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Comparison and analysis of the efficacy of drug therapy for liver cancer

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Abstract

Hepatocellular carcinoma (HCC) is a poor prognosis tumor when not accessible to potentially curative treatments such as surgical resection, thermal ablations or liver transplantation. Systemic cytotoxic chemotherapies have shown inconsistent clinical benefit. In 2007, sorafenib, a tyrosine kinase inhibitor (TKI), was the first systemic therapy able to significantly improve the outcome of HCC patients non-eligible for curative or loco-regional therapies, despite a modest tolerance and low tumor objective response rate (ORR). Among the newer TKIs approved after 2017, lenvatinib was the first to show a striking ORR and demonstrate non-inferiority vs. sorafenib in the first-line setting. Furthermore, phase 3 trials showed the benefit of other TKIs, regorafenib and cabozantinib, and the anti-angiogenic ramucirumab monoclonal antibody, in systemic second-line therapy. Immune checkpoint inhibitors targeting PD1, achieved striking tumor shrinkage in some patients in monotherapy, seeming to be associated with exciting outcomes. Unfortunately, this occurred in too few patients to improve the median overall survival. More recently, the combination of anti-angiogenic drugs targeting the liver microenvironment with PD-1/PD-L1 inhibitors, such as the combination of bevacizumab and atezolizumab, proved to be substantially effective in phase 3, and other combinations of PD-1/PD-L1 and CTLA-4 inhibitors or TKIs have raised a lot of hopes for the systemic treatment of HCC.

Keywords: Hepatocellular carcinoma, therapy, immune checkpoint inhibitors, tyrosine kinase inhibitors



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INTRODUCTION

Hepatocellular carcinoma (HCC) is a poor prognosis tumor ranking fourth as the leading cause of cancer death worldwide, with about 841,000 new cases and 782,000 deaths annually inventoried in 2018^[1]. Due to the frequently silent clinical character and the low sensitivity of currently available diagnostic biomarkers, HCC is commonly diagnosed at an advanced stage when curative treatments, i.e., surgical resection, ablations, and liver transplantation, or radiologic palliative loco-regional therapies are not feasible. Thus, these patients are eligible for systemic strategies^[2]. Until 2007, treatment options for advanced HCC were lacking. No systemic cytotoxic chemotherapies, including new compounds loaded onto nanoparticles^[3], have ever shown to significantly improve overall survival (OS) of HCC patients. Similarly, hormone therapy and somatostatin analogs have failed to definitely benefit OS^[2]. The approval in 2007 of the first oral tyrosine kinase inhibitor (TKI) and antiangiogenic agent (AAA), sorafenib, and the more recent development of other TKIs and immune checkpoint inhibitors (ICIs) as well, have completely revolutionized the therapeutic paradigm for HCC. The perspectives for advanced HCC patients have changed from palliative short-term mortality towards long-term survival expectations. Several drugs are now available, and in this review, we will compare their efficacy with respect to OS and other surrogate endpoints as well, keeping in mind that they are still controversial and their pertinence must be carefully discussed. We will only focus on data emerging from positive phase 3 trials, and from those phase 1b/2 studies that led to an early US-FDA approval.

EFFICACY OF DRUGS: ENDPOINTS OF CLINICAL TRIALS

Clinical trials in HCC have been originally designed according to conventional biostatistical rules applied in oncology trials^[4], following the traditional linear model of cancer drug development in which drug activity assessment occurs in randomized confirmatory phase 2 and 3 clinical trials with OS as the most important endpoint for demonstrating clinical benefit. Nevertheless, OS has some disadvantages such as the requirement for long follow-up time, the need for a high number of patients and the possibility to be affected by sequential therapies administered after tumor progression. The need to achieve a more rapid development of new targeted antitumor agents led to the adoption of innovative clinical trial designs and the identification of surrogate endpoints of survival such as progression-free survival (PFS), time to progression (TTP) and objective response rate (ORR).

Objective response rate

ORR directly reflects the treatment antitumor activity and is usually defined as the sum of complete (CR) and partial response (PR) rates. In HCC, ORR is measured according to Recist (Response Evaluation Criteria In Solid Tumors) version and/or liver modified-Recist (mRecist) criteria^[5]. ORR has been considered to be the primary endpoint for phase 2 studies dealing with local ablations or loco-regional therapies studies in HCC where this endpoint is consistently associated with OS^[6]. Whereas with the introduction of molecularly targeted treatments with TKIs, reliance on ORR needs to be reconsidered because clinically significant survival advantages are reported despite faint ORRs. Of course, long-lasting stable disease with the absence of progression is a beneficial characteristic, as death due to progression would not occur. In contrast, ORR has shown to be a potentially promising endpoint to obtain clinical benefit from some systemic drugs and in particular ICIs in HCC^[7,8].

Although Recist 1.1 and mRecist criteria can both be used to assess ORR in HCC, Recist 1.1 remains the gold-standard in phase 3 trials with systemic therapies. Of course, it is quite simple to apply Recist 1.1 after liver resection or transplantation. In contrast, local thermoablations or loco-regional intra-arterial therapies induce tumor necrosis, and thus, Recist 1.1 is not appropriate any more since it is unable to capture such an effect since relying on size reduction and ignoring necrosis. That is the reason why the EASL introduced criteria including the use of absence of contrast uptake in dynamic imaging to register response^[9],

Table 1. Objective response rate per Recist 1.1 and/or mRecist

	Led to committee approval	Systemic line	ORR (%) (95%CI)	Median duration of response in months (95%CI)	DCR (%)	First author (TRIAL)
Sorafenib (vs. placebo)	US-FDA, EMA	1L	IRF Recist 1.1 2%	ND	IRF Recist 1.1 71%	Llovet <i>et al.</i> ^[10] (Ph 3, SHARP)
Lenvatinib (vs. sorafenib)	US-FDA, EMA	1L	IRF Recist 1.1 18.8% (15.3-22.3) vs. 6.5% (4.3-8.7) IRF mRecist 40.6% (36.2-44) vs. 12.4% (9.4-15.4)	ND	IRF Recist 1.1 72.8% (68.8-76.8) vs. 59.0% (54.6-63.5) IRF mRecist 73.8% (69.9-77.8) vs. 58.4% (54.0-62.8)	Kudo <i>et al.</i> ^[11] (Ph 3, REFLECT)
Regorafenib (vs. placebo)	US-FDA, EMA	2L	Per investigator Recist 1.1 7%	Per investigator mRecist 3.5 (1.9-4.5)	Per investigator Recist 1.1 66%	Bruix <i>et al.</i> ^[12] (Ph 3, RESORCE)
Cabozantinib (vs. placebo)	US-FDA, EMA	2L or 3L	Per investigator Recist 1.1 4%	ND	Per investigator Recist 1.1 64%	Abou-Alfa <i>et al.</i> ^[13] (Ph 3, CELESTIAL)
Ramucirumab (vs. placebo)	US-FDA, EMA	2L	Per investigator Recist 1.1 5%	Per investigator Recist 1.1 at 6 months 59.9%	ND	Zhu <i>et al.</i> ^[14] (Ph 3, REACH-2)
Nivolumab	US-FDA	1L or 2L	Per investigator Recist 1.1 19%	Per investigator Recist 1.1 9.9 months (8.3-NE)	Per investigator Recist 1.1 64%	El-Khoueiry <i>et al.</i> ^[19] (Ph 1/2, CheckMate-040, dose-expansion phase)
Nivolumab (vs. sorafenib)	-	1L	IRF Recist 1.1 15%	IRF Recist 1.1 23.3 (3.1-34.5+) vs. 23.4 (1.9+-28.7+)	IRF Recist 1.1 55% vs. 55%	Yau <i>et al.</i> ^[20] (Ph 3, CheckMate-459)
Pembrolizumab	US-FDA	2L	IRF mRecist 17% (11-26)	IRF mRecist NR (3.1-14.6+)	IRF mRecist 61%	Zhu <i>et al.</i> ^[17] (Ph 2, KEYNOTE-224)
Pembrolizumab (vs. placebo)	-	2L	IRF Recist 1.1 18.3% (14-23.4)	IRF Recist 1.1 13.8 (1.5+-23.6+)	IRF Recist 1.1 62.2%	Finn <i>et al.</i> ^[18] (Ph 3, KEYNOTE-240)
Atezolizumab + bevacizumab (vs. sorafenib)	Ongoing for US-FDA and EMA	1L	IRF Recist 1.1 27% (23-33) IRF mRecist 33% (28-39)	IRF Recist 1.1 NR IRF mRecist NR	IRF Recist 1.1 74% IRF mRecist 72%	Finn <i>et al.</i> ^[16] (Ph 3, IMbrave150)
Nivolumab + ipilimumab	US-FDA	2L	IRF Recist 1.1 32%	IRF Recist 1.1 17.5 (4.6-30.5+)	IRF Recist 1.1 50%	Yau <i>et al.</i> ^[8] (Ph 1/2 CheckMate-040, Arm A)

US-FDA: American Federal Drug Administration; EMA: European Medicines Agency; NR: not reached; NE: not estimable; ND: not determined; ORR: objective response rate; CR: complete response; PR: partial response; SD: stable disease; DCR: disease control rates; CR+PR+SD; IRF: independent review facility; First (1L), second (2L) or third (3L) systemic therapeutic line; Ph: phase

which corresponds to mRecist criteria. If Recist 1.1 can miss the initial antitumor effect on HCC such as devascularization, no study has definitely demonstrated its correlation with OS. Antiangiogenic agents may prompt a variable degree of vascular shutdown - i.e., sorafenib, regorafenib, cabozantinib, ramucirumab - and have marginal impact in terms of response as *per* Recist 1.1^[10-14].

Further, another issue comes from the inter-observer variability in tumor response assessment *per* Recist 1.1 and mRecist for HCC. However, although it remains poorly known and warrants prospective assessment, it is possible that concordance is good between operators with expertise in liver imaging and lower with non-specifically trained operator, independently of the response criteria^[15].

As detailed in Table 1, in ORR assessed by Recist 1.1, atezolizumab/bevacizumab^[16] and nivolumab/ipilimumab^[8] combinations displayed the best ORR (27% and 32%, respectively), followed by lenvatinib/TKI (18.8%)^[11], ICI monotherapy with pembrolizumab (17%-18.3%)^[17,18] and nivolumab (15%-19%)^[19,20], and at a disappointing lower level all the remaining TKIs such as sorafenib (2%-6.5%)^[10,11], regorafenib (7%)^[12] and cabozantinib (4%)^[13], and finally the monoclonal antibody ramucirumab (5%)^[14]. These data suggest that these latter drugs have mostly a tumor-static rather than tumoricidal activity by comparison to the

former. In those, comprising atezolizumab/bevacizumab^[16] and nivolumab/ipilimumab^[8] combinations, durations of response were long-lasting (median not reached and 17.5 months, respectively) as well as with ICI monotherapies (median 23.3 months with nivolumab^[20], 13.8 months with pembrolizumab^[18]), and unfortunately not determined with lenvatinib^[11].

ORR might be a surrogate endpoint of drug efficacy in some cases. In phase 1/2 trials with ICIs, ORR by Recist 1.1 seemed to deeply correlate with OS of patients treated either with nivolumab monotherapy^[7] or with the nivolumab/ipilimumab combination^[8]. In both cases, tumor responders (CR + PR) had the best OS [median non-reached (NE-NE) for both cases]. Patients in progression disease (PD) did not seem to have any benefit on OS by comparison to well known patients randomized in the placebo arms in controlled trials [8.9 months (7.3-13.4) and 8.3 months (6.6-10.8), respectively]. Intermediately, stable diseases (SD) had better but not striking data [16.7 (13.8-20.2) and 14.5 (8.4-29.6), respectively]. However, it has not been assessed so far in the atezolizumab/bevacizumab phase 3 trial^[16] or other kind of ICI plus AAA combination in phase 1/2 studies, whether ORR has the same predictive value on the outcome of HCC patients. Furthermore, no data on the field are available regarding the correlation between ORR by mRecist and OS of HCC patients treated with ICIs.

These observations do not seem so evident with TKIs, which have the disadvantage of resulting in very low levels of ORR except for lenvatinib^[11]. ORR (and TTP) have been suggested as potential surrogate endpoints for OS in advanced HCC with brivanib^[21,22], and seemed to be confirmed with sorafenib and lenvatinib in REFLECT^[11,23]. However, a weak correlation was reported between ORR, TTP/PFS and OS in SHARP with sorafenib^[10], and with regorafenib in RESORCE^[12,24]. In this later study, since ORR was rather low either by Recist 1.1 (2%) or mRecist (10%), a bootstrap approach was applied to simulate 10,000 trials of patients with advanced HCC from RESORCE ($n = 573$), and the mean simulated results were calculated. A Pearson correlation was calculated between estimated median OS and estimated ORR for regorafenib and placebo arms separately. The Pearson correlation of log-rank test statistics was calculated comparing regorafenib and placebo. The Pearson correlation of log-rank test statistics comparing the two arms for OS was used and the Cochran-Mantel-Haenszel test statistic used to compare the two treatment arms for ORR. Finally, a weak correlation between median OS and ORR was found for regorafenib and placebo in RESORCE, indicating that mRecist/Recist 1.1 ORR may not be a reliable surrogate endpoint for OS in patients with advanced HCC. The same observation was found for TTP in this study.

In summary, ORR could be as a good surrogate marker for OS in HCC patients under lenvatinib or ICI therapy, which give high levels of ORR, whereas it is more complex, debatable and doubtful for drugs with low level of ORR such as sorafenib and regorafenib, keeping in mind that this research has not been performed so far for cabozantinib and ramucirumab.

Progression-free survivals and/or time to radiologic progression

In HCC, progression-free survival (PFS) is frequently used in phase 2 trials. PFS is a composite endpoint that includes: (1) radiologic progression as defined by Recist 1.1 or mRecist; and (2) death due to tumor progression or the terminal natural history of the underlying chronic liver disease. In general, regulatory agencies prefer PFS to TTP for drug approval because the former endpoint may be better correlated with OS^[25]. However, in HCC, PFS might not be reliable because death resulting from the natural history of cirrhosis might confound the detection of potential benefits from effective drugs. The risk of bias in detection of potential benefits from effective antitumor drugs due to death related to liver failure despite a relevant antitumor response can be avoided using restrictive inclusion criteria for evaluation of liver function^[25].

Time to radiologic progression (TTP), on the other hand, is a pure radiologic endpoint^[26], and requires repeated radiologic measurements to capture relevant differences between groups that can be missed if the

Table 2. Median PFS and/or TTP following Recist 1.1 and/or mRecist

	PFS in months (95%CI)	TTP in months (95%CI)	Authors (Trial)
Sorafenib <i>vs.</i> placebo	ND	IRF Recist 1.1 5.5 <i>vs.</i> 2.8; HR = 0.58, 95% CI: 0.45-0.74; <i>P</i> < 0.001	Llovet <i>et al.</i> ^[10] (Ph 3, SHARP)
Lenvatinib <i>vs.</i> sorafenib	IRF Recist 1.1 7.3 <i>vs.</i> 3.6 HR = 0.65, 95% CI: 0.56-0.77; <i>P</i> < 0.0001 IRF mRecist 7.3 <i>vs.</i> 3.6 HR = 0.64, 95% CI: 0.55-0.75; <i>P</i> < 0.0001	IRF Recist 1.1 7.4 <i>vs.</i> 3.7 HR = 0.61, 95% CI: 0.51-0.72; <i>P</i> < 0.0001 IRF mRecist 7.4 <i>vs.</i> 3.7 HR = 0.60, 95% CI: 0.51-0.71; <i>P</i> < 0.0001	Kudo <i>et al.</i> ^[11] (Ph 3, REFLECT)
Regorafenib <i>vs.</i> placebo	Per investigator Recist 1.1 3.4 <i>vs.</i> 1.5 HR = 0.43, 95%CI: 0.35-0.52; <i>P</i> < 0.0001 Per investigator mRecist 3.1 <i>vs.</i> 1.5 HR = 0.46, 95% CI: 0.37-0.56; <i>P</i> < 0.0001	Per investigator Recist 1.1 3.9 <i>vs.</i> 1.5 HR = 0.41, 95%CI: 0.34-0.51; <i>P</i> < 0.0001 Per investigator mRecist 3.2 <i>vs.</i> 1.5 HR = 0.44, 95% CI: 0.36-0.55; <i>P</i> < 0.0001	Bruix <i>et al.</i> ^[12] (Ph 3, RESORCE)
Cabozantinib <i>vs.</i> placebo	Per investigator Recist 1.1 5.2 <i>vs.</i> 1.9 HR = 0.44, 95%CI: 0.36-0.52; <i>P</i> < 0.001	ND	Abou-Alfa <i>et al.</i> ^[13] (Ph 3, CELESTIAL)
Ramucirumab <i>vs.</i> placebo	Per investigator Recist 1.1 2.8 <i>vs.</i> 1.5 HR = 0.57, 95%CI: 0.47-0.69; <i>P</i> < 0.0001	ND	Zhu <i>et al.</i> ^[14] (Ph 3, REACH-2)
Nivolumab	Per investigator Recist 1.1 4.0 (2.9-5.4)	ND	El-Khoueiry <i>et al.</i> ^[19] (Ph 1/2, CheckMate-040, dose-expansion phase)
Nivolumab <i>vs.</i> sorafenib	Per investigator Recist 1.1 3.7 <i>vs.</i> 3.8 HR = 0.93, 95%CI: 0.79-1.10	ND	Yau <i>et al.</i> ^[20] (Ph 3, CheckMate-459)
Pembrolizumab	IRF mRecist 4.9 (3.4-7.2)	IRF mRecist 4.9 (3.9-8.0)	Zhu <i>et al.</i> ^[17] (Ph 2, KEYNOTE-224)
Pembrolizumab <i>vs.</i> placebo	IRF Recist 1.1 3.0 <i>vs.</i> 2.8 HR = 0.72, 95%CI: 0.57-0.90; <i>P</i> = 0.0022	IRF Recist 1.1 3.8 <i>vs.</i> 2.8 HR = 0.69, 95%CI: 0.54-0.87; <i>P</i> = 0.0011	Finn <i>et al.</i> ^[18] (Ph 3, KEYNOTE-240)
Atezolizumab + bevacizumab <i>vs.</i> sorafenib	IRF Recist 1.1 6.8 <i>vs.</i> 4.3 HR = 0.59, 95%CI: 0.47-0.76; <i>P</i> < 0.0001	ND	Finn <i>et al.</i> ^[16] (Ph 3, IMbrave150)
Nivolumab + ipilimumab	ND	ND	Yau <i>et al.</i> ^[8] (Ph 1/2 CheckMate-040, Arm A)

PFS: progression-free survival; TTP: time to radiologic progression; IRF: independent review facility; ND: not determined

intervals between measurements are too long. Symmetric assessment should be ensured between treatment arms. TTP can be recommended as the main time-to-event endpoint to capture possible antitumor benefits in phase 2 trials testing systemic therapies in HCC because it is less vulnerable (only progression is captured) than composite endpoints. However, TTP has been measured less commonly than PFS in HCC phase 3 studies.

In the present review, PFS has been assessed in 7 out of 8 phase 3 studies, and TTP in only 4 of them [Table 2]. When both were available, a close correlation existed between PFS and TTP, thus suggesting that the drugs tested in those trials were not toxic enough to engender death independently of tumor radiologic progression. Taking into account PFS only, atezolizumab/bevacizumab combination clearly gave the best PFS (6.8 months)^[16] as well as lenvatinib (7.3 months)^[11], although comparison of PFS between trials should

be done with considerable caution. However, the long duration of tumor response under atezolizumab/bevacizumab combination as discussed above in “ORR” paragraph, was clearly of huge importance to impact on the long median OS (not reached)^[16], whereas the quite similar PFS under lenvatinib was associated with a much lower OS (13.6 months)^[11]. Unfortunately, the duration of response under lenvatinib has not been assessed, although it is likely shorter than under ICIs and similar to those of other TKIs [Table 1], for instance 3.5 months with regorafenib^[12]. This difference in OS cannot be explained by the disease control rate (DCR by Recist 1.1) since very similar in both trials (74% for atezolizumab/bevacizumab^[16] vs. 72.8% for lenvatinib^[11]) [Table 1].

PFS by Recist 1.1 for monotherapies of ICI gave values around 4 months (3.0-4.9)^[17-20], quite similar to those of TKIs such as sorafenib (3.6 months)^[11] and regorafenib (3.4 months)^[12]. PFS seems to be better with cabozantinib (5.2 months)^[13], but worse with ramucirumab (2.8 months)^[14], which supported a poor prognosis subpopulation. When available, TTP was in accordance with PFS. It is important to underline that ICI monotherapy responders have a long duration of response [Table 1], but the number of responders was too low in the trials to have a significant impact on median PFS or median TTP, and finally on median OS. Differences on PFS/TTP/OS cannot be explained by different DCRs [Table 1] since they were quite the same between ICI and TKI schedules: atezolizumab/bevacizumab (74%)^[16], nivolumab/ipilimumab (50%)^[8], nivolumab (55%-64%)^[19,20], pembrolizumab (61%-62.2%)^[17,18], lenvatinib (72.8%)^[11], sorafenib (59-71%)^[10,11], regorafenib (66%)^[12], and cabozantinib (64%)^[13].

Overall survival

Overall survival (OS), defined as the time from randomization to death, is a direct measure of clinical benefit to a patient and the gold standard primary endpoint to evaluate the outcome in oncologic clinical trials. OS is easily measured, unambiguous, objective, not subjected to researcher bias and it is used by the international authorities worldwide for cancer drug approval. OS is the primary endpoint recommended for all phase 3 studies in HCC. When selecting endpoints in HCC clinical trials, it must be also considered that OS is impacted by liver failure due to both the end stage natural history of underlying chronic liver disease and the HCC loco-regional spread, which in turn promotes liver failure and leads to death. Thus, if the treatment aims to reduce HCC-related death (i.e., the endpoint is cancer-related death), but the competing mortality from progressive liver failure is high in both the active treatment and in the control arms, the risk ratio will be reduced and the required sample size increases. Thus, phase 3 studies in HCC require a larger sample size to include competing risk analysis and assess cancer-related deaths as compared to OS evaluation.

In the present review, regarding OS [Table 3] and taking into account potential confounding factors that may influence the median OS, atezolizumab/bevacizumab therapy has not reached median OS so far taking into account that the median follow-up is only 17 months^[16], the nivolumab/ipilimumab combination (22 months)^[8], nivolumab (16.4 months)^[20], pembrolizumab (12.9-13.9 months)^[17,18], lenvatinib (13.6 months)^[11], sorafenib (10.7 months)^[10], regorafenib (10.6 months)^[12] and cabozantinib (10.2 months)^[13], while worse with ramucirumab (8.5 months) due to the poor prognosis assessed subpopulation^[14]. The 1L or 2L design of the trials does not impact much the spontaneous OS of patients since in the placebo arms of randomized controlled trials, median OS is quite the same in 1L or 2L for HCC patients eligible for systemic therapies with ECOG PS status 0-1 and Child-Pugh A liver functions. Indeed, OS of placebo arms seems similar in 1L phase 3 trials (7.9 months in SHARP^[10], 8.5 months in SEARCH^[27]) by comparison to 2L/3L phase 3 trials (7.9 months in RESORCE^[12], 8 months in CELESTIAL^[13], 10.6 months in KEYNOTE-240^[18], 8.2 months in BRISK-PS^[21], 7.3 months in EVOLVE-1^[28], 7.6 months in REACH^[29], and 9.1 months in METIV-HCC^[30]).

The control arm and subsequent therapies administered after trial withdrawal are of prominent importance. Indeed, OS in HCC randomized controlled trials depends on the target population, the parameters assessed

Table 3. Median overall survival

	OS in months (95%CI)	Subsequent systemic therapy after trial withdrawal	Authors (Trial)
Sorafenib vs. placebo	10.7 vs. 7.9 HR = 0.69, 95%CI: 0.55-0.87; <i>P</i> < 0.001	Absence of active drug against HCC	Llovet <i>et al.</i> ^[10] (SHARP)
Lenvatinib vs. sorafenib	13.6 vs. 12.3 HR = 0.92, 95%CI: 0.79-1.06; meeting criteria for non-inferiority	32.6% (sorafenib 25%; investigational therapy) vs. 38.7% (sorafenib 12%; investigational therapy)	Kudo <i>et al.</i> ^[11] (Ph 3, REFLECT)
Regorafenib vs. placebo	10.6 vs. 7.8 HR = 0.63, 95%CI: 0.50-0.79; <i>P</i> < 0.0001	ND	Bruix <i>et al.</i> ^[12] (Ph 3, RESORCE)
Cabozantinib vs. placebo	10.2 vs. 8.0 HR = 0.76, 95%CI: 0.63-0.92; <i>P</i> = 0.005	25% [anti-PD1/PD-L1 5%; TKI (sorafenib, lenvatinib, regorafenib) 6.5%; systemic chemotherapy 12%; investigational agents 6%] vs. 30% [anti-PD1/PD-L1 6%; TKI (sorafenib, lenvatinib, regorafenib) 3%; systemic chemotherapy 17%; investigational agents 7%]	Abou-Alfa <i>et al.</i> ^[13] (Ph 3, CELESTIAL)
Ramucirumab vs. placebo	8.1 vs. 5.0 HR = 0.69, 95%CI: 0.57-0.84; <i>P</i> = 0.0002	26.9% [immunotherapy 6.6%; TKI (regorafenib, sorafenib, cabozantinib, BLU-554, lenvatinib) 13.7%; systemic chemotherapy 11.2%; investigational drug 2.5%; other 0.5%] vs. 28.4% [immunotherapy 6.3%; TKI (regorafenib, sorafenib, cabozantinib, BLU-554, lenvatinib) 6.3%; systemic chemotherapy 15.8%; investigational drug 2.1%; other 1.1%]	Zhu <i>et al.</i> ^[14] (Ph 3, REACH-2)
Nivolumab	NR	ND	El-Khoueiry <i>et al.</i> ^[19] (Ph 1/2, CheckMate-040, dose-expansion phase)
Nivolumab vs. sorafenib	16.4 vs. 14.7 HR = 0.85, 95%CI: 0.72-1.02; <i>P</i> = 0.0752	49% (ICI 2%; TKI 36%; systemic chemotherapy 4%; investigational agent 3%; other 1%) vs. 53% (ICI 20%; TKI 23%; systemic chemotherapy 7%; investigational agent 11%; other 1%)	Yau <i>et al.</i> ^[20] (Ph 3, CheckMate-459)
Pembrolizumab	12.9 (95%CI: 9.7-15.5)	ND	Zhu <i>et al.</i> ^[17] (Ph 2, KEYNOTE-224)
Pembrolizumab vs. placebo	13.9 vs. 10.6 HR = 0.78, 95%CI: 0.61-0.99; <i>P</i> = 0.0238	41.7% [approved anticancer medication 31.7%: ICI 6.8%, others (lenvatinib, regorafenib, ramucirumab) 31.7%] vs. 47.4% [approved anticancer medication 31.9%, ICI 10.4%, others (lenvatinib, regorafenib, ramucirumab) 31.9%]	Finn <i>et al.</i> ^[18] (Ph 3, KEYNOTE-240)
Atezolizumab + bevacizumab vs. sorafenib	NR vs. 13.2 HR = 0.58, 95%CI: 0.42-0.79; <i>P</i> = 0.0006	ND	Finn <i>et al.</i> ^[16] (Ph 3, IMbrave150)
Nivolumab + ipilimumab	22.8 (95%CI: 9.4-NE)	ND	Yau <i>et al.</i> ^[8] (Ph 1/2 CheckMate-040, Arm A)

OS: overall survival; NR: not reached; NE: not evaluable; ND: not determined; TKI: tyrosine kinase inhibitor; ICI: immune checkpoint inhibitor

and reported in the trial, the stratification before randomization in both the active and the control arms. For most HCC trials, the study population is composed of approximately 80% BCLC-C and 20% BCLC-B HCCs, with a good general status (PS ECOG 0-1) and conserved liver functions (Child-Pugh A). A critical element that can substantially affect the interpretation of trial results is whether patients are allowed to receive medications or undergo procedures potentially active against HCC after trial withdrawal.

As far as control arms are considered, the SHARP trial^[10] still represents a paradigm since patients were treated in both arms up to symptomatic progression, and patients could not be treated by other active drugs after radiologic progression since such drugs were not existing [Table 3]. Thus, in SHARP, OS of the control arm (composed of placebo only or subsequent inactive drugs against HCC) was 7.9 months, and sorafenib

increased OS *vs.* placebo with a hazard ratio (HR) of 0.69 (95%CI: 0.55-0.87, $P < 0.0001$)^[10]. REFLECT was a head-to-head comparison of lenvatinib and sorafenib, within a non-inferiority trial^[11], but after trial withdrawal, 33% and 39% of patients received potentially active medications against HCC, likely one of the reasons why the OS of sorafenib improved from SHARP (10.7 months) conducted a couple of years before 2008^[10], towards REFLECT (12.3 months) conducted 10 years later^[11] [Table 3]. In the other 1L systemic therapies with control arm, the same comments can arise from CheckMate-459 comparing nivolumab to sorafenib^[20]. It was an open label trial, and at radiologic progression, patients were withdrawn and received potentially active subsequent medications [Table 3]. That explains, at least in part, the high OS value in the sorafenib arm (14.7 months), that maybe led to conceal the benefit of nivolumab (OS 16.4 months) *vs.* sorafenib (HR 0.85 [95%CI: 0.72-1.02]; $P = 0.0752$)^[20]. The same conclusions can be drawn from the IMBrave150 trial^[16] [Table 3] where OS under sorafenib was surprisingly high at 13.2 months, and the atezolizumab/bevacizumab combination increased OS (not reached) *vs.* sorafenib (13.2 months) with HR of 0.58 (95%CI 0.42-0.79, $P < 0.0006$)^[16], the efficacy of the atezolizumab/bevacizumab combination being high enough to prevent any concealing by the overestimated value of OS in the sorafenib arm.

However, operator experience acquired over time is also likely a relevant factor that has a greater impact on OS in the sorafenib arms

In 2L setting, all control arms were placebo arms, also debatable due to post-withdrawal medications [Table 3]. In spite of the overestimated values of OS in placebo arms in 2L, regorafenib increased OS with HR of 0.63 (95%CI: 0.50-0.79, $P < 0.0001$)^[12], cabozantinib improved OS with HR of 0.76 (95% CI 0.63-0.92, $P < 0.005$)^[13], and ramucirumab improved OS with HR of 0.71 (95%CI: 0.53-0.95, $P = 0.0199$)^[14]. In the KEYNOTE-240 phase 3 study, the trial did not meet the statistical criteria for either of the dual endpoints (OS and PFS) although pembrolizumab improved OS over placebo with HR of 0.78 (95% CI 0.61-0.99, $P = 0.0238$)^[18], but the placebo arm showed abnormally high OS value of 10.6 months, in part due to post-withdrawal trial medication [Table 3].

CONCLUSION

For more than a decade, huge improvements have arisen in the systemic strategy of HCC therapy. The coming 1L will associate atezolizumab and bevacizumab. Of course, a lot a work remains to be done to improve this combination and find some strategies overwhelming primary or secondary resistances. Results are soon expected from other 1L combinations in phase 3: pembrolizumab/lenvatinib (NCT03713593), atezolizumab/cabozantinib (NCT03755791), durvalumab/tremelimumab (NCT03298451), and nivolumab/ipilimumab (NCT 04039607). At the moment, there is also an urgent need for prospective controlled trials to identify the best TKI therapy following progression under any ICI combination schedule. Sorafenib and lenvatinib were the two possible 1L. Will they remain the gold standard after ICI combination schedule failure? If yes, the subsequent TKIs after their own failure would likely remain regorafenib, cabozantinib or ramucirumab, if not used in the prior ICI combination schedules of 1L. Only randomized controlled trials will guide the future ways of research and draw the future therapeutic algorithms to improve more and more the treatment of HCC.

DECLARATIONS

Authors' contributions

Made substantial contribution to conception and design of the review article, and performed data analysis and interpretation: Merle P, Subic M

Availability of data and materials

Not applicable.

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Conflicts of interest

Merle P has to declare AbBoard with Bayer, Ipsen, Exelixis, Eisai, Lilly, Roche, Bristol Myers Squibb, AstraZeneca, and Onxeo. Subic M declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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