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Hepatocellular Carcinoma Immunotherapy

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Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and the third leading cause of cancer-related death worldwide. Single-agent anti-PD-1 immune checkpoint inhibitors (ICIs) demonstrated promising efficacy in early-phase trials, a finding that was not confirmed in phase III studies. The combination of atezolizumab (an anti-PD-L1 ICI) with bevacizumab (an anti-VEGF antibody) was approved as first-line therapy in 2020, however, with significant improvement in response rate, progression-free survival, and overall survival in comparison with the previous standard of care, sorafenib. Numerous ongoing clinical trials are assessing ICIs in combination with each other or with targeted agents, and also in earlier stages with local therapies. This review summarizes the latest concepts in the use of ICIs for the management of HCC.

INTRODUCTION

Globally, hepatocellular carcinoma (HCC) was the sixth most diagnosed cancer and the third leading cause of cancer-related death in 2020, with approximately 906,000 new cases and 830,000 deaths (1). The major risk factor is cirrhosis, which may have numerous causes, including viral hepatitis, alcohol abuse, environmental toxins, and nonalcoholic fatty liver disease (2). The management of HCC is complex, as this heterogeneous disease usually affects a chronically inflamed liver and often requires a team of clinicians from different areas. Early-stage HCC can be cured with surgical resection, ablation, or liver transplantation; unfortunately, <20% of patients are diagnosed in such early phases of their disease (3). Overall survival when disease is already locally advanced or metastatic is <10% in 5 years (4). Moreover, disease recurs in up to 70% of patients following curative-intent therapy (5). HCC is a chemotherapy-refractory tumor, and no effective systemic therapies had meaningfully improved survival until recently (6, 7). Auspiciously, as knowledge of HCC biology forges ahead, new drugs have been integrated into standard treatment paradigms, from targeted therapies, including monoclonal antibodies and tyrosine kinase inhibitors (TKIs) targeting vascular endothelial growth factor (VEGF), to immune checkpoint inhibitors (ICIs) (**Figure 1**).

Evolving understanding of the pathophysiology of HCC placed angiogenesis under the spotlight as a potential therapeutic target. Hypervascularity and vascular abnormalities, e.g., arterialization and sinusoidal capillarization, which are mediated by the action of proangiogenic factors such as VEGF, are common findings in HCC (8). In the early 2000s, the HCC treatment paradigm was revolutionized with the development of small molecules blocking the VEGF pathway, culminating with the SHARP phase III trial and the demonstration of benefit with the use of sorafenib. This orally available TKI modestly—though significantly—improved overall survival versus best supportive care alone [10.7 versus 7.9 months, hazard ratio (HR) 0.69] (9), establishing a clear standard of care. In 2018, lenvatinib was also approved as first-line treatment after the phase III REFLECT study demonstrated noninferiority versus sorafenib (10). In addition, a myriad of antiangiogenic agents was approved in second-line settings subsequently (**Figure 1**), including regorafenib (11), ramucirumab (for patients with alpha-fetoprotein >400) (12), and cabozantinib (13), with overall survival improvements versus placebo ranging from 1.6 to 2.8 months. However, no appropriate molecular biomarker for better selection of patients who might derive the largest benefit has been identified, and, perhaps for this reason, these agents offer only a modest improvement in overall survival.

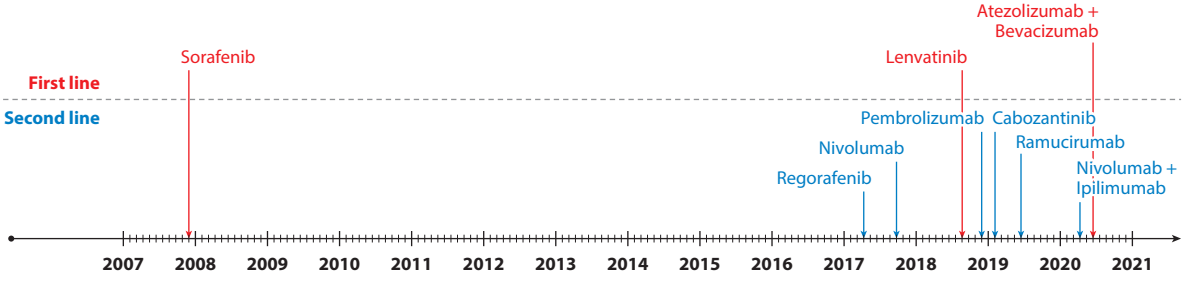

Figure 1

Timeline of US Food and Drug Administration approvals for the systemic treatment of hepatocellular carcinoma. Sorafenib was the first drug to demonstrate an overall survival benefit in patients with advanced hepatocellular carcinoma, in 2007. Ten years later, regorafenib demonstrated overall survival gains in the second-line setting. Since then, multiple new agents from have been approved, significantly expanding the therapeutic arsenal.

It is well established that cancer is an immunogenic disease, and immune modulation as a form of cancer therapy is increasingly explored. A few decades ago, local and systemic immunotherapy with interferon (IFN) and cytokines such as interleukin (IL)-12 were studied with poor results (14, 15). Identification of immune checkpoints and the development of ICIs revolutionized the treatment landscape of many malignancies (16). This class of agents was particularly successful in melanoma (17), renal cell carcinoma (18), and non–small cell lung cancer (NSCLC) (19) by inducing blockade of immune inhibitory pathways and therefore compromising the capacity of the tumor and its stroma to suppress infiltrating lymphocytes, allowing for effective eradication of malignancies by the immune system. For the patients who respond, ICIs have also demonstrated potential for long-term disease control, including cures in metastatic chemotherapy-refractory solid tumors (20). A more refined understanding of the immune microenvironment of the normal and cancerous liver has led to an increased interest in ICI agents.

Rationale of Immune Checkpoint Inhibitors in Cancer Treatment

The role of innate and adaptive immune surveillance in cancer development is the foundation for many therapeutic advances for numerous cancer types (21). The initial step depends on the immune system's capacity of recognizing self and nonself antigens, mediated at the immune synapse. The immune synapse comprises the interface between the tumor cells and immune effectors in a process that will ultimately define the activation or inhibition of the immune response mediated by antigen-presenting cells (APCs) and major histocompatibility complex (MHC) classes I and II. The primary binding between T cells and APCs happens between the MHC and the T cell receptor complexes (22). This initial signal requires additional costimulatory and coinhibitory binding interactions, collectively known as immune checkpoints. After this step, two opposing results may occur: immune activation by effector T cells or exhaustion of these cells coupled with immune evasion due to recruited regulatory and immunosuppressive cells (23). The most representative negative immune checkpoints to date are programmed cell death receptor 1 (PD-1); its ligand, programmed cell death ligand 1 (PD-L1); and cytotoxic T lymphocyte associated protein 4 (CTLA-4) (24).

Regulatory T cells and activated $CD4^+$ and $CD8^+$ lymphocytes express CTLA-4, which competitively binds to CD80 (also known as B7–1) and CD86 (B7–2), thereby decreasing the costimulatory signal of CD28 on APCs (25). Pro-effector cytokines IL-12 and IFN-γ, as well as T cell receptor activation, all act to upregulate CTLA-4, leading to a feedback inhibition loop on effector T cells and, consequently, weakening of the immune response (26).

Alternatively, lymphocytes (T cells, B cells, and natural killer cells) express PD-1, which is the preeminent target of T cell suppressive immunomodulation in the tumor microenvironment. It is also a coinhibitory receptor that is engaged by both PD-L1 (also known as B7-H1 or CD274) and PD-L2 (B7-H2 or CD273), stimulating peripheral T effector cell exhaustion (27). PD-L2 is primarily expressed by cells of the hematopoietic system, while PD-L1 is expressed across numerous cell types, including tumor cells. IL-12 and IFN-γ enhance PD-L1 expression in the tumor microenvironment, highlighting its role as a physiological brake to effector T cells and as a mechanism for immune evasion (28, 29). Feedback inhibition of effector T cells may also be induced by chronic presentation of antigens, seen in chronic viral infections or neoplastic clones, in a process known as immune exhaustion (23).

The Liver Immune Microenvironment

The initial step for the development of a cancer-specific cellular immune response is the recognition of neoantigens. In fact, solid tumors with high mutational burden, such as melanoma and

NSCLC, demonstrated better response to ICI treatment, theoretically due to the ability of immune effector cells to recognize the higher burden of neoantigens in these malignancies. Although the overall mutational burden of HCC is defined as intermediate, the exact characterization of neoantigens in HCC is yet to be fully described (30).

The hepatic tumor microenvironment also presents particular issues, as nonparenchymal liver cells (e.g., Kupffer, hepatic stellate, and liver sinusoidal endothelial cells) cooperate with tumor cells, immune infiltrate, and tumor-associated fibroblasts to enable immune evasion. These resident cells play an important role in maintaining immune tolerance, which is desirable under normal circumstances as nonself, exogenous molecules such as food and bacterial antigens are filtered through the liver. The immune microenvironment in HCC also includes upregulation and overexpression of PD-1 in intrahepatic lymphocytes, as well as of PD-L1 and PD-L2 in Kupffer cells, liver sinusoidal endothelium, and leukocytes (31).

It is important to highlight that phenotype classification, based on gene profiling, gene signatures, and other molecular features, may help select subsets of patients more likely to respond to specific therapies, which is especially necessary in a heterogeneous disease with multiple predisposing factors. In HCC, it is possible to classify microenvironment-based immune subtypes in distinct phenotype groups. Inflammatory response with overexpression of PD-1 and PD-L1 was found in 25% of HCC samples. This so-called immune class can be subdivided into two groups according to immune status: active status (65%, with overexpression of adaptive immune response genes) and exhaustion of immunological activity (35%, with predominance of immunosuppressive features such as TGF-β expression and M2 macrophage infiltration) (32).

SAFETY AND EFFICACY DATA OF IMMUNE CHECKPOINT INHIBITORS IN ADVANCED DISEASE

The first study of ICIs in HCC, published in 2017, was CheckMate 040, a phase I/II study evaluating the use of nivolumab (an anti-PD-1 ICI) after sorafenib failure in 262 patients (33). With an overall response rate of 20%, disease control rate of 64%, progression-free survival of 4.0 months, and median duration of response of 9.9 months, it drew attention to ICIs' potential for eliciting long-term responses. Overall survival was 83% at 6 months and 74% at 9 months, which compared favorably to trials in the second-line setting of non-immunotherapy agents. In addition, the drug was well tolerated; only 3% of subjects discontinued therapy because of drug-related adverse events. Specifically, immune-related hepatitis was rare and mostly low grade (34).

In 2018, additional data highlighted the potential of ICIs in the liver cancer setting. The single-arm phase II KEYNOTE-224 trial evaluated 104 HCC cases that had progressed on sorafenib and were treated with pembrolizumab (an anti-PD-1 ICI). The overall response rate was 17%, with disease control rate 62%. Median time to response was 2.1 months, and 77% of patients continued to respond for ≥9 months, with median duration of response not reached. Median overall survival was 12.9 months. Side effects attributable to immune-mediated hepatitis were similar to those associated with nivolumab, seen in only 3% of patients (35).

Unfortunately, the promising initial results of single-agent anti-PD-1 ICIs were not confirmed by larger confirmatory trials, in both first- and second-line settings. In the second-line setting, a multicenter, randomized phase III study (KEYNOTE-240) assigned 413 patients to pembrolizumab or placebo, after progression on sorafenib. Unfortunately, the trial did not meet the threshold for superiority in overall or progression-free survival, defined as coprimary endpoints. Secondary efficacy and safety data endorsed prior reports: The response rate was 16.9%, with median duration of response of 13.8 months, and therapy was well tolerated with no new

safety signals (36). The results regarding first-line treatment with single-agent anti-PD-1 ICIs were not encouraging either. CheckMate 459 was a phase III trial comparing nivolumab versus sorafenib for 743 systemic therapy-naive patients with advanced HCC. This study also failed to meet its primary endpoint of superior overall survival, with median overall survival of 16.4 months for the nivolumab group versus 14.8 months for the sorafenib group (HR 0.85). At 33 months, nivolumab had an overall survival rate of 29% and sorafenib 21%. Consistent with prior reports, severe adverse events were more common in the TKI group—reported in 82 patients (22.3%) of the nivolumab group and in 180 patients (49.6%) of the sorafenib group (37).

In summary, despite encouraging initial efficacy data with relatively high response and disease control rates, anti-PD-1 ICIs as single agents failed to improve survival endpoints in confirmatory phase III studies. Hence, interest shifted toward diversifying strategies and combining agents to improve efficacy. The efficacy data of approved ICIs in HCC are summarized in **Table 1**.

Although both nivolumab and pembrolizumab are still conditionally approved for HCC, the Oncology Drug Advisory Committee of the US Food and Drug Administrations (FDA) has reviewed the data, most recently in April 2021 (38), and a decision on whether to keep or withdraw the approval is expected in the near future.

Table 1 Efficacy of immune checkpoint inhibitors approved by the US Food and Drug Administration

Drug	Trial	Phase	*n*	Characteristics	Efficacy data
Pembrolizumab	KEYNOTE-224 (57)	II	156	Second line, single arm	ORR 17% (95% CI 11–26%), DoR median NR (95% CI 3.1–14.6+ mo)
	KEYNOTE-240 (58)	III	413	Second line versus placebo	mOS: pembrolizumab 13.9 mo (95% CI 11.6–16.0) versus placebo 10.6 mo (95% CI 8.3–13.5); HR 0.781 (95% CI 0.611–0.998; $p = 0.0238$) mPFS: pembrolizumab 3.3 mo (95% CI 2.8–4.1) versus placebo 2.8 mo (95% CI 1.6–3.0); HR 0.7 (95% CI 0.56–0.89; $p = 0.0011$)
Nivolumab	CheckMate 040 (59) (NCT01658878)	II	1,097	Single arm, mostly pretreated (74%)	ORR 20% (95% CI 9–21%), DoR median NR (95% CI 3.2–51.1+ mo), 59% responded for 12 months or longer
	CheckMate 459 (37)	III	743	First line versus sorafenib	mOS: nivolumab 16.4 mo (95% CI 13.9–18.4) versus sorafenib 14.7 mo (95% CI 11.9–17.2); HR 0.85 (95% CI 0.71–1.02; $p = 0.0752$)
Atezolizumab + bevacizumab	IMbrave150 (60)	III	558	First line versus sorafenib	mOS: atezolizumab/bevacizumab 19.2 mo (95% CI 17.0–23.7) versus sorafenib 13.4 mo (95% CI 11.4–16.9); HR 0.58 (95% CI 0.52–0.85; $p = 0.0009$) mPFS: atezolizumab/bevacizumab 6.9 mo (95% CI 5.7–8.6) versus sorafenib 4.3 mo (95% CI 4.0–5.6); HR 0.59 (95% CI 0.53–0.81; $p = 0.0001$)
Nivolumab + ipilimumab	CheckMate 040 (61) (NCT01658878)	II	1097	Second line	ORR 33% (95% CI 20–48%), DoR 17.5 mo (95% CI 4.6–30.5+ mo), 56% responded for 12 months or longer

Abbreviations: CI, confidence interval; DoR, duration of response; HR, hazard ratio; mo, months; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; ORR, overall response rate.

Combination Immune Checkpoint Inhibitors in Hepatocellular Carcinoma

The VEGF pathway plays a pivotal role in establishing and maintaining an immunosuppressive tumor microenvironment. Therefore, a strategy using combined VEGF/PD-(L)1 blockade may be advantageous in various solid cancers, especially in HCC given its nature as a highly vascularized tumor. In May 2020, following results from the phase III IMbrave150 trial, a new standard of care for advanced and unresectable HCC was approved by the FDA: atezolizumab (an anti-PD-L1 ICI) plus bevacizumab (an anti-VEGF monoclonal antibody) (39). The IMbrave150 study assessed this combination versus sorafenib as a first-line treatment in 501 previously untreated patients, with median overall survival significantly better for the combined therapy [not reached (NR) versus 13 months; HR 0.58], and an overall survival benefit of 12% at 1 year (67% versus 55%). Combination therapy also improved secondary efficacy endpoints: It doubled the objective response rate (27% versus 12%) (40) and also improved progression-free survival (6.8 versus 4.3 months; HR 0.59). Moreover, authors reported a benefit in quality of life and physical/role performance (41). Other combinations of anti-VEGF agents and ICIs have been explored; particularly, the combination of lenvatinib plus pembrolizumab has demonstrated promising antitumor activity in a phase Ib trial enrolling 106 patients with unresectable HCC (42). The overall response rate was 46%, with median duration of response of 8.6 months; moreover, treatment was reasonably well tolerated, with no unexpected safety signals identified.

Additionally, the association of two ICIs has been explored. Combining an anti-PD-1 with an anti-CTLA-4 ICI has demonstrated intriguing activity in NSCLC (43), melanoma (44) and microsatellite instability-high colon cancer (45), among other solid tumors, and has also yielded promising results in HCC. In fact, in March 2020, based on the CheckMate 040 study, the FDA granted accelerated approval to the combination of nivolumab and ipilimumab as second-line therapy for previously treated advanced HCC patients (46). With 4 complete and 12 partial responses, the overall response rate was 33%. Importantly, more than 30% of responses persisted for at least 24 months, with median response duration of 17 months. Nevertheless, the combination elicited a higher occurrence of immune-related adverse events, including grade 3–4 increased levels of aspartate aminotransferase and lipase; 18% of patients had to discontinue this combination due to such adverse events (47).

PERSPECTIVES

Despite the promising improvement that the combination of atezolizumab and bevacizumab showed as a first-line option, the exclusion criteria—e.g., untreated large esophageal varices, bleeding in the previous 6 months, autoimmune diseases, or more advanced uncompensated cirrhosis beyond Child-Pugh A class—imply that approximately 15–20% of patients are ineligible for this treatment (40). In such cases, the first-line alternatives remain sorafenib, lenvatinib, or best supportive care alone (48). Meanwhile, more studies are being conducted for other monotherapy and combination ICI treatments for first- and second-line therapy (**Table 2**). For patients who did not respond to sorafenib as first-line treatment, there are ongoing studies for the use of pembrolizumab (KEYNOTE-394, NCT03062358) and nivolumab with ipilimumab (47). The use of nivolumab alone for second-line treatment after sorafenib remains under debate, and the Oncology Drug Advisory Committee recently voted against keeping its accelerated approval valid (38). Other trial results regarding combinations of ICIs for first-line treatment are eagerly expected, such as CheckMate 9DW (NCT04039607), comparing nivolumab with ipilimumab to sorafenib or lenvatinib, and LEAP-002 (NCT03713593), comparing pembrolizumab with lenvatinib against lenvatinib alone.

Table 2 Upcoming phase III studies on immune checkpoint inhibitors for advanced hepatocellular carcinoma (HCC)

Study	Description	National Clinical Trial number	Status	Estimated primary completion date
Lenvatinib in Combination With Pembrolizumab Versus Lenvatinib in First-line Therapy of Participants With Advanced HCC (LEAP-002)	Lenvatinib (E7080/MK-7902) in combination with pembrolizumab (MK-3745) versus lenvatinib in combination with placebo as first-line therapy for the treatment of advanced HCC	03713593	Active	May 13, 2022
Cabozantinib in Combination With Atezolizumab Versus Sorafenib in Subjects With Advanced HCC Who Have Not Received Previous Systemic Anticancer Therapy (COSMIC-312) (62)	Cabozantinib in combination with atezolizumab versus the standard of care sorafenib in HCCs that have not received previous systemic therapy	03755791	Recruiting	June 1, 2021
Durvalumab and Tremelimumab as First-line Treatment in Patients With Advanced Hepatocellular Carcinoma (HIMALAYA)	Durvalumab plus tremelimumab combination therapy and durvalumab monotherapy versus sorafenib in the treatment of unresectable HCC	03298451	Recruiting	Dec. 30, 2021
CS1003 in Subjects With Advanced Hepatocellular Carcinoma	CS1003 in combination with lenvatinib versus placebo in combination with lenvatinib in first-line treatment of unresectable advanced HCC	04194775	Recruiting	June 30, 2023
Atezolizumab With Lenvatinib or Sorafenib Versus Lenvatinib or Sorafenib Alone in Hepatocellular Carcinoma Previously Treated With Atezolizumab and Bevacizumab (IMbrave251)	Atezolizumab plus lenvatinib or sorafenib versus lenvatinib or sorafenib alone in locally advanced or metastatic and/or unresectable HCCs that have progressed following prior treatment with atezolizumab and bevacizumab	04770896	Recruiting	Oct. 8, 2024
IBI310 Combined With Sintilimab Versus Sorafenib in the First-line Treatment of Advanced HCC	IBI310 combined with sintilimab versus sorafenib in patients with locally advanced or metastatic HCC without previously systemic therapy	04720716	Recruiting	Dec. 1, 2023
Tislelizumab Versus Sorafenib in Participants With Unresectable HCC (RATIONALE 301) (63)	Tislelizumab versus sorafenib as first-line systemic treatment in participants with unresectable HCC	03412773	Active	June 20, 2021
Evaluate the Safety and Efficacy of Toripalimab Combined With Bevacizumab Versus Sorafenib Therapy for HCC	Toripalimab combined with bevacizumab versus sorafenib as first-line therapy for advanced HCC	04723004	Recruiting	Aug. 31, 2022

(*Continued*)

Table 2 (*Continued*)

Study	Description	National Clinical Trial number	Status	Estimated primary completion date
SCT-I10A Plus SCT510 Versus Sorafenib as First-Line Therapy for HCC	SCT-I10A in combination with SCT510 in patients with HCC who have not received prior systemic therapy	04560894	Recruiting	Apr. 2024
Sintilimab in Combination With IBI305 (Anti-VEGF Monoclonal Antibody) Compared to Sorafenib as the First-Line Treatment for Advanced HCC (ORIENT-32)	Sintilimab in combination with IBI305 in patients with HCC as first-line treatment compared with sorafenib	03794440	Active	Dec. 2022
Toripalimab Combined With Lenvatinib for Advanced HCC	Toripalimab combined with lenvatinib versus placebo combined with lenvatinib as first-line therapy for advanced HCC	04523493	Recruiting	May 25, 2024
SHR-1210 in Combination With Apatinib as First-Line Therapy in Patients With Advanced HCC	SHR-1210 plus apatinib mesylate versus sorafenib as first-line therapy in patients with advanced HCC	03764293	Recruiting	Dec. 2021

Moreover, ICI therapy has been increasingly incorporated into the treatment of locoregional solid tumors, with improvement in survival endpoints described in melanoma (49), esophageal cancer (50), and NSCLC (51). The incorporation of ICIs in early-stage HCC is also appealing due to the opportunity to increase the cure rate, especially in tumors with high recurrence after intra-arterial therapies, such as transarterial chemo-embolization (TACE) (NCT04340193); or after radio-embolization with yttrium-90 (NCT03812562); or after other curative-intent therapies, such as ablation or resection (NCT03383458, NCT03867084, NCT04102098). Ongoing trials are evaluating ICIs alone or in combinations in the (neo)adjuvant settings, with encouraging early results. Of note, prior preclinical data by Liu et al. (52) suggested increased efficacy of neoadjuvant immune checkpoint inhibition when compared to the same treatment in the adjuvant setting, and feasibility of neoadjuvant immune checkpoint blockage has been demonstrated in melanoma, NSCLC, breast cancer, and colorectal cancer (53, 54). Intriguingly, these studies demonstrate impressive long-term results in responders to neoadjuvant ICIs; for illustration, among patients who received neoadjuvant ICIs for melanoma and achieved a pathological complete response, the 2-year recurrence-free survival was 96% (53). This paradigm has been increasingly explored in HCC. One example is a phase II trial incorporating a perioperative ICI regimen (nivolumab alone or in combination with ipilimumab). In this study, neoadjuvant ICI therapy was safe and achieved an encouraging rate of pathological response in 21 evaluable patients—24% achieved a pathological complete response (55). Interestingly, early correlative reports suggest that pathological response in HCC correlates with expansion in $CD8^+$ T cell infiltration, specifically in effector T cell clusters (56).

CONCLUSION

Application of immunotherapy in HCC is a burgeoning field of study that has now displaced TKI monotherapy as standard of care for advanced disease. Further progress may be particularly

difficult due to the challenges of treating specific patient populations with underlying uncompensated cirrhosis and portal hypertension complications. Moreover, survival rates are still suboptimal, and there is an unmet need for improvement regarding treatment plans. Therefore, current ongoing studies of combination systemic therapies in advanced HCC in first- and second-line settings and combinations of systemic and local therapies in localized disease may change the current landscape and improve the dismal outcome of unresectable HCC. Finally, ICI incorporation into very early-stage HCC, which is amenable to ablation and resection, may lower recurrence rates and offer cure for this patient population.

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