


# Real-World Use of Immunotherapy for Hepatocellular Carcinoma

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**Abstract:** Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related mortality worldwide and accounts for 90% of all primary liver cancers. Chronic inflammation is the hallmark across most prevalent etiologies among which HBV is the leading cause worldwide (33%), followed by alcohol (30%), HCV (21%), other factors like non-alcoholic steatohepatitis linked to insulin resistance/metabolic syndrome, and obesity associated inflammation (16%). Deregulation of the tightly controlled immunological network leads to liver disease, including chronic infection, autoimmunity, and tumor development. While inflammation drives oncogenesis in the liver, HCC also recruits ICOS+ FOXP3+ Tregs and MDSCs and upregulates immune checkpoints to induce a state of immunosuppression in the tumor microenvironment. As such, research is focused on targeting and modulating the immune system to treat HCC. The Checkmate 040 and Keynote 224 studies established the role of immunotherapy in the treatment of patients with HCC. In Phase I and II trials, nivolumab and pembrolizumab demonstrated durable response rates of 15–20% and were subsequently approved as second-line agents after sorafenib. Due to the success of the IMbrave 150 and HIMALAYA trials, which examined the combination of atezolizumab/bevacizumab and tremelimumab/durvalumab, respectively, the FDA approved these regimens as first-time treatment options for patients with advanced HCC. The encouraging results of immunotherapy in the management of HCC has led researchers to evaluate if combination with locoregional therapies may result in a synergistic effect. Real-world studies represent an invaluable tool to assess and verify the applicability of clinical trials in the bedside setting with a more varied patient population. We herein review current real-life use of ICIs in the management of HCC and highlight some of the ongoing clinical trials that are expected to change current recommended first-line treatment in the near future.

**Keywords:** hepatocellular carcinoma, immunotherapy, real-world data, immunotherapy biomarkers, liver microenvironment

## Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related mortality worldwide and accounts for 90% of all primary liver cancers<sup>1</sup> HCC is a serious healthcare challenge as it accounted for 830,180 deaths in 2020 and has a projected increase in incidence from 13.5 in 2013 to 17.0 in 2020 and 21.2 in 2030 per 100,000 person-years.<sup>2,3</sup> HCC oncogenesis is driven by inflammation.<sup>4</sup> Chronic inflammation secondary to Hepatitis B infection (HBV), alcohol, hepatitis C infection (HCV), and non-alcoholic steatohepatitis linked to insulin resistance/metabolic syndrome or obesity associated inflammation is the underlying driver of HCC development.<sup>5,6</sup> These etiologies lead to a unique microenvironment through alterations to immune cells, the cytokine milieu, and tumor cell signaling pathways.<sup>4</sup>

While inflammation drives oncogenesis in the liver, HCC tumor cells also adjust the surrounding microenvironment by recruiting ICOS+ FOXP3+ Tregs and MDSCs and upregulating immune checkpoints (eg PD-1 and CTLA-4) in order to induce a state of immunosuppression.<sup>7,8</sup> As such, research is focused on targeting and modulating the immune system to treat HCC. For over a decade, several HCC systemic therapeutic drugs have been developed and have demonstrated modest survival benefits as single agents. However, recent landmark trials with immune-checkpoint inhibitors (ICIs) have

revolutionized the management of HCC and changed the standard of care. To this point, HCC clinical research across all stages has increasingly focused on immunotherapy with more than 30 Phase III trials currently ongoing.<sup>4,9–11</sup>

In addition, the updated Barcelona Clinic Liver Cancer (BCLC) guidelines now incorporate immune checkpoint inhibitor-based combination therapies as first-line treatment for advanced HCC. The spectrum of immunotherapy success in the management of advanced HCC has resulted in a new goal of treating with immunotherapy ± locoregional therapies to downstage patients to enhance resectability. Additionally, immunotherapy is now being leveraged in clinical trials to prevent recurrence after curative-intent resection.<sup>12–15</sup> Despite progress in the application of immunotherapy for cancer treatment, reliable response biomarkers to define patients who might benefit the most from immunotherapy are still lacking. We herein review current real-life use of ICIs in the management of HCC and highlight some of the ongoing clinical trials that are expected to change current recommended first-line treatment.

## Liver Microenvironment

The liver is the largest reticuloendothelial system in the body. The liver is continuously challenged by a large burden of antigens and pathogens from both the gastrointestinal tract via the portal vein and the circulatory system via the hepatic artery. As such, the liver needs to maintain a physiologically tolerogenic immunosuppressed niche to downregulate any immunogenic responses and avoid autoimmunity.<sup>16</sup> Deregulation of this tightly controlled immunological network can lead to chronic infection, autoimmunity and tumor development.<sup>17</sup> Chronic inflammation leads to a persistent pro-inflammatory state, which stimulates liver cell death and regeneration leading to fibrosis and/or subsequent cirrhosis. In turn, fibrosis and cirrhosis often eventually induce the development of dysplastic nodules and tumorigenesis.<sup>16</sup>

Overall, 80% of the liver parenchyma is constituted of hepatocytes, followed by cholangiocytes, liver sinusoidal endothelial cells (LSECs), hepatic stellate cells (HSCs), and liver-resident immune cells.<sup>18</sup> Major immunosuppressive cells implicated in HCC immune evasion include tissue-resident macrophages (mainly Kupffer cells), monocyte-derived macrophages, regulatory T (T<sub>reg</sub>) cells and myeloid-derived suppressor cells (MDSCs).<sup>16,17,19,20</sup> Dysfunctional dendritic cells (DCs), CD8<sup>+</sup>PD1<sup>+</sup> T cells (in the context of NASH), neutrophils, and regulatory B (B<sub>reg</sub>) cells produce metalloproteinases and limit the effectiveness of innate and adaptive immunity. Subsequently, this allows for uncontrolled cell growth.<sup>21</sup> In turn, this process can produce mitotic mediators (eg EGFR ligands, IL-6, TNF $\alpha$ , FGFs, TGF $\beta$  and HGF),<sup>22</sup> angiogenesis mediators (eg VEGF, bFGF, TNF $\alpha$ , TGF $\beta$ , platelet-derived growth factor and placental growth factor),<sup>23</sup> and mediators that support cancer stem cells (eg IL-6 to interact with STAT3).<sup>24</sup>

## Development of Hepatocellular Carcinoma Systemic Treatment

HCC treatment is driven by disease stage and liver function. Early-stage HCC can often undergo curative-intent treatment with surgical resection, liver transplantation, and/or ablation, while intermediate stage disease may require additional treatments modalities like embolization and/or radiation therapy. Systemic therapy (chemotherapy, molecular targeted therapy, immunotherapy, and gene therapy) has been the mainstay treatment for intermediate or advanced-stage HCC patients.<sup>25</sup>

Published in 2008, the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) was the first Phase III, randomized, placebo-controlled trial to demonstrate an overall survival (OS) benefit for patients with advanced HCC and well-preserved liver function (>95% Child-Pugh A) who were treated with a targeted agent. Compared to a placebo, patients treated with sorafenib had improved median OS (sorafenib: 10.7 months versus placebo: 7.9 months, HR in sorafenib cohort: 0.69;  $p < 0.001$ ).<sup>26</sup> Raoul et al published a SHARP trial sub-analysis in 2012 that demonstrated the efficacy of sorafenib irrespective of disease etiology, liver enzyme levels,  $\alpha$ -fetoprotein (AFP) levels, bilirubin levels, tumor size or stage.<sup>27</sup> Sorafenib was, however, associated with primary and acquired resistance that limited its use and contributed to poor outcomes.<sup>28</sup> Subsequently, based on data from the RESORCE and CELESTIAL studies, Regorafenib and Cabozantinib, respectively, received approval for use in patients who were resistant to or intolerant to sorafenib. Cabozantinib has also received approval as a third-line therapeutic option.<sup>29,30</sup> Specifically, these agents demonstrated improved OS (26 months) as a second-line therapy to sorafenib compared to placebo as a second-line therapy (OS: 19 months).<sup>29,30</sup>

The phase III REFLECT randomized trial demonstrated that OS associated with the TKI lenvatinib was noninferior to sorafenib. Lenvatinib also demonstrated a higher objective response rate (ORR: 18% vs 6%) and fewer cases of palmar-plantar erythrodysesthesia. Based on this trial, Lenvatinib is an acceptable alternative to sorafenib as first-line therapy.<sup>31</sup> Interestingly, OS related to TKI use in the post-approval phase has been reported to be slightly longer in both clinical trials and in real-life.<sup>32–35</sup> Antiangiogenic monoclonal antibodies, such as ramucirumab and bevacizumab, which target VEGF to inhibit the angiogenesis, have also been approved for patients who progressed on sorafenib with AFP levels of  $\geq 400$  ng/mL based on data demonstrating improved overall survival versus placebo.<sup>36–38</sup>

## Immunotherapy in Hepatocellular Carcinoma

Immunotherapy has redefined and revolutionized the field of oncology with unprecedented potential to benefit patients with advanced disease. It has proven to be more effective and with a better safety profile than TKIs among patients with advanced HCC (Table 1).

### Single Agent Immunotherapy

The Checkmate 040 and Keynote 224 studies established the role of immunotherapy in the treatment of patients with HCC. In phase I and II trials, nivolumab and pembrolizumab demonstrated response rates of 15–20% and were subsequently approved as second-line agents.<sup>43,44</sup> However, the phase III CheckMate 459 study failed to demonstrate an improved OS for nivolumab versus sorafenib.<sup>45</sup> In the phase III Keynote 240 trial, pembrolizumab was investigated as a second-line therapy, but failed to demonstrate a survival benefit compared to placebo.<sup>46</sup> The phase III Keynote 394 trial compared best supportive care with pembrolizumab versus placebo as second-line therapy among patients in Asia with advanced HCC. Compared to the placebo, pembrolizumab significantly improved OS, PFS, and ORR.<sup>47</sup> In a Phase II trial, another anti-PD-1 inhibitor camrelizumab demonstrated promise to be utilized as a new treatment in pretreated patients with advanced HCC.<sup>48</sup> Atezolizumab, an anti-PDL1 inhibitor, has also been investigated among patients with unresectable HCC, yet the results are pending.<sup>49</sup>

### Combined Agent Immunotherapy

Because single-agent anti-PD1/anti-PDL1 inhibitors have demonstrated limited activity in an immunosuppressive microenvironment like HCC, new immunotherapy combinations have been tested. Combination therapy provides simultaneous blockade of multiple immune checkpoints.

To this point, the IMbrave 150 trial examined the combination of atezolizumab and bevacizumab.<sup>39</sup> Compared to sorafenib, this combination treatment regimen demonstrated improved OS (atezo/bev median OS not reached vs 13.2 months with sorafenib) and improved PFS (atezo/bev median PFS: 6.8 months vs 4.3 months with sorafenib). In turn, the FDA approval of this regimen as first-line therapy for advanced HCC.<sup>39</sup> An updated analysis with a median follow-up of 15.6 months demonstrated a median overall survival of 19.2 months with atezolizumab and bevacizumab versus 13.4 months with sorafenib alone.<sup>40</sup> Of note, the IMbrave 150 study cohort included a patient population with varying etiologies (50% HBV, 20% HCV, and 30% non-viral etiology). Importantly, a recent report noted patients with HCC due

**Table 1** Reported Median Overall Survival and Median Progression Free Survival in HCC Immunotherapy Trials

Reference	Study Arm	Median OS/ Median PFS (Months)	Comparison Arm	Median OS/ Median PFS (Months)	Statically Significant
Finn et al, 2020 (IMBrave) <sup>39</sup>	Atezolizumab + Bevacizumab	NR/ 6.8	Sorafenib	13.2/ 4.3	Yes
Cheng et al, 2022 <sup>40</sup>	Atezolizumab + Bevacizumab	19.2/ 6.9	Sorafenib	13.4/ 4.3	Yes
Qin et al, 2022 <sup>41</sup>	Camrelizumab + Rivoceranib	22.1/ 5.6	Sorafenib	15.2/ 3.7	Yes
Finn et al, 2022 <sup>42</sup>	Lenvatinib + Pembrolizumab	21.2/ 8.2	Lenvatinib	19/ 8.1	No
Abou-Alfa et al, 2022 (HIMALAYA) <sup>30</sup>	Tremelimumab + Durvalumab	16.4	Sorafenib	13.8	Yes

**Abbreviations:** OS, overall survival; PFS, progression free survival; NR, not reached.

to a viral etiology derived a therapeutic benefit from ICI use [HR 0.64], whereas patients with a nonviral HCC etiology (NAFLD/NASH) did not [HR 0.92] ( $P = 0.03$ ).<sup>50</sup> In turn, results of IMbrave 150 need to be interpreted in light of this information as the trial results may be more applicable to viral-induced HCC tumors that are more sensitive to immune microenvironment alterations.<sup>39</sup> Two Phase Ib first-line trials examined pembrolizumab plus regorafenib (REG-PEMBRO-HCC) and pembrolizumab plus Lenvatinib (Keynote 524/Study 116), respectively, for advanced HCC.<sup>42,51</sup> Both regimens demonstrated promising anti-tumor activity with reported disease control rates of ~90% with no major safety issues.<sup>42,51</sup> As such, these combination therapies may be attractive options for NASH-associated HCC. In a phase III trial, Camrelizumab demonstrated improved survival outcomes when received in combination with Rivoceranib (anti-angiogenic TKI) as first-line treatment in a cohort of patients with unresectable HCC.<sup>41</sup>

Anti-CTLA-4 monoclonal antibodies such as tremelimumab and ipilimumab have also emerged as potential effective ICIs. To this end, based on the CheckMate 040 trial, ipilimumab with nivolumab received accelerated approval by the FDA in 2020 for patients with HCC already treated with sorafenib.<sup>52</sup> The phase II CheckMate 040 trial demonstrated that nivolumab-ipilimumab combination had a manageable safety profile and promising ORR.<sup>52</sup> Nivolumab/ipilimumab versus sorafenib/lenvatinib is currently being studied in a phase III trial (CheckMate 9DW, NCT04039607).

Recently, cohort 6 of the Checkmate 040 trial reported that nivolumab/cabozantinib with or without ipilimumab had encouraging preliminary antitumor activity.<sup>53</sup> Nivolumab plus cabozantinib had a consistent safety profile compared with other established individual drugs used to treat patients with advanced HCC.<sup>53</sup> The phase III LEAP-002 trial demonstrated no difference in OS or PFS when comparing Lenvatinib plus Pembrolizumab versus Lenvatinib alone as first-line treatment.<sup>32</sup>

The study 22 (a phase II) and HIMALAYA (a phase III) second-line trials demonstrated that a single dose of tremelimumab (anti-CTLA-4) plus durvalumab (anti PD-L1) administered at regular intervals (STRIDE regimen) yielded a median OS of 16.4 versus 13.8 months for patients treated with sorafenib.<sup>54,55</sup> HIMALAYA was conducted in 190 centers across 16 countries. Notably, the study population was externally validated and 31% of the patients had HBV, 27% had HCV, and 42% had a non-viral etiology of their chronic liver inflammation.<sup>56</sup>

A synergistic effect may be the reason for increased efficacy related to combining ICIs and anti-VEGF therapy versus TKIs alone. ICIs block checkpoint inhibition of the immune system, thereby increasing the activation and recruitment of killer lymphocytes. VEGF inhibitors transiently normalize tumor vasculature to convert the immunosuppressive tumor microenvironment to a more immune-supportive one via upregulation of adhesion molecules (ICAM, VCAM), selectins and integrins that facilitate migration of effective killer lymphocytes into the tumor microenvironment.<sup>57</sup> Additionally, VEGF inhibitors also decrease the expression of PD-L1 on dendritic cells; in mouse models, VEGF inhibitors have been demonstrated to decrease the expression of inhibitory molecules like PD-1, Tim-3, CTLA-4, and Lag-3, thus leading to increased activation of CD8<sup>+</sup> T cells and CD8<sup>+</sup>/T-Reg ratio.<sup>57</sup> CTLA-4 is an immune checkpoint that inhibits T-cell activation at secondary lymphoid organs and at the time point of T-cell development. A complementary or synergistic effect may be related to dual ICI therapy based on observation of a distinct immune environment that involves increased CD8<sup>+</sup> T-cell recruitment and activation, increased IL-8 and HLA-DR, soluble IL-2R and anti-CTLA-4 upregulated gene expression, and B cell phenotype modulation in the periphery and the cancer TME leading to enhanced tumor rejection.<sup>58</sup>

## Immunotherapy Combined with Locoregional Therapies

The combination of immunotherapy and regional therapies (eg, trans-arterial embolization (TACE), ablation, Yttrium-90 radioembolization (Y90), and/or radiation therapy (RT)) may have a potentially synergistic effect. Regional therapies can alter the microenvironment by inducing necrosis of tumor cells and the release of tumor neo-antigens. In turn, the microenvironment and tumor may be more primed for immune checkpoint inhibitors.<sup>59</sup> Currently, this effect of combination therapy has been demonstrated in pre-clinical studies with mouse HCC models and is also being investigated in early phase trials.<sup>60,61</sup> Zhu et al treated twenty HCC patients with neoadjuvant TACE and a PD-1 inhibitor as a bridge to surgery.<sup>15</sup> Fourteen of patients were successfully downstaged, suggesting that there may be a benefit to this combination therapy. In a separate study, Mizukoshi et al analyzed immune response before and after radiofrequency ablation in 69 patients with HCC.<sup>14</sup> Radiofrequency ablation enhanced T cell response to tumor-specific antigens. At 24 weeks post-radiofrequency ablation, there was, however, a decrease in these T cells. These data suggest an association between ablation and change in T cell response, which may be transient in nature. Duffy et al treated 32 HCC patients

with tremelimumab and either radiofrequency ablation or chemoablation<sup>13</sup> The combination of immunotherapy and ablation was safe and led to the accumulation of intra-tumoral CD8+ T cells. One case report demonstrated the potential of combination of immune checkpoint inhibitors and radiation therapy.<sup>62</sup> There are several ongoing trials examining the combination of regional therapy and immune checkpoint inhibitors (NCT 04246177, NCT03482102, NCT03203304, NCT03316872, NCT03817736, NCT04611165, NCT05225116, NCT05185531).

## Real World Data of Immunotherapy Efficacy and Safety in Advanced HCC

Real-world studies are crucial to demonstrating that novel therapies can be employed in clinical practice outside strict trial criteria. Liver function is typically assessed with Child-Pugh classification system. Unfortunately, preserved liver function is often a criterion for these clinical trials and patients with a Child Pugh class B and C are commonly excluded or enrolled in limited numbers.<sup>26,31,39,45</sup> Thus, there is limited data on the safety and efficacy of many first-line therapies in patients with Child-Pugh B and C. For this reason, many real-world studies across the globe have been conducted trying to address these questions (Table 2).

**Table 2** Reported Median Overall Survival and Median Progression Free Survival in HCC Immunotherapy Real-World Studies

Reference	Arm-1	Median OS/ Median PFS (Months)	Arm-2	Median OS/ Median PFS (Months)	Comments
DeCastro et al 2022 <sup>63</sup>	IMBrave-in	15/ 8.7	IMBrave-out	6/ 3.7	IMBrave-out group showed increased risk for ascites and hepatic encephalopathy
Rimini et al, 2023 <sup>64</sup>	IMBrave-in	16.3/ 8.3	IMBrave-out	14.3/ 6	No statistically significant difference in safety profile
Tanaka et al, 2022 <sup>65</sup>	Atezolizumab + Bevacizumab in CP-A	NR/ 9.5	Atezolizumab + Bevacizumab in CP-B	14/ 5.1	Therapeutic efficacy correlated with worsening liver function (mALBI score grade 2b-3).
Kim et al, 2022 <sup>66</sup>	Atezolizumab + Bevacizumab in CP-A	NR/ 6	Atezolizumab + Bevacizumab in CP-B	6/ 3	CP-B showed increase rate of grade 3 adverse effects compared to CP-A
D'Alessio et al, 2022 <sup>67</sup>	Atezolizumab + Bevacizumab in CP-A	16.8/ 7.6	Atezolizumab + Bevacizumab in CP-B	6.7/ 3.4	
Cheon et al, 2023 <sup>68</sup>	Atezolizumab + Bevacizumab in CP-A	NR/ 9.6	Atezolizumab + Bevacizumab in CP-B	7.7/ 3	CP-B showed increase rate of grade 3 adverse effects compared to CP-A
Rimini et al, 2023 <sup>69</sup>	Atezolizumab + Bevacizumab in CP-B	8.2/ 6.9	Lenvatinib in CP-B	13.8/ 8.2	No statistically significant difference in PFS
Casadei- Gardini et al, 2023 <sup>70</sup>	Atezolizumab + Bevacizumab	16.4 (OS)	Lenvatinib	16.1 (OS)	ATE/BEV improved OS in HCC patients with viral etiology. Lenvatinib improved OS in HCC patients with NASH/ NAFLD etiology.
Wong et al, 2021 <sup>71</sup>	Single agent Nivolumab/ Pembrolizumab in CP-B	3.1 (OS)	Single agent Nivolumab/ Pembrolizumab in CP-C	1.7 (OS)	ORR for CP-B and CP-C was 6.8% and 0% respectively. TTP 2.1 and 1.4 months, respectively.
Fessas et al, 2020 <sup>72</sup>	Nivolumab in CP-A	16.3 (OS)	Nivolumab in CP-B	7.3 (OS)	
Chapin et al, 2023 <sup>73</sup>	Nivolumab in CP-B	5 (OS)	Sorafenib in CP-B	4 (OS)	Decreased hazard of death with nivolumab compared to sorafenib HR: 0.69

**Abbreviations:** OS, overall survival; PFS, progression free survival; ORR, objective response rate; TTP, time to progression; HR, hazard ratio; NR, not reached; ATE, atezolizumab; BEV, bevacizumab; CP, Child-Pugh; mALBI, modified albumin-bilirubin score.



In 2022, a retrospective study by De Castro et al, the efficacy and safety of atezolizumab/bevacizumab was evaluated in 147 HCC patients from Germany and Austria. This study divided the patients into two cohorts: patients who met the inclusion criteria of IMBrave150 (IMBrave-IN) versus patients with at least one major exclusion criteria of the IMBrave150 trial (IMBrave-OUT). The IMBrave-OUT group had 35 Child-Pugh B pts (23.8%), 6 Child-Pugh C pts (4.1%), 7 BCLC D Pts (4.8%), and 13 ALBI III Pts (8.8%). The IMBrave-IN cohort had improved median OS and median PFS compared to the IMBrave-OUT cohort (mOS: 15.0 months versus 6.0 months and mPFS: 8.7 months versus 3.7 months). Additionally, the impact on OS also corresponded with worsening liver function (CPS >7 and ALBI grade >2), which was in line with consistent with other real-world studies.<sup>71,74</sup> Finally, the IMBrave-OUT group had increased risk for hepatic encephalopathy and/or ascites.<sup>63</sup> Following this study, a recent similar evaluation conducted by Rimini et al noted that adherence to the IMBrave150 trial inclusion criteria was associated with improved prognosis of patients receiving atezolizumab/bevacizumab. Of note, patients with Child-Pugh class A had improved OS and PFS compared to patients with Child-Pugh class B (OS: 16.3 months vs 5.9 months; PFS 7.9 months vs 5.3 months).<sup>64</sup> In another retrospective study, Tanaka et al reported on 457 Japanese patients with unresectable HCC, 89 of whom were classified as Child-Pugh B, while the remainder were classified as Child-Pugh.<sup>65</sup> PFS and OS among CP-A patients were better than that of patients with CP-B disease, with the therapeutic efficacy correlating with worsening liver function (mALBI grade of 2b or 3).<sup>65</sup>

Separate reports by Kim et al and D'Alessio et al noted that the Atezolizumab/Bevacizumab regimen was a safe option as a first-line treatment for unresectable HCC.<sup>66,67</sup> OS was, however, inferior among patients with Child-Pugh B versus Child-Pugh A disease. The rate of grade 3 or 4 adverse events was higher among patients with Child-Pugh B.<sup>66,67</sup> Cheon et al reported similar findings in which patients with Child-Pugh B HCC receiving first-line Atezolizumab/Bevacizumab had an ORR of 11.1%, a median PFS of 3.0 months, and a median OS 7.7 months, while Child-Pugh A patients had an ORR of 34.1%, a median PFS of 9.6 months, and a median OS that was not reached.<sup>68</sup> Again, grade 3–4 adverse events were more commonly observed among patients with Child-Pugh B versus patients with Child-Pugh A. In addition, there were differences even within the Child-Pugh B subset; patients with Child-Pugh B7 demonstrated a trend toward better ORR, median PFS, and OS results compared with the Child-Pugh B8–B9 group.<sup>68</sup>

Jost-Brinkmann et al evaluated the efficacy of Atezolizumab plus bevacizumab as a second-line therapy after either sorafenib or Lenvatinib.<sup>75</sup> In this study, the Atezolizumab/Bevacizumab regimen was noted to be safe among patients with liver disease. Of note, patients with Child-Pugh B had similar ORR (objective response rate) yet shorter median OS and PFS versus patients with preserved liver function.<sup>75</sup> In another study, Rimini et al reported that patients with unresectable HCC and Child-Pugh B liver disease, had better outcomes following treatment with Lenvatinib versus atezolizumab/bevacizumab.<sup>69</sup> The study recruited 217 CP B HCC patients from Italy, Germany, Republic of Korea and Japan. The median OS among patients receiving Lenvatinib was 13.8 months versus 8.2 months among patients receiving atezolizumab/bevacizumab as first-line treatment and there was no difference in median PFS. Additional analysis demonstrated that patients who received first-line Lenvatinib had longer median OS compared to patients receiving atezolizumab/bevacizumab.<sup>69</sup> These findings were in line with another recent study by Casadei-Gardini et al, which noted that atezolizumab plus bevacizumab was not associated with a survival advantage over Lenvatinib.<sup>70</sup> This study included a total of 214 Child-Pugh B patients, 62 of whom were in atezolizumab plus bevacizumab arm (7.2%), and 152 in the Lenvatinib arm (11.4%). OS was prolonged by atezolizumab plus bevacizumab over lenvatinib among patients with a viral etiology of HCC; in contrast, OS was better among patients treated with lenvatinib in the setting of non-alcoholic steatohepatitis/non-alcoholic fatty liver disease.<sup>70</sup> Chen et al noted that among patients with HCC in a real-world clinical practice, Lenvatinib was safe and efficacious as a second-line systemic therapy after progression on atezolizumab/bevacizumab.<sup>76</sup> The IMBrave050, a phase III trial by Chow et al published very recently showed that adjuvant treatment ATE/BEV combination achieved a statistically significant recurrence free survival compared to active surveillance alone in patients with high-risk HCC following resection or ablation. 12-month recurrence free survival rate was 78% in ATE/BEV group vs 65% in active surveillance group.<sup>12</sup>

The efficacy of nivolumab and pembrolizumab for treatment of unresectable HCC has also been evaluated in the real-world clinical setting. Wong et al studied 61 patients with unresectable HCC; 72.1% (n=44) were Child-Pugh B and 27.9% (n = 17) were of Child-Pugh C.<sup>71</sup> Patients received either single agent nivolumab or pembrolizumab. The ORR of

Child-Pugh B and Child-Pugh C patients were 6.8% and 0%, respectively, and time to progression were 2.1 months and 1.4 months, respectively. Child-Pugh B patients had a better OS than Child-Pugh C patients (3.1 months, vs 1.7 months).<sup>71</sup> A different retrospective, international, multicenter observational study evaluated the safety and efficacy of nivolumab in 233 patients (n=75, 32.2% Child-Pugh B) treated outside clinical trials from eight centers in North America, Europe, and Asia.<sup>72</sup> In this study, nivolumab was noted to be safe and effective in advanced HCC across various lines of therapy and degrees of liver dysfunction, however, OS was shorter among patients with Child-Pugh B versus A disease (7.3 months vs 16.3 months).<sup>72</sup> Choi et al indicated that Child-Pugh class B was an independent negative predictor for objective response to nivolumab among patients with HCC.<sup>74</sup> Chapin et al also recently compared nivolumab to sorafenib for first systemic therapy among patients with HCC and Child-Pugh B cirrhosis.<sup>73</sup> Among patients with HCC and Child-Pugh B cirrhosis, nivolumab was associated with improved OS and tolerability compared to sorafenib. Therefore, nivolumab should be considered first-line in this patient population.<sup>73</sup> A recent study assessed the efficacy and safety of ipilimumab plus nivolumab in advanced HCC patients who received pembrolizumab alone or with the addition of TKI. Results showed improved OS and PFS with reasonable safety data suggesting that ipi/nivo combination could represent a reasonable second-line regimen in advanced HCC.<sup>77</sup>

## Current Guidelines for the Treatment of HCC, BCLC 2022 Recommendations

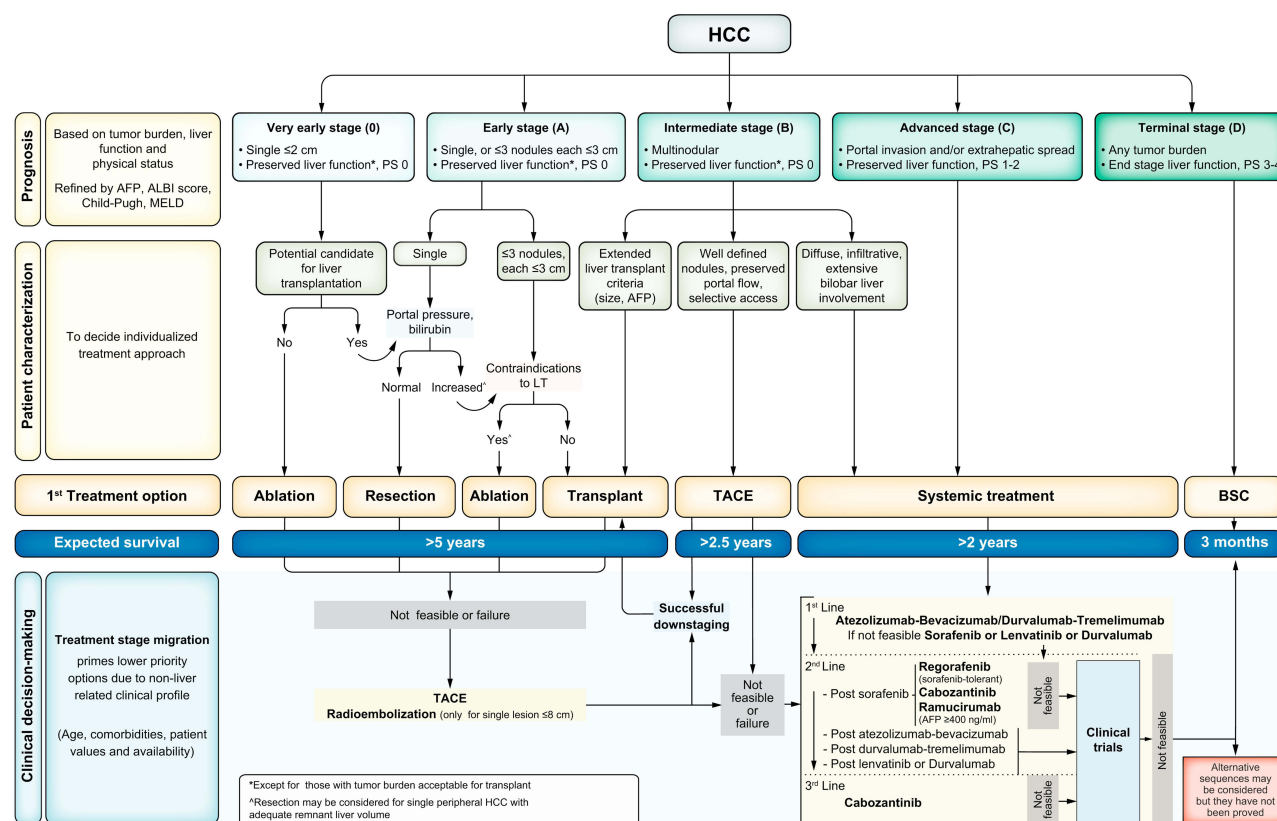
The BCLC guidelines divide HCC into 5 stages: 0 (Very Early), A (Early), B (Intermediate), C (Advanced), D (Terminal) (Figure 1). These 5 stages are linked to prognosis and treatment recommendations. The BCLC was most recently updated in 2022.<sup>78,79</sup> For very early stage (BCLC 0) disease, defined as a solitary HCC < 2 cm without vascular invasion or extrahepatic spread in a patient with preserved liver function and no cancer-related symptoms, liver transplant (LT) is the first choice followed by ablation/resection if LT is not feasible.<sup>78</sup> For early stage (BCLC A), disease defined as solitary HCC irrespective of size or as a multifocal HCC up to 3 nodules (none of them >3 cm), without macrovascular invasion, extrahepatic spread or cancer-related symptoms (PS-0), surgical resection and LT are considered depending on number, location, burden of hepatic lesions, and presence of clinically significant portal hypertension (CSPH) defined by a hepatic venous pressure gradient [HVPG] >10 mmHg.<sup>78</sup>

Intermediate stage (BCLC-B) is defined as multifocal HCC outside of BCLC A criteria with preserved liver function, no cancer-related symptoms, and no vascular invasion or extrahepatic spread. This stage is divided into three groups. The first cohort meets extended liver transplant criteria and LT should be considered for these patients. The second cohort includes patients who have preserved portal flow and defined tumor burden, suggesting the feasibility of selective access to feeding tumor arteries, but are not candidates for LT. These patients are candidates for arterial based therapies like trans-arterial chemoembolization (TACE). If patients meet neither the “extended liver transplant criteria” nor TACE criteria, then systemic therapy should be considered. The third subgroup within BCLC-B includes patients with diffuse, infiltrative, extensive HCC liver involvement. These patients should be referred for systemic therapy.<sup>78</sup>

Advanced stage (BCLC-C) patients are defined as having vascular invasion or extrahepatic spread who are still relatively fit with preserved liver function. BCLC-C patients should be evaluated for systemic therapy.<sup>78</sup> Based on the positive results from IMBrave and HIMALAYA studies, the current recommended first-line option in the updated BCLC algorithm should be targeted therapy. For advanced stage HCC, first-line treatments include atezolizumab plus bevacizumab or durvalumab plus tremelimumab. If these options are not feasible, then sorafenib, lenvatinib, or durvalumab are other options. Second-line therapy post sorafenib typically involves regorafenib, cabozantinib, or ramucirumab.<sup>78,79</sup>

## Immunotherapy Response Biomarkers

Despite the encouraging results of the IMBrave 150 and HIMALAYA trials, identifying biomarkers that predict clinical response to immunotherapy remains crucial to identify which patients may benefit the most. Biomarkers will improve patient selection and treatment outcomes, which is critical as roughly 25% of patients will develop grade 3–4 adverse events from immunotherapy.



**Figure 1** The BCLC system establishes a prognosis in accordance with the 5 stages that are linked to first-line treatment recommendation. The expected outcome is expressed as median survival of each tumour stage according to the available scientific evidence. Individualised clinical decision-making, according to the available data on November 15, 2021, is defined by teams responsible for integrating all available data with the individual patient's medical profile. Note that liver function should be evaluated beyond the conventional Child-Pugh staging. \*Except for those with tumor burden acceptable for transplant. \*Resection may be considered for single peripheral HCC with adequate remnant liver volume. Reprinted with copyright permission from Reig M, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. *J Hepatol*. 2022;76(3):681–693. © 2021 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.<sup>78</sup>

**Abbreviations:** AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; ECOG-PS, Eastern Cooperative Oncology Group-performance status; LT, liver transplantation; MELD, model of end-stage liver disease; TACE, transarterial chemoembolisation.

In general, there is no standard biomarker to predict ICIs outcomes among patients with HCC. Tumor PD-L1 expression is the most widely studied biomarker in HCC, but the data on its predictive potential is controversial.<sup>80,81</sup> Other potential biomarkers related to HCC include infiltrating lymphocytes,<sup>13,80,82</sup> tumor mutational burden (TMB),<sup>83–85</sup> neutrophil-to-lymphocytes ratio and platelet-to-lymphocytes ratio,<sup>80</sup> circulating tumor DNA (ctDNA),<sup>86–89</sup> circulating tumor cells (CTCs),<sup>90</sup> and gut microbiota.<sup>91,92</sup> Unfortunately, the evidence is not yet strong enough to support implementation of these biomarkers in the clinical setting, thus more studies are needed beyond the pre-clinical setting.

Analysis of histopathology, imaging, and immune signatures is likely the most comprehensive way to assess treatment effect.<sup>93</sup> A recent study classified HCC into four groups based on microenvironment lymphocytic infiltration and angiogenic factor expression. These studies included immune-high/angiostatic (IH/AS), immune-mid/angio-mid (IM/AM), immune-low/angiogenic (IL/AG), and immune-low/angio-low (IL/AL). A reciprocal interaction between antitumor immunity and tumor angiogenesis, and an association between poor prognosis with decreased lymphocyte infiltration, and increased vessels encapsulating tumor clusters (VETC)/macrotrabecular-massive (MTM) pattern formation was noted. In turn, this classification may potentially be used to better identify patients expected to respond to immunotherapy alone.<sup>94</sup> Mutations in the CTNNB1 gene lead to activation of the Wnt/ $\beta$ -catenin pathway and may serve as a predictor of response to ICIs. Mutations in Wnt/ $\beta$ -catenin were associated with increased resistance to immunotherapy and poorer prognosis in both pre-clinical and clinical setting.<sup>95,96</sup> These mutations have been observed in “cold” HCC tumors and were associated with IL/AG subtype and VETC positivity, which correlated with tumors that were devoid of CD8<sup>+</sup> T-cells and NK cells and rich in T-Regs.<sup>94,97</sup>



## Conclusion/Expert Opinion

HCC is a rare and aggressive tumor with a high incidence of recurrence and poor prognosis. The unique environment of the liver is balanced between immune tolerance and activation. When this balance is disrupted by chronic inflammation, immune cell exhaustion and fibrosis can occur making the liver vulnerable to carcinogenesis. This perturbation may prove, however, an opportunity to leverage immunotherapy to treat HCC. The IMbrave150 and HIMALAYA trials established that atezolizumab/bevacizumab and durvalumab/tremelimumab can effectively treat advanced HCC. Real-world data has further confirmed the survival benefit of immunotherapy in advanced HCC, as well as patients with more advanced underlying liver disease. Unfortunately, only about 30–40% of patients with HCC respond to immunotherapy and a large proportion of individuals will eventually progress even after demonstrating an initial response. Recent research has focused on overcoming primary and secondary resistance, but the mechanisms remain poorly understood and reliable response biomarkers are still needed. Future progress will require close collaboration and translational work between basic science labs and clinical trial investigators.

Given the propensity for HCC to arise in a dysfunctional liver, patients are prone to recurrence even after a successful resection or ablation. In particular, the underlying non-tumorous environment can promote ongoing carcinogenesis and give rise to either new or recurrent disease. In turn, trials that involve the neoadjuvant and adjuvant setting have been an area of increased interest to treat micrometastatic disease and/or prevent recurrence. In addition, given the relatively high number of patients who present with advanced HCC, there is also interest in using immunotherapy to downstage patients to a resection. Several, small neoadjuvant trials have demonstrated promising results and are currently ongoing. The IMbrave050 trial, a randomized controlled phase III trial designed to study the use of atezolizumab/bevacizumab in the adjuvant setting after resection or ablation of high-risk HCC, recently demonstrated promising results on the interim analysis. To advance treatment, patients with HCC need to be screened and accrued for appropriate clinical trials to accelerate innovation and discovery related to HCC.

## Disclosure

Dr Anne M Noonan is a member of steering committee for clinical trial for Astra Zeneca, and a member of the Advisory Board for Elevar Therapeutics and Eisai, outside the submitted work. The authors report no conflict of interest in this work.

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