Frontline therapy for advanced hepatocellular carcinoma: an update

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Abstract: Hepatocellular carcinoma (HCC) is the fastest increasing cause of cancer-related mortality in the United States and is projected to be the third leading cause of cancer-related mortality in the United States by 2030. Main risk factors include alcoholic cirrhosis, chronic hepatitis B, hepatitis C, and nonalcoholic steatohepatitis (NASH). More than half of the patients have advanced-stage disease at presentation. Currently approved frontline systemic therapy options include sorafenib, lenvatinib, and atezolizumab/bevacizumab. Over the past decade, there has been a significant improvement in survival with a median overall survival of 19.2 months reported with first-line treatment with atezolizumab/bevacizumab. Based on positive results of randomized phase III HIMALAYA trial, durvalumab and tremelimumab combination could become another frontline option. Multiple frontline clinical trials with immune checkpoint inhibitor (ICI) or ICI combined with other novel agents are underway. In the frontline setting, identifying predictive biomarkers for ICI-based or tyrosine kinase (TKI)-based therapy is an unmet need. Subsequent treatment is poorly defined in patients with prior ICI-based therapy since all the available second-line and beyond therapy was studied after first-line sorafenib. Frontline systemic therapy is poorly defined in certain subgroups of HCC such as Child–Pugh B and post-transplant recurrent HCC. The landscape of frontline HCC treatment is rapidly changing, and this article reviews the most recent treatment approaches to frontline therapy for advanced HCC.

Keywords: Hepatocellular carcinoma, immunotherapy, frontline treatment

Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related mortality in the world.[1] In North America and Europe, hepatitis C virus (HCV) is the most common cause of HCC and the majority of HCC develops in the setting of cirrhosis.[2] Autoimmune liver diseases such as autoimmune hepatitis and primary biliary cholangitis are also associated with increased risk of HCC development.[3] HCC is the fastest increasing cause of cancer-related mortality in the United States and 5-year survival is less than 12%.[2] About 40% of patients with HCC can be candidates for curative treatments which include ablation, surgical resection, and liver transplantation.[4] For the majority of patients who present with advanced-stage disease, current US Food and Drug Administration (FDA)-approved systemic treatment options include sorafenib, lenvatinib, and atezolizumab/bevacizumab in the first-line setting. Clinical trials are underway to expand frontline systemic treatment options by combining immune checkpoint inhibitors (ICIs) with tyrosine kinase inhibitors (TKIs) or other novel agents. Nivolumab/ipilimumab, regorafenib, cabozantinib, pembrolizumab, and ramucirumab (for patients AFP > 400) are approved in the second-line setting after failure of sorafenib[5–11] None of the currently approved agents have been studied in patients who failed atezolizumab/bevacizumab combination or other prior anti-PD-1/PD-L1 antibody-based treatment.[12] Therefore, novel therapies exploring rational combinations in immunotherapy refractory HCC patients is an

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area of unmet need. Furthermore, all the approved agents were studied in patients with compensated cirrhosis or Child–Pugh A status. Patients with uncompensated cirrhosis [Child–Pugh Score (CPS) B or CPS C] and patients with prior liver transplant were excluded from HCC trials. Frontline systemic therapy options in these special HCC subgroups are lacking. The current manuscript aims to provide a review of the current approach to frontline systemic therapy of advanced HCC and provides an update on the ongoing research in this very rapidly evolving field.

Overview of currently approved frontline systemic therapy options

Based on the Study of Heart and Renal Protection (SHARP)[5] trial, frontline systemic therapy of HCC was limited to sorafenib. Recently reported landmark trials REFLECT[8] and IMbrave150[10] resulted in the approval of the lenvatinib and atezolizumab/bevacizumab (Table 1).

Sorafenib

Sorafenib is a multikinase inhibitor targeting vascular endothelial growth factor receptor (VEGFR) 1–3, platelet-derived growth factor receptor-beta (PDGFR-β), and RAF-MEK-ERK pathway. The landmark SHARP trial established multikinase inhibitor sorafenib as the first FDA-approved systemic therapy for advanced HCC.[5] This randomized double-blind placebo-controlled trial of 602 patients with advanced HCC with no prior systemic therapy randomized patients sorafenib *versus* placebo in one-to-one ratio. The majority of patients were accrued from Europe. In total, 97% of patients had Child–Pugh A disease. The most common etiology of HCC was hepatitis C, alcohol, and hepatitis B. In total, 51% of patients had extrahepatic disease and almost half of the patients had not received any treatment of HCC. Sorafenib improved median overall survival (mOS) significantly compared with placebo [mOS 10.7 *versus* 7.9 months; hazard ratio (HR) = 0.69; 95% confidence interval (CI) 0.55–0.87; $p < 0.001$] and became the first FDA-approved systemic therapy for advanced HCC. Objective response rate (ORR) was 2% *versus* 1% and disease control rate (DCR) was 43% *versus* 32% ($p = 0.002$), respectively. No complete response was seen in either group. Grade III drug-related adverse events were more common in sorafenib 8% *versus* 2% ($p < 0.001$). Diarrhea,

Table 1. Key findings of landmark clinical trials in frontline treatment of advanced HCC.

Trial name	Treatment arms	Primary endpoint	Patient number	ORR (%)	DCR (%)	PFS (months)	OS (months)	HR	Reference
SHARP	Sorafenib versus placebo	OS	602	2 versus 1	43 versus 32	5.5 versus 2.8	10.7 versus 7.9	0.69	Llovet et al.[5]
REFLECT	Lenvatinib versus sorafenib	OS	954	24.1 versus 9.2	75.5 versus 60.5	7.4 versus 3.7	13.6 versus 12.3	0.92	Bruix et al.[6]
IMbrave150	Atezolizumab + bevacizumab versus sorafenib	OS, PFS	501	27.3 versus 11.9	73.6 versus 55.3	6.8 versus 4.3	19.2 versus 13.4	0.66	Finn et al.[10]
HIMALAYA	Tremelimumab + Durvalumab versus Sorafenib vs durvalumab	OS for tremelimumab + durvalumab vs sorafenib	1324	20.1 versus 5.1 vs 17.0	60.1 vs 60.7 versus 54.8	3.78 versus 4.07 versus 3.65	16.4 versus 13.8 versus 16.6	0.78	Abou-Alfa et al.[42]
COSMIC 312	Cabozantinib and atezolizumab versus sorafenib versus cabozantinib	OS, PFS	837	11 versus 6.4	78 versus 65	6.8 versus 4.2 versus 5.8	15.4 versus 15.5 vs NA	0.90	Kelley et al.[49]

DCR, disease control rare; HCC, hepatocellular carcinoma; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; REFLECT, A phase 3, multinational, randomized, non-inferiority trial; SHARP, Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol.

hand–foot skin reaction, and hypertension were the most common grade III adverse events. The majority of patients included in the SHARP trial were from predominantly Western countries with HCV and alcohol as the etiology of HCC and a randomized double-blind placebo-controlled trial with sorafenib was later conducted in Asia Pacific region where hepatitis B is the predominant etiology of HCC. Survival benefit of sorafenib was shown in this trial as well. mOS was 6. 5 months (95% CI 5.56–7.56) *versus* 4.2 months (3.75–5.46) (HR = 0.68, 95% CI 0.50−0.93, *p* = 0.014). Proper management of treatment-related AEs was shown to translate into longer treatment duration and survival benefit with sorafenib in subsequent studies.[13]

Lenvatinib

Following the SHARP trial for almost a decade, a series of randomized clinical trials failed to identify a new agent in the frontline setting.[8,14] The REFLECT trial evaluated lenvatinib, a multikinase inhibitor targeting VEGFR1–3, fibroblast growth factor receptor (FGFR) 1–4, PDGFR alpha (α), ret proto-oncogene (RET), and kit-proto-oncogene (KIT) in previously untreated advanced-stage HCC. REFLECT study was an open-label randomized phase III noninferiority study comparing lenvatinib with sorafenib in 954 patients with advanced HCC with no prior systemic therapy. In total, 33% of patients enrolled were from Western countries and 99% of patients had Child–Pugh A disease. Extrahepatic spread was present in 61% of patients. The most common etiology was hepatitis B (53% *versus* 48%), then hepatitis C (19% *versus* 26%), respectively. Approximately one-third of patients did not receive any prior regional treatment for HCC. Of note, patients with 50% or higher liver tumor burden, gross invasion of the bile duct, or invasion at the main portal vein were excluded from the study. mOS was 13.6 months (95% CI 12.1–14.9) with lenvatinib compared with 12.3 months with sorafenib (95% CI 10.4–13.9; HR = 0.92, 95% CI 0.79–1.06) and met the noninferiority criteria. Median progression-free survival (PFS) was superior in lenvatinib group compared with sorafenib, 7.4 *versus* 3.7 months (HR = 0.66, 95% CI 0.57–0.77, *p* < 0.0001). ORR was 18.8% *versus* 6.5%, *p* < 0.0001, and DCR was 72.8% *versus* 59.0%, median time to progression was 7.4 months *versus* 3.7 months (HR = 0.61, 95% CI 0.51–0.72, *p* < 0.0001) favoring lenvatinib per

masked independent reviewing per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Grade II adverse events were similar in both groups. Hypertension (42%), diarrhea (39%), decreased appetite (34%) and decreased weight (31%) were the most common any grade adverse events in lenvatinib group, palmar–plantar erythrodysesthesia (52%), diarrhea (46%), hypertension (30%), and decreased appetite (27%) were the most common any grade adverse events in sorafenib group. Based on the results of the REFLECT study, lenvatinib was approved as a frontline systemic therapy option in advanced HCC by FDA.

Atezolizumab/bevacizumab

Immune checkpoints are expressed on lymphocytes and contribute to immune exhaustion during chronic inflammation.[15] Tumor cells utilize this physiological mechanism to create immune evasion and a more tumor favorable microenvironment. ICIs are monoclonal antibodies that block programmed cell death protein-1 (PD-1), programmed cell death ligand-1 (PD-L1), and or cytotoxic T lymphocyte–associated antigen-4 (CTLA-4). This blockade induces T-cell rejuvenation and unleashes the cytotoxic T-cell activity against tumor cells.[16,17] Preclinical and clinical studies revealed synergistic effects of VEGF and PD-1/PD-L1 blockade.[18–20] Atezolizumab is a monoclonal antibody (Ab), which blocks PD-L1 and bevacizumab is a monoclonal antibody against VEGF-A. In a phase Ib trial, the combination of atezolizumab and bevacizumab was found to be safe and preliminary activity was seen in patients with advanced HCC. Based on synergistic effect of PD-1/PD-L1 and VEGF pathway inhibition and encouraging phase Ib trial[21] data, an open-label phase III trial (IMbrave150) randomized 336 patients with previously untreated advanced HCC to atezolizumab and bevacizumab combination or sorafenib in a 2:1 ratio.[10] All patients had Child–Pugh A disease. In total, 40% of patients were from Asia; hepatitis B (49% *versus* 46%) was the most common underlying etiology. Approximately 60% had extrahepatic metastasis. Patients were required to have baseline evaluation and treatment for esophageal varices per local standards. Atezolizumab/bevacizumab was shown to have superior mOS (estimated survival at 12 months: 84.8%, 95% CI 80.9–88.7 *versus* 54.6%, 95% CI 45.2–64.0), and median PFS (6.8 months: 95% CI 5.7–8.3 *versus*

4.3 months: 95% CI 4.0–5.6; HR = 0.59, 95% CI 0.47–0.76, $p < 0.001$) as compared with sorafenib. DCR was superior in atezolizumab/bevacizumab group, 73.6% *versus* 55.3%. Similarly, ORR (27.3% *versus* 11.9%) and complete response rate (5.5% *versus* 0%) were higher in the combination arm. Grade 3–4 adverse events occurred in 56.5% with atezolizumab/bevacizumab group *versus* 55.1% with sorafenib group. Incidence of upper gastrointestinal tract bleeding was 7% in combination group *versus* 4.5% in sorafenib group. With the approval of several frontline therapy options as single-agent TKI, ICI, and anti-VEGF combination and potentially upcoming anti-PD-L1/CTLA-4 Ab combination identification of patients who would benefit from each approach the most is a major area of unmet need in frontline HCC management.

Emerging systemic therapeutic options on the horizon

Immunosuppressive tumor microenvironment in HCC

Chronic inflammation and hypervascularity are hallmarks of HCC.[22] These hallmarks are associated with immunosuppressed tumor microenvironment (TME) and CD8+ T-cell exhaustion, which is at least partly driven through signaling *via* the VEGF/VEGFR2 pathway. While this pathway is most notable in regulating angiogenesis, it is also connected closely to T-cell exhaustion *via* multiple mechanisms and VEGF pathway blockade can improve T-cell exhaustion.[19,23] Chronic inflammation and hypervascularity are associated with impaired antitumor immune responses, in part mediated by increased expression of immune checkpoints such as PD-1 and CTLA-4 on effector cells which result in tumor immune escape in HCC.[19,24] High proportions of immune inhibitory cells including tumor-associated macrophages (TAMs),[25] myeloid-derived suppressor cells (MDSCs),[26,27] and T-regulatory (T-regs)[28] cells in the HCC TME contribute to resistance to checkpoint blockade. Furthermore, HCC cells secrete soluble mediators such as VEGF, colony-stimulating factor 1 (CSF 1),[29] platelet-derived growth factor (PDGF), and transforming growth factor-beta (TGF-β)[30] which promote the development of this immunosuppressive environment.[25] Other immune checkpoints such as lymphocyte-activation gene 3 (LAG-3)[31] and mucin domain containing-3 (TIM-3)[32–34] also contribute to immunosuppressive TME and emerged as potential treatment targets in HCC. Frontline therapy with ICI-based therapy has become standard of care in HCC; however, this approach induces objective responses in up to one-third of patients; therefore, novel approaches to increase the efficacy of ICI-based therapy are being explored in multiple frontline clinical trials. Select ongoing clinical trials with single or dual ICIs, ICI combined with TKIs, or ICI combined with other novel agents are summarized in Table 2.

Monotherapy with ICIs

Monotherapy with anti-PD-1/PD-L1 or anti-CTLA-4 Ab treatment has achieved up to 20% ORR in advanced HCC after sorafenib treatment.[7,35–37] Based on promising response rates with single-agent ICIs in the second-line setting, this approach has been explored in frontline treatment. CheckMate 459 trial explored frontline single-agent anti-PD-1 Ab in advanced HCC. In this study, nivolumab was compared with sorafenib in 743 patients with advanced HCC with no prior systemic therapy.[38] All patients had Child–Pugh A disease. ORR was 15% *versus* 7%, mOS was 16.4 *versus* 14.7 months, and median PFS was 3.7 *versus* 3.8 months. The primary endpoint of overall survival (OS) was not achieved in this trial indicating novel combination approaches with ICIs are needed in frontline HCC treatment. A randomized phase III RATIONALE 301 trial is comparing anti-PD-1 antibody tislelizumab with sorafenib[39] (NCT03412773). Tislelizumab is an Ig-G4 monoclonal antibody against PD-1, which is designed to escape Fcγ receptor-1-mediated resistance to anti-PD-1 Ab treatment.

Dual ICI therapy

PD-1/PD-L1 and CTLA-4 blockade by ICIs can induce T-cell rejuvenation and unleash cytotoxic T-cell activity against tumor cells.[16,17] ICIs regulate different subsets of T-cell populations to induce antitumor activity.[40] While anti-PD-1 Ab has been proposed to induce reinvigoration and expansion of effector-like CD8 T cells, anti-CTLA-4 Ab may act at the level of T-cell priming and can invigorate T helper type 1 (Th1)-like effector CD4 T cells in addition to CD8 T cells in human melanoma and murine tumor models.[40] Based on this rational multicohort, CheckMate 040 trial evaluated dual checkpoint inhibition by nivolumab and

Table 2. Select ongoing clinical trials in frontline treatment of advanced HCC.

Clinical trial identifier	Phase	Agent(s)	Primary endpoint(s)	Setting	Recruitment status
CheckMate 9DW (NCT04039607)	3	Nivolumab + ipilimumab *versus* sorafenib *versus* lenvatinib	OS	First line	Active, not recruiting
LEAP-002 (NCT03713593)	3	Lenvatinib + pembrolizumab *versus* lenvatinib + placebo	PFS, OS	First line	Active, not recruiting
RATIONALE 301 (NCT03412773)	3	Tislelizumab *versus* sorafenib	OS, Safety	First line	Active, not recruiting
NCT03680508	2	Cobolimab (anti-TIM-3 Ab) + dostarlimab	ORR	First line	Recruiting
NCT03764293	3	Apatinib + camrelizumab *versus* sorafenib	PFS, OS	First line	Recruiting
DEDUCTIVE (NCT03970616)	1b/2	Tivozanib + durvalumab	Safety	First line and second line	Recruiting
NCT04183088	2	Regorafenib + tislelizumab	Safety, ORR, PFS	First line	Recruiting
GOING (NCT04170556)	½	Regorafenib followed by nivolumab	Safety	Second line	Recruiting
RENOBATE (NCT04310709)	2	Regorafenib + nivolumab	ORR	First line	Recruiting
REGSIN (NCT04718909)	2	Regorafenib + sintilimab	PFS	Second line	Recruiting
ORIENT-32 (NCT03794440)	2/3	Sintilimab + IBI305 *versus* sorafenib	PFS, OS	First line	Active, not recruiting
NCT04050462	II	Cabiralizumab + nivolumab *versus* nivolumab *versus* nivolumab + BMS-986253	ORR	First line	Recruiting

HCC, hepatocellular carcinoma; ORR, overall response rate; OS, overall survival; PFS,

ipilimumab in 148 advanced HCC patients with prior sorafenib treatment in three different dosing schedules. The treatment arm with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks followed by nivolumab 240 mg every 2 weeks schedule achieved 31% ORR, 54% DCR, and 22.8 months mOS.[41] Any grade and III–IV immune-mediated adverse events were seen in 94% and 53% in the same cohort. Subsequently, this dual ICI therapy received accelerated approval for second line for advanced HCC treatment post-sorafenib in the United States. Immune-mediated adverse events occur more frequently with dual ICI therapy compared with single-agent ICI and emerging role of Treg inhibition in immune-mediated adverse event development is suggested.[3] Currently, a randomized phase III CheckMate 9DW trial compares nivolumab and ipilimumab combination with sorafenib *versus* lenvatinib in the frontline treatment of advanced HCC (NCT04039607). The phase III randomized HIMALAYA trial compared durvalumab (anti-PD-L1) with and without tremelimumab (anti-CTLA-4 Ab) to sorafenib in frontline treatment of advanced HCC (NCT03298451). The results of this study were recently reported at ASCO Gastrointestinal Cancers Syposium.[42] The combination therapy improved survival compared with sorafenib (16.4 months *versus* 13.8 months, HR = 0.78, 95% CI 0.65–0.92, $p = 0.0035$). Single-agent durvalumab was found to be noninferior to sorafenib (HR = 0.86; 95% CI 0.73–1.03). ORRs were 20.1%, 17.0%, and 5.1% with the dual ICI combination, single-agent durvalumab, and sorafenib, respectively. Potential approval of durvalumab and tremelimumab combination and single-agent durvalumab would establish an ICI-only based therapy in frontline treatment of HCC.

ICI and TKI combination

Lenvatinib was shown to decrease TAMs and increase CD8$^+$ T cells in the TME in preclinical studies.[43] Combination of lenvatinib and anti-PD-1 Ab revealed increased activation CD8$^+$ T cells, decreased TAMs, and achieved synergistic antitumor activity in murine HCC models.[44] Based on immunomodulatory effects of lenvatinib, a phase Ib trial explored lenvatinib plus pembrolizumab in 104 patients with previously untreated advanced HCC.[45] ORR of 36% and DCR of 88% were achieved. Following promising results of this study, an ongoing randomized double-blinded phase III LEAP-002 trial compares lenvatinib and pembrolizumab with lenvatinib plus placebo (NCT03713593).

Cabozantinib was shown to have immune-permissive properties in preclinical and clinical studies which can create a synergistic effect with ICIs.[46] Cabozantinib improved the tumor cell sensitivity to immune-mediated lysis by cytotoxic T lymphocytes in MC38-carcinoembryonic antigen (CEA) cell model, upregulated expression of MHC-I molecules on the tumor cells, and increased the potential for antigen presentation and T-cell recognition of the tumor cells.[47] As single-agent cabozantinib increased the frequency of peripheral CD8$^+$ T cells, decreased T-regs and MDSCs in C57BL/6 mice preclinical model, and improved peripheral T-cell proliferation and function when combined with a therapeutic cancer vaccine.[47] Cabozantinib increased infiltrating CD8$^+$ T cell, decreased TAMs and MDSCs infiltration into the TME, decreased tumor vascular density in the MC38-CEA preclinical model, and enhanced antitumor effects as a single agent and in combination with a cancer vaccine in the same model.[47] The encouraging data from preclinical studies translated into multiple clinical trials with cabozantinib combined with ICIs in advanced HCC. CheckMate 040 trial evaluated the efficacy of nivolumab and cabozantinib with or without ipilimumab in 71 sorafenib naïve or experienced advanced HCC patients.[48] Thirty-six patients received cabozantinib and nivolumab and 35 patients received cabozantinib, nivolumab, and ipilimumab. Doublet regimen achieved 17% ORR and triplet regimen achieved 26% ORR. DCR was 81% *versus* 83%, respectively. More frequent grade III/IV treatment-related AEs were reported in triplet arm (71% *versus* 42%). Randomized phase III COSMIC-312 trial evaluated the efficacy of cabozantinib 40 mg daily and atezolizumab 1200 mg every 3 weeks *versus* sorafenib 400 mg twice daily *versus* cabozantinib 60 mg daily as first-line treatment in advanced HCC.[49] PFS and OS were dual primary endpoints. Eight hundred and thirty-seven patients were randomized, 39% had nonviral etiology, and 29% were enrolled from Asia. Cabozantinib and atezolizumab combination improved PFS compared with sorafenib, median PFS 6.8 *versus* 4.2 months. The interim analysis did not reveal improvement in OS and the final analysis is still ongoing (NCT01658878).

Regorafenib inhibits vascular VEGFR 1–3, angiopoietin-1 receptor (TIE2), c-KIT, RET, PDGFR alpha and beta, FGFR 1–2, and BRAF.[50,51] Therefore, it is involved in tumor angiogenesis, metastasis, oncogenesis, tumor immunity, and immunomodulation as shown in preclinical and clinical studies.[52–54] Based on this rationale, a phase Ib study examined regorafenib and pembrolizumab combination in frontline setting.[55] Thirty-five patients were treated at 120 mg regorafenib dose and 22 patients were treated at 80 mg regorafenib dose; pembrolizumab was a standard dose of 200 mg every 2 weeks. Of 32 evaluable patients on the 120 mg cohort, 31% ORR and 88% DCR were reported. Of 22 patients on the 80 mg cohort, 18% ORR and 91% DCR were reported. Less treatment-related AEs were reported in the 80 mg cohort.

Considering promising efficacy and tolerability data with TKI and ICI combinations, several other agents are being explored in frontline setting in similar study designs worldwide as summarized in Table 2. For example, a phase II study examines regorafenib and nivolumab (NCT04310709), a randomized phase III trial explores apatinib plus camrelizumab (anti-PD-1 Ab) *versus* sorafenib (NCT03764293), phase I/II study examines tivozanib (oral VEGF inhibitor) plus durvalumab (NCT03970616), and a phase II study explores regorafenib plus tislelizumab (anti-PD-1 Ab) (NCT04183088).

ICI and novel agent combination

Multiple pathways and soluble factors play a key role in immune evasion and resistance to single or dual ICI therapy in HCC TME.[15,32] Novel clinical trials are underway to explore the potential of these targets to improve the efficacy of ICIs therapy in advanced HCC. For example, a phase II

trial with relatlimab (anti-LAG-3 Ab) and nivolumab is ongoing in immunotherapy naïve patients but after prior TKI (NCT04567615). A phase II study is examining the efficacy of cobolimab (anti-TIM-3 Ab) and dostarlimab (anti-PD-1 Ab) in previously untreated advanced HCC (NCT0680608). A phase II study of cabiralizumab (anti-CSF1R antibody) and nivolumab *versus* nivolumab *versus* BMS-986253 (anti-IL-8 Ab) *versus* nivolumab in frontline setting (NCT04050462).

Unaddressed challenges in frontline treatment of advanced HCC

Identifying predictive biomarkers in an area of unmet need

Predictive biomarkers for ICI-based or TKI-based frontline therapy have not been identified. Such biomarkers could enrich responders and help in the development of a more rational approach for treatment selection in the frontline setting. Microsatellite instability sensitizes tumors to checkpoint inhibitors but the incidence of this molecular subtype in HCC is rare. Recently, β-catenin activation was shown to lead to ICI resistance.[56,57] CTNNB1 (β-catenin pathway)-mutated HCC was shown to have decreased tumoral T-cell infiltration.[58] Furthermore, β-catenin activation-induced immune escape by decreasing dendritic and T-cell recruitment and caused resistance to anti-PD-1 Ab treatment in preclinical study by Ruiz de Galarreta *et al.* in a novel genetically engineered mouse model (GEMM).[59] In a small cohort of patients with advanced HCC activated β-catenin signaling was associated with decreased response to single-agent anti-PD-1 and anti-PD-L1 Ab treatment.[60]

Emerging literature suggests a potential predictive role of HCC etiology in outcomes with ICIs.[61] In the preclinical study with nonalcoholic steatohepatitis (NASH)-induced HCC mouse model by Pfister *et al.*, unconventionally activated exhausted $CD8^+$ $PD1^+$ T-cell population was identified. Prophylactic anti-PD-1 antibody treatment of this tumor model resulted in increased incidence of NASH-induced HCC. Furthermore, in the same study, a meta-analysis of three randomized trials examining anti-PD-1 Ab treatment revealed that patients with nonviral etiology did not respond to anti-PD-1 therapy and NASH-induced HCC patient had decreased survival.

Advanced HCC patients with Child–Pugh class B

In frontline management of advanced HCC, all available systemic therapy options were studied and approved in patients with Child–Pugh class A (CPA) cirrhosis.[5–11] Limited data are available with sorafenib in patients with Child–Pugh class B (CPB).[62–64] In the prospective registry, GIDEON study, better OS was reported in CPA (13.6 months) than class B (5.2 months) and class C (2.6 months).[62] Treatment-related adverse events (TRAEs) leading to drug discontinuation were similar between CPA and CPB (17% *versus* 21%). A retrospective study of 98 patients with advanced HCC and CPA and CPB ($n = 38$) treated with sorafenib revealed poorer outcomes in CPB.[65] Metronomic capecitabine *versus* best supportive care was also studied in a retrospective multicenter study in HCC with CPB and no prior systemic therapy and was noted be tolerated well.[66] A prospective trial evaluated nivolumab in advanced HCC patients with further liver dysfunction. In a cohort of CheckMate 040 study, nivolumab was studied in 49 patients with advanced HCC with CPB 7, 8. An overall response rate (ORR) of 10.2% and DCR of 55.1% were reported.[67] TRAEs were reported in 51% of patients and 8.2% hepatic TRAEs. The safety profile was comparable with cohorts of patients with CPA cohorts. A retrospective study of 18 patients with advanced HCC and CPB status who were treated with nivolumab revealed 17% ORR including two partial responses and one complete response.[63] Clinical trials examining the role of ICIs in this patient population are needed.

Post-transplant recurrent advanced HCC

Liver transplantation is a curative option in HCC with 5-year OS between 65% and 85%.[68] However, up to 20% of patients develop recurrent disease in 5 years and prognosis remains poor.[68–70] HCC recurrence post-transplant is usually extrahepatic (up to 67%) hence requires effective systemic therapy options.[70,71] Recurrent HCC after transplantation is defined as metastasis from the native liver that could occur due to undetected extrahepatic metastasis that was present before liver transplantation or due to circulating HCC cell clones engrafting into target organ.[69,70] Although frontline systemic treatment of advanced HCC has several options, management of patients with recurrent HCC after liver

transplantation poses a unique challenge for routine clinical practice due to the absence prospective clinical trial data.[72] The data in this setting are limited to retrospective case series with TKIs and predominantly sorafenib.[69,73–76] In a systematic review of the literature including 1021 patients with recurrent HCC after liver transplantation, sorafenib was utilized in 20% of patients, 42.1% of the patients required dose reductions, and 46.5% achieved stable disease.[70] Regorafenib was studied in 28 patients who progressed on sorafenib in recurrent HCC post-transplant setting and revealed mOS of 12.9 months.[77] As more novel and better tolerated agents emerge in advanced HCC treatment, it is warranted to explore these agents in recurrent HCC after liver transplantation in a prospective manner. Prospective clinical trials mainly with TKIs are underway in this challenging clinical setting (NCT04204850) and (NCT05103904).

Conclusion

Frontline systemic therapy of advanced HCC is rapidly changing. Identification of biomarkers to identify patients for most suitable for ICI-based *versus* TKI-based frontline therapy, developing treatment strategies to improve the efficacy of immunotherapy, developing frontline systemic therapy options in patients with CPB, and post-transplant recurrent HCC are areas of active research. Recently completed and ongoing clinical trials have the potential to expand frontline systemic therapy options in advanced HCC and shed light on special HCC populations.

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