10.21037/hbsn-21-350.
7. Reveron-Thornton RF, Teng ML, Lee EY, Tran A, Vajanaphanich S, Tan EX, Huang DQ. Global and regional long-term survival following resection for HCC in the recent decade: a meta-analysis of 110 studies. Hepatol Commun. 2022;6(7):1813–1826. doi:10.1002/hep4.1923.
8. Tan DJH, Lim WH, Yong JN, Ng CH, Muthiah MD, Tan EX, Huang DQ. UNOS Down-Staging Criteria for Liver Transplantation of Hepatocellular Carcinoma: systematic Review and Meta-Analysis of 25 Studies Clin Gastroenterol Hepatol. 2022;21(6): 1475–1484. doi:10.1016/j.cgh.2022.02.018.
9. Forner A, Reig ME, Rodriguez de Lope C, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis. 2010;30(1):61–74. doi:10.1055/s-0030-1247133.
10. Sangro B, Sarobe P, Hervás-Stubbs S, Melero I. Advances in immunotherapy for hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol. 2021;18(8):525–543. doi:10.1038/s41575-021-00438-0.
11. Tan DJH, Ng CH, Lin SY, Pan XH, Tay P, Lim WH, Teng M, Syn N, Lim G, Yong JN, et al. Clinical characteristics, surveillance, treatment allocation, and outcomes of non-alcoholic fatty liver disease-related hepatocellular carcinoma: a systematic review and meta-analysis. Lancet Oncol. 2022;23(4):521–530. doi:10.1016/S1470-2045(22)00078-X.
12. Tu T, Budzinska M, Maczurek A, Cheng R, Di Bartolomeo A, Warner F, McCaughan G, McLennan S, Shackel N. Novel aspects of the liver microenvironment in hepatocellular carcinoma pathogenesis and development. Int J Mol Sci. 2014;15(6):9422–9458. doi:10.3390/ijms15069422.
13. Pinzani M, Marra F. Cytokine receptors and signaling in hepatic stellate cells. Semin Liver Dis. 2001;21(03):397–416. doi:10.1055/s-2001-17554.
14. Zheng M, Tian Z. Liver-mediated adaptive immune tolerance. Front Immunol. 2019;10:10. doi:10.3389/fimmu.2019.02525.
15. Li F, Li C, Cai X, Xie Z, Zhou L, Cheng B, Liang W. The association between CD8+ tumor-infiltrating lymphocytes and the clinical outcome of cancer immunotherapy: A systematic review and meta-analysis. eClinicalMedicine, 2021. 41.
16. Yau T, Zagonel V, Santoro A, Acosta-Rivera M, Choo SP, Matilla A, He AR, Cubillo Gracian A, El-Khoueiry AB, Sangro B, et al. Nivolumab plus cabozantinib with or without ipilimumab for advanced hepatocellular carcinoma: results from Cohort 6 of the CheckMate 040 Trial. J Clin Oncol. 2023;41(9):1747–1757. doi:10.1200/JCO.22.00972.
17. El-Khoueiry AB, Yau T, Kang Y-K, Kim T-Y, Santoro A, Sangro B, Melero I, Kudo M, Hou M-M, Matilla A, et al. Nivolumab (NIVO) plus ipilimumab (IPI) combination therapy in patients (Pts) with advanced hepatocellular carcinoma (aHCC): long-term results from CheckMate 040. J Clin Oncol. 2021;39(3_suppl):269. doi:10.1200/JCO.2021.39.3_suppl.269.
18. Pathak S, Sonbol MB. Second-line treatment options for hepatocellular carcinoma: current landscape and future direction. J Hepatocell Carcinoma. 2021;8:1147–1158. doi:10.2147/JHC.S268314.
19. Leighl NB, Bennouna J, Yi J, Moore N, Hambleton J, Hurwitz H. Bleeding events in bevacizumab-treated cancer patients who received full-dose anticoagulation and remained on study. Br J Cancer. 2011;104(3):413–418. doi:10.1038/sj.bjc.6606074.
20. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T-Y, Kudo M, Breder V, Merle P, Kaseb AO, et al. Atezolizumab plus Bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020;382(20):1894–1905. doi:10.1056/NEJMoa1915745.
21. Cheng A-L, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T-Y, Lim HY, Kudo M, Breder V, Merle P, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol. 2022;76(4):862–873. doi:10.1016/j.jhep.2021.11.030.
22. Kelley RK, Sangro B, Harris W, Ikeda M, Okusaka T, Kang Y-K, Qin S, Tai DWM, Lim HY, Yau T, et al. Safety, efficacy, and pharmacodynamics of tremelimumab plus durvalumab for patients with unresectable hepatocellular carcinoma: randomized

Expansion of a Phase I/II Study. J Clin Oncol. 2021;39 (27):2991–3001. doi:10.1200/JCO.20.03555.
23. Bang Y-J, Golan T, Dahan L, Fu S, Moreno V, Park K, Geva R, De Braud F, Wainberg ZA, Reck M, et al. Ramucirumab and durvalumab for previously treated, advanced non–small-cell lung cancer, gastric/gastro-oesophageal junction adenocarcinoma, or hepatocellular carcinoma: an open-label, phase Ia/b study (JVDJ). Eur J Cancer. 2020;137:272–284. doi:10.1016/j.ejca.2020.06.007.
24. Okusaka T, Ikeda M. Immunotherapy for hepatocellular carcinoma: current status and future perspectives. ESMO Open. 2018;3:e000455. doi:10.1136/esmoopen-2018-000455.
25. Abou-Alfa GK, Lau G, Kudo M, Chan SL, Kelley RK, Furuse J, Sukeepaisarnjaroen W, Kang Y-K, Van Dao T, De Toni EN, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. NEJM Evidence. 2022;1(8):EVIDoa 2100070. 10.1056/EVIDoa2100070.
26. Administration UFAD. *FDA grants accelerated approval to pembrolizumab for hepatocellular carcinoma*. 2018 [accessed 2022 Mar 8]. https://www.fda.gov/drugs/fda-grants-accelerated-approval-pembrolizumab-hepatocellular-carcinoma.
27. Administration UFAD. *FDA approves ramucirumab for hepatocellular carcinoma*. 2019 [accessed 2022]. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ramucirumab-hepatocellular-carcinoma.
28. Zhu AX, Kang Y-K, Yen C-J, Finn RS, Galle PR, Llovet JM, Assenat E, Brandi G, Pracht M, Lim HY, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019;20(2):282–296. doi:10.1016/S1470-2045(18)30937-9.
29. Saung MT, Pelosof L, Casak S, Donoghue M, Lemery S, Yuan M, Rodriguez L, Schotland P, Chuk M, Davis G, et al. FDA approval summary: nivolumab plus ipilimumab for the treatment of patients with hepatocellular carcinoma previously treated with sorafenib. Oncologist. 2021;26(9):797–806. doi:10.1002/onco.13819
30. Yau T, Kang Y-K, Kim T-Y, El-Khoueiry AB, Santoro A, Sangro B, Melero I, Kudo M, Hou M-M, Matilla A, et al. Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib: the checkmate 040 randomized clinical trial. JAMA Oncology JAMA Oncol. 2020;6(11):e204564. 10.1001/jamaoncol.2020.4564.
31. Finn RS, Ikeda M, Zhu AX, Sung MW, Baron AD, Kudo M, Okusaka T, Kobayashi M, Kumada H, Kaneko S, et al. Phase Ib study of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma. J Clin Oncol. 2020;38 (26):2960–2970. doi:10.1200/JCO.20.00808.
32. Finn R, Kudo M, Merle P, Meyer T, Qin S, Ikeda M, Xu R, Edeline J, Ryoo B-Y, Ren Z, et al. *LBA34 - Primary results from the phase III LEAP-002 study: lenvatinib plus pembrolizumab versus lenvatinib as first-line (1L) therapy for advanced hepatocellular carcinoma (aHCC)*. Ann Oncol. 2022;33(suppl_7):S808–869. doi:10.1016/annonc/annonc1089,2022.
33. Pompili M, Francica G, Ponziani FR, Iezzi R, & Avolio AW. Bridging and downstaging treatments for hepatocellular carcinoma in patients on the waiting list for liver transplantation. World J Gastroenterol. 2013;19(43):7515–7530. doi:10.3748/wjg.v19.i43.7515.
34. Coletta M, Nicolini D, Cacciaguerra AB, Mazzocato S, Rossi R. Bridging patients with hepatocellular cancer waiting for liver transplant: all the patients are the same? Transl Gastroenterol Hepatol. 2017;2:78. doi:10.21037/2Ftgh.2017.09.01.
35. Ho WJ, Zhu Q, Durham J, Popovic A, Xavier S, Leatherman J, Mohan A, Mo G, Zhang S, Gross N, et al. Neoadjuvant cabozantinib and nivolumab converts locally advanced HCC into resectable disease with enhanced antitumor immunity. Nat Cancer. 2021;2 (9):891–903. doi:10.1038/s43018-021-00234-4.
36. Marron TU, Fiel MI, Hamon P, Fiaschi N, Kim E, Ward SC, Zhao Z, Kim J, Kennedy P, Gunasekaran G, et al. Neoadjuvant cemiplimab for resectable hepatocellular carcinoma: a single-arm, open-label, phase 2 trial. The Lancet Gastroenterol Hepatol. 2022;7 (3):219–229. doi:10.1016/S2468-1253(21)00385-X.
37. Bruix J, Takayama T, Mazzaferro V, Chau G-Y, Yang J, Kudo M, Cai J, Poon RT, Han K-H, Tak WY, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2015;16(13):1344–1354. doi:10.1016/S1470-2045(15)00198-9.
38. Kudo M. Adjuvant immunotherapy after curative treatment for hepatocellular carcinoma. Liver Cancer. 2021;10(5):399–403. doi:10.1159/000518584.
39. Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul J-L, Schirmacher P, Vilgrain V. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2018;69 (1):182–236. doi:10.1016/j.jhep.2018.03.019.
40. Lee JJX, Tai DWM, Choo SP. Locoregional therapy in hepatocellular carcinoma: when to start and when to stop and when to revisit. ESMO Open. 2021;6(3):100129.10.1016/j.esmoop.2021.100129
41. Li X, Wang Y, Ye X, Liang P. locoregional combined with systemic therapies for advanced hepatocellular carcinoma: an inevitable trend of rapid development. Frontiers In Molecular Biosciences. 2021;8:8. doi:10.3389/fmolb.2021.635243.
42. Lee Y, Auh SL, Wang Y, Burnette B, Wang Y, Meng Y, Fu YX. Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. Blood. 2009;114(3):589–595. doi:10.1182/blood-2009-02-206870.
43. Esposito A, Criscitiello C, Curigliano G. Immune checkpoint inhibitors with radiotherapy and locoregional treatment: synergism and potential clinical implications. Curr Opin Oncol. 2015;27 (6):445–451. doi:10.1097/CCO.0000000000000225.
44. Kwon ED, Drake CG, Scher HI, Fizazi K, Bossi A, van den Eertwegh AJM, Krainer M, Houede N, Santos R, Mahammedi H, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2014;15 (7):700–712. doi:10.1016/S1470-2045(14)70189-5.
45. Twyman-Saint Victor C, Rech AJ, Maity A, Rengan R, Pauken KE, Stelekati E, Benci JL, Xu B, Dada H, Odorizzi PM, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature. 2015;520(7547):373–377. doi:10.1038/nature14292.
46. Marinelli B, Kim E, D'Alessio A, Cedillo M, Sinha I, Debnath N, Kudo M, Nishida N, Saeed A, Hildebrand H, et al. Integrated use of PD-1 inhibition and transarterial chemoembolization for hepatocellular carcinoma: evaluation of safety and efficacy in a retrospective, propensity score-matched study. J ImmunoTher Cancer. 2022;10(6):e004205. doi:10.1136/jitc-2021-004205.
47. Chiang CL, Chiu KWH, Chan KSK, Lee FAS, Li JCB, Wan CWS, Dai WC, Lam TC, Chen W, Wong NSM, et al. Sequential transarterial chemoembolisation and stereotactic body radiotherapy followed by immunotherapy as conversion therapy for patients with locally advanced, unresectable hepatocellular carcinoma (START-FIT): a single-arm, phase 2 trial. The Lancet Gastroenterology & Hepatology The Lancet Gastroenterol Hepatol. 2023;8(2):169–178. 10.1016/S2468-1253(22)00339-9.
48. Zhan C, Ruohoniemi D, Shanbhogue KP, Wei J, Welling TH, Gu P, Park JS, Dagher NN, Taslakian B, Hickey RM. Safety of combined yttrium-90 radioembolization and immune checkpoint inhibitor immunotherapy for hepatocellular carcinoma. J Vasc Interv Radiol. 2020;31(1):25–34. doi:10.1016/j.jvir.2019.05.023.
49. Schmid AS, Neri D. Advances in antibody engineering for rheumatic diseases. Nat Rev Rheumatol. 2019;15(4):197–207. doi:10.1038/s41584-019-0188-8.
50. Wang S, Chen K, Lei Q, Ma P, Yuan AQ, Zhao Y, Jiang Y, Fang H, Xing S, Fang Y, et al. The state of the art of bispecific antibodies for treating human malignancies. EMBO Mol Med. 2021;13(9):e14291. doi:10.15252/emmm.202114291.

51. Lindner SE, Johnson SM, Brown CE, Wang LD. Chimeric antigen receptor signaling: functional consequences and design implications. Sci Adv. 2020;6(21). eaaz3223. doi:10.1126/sciadv.aaz3223.
52. Hou AJ, Chen LC, Chen YY. Navigating CAR-T cells through the solid-tumour microenvironment. Nat Rev Drug Discov. 2021;20(7):531–550. doi:10.1038/s41573-021-00189-2.
53. Armstrong S, Prins P, He AR. Immunotherapy and immunotherapy biomarkers for hepatocellular carcinoma. Hepatoma Research. 2021;7:18. doi:10.20517/2394-5079.2020.118.
54. Pessoa LS, Heringer M, Ferrer VP. ctDNA as a cancer biomarker: a broad overview. Crit Rev Oncol Hematol. 2020;155:103109. doi:10.1016/j.critrevonc.2020.103109.
55. Hsu C-H, Lu S, Abbas A, Guan Y, Zhu AX, Aleshin A, Lee K-H, Lee MS, Mahipal A, Ryoo B-Y, et al. Longitudinal and personalized detection of circulating tumor DNA (ctDNA) for monitoring efficacy of atezolizumab plus bevacizumab in patients with unresectable hepatocellular carcinoma (HCC). J Clin Oncol. 2020;38(15_suppl):3531. doi:10.1200/JCO.2020.38.15_suppl.3531.
56. Tang J-C, Feng Y-L, Guo T, Xie A-Y, Cai X-J. Circulating tumor DNA in hepatocellular carcinoma: trends and challenges. Cell & Bioscience. 2016;6(1):32. doi:10.1186/s13578-016-0100-z.
57. Sia D, Jiao Y, Martinez-Quetglas I, Kuchuk O, Villacorta-Martin C, Castro de Moura M, Putra J, Camprecios G, Bassaganyas L, Akers N, et al. Identification of an immune-specific class of hepatocellular carcinoma, based on molecular features. Gastroenterology. 2017;153(3):812–826. doi:10.1053/j.gastro.2017.06.007.
58. Cai Q, Zhu M, Duan J, Wang H, Chen J, Xiao Y, Wang Y, Wang J, Yu X, Yang H. Comprehensive analysis of immune-related prognosis of TK1 in hepatocellular carcinoma. Front Oncol. 2022;11:11. doi:10.3389/fonc.2021.786873.
59. Yu Z, Zhang Y, Shao S, Liu Q, Li Y, Du X, Zhang K, Zhang M, Yuan H, Yuan Q, et al. Identification of CDCA2 as a diagnostic and prognostic marker for hepatocellular carcinoma. Front Oncol. 2021;11:11. doi:10.3389/fonc.2021.755814.
60. Liu S, Zhao W, Li X, Zhang L, Gao Y, Peng Q, Du C, Jiang N. AGTRAP is a Prognostic Biomarker Correlated with Immune Infiltration in Hepatocellular Carcinoma. Front Oncol. 2021;11:11. doi:10.3389/fonc.2021.713017.
61. Rizzo A, Ricci AD, Di Federico A, Frega G, Palloni A, Tavolari S, Brandi G. Predictive biomarkers for checkpoint inhibitor-based immunotherapy in hepatocellular carcinoma: where do we stand? Front Oncol. 2021;11:11. doi:10.3389/fonc.2021.803133.
62. Yau T, Park J-W, Finn RS, Cheng A-L, Mathurin P, Edeline J, Kudo M, Harding JJ, Merle P, Rosmorduc O, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol. 2022;23(1):77–90. doi:10.1016/S1470-2045(21)00604-5.
63. Kim H-D, Song G-W, Park S, Jung MK, Kim MH, Kang HJ, Yoo C, Yi K, Kim KH, Eo S, et al. Association between expression level of PD1 by tumor-infiltrating CD8$^+$ T cells and features of hepatocellular carcinoma. Gastroenterology. 2018;155(6):1936–1950.e17. doi:10.1053/j.gastro.2018.08.030.
64. Calderaro J, Rousseau B, Amaddeo G, Mercey M, Charpy C, Costentin C, Luciani A, Zafrani E-S, Laurent A, Azoulay D, et al. Programmed death ligand 1 expression in hepatocellular carcinoma: relationship with clinical and pathological features. Hepatology. 2016;64(6):2038–2046. doi:10.1002/hep.28710.
65. Marrero JA, Kudo M, Venook AP, Ye S-L, Bronowicki J-P, Chen X-P, Dagher L, Furuse J, Geschwind JFH, de Guevara LL, et al. Observational registry of sorafenib use in clinical practice across child-Pugh subgroups: the GIDEON study. J Hepatol. 2016;65(6):1140–1147. doi:10.1016/j.jhep.2016.07.020.
66. Choi WM, Lee D, Shim JH, Kim KM, Lim Y-S, Lee HC, Yoo C, Park SR, Ryu M-H, Ryoo B-Y, et al. Effectiveness and safety of nivolumab in child–Pugh b patients with hepatocellular carcinoma: a real-world cohort study. Cancers (Basel). 2020;12(7):1968. doi:10.3390/cancers12071968.
67. Kudo M, Matilla A, Santoro A, Melero I, Gracián AC, Acosta-Rivera M, Choo S-P, El-Khoueiry AB, Kuromatsu R, El-Rayes B, et al. CheckMate 040 cohort 5: a phase I/II study of nivolumab in patients with advanced hepatocellular carcinoma and Child-Pugh B cirrhosis. J Hepatol. 2021;75(3):600–609. doi:10.1016/j.jhep.2021.04.047.
68. Yuan L, Feng J, Zhang Y, Lu C, Xu L, Liang C, Liu Z, Mao F, Xiang Y, Wang W, et al. Transarterial chemoembolization plus immune checkpoint inhibitor as postoperative adjuvant therapy for hepatocellular carcinoma with portal vein tumor thrombus: a multicenter cohort study. Eur J Surg Oncol. 2023. doi:10.1016/j.ejso.2023.01.020.
69. Gao Q, Anwar IJ, Abraham N, Barbas AS. Liver transplantation for hepatocellular carcinoma after downstaging or bridging therapy with immune checkpoint inhibitors. Cancers (Basel). 2021;13(24):6307. doi:10.3390/cancers13246307.
70. 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(3):879–883. doi:10.1111/ajt.15617.
71. Schwacha-Eipper B, Minciuna I, Banz V, Dufour JF. Immunotherapy as a Downstaging Therapy for Liver Transplantation. Hepatology. 2020;72(4):1488–1490. doi:10.1002/hep.31234.
72. Chen GH, Wang GB, Huang F, Qin R, Yu XJ, Wu RL, 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. doi:10.1016/j.trim.2021.101386.
73. Qiao ZY, Zhang Z-J, Lv Z-C, Tong H, Xi Z-F, Wu H-X, Chen X-S, Xia L, Feng H, Zhang J-J, et al. Neoadjuvant programmed cell death 1 (PD-1) inhibitor treatment in patients with hepatocellular carcinoma before liver transplant: a cohort study and literature review. Front Immunol. 2021;12:653437. doi:10.3389/fimmu.2021.653437.
74. Sogbe M, López-Guerra D, Blanco-Fernández G, Sangro B, Narváez-Rodriguez I. Durvalumab as a successful downstaging therapy for liver transplantation in hepatocellular carcinoma: the importance of a washout period. Transplantation. 2021;105(12):e398–400.10.1097/TP.0000000000003855
75. Tabrizian P, Florman SS, Schwartz ME. PD-1 inhibitor as bridge therapy to liver transplantation? Am J Transplant. 2021;21(5):1979–1980. doi:10.1111/ajt.16448.
76. Johnson DB, Nebhan CA, Moslehi JJ, Balko JM. Immune-checkpoint inhibitors: long-term implications of toxicity. Nat Rev Clin Oncol. 2022;19(4):254–267. doi:10.1038/s41571-022-00600-w.