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MINIREVIEWS

Present and future of new systemic therapies for early and intermediate stages of hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is a high mortality neoplasm which usually appears on a cirrhotic liver. The therapeutic arsenal and subsequent prognostic outlook are intrinsically linked to the HCC stage at diagnosis. Notwithstanding the current deployment of treatments with curative intent (liver resection/local ablation and liver transplantation) in early and intermediate stages, a high rate of HCC recurrence persists, underscoring a pivotal clinical challenge. Emergent systemic therapies (ST), particularly immunotherapy, have demonstrate promising outcomes in terms of increase overall survival, but they are currently bound to the advanced stage of HCC. This review provides a comprehensive analysis of the literature, encompassing studies up to March 10, 2024, evaluating the impact of novel ST in the early and intermediate HCC stages, specially focusing on the findings of neoadjuvant and adjuvant regimens, aimed at increasing significantly overall survival and recurrence-free survival after a treatment with curative intent. We also investigate the potential role of ST in enhancing the downstaging rate for the intermediate-stage HCC initially deemed ineligible for treatment with curative intent. Finally, we critically discuss about the current relevance of the results of these studies and the encouraging future implications of ST in the treatment schedules of early and intermediate HCC stages.

Key Words: Hepatocellular carcinoma; Early stage; Intermediate stage; Neoadjuvant; Adjuvant; Systemic therapy

Core Tip: This review provides an updated analysis (up to March 2024) of the current data about the new systemic therapies for the hepatocellular carcinoma (HCC) in the early and intermediate stages; specially focusing on the findings of neoadjuvant and adjuvant systemic therapies after a treatment with curative intent, for prevention of HCC recurrence. Finally, we discuss about the potential benefits of these new systemic therapies for early and intermediate stages of HCC and their future impact in the HCC treatment schedules.

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INTRODUCTION

Hepatocellular carcinoma as a health problem of the first order

Cancer is the current leading cause of death, with 10 million deaths per year[1]. Among neoplasms, primary liver cancer ranks seventh in incidence (9.5 per 100000 inhabitants) and fourth in mortality (8.7 per 10000 inhabitants) worldwide. It accounts for 8.3% of all cancer deaths and is the most prevalent neoplasm in some places, such as Egypt or Southeast Asia [1-3].

The most common primary liver cancer, far exceeding other types (75%–85% of the total), is hepatocellular carcinoma (HCC)[2]. Its incidence and mortality rates are 2–3 times higher in men than in women and it usually appears in the sixth or seventh decades of life[4]. In addition, HCC usually occurs after liver cirrhosis, which increases its morbidity and mortality[5].

There are identified risk factors for the development of HCC such as the hepatitis B and C viruses, chronic alcohol consumption, and metabolic syndrome, all of which can be controlled as preventive measures[6-8]. Nevertheless, the incidence of HCC has increased or stabilized at its highest level in western countries (Europe, North America and Australia), due to the progressive increase in metabolic liver disease[8,9]. In the latter disease, HCC has a different molecular pathway of pathogenesis to the other aetiologies, thus hindering the early diagnosis and treatment of HCC[10-13], which can occur in patients without liver cirrhosis[14].

Treatment of HCC

Use of the Barcelona Clinic Liver Cancer (BCLC) algorithm, which distinguishes between five stages (very early, early, intermediate, advanced and terminal) depending on the tumor burden, liver function and physical status of the patient, is deeply rooted in western countries. Its latest version was published in 2022[15]. The patient's expected survival is conditioned by the treatment received and is significantly greater among patients with potentially resectable HCC who are candidates for treatment with curative intent (TCI)[16,17]. The latter consists of two options: Liver resection (LR) with local ablation as an alternative, and liver transplantation (LT). LT indications have traditionally been based on the Milan criteria, which have expanded over the years[18].

HCC patients can be classified into three groups under the BCLC system and according to their treatment (excluding the terminal stage). The first group involves TCI candidates. These are patients in early stages and select intermediate-stage cases, and have the highest expected survival (> 5 years)[15]. Despite this, their expected survival is limited by a high rate of post-surgical recurrence of up to 70% at the 5-year mark, due to microscopic vascular invasion and/or satellitosis[19-21].

The second group involves intermediate-stage patients who are not initially candidates for TCI but who may benefit from downstaging, i.e. reducing their stage by locoregional treatment to eventually receive an LT. There are several treatments used for downstaging[22-27] and the radiological response is usually assessed using mRECIST criteria[28].

The last group involves patients who are not candidates for these treatments, and has the aim of increasing their expected survival through systemic therapy (ST). These are patients in the advanced stage, as well as patients in the intermediate stage who cannot be treated with locoregional treatment such as downstaging, who fail locoregional treatment, or who present diffuse, infiltrative or extensive bilobar tumor involvement. This group presents an expected survival that is much lower than the previous ones (> 2 years)[15], but significantly higher than the one described in the previous versions of the BCLC staging system[29].

The benefits of ST in advanced HCC

ST scenario has undergone a revolution in the last six years with the emergence of new drugs, as we briefly summarize in the following. In addition, the main studied combination of ST molecules and the approved first-line drugs median overall survival (OS) achieved in clinical trials (CT) are shown in Figures 1 and 2, respectively.

Sorafenib was the first one to achieve in a CT an OS greater than the placebo[30,31]. Subsequently, lenvatinib was the first to show non-inferiority to sorafenib in terms of OS as first-line treatment[32]; although other many drugs did not achieve this advantage[33-37]. The immunotherapy, drugs with immune checkpoint inhibition capabilities that are programmed for tumor cell removal by immune system stimulation[38-40], did not show a clear benefit of OS in monotherapy CTs[41-43]. However, the combination of the immunotherapy with the drugs of the previous groups

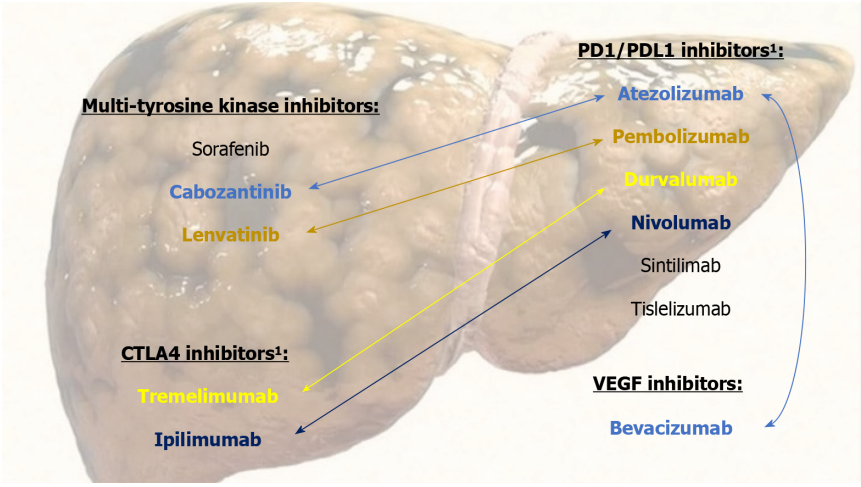

Figure 1 Drugs available for systemic therapy classified according to their mechanism of action, indicating by arrows and colors the main drug combinations studied. [1]Immunotherapy. PD1: Programmed cell death protein 1; PDL1: Programmed death-ligand 1; CTLA4: Cytotoxic T-lymphocyte associated protein 4; VEGF: Vascular endothelial growth factor.

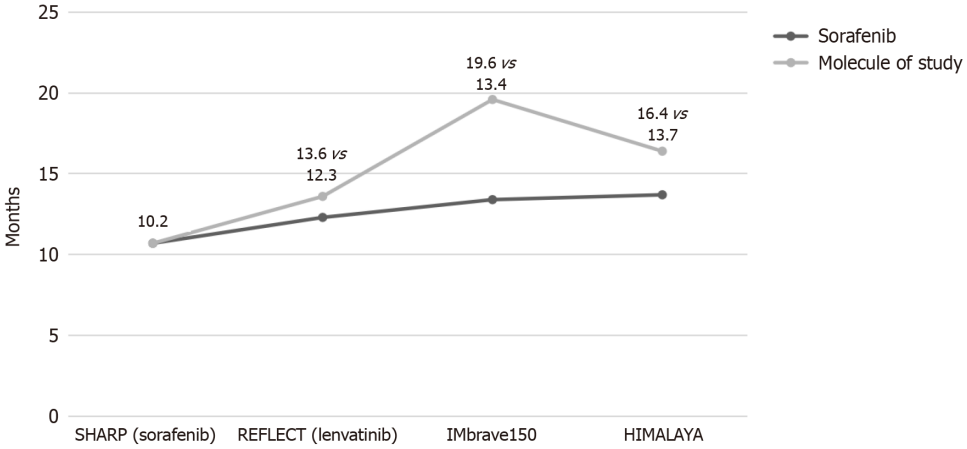

Figure 2 Median overall survival shown in clinical trials by drugs approved as first-line systemic therapy, compared with sorafenib. IMbrave150 analyzed atezolizumab + bevalizumab. HIMALAYA investigated durvalumab + tremelimumab.

presents a synergistic effect with clinical benefits[44].

In this respect, two combination therapies stand out that have shown a significant increase in OS. The phase III CT IMbrave150[45] compared atezolizumab + bevacizumab versus sorafenib in patients with advanced HCC, and showed a significantly higher OS in the first group. This combination was subsequently evaluated in real life in a cohort of Child-Pugh A-B cirrhosis[46], verifying the efficacy and tolerance profile shown in the CT. The phase III CT HIMALAYA[47] evaluated the double immunotherapy durvalumab + tremelimumab versus sorafenib showing a higher OS in the first group. In this same CT, durvalumab as monotherapy had OS similar to that of sorafenib.

In addition, ipilimumab + nivolumab achieved survival of 24 months among 40% of its subjects[48]. Lenvatinib + pembrolizumab showed no difference in OS compared with lenvatinib in advanced HCC[49]. Finally, a triple drug combination with nivolumab + cabozantinib ± ipilimumab yielded a similar OS in the 2- and 3-drug arms[50].

A potential new scenario for ST

The encouraging previous results of the new ST drugs have recently modified the treatment algorithm for advanced-stage HCC providing lengthy OS. Currently, atezolizumab + bevacizumab and durvalumab + tremelimumab are primarily indicated; as well as other first-, second- and third-line options available[15,17,51-54]. It should be noted that up to 50% of patients with HCC eventually receive ST[39].

Despite the potential benefits of these new drugs, ST is still bounded for advanced-stage HCC with the aim of increasing OS. Although the early and some intermediate stage HCC can be initially candidates for TCI, the OS in these group is clearly limited due to a high rate of post-surgical recurrence[19-21]. Furthermore, in the intermediate stage there is a subgroup of initially unresectable HCC that are not initially deemed eligible or failed to downstaging with locoregional treatment and cannot benefit from a TCI[15]. Thus, the therapeutic management of these stages is still a challenge, and new effective therapies are needed.

For all these reasons, the promising results of the new ST in HCC advanced-stage make it inevitable to consider its possible impact on potentially resectable HCC (early and intermediate stages as per BCLC), with the aims of increasing OS and recurrence-free survival (RFS) after TCI and the downstaging rate for LT or LR in initially unresectable tumors, both in neoadjuvant and adjuvant therapy[55]. For this purpose, it is highly relevant to analyze the recent studies, mainly CTs, that are being developed to evaluate the potential benefits of ST in this field.

THE NEW PRESENT STATUS OF SYSTEMIC THERAPY IN THE EARLY AND INTERMEDIATE STAGES OF HEPATOCELLULAR CARCINOMA

Below, following a literature search updated to March 10th, 2024, focusing on our keywords, we show the main results from a selection of studies that we consider representative of these clinical scenarios.

CTs with the new ST drugs have used the term "major pathological response" (MPR) to define significant tumor necrosis following treatment, and although its definition varies among studies, it is usually > 70%.

Neoadjuvant therapy to treatment with curative intent

Cabozantinib + nivolumab: Phase Ib CT for locally advanced/borderline HCC[56].

Fifteen patients with locally advanced HCC, who were initially ineligible for curative LR, were included and received cabozantinib + nivolumab neoadjuvant therapy. Eighty percent subsequently underwent LR, all with free resection margins. In addition, the surgical portion in five of these patients showed an MPR of > 90%. Grade 3 adverse events occurred in 13%.

Anti-programmed cell death protein 1 antibody (nivolumab, camrelizumab, pembrolizumab or sintilimab) + tyrosine kinase inhibitor (lenvatinib or apatinib): Series of cases in unresectable or advanced HCC[57].

A total of 63 with initially unresectable HCC received neoadjuvant combination therapy with these drugs. Of these, only 15.9% (10/63) were finally able to undergo LR, but the surgical portion showed partial MPR in 60% of these patients and complete MPR in the other 40%.

Anti-programmed cell death protein 1 antibody (pembrolizumab, toripalimab or sintilimab) + tyrosine kinase inhibitor (lenvatinib or apatinib): Pilot study in unresectable intermediate-stage HCC[58].

In this study with 10 Child-Pugh A patients with initially unresectable HCC, it was found that 80% were made eligible for LR following neoadjuvant therapy. Partial MPR was observed in 70% and complete MPR in 30% following treatment. Finally, the post-surgical RFS rate at the 12-month follow-up mark was 75%.

Nivolumab + ipilimumab: Phase Ib CT in resectable HCC[59].

After adjuvant therapy and subsequent LR, liver tissue was available for histological analysis in nine patients. Partial MPR (> 70%) was observed in 78% of patients and complete MPR in 22%. The six-month post-operative follow-up showed an RFS of 92%.

Dovitinib: Phase II CT in early- and intermediate-stage HCC[60].

A total of 24 patients received neoadjuvant therapy with dovitinib, followed by locoregional therapy. Following neoadjuvant therapy, the rate of partial or complete radiological response (as per mRECIST criteria) was 70% (7/10) in the early stage and 22% (2/9) in the intermediate stage; while the remaining patients showed radiological stability. In addition, seven patients were able to receive LT after neoadjuvant therapy.

Sorafenib: Phase II CT in resectable HCC[61].

Nineteen patients were included, with a 32% radiological response as per mRECIST and no cases of radiological progression being observed. After LR, disease-free surgical margins were observed in 88% of patients and an MPR ≥ 50% in 24%.

Adjuvant therapy after local resection/ablation

Atezolizumab + bevacizumab following TCI: Phase III CT in HCC with high risk of recurrence (IMbrave050)[62].

Multicenter study with 668 Child-Pugh A adult patients with HCC with a high risk of recurrence who underwent TCI *via* LR or local ablation. They were subsequently randomized to 12-month adjuvant therapy with atezolizumab + bevacizumab (n = 334) *vs* active follow-up (n = 334). At 12 months of follow-up, the RFS was higher in the adjuvant therapy group (78% *vs* 65%, hazard ratio 0.71, P value = 0.012). However, the mortality rate was also slightly higher in the adjuvant group (27 *vs* 20 patients). In addition, grade 3–4 adverse effects were more frequent in the adjuvant group (41% *vs* 13%), requiring the drug to be discontinued in 9% (29/334). This is the first phase III CT to show positive results for RFS with adjuvant therapy following TCI.

Sorafenib following TCI: Phase III CT[63].

More than 1000 patients were included, undergoing LR or ablation, followed by adjuvant therapy with sorafenib *vs* placebo. The RFS was similar in both groups (33.3 *vs* 33.7 months).

Neoadjuvant and adjuvant therapy associated to treatment with curative intent

Nivolumab + ipilimumab: Phase II CT in resectable HCC[64].

Twenty-seven patients with resectable HCC were included, who were then randomized to two arms with neoadjuvant and adjuvant therapy with nivolumab (13 patients) *vs* nivolumab + ipilimumab (14 patients). Seventy-four percent finally received an LR (20/27) and grade 3–4 adverse effects were observed in both arms (43% *vs* 23%), not presenting delays to surgery.

An MPR > 70% was achieved in 6 patients (3 in each arm) with no tumor recurrence observed in these patients at 24 months of follow-up. Conversely, half of those with tumor necrosis < 70% did present a recurrence. The median RFS was 9.4 months in the nivolumab group versus 19.5 months in the nivolumab + ipilimumab group. It is noteworthy that four out of the seven patients who did not receive LR presented radiological progression; although we must take into account that this CT included 8 patients with HCC diameters > 10 cm.

Camrelizumab + apatinib: Phase II CT in resectable HCC[65].

Eighteen patients received neoadjuvant therapy, 17 of whom underwent LR and a final 13 completed adjuvant therapy. Six patients presented complete radiological response after neoadjuvant therapy, as per mRECIST criteria. After LR, an MPR > 90% was achieved in four patients. Grade ≥ 3 adverse events occurred in three patients. The recurrence rate was greater in the group that did not achieve these tumor necrosis rates.

Cemiplimab: Phase II CT in resectable HCC[66].

Twenty patients undergoing LR were included. An MPR > 70% was achieved in 20% and an MPR > 50% was achieved in 15%. Grade 3 adverse effects occurred in 33% of patients, with no grade 4–5 cases. This study found that immune infiltration in pre-treatment tumor specimens was greater in patients who achieved high rates of necrosis.

Neoadjuvant therapy for downstaging to LT

Dovitinib: Phase IIb/III CT in HCC outside of Milan criteria[67].

This trial included 74 patients with HCC exceeding Milan criteria, no macrovascular invasion or extrahepatic involvement, Child-Pugh ≤ B7, and < 50% of patients with an estimated post-transplant OS < 5 years. Patients underwent neoadjuvant therapy with dovitinib and subsequent downstaging with the treatment deemed appropriate by a multidisciplinary team.

After dovitinib, the response rate as per mRECIST was 48%, including 13% with complete radiological remission. Despite reduction/discontinuation of the dovinitib dose in 83% of patients due to grade 3–4 adverse events, all patients were able to receive the planned locoregional treatment. OS was greater in the transplant group (34.8 *vs* 16.8 months).

Combination of ST with locoregional therapy

Several studies have analyzed the combination of ST and locoregional treatments, with promising results. We highlight the phase III CT EMERALD-1[68] with unresectable HCC eligible for transarterial chemoembolization (TACE). Six hundred sixteen patients with early or intermediate HCC stages and no evidence of extrahepatic disease were randomized to durvalumab + bevacizumab + TACE, durvalumab + TACE or TACE alone. RFS was significantly improved for durvalumab + bevacizumab + TACE *vs* TACE alone (15.0 *vs* 8.2 months, *P* value = 0.032).

Worthy of mention is a CT comparing TACE *vs* TACE + sorafenib in unresectable HCC, which achieved a significantly higher RFS in the second group (13.5 *vs* 25.2 months)[69]. Another CT studied radioembolization with nivolumab adjuvant therapy in patients with unresectable HCC, presenting an encouraging response rate[70].

Ongoing studies

There is currently significant research activity in this field. Table 1 shows the main results of ongoing CTs, which can be found on clinicaltrials.gov and cilinicaltrialsregister.eu.

THE FUTURE OF SYSTEMIC THERAPY IN THE EARLY AND INTERMEDIATE STAGES OF HEPATOCELLULAR CARCINOMA

The morbidity and mortality associated with HCC are significant in all BCLC stages, despite the wide range of treatments available. Therefore, the results we have observed with ST at early- and intermediate-stage CTs, with the intention of decreasing post-surgical recurrence in resectable patients as well as increasing the downstaging rate in initially unresectable patients, are encouraging with the aim of increasing OS and RFS.

There is no doubt that the indications for ST are expanding, mainly due to its ability to induce tumor necrosis. In this respect, the American Association of the Study of the Liver guidelines[71], published following the results of IMbrave050, already recommends ST in patients at high risk of recurrence after LR or local ablation. In addition, the use of these drugs in neoadjuvant surgery allows for the possibility of identifying immunity tumor markers that are predictive of treatment response[72]. Some of these, such as immune infiltration, have already been suggested[66,73,74].

Even though the results available are promising, we believe they should be interpreted with caution. As we have seen, these mainly stem from phase I-II CTs with few patients, short follow-up periods and heterogeneous HCC samples. In addition, each CT analyzes a different drug or combination of drugs, and the methodology and objectives among them often vary. Finally, while the results are striking in terms of achieving MPR, their impact on OS and RFS in the long term has not been clearly defined.

Table 1 Summary of key characteristics of ongoing clinical trials for early- and intermediate-stage systemic therapy for hepatocellular carcinoma

Trial number (phase)	Treatment	Clinical condition	Patients included
NCT03510871 (II)	Nivolumab + ipilimumab	Surgical NeAd	Potentially resectable HCC with high-risk recurrence
NCT048 50040 (II)	Camrelizumab + apatinib + oxaliplatine	Surgical NeAd	Potentially resectable HCC with high-risk recurrence
NCT03578874 (II)	Sorafenib + capecitabine + oxaliplatine	Surgical NeAd	Unilobar no potentially curative HCC
NCT04174781 (II)	Sintilimab + TACE	Surgical NeAd	Unresectable HCC stage A/B BCLC
NCT01507064 (II)	Sorafenib + laser ablation *vs* laser ablation	Surgical NeAd	Unresectable HCC with single > 4 cm nodule
NCT04857684 (I)	Atezolizumab + bevacizumab + radiotherapy	Surgical NeAd	Resectable HCC
NCT04888546 (Ib)	Anlotinib + TQB2450 (PDL1 antibody)	Surgical NeAd	Potentially resectable HCC with high-risk recurrence
NCT04721132 (II)	Atezolizumab + bevacizumab	Surgical NeAd	Resectable HCC
NCT03847428 (III)	Durvalumab + bevacizumab	Surgical Ad	Potentially curative HCC (resection/ablation)
NCT03383458 (III)	Nivolumab	Surgical Ad	Potentially curative HCC (resection/ablation)
NCT03867084 (III)	Pembrolizumab	Surgical Ad	Potentially curative HCC (resection/ablation)
NCT04639180 (III)	Camrelizumab + apatinib	Surgical Ad	Potentially curative HCC (resection/ablation)
NCT05367687 (II)	Camrelizumab + apatinib *vs* camrelizumab	Surgical Ad	Potentially curative HCC (resection/ablation)
NCT05545124 (II)	Donafenib + tislelizumab	Surgical Ad	Potentially curative resection HCC
NCT05407519 (II)	Tislelizumab + sitravatinib	Surgical Ad	Potentially curative resection HCC
NCT04418401 (I)	Donafenib + anti-PD-1 antibody	Surgical Ad	Potentially curative resection HCC
NCT0544086 (II)	Tremelimumab NeAd + durvalumab Ad	Surgical NeAdAd	Resectable HCC
NCT03630640 (II)	Nivolumab NeAd + nivolumab Ad	Surgical NeAdAd	Resectable HCC
NCT04727307 (II)	Atezolizumab NeAdAd + bevacizumab Ad	Surgical NeAdAd	Ablation of HCC
NCT04930315 (II)	Camrelizumab NeAdAd + apatinib Ad	Surgical NeAdAd	Resectable HCC
NCT04834986 (II)	Tislelizumab NeAd + lenvatinib NeAdAd	Surgical NeAdAd	Resectable HCC
NCT04658147 (I)	Nivolumab NeAdAd *vs* nivolumab NeAdAd + relatlimab NeAdAd	Surgical NeAdAd	Resectable HCC
NCT05185739 (II)	Pembrolizumab NeAdAd + lenvatinib Ad	Surgical NeAdAd	Resectable HCC
NCT03867370 (Ib/II)	Toripalimab NeAdAd + lenvatinib NeAdAd	Surgical NeAdAd	Resectable HCC
NCT04615143 (II)	Tislelizumab NeAdAd + lenvatinib NeAdAd	Surgical NeAdAd	Resectable HCC
NCT04954339 (II)	Atezolizumab NeAdAd + bevacizumab NeAdAd	Surgical NeAdAd	Resectable HCC
NCT04521153 (II)	Camrelizumab NeAd + TACE + camrelizumab Ad + apatinib Ad	Surgical NeAdAd	Resectable HCC
NCT04425226 (UK)	Pembrolizumab + lenvatinib	NeAd LTD	Unresectable HCC
NCT04035876 (UK)	Camrelizumab + apatinib	NeAd LTD	Unresectable HCC

NeAd: Neoadjuvant; HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolization; Ad: Adjuvant; NeAdAd: Neoadjuvant plus adjuvant; UK: Unknown; LTD: Liver transplantation downstaging; PDL1: Programmed death-ligand 1; PD1: Programmed cell death protein 1.

The most representative study to date, the IMbrave050, can be used as example to illustrate these limitations. Despite showing superiority in RFS following TCI in the adjuvant group, the follow-up period was relatively short, so the duration of this beneficial effect is unknown. In addition, mortality during follow-up was low and similar in both groups, reason for which it will be a long time before we know their true impact on OS. Finally, a considerable percentage of grade ≥ 3 adverse effects was obtained in the adjuvant arm, which could be considered inadmissible depending on the OS and RFS that are ultimately reported.

Therefore, we need to know the OS and RFS results after long follow-up periods in current and future studies to be able to assess the actual potential of ST in the early and intermediate stages of HCC and, on this basis, be able to determine its indications and position among the treatment schedules. Important issues, such as the ideal moment for their use in patients with resectable tumors (before or after surgery), remain unresolved[55]. However, it is expected that in the next 5-years period several phase III CTs will be completed, and their results could shed a necessary light on those questions[75].

In our view, the future of HCC treatment will be based on personalized therapy as a function of patient and tumor characteristics. This therapy will allow a significant increase in OS and RFS, as well as a good treatment tolerance profile. However, to achieve personalized therapy, it will be necessary to define accurate and easy-to-use biomarkers, both of the host, as well as tumor-based or predictive of ST response. Research in this respect is currently flourishing[72,76-80].

Considering the findings described in this review, we posit that neoadjuvant and/or adjuvant ST with these novel drugs will play an important role in the personalized therapy for the early and intermediate stages of HCC.

CONCLUSION

Concerning the application of ST in the early and intermediate stages of HCC, the outcomes delineated in this review signal a promising enhancement in the prognosis for these patients in the near future. Nevertheless, deeper research in this field has to be done, before we are able to integrate this approach into clinical practice.

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FOOTNOTES

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