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Review Article

Immune Checkpoint Inhibitors, New Therapies for HCC: A Systematic Review of Clinical Registered Trials and Trials on-Going

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Abstract

Hepatocellular carcinoma (HCC) is a major cause of liver cancer-related death worldwide. In the last decade, systemic therapy for advanced stage HCC remained poor of new treatments, except for few molecular target therapies, and only in the last 2 years a new approach with immune checkpoint inhibitors (ICIs) started to gain attention.Our review wants to describe the evidences collected from the new drugs used to treat HCC, in monotherapy or in association, and to present the ongoing trials.

Introduction

Hepatocellular carcinoma (HCC) is a major cause of liver cancer-related death worldwide. It usually occurs in the setting of chronic liver disease and cirrhosis with different aetiopathogenesis (metabolic, viral, alcoholic, autoimmune, genetic and other minor causes). Primary liver cancer is the seventh-most frequently occurring cancer in the world and the second-most common cause of cancer mortality [1]. Asia and Africa are the nations with registered the highest inci-dence worldwide [2].

Globally, hepatocellular carcinoma (HCC) is the dominant type of liver cancer, accounting for ~75% of all liver cancers [2]. In the last decade HCC incidence declined in many Asian countries and Italy, but increased in India, the Americas, Oceania, and most European countries [3]. Incidence and mortality rates are roughly equivalent. In 2018, the estimated global incidence rate of liver cancer per 100,000 person-years was 9.3 whereas the corresponding mortality rate was 8.5 [4].

Treatment options for HCC can be divided into surgical therapies (resection, cryoablation, and liver transplantation) and non-surgical therapies, which may be liver directed (percutaneous ethanol injection, radiofrequency/microwave ablation, trans-arterial embolization, external beam radiation therapy), or systemic (chemotherapy, molecularly targeted therapy, immunotherapy). A general approach to the treatment of HCC has been proposed by the Barcelona Clinic (BCLC) [5].

In the last decade, systemic therapy for advanced stage HCC remained poor of new treatments, except for few molecular target therapies, and only in the last 2 years a new approach with immune checkpoint inhibitors (ICIs) started to gain attention. ICIs target a class of membrane-bound molecules called immune checkpoints. Immune checkpoints are highly expressed in different immune cells types, such as T and B cells, dendritic cells, monocytes, natural killer cells, tumor-associated macrophages and dendritic cells, and play a central role in preventing autoimmune reactions to self-antigens. In the last few years, a growing number of evidence indicate that tumors cells can interfere with certain different immune checkpoint pathways (e.g. PD-1/PD-L1 and CTLA-4/B7-1/B7-2) suppressing antitumor immune response. Blocking the interaction between ligands and receptors, ICIs can restore cancer immune surveillance and promote tumor cells elimination [6].

Our review wants to describe the evidences collected from the new drugs used to treat HCC, in monotherapy or in association, and to present the ongoing trials.

Monotherapy with Immune Checkpoint Inhibitors in First or Second Line (Table 1)

Nivolumab

Nivolumab is a fully human monoclonal antibody that targets the programmed cell death 1 receptor (PD-1), restoring T cell immune activity directed against tumour cells. The efficacy of nivolumab monotherapy was addressed in a phase I/II study (CheckMate 040), Open-Label, Non-Comparative trial that included patients with advanced HCC and Child-Pugh A or B7 on cirrhosis whose disease had progressed on sorafenib or who refused or were intolerant of the drug [7].48 patients were treated in the dose-escalation part of the study and 214 in the expansion cohort. Nivolumab was administered IV every two weeks for up to two years at doses ranging from 0.1 to 10 mg/kg, although a maximally tolerated dose was not reached and the expansion cohort (as long as not HBV-infected) was treated at a dose of 3 mg/kg.Overall, 68% of patients in the expansion cohort had received sorafenib in first line. 45 of the 255 patients assessable for response had an objective antitumor response to nivolumab (15 % of the escalated-dose cohort and 20 percent of the expansion cohort), with six of them having a complete one. An additional 50% had stable disease. In the dose-escalation group, the median duration of response was 17 months (95% CI 6-24), and the median overall survival was 15 months. In the expansion cohort, the median duration of response was 9.9 months, and the data were insufficiently mature for calculation of median survival. However, 74 % of patients were still alive at nine months.

Most adverse events (AEs) were mild and transient. The most common grade 3 or 4 toxicities in the dose-escalation phase patients were increased aspartate aminotransferase (AST) (10%), increased alanine aminotransferase (ALT) (3%), increased lipase (3%), and increased amylase (2%). Immune-mediated hepatitis requiring systemic glucocorticoids occurred in 5 % of treated patients. Toxicity was similar in the expansion cohort.

In a later analysis of the entire cohort, the durable benefits of nivolumab were observed both in sorafenib-naïve (objective response rate (ORR) 23 %, with 44% of responses ongoing) and sorafenib-experienced patients (ORR 16% to 19 %) [8].

Largely based on these data, in September 2017, the FDA expanded the indications for nivolumab to include treatment of HCC in patients who have been previously treated with sorafenib [4], at the dose of 240 mg every two weeks. However, an alternative dose of 480 mg every four weeks has been added to most indications, including HCC, based on manufacturer pharmacokinetic data [9,10].

In the subsequent phase III CheckMate 459 trial, nivolumab was compared to sorafenib in 743 patients with advanced, previously untreated HCC [11].

In a preliminary report presented at the 2019 European Society for Medical Oncology (ESMO) meeting, nivolumab was associated with a twofold higher objective response rate (15% versus 7 %) and more complete responses (4% versus 1%), but without any significant benefit in either progression-free survival (PFS) (median 3.7 versus 3.8 months) or overall survival (OS) (median 16.4 versus 14.7 months).

Compared with sorafenib, grade 3 or 4 treatment-related adverse events were reported in fewer nivolumab-treated patients (22% versus 49%), with a reduction in discontinue therapy (4% versus 8 %). Up to date nivolumab is approved in patients with advanced HCC previously treated with sorafenib but consensus-based guidelines from The National Comprehensive Cancer Network (NCCN) suggest that patients with Child-Pugh class B disease and a total score >7 are not good candidates to receive nivolumab [12].

Table 1. Trials on monotherapy

Trial identifier	Enrollment	Status	Phase	Regimen	Control arm	Line	Study description
NCT03232593	3000 participants (estimated)	Recruiting	4	Atezolizumab			Evaluation of the the safety and effectiveness of atezolizumab
NCT03829501	412 participants (estimated)	Recruiting	1/2	KY1044 (human anti-ICOS mono-clonal antibody)	KY1044 and atezolizu-mab	2	Evaluation of the safety, efficacy and tolerability of KY1044 as single agent and in combination with atezolizumab in adult patients with selected advanced malignancies
NCT03841110	76 participants (estimated)	Recruiting	1	FT500 (iPSC-derived NK cell product)	FT500 + Immune Check-point Inhibitor	1	Evaluation of the maximum tolerated dose and objective response rate of FT500 as monotherapy and in combination with ICI in subjects with advanced solid tumors.

NCT03222076	46 participants (estimated)	Recruiting	2	Nivolumab	Nivolumab +Ipilimumab	1	Evaluation of the side effects and efficacy of nivolumab with or without ipilimumab in treating patients with liver cancer that can be removed by surgery.
NCT03419481	30 participants (estimated)	Recruiting	2	Pembrolizumab		1	Evaluation of efficacy of pembrolizumab in patients with hepatitis B virus-related hepatocellular carcinoma with parallel study on baseline and serial change in the immune environment.
NCT02658019	29 participants (estimated)	Active, not recruiting	2	Pembrolizumab		1	Evaluation of therapeutic efficacy of Pembrolizumab in patients with advanced, unresectable hepatocellular carcinoma.
NCT03163992	60 participants (estimated)	Recruiting	2	Pembrolizumab		2	Evaluation of the efficacy of pembrolizumab in subjects with advanced hepatocellular carcinoma as second-line treatment after failure of sorafenib.
NCT03867084/ KEYNOTE-937	950 participants (estimated)	Recruiting	3	Pembolizumab	Placebo	1	Evaluation of the safety and efficacy of pembrolizumab versus placebo as adjuvant therapy in participants with hepatocellular carcinoma and complete radiological response after surgical resection or local ablation. The primary hypotheses of this study are that adjuvant pembrolizumab is superior to placebo with respect to recurrence-free survival and overall survival.
NCT02702414/ KEYNOTE-224 [10]	150 participants (estimated)	Active, not ecruiting	2	Pembrolizumab		2	Evaluation of the efficacy and safety of pembrolizumab as monotherapy in participants with hepatocellular carcinoma in two cohorts: participants with advanced HCC and with no curative option after disease progression on sorafenib or intolerance of sorafenib (Cohort 1) or who had not received treatment for systemic disease (Cohort 2).
NCT02702401/ KEYNOTE-240 [19]	413 participants (estimated)	Active, not recruiting	3	Pembrolizumab	Placebo	2	Determination of Progression Free Survival and Overall Survival of pembrolizumab plus best supportive care (BSC) compared with placebo plus BSC.
NCT03939975	50 participants	Completed	2	Pembrolizumab	Nivolumab	2	This study aimed to analyze outcomes of advanced HCC treated with anti PD-1 inhibitors in combination with incomplete thermal ablation.
NCT01658878 [7]	1097 participatns	Active, not recruiting	1	Nivolumab		2	Evaluation of the safety of nivolumab at different dose levels for each of the three cohorts (uninfected hepatocellular carcinoma subjects, HCV-infected HCC subjects, and HBV-infected subjects).
NCT02576509/CheckMate 459	1723 participants (estimated)	Active, not recruiting	3	Nivolumab	Sorafenib	1	Evaluation of the efficacy of nivolumab versus sorafenib in the treatment of advanced hepatocellular carcinoma.
NCT03383458	530 participants (estimated)	Recruiting	3	Nivolumab	Placebo	1	Evaluation of recurrence-free survival with nivolumab versus placebo in participants with HCC who have undergone complete resection or have achieved a complete response after local ablation, and who are at high risk of recurrence.

Pembrolizumab

Pembrolizumab (another anti-PD-1 monoclonal antibody) is a reasonable alternative ICI in patients who have failed initial sorafenib. Pembrolizumab is a first-line treatment if the cancer overexpresses PD-L1, a PD-1 receptor ligand, and the cancer has no mutations in EGFR or in ALK; Results from the Open-Label phase II Keynote-224 trial Non-Randomised, of pembrolizumab in patients previously treated with sorafenib support benefits for this alternative PD-1 inhibitor (objective response rate 17 %, with 44 % stable disease) [13]. The median duration of pembrolizumab therapy was 4.2 months (interquartile interval 2.1 to 7.7 months).

At least one AE was observed in 97% of patients enrolled. Treatment-related AEs (TRAEs) were observed in 76 (73%) subjects, of whom 16 (15%) were classified as serious. 28 (27%) deaths were reported in the study, 12 of which were attributed to AEs; moreover a case of treatment-related death from ulcerative esophagitis was reported to be possibly treatment-related.

Dose interruptions because of AES were necessary in 26 (25%) of patients; the most frequent of AEs included increase concentration of AST (4%) or ALT (3%), hypothyroidism (2%) and rash (2%). Immune-mediated events (IREs) occurred in 15 (14%) participants, and the most common events of any grade of severity were hypothyroidism (8% of participants) and adrenal insufficiency (3% of patients). Immune-mediated hepatitis was seen in three (3%) participants. No cases of flares of hepatitis B virus or hepatitis C virus occurred.

Grade 3 IREs were also reported, including 2 cases of adrenal insufficiency, one 1 skin toxicity and one type 1 diabetes mellitus. No IREs worse than grade 3 severity occurred. These results were confirmed in the international phase III KEYNOTE-240 trial of best supportive care plus either pembrolizumab or placebo for second-line therapy of advanced HCC with Child-Turcotte-Pugh A cirrhosis after radiologic progression/intolerance of sorafenib [14]. Overall, 413 patients were randomly assigned on a 2:1 basis to pembrolizumab or placebo. Despite clinically significant improvements in median OS (13.9 versus 10.6 months, HR 0.78, 95% CI 0.61-0.998) and PFS (3 versus 2.8 months), results did not reach the prespecified efficacy boundaries. However, the ORR was higher for pembrolizumab (18.3 versus 4.4 percent), there were more complete responders with it (six versus none), and responses were durable (median duration of response 13.8 months, range 1.5 to 23.6+ months). Grade 3 or higher adverse events were reported in 147 (52.7%) and 62 patients (46.3%) for pembrolizumab versus placebo. Among them, TRAE occurred in 52 (18.6%) and 10 patients (7.5%), respectively. No hepatitis C or B flares were identified.

Largely based on the early KEYNOTE-224 data, pembrolizumab monotherapy was approved by the FDA in November 2018 for treatment of patients with HCC who have been previously treated with sorafenib. There are no studies that assist the clinician in the selection between nivolumab and pembrolizumab. However, consensus-based guidelines from the NCCN suggest limiting pembrolizumab use to individuals with Child-Pugh class A cirrhosis, but patients with Child-Turcotte-Pugh class B cirrhosis and a score no higher than 7 can be candidates for nivolumab [12].

Notably, although patients with HCC who are treated with ICIs show a substantial increase in transaminases as compared with patients receiving these drugs for other indications (eg, lung cancer, melanoma), this does not translate into premature treatment discontinuation or treatment-related mortality [15]. Nevertheless, liver function tests should be monitored while using these agents.

Cemiplimab

Cemiplimab is a new human monoclonal anti-PD-1. Cemiplimab targets the cellular pathway PD-1. In a recent phase I study [16], 26 HCC patients in progression with first line sorafenib, regorafenib and nivolumab, received cemiplimab 3 mg/kg Q2W for up to 48 weeks. By investigator assessment, 19.2% had partial response, 53.8% had stable disease, 23.1% had progressive disease. Median progression-free survival was 3.7 months (95% CI: 2.3–9.1). The most common treatment-emergent adverse events of any grade were fatigue (26.9%), decreased appetite, increased aspartate aminotransferase (AST), abdominal pain, pruritus, and dyspnoea (each 23.1%). Grade ≥3 TEAEs occurring in ≥ 2 pts were hyponatraemia (3 pts), autoimmune hepatitis (2 pts) and increased AST (2 pts). Cemiplimab demonstrated a safety profile comparable with that of other anti-PD-1 inhibitors.

Durvalumab

Durvalumab is an anti-PD-L1 agent. It is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that blocks the interaction of programmed cell death ligand 1 (PD-L1) with the PD-1 (CD279). In a Phase 1/2, multicenter, open-label study 40 patients with HCC (Child-Pugh class A), 93% of whom had prior sorafenib, received durvalumab 10 mg/kg i.v. q2w for 12 months or until confirmed progressive disease. seven (17.5%) pts completed the initial 12-month treatment, while 7 (17.5%) pts discontinued treatment because of an AE.

The study has reported an ORR of 10%, a median OS of 13.2 months (6.3–21.1- 95% CI) and a 56% 1-year survival rate. Treatment-related AEs occurred in 80.0% of pts, the most common being fatigue (27.5%), pruritus (25.0%) and elevated AST (22.5%). Grade 3–4 treatment-related AEs were reported in 20.0% of pts, elevated liver enzymes (AST 7.5% and ALT 5.0%) above all.

Authors concluded that Durvalumab had an acceptable safety profile and showed promising antitumor activity in pts with HCC, especially in presence of HCV-related aetiology [17].

Tremelimumab

Tremelimumab is a monoclonal antibody that blocks cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), an inhibitory co-receptor that interferes with T cell activation and proliferation. Tremelimumab was the first immune checkpoint blocker to be tested in advanced HCC.

In a recent pilot clinical trial phase II [10]. 37 patients with HCV-related HCC were assessable for toxicity, HCV viral response and tumor response. Most patients had advanced stage disease and 43% had Child-Pugh class B. Despite a modest response rates (17.6%), mirrored by a median time to progression (TTP) of 6.5 months (95% CI 3.95-9.14), a good safety profile was recorded for the CTLA-4 and interestingly a significant drop in viral load was observed. However, anti-CTLA-4 monotherapy has not undergone further testing in the context of large phase III studies leaving open questions around its efficacy in HCC patients and across different etiologies of chronic liver disease.

ICIs have consistently demonstrated ORR ranging from 14 to 20% as monotherapy in HCC [7,10]. Despite promising clinical activity, phase 3 trials of single agent ICIs failed to show survival benefits in first and second line setting [18,19].

Thus, both novel biomarkers as well as different treatment strategies are needed to improve patients' outcome. Multiple non-redundant mechanisms synergies have been addressed in determining a barrier to immunotherapy, involving intrinsec liver immunosuppressive properties and the peculiar tumor microenvironment (TME) of HCC. The presence of multiple pathways constitutes the rationale for a combined approach for HCC [20,21]. Therefore, several combination strategies have been studied and include targeting multiple co-inhibitor receptors, ICIs and non-immunological systemic therapies combination, or local treatments. Unfortunately, at present, these combinations have been tested mainly in the context of small, single-arm studies.

Combined Therapy

Dual Immune checkpoint blockade

Combining agents with different mechanisms of action offers the possibility of a synergistic effect. For instance, PD-1 and CTLA4 are both co-inhibitory agents but evidence suggests that they exert their effect on T-cells in different ways, thus providing a rationale for a combined strategy. Treatment with anti PD1 and anti CTLA4 agents has shown efficacy in many cancer types and data from early trials confirmed an acceptable safety profile and efficacy even in the HCC setting.

Based on the data from the phase I/II Checkmate-040, in November 2019 the FDA approved the combination of nivolumab and ipilimumab in advanced HCC after sorafenib failure [9]. Similar results were obtained with the combination of the anti PDL1 durvalumab and the anti CTLA4 tremelimumab, leading to FDA approval in January 2020.

Other inhibitory receptors shared by natural killer and T-cells including TIGIT, LAG-3, TIM-3, BTLA and NKG2A have been identified as novel checkpoint blockade [22] appearing particularly promising in combination with anti-PD-1/PD-L1 or anti-CTLA-4 agents [23].

Furthermore, the combination with agonist antibodies targeting costimulatory molecules (4-1BB, CD40 and OX40) and a triple combination targeting 4-1BB, OX40 and anti PDL1 showed interesting results in murine models [24], leading evidences for further exploring this strategy.

Antivascular therapy and ICIs

Combining ICIs and targeted therapies is justified both by evidence of single-agent activity and also by the complex bidirectional relationship between angiogenesis and immunity [25]. Vascular endothelial growth factor (VEGF) overexpression constitutes one of the intrinsic immune-evasion pathways [26,27] and on the other hand the presence of an immune-suppressive microenvironment contributes to anti-angiogenic therapies resistance [28]. Moreover, the expression of PD-L1 itself is strongly placed under the transcriptional regulation of hypoxia inducible factor 1-alpha [29].

Anti-vascular therapy has been demonstrated to exert a role in normalizing tumor vasculature, modeling both TME and immune infiltrate by activating dentritic cells and decreasing T-regs and myeloid derived suppressor cells (MDSCs) [30]. In addition, anti-VEGF therapy avoids effector T cells exhaustion [31].

Preclinical studies indicate that anti-VEGF antibody bevacizumab may enhance the activity of anti PD1/PDL1, by reversing VEGF-induced immunosuppression and promoting immune infiltrate [32]. Results from trials in renal cell carcinoma and non-small cell lung cancer support this data [33,34]. Therefore, the combination of anti-VEGF therapies (small molecules or monoclonal antibodies (mAbs)) with ICIs has a strong biological rationale.

After the promising results of a phase Ib trial in terms of response rate and safety profile in patients with advanced HCC [16], a phase III trial (IMbrave 150) comparing atezolizumab-bevacizumab to standard first line sorafenib was conducted. Results from this trial [34] clearly showed the benefit of this strategy over single agent. Trials are now ongoing to evaluate similar combination also in the adjuvant setting.

Multikinase inhibitors and immunotherapy

TKIs have several roles in the regulation of the immune sys-

-tem through direct and indirect effects. In particular, they promote dentritic cell maturation, T-cell priming, activation and differentiation. Moreover, they exert a role in enhancing tumor immunogenicity [35]. Immuno-modulatory effects of cabozantinib have been described in vitro and in murine models for several cancers including renal, colorectal and prostate cancer. Cabozantinib appears to exert its effect on T-reg via the HGF/c-Met pathway [36].

In murine models, cabozantinib was shown to alter the composition of peripheral immune cells by increasing activated T cell, reducing T-reg and MDSCs and finally increasing the sensitivity of cancer cells to T-cell mediated killing [37]. An increase in tumor infiltration of CD8+ T cells and T-regs accompanied by a decrease in tumor infiltration of MDSCs and Tumor-associated macrophages (TAMs) was also observed.

Moreover, cabozantinib increased the expression of major histocompatibility complex class 1 and cell surface molecules Fas, intercellular adhesion molecule 1, and calreticulin, which are involved in immune cell recognition and can also raise sensitivity to T-cell mediated lysis [37].

Therefore, these results suggest that TKIs can induce a more immune permissive environment in tumor periphery. Moreover, the effect of TKI on angiogenesis may also affect immune response by increasing the expression of adhesion molecule on endothelial cells and immune cell infiltration in the TME [20].

Taken together these data strongly support the combination of TKI and immunotherapy and several trials are ongoing to test this hypothesis. In recent studies, cabozantinib combined with nivolumab with or without ipilimumab in genitourinary tumors showed an ORR of 36% [38].

Promising results in terms of response rate and survival were reported with the combination of levantinib and pembrolizumab in a recent phase Ib trial [39] and a multicenter, double-blinded, phase III trial, LEAP-002 (NCT03713593), is currently underway to examine this combination in the front-line setting for patients with advanced HCC [40]. Given these promising results with combined therapies, several studies are now ongoing in first and second-line setting (Table 2).

Table 2. Trials on combined therapy

Trial identifier	Phase	Regimen	Control arm	Line	Number of patients	Status	Results
NCT03298451 (HIMALAYA)	III	Tremelimumab Durvalumab	Sorafenib	1	Actual enrollment 1324 pts	Active, not recruiting	NA
NCT03794440 (ORIENT-32)	II/III	Sintilimab Bevacizumab (biosimilar)	Sorafenib	1	Estimated enrollment 566 pts	Ongoing	NA
NCT03713593	III	Pembrolizumab Lenvatinib	Lenvatinib	1	Estimated enrollment 750 pts	Active, not recruiting	NA
NCT03764293	III	Camrelizumab Apatinib	Sorafenib	1	Estimated enrollment 510 pts	Ongoing	NA
NCT03434379 [34]	III	Atezolizumab Bevacizumab	Sorafenib	1	Estimated enrollment 480 pts	Active, not recruiting	Increase overall and progression-free survival with the combination
NCT01658878 [7]	I/II	Ipilimumab Nivolumab		2	Actual enrollment 1097 pts	Active, not recruiting	Positive results in terms of safety and activity (objective response and, response duration)
NCT04472767	II	Cabozantinib Ipilimumab Nivolumab + TACE		1	Estimated enrollment 35 pts	Ongoing	NA
NCT03755791 (COSMIC-312) [41]	III	Cabozantinib Atezolizumab	Sorafenib	1	Estimated enrollment 740 pts	Ongoing	NA

NCT01658878	I/II	Nivolumab + Cabozantinib +/- ipilimumab	Sorafenib	1 o 2	Actual enrollment 1097 pts	Active, not recruiting	Positive results in terms of safety and activity (objective response and, response duration) with Nivolumab plus ipilimumab
NCT03347292	I	Regorafenib Pembrolizumab		1	Estimated enrollment 57 pts	Active, not recruiting	Positive data in terms of safety profile
NCT03539822 (CAMILLA)	I	Cabozantinib Durvalumab		2	Estimated enrollment 93 pts	Ongoing	NA
NCT02572687	I	Ramucirumab Durvalumab		2	Actual enrollment 114 pts	Active, not recruiting	Positive data in terms of safety profile
NCT02856425	Ib	Pembrolizumab Nintedanib			Estimated enrollment 18 pts	Ongoing	NA
NCT04442581	II	Cabozantinib Pembrolizumab		1	Estimated enrollment 29 pts	Not yet recruiting	NA
NCT02519348	II	Durvalumab + Tremelimumab Durvalumab Tremelimumab Durvalumab + Bevacizumab		2	Actual enrollment 433 pts	Active, not recruiting	Positive data in terms of safety profile
NCT03841201	II	Nivolumab Lenvatinib		1	Estimated enrollment 50 pts	Ongoing	Positive results in term of safety and tolerability after the first 6 pts enrolled

Conclusion

Patients with advanced HCC show a very poor prognosis with a median overall survival times of 6-8 month and a one-year survival rate of 25% [42]. At the present, if there are no contraindication to immunotherapy, we believe that the best first-line treatment option for advanced HCC could be the combination between atezolizumab/bevacizumab as sated in a very recent meta-analysis (cit). To date, regarding second-line treatment for advanced HCC, the superiority of ICIs over other agents, such as TKIs or anti-VEGF, was not clearly demonstrated. Sonbol and colleagues found that in these patients only regorafenib and cabozantinib showed a significant overall survival benefit compared to placebo. Furthermore, patients treated with regorafenib and cabozantinib showed a greater PFS compared to those treated with ramucirumab or pembrolizumab [43]. Therefore, it is our opinion that, for patients with progressive disease after first line therapies, treatment with ICIs (Pembrolizumab or Nivolumab) should be consider as an alternative to regorafenib or cabozantinib and should be limited to patients that did not receive PD-1 or PDL-1 blockade as first line treatment.

Although the emergence of ICIs in mono or combined therapy have profoundly changed the landscape of treatments options for advanced HCC, there is an urgent need to understand the determinants behind response to ICIs in this setting since response to anti-PD1 inhibitors could be extremely heterogenous. As an example, despite the promising results of the CheckMate 040 trial [7], in the phase III CheckMate 459 trial [18] Nivolumab failed to show a significant survival benefit, as compared with Sorafenib, in treatment naïve patients with advanced HCC. The failure of phase III confirmatory trial might be due to high tumour heterogeneity in terms of tumour microenvironment (TME). In this context, Sangro and colleagues [11] undertook an interestingly retrospective analysis using tumour and blood samples of dose-escalation and dose-expansion phases of the CheckMate 040 trial in order to elucidate the identify tumour and systemic inflammation markers potentially associated with clinical outcomes. They found that several biomarkers related to T cell inflamed TME and systemic inflammation might be predictive of greater survival and response rates in Nivolumab treated patients. Another interesting issue that must be considered before starting ICIs is the possibility of dramatic tumor progression during treatment with PD1-blockaed, a phenomenon called hyperprogressive disease (HPD). As stated in a very recent study HPD can occur in a fraction of patients with advanced HCC treated with PD1-inhibithors. HPD development was associated with a rapid clinical deterioration that precluded the initiation of another treatment. Furthermore, patients with HPD exhibited an extremely poor prognosis (median OS of 59 days). Thus, the identification of potential predictive factors of HPD is critical before starting treatment with PD-1 blockade [44].

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