Therapy for Hepatocellular Carcinoma

Subjects: Oncology

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Advanced hepatocellular carcinoma is a prevalent and potentially aggressive disease. For more than a decade, treatment with sorafenib has been the only approved therapeutic approach. Moreover, no agent has been proven to prolong survival following the progression of disease after sorafenib treatment. However, in recent years, this scenario has changed substantially with several trials being conducted to examine the effects of immunotherapy and novel targeting agents. Several immune checkpoint inhibitors have shown promising results in early-stage clinical trials. Moreover, phase III trials with large cohorts have demonstrated remarkable improvement in survival with the use of new targeted therapies in second-line treatment. Treatment regimens involving the combination of two immune checkpoint inhibitors as well as immune checkpoint inhibitors and anti-angiogenic targeted therapies have shown potential to act synergistically in clinical trials. Recently, the combination of atezolizumab and bevacizumab evaluated in a phase III clinical trial has demonstrated survival superiority in the first-line treatment; it is the new considered standard of care.

Keywords: hepatocellular carcinoma ; immune checkpoint inhibitors ; targeted therapy ; biomarkers

1. Introduction

Hepatocellular carcinoma (HCC) is a major health problem worldwide. It is estimated to be the sixth most common cancer, the fourth leading cause of cancer-related deaths [1], and the most common primary liver cancer, accounting for up to 90% of the cases [2]. HCC often originates in an inflamed cirrhotic liver, frequently due to chronic hepatitis B or C, chronic exposure to toxic agents (alcohol and aflatoxins), metabolic syndromes (non-alcoholic fatty liver disease and diabetes), and diseases associated with the immune system (primary biliary cirrhosis and autoimmune hepatitis) [2][3]. Despite the advances made in the development of approaches to the early detection of HCC, many patients are first diagnosed at an advanced stage [4][5].

Several staging systems have been proposed for clinical classification and prediction of survival. Among these, the Barcelona Clinic Liver Cancer (BCLC) staging system has been the most commonly used method to guide treatment decisions [6]. Liver function is also crucial for making treatment decisions and is usually assessed according to the Child–Turcotte–Pugh criteria, which evaluate the degree of ascites, concentrations of albumin and bilirubin in the serum, prothrombin time, and degree of encephalopathy. A scoring system is applied to each category and patients are classified into three groups that correlate with survival: Child–Pugh score of 5 to 6 is considered class A (well-compensated illness), 7 to 9 is class B (significant functional impairment), and 10 to 15 is class C (decompensated disease) [7][8].

For early-stage HCC (BCLC A), curative treatment includes liver transplantation, surgical resection, or radiofrequency ablation [9][10]. For intermediate-stage HCC (BCLC B), which presents a large or multifocal tumor mass without extrahepatic invasion, transarterial chemoembolization or selective internal radiation therapy is the recommended treatment [11].

For patients with advanced disease (BCLC C), treatment with sorafenib has been the standard of care for more than a decade based on the findings of two phase III trials (SHARP and Asia–Pacific) showing improved overall survival (OS) in patients who received sorafenib treatment. The SHARP trial randomly assigned 602 patients with advanced HCC, Child–Pugh liver function class A, who had not received previous systemic treatment to receive either sorafenib (400 mg twice daily) or placebo. Median OS was 10.7 months in the sorafenib group and 7.9 months in the placebo group (HR: 0.69; $p < 0.001$) [12]. The Asia–Pacific trial enrolled 226 patients with advanced HCC who had not received previous systemic therapy and had Child–Pugh liver function class A. Patients were randomly assigned to receive either oral sorafenib (400 mg) or placebo twice daily in 6-week cycles. Median OS was 6.5 months in patients treated with sorafenib, compared with 4.2 months in those who received placebo (HR: 0.68; $p = 0.014$) [13]. Fortunately, treatment options for patients with advanced HCC have recently improved with the approval of new targeted agents and immune checkpoint inhibitors (ICIs). This paper aims to review the latest new treatment options in first- and second-line therapies for HCC.

2. Targeted Therapies

HCC has a complex molecular pathogenesis involving several signaling cascades such as epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), hepatocyte growth factor (HGF/MET), and mechanistic target of rapamycin (mTOR) among others [14]. The growing knowledge of such molecular alterations harboring potential therapeutic targets gave us the rationale to clinically test tyrosine kinase inhibitors (TKI) targeting one or several of these pathways. The survival benefit of sorafenib [12] was the first successful targeted therapy approved in HCC and paved the way for the development of other targeted therapies. Table 1 is summarizing the results of the most relevant trials involving targeted therapies in advanced HCC patients.

Table 1. Results of selected studies testing targeted therapies in HCC patients.

Study (Year)	Phase	*n*	Population	Drug	Median Overall Survival	Median Progression-Free Survival	Objective Response Rate
REFLECT trial (2018) [15]	III non-inferiority	954	Unresectable HCC and no prior systemic therapy (99% Child–Turcotte–Pugh class A)	Lenvatinib vs. sorafenib	13.6 mo for lenvatinib vs. 12.3 mo for sorafenib (HR: 0.92, 95% CI: 0.79−1.06)	7.4 mo for lenvatinib vs. 3.7 mo for sorafenib (HR: 0.66; $p < 0.0001$)	24.1% for lenvatinib vs. 9.2% for sorafenib ($p < 0.0001$)
Feng Bi et al. (2020) [16]	II/III	668	Unresectable or metastatic HCC, Child–Pugh liver function score ≤ 7, and no prior systemic therapy	Donafenib vs. sorafenib	12.1 mo for donafenib vs. 10.3 mo for sorafenib (HR: 0.831; $p = 0.0363$)	3.7 mo for donafenib vs. 3.6 mo for sorafenib ($p = 0.2824$)	4.6% for donafenib vs. 2.7% for sorafenib ($p = 0.2448$)
CELESTIAL trial (2018) [17]	III	707	Advanced and progressing HCC and not worse than Child–Pugh A	Cabozantinib vs. placebo	10.2 mo for cabozantinib vs. 8.0 mo for placebo (HR: 0.76; $p = 0.005$)	5.2 mo for cabozantinib vs. 1.9 mo for placebo (HR: 0.44; $p < 0.001$)	4% for cabozantinib vs. less than 1% for placebo ($p = 0.009$)
RESORCE trial (2017) [18]	III	573	Advanced HCC that progressed after first-line treatment with sorafenib, Child–Pugh A	Regorafenib vs. placebo	10.6 mo for regorafenib vs. 7.8 mo for placebo (HR: 0.63; $p < 0.0001$)	3.1 mo for regorafenib vs. 1.5 mo for placebo (HR: 0.46; $p < 0.0001$)	11% for regorafenib vs. 4% for placebo ($p = 0.0047$)
REACH trial (2015) [19]	III	565	Advanced HCC following first-line therapy with sorafenib and Child–Pugh A	Ramucirumab vs. placebo	9.2 mo for ramucirumab vs. 7.6 mo for placebo (HR: 0.87; $p = 0.14$).	2.8 mo for ramucirumab vs. 2.1 mo for placebo (HR 0.63; $p<0.0001$)	7% for ramucirumab vs. < 1% for placebo ($p<0.0001$)
REACH-2 trial (2019) [20]	III	292	Advanced HCC, Child–Pugh class A, and serum AFP ≥ 400 ng/mL in patients who had disease progression under first-line sorafenib	Ramucirumab vs. placebo	8.5 mo for ramucirumab vs. 7.3 mo for placebo (HR: 0.71; $p = 0.0199$	2.8 mo for ramucirumab vs. 1.6 mo for placebo (HR: 0.452; $p < 0.0001$)	5% for ramucirumab vs. 1% for placebo ($p = 0.1697$)
Qiu Li et al. (2020) [21]	III	393	Advanced HCC after failure of sorafenib and oxaliplatin-based chemotherapy and Child–Pugh liver function class A or B ≤ 7 points	Apatinib vs. placebo	8.7 mo for apatinib vs. 6.8 mo for placebo (HR: 0.785; $p = 0.0476$)	4.5 mo for apatinib vs. 1.9 mo for placebo (HR: 0.471; $p < 0.0001$)	10.7% for ramucirumab vs. 1.5% for placebo

Abbreviations: HCC: hepatocellular carcinoma; mo: months; HR: hazard ratio.

2.1. Lenvatinib

Lenvatinib is a potent multi-TKI inhibitor that targets VEGF receptors (VEGFR1-3) and other pro-oncogenic tyrosine kinases, including fibroblast growth factor receptors (FGFR1-4), PDGFRα, KIT, and rearranged during transfection (RET) tyrosine kinases [22]. Recently, the use of levantinib as a first-line treatment for advanced HCC was approved based on the results of the phase III non-inferiority REFLECT trial, which compared lenvatinib (12 mg once daily for body weight ≥ 60 kg, 8 mg daily for <60 kg) versus sorafenib (400 mg twice daily for all patients). A total of 954 patients with unresectable HCC and no prior systemic therapy (99%Child–Pugh class A) were included in the trial. Patients with involvement of >50% of the liver or invasion of the main portal vein or biliary tree were excluded. Patients were randomly assigned to treatment with lenvatinib (n = 478) or sorafenib (n = 478). The median OS was 13.6 months for patients treated with levantinib and 12.3 months for patients treated with sorafenib (HR 0.92; 95% CI: 0.79−1.06 months). Median PFS was 7.4 months for patients treated with lenvatinib vs. 3.7 months for patients treated with sorafenib (HR: 0.66; p < 0.0001), and the ORR was 24.1 vs. 9.2% for lenvatinib and sorafenib treatments, respectively (OR 3.13; p < 0.0001). Grade 3 or higher TRAEs occurred in 57% of patients in the lenvatinib arm and 49% of patients in the sorafenib arm. The most common grade 3 or higher TRAEs in the lenvatinib arm were hypertension (23%) and decreased weight (8%) [15].

2.2. Donafenib

Donafenib is a multikinase inhibitor that targets Raf kinase and various receptor tyrosine kinases. This mechanism inhibits cell proliferation in Raf-expressing tumor cells. The efficacy of donafenib has been demonstrated according to an open-label randomized multicenter phase II/III trial with 668 patients with unresectable or metastatic HCC, Child–Pugh liver function score ≤ 7, and no prior systemic therapy. Patients were randomized to receive oral donafenib (0.2 g) or sorafenib (0.4 g) twice daily until intolerable toxicity or disease progression. The primary endpoint was OS. Donafenib showed potential benefits and significantly improved OS compared to sorafenib (12.1 vs. 10.3 months, HR 0.831; p = 0.0363). No significant differences were observed in median PFS (3.7 vs. 3.6 months for donafenib and sorafenib, respectively; p = 0.2824), ORR (4.6% vs. 2.7% for donafenib and sorafenib, respectively; p = 0.2448), and disease control rate (30.8% vs. 28.7% for donafenib and sorafenib, respectively; p = 0.5532). Grade 3 or higher TRAEs were reported in 57.4% and 67.5% of patients (p = 0.0082), respectively. Common adverse events reported in patients who received donafenib included skin reaction in hands and feet, increased aspartate aminotransferase levels, increased blood bilirubin levels, decreased platelet count, and diarrhea [16].

2.3. Cabozantinib

Cabozantinib is a potent inhibitor of several receptor tyrosine kinases, including HGF/c-MET, VEGFR-1, VEGFR-2, and VEGFR-3. The efficacy of cabozantinib in patients with previously treated advanced HCC was shown in phase III CELESTIAL trial. A total of 707 patients were enrolled with advanced and progressive HCC and no worse than Child–Pugh A cirrhosis. Patients were randomly assigned to cabozantinib (60 mg once daily) or placebo treatment groups. Eligible patients had received previous treatment with sorafenib, had disease progression after at least one systemic treatment for HCC, and may have received up to two previous systemic regimens for advanced HCC. The primary endpoint was OS. Treatment with cabozantinib prolonged median OS (10.2 vs. 8.0 months, HR 0.76; p = 0.005). Median PFS was 5.2 months in patients who were treated with cabozantinib and 1.9 months in patients treated with placebo (HR 0.44; p < 0.001). The ORR was 4% for cabozantinib and less than 1% for placebo treatment (p = 0.009). Grade 3 or 4 TRAEs were reported in 68% of patients included in the cabozantinib treatment group and 36% of the patients included in the placebo group. Palmar–plantar erythrodysesthesia, hypertension, fatigue, increased aspartate aminotransferase levels, and diarrhea were the most commonly reported high-grade TRAEs with cabozantinib treatment [17].

2.4. Regorafenib

Regorafenib is an orally active inhibitor of angiogenic (including VEGFR-1, VEGFR-2, and VEGFR-3), stromal, and oncogenic receptor tyrosine kinases. It is structurally similar to sorafenib and targets a variety of kinases implicated in angiogenic and tumor growth-promoting pathways. The advantage of regorafenib treatment in patients showing disease progression after first-line treatment with sorafenib was demonstrated in the RESORCE trial. A total of 573 patients were enrolled in this study. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, Child–Pugh A score, and were randomly assigned to oral regorafenib 160 mg or placebo once daily during weeks 1−3 of each 4-week cycle. The primary endpoint was OS. Regorafenib was associated with significant prolongation of median OS (10.6 versus 7.8 months, HR 0.63; p < 0.0001). Median PFS was 3.1 months for patients treated with regorafenib and 1.5 months for patients treated with placebo (HR 0.46; p < 0.0001), and ORR was 11 vs. 4% for regorafenib and placebo,

respectively (p = 0.0047). Grade 3 or 4 TRAEs were reported in 67% of patients in the regorafenib arm and 39% in the placebo arm. Most common grade 3 or higher TRAEs in regorafenib arm were hypertension (15%), hand–foot skin reaction (13%), and increased AST [18].

2.5. Ramucirumab

Ramucirumab is a recombinant monoclonal antibody belonging to immunoglobulin G subclass 1 (IgG1) that binds to VEGFR-2 and blocks receptor activation. In the REACH study, 565 patients who had failed previous treatment with sorafenib and continuously demonstrated Child–Pugh A score were randomly assigned to ramucirumab (8 mg/kg) or placebo every 2 weeks. The primary endpoint was OS. In the intention-to-treat population, the use of ramucirumab did not result in a significant gain in OS (9.2 vs. 7.6 months for ramucirumab and placebo, respectively; HR 0.87; p = 0.14). Median PFS was 2.8 months in the ramucirumab group versus 2.1 months in the placebo group (HR 0.63; p < 0.0001). The ORR was 7% for ramucirumab and < 1% for placebo (p < 0.0001). In this study, the analysis of a pre-specified subgroup of patients with alpha-fetoprotein levels (AFP) > 400 ng/mL indicated a potential benefit in OS upon treatment with ramucirumab (7.8 vs. 4.2 months; HR 0.67; p = 0.0059) [19]. A follow-up phase III trial (REACH-2) randomly assigned 292 HCC patients, Child–Pugh class A liver disease, who demonstrated disease progression after first-line sorafenib treatment and serum AFP ≥ 400 ng/mL. The patients received 8 mg/kg intravenous ramucirumab every 2 weeks or placebo treatment groups. The primary endpoint was OS. Ramucirumab was associated with a significantly better median OS, which was reported as 8.5 vs. 7.3 months in patients who received ramucirumab and placebo treatments, respectively (HR 0.71; p = 0.019). Median PFS was 2.8 months for ramucirumab vs. 1.6 months for placebo (HR 0.452; p < 0.0001). The ORR was 5 and 1% for ramucirumab and placebo, respectively (p = 0.1697). The most frequently reported TRAEs in ramucirumab arm were fatigue (27%), peripheral edema (25%) and decreased appetite (23%) [20]. Based on this trial, ramucirumab was approved in May 2019 for second-line treatment of HCC in patients with an AFP level ≥ 400 ng/mL.

2.6. Apatinib

Apatinib is an orally active VEGFR-2 inhibitor approved for second-line treatment of advanced gastric cancer in China. The efficacy of second-line treatment for advanced HCC after the failure of sorafenib and oxaliplatin-based chemotherapy was shown in a phase III randomized placebo-controlled trial of 393 patients with Child–Pugh A or B (≤7) cirrhosis. The patients received 750 mg apatinib orally once daily or placebo. The primary endpoint was OS. Apatinib significantly prolonged median OS (8.7 months in the apatinib arm versus 6.8 months in the placebo arm, HR 0.785; p = 0.0476) and median PFS (4.5 months with apatinib vs. 1.9 months with placebo; HR 0.471; p˂ 0.0001). The ORR was 10.7% (95% CI: 7.2−15.1%) in the apatinib group vs. 1.5% (95% CI: 0.2−5.4%) in the placebo group. TRAEs were reported in 97.3% of patients who received apatinib, with the most common AEs of grade 3 and 4 including hypertension, hand–foot syndrome, decreased platelet count, and decreased neutrophil count [21].

3. Combination of Immunotherapy and Targeted Therapies

The angiogenic pathway has immunosuppressive effects on the tumor microenvironment (TME) [23]. The VEGF pathway can negatively affect effector T cells and antigen-presenting cells and enhance the activity of immune suppressive cells such as regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSCs) [24]. Anti-angiogenic targeted therapies can induce immunogenic alterations in the TME that can synergize with the effects of ICIs. Preclinical studies have demonstrated that anti-angiogenic TKIs can reduce the percentage of immunosuppressive Treg cells and MDSCs and increase T cell infiltration [25][26]. These findings were also confirmed in clinical studies [27] and successful combinations have been reported in multiple cancer types, such as clear cell renal cell carcinoma (ccRCC) [28][29][30], urothelial carcinoma [31], and endometrial carcinoma [32]. Both ICIs and anti-angiogenic targeted therapies are active in patients with metastatic HCC, making the combination of these two classes of treatment very attractive for these patients. Recent clinical data have confirmed the advantages. Table 2 summarizes the studies combining ICI and targeted therapy.

Table 2. Results of selected studies testing the combination of immune checkpoint inhibitors and targeted therapies in advanced HCC patients.

Study (Year)	Phase	*n*	Population	Drug	Median Overall Survival	Median Progression-Free Survival	Objective Response Rate
GO30140 (2019) [33]	Ib	Arm F: 119 Arm A: 104	Unresectable HCC, Child–Pugh A, and naïve to systemic treatment	Atezolizumab + bevacizumab		Arm F: 5.6 mo for atezolizumab + bevacizumab vs. 3.4 mo for atezolizumab alone (HR: 0.55; $p = 0.0108$) Arm A: 7.3 mo	Arm A: 36%
IMbrave 150 (2020) [34]	III	501	Unresectable HCC, Child–Pugh A, and naïve to systemic treatment	Atezolizumab + bevacizumab vs. sorafenib	NR for the atezolizumab/bevacizumab group vs. 13.2 mo for the sorafenib group (HR: 0.58, $p < 0.001$)	6.8 vs. 4.3 mo for the atezolizumab/bevacizumab group and the sorafenib group, respectively (HR: 0.59; $p < 0.001$)	27.3% for the atezolizumab/bevacizumab group and 11.9% for the sorafenib group
Finn et al. (2020) [35]	Ib	30	Advanced HCC BCLC B/C, Child–Pugh A, in the first-line setting	Pembrolizumab + levantinib	22.0 mo	9.3 mo	46%
CheckMate 040 (2020) [36]	I/II	71	Advanced HCC patients that were treatment-naïve or that received sorafenib previously	Arm 1: CaboNivo Arm 2: CaboNivoIpi	NR in both arms	Arm 1: 5.5 mo Arm 2: 6.8 mo	Arm 1: 17% Arm 2: 26%
VEGF Liver 100 (2019) [37]	Ib	22	Advanced HCC, Child–Pugh A in the first-line setting	Avelumab + axitinib		5.5 mo per RECIST	13.6%
Xu et al. (2019) [38]	I	18	HCC patients, Child–Pugh A, and previously treated with sorafenib	SHR-1210 + apatinib	NR	5.8 mo	50%

Abbreviations: HCC: hepatocellular carcinoma; mo: months; HR: hazard ratio; NR: not reached; BCLC: Barcelona Clinic Liver Cancer; Cabo: Cabozantinib; Nivo: nivolumab; Ipi: ipilimumab.

3.1. Atezolizumab + Bevacizumab

The combination of atezolizumab and bevacizumab showed effective results in patients with metastatic ccRCC [29]. This combination was also evaluated in patients with HCC. The phase IB study GO30140 evaluated atezolizumab alone or in combination with bevacizumab in patients with advanced HCC and no previous systemic treatment. Arm F randomized 119 patients 1:1 to 1200 mg i.v. of atezolizumab alone or in combination with 15 mg/kg i.v. of bevacizumab every 3 weeks. Arm A evaluated the combination of atezolizumab and bevacizumab (same dose as arm F) in 104 patients. The results showed a statistically significant benefit in median PFS, which was the primary endpoint for arm F, in favor of the combination over atezolizumab monotherapy (5.6 vs. 3.4 months; HR: 0.55; $p = 0.0108$). Arm A showed an ORR of 36% (primary endpoint) and a median PFS of 7.3 months (95% CI: 5.4−9.9 months) for patients that received the combination of atezolizumab and bevacizumab. Grade 3 or 4 TRAEs occurred in 20% of patients treated with the combination in arm F and 39% in arm A [33].

The phase III trial IMBRAVE 150 randomly assigned 501 previously untreated patients with advanced unresectable HCC and Child–Pugh A 2:1 to atezolizumab (1200 mg i.v. every three weeks) plus bevacizumab (15 mg/kg i.v. every three weeks) or sorafenib (400 mg orally daily) treatment groups [34]. The median OS was not reached for the patients included in the atezolizumab/bevacizumab arms and was 13.2 months among the patients included in the sorafenib arm (HR: 0.58, $p < 0.001$). Median PFS was 6.8 vs. 4.3 months for atezolizumab/bevacizumab and sorafenib treatment groups, respectively (HR: 0.59; $p < 0.001$). The ORR was 27.3% (95% CI: 22.5−32.5%) in patients treated with atezolizumab/bevacizumab patients vs. 11.9% (95% CI: 7.4−18.0%) in patients treated with sorafenib, based on the independent assessment performed in accordance with RECIST 1.1 ($p < 0.001$). In addition to the aforementioned results, the same trial showed that atezolizumab/bevacizumab was significantly associated with improved physical functioning (13.1 versus 4.9 months), role functioning (9.1 versus 3.6 months), and with longer delays in the median time to deterioration of quality of life (11.2 versus 3.2 months). Grade 3 or 4 TRAEs were reported in a similar percentage of patients in both groups (56.6% and 55.1% for atezolizumab/bevacizumab and sorafenib, respectively) [34]. Given the results of this trial, the FDA approved this treatment regimen in May 2020 for patients with unresectable or metastatic HCC who have not received prior systemic therapy.

3.2. Pembrolizumab + Lenvatinib

Pembrolizumab in combination with lenvatinib demonstrated effective results in patients with recurrent endometrial cancer [32], patients with ccRCC previously treated with ICIs [39], and patients with advanced gastric cancer [40]. Recently, a phase IB study aiming to evaluate the effects of lenvatinib (at a dose of 12 mg orally daily if body weight > 60 kg and 8 mg if < 60 kg) plus pembrolizumab (200 mg i.v.; every 3 weeks) in a single arm comprising 100 patients showed promising antitumor activity in unresectable or metastatic HCC. The ORR analyzed by independent imaging review (IIR) was 46% per modified Response Evaluation Criteria in Solid Tumors (mRECIST) with 11% of CR. Per RECIST version 1.1. (v1.1), the ORR was 36% with 1% CR. Median PFS according to the IIR was 9.3 months (95% CI: 5.6−9.7 months) per mRECIST and 8.6 months (95% CI: 7.1−9.7 months) per RECIST v1.1. Median OS was 22.0 months (95% CI: 20.4−NR months) per

mRECIST criteria. Moreover, responses were considered durable with median DOR of 8.6 months (95% CI: 6.9–NR months) per mRECIST and 12.6 months (95% CI: 6.9−NR months) per RECIST v1.1, as evaluated by IIR. Grade 3 or 4 TRAEs were reported in 67% of patients, with hypertension being the most common adverse effect (17%), followed by AST increase (11%) and diarrhea (5%) [35].

3.3. Cabozantinib + Nivolumab and Cabozantinib + Nivolumab + Ipilimumab

Cabozantinib in combination with nivolumab with or without ipilimumab was evaluated in patients with metastatic urothelial carcinoma and other genitourinary tumors in a phase I trial. The treatment demonstrated manageable toxicity profiles and promising results [31]. These regimens are also being evaluated in patients with HCC. The CheckMate 040 study evaluated patients with advanced HCC that were treatment-naïve or had previously received sorafenib. Patients were randomly assigned to two treatment groups: The first group received nivolumab treatment at a dose of 240 mg i.v. every 2 weeks along with daily oral administration of 40 mg cabozantinib. The second group involved treatment with 3 mg/kg i.v. nivolumab every 2 weeks along with 40 mg cabozantinib and 1 mg/kg i.v. ipilimumab every 6 weeks. A total of 71 patients were enrolled, 36 for the doublet and 35 for the triplet regimen. The ORR was 17% and 26% for the doublet and triplet regimens, respectively. The median PFS was 5.5 months in patients treated with cabozantinib + nivolumab and 6.8 months in patients treated with cabozantinib, nivolumab + ipilimumab. The median OS was not reached in patients included in either arm. As expected, patients subjected to treatment with the triplet regimen demonstrated more grade 3 or 4 TRAEs (71% versus 42% for triplet versus doublet) [36].

3.4. Avelumab + Axitinib

Avelumab in combination with axitinib has shown promising results in patients with ccRCC with significant improvements in PFS [28]. This combination is also being evaluated in the phase IB VEGF liver 100 trial. This trial enrolled advanced HCC patients with an ECOG performance status of 0 or 1 and Child–Pugh class A who were subjected to treatment with 10 mg/kg i.v. avelumab every 2 weeks in combination with axitinib 5 mg that was administered twice daily via the oral route. Interim results presented in 2019 showed that the most common grade 3 TRAEs were hypertension (50.0%) and hand–foot syndrome (22.7%). The ORR per RECIST was 13.6% (95% CI: 2.9−34.9%), per mRECIST—31.8% (95% CI: 13.9−54.9%). Median PFS was 5.5 months per RECIST (95% CI: 1.9−7.3 months) and 3.8 months per mRECIST (95% CI: 1.9−7.3 months) [37].

3.5. Camrelizumab + Apatinib

The anti-PD-1 antibody camrelizumab (SHR-1210) is being evaluated in combination with apatinib in patients with advanced HCC and gastric cancer (GC) or esophagogastric junction cancer (EGJC). The results of a phase I trial with a dose escalation and expansion cohorts were recently reported [38]. A total of 43 patients were enrolled in the study (18 with HCC and 25 with GC/EGJC). Fifteen patients (83.3%) demonstrated disease progression or were intolerant to sorafenib and 13 had Child–Pugh A score. The recommended phase II dose for apatinib was 250 mg and the dose of camrelizumab was 200 mg i.v. every 2 weeks. The most common grade 3 or higher TRAEs were hypertension (15.2%) and elevated aspartate aminotransferase levels (AST; 15.2%). Among patients with HCC, 16 were considered evaluable. Among them, eight patients demonstrated PR (50%) and 7 patients showed SD (43.7%). The median PFS of patients with HCC was 5.8 months (95% CI: 2.6−NR months), and the median OS was not reached.

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