

Drug Treatment for Advanced Hepatocellular Carcinoma

Subjects: **Oncology**

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Hepatocellular carcinoma (HCC) has high mortality and a high risk of recurrence after radical treatment. It is recognized as the fourth most common cause of death in cancer patients and has been a healthcare burden globally. Unfavorable outcomes are largely due to the asymptomatic presentation of disease until a later stage, and a lack of effective systemic treatments in advanced HCC. For early-stage disease, curative intent treatments include surgery, radiofrequency ablation, and liver transplant. For advanced disease, conventional cytotoxic chemotherapy is ineffective, with limited clinical benefits. In the era before multikinase inhibitors, the overall survival (OS) for HCC patients with advanced disease was expected to be a few months only.

advanced hepatocellular carcinoma

systemic therapies

immunotherapy

multikinase inhibitor

1. Systemic Therapies for Advanced Hepatocellular Carcinoma (HCC)

1.1. First-Line Systemic Therapy

1.1.1. Single Agent Multikinase Inhibitor

Sorafenib

Until 2017, the only first-line treatment in unresectable HCC was sorafenib. Sorafenib is a multikinase inhibitor which inhibits the activities of kinases and pathways involved in angiogenesis and cell proliferation. It inhibits platelet-derived growth factor receptor (PDGFR), c-KIT, vascular endothelial growth factor receptor (VEGFR) 2/3, RET, RAS/RAF/mitogen-activated protein kinase (MAPK), FLT-3, and Janus kinase (JAK)/signal transducer and activator of transcription protein (STAT) [1][2]. The benefit of first-line sorafenib for inoperable HCC patients with Child A cirrhosis was demonstrated in the multicenter phase III European SHARP trial and the Asia-Pacific trial [3][4]. In the SHARP trial, the sorafenib group showed a better median OS of 10.7 months and time to radiologic progression of 5.5 months, compared with those in the placebo group, which were 7.9 months and 2.8 months, respectively [3]. The time to progression (TTP) and survival benefit were similarly seen in the Asia-Pacific trial which included mostly hepatitis B patients, with median OS and TTP of 6.5 months and 2.8 months in the treatment group, and 4.2 months and 1.4 months in the placebo group, respectively [4]. However, according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, the partial response (PR) was low (SHARP: 2%; Asia-Pacific: 3.3%), and complete response (CR) was not seen in both trials [3][4]. With respect to the benefit based on

the etiology of liver disease, the SHARP trial identified that the difference between treatment and placebo group in median OS was most significant in the hepatitis C-HCC group at 6.6 months. The differences in OS were smaller in hepatitis B-HCC at 3.6 months and alcoholic HCC at 2.3 months [5].

Regarding the safety profile for sorafenib, adverse events (AEs) were generally manageable. The most common grade 3/4 AEs included hand–foot syndrome (HFS) (SHARP: 8%; Asia–Pacific: 11%) and diarrhea (SHARP: 8%; Asia–Pacific: 6%) [3][4].

Although sorafenib increases survival in advanced HCC patients, drug resistance is commonly encountered [6]. Clinical evidence supporting the presence of hypoxia is essential in HCC development. The persistent antiangiogenic effect exerted by the long-term use of sorafenib can lead to hypoxia-inducible factors (HIFs)—mediated cellular responses which promote and select resistant cells adaptive to hypoxic microenvironment. Therefore, HIF-1 α and HIF-2 α overexpression are recognized as poor prognostic markers in HCC patients [6].

Lenvatinib

Lenvatinib is another multikinase inhibitor which inhibits vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), KIT, RET and fibroblast growth factor receptor (FGFR) activities [7]. In 2018, the REFLECT trial revealed non-inferiority median OS of lenvatinib at 13.6 months compared with 12.3 months in the sorafenib group [8]. Regarding secondary endpoints, determined by investigator review according to modified RECIST (mRECIST), lenvatinib was associated with higher ORR of 24.1%, better PFS of 7.4 months and longer median TTP of 8.9 months. For the sorafenib group, the results were 9.2%, 3.7 months and 3.7 months. A masked independent imaging review according to mRECIST confirmed the above results. Lenvatinib significantly improved ORR at 40.6%, PFS at 7.3 months and median TTP at 7.4 months. In the sorafenib group, the results were 12.4%, 3.6 months and 3.7 months, respectively [8]. In terms of treatment-related toxicities, lenvatinib was associated with more common grade 3/4 hypertension (23% vs. 14%), while sorafenib had more HFS (52% vs. 37% any grade, 11% vs. 3% grade 3 or worse) and alopecia of any grade (25% vs. 3%).

Based on this finding, lenvatinib is now an alternative first-line multikinase inhibitor for advanced HCC. Japan approved its use in March 2018. Subsequently, it received approval in the U.S. for the same indication in August 2018. The American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN) and European Association for the Study of the Liver (EASL) also supported its use in the first-line setting, but limited to individuals with Child A cirrhosis [9][10][11].

1.1.2. Combining ICI with an Anti-VEGF Antibody

Atezolizumab and Bevacizumab

Atezolizumab is a PD-L1 blocker, and bevacizumab is a VEGF inhibitor. Both are monoclonal antibodies. This combination is now Food and Drug Administration (FDA) approved and has superseded sorafenib as the gold-standard first-line treatment in unresectable HCC. This approval was based on the findings from the IMBrave 150

trial which compared atezolizumab and bevacizumab with sorafenib in the first-line setting [12]. The combination therapy demonstrated a significantly better median PFS of 6.8 months vs. 4.3 months for sorafenib. The median OS was also improved to 19.2 months with combination therapy vs. 13.4 months for sorafenib. The ORR was almost threefold better with atezolizumab and bevacizumab (30%), compared with sorafenib (11%) [13]. In the atezolizumab and bevacizumab group, 5.5% achieved CR, and 21.8% achieved PR. There was no CR in the sorafenib group.

The overall grade 3/4 AEs were similar in both groups (atezolizumab–bevacizumab: 57%; sorafenib: 55%), but hypertension (atezolizumab–bevacizumab: 15.2%; sorafenib: 12.2%), proteinuria (atezolizumab–bevacizumab: 3.0%; sorafenib: 0.6%), raised aspartate aminotransferase (AST) (atezolizumab–bevacizumab: 7.0%; sorafenib: 5.1%) and elevated alanine aminotransferase (ALT) (atezolizumab–bevacizumab: 3.6%; sorafenib: 1.3%) were more common with combination therapy [12]. There were no unexpected safety signals.

In summary, for Child A cirrhosis patients with satisfactory performance status, atezolizumab–bevacizumab is now recommended as the first-line therapy. This is consistent with the ASCO 2020 guideline [9], the Society for Immunotherapy of Cancer 2021 guideline [14], and the recommendation from the EASL [15].

Atezolizumab and Cabozantinib

The COSMIC-312 phase III trial compared cabozantinib monotherapy 60 mg daily, sorafenib monotherapy 400 mg twice daily, and intravenous atezolizumab 1200 mg every three weeks and cabozantinib 40 mg daily in the first-line setting. It randomized 837 patients into the three groups. According to RECIST v1.1, PFS reviewed by a blinded independent review committee (BIRC) was met at a median follow-up of 15.8 months. Atezolizumab–cabozantinib demonstrated a significantly longer median PFS of 6.8 months and reduced disease progression risk by 37% in comparison with sorafenib with a median PFS of 4.2 months (Hazard ratio (HR) 0.63; 99% confidence interval (CI) 0.44–0.91; $p = 0.0012$). The ORRs were 11%, 3.7% and 6.4% in the atezolizumab-cabozantinib, sorafenib and cabozantinib groups, respectively [16]. However, the median OS for the atezolizumab-cabozantinib group and sorafenib group were similar, at 15.4 months and 15.5 months, respectively (HR 0.90; 96% CI 0.69–1.18; $p = 0.438$). The final analysis did not yield a statistically significant OS benefit for cabozantinib plus atezolizumab group compared with sorafenib [17]. A total of 54% and 32% of patients in the atezolizumab–cabozantinib and sorafenib groups experienced grade 3/4 TRAEs. The most common toxicities included HFS (atezolizumab-cabozantinib: 7.9%; sorafenib: 8.2%), hypertension (atezolizumab–cabozantinib: 7.0%; sorafenib: 6.3%), AST elevation (atezolizumab–cabozantinib: 6.5%; sorafenib: 2.4%) and ALT elevation (atezolizumab–cabozantinib: 6.3%; sorafenib: 1.9%), all of which were less than 10% [18]. In summary, COSMIC-312 demonstrated that atezolizumab–cabozantinib was superior to sorafenib regarding PFS rather than OS in the first-line setting with a manageable safety profile.

1.1.3. PD-1 and CTLA-4 Antibodies Combination

Durvalumab and Tremelimumab

A number of studies demonstrated that prolonged exposures to CTLA-4 inhibitors might not be necessary for sustained anti-tumor effects. Zeynep et al. reported that a single dose of CTLA-4 inhibitor tremelimumab could lead to very long duration of objective anti-tumor responses beyond 12 years in advanced melanoma [19]. A phase Ib study showed tremelimumab 1 mg/kg combined with durvalumab (anti-PD-L1) 20 mg/kg every 4 weeks exerted anti-tumor effect with manageable tolerability in advanced non-small cell lung cancer [20]. Recently, a phase I/II trial evaluated durvalumab (20 mg/kg or 1500 mg) and tremelimumab (1 mg/kg or 75 mg) every 4 weeks for four doses followed by durvalumab 20 mg/kg every 4 weeks alone with tolerable toxicity profile and promising initial efficacy in the second-line setting [21]. Expansion phase II trial studied combination 75 mg tremelimumab (T) plus 1500 mg durvalumab (D) (T-75/D-1500) and T-300/D1500, and the high-dose T-300/D1500 combination group showed the best risk and benefit profile with a median OS and ORR of 18.7 months and 22.7%, respectively. The T-300/D-1500 group was further evaluated as first-line therapy in the phase III HIMALAYA trial which was recently published at the ASCO gastroenterology (GI) 2022 meeting [22]. Treatment-naïve patients with inoperable HCC were randomized into four groups: (1) STRIDE (single T regular interval D) regimen: T-300/D-1500 (one dose) and then D-1500 every four weeks; (2) D-1500 every four weeks; (3) sorafenib 400 mg twice daily; (4) T-75 every four weeks (4 doses) and D-1500 every four weeks (T-75/D). Recruitment to T-75/D was discontinued because a planned analysis demonstrated no significant difference between T-75/D and D-1500. The STRIDE group showed a significantly better 3-year OS benefit of 30.7% compared with D-1500 of 24.7% and sorafenib of 20.2%. STRIDE led to a significantly better OS of 16.4 months compared with sorafenib alone at 13.8 months (HR 0.78; 96% CI, 0.65–0.92; $p = 0.0035$). D showed noninferiority to sorafenib alone regarding OS (16.6 vs. 13.8 months; HR, 0.86; 96% CI, 0.73–1.03). The ORR was 20.1% for the T-300/D-1500, 17% for durvalumab alone, and 5.1% for sorafenib alone. However, there was no significant difference in PFS. Durvalumab was non-inferior to sorafenib with favorable safety [22]. The combination group led to grade 3/4 AEs in 25.8% of patients, durvalumab in 12.9% and sorafenib in 36.9% of patients [22]. Therefore, durvalumab and tremelimumab combination is a promising first-line option for patients who are not suitable for atezolizumab and bevacizumab, such as elevated bleeding risk [23].

1.1.4. Summary in First-Line Systemic Therapy

In short, current guidelines from ASCO and ESMO support the use of first-line combination therapy with atezolizumab–bevacizumab rather than monotherapy with lenvatinib or sorafenib, in unresectable HCC patients with Eastern Cooperative Oncology Group (ECOG) of 0 or 1, Child A cirrhosis without receiving anticoagulant, and following treatment for esophageal varices. For those who are contraindicated to receive bevacizumab, tremelimumab–durvalumab is an alternative option. For patients with Child–Pugh B cirrhosis but no worse than score 7, or when dual immunotherapy is contraindicated, or if clinically the patients were less fit such as marginal performances status 1 or with multiple medical comorbidities with expected poor tolerance to dual immunotherapy, monotherapy with sorafenib or lenvatinib are alternative options. Lenvatinib is only recommended in patients with no worse than Child–Pugh A cirrhosis. In general, lenvatinib has a better toxicity profile compared with sorafenib, such as less HFS and alopecia. It also has a higher ORR, better PFS and longer TTP as per the REFLECT trial. As a result, most clinicians nowadays would prefer to start with lenvatinib if monotherapy is indicated. However, sorafenib might still be preferred given the longer duration of experience and the noninferior median OS demonstrated in the REFLECT trial.

1.2. Second-Line Systemic Therapy

1.2.1. Single-Agent Multikinase Inhibitor

Regorafenib

Regorafenib is an oral multikinase inhibitor which shares similarities in structure with sorafenib but demonstrates more profound antiangiogenic effects and tumor growth inhibition (TGI) in preclinical models [24]. Similar to sorafenib, it also targets kinases and cellular pathways involved in angiogenesis and tumor growth, such as the VEGFR, FGFR1, KIT, PDGFR, RET, and BRAF. The US FDA approved second-line use of regorafenib in April 2017 for those who failed sorafenib based upon the RESORCE trial [25]. The trial randomized 573 patients who progressed on sorafenib with ECOG 0–1 and Child A liver function, into either regorafenib or placebo group [25]. Regorafenib showed a significantly better median PFS of 3.1 months, longer median OS of 10.6 months, better ORR of 11% and disease control rate (DCR) of 65%, compared with 1.5 months, 7.8 months, 4% and 36%, respectively, in the placebo group.

In terms of toxicity, regorafenib had more grade 3/4 TRAEs in hypertension (regorafenib 15%, sorafenib 5%), HFS (regorafenib 13%, sorafenib 1%), fatigue (regorafenib 9%, sorafenib 5%), and diarrhea (regorafenib 3%, sorafenib 0%). 68% of patients in the treatment group required dose reduction, while only 31% of patients had dose reduction in the placebo group [25].

Cabozantinib

Cabozantinib is another multikinase inhibitor which inhibits VEGFR, MET, RET, AXL and KIT [26]. Exposure to sorafenib may upregulate MET expression and it has been shown as one of the resistance mechanisms to sorafenib in preclinical models [26][27][28]. While low baseline levels of MET were prognostic of better OS, cabozantinib has been shown to associate with better PFS and OS as a second-line post-sorafenib therapy in unresectable HCC regardless of baseline tumor-marker levels. It was granted approval in January 2019 [29]. Its efficacy was demonstrated in the CELESTIAL trial involving 707 patients, which compared cabozantinib with placebo in the second-line post-sorafenib setting [30]. Cabozantinib demonstrated longer median PFS of 5.2 months, improved median OS of 10.2 months and better ORR of 4%. The results were 1.9 months, 8 months and <1% for placebo, respectively. In a later analysis, cabozantinib improved outcomes in those with baseline alpha fetoprotein (AFP) ≥ 400 ng/mL significantly with median OS of 8.5 months compared with placebo at 5.2 months (HR 0.71; 95% CI 0.54–0.94); while for those with baseline AFP < 400 ng/mL, cabozantinib still showed a trend of a longer median OS to 13.9 months comparing with 10.3 months for placebo, but statistically it did not reach significance (HR, 0.81; 95% CI, 0.62–1.04). As a whole, cabozantinib improved outcomes across the whole spectrum of baseline AFP levels. In addition, it was shown that patients with AFP response in the 8th week were associated with a longer OS at 16.1 months, compared with those without an AFP response at 9.1 months [31].

The most frequent grade 3/4 TRAEs of cabozantinib include HFS (cabozantinib 17%, sorafenib 0%), hypertension (cabozantinib 16%, sorafenib 2%), AST elevation (cabozantinib 12%, sorafenib 7%), fatigue (cabozantinib 10%,

sorafenib 4%) and diarrhea (cabozantinib 10%, sorafenib 2%) [29]. 62% and 16% of patients treated with cabozantinib required dose reductions and treatment discontinuation because of TRAEs. The major causes for cabozantinib discontinuation were HFS, fatigue, poor appetite, and diarrhea [30].

1.2.2. Single VEGF Antibody

Ramucirumab

Ramucirumab is a recombinant immunoglobulin G subclass 1 (IgG1) class which specifically targets VEGFR-2 and inhibits its activation. Ramucirumab was approved in May 2019 as a second-line option upon progression on sorafenib in those with a high baseline level of AFP ≥ 400 ng/mL [32]. The REACH trial initially failed to show a benefit of ramucirumab [33]. Interestingly, an unplanned subset analysis demonstrated significant better OS of 7.8 months in those with high levels of AFP in the ramucirumab group compared with 4.2 months for placebo [33]. Thereafter, a phase III REACH-2 trial was planned to evaluate the efficacy of ramucirumab in patients who had a baseline AFP ≥ 400 ng/mL after progression on sorafenib [34]. This was a positive study. Compared with placebo, ramucirumab demonstrated significantly better median OS of 8.5 months vs. 7.3 months in the placebo group. Ramucirumab also showed a higher ORR (5% vs. 1%) and overall DCR (60% vs. 39%) [34].

Regarding the toxicity profile, grade 3/4 TRAEs were hypertension (ramucirumab 13%; placebo 5%), hyponatremia (ramucirumab 6%; placebo 0%) and elevated AST (ramucirumab 3%; placebo 5%). It is worth mentioning that, unlike other molecularly targeted treatments, ramucirumab does not cause HFS [34].

1.2.3. Single ICI

Pembrolizumab

Pembrolizumab (anti-PD-1) is another ICI that had been evaluated in treating advanced HCC. In November 2018, US FDA approved second-line pembrolizumab. In the phase II KEYNOTE-224, pembrolizumab showed benefits in median OS and ORR with 12.9 months and 17%, respectively [35]. The corresponding phase III trial KEYNOTE-240 compared second-line pembrolizumab with best supportive care in unresectable HCC patients who failed first-line sorafenib, however, was a negative trial [36]. Pembrolizumab was associated with numerically better median OS and PFS of 13.9 months and 3 months, respectively, compared with 10.6 months and 2.8 months for best supportive care (BSC). Unfortunately, the pre-specified statistical significance boundary was not reached, so it was technically a negative trial. Yet, pembrolizumab yielded a higher ORR of 18.3% compared with 4.4% for the placebo group, a better median DOR (13.8 months) and more complete responders (six vs. none in the BSC group).

1.2.4. PD-1 and CTLA-4 Antibodies Combination

Nivolumab and Ipilimumab

Ipilimumab is an ICI which targets the CTLA-4 molecule, an essential signaling checkpoint required to activate T-cells. When combined with nivolumab, they effectively target two different immune checkpoints and thus release the adaptive immune response. In March 2020, US FDA approved second-line therapy nivolumab plus ipilimumab [37]. The benefits of combined therapy were demonstrated in phase I/II CHECKMATE-040 (cohort 4) that involved 148 sorafenib-treated patients with no worse than a Child A cirrhosis. The trial tested three different regimens: nivolumab 1 mg/kg plus same day ipilimumab 3 mg/kg every three weeks for four cycles then biweekly nivolumab 240 mg (arm A); nivolumab 3 mg/kg plus same day ipilimumab 1 mg/kg every three weeks for four cycles, followed by biweekly nivolumab 240 mg (arm B); or nivolumab 3 mg/kg every two weeks plus ipilimumab 1 mg/kg every six weeks (arm C). The recommended regimen is arm A. The results indicated that the recommended regimen showed the best ORR of 32% [38]. A total of 8% of patients achieved CR and 24% PR. The median DOR was 17 months. The DCR was similar in the three groups. However, trials with a larger sample size are necessary to confirm this result in the future. The recommended regimen is currently being investigated as a first-line therapy in the phase III CHECKMATE-9DW trial.

The different arms evaluated in this CHECKMATE-040 cohort demonstrated similar patterns of AEs in patients with or without hepatitis B or C, but arm A was associated with more TRAEs. Treatment discontinuation owing to TRAEs occurred in 18% of patients in arm A, 6% in arm B and 2% in arm C. Common immune-mediated side effects included rash in 35%, adrenal insufficiency in 18%, hypothyroidism or thyroiditis in 22%, colitis in 10%, pneumonitis in 10%, and infusion-related reactions in 8% [38].

1.2.5. Summary in Second-Line Systemic Therapy

The best regimen and optimal sequence of second-line therapy is not well established yet and it depends on patients' performance status, liver function and the choice of first-line therapy. ASCO guidelines recommend that second-line options for those patients who are initially treated with atezolizumab-bevacizumab or durvalumab-tremelimumab include TKIs such as sorafenib, lenvatinib, regorafenib or cabozantinib [9]. For those patients who progressed on TKIs such as sorafenib or lenvatinib, dual immunotherapy nivolumab-ipilimumab is preferred given the potential for a higher ORR, or pembrolizumab monotherapy as an alternative if the patients are unable to tolerate dual ICIs. If sorafenib or lenvatinib has been chosen as the first-line therapy, regorafenib or cabozantinib can be considered as second-line options if the patients have contraindications to immune checkpoint inhibitors. Ramucirumab is recommended in patients with AFP level more than 400 ng/mL.

2. Ongoing Trials in Combination Systemic Treatment

Combining checkpoint inhibitors with multikinase inhibitors, especially anti-angiogenesis therapy, has become mainstream since accelerated FDA approval of atezolizumab and bevacizumab. Multiple studies have demonstrated that the combination of ICIs and TKIs is synergistic by facilitating vascular remodeling and tumor immune stimulation [39][40][41][42]. Lenvatinib and pembrolizumab were studied in a phase Ib trial [43]. This combination showed strong anti-tumor activity with median PFS, OS and ORR of 9.7, 20.4 months and 46%,

respectively. Most AEs were manageable by dose modifications. Currently, a direct comparison between this regimen and lenvatinib is underway in the phase III LEAP-002 trial [\[44\]](#).

Combination of apatinib (an orally active VEGFR-2 inhibitor) and camrelizumab (SHR1210) (an anti-PD-1 antibody) has also been evaluated in a dose-expansion and escalation phase I trial [\[45\]](#). The recommended dose with apatinib 250 mg daily and camrelizumab 200 mg every two weeks demonstrated clinical benefits with an ORR of 50%. As a result, this regimen was examined in the phase II RESCUE trial [\[46\]](#). Treatment-naïve inoperable HCC patients or those who failed or were intolerant to previous TKIs were treated with intravenous camrelizumab 200 mg (body weight \geq 50 kg) or 3 mg/kg (body weight < 50 kg) every two weeks and apatinib 250 mg daily orally. A total of 70 patients and 120 patients who were predominantly infected with HBV (88.3%) were enrolled in the first-line and second-line setting, respectively. An updated result of the RESCUE trial was recently published in the ASCO meeting 2021. The median time to data cutoff was 29.1 months. In the first-line setting, the median OS was 20.1 months and 2-year OS was 43.3%. In the second-line setting, the median OS was 21.8 months and the 2-year OS was 44.6% [\[47\]](#). An ongoing phase III trial (NCT03764293) has been designed to directly compare its efficacy with sorafenib in the first-line setting.

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