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CURRENT HEPATOCELLULAR CARCINOMA SYSTEMIC PHARMACOLOGICAL TREATMENT OPTIONS

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Abstract – *Liver cancer is the sixth common cancer and the second leading cause of cancer death worldwide. Hepatocellular carcinoma (HCC) accounts for ~90% of cases of liver cancer and is the fourth most common cause of cancer-related death in the world. Up to now, 4 oral multityrosine kinase inhibitors (sorafenib, lenvatinib, regorafenib and cabozantinib), 1 anti-angiogenic antibody (ramucirumab) and 5 immune checkpoint inhibitors, alone or in combination (atezolizumab in combination with bevacizumab, ipilimumab in combination with nivolumab, tremelimumab in combination with durvalumab, nivolumab and pembrolizumab in monotherapy) have been commercialized for advanced HCC patients' treatment. The aim of this editorial is to provide an insight in current hepatocellular carcinoma systemic pharmacological treatment options.*

KEYWORDS: *Hepatocellular carcinoma, Systemic pharmacological treatment, Sorafenib, Lenvatinib, Regorafenib, Cabozantinib, Ramucirumab, Atezolizumab plus bevacizumab, Ipilimumab plus nivolumab, Nivolumab, Pembrolizumab, Tremelimumab plus durvalumab.*

Liver cancer is the sixth common cancer and the second leading cause of cancer death worldwide[1]. Hepatocellular carcinoma (HCC) accounts for ~90% of cases of liver cancer and is the fourth most common cause of cancer-related death in the world[2]. Incidence is extremely variable worldwide, due to several factors (e.g., environmental factors, viral infections prevalence, metabolic factors, healthcare resources availability) with almost 85% of the diagnosed HCC occurring in low-income or middle-income countries, in particular in the Eastern Asia and sub-Saharian Africa[3-5]. HCC age of onset is extremely variable as well, with a later occurrence in Japan, North America and European countries (median age above 60 years), and with an early occurrence in some parts of Asia and Africa (30-60 years)[6,7]. HCC management is still challenging, requiring a complex decision-making process, involving tumour extent, patient's comorbidities, healthcare resources and, most importantly, liver disfunction, including liver transplant recipients, as most treatment can worsen underlying liver disease[2,8-10].

HCC systemic pharmacological treatment options are increasing in the recent years[11-19]. The introduction of new molecules, such as immune checkpoint inhibitors, has given rise to new hope and has given a signal that research in the oncological field is progressing, albeit not with little difficulty[20]. Up to now, 4 oral multityrosine kinase inhibitors (sorafenib, lenvatinib, regorafenib and cabozantinib), 1 anti-angiogenic antibody (ramucirumab) and 5 immune checkpoint inhibitors, alone or in combination (atezolizumab in combina-

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tion with bevacizumab, ipilimumab in combination with nivolumab, tremelimumab in combination with durvalumab, nivolumab and pembrolizumab in monotherapy) have been commercialized for advanced HCC patients' treatment[21].

SORAFENIB

Sorafenib is a small molecule multikinase inhibitor that directs against vascular endothelial growth factor receptors 1-3 (VEGFR), platelet-derived growth factor receptor-β (PDGFRβ) and the Raf family kinases (mainly C-Raf)[22]. Sorafenib was approved in Europe and United States of America in 2007 following the results of the SHARP trial, a multicenter, phase 3, double-blind, placebo-controlled trial, involving 602 patients with advanced HCC, naïve to systemic treatment and Child-Pugh Class A cirrhosis. The primary endpoint was the median overall survival, which showed an improvement of 2-3 months (10.7 *vs.* 7.9 months in the sorafenib group and placebo group respectively; hazard ratio: 0.69; 95% CI, 0.55 to 0.87; p=0.0001)[23]. Similar findings were also reported by the Asia-Pacific trial (6.5 *vs.* 4.2 months in the sorafenib group and placebo group respectively)[24]. However, phase 3 randomized control trials reported no added benefit as an adjuvant therapy in patients treated with curative resection (STORM trial)[25], or with transcatheter arterial chemoembolization concurrent treatment (SPACE trial)[26].

LENVATINIB

Lenvatinib was approved by both European Medical Agency (EMA) and Food and Drug Administration (FDA) in 2018 for the first-line treatment of people with unresectable HCC. Lenvatinib acts as an inhibitor of VEGFR 1-3, PDGFRα, c-KIT, RET multikinase, and fibroblast growth factor receptor 1-4 (FGFR), and proved to be non-inferior in the median overall survival to sorafenib in an open-label, phase 3, multicenter trial (13.6 *vs.* 12.3 months in the Lenvatinib versus sorafenib group respectively)[27]. In addition, it has been reported that Lenvatinib was associated with a higher objective response rate (24.1%), a better progress free survival (7.4 months), as well as a prolonged median time to progression (8.9 months)[20].

REGORAFENIB

Regorafenib, a multikinase inhibitor chemically related to sorafenib, exert its antitumor effect by targeting angiogenic, stromal and oncogenic receptor tyrosine kinase. In particular, the antiangiogenetic effect is driven by its dual targeted VEFFR2-TIE2 tyrosine kinase inhibition. In the RESORCE trial regorafenib showed an improvement in median survival *vs.* placebo (10.6 months *vs.* 7.8 months respectively) in HCC patients progressing on sorafenib treatment, thus receiving approval as second line treatment[28]. Thus, in 2017 regorafenib was approved as second line treatment for patients with advanced HCC and previously treated with sorafenib in United States, Europe, and most Asian countries[20]. Recent evidence from a retrospective study has shown that Regorafenib plus programmed cell death protein-1 (PD-1) increased progression-free survival, objective response rate but did not improve overall survival, though further studies are needed[29].

CABOZANTINIB

Cabozatinib is a small molecule multikinase inhibitor that directs against c-Met, VEGFR 1-3, AXL and RET. In the CELESTIAL trial, a double-blind, phase 3 trial, patients receiving cabozantinib showed a significantly longer overall survival compared to placebo (10.2 *vs.* 8.0 months respectively; HR 0.76, 95% CI 0.63–0.92, p=0.005). However, cabozatinib treatment was associated with an increased report of grade 3 or grade 4 adverse events (68% *vs.* 36% respectively). Of note, in the subgroup analysis of the same trial it was reported that the HR for death was 0.69 in HCC patients with HBV infection and 1.11 in the ones infected with HCV, making it suggest that cabozatinib could be beneficial as second line therapy in HBV patients, as well as it could be possible different response according to the underlying liver disease[30]. Furthermore, in another subgroup analysis cabozantinib also proved to improve efficacy outcomes *vs.* placebo in patients who had been previously treated with sorafenib, regardless of prior sorafenib treatment duration[31]. Cabozatinib received EMA approval in 2018 and FDA approval in 2019 for HCC patients previously treated with sorafenib and had Child Pugh Class A liver impairment and is the only third-line treatment for patients with advanced HCC.

RAMUCIRUMAB

Ramucirumab is a fully human monoclonal antibody of the IgG1 family, which plays an antiangiogenetic action by blocking the ligand of VEGFA, VEGFC and VEGFD to VEGFR2[32]. In 2019 ramucirumab received FDA approval as second line treatment in patients with HCC and α-fetoprotein levels ≥ 400 ng/mL and previously treated with sorafenib, following the results of the REACH-2 trial. It was reported

a significantly improvement in the ramucirumab group compared with the placebo group in median overall survival (8.5 *vs.* 7.3 months) and progression free survival (2.8 *vs.* 1.6 months)[33].

NIVOLUMAB

Nivolumab is a PD-1 immune checkpoint inhibitor that showed a 15% objective response rate in the dose-escalation phase and of 20% in patients treated with 3 mg/kg nivolumab in the dose expansion phase, manageable safety, and promising survival in patients with HCC in the phase 1-2 CheckMate 040 study[34]. In the 2017 nivolumab was granted accelerated approval by FDA for second line treatment of advanced HCC patients, based on these results. An attempt to use it in first line therapy was made in the phase 3 CheckMate 459 trial, though nivolumab treatment did not significantly improve overall survival compared with sorafenib, thus making it a possible therapeutic option in patients in whom other first line therapies are contraindicated[35]. However, in July 2021, in consultation with the FDA, Bristol Myers Squibb (New York, NY, USA) decided for the withdrawal of nivolumab indication for advanced HCC monotherapy treatment, due to the lack of confirmatory benefit evidence during the post-marketing period[36]. The European Committee for Medicinal Products for Human Use, instead, believed the results provided by the study were insufficient, as there was no direct comparison with other treatments and that they were unable to compare study results with others due to insufficient patient's information, leading to company application withdrawal in July 2017[37].

PEMBROLIZUMAB

Pembrolizumab is a PD-1 immune checkpoint inhibitor that similarly to Nivolumab, received in the 2018 the accelerated FDA approval for the treatment of advanced HCC patients, who underwent previous sorafenib treatment. This decision followed the results of the KEYNOTE-224, a non-randomized, multicenter, open-label, phase 2 trial enrolling 104 Child-Pugh class A HCC patients, who were previously treated with sorafenib or were intolerant. The objective response rate was 17%, with occurrence of grade 3 and 4 adverse events were 24% and 1%, respectively. In addition, it was reported a single death with ulcerative esophagitis, which was attributed to the treatment[38]. Similar findings supporting the favorable risk-to-benefit were also reported by KEYNOTE-240, a randomized, double-blind, phase III trial enrolling 413 HCC patients randomized either to pembrolizumab and to placebo was found a longer median overall survival (13.9 *vs.* 10.6 months), and a higher objective response rate by RECIST 1.1 (18.3% *vs.* 4.4%)[39]. Furthermore, a randomized, double-blind, phase III trial enrolling 453 previously treated HCC patients from Asia reported consistent findings, showing a longer overall survival (14.6 *vs.* 13.0 months), progression-free survival (2.6 *vs.* 2.3 months), and objective response rate (12.7% *vs.* 1.3%)[40]. Up to now, pembrolizumab it seems that has not yet been evaluated nor proposed for indication extension by the pharmaceutical company. We will surely have in the future an EMA opinion, also according to newer post marketing evidence.

ATEZOLIZUMAB PLUS BEVACIZUMAB

Atezolizumab blocks the interaction of PD-L1 with PD-1 and CD80 receptors (B7-1Rs), whilst bevacizumab is a monoclonal antibody that targets VEGFA, thus inhibiting neoangiogenesis. In the Imbrave, a global, open-label, phase 3 trial, 336 and 165 naïve patients with unresectable HCC were randomized to atezolizumab–bevacizumab group and sorafenib group, respectively. The combination therapy proved to be a better in both overall 12-months survival (67.2% *vs.* 54.6%) and progression-free survival (6.8 *vs.* 4.3 months)[41]. In 2020 the FDA and EMA approved atezolizumab in combination with bevacizumab as first line therapy for patients with unresectable or metastatic hepatocellular carcinoma. Finally, the clinical benefit from the combination therapy compared to sorafenib was maintained after a longer follow-up, as reported by a recent update of the same trial[42].

IPILIMUMAB PLUS NIVOLUMAB

Ipilimumab is a monoclonal antibody that exert its action by inhibiting cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) immune checkpoint. It was approved in 2020 by FDA in combination therapy with nivolumab for the treatment of HCC patients, previously treated with sorafenib. This accelerated approval was due to the results presented by CheckMate 040 trial, in which 148 patients, affected with advanced HCC or metastatic HCC and previously treated or intolerant to sorafenib treatment, were randomized to receive 3 different dosing regimens of the combination of ipilimumab and nivolumab. The arm A regimen (4 doses nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks then nivolumab 240 mg every 2 weeks) showed the best objective response rate (32% *vs.* 27% and 29%), while the duration of response ranged from 17.5 to 22.2 months across the three arms (overlapping 95%

confidential intervals), with adverse events reports consistent with what was already known for the single drug safety profile[43]. The decision of starting single therapy nivolumab or in combination with ipilimumab should be made in accordance with patient's will. In fact, it should be taken into consideration both the potential response benefits and the potential increased rate of adverse events[44]. Up to now, EMA have not released any opinion for the use of the combination therapy in advanced HCC treatment.

TREMELIMUMAB PLUS DURVALUMAB

Tremelimumab is a fully human monoclonal antibody that acts by blocking CTLA-4, whilst durvalumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that blocks the interaction between PD-L1 and PD-1. This combination therapy was approved as first line therapy in 2022 for patients with unresectable HCC by both FDA and EMA. The commercialization trial called HIMALAYA (a randomized, open-label, multicenter study on treatment naïve HCC patients) proved a better median overall survival compared to sorafenib treatment (16.4 *vs.* 13.8 months; HR 0.78, 95% CI 0.66 to 0.92, p=0.0035), a similar progression-free survival (3.8 *vs.* 4.1 months, respectively) and an increased overall response rate (20.1% *vs.* 5.1%)[45].

CONCLUSIONS

Multiple systemic drugs have emerged to treat unresectable HCC (**Table 1**), rising new hopes of suffering patients and of the doctors and family members

TABLE 1. Systemic pharmacological treatment with therapeutic posology approved for HCC treatment.

SPT	FDA	EMA	Treatment Line	Posology*	Outcomes
Sorafenib	Yes	Yes	First Line	400 mg BID	Median OS: 10.7 months[20] Median PFS: 4.1 months[20]
Lenvatinib	Yes	Yes	First Line	>60 kg 12 mg SID <60 kg 8 mg SID	Median OS: 13.6 months[24] Median PFS: 7.4 months[24]
Regorafenib	Yes	Yes	Second Line	Cycles of 160 mg SID for 3 weeks and 1 week wash-out	Median OS: 10.6 months[25] Median PFS: 3.1 months[25]
Cabozantinib	Yes	Yes	Second Line/ Third Line	60 mg SID	Median OS: 10.2 months[27] Median PFS: 5.2 months[27]
Ramucirumab	Yes	Yes	Second Line	8 mg/kg IV every 2 weeks	Median OS: 8.5 months[30] Median PFS: 2.8 months[30]
Nivolumab	Withdrawal	No	Second Line	240 mg IV every 2 weeks, or 480 mg IV every 4 weeks	Median OS: 15 months[31] Median PFS: 4.0 months[31]
Pembrolizumab	Yes	No	Second Line	200 mg IV every 3 weeks	Median OS: 13.9 months[34] Median PFS: 3.0 months[34]
Atezolizumab plus Bevacizumab	Yes	Yes	First Line	Atezolizumab 840 mg IV every 2 weeks, or 1200 mg IV every 3 weeks, or 1680 mg IV every 4 weeks	Bevacizumab 15 mg/kg every 3 weeks OS at 6 and 12 months: 84.8% and 67.2%[36] Median PFS: 6.8 months[36]
Ipilimumab plus Nivolumab	Yes	No	Second Line	Nivolumab 1 mg/kg IV every 3 weeks PLUS Ipilimumab 3 mg/kg IV on the same day for 4 doses After completing 4 doses of combination therapy, continue with single therapy: Nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks	Median OS: 22.8 months[38] Median PFS: NA[38]
Tremelimumab plus Durvalumab	Yes	Yes	First Line	Tremelimumab 300 mg IV as a single dose in combination with durvalumab 1500 mg, followed by durvalumab 1500 mg IV every 4 weeks	Median OS: 16.4 months[40] Median PFS: 3.8 months[40]

*Posology and treatment duration may change in special populations and according to adverse events onset. Abbreviations – SPT: Systemic Pharmacological Treatment; FDA: Food and Drug administration; EMA: European Medicines Agency; OS: overall survival; PFS: progression free survival; BID: bis in die; SID: semel in die; IV: intra venous.

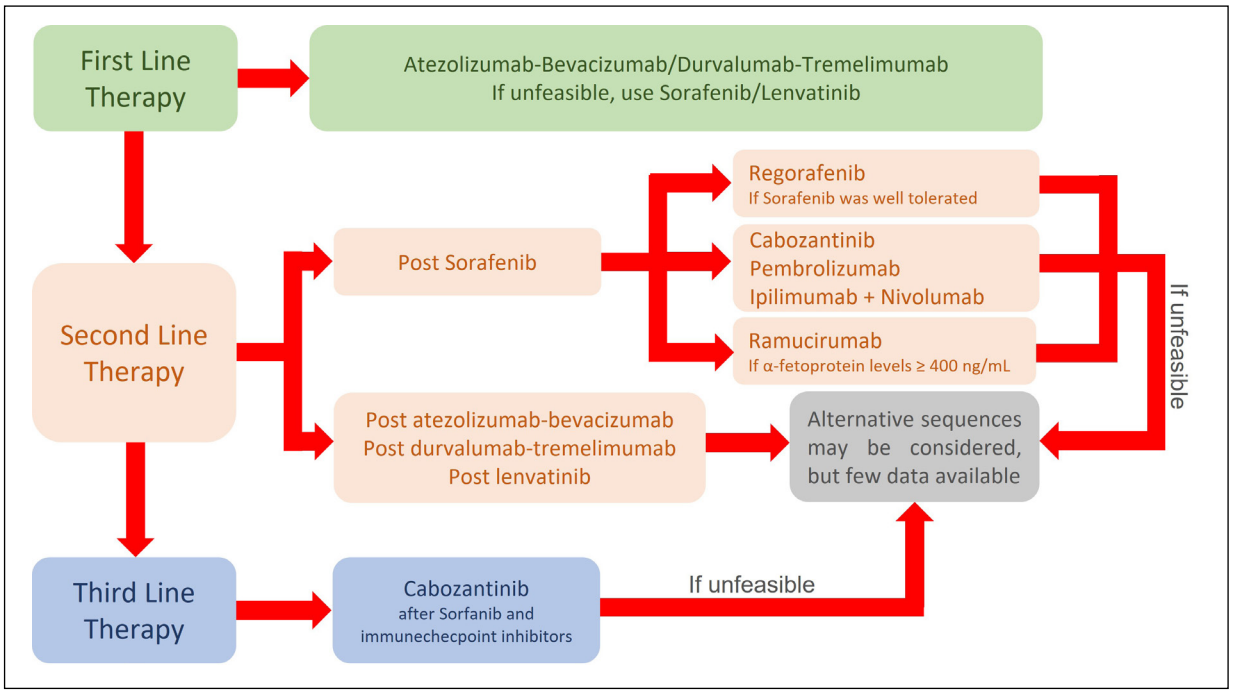

Fig. 1. Systemic pharmacological treatment algorithm for advanced HCC patients, according to current evidence.

who assist them. However, we are still in need of newer therapies and evidence that might lead us to a better HCC management with improved outcomes (**Figure 1**), also considering the healthcare resources and drug availability worldwide. In addition, still little is known on how to ameliorate our patients' conditions, once all the aforementioned drugs fail. Moreover, future research should focus on the identification of several biomarkers which could lead decision making, improving tailored medicine approaches, and reducing adverse events onset. Currently, the role of complementary therapies does not yet seem to have significant weight[46-48]. Furthermore, we do believe that in lack of definitive treatments, the correct management of the predisposing factors leading to HCC development should be physician first goal to improve outcomes.

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The authors have reviewed literature data and have reported results coming from studies approved by local Ethics Committee.

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