Chapter

Systemic Therapy in Hepatocellular Carcinoma

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Abstract

Systemic therapy of advanced stage hepatocellular carcinoma (HCC) was limited to the sorafenib in the past decade since 2007. Novel agents including multiple targeting agents, immune checkpoint inhibitors and anti-angiogenesis reported efficacy in treatment. This is the first time, the combination of atezolizumab and bevacizumab as first-line treatment is superior to sorafenib. Standard guideline in advanced HCC was changing. New novel drugs increase in available including multiple targeting agents and immune checkpoint blockade such as Lenvatinib, regorafenib, cabozantinib, ramucirumab and immunotherapy as first line or second line therapy will benefit in term of survival benefit and quality of life in advanced stage or unresectable hepatocellular carcinoma.

Keywords: hepatocellular carcinoma, immunotherapy, targeted therapy, systemic therapy, advanced stage

1. Introduction

During the many years, numerous randomized control clinical studies have been performed for testing treatments for advanced hepatocellular carcinoma (HCC) [1]. Historical studies performed to prove efficacy of cancer chemotherapy as single agent or in combination. However, this class of cancer therapy have had no proven benefits on overall survival in advanced stage HCC. Sorafenib a multi-tyrosine kinase inhibitor with antiangiogenesic effects showed a survival benefit and it was established as first-line systemic therapy for advanced stage HCC patients or progression form locoregional therapy since 2007. In recent years, there are new agents has been approved for advanced stage HCC as first line and second line options. Exploratory analyses of these drugs indicate that a cumulative median overall survival more than 20 months with good liver function and quality of life.

2. Systemic chemotherapy

Historically, systemic chemotherapy has not shown survival efficacy in treatment of HCC when used in advance stage HCC. This result comes from single-arm, open label studies evaluating the use of some traditionally chemotherapeutic, that did not lead in the past years and limiting their use in palliative setting or some situations. Single agent anthracyclines and fluoropyrimidines have been most widely used in clinical practice in the past. Unfortunately, that result reported poor response rates and short timing in tumor progression [2]. New chemotherapeutic

agents, such as oxaliplatin, have shown clinical benefit in cancers of gastrointestinal tract (stomach cancer, colorectal cancer, or pancreatic cancer). These drugs have also been evaluated for the treatment of advanced stage setting with some benefit findings. As previously said, rational of combination use of chemotherapy might be a valuable option for advance stage HCC. FOLFOX4 regimen (Fluorouracil, leucovorin, oxaliplatin) was evaluated efficacy in comparison with single agent of doxorubicin for advanced stage HCC patients whom ineligible for locoregional therapies or surgery in Phase III EACH study [3]. FOLFOX4 had better results in term of progression free survival (PFS) (2.93 mons vs. 1.77 mons, $P < 0.001$) and in response rate and disease control rate. Although, these positive results and good safety profile in adverse effect but do not necessarily translate to better overall survival that is primary endpoint of the study (6.40 mons vs. 4.97 mons, $P = 0.07$), leading to a negatively result of study. Still, an unplanned subsequent analysis performed at 7 months after the end of the previous study has shown an improvement of survival outcomes (6.46 mons vs. 4.90 mons, $P = 0.04$) but progression free survival, response rate and disease rate control in the Chinese populations [4], leading to FOLFOX4 approval in Chines FDA for advanced HCC. Others, combination drug, GEMOX regimen (Gemcitabine, oxaliplatin) was evaluated in a large, multicenter retrospective study (AGEO) [5]. Results of the study had high response rate with 22%, 66% disease control rate and 4.5 months with 11.0 months in term of progression free survival and overall survival. This interesting result should be considered, response to GEMOX led to better overall survival in comparison with lack of response but possible serious side effects of this regimen (Neurotoxicity, thrombocytopenia, neutropenia, and diarrhea). Furthermore, studies are therefore required in phase III trial to assess the role of this regimen in treatment of advanced stage HCC. Some other oxaliplatin-based regimens have been studies in phase II studies, showing interesting results, such as XELOX (oxaliplatin plus capecitabine) or GP (Gemcitabine plus cisplatin) [6, 7]. Meta-analysis study defined the efficacy of oxaliplatin-based regimens but it as an important limitation having evaluated only small single arm studies [8].

All this result suggests that better efficacy in some situation could be obtained with oxaliplatin-base regimen and GEMOX combination in some setting. But current trials are emerging and focusing on targeted therapies and immunotherapy that have significantly improve survival outcome.

3. Targeted therapies

The vascular nature of HCC and that vascular endothelial growth factor (VEGF) play role of HCC development and metastasis, anti-angiogenesis agents have been studies extensively in the setting of advanced HCC. All, this knowledge dramatically leaded changing of systemic therapies form chemotherapy to molecular targeted agent. Since sorafenib was established as standard first line therapy in advanced HCC.

3.1 Targeted first line therapies

3.1.1 Sorafenib

Sorafenib, a multi-tyrosine kinase inhibitor with antiangiogenic effects is thought to be mediated by the blockade of VEGFR 2–3, platelet-derived growth factor receptor (PDGFR)-B, and other receptor tyrosine kinases. Sorafenib was approved in 2007 by the FDA as first-line therapy for unresectable HCC with BCLC stage C,

Child-Pugh class A or BCLC stage B that progressing after locoregional therapy. It was recommended in patient with well performance status (Eastern cooperative oncology group or ECOG PS 0–2) and preserve liver function test. The efficacy of this drug was demonstrated in two phase III, randomized, placebo-controlled clinical trials: the SHARP study [9] and the Asia-Pacific study (ORIENTAL) [10]. The patient population was mainly recruited form Europe and North America in SHARP study and Asian population in Asia-Pacific study. In the SHARP phase III studies, Sorafenib treatment with dose 400 mg twice a day compared to placebo. Among 602 patients, sorafenib significantly improved overall survival compared with placebo (HR 0.69; 10.7 mons vs. 7.9 mons, $P < 0.001$), DCR (disease control rate) about 43% in sorafenib arm compared to 32% in placebo arm ($P = 0.002$). Sorafenib study arm had significantly prolong time to radiologic progression in 5.5 mons compared with 2.8 mons in placebo arm ($P < 0.001$), Even though sorafenib prolong time to radiologic progression but there is no significant difference in term of time to symptomatic progression. Population of this trial was mostly patients with advanced stage HCC including 35% with macrovascular invasion and 50% with extrahepatic disease. The observed side effects were diarrhea, weight loss, hand-foot syndrome and hypophosphatemia. The result of the SHARP trial was subsequently confirmed in Asia-Pacific study and in 10 subsequent trials with and median overall survival in the range of 10–12 months. Efficacy of sorafenib was conducted in Asia-Pacific region population (The ORIENTAL study). The study was performed with the same design study to the SHARP trial. The Sorafenib arm group had significantly increase overall survival with 6.5 mons compared to 4.2 mons in placebo arm ($P = 0.014$). The overall survival-time and progression free survival time was lower compared to the SHARP study. Unfortunately, objective responses rate is poor with 2% by Response Evaluation Criteria in Solid Tumors (RECIST) and 10% by modified RECIST (mRECIST) [11] and no predictive biomarkers of responsiveness to sorafenib have been identified.

From the positively result, Sorafenib was approved with patient who has well Child-Pugh score (CTP A only); however, result for the GIDEON (Global investigation of therapeutic decision in Hepatocellular Carcinoma and its Treatment with Sorafenib) study, a large observational study assessing the safety profile and efficacy in patients with poor liver dysfunction, the result had a similar safety profile irrespective of Child-Pugh scoring [12]. However, Clinical practice guideline recommended that sorafenib in patient with underlying liver dysfunction is not recommended based on these data alone. The risks and benefits of sorafenib should be carefully consideration prior to start.

The recommended dose of sorafenib is 800 mg. Median treatment duration is estimated 5–6 months, but early recognition and prevention of toxicities can enhance tolerability. Sorafenib toxicities can be manageable. Common toxicities are diarrhea, hand-foot skin reaction (HFS), fatigue and hypertension. 35% of the patient in the study needed dose reduction and 15% of patients need to withdraw from the study due to adverse side effect sorafenib. Liver failure that related to sorafenib complications are marginal. Considering the restrictive indication of sorafenib in Child-Pugh A class only. However, because of its poor antitumor effect and relatively toxicity, developing a new targeted agent with superior efficacy and/or lower toxicity has been a critical issue.

3.1.2 Lenvatinib

After sorafenib has been approved for advanced HCC then several studies have been conducted to compare sorafenib in front line therapy such as sunitinib [13], brivatinib [14], erlotinib [15], linifanib [16] or everolimus [17] without

showing superiority (or at least non-inferiority) to sorafenib. Lenvatinib has only recently shown non-inferior clinical benefit in REFLECT study [18]. Lenvatinib is an oral multi-kinase inhibitor that targets VEGFR 1–3 and fibroblast growth factor receptor (FGFR) 1–4, among others. REFLECT study is an open-label, Phase III, multicenter, non-inferiority study demonstrated efficacy in Lenvatinib compared with sorafenib in patients with advanced HCC (excluding main portal vein invasion, clear bile duct invasion and > 50% of tumor to total liver volume occupancy). Lenvatinib was adjusted to body weight of patient. The study was evaluated in the first line therapy. The study met the primary endpoint of non-inferiority in overall survival (HR = 0.92, 13.6 mons, Lenvatinib compared 12.3 mons, sorafenib, 95% CI = 0.79–1.06). Secondary outcomes in PFS and time to progression were better for Lenvatinib. Overall response rate (ORR) by mRECIST had significant better response (24% versus 9.2% for sorafenib, $P < 0.001$). This drug has shown a higher response rate compared with other tyrosine kinase inhibitors (TKIs) and sorafenib. Most common adverse effects compared with sorafenib were as follows: hypertension (42% versus 30%), diarrhea (39% versus 45%) and HFS (27% versus 52%). These results, Lenvatinib was approved as an option in first line therapy for advanced HCC.

Arguing for a use of Lenvatinib when rapid tumor shrinkage is warranted. Further subgroup analyses showed that Asian populations, patients with hepatitis B infection and high serum AFP > 200 ng/mL demonstrated a particular benefit form treatment with Lenvatinib. Comparing in term of side effects Lenvatinib was associated with more frequent side effects than sorafenib but manageable. More important high side effects were hypertension and weight loss for Lenvatinib. Based on these documents, current clinical practice guidelines recommended both Lenvatinib and sorafenib as frontline therapy for unresectable or advance stage HCC that are not amendable to surgery or locoregional therapies [19].

3.2 Targeted second-line therapies

In the SHARP/ASIAN-Pacific and REFLECT studies, it was shown that administration of TKIs only leads to relatively short periods of tumor control. The recent data evaluated the efficacy of targeted therapies in second-line therapy that shown clinical benefit in patients with advanced HCC that progressed on prior sorafenib therapy in front-line treatment, drugs that considered in this setting was regorafenib, carbozantinib and ramucirumab.

3.2.1 Regorafenib

Regorafenib, a multi-kinase inhibitor targeting similar kinases as sorafenib. Phase III study (RESOUCE) study [20] was conducted to comparing regorafenib with placebo in advanced HCC patients progressing despite sorafenib. The starting dose of regorafenib is 160 mg/day (3 weeks on and 1 week off). The primary endpoint of this study is overall survival. The study was positive for its primary end points (HR = 0.62, P < 0.001, 10.6 months in the regorafenib group vs. 7.8 months in the placebo). The secondary endpoints were PFS, ORR and safety profile. Regorafenib had significantly prolonged time to disease progression (3.1 versus 1.5 months). The efficacy of treatment improved survival in all subgroups of patients. Population in this trial, 88% were BCLC stage C and 12% were BCLC stage B, with all of them tolerant to sorafenib but progression on treatment. 70% of patients had extrahepatic spread and 30% had macrovascular invasion. Around half of patients has high AFP more than 400 ng/dL. The response rate was only 10%, based on mRECIST. Median time on treatment was 3.5 months. Hypertension was the most common adverse

effect, occurring in 15% of patients on regorafenib, followed by HFS. Adverse effects led to 51% dose reductions and 10% treatment discontinuation. Sequential administration of sorafenib and regorafenib resulted in an OS of 26 months compared with 19 months in patients receiving only sorafenib as first-line and placebo as second line treatment [21].

Regorafenib is the standard of care for patients with advanced HCC who have tolerated sorafenib but progressed and recommended in patients with well-preserved liver function test (Child-Pugh A class) and good ECOG PS 0–1.

3.2.2 Cabozantinib

Cabozantinib is another TKI targeting VEGFR 1–3, MET, RET and AXL [22]. Carbozantinib was approved for thyroid and renal cancer. Phase III study (CELESTIAL) [23] compared the efficacy of carbozantinib as second- and third-line therapy in advanced HCC patients after failure of a sorafenib compared with placebo. In contrast to regorafenib, this study allowed the inclusion of patients that were intolerant to sorafenib and who had progressive disease on one or two systemic therapies. Carbozantinib led to a significant improvement in overall survival (HR = 0.76, 95% CI = 0.63–0.92, P = 0.0049, 10.2 mons versus 8.0 mons). Other secondary end points such as PFS and ORR were also positive. It is worth noting that 27% of the patients had received 2 previous systemic agents. 30% of populations in this study presented with macrovascular invasion, 78% with extra-hepatic spreading and 45% with AFP > 400 ng/dL. Response rate was only 4% with carbozantinib based upon RECIST criteria. The most common adverse effects are HFS, hypertension, increased level of aspartate aminotransferase (AST), fatigue and diarrhea. These adverse effects led to 62% dose reduction and 16% treatment discontinuation.

Carbozantinib can be considered for patients who had progressive disease on one or two systemic therapies with well-preserve liver function and good ECOG PS 0–1.

Because RESORCE and CELESTIAL compared with a placebo arm, it is no data shown that which is superior or inferior in term of efficacy to the other. Biomarkers have not yet been identified. The RESORCE study recently identified a total of five proteins (angiopoietin 1, cystatin B, the latency-associated peptide of TGF-β1, oxidized low-density lipoprotein receptor 1 and C-C motif chemokine ligand 3) that were associated with prolonged survival with regorafenib [24]. In addition, nine plasma miRNAs (MIR30A, MIR122, MIR125B, MIR200A, MIR374B, MIR15B, MIR107, MIR320 and MIR645) were correlated with an improved survival. To what extent these findings will become clinically relevant remains to be seen.

3.2.3 Ramucirumab

Ramucirumab is a human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that inhibits ligand activation of VEGFR2. Phase III study (REACH) [25] conducted for tested efficacy of ramucirumab in term of overall survival in advanced HCC after the failure of sorafenib. The primary end point of the study is OS was not statistically significant, but a meaningful improvement was observed in sub-group patients with baseline AFP > 400 ng/mL. Based on these data, the REACH-2 phase III study [26] analyzed the efficacy of ramucirumab in patients with baseline AFP > 400 ng/mL after failure with sorafenib. Result of this study shown ramucirumab significantly improved overall survival from 7.3 mons to 8.5 mons (HR = 0.71, 95% CI = 0.53–0.95) and median PFS from 1.6 mons to 2.8 mons (HR = 0.45, 95% CI = 0.34–0.60) compared with placebo. Overall response rate was 4.6%. The safety

profile observed in this study was consistent with previously study, only grade III adverse effects occurring were hypertension (12.2%) and hyponatremia (5.6%)

Ramucirumab can be considered for patients in second-line therapy with baseline AFP > 400 ng/mL with well-preserved liver function and good ECOG PS 0–1, thus, the AFP may serve as a marker for the benefit of ramucirumab in the second line setting for advanced hepatocellular carcinoma. Ramucirumab remains the only systemic agent that demonstrated clinical benefit in biomarker selected population in HCC.

3.3 Immunotherapy

The most promising immunotherapeutic approach has been the use of immune checkpoint inhibitors in vary of cancer type including gastrointestinal malignancies. Immune checkpoint inhibitor can change paradigm of treatment and improve survival and quality of life in many type of cancer. Tumor-infiltrating lymphocytes (TILs) in the tumor microenvironment was demonstrated in hepatocellular carcinoma cell, which shown that HCC is also immunogenic cancer [27]. Some studies have also shown the presence of an immunosuppressive intratumoral milieu driven by constant exposure of the liver to antigens via the portal system and immune dysfunction related to cirrhosis [28]. These results of a phenomenon of immune escape might predict that HCC could be response to immunotherapy and immune checkpoint inhibitor drugs.

3.4 First-line immunotherapy

Single agent of Immunotherapy has been conducted in two phase III studies as first line therapy. The Checkmate 459 trial, Nivolumab compared to standard of care as sorafenib, failed to meet the primary endpoint as overall survival [29]. Also, with, The KEYNOTE-240 trial of pembrolizumab as second line treatment of advance HCC after failure to sorafenib compared with placebo, failed to meet endpoints of OS and progression free survival [30]. They are not recommended as monotherapy for the treatment of advanced HCC.

To date, new combination immunotherapy with Atezolizumab plus bevacizumab were change paradigm of treatment in advanced HCC. This combination therapy is the first treatment to demonstrate a significant OS benefit compared with sorafenib in Phase III international, open label of patients with locally advanced or metastatic and/or unresectable HCC (IMbrave 150 study) [31]. Patients were allocated randomization with 2:1 ratio to compare efficacy of Atezolizumab plus bevacizumab to sorafenib. The coprimary endpoints were overall survival and progression free survival. The combination therapy demonstrated a significant overall survival benefit (HR = 0.66, 95% CI = 0.52–0.85). The median overall survival was not reached (Not estimate or NE) in the Atezolizumab plus bevacizumab arm, whereas sorafenib arm had median overall survival at 13.2 months. The study reported a significantly PFS of combination therapy compared to sorafenib (6.8 mons vs. 4.3 mons, HR = 0.59, 95% CI = 0.47–0.76, P < 0.0001). The difference in overall response rate was significant (stratified $P < 0.0001$): Atezolizumab plus Bevacizumab arm = 27%, and sorafenib arm = 12%. Complete response was achieved in 18 patients (6%), which is quite promising. The median duration of response of NE and the proportion (80%) of responders with a DOR of >6 months by Atezolizumab plus Bevacizumab arm therapy indicate a considerable durable response to this treatment. Successful benefit both the OS and PFS endpoints at first analysis was surprising and coming to a new era of systemic therapy for HCC as standard of care in first-line therapy due to meet primary endpoint of overall survival benefit.

Treatment related adverse effects especially grades III or IV were found more in sorafenib arm (46%) compared to Atezolizumab plus Bevacizumab arm (36%). Immune-related adverse effects were rarely observed in the Atezolizumab plus Bevacizumab arm (expect for infusion reaction in 10.9%, AIHA in 0.3% and adrenal insufficiency in 0.3%). Bleeding events form bevacizumab was minimal occurring at 6.4%. The data suggest that the acceptable safety profile in Atezolizumab plus Bevacizumab.

However, the median progression free survival is only 6.8 months and only 20% of patients do not response to atezolizumab plus bevacizumab, experimental studies need to define options for second-line therapy after progression on immunotherapy. Most of drugs only been tested after sorafenib intolerance or progression and there are currently no phase III study to inform the choice of therapy in this setting. However, a clear rationale for offering a targeted therapy given the existing evidence for efficacy in first- and second-line therapy.

3.5 Other combination immunotherapies

To current knowledge of combination immune checkpoint blockade plus anti-angiogenesis translate to new combination therapy that need to find out the clinical benefit. Basic research studies show that lenvatinib and anti-PD-1 antibodies have synergistic effects [32]. Immunotherapy and Molecular targeting agents as combination therapy might have a role in the treatment of HCC in the future. A phase Ib trial of combination use of lenvatinib plus pembrolizumab reported promising results [33]. This combination had a median progression free survival and overall survival of 9.3 months (95% CI: 5.6–9.7) and 22.0 months (95% CI: 20.4–NE), respectively. Overall response rate was higher in 46% (95% CI: 36.0–56.3). A phase III trial (LEAP002) of this combination is currently ongoing. On the other hand, rationale of dual combination immune checkpoint blockade (PD-L1 plus CTLA-4 inhibitor) might have a clinical response too. The results of combination therapy with the durvalumab (PD-L1 antibody) and the tremelimumab (CTLA-4 antibody). The study revealed a median PFS and OS of 2.17 months (95% CI: 1.91–5.42) and 18.73 months (95% CI: 10.78–27.27), respectively. ORR this combination therapy was 24.0% (95% CI, 14.9–35.3). Therefore, this combination therapy is promising, and the phase III HIMALAYA trial of this combination is ongoing too.

3.6 Second-line immunotherapy

Second-line therapy after the failure of sorafenib apart from molecular targeting agents. Data of immunotherapy both pembrolizumab (an anti-PD-1 monoclonal antibody) and nivolumab (a fully humanized monoclonal antibody against PD-1) shown efficacy in Phase Ib studies (CheckMate-040 [34] and Keynote-224 [35]). Unfortunately, for pembrolizumab, these results were negative in the Phase III study, randomized double-blind keynote-240 study, which included a total of 413 patients with pretreated advanced HCC. The study was comparable with pembrolizumab or placebo. The median OS was 13.9 months in the pembrolizumab arm versus 10.6 months in the control arm (HR: 0.78; $P = 0.024$), the median PFS was 3.0 mons versus 2.8 mons (HR: 0.72; $P = 0.002$). However, since the prespecified alpha level was significantly lower, the study must be considered statistically negative. CTLA-4 antibodies were also tested in second-line therapy of advance stage HCC; The study reported results (response rate was 17.6% and a median time to progression was 6.48 months) from patients treated with tremelimumab [36]. Nivolumab as single agent in advance HCC treated with sorafenib reported an ORR of 14% and median OS of 16 months. Due to the promising results the study was conducted

the efficacy and safety of the combination of nivolumab and ipilimumab [37]. The study was randomized into three different dose and time arms of nivolumab and ipilimumab. Of note, the first arm (Nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (Q3W) followed by n 240 mg Q2W) demonstrated the most promising efficacy in term of OS (23 months). ORR and disease control rate were 31% and 49%, respectively. Interestingly, the different combinations were well tolerated, potentially offering a novel treatment option for patients with pretreated HCC.

4. Conclusion

Current data of systemic therapy in advanced stage/unresectable or failure to locoregional therapy HCC shown efficacy and safety profile of multiple targeting agents such as Lenvatinib, regorafenib, cabozantinib and ramucirumab in addition to standard treatment with sorafenib. New emerging current standard of care in advanced HCC is change to combination therapy with Bevacizumab plus atezolizumab as first line therapy due to improvement of progression free survival and with overall survival. The increase in available multiple targeting agents and immune checkpoint blockade will benefit in many patients. Sequential therapy and drug selection will become more challenging as **Figure 1**. New strategies of systemic therapy with new combination therapy are needed to explore.

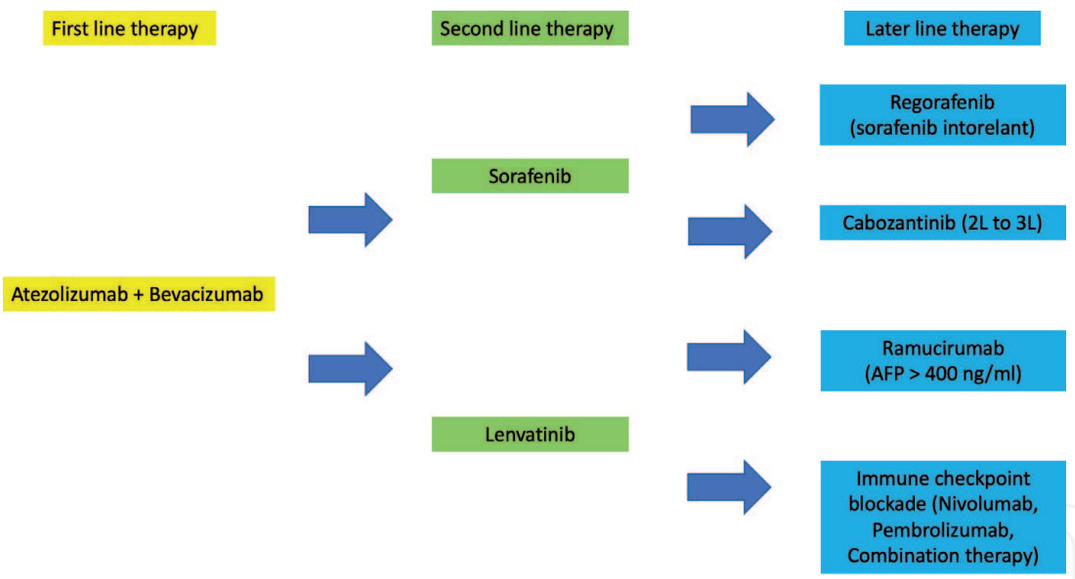

Figure 1.
Possible sequential systemic therapy for advanced stage/unresectable or failure to locoregional treatment HCC, hepatocellular carcinoma; 2 L, second line; 3 L, third line; AFP, alpha-fetoprotein.

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Conflict of interest

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