






# Assessment and Monitoring of Response to Systemic Treatment in Advanced Hepatocellular Carcinoma: Current Insights

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**Abstract:** Advanced hepatocellular carcinoma (HCC) management has become more complex as novel therapies have been proven effective. After sorafenib, the approval of other multikinase inhibitors (MKIs) and immune checkpoints inhibitors (ICIs) has considerably increased the number of systemic therapies available. Therefore, careful assessment and monitoring of response to systemic treatment are essential to identify surrogate endpoints of overall survival (OS) in clinical trials and reliable tools to gauge treatment benefit in clinical practice. Progression-free survival (PFS) and objective response rate (ORR) are early informative parameters of efficacy that are not influenced by further lines of therapy. However, none of them has shown sufficient surrogacy to be recommended in place of OS in phase 3 trials. With such a wealth of therapeutic options, the prime intent of tumor assessments is no longer limited to identifying progressive disease to spare ineffective treatments to non-responders. Indeed, the early detection of responders could also help tailor treatment sequencing. Tumor assessment relies on the Response Evaluation Criteria for Solid Tumors (RECIST), which are easy to interpret – being based on dimensional principles – but could misread the activity of targeted agents. The HCC-specific modified RECIST (mRECIST), considering both the MKI-induced biological modifications and some of the cirrhosis-induced liver changes, better capture tumor response. Yet, mRECIST could not be considered a standard in advanced HCC. Further prognosticators including progression patterns, baseline and on-treatment liver function deterioration, and baseline alpha-fetoprotein (AFP) levels and AFP response have been extensively evaluated for MKIs. However, limited information is available for patients receiving ICIs and regarding their predictive role. Finally, there is increasing interest in incorporating novel imaging techniques which go beyond sizes and novel serum biomarkers in the advanced HCC framework. Hopefully, multiparametric models grouping dimensional and functional radiological parameters with biochemical markers will most precisely reflect treatment response.

**Keywords:** AFP, HCC, RECIST, mRECIST, surrogate endpoints, systemic therapy

## Introduction

Hepatocellular carcinoma (HCC) represents the third leading cause of cancer-related death worldwide and generally arises within a condition of chronic liver disease and cirrhosis.<sup>1</sup> Specific risk factors encompass hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, alcohol misuse, aflatoxin exposure, and metabolic conditions, including diabetes, obesity, non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH). Most HCC patients are diagnosed with advanced disease, defined according to the Barcelona Clinic Liver Cancer (BCLC) staging system as BCLC C or BCLC B unsuitable for further locoregional treatments.<sup>2</sup> At this stage, systemic therapy represents the sole therapeutic option, and the prognosis remains overall dismal. For more than a decade, sorafenib, a multi-kinase inhibitor (MKI) with antiangiogenic activity, has been the mainstay, being approved in 2008 following the results of two phase 3 randomized trials.<sup>3,4</sup> However, in

recent years, the therapeutic scenario has been enriched with a multitude of novel treatments either in first-line,<sup>5,6</sup> or in further-lines,<sup>7-12</sup> so that the survival threshold for patients suitable for treatment sequences surpasses now two years.<sup>13-15</sup> In the first-line setting, lenvatinib, another MKI with antiangiogenic activity, was proven non-inferior to sorafenib in the phase 3 REFLECT trial,<sup>5</sup> and in 2020, the combination of atezolizumab, an anti-programmed death-ligand 1 (PD-L1) monoclonal antibody (mAb), plus bevacizumab, anti-vascular endothelial growth factor (VEGF) mAb, outperformed sorafenib in the phase 3 IMbrave150 trial, becoming the new first-line standard of care.<sup>6,16</sup> More recently, the combination of a single priming dose of tremelimumab, an anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) mAb, plus durvalumab, an anti-PD-L1 mAb (STRIDE regimen) led to a significant overall survival (OS) advantage over sorafenib in the phase 3 HIMALAYA trial.<sup>17</sup> Of note, single-agent durvalumab was proven non-inferior to sorafenib in the same study.<sup>17</sup> Furthermore, cabozantinib plus atezolizumab significantly improved progression-free survival (PFS), one of the dual primary endpoints of the study, but not OS against sorafenib in the phase 3 COSMIC-312 trial.<sup>18</sup> As further-line options after sorafenib, two other MKIs, regorafenib and cabozantinib, and a VEGF receptor 2 (VEGFR-2) mAb, ramucirumab, received approval following the positive results of their respective phase 3 trials.<sup>7-9</sup> Of note, regorafenib was tested only in a sorafenib-tolerant population,<sup>7</sup> cabozantinib was proven effective even in the third-line setting,<sup>8</sup> and ramucirumab worked only in patients with elevated baseline alpha-fetoprotein (AFP) levels ( $\geq 400$  ng/mL).<sup>9</sup> Nivolumab plus ipilimumab and pembrolizumab are other approved agents after sorafenib in the United States (US), based upon the advantage provided in early-phase studies.<sup>10-12</sup> However, both nivolumab and pembrolizumab failed their subsequent phase 3 trials, with the notable exception of the KEYNOTE-394 trial testing pembrolizumab in Asian patients.<sup>19-21</sup> Nevertheless, they were deemed to yield a substantial clinical benefit over the standard of care.<sup>19,20</sup> Other phase 3 studies with immune checkpoint inhibitors (ICIs) either as single-agent or in combinations are underway in the front-line setting and will hopefully further broaden the treatment landscapes in the following years.<sup>22-24</sup>

All of the approved treatments provided a survival advantage or at least a non-inferiority versus the standard of care since OS remains the gold-standard outcome to be met in phase 3 trials.<sup>25</sup> However, with the increased number of sequential treatments available, OS could be affected by the further lines of treatment offered. Therefore, refining the available tools to assess and monitor treatment response is crucial to validate potential surrogate endpoints that could be used in clinical trials and inform treatment decisions in clinical practice. Moreover, in light of the failure of several phase 3 trials in the advanced setting, there is growing recognition that a deeper understanding of the determinants of HCC outcomes is needed to achieve advantageous results in HCC research and introduce practice-changing treatments in the clinical setting.<sup>19,20,26-29</sup>

In this review, we discuss the well-established, evolving, and emerging radiological and biochemical means that have been adopted to determine treatment response and their challenges in advanced HCC.

## Radiological Criteria to Assess Tumor Response: RECIST, Modified RECIST, and Immune-RECIST

### RECIST

The extent of tumor shrinkage has been assumed as one of the first signs of activity of anticancer agents due to the expectation that a reduction in tumor burden will reasonably provide a survival benefit. In drug development, tumor response is regarded as a valuable endpoint in phase 2 trials to screen the therapeutics that warrant further testing in larger phase 3 trials.<sup>30</sup> Accordingly, time to progression (TTP) and PFS are other relevant endpoints in clinical trials. However, these measures could be helpful as long as they are based on uniform, commonly accepted, and quickly applied criteria.

A first attempt to homogenize tumor assessment and the reporting of response (or progression) was proposed by the World Health Organization (WHO) in 1981, which introduced the notion that the tumor burden should be classified into measurable and non-measurable disease and tumor response quantified as a result of the dimensional modifications from baseline.<sup>31</sup> To adapt to novel technologies, such as computed tomography (CT) and magnetic resonance imaging (MRI), and tackle ambiguous sections of the previous guidelines, further reworking was provided with the appointment of the Response Evaluation Criteria in Solid Tumors (RECIST) in 2000.<sup>32</sup> They promoted the adoption of the unidimensional measurement (longest diameter) of tumor lesions, standardized tumor response according to certain predefined thresholds, and introduced the notion of target and non-target lesions according to their suitability for repeated assessments. Additional refinements were brought by the revised RECIST (version [v] 1.1) in 2009, which amended the number of

target lesions to be assessed, introduced pathological lymph nodes (with a short axis  $\geq 15\text{mm}$ ) in the bulk of target lesions, and clarified that a 5 mm absolute growth would have been required to claim progressive disease (PD) besides the  $\geq 20\%$  increase in the sum of target disease.<sup>33</sup>

### Modified RECIST (mRECIST)

To acknowledge the peculiar mechanism of action of molecular-targeted therapies, which might initially suppress tumor growth by downregulating angiogenesis instead of causing substantial tumor shrinkage, a further formal amendment of RECIST – the modified RECIST (mRECIST) for HCC – was proposed.<sup>34</sup> This novel set of guidelines incorporated treatment-induced tumor necrosis as an early image biomarker of the antitumor activity that can precede the dimensional changes of the lesions. Therefore, the reporting of tumor response or progression was readapted according to the modifications in the viable tumor, which is restricted to the part of the lesions that shows contrast enhancement in the arterial phase, and a cytopathological confirmation of the neoplastic nature of pleural effusion and ascites was required to define PD when the target lesions meet the criteria for complete response (CR), partial response (PR), or stable disease (SD). Furthermore, to avoid a misreporting of intrahepatic progression in cirrhotic patients, the appearance of new lesions – a criterion sufficient to determine PD per conventional RECIST – should comply with the specific diagnostic criteria of HCC, which takes into account both the dimension and the vascular pattern of the nodule. Indeed, either a  $\geq 1\text{cm}$  nodule with a typical vascular pattern on dynamic imaging or a  $\geq 1\text{-cm}$ -interval growth in subsequent scans for nodules with an atypical pattern should be documented to define a liver lesion as a novel HCC nodule.

### Immune-RECIST (iRECIST)

The entry of immunotherapy in the treatment scenario of advanced HCC raised further uncertainties concerning the use of RECIST. In fact, patterns and timing of the response to ICIs can still be observed in conditions that would have met the requirements for the definition of PD. With this regard, immune-RECIST (iRECIST) introduced the request that tumor progression should be confirmed to help distinguish pseudoprogression from real PD.<sup>35</sup> Indeed, the first evidence of PD per RECIST, a condition known as immune unconfirmed PD (iUPD) per iRECIST, would require a subsequent confirmatory scan within 4–8 weeks to rule out (in case the disease appears unchanged or even reduced) or confirm (in case of further increase of the tumor burden) tumor progression. A prospective assessment is recommended to inform treatment decisions, although a retrospective evaluation is not unusual, especially outside of clinical trials.<sup>36–38</sup> The allowance to continue treatment despite initial radiologic PD (iUPD) in clinically stable patients comes from the observation that a transient tumor flare might occur in the first few months after the start of immunotherapy and does not preclude the possibility to achieve tumor response at a later assessment. This apparent initial increase in tumor burden is deemed related to immune infiltrate, edema, and necrosis induced by ICIs. However, despite being reported in up to 15.8% of the patients in trials with ICIs, pseudoprogression in HCC is overall a rare event ( $<10\%$ ).<sup>36–39</sup> The main differences between the RECIST v1.1, mRECIST, and iRECIST are summarized in Table 1.

## Assessment of Drug Activity in Clinical Trials for Hepatocellular Carcinoma: Radiological Endpoints

Even though OS remains an unquestionable and solid endpoint, several surrogate endpoints of survival are gaining recognition in clinical trials.<sup>40</sup> In the context of advanced, unresectable HCC, these endpoints are traditionally based on the radiological definition of tumor progression (or response) according to pre-specified criteria, which can be otherwise summarized in terms of objective response rate (ORR), TTP, and PFS. Despite being subject to interpretation bias, which can be mitigated by central radiology review, and, therefore, less robust than a hard endpoint such as OS, surrogate endpoints are being increasingly used to predict a survival benefit when long-time intervals are needed before a predefined number of survival events occur.<sup>25,41</sup> Additional advantages related to surrogate endpoints in clinical trials include that they can be assessed during the treatment course, which potentially informs further clinical decisions, and will require a relatively shorter follow-up period and smaller sample size for the trial design.

Surrogate endpoints may also serve as a parameter leading to accelerated regulatory approval. Indeed, these are significant tools leading to regulatory approval of cancer drugs in the US. Between 2009 and 2014, 66% of anticancer

**Table 1** Comparison Between RECIST Version 1.1, mRECIST, iRECIST

	RECIST Version 1.1 <sup>33</sup>	mRECIST for HCC <sup>34</sup>	iRECIST <sup>35</sup>
<b>Target Lesion</b>			
	Unidimensional measurement, at least 10 mm in the longest diameter For lymph nodes, at least 15 mm in the short axis	Unidimensional measurement, at least 10 mm in the longest viable tumor <sup>a</sup> diameter For porta hepatis lymph nodes, at least 20 mm in the short axis	As per RECIST version 1.1
<b>Response assessment</b>			
Complete response (CR)	Disappearance of all target lesions	Disappearance of any intratumoral arterial enhancement in all target lesions	Disappearance of all target lesions (iCR)
Partial response <sup>b</sup> (PR)	≥ 30% decrease in the sum of diameters of target lesions	≥ 30% decrease in the sum of diameters of viable target lesions	≥ 30% decrease in the sum of diameters of target lesions (iPR)
Stable disease (SD)	Any cases that do not qualify as either partial response or progressive disease	Any cases that do not qualify as either partial response or progressive disease	Any cases that do not qualify as either partial response or progressive disease (iSD)
Progressive disease <sup>c</sup> (PD)	≥ 20% increase in the sum of the diameters of target lesions, with at least ≥5 mm increase in size, or the appearance of new lesions	≥ 20% increase in the sum of the diameters of viable target lesions, or the appearance of new lesions For new hepatic lesions in cirrhotic liver: <i>Typical lesions<sup>d</sup></i> : at least 1 cm in diameter and two imaging techniques (CT and MRI) for lesions of 1 to 2 cm in diameter <i>Atypical lesions</i> : at least 1-cm-interval growth in subsequent scans	≥ 20% increase in the sum of the diameters of target lesions, with at least ≥5 mm increase in size, or the appearance of new lesions (iUPD)
<b>Confirmation of PD</b>	Not required	Required cytopathological confirmation for pleural effusion or ascites if the disease otherwise qualifies at least as SD	Required, 4–8 weeks later (iCPD) <sup>e</sup>
<b>Clinical status assessment</b>	Not required	Not required	Clinical stability required when treatment beyond progression is considered

**Notes:** <sup>a</sup>Only lesions that show contrast enhancement in the arterial phase are considered viable tumor. <sup>b</sup>For PR, the evaluation is made taking as reference the baseline sum of the diameters of target lesions. <sup>c</sup>For PD, the evaluation is made taking as reference the smallest sum of the diameters of target lesions recorded since treatment started. <sup>d</sup>Typical lesions show the characteristic vascular features of HCC (arterial hypervascularization with washout in the portal venous or the late phase) at dynamic imaging studies. <sup>e</sup>Evidence of new lesions or a further increase in a new lesion from iUPD (sum of measures increase in new lesion target ≥5 mm, any increase for new lesion non-target) would be necessary to define iCPD. Data from <sup>33–35</sup>.

**Abbreviations:** RECIST, Response Evaluation Criteria for Solid Tumors; mRECIST, modified RECIST; iRECIST, immune-RECIST; CR, complete response; iCR, immune complete response; PR, partial response; iPR, immune partial response; SD, stable disease; iSD, immune stable disease; PD, progressive disease; iUPD, immune unconfirmed progressive disease; iCPD, immune confirmed progressive disease.

drugs were approved by the US Food and Drug Administration (FDA) based on surrogate endpoints, principally ORR.<sup>42</sup> Among drugs approved over the last years, 55% were eventually confirmed by regular approval, while the remaining indications were either withdrawn,<sup>43</sup> or the approval process did not proceed further.<sup>44</sup> This was the case for nivolumab in second-line HCC, withdrawn after having been granted accelerated approval by the FDA due to the lack of confirmatory data.<sup>45</sup>

In the HCC field, surrogate endpoints are achieving significance, given the availability of additional lines of therapy after progression, which would contribute to the net survival benefit. Indeed, this might have confounded the survival outcomes in patients who had received further lines of therapy, which accounted for nearly one-third of the patients in the REFLECT trial and up to 50% of the patients in the CheckMate 459 trial.<sup>5,13,19</sup> However, the radiological outcomes have been misaligned with OS across many clinical trials for advanced HCC. As such, despite successfully improving survival, most of the MKIs displayed only low response rates.<sup>3,7,8</sup> On the other hand, both nivolumab and pembrolizumab showed decent ORR albeit failing to improve survival in large phase 3 trials.<sup>19,20</sup> In addition, even when these parameters were aligned with OS, there was relatively little agreement in terms of the magnitude of benefit. Indeed, lenvatinib substantially outperformed sorafenib in ORR and PFS though it was only non-inferior in OS.<sup>5</sup> Similarly, durvalumab plus tremelimumab (STRIDE regimen) yielded quite a short median PFS compared with the other positive phase 3 trials in the front-line setting, albeit significantly improving OS.<sup>5,6,17,18</sup> Furthermore, divergent tumor responses according to the different radiological criteria adopted add further complexity. If mRECIST might better identify responders but do not affect PD as compared with RECIST, iRECIST, reclassifying as tumor response some of the cases identified as PD by RECIST, make the evaluation of ORR as a surrogate endpoint of OS rather complex.<sup>5-7,12,38</sup> Therefore, such discrepancies between the endpoints recapitulating tumor response and survival improvement hamper their value as surrogate endpoints in advanced HCC.<sup>39</sup>

The evaluation of treatment efficacy is strongly related to the assumption that changes in tumor burden would eventually translate into survival outcomes. Regardless of the criteria adopted, tumor growth and metastatic spread clearly indicate poor prognosis since they may eventually lead to death. This concept was particularly true when post-progression therapies which may delay the time to death were not available. However, as a consequence of the improvement of the radiological technologies, the assessment of progressive disease (PD) is currently made well before symptomatic progression, allowing earlier initiation of further-line treatments. As such, survival after progression might be artificially prolonged – albeit partially – as an effect of the earlier radiological diagnosis (lead time bias), hindering the surrogacy of PFS. Moreover, the availability of novel treatments now approved beyond the first line for HCC might further exaggerate the distance between PD on a front-line agent and death contributing to the lack of correlation between PFS and survival.<sup>40</sup> On the other hand, while PRs or CRs suggest a reduction in tumor burden, the activity of a given anticancer agent cannot be ruled out when the disease is stable and the ORR is as low as <10%, as exemplified by the sorafenib experience,<sup>3</sup> and by targeted agents approved after sorafenib.<sup>7-9</sup>

Furthermore, the use of TTP as a surrogate for OS can be regarded as controversial and its use has been discouraged in the field of advanced HCC research.<sup>25</sup> In fact, peculiar to HCC, which generally arises from chronic liver disease, the definition of progression due to the appearance of new hepatic nodules might be complex. Therefore, it has been readapted to consider, for example, macroregenerative nodules within a cirrhotic liver, possibly misinterpreted as false-positive cases.<sup>46</sup> Additionally, some analyses suggested that the pattern of progression on sorafenib or ramucirumab might be more informative to predict the outcomes, with the occurrence of vascular invasion (MVI) and/or extrahepatic lesions (EHS) heralding the worst prognosis.<sup>7,47,48</sup> Therefore, such findings might be even more relevant than the evidence of PD per se in the decision-making process as to the adequate timing to switch to a further line of treatment. Indeed, most research trials foresee treatment interruption in the case of PD, whereas maintaining treatments beyond progression could be an option if the investigator believes that the patient still benefits from that treatment. On the contrary, in clinical practice, the evidence of “marginal progression” might be disregarded as not indicative of treatment failure.<sup>49</sup> This may be particularly useful with ICIs that might induce distinctive patterns and timing of response, the most peculiar of which is pseudoprogression.<sup>38</sup> Although overall infrequent, this condition recognizes the possibility that an enlargement of tumor lesions could be owed to immune cell infiltration rather than true tumor progression, and, thus, it might not necessarily be confirmed at a later time point.<sup>35</sup>



Regarding PFS, several attempts have been made to correlate this endpoint with OS. The value of PFS as a surrogate for OS is debated given the composite nature of PFS, which captures both death and PD.<sup>41,50</sup> However, the risk of death due to liver decompensation – potentially masking the net benefit of anticancer treatments – is reduced by the strict inclusion criteria of clinical trials where the enrollment is limited to patients with well-preserved liver function. Furthermore, the assessment of tumor response at variable time intervals across trials might challenge the comparison of the studies. It has been recently postulated that a benefit in PFS may predict a subsequent benefit in OS based on certain hazard ratio thresholds.<sup>25</sup> However, the analysis acknowledged several limitations, and, therefore, a thorough validation is still pending.<sup>50</sup>

## AFP Response as an Alternative Criterion to Radiological Endpoints

The AFP gene belongs to the albumin gene family,<sup>51</sup> and its expression is essentially regulated at a transcriptional level by the inhibitory control operated by the transcription factor p53.<sup>52</sup> Of note, AFP determines the malignant transformation and the development of HCC and may promote immune evasion through a variety of mechanisms including the induction of PD-L1 expression in immune cells.<sup>53</sup> Though a cut-off has not been universally established, increased serum levels of AFP are associated with poor prognosis in HCC patients across all stages of the disease.<sup>54</sup> Furthermore, several relationships between baseline AFP levels and tumor size, pathologic grade, and tumor stage have been recently integrated with molecular subtypes.<sup>55</sup> Among them, the HCC S2 subtype is characterized by elevated AFP and aggressive behavior.<sup>56</sup> Preoperative elevated AFP levels are predictors of recurrence after surgical resection or transplant,<sup>57,58</sup> whereas post-procedure declines of AFP identify better outcomes after transarterial chemoembolization,<sup>59</sup> radiofrequency ablation,<sup>60</sup> and systemic therapy.<sup>61,62</sup> Due to its prognostic significance, baseline AFP concentration has been increasingly identified as a stratification factor in the frame of several phase 3 clinical trials evaluating systemic treatments in HCC,<sup>5–8</sup> and has been recognized as a predictive biomarker of outcomes on ramucirumab.<sup>9</sup> Radiographic assessment of response can be challenging due to the cirrhotic liver morphology, scarring or devascularization derived from prior procedures, or diverse time intervals occurring between the injection of contrast dye and further image acquisition.<sup>63</sup> The use of serum biomarkers as an adjunct to the radiographic assessment may help overcome these limitations. Moreover, serum biomarkers may provide an early read-out of treatment efficacy that may be particularly useful to guide clinical decisions with therapies, such as MKIs, which typically induce only modest ORR. Serial serum AFP measurements during systemic treatments are easily reproducible, and retrospective investigations suggest an association between AFP decline (also known as “AFP response”) and improved survival.<sup>64–71</sup> Of note, only patients with  $\geq 10$ –20 ng/mL baseline AFP – nearly 70% of patients with advanced HCC – could be considered, given that a “background noise” due to active viral hepatitis or other causes of hepatic inflammatory damage contributes to AFP elevation, particularly at low levels. Furthermore, there is no consensus yet on the definition of AFP-based response or progression. Criteria to quantify the AFP response vary across studies, with reductions that range between 20% and 75% from the baseline AFP levels, and variable are the timepoints employed to measure AFP levels that spread over 4 to 8-week intervals.

## Tumor Response in Clinical Trials: Comparison Between Radiologic Criteria (RECIST Version 1.1 and mRECIST)

Most of the pivotal trials leading to the approval of MKIs in advanced HCC exclusively adopted RECIST. With the notable exception of the SHARP trial, which included a modified ad-hoc version of the RECIST,<sup>3</sup> conventional RECIST were used in the Asia-Pacific trial,<sup>4</sup> investigating sorafenib versus placebo as a front-line option in Asian patients, and RECIST v1.1 in the CELESTIAL trial,<sup>8</sup> testing cabozantinib versus placebo as a second- or third-line agent, and in the REACH-2 trial,<sup>9</sup> evaluating ramucirumab versus placebo as a second-line option for patients with baseline AFP levels of 400 ng/mL or greater. Overall, ORR by RECIST was 2–3.3% with sorafenib (all PRs), 4% with cabozantinib (all PRs), and 4.6% with ramucirumab (all PRs) compared with 1–1.3% (all PRs), less than 1% (1 PR), and 1.1% (1 PR) with placebo in each study, respectively. Despite the limited response rates, disease control rate (DCR), PFS, and OS were significantly improved with the active investigational agent compared to placebo in each study. Therefore, although the overall tumor burden appeared substantially unchanged, these compounds were proven effective in slowing down tumor progression and prolonging survival, which remains the ultimate purpose for patients with unresectable disease.

With the aim to overcome some of the intrinsic limitations of conventional RECIST in the assessment of tumor response and time-to-event outcomes in the advanced HCC field, a relatively small number of phase 3 trials exclusively employed mRECIST.<sup>26,29,72</sup> However, despite the higher ORRs reported, they failed to improve survival.

On the other hand, the phase 3 REFLECT, IMbrave150, and RESORCE trials adopted both RECIST v1.1 and mRECIST.<sup>5–7</sup> Their results are summarized in Table 2. Notably, mRECIST were primarily adopted to assess the efficacy outcomes in the REFLECT and RESORCE trials whereas were included among the exploratory endpoints in the IMbrave150 trial. In the REFLECT study,<sup>5</sup> the ORR by masked independent central imaging review was 40.6% and 12.4% per mRECIST and 18.8% and 6.5% per RECIST v1.1 for sorafenib and lenvatinib, respectively. Interestingly, investigator-assessed ORR per mRECIST was noticeably lower (24.1% with lenvatinib and 9.2% with sorafenib), showing to which extent the interpretation bias might play a relevant role in the assessment of the radiological endpoints. Although the response rate was remarkably higher per mRECIST, median PFS and TTP, which significantly favored lenvatinib, were similar both by mRECIST (PFS: HR 0.64, 95% CI, 0.55–0.75,  $p < 0.0001$  and TTP: HR 0.60, 95% CI, 0.51–0.71,  $p < 0.0001$ ) and RECIST v1.1 (PFS: HR 0.65, 95% CI, 0.56–0.77,  $p < 0.0001$  and TTP: HR 0.61, 95% CI, 0.51–0.72,  $p < 0.0001$ ). Additionally, OS was not significantly different (HR 0.92, 95% CI, 0.79–1.06) establishing the non-inferiority of lenvatinib.

Moving forward, in the IMbrave150 trial, ORR was 30% versus 11% by RECIST v1.1 and 35.4% versus 13.9% by mRECIST for atezolizumab plus bevacizumab versus sorafenib, respectively, according to the updated analysis.<sup>6,16</sup> Of note, the CR rate increased from 8% to 12% for atezolizumab plus bevacizumab and from <1% to 3% for sorafenib when ORR was assessed per mRECIST. Furthermore, median duration of response (DOR) was significantly longer in the combination arm both per RECIST v1.1 (18.1 months versus 14.9 months) and per mRECIST (16.3 months versus 12.6 months), with an estimated rate of responders for  $\geq 18$  months roughly doubled with atezolizumab plus bevacizumab compared with sorafenib (51% and 22%, respectively). Interestingly, even if more than 50% of the radiological responses were achieved within the first 3 months in both arms, 19% of first responses in the atezolizumab plus bevacizumab arm occurred after 6 months, with 1 patient (1%) achieving a CR at week 54. Superior outcomes for the combination were also reported in median PFS (HR 0.65, 95% CI, 0.53–0.81,  $p < 0.001$ ) and in median OS (HR 0.66, 95% CI, 0.52–0.85,  $p < 0.001$ ) setting a new front-line standard of care. Of note, more than half of the patients continued to receive atezolizumab plus bevacizumab beyond disease progression with sustained benefit and prolonged survival.<sup>16</sup>

Concerning the RESORCE trial,<sup>7</sup> ORR was 11% and 4% per mRECIST, and 7% and 3% per RECIST v1.1 for regorafenib and placebo, respectively. Interestingly, 2 CRs were exclusively reported by mRECIST, which exclude the necrosis of the target lesions from tumor measurement. Again, median PFS and TTP, which significantly favored regorafenib against placebo, were comparable regardless of the criteria adopted. Of note, clinical progression, which was included in the evaluation of both PFS and TTP, was reported for approximately 1 in 5 patients. Median OS was significantly longer for regorafenib (HR 0.63, 95% CI, 0.50–0.79, one-sided  $p < 0.0001$ ).

To date, iRECIST have been introduced exclusively in the phase 2 KEYNOTE-224 trial, testing pembrolizumab over placebo in the second-line setting.<sup>12</sup> Indeed, the trial evaluated ORR, its primary endpoint, by RECIST v1.1 and incorporated as preplanned exploratory analysis of tumor response by iRECIST and mRECIST. No major discrepancies were reported irrespective of the adopted criteria (ORR per RECIST v1.1: 18%; ORR per mRECIST: 15%; ORR per iRECIST: 17%), although, concordantly to previous observations,<sup>7,16</sup> the highest CR rate was recorded using mRECIST. On the contrary, PD rates were sensibly lower with iRECIST (25%) as compared to those reported with RECIST v1.1 (33%) and mRECIST (43%).<sup>12</sup> Responses were durable with 77% of responders showing a DOR of at least 9 months and, even though the vast majority of responders (67%) achieved an objective response within 8–10 weeks, late responses were not exceptional events with two CRs (1 confirmed and 1 unconfirmed) being reported during weeks 15–37 of treatment.<sup>12</sup>

## Correlation Between Tumor Response and Survival and Other Determinants of Survival in HCC

The identification of responders represents a significant endpoint in clinical trials and precious information for clinical decisions. In early and intermediate HCC, ORR has been shown to be an independent predictor of OS.<sup>25</sup> However, its role as a surrogate endpoint for survival is still poorly defined, especially in the field of advanced HCC. With both MKIs and the combination of atezolizumab plus bevacizumab, ORR qualified as an independent predictor of survival,<sup>73–76</sup>

**Table 2** Efficacy Outcomes by RECIST v1.1 and mRECIST in Phase 3 Trials for Advanced HCC

	REFLECT <sup>5</sup>		IMbrave150 <sup>6</sup>		RESORCE <sup>7</sup>	
	Lenvatinib (n=478)	Sorafenib (n=476)	Atezolizumab + Bevacizumab (n=326)	Sorafenib (n=159)	Regorafenib (n=379)	Placebo (n=194)
<b>ORR per RECIST v1.1, % (95% CI)</b>	18.8% <sup>a</sup> (15.3–22.3)	6.5% <sup>a</sup> (4.3–8.7)	30% (25–35)	11% (7–17)	7%	3%
CR	<1%	<1%	8%	<1%	0	0
PR	18%	6%	22%	11%	7%	3%
SD	54%	53%	44%	43%	59%	32%
DCR	72.8%	59%	74%	55%	66%	35%
<b>ORR per mRECIST, % (95% CI)</b>	40.6% <sup>a</sup> (36.2–45.0)	12.4% <sup>a</sup> (9.4–15.4)	35.4% (30.2–40.9)	13.9% (8.9–20.3)	11% (p<0.0047)	4% (p<0.0047)
CR	2%	1%	12%	2.5%	1%	0
PR	38%	12%	23.4%	11.4%	10%	4%
SD	33%	46%	37.2%	41.1%	54%	32%
DCR	73.8%	58.4%	72.6%	55%	65% (p<0.0001)	36% (p<0.0001)
<b>DOR per RECIST v1.1</b> Median, months (95% CI)	–	–	18.1 (14.6–NE)	14.9 (4.9–17.0)	–	–
<b>DOR per mRECIST</b> Median, months (95% CI)	–	–	16.3 (13.1–21.4)	12.6 (6.1–17.7)	3.5 (1.9–4.5) <sup>b</sup>	2.7 (1.9–NE) <sup>b</sup>
<b>PFS per RECIST v1.1</b> Median, months	7.3 <sup>a</sup>	3.6 <sup>a</sup>	6.9	4.3	3.4	1.5
HR (95% CI)	0.65 (0.56–0.77)		0.65 (0.53–0.81)		0.43 (0.35–0.52)	
p value	p<0.0001		p<0.001		p<0.0001	
<b>PFS per mRECIST</b> Median, months	7.3 <sup>a</sup>	3.6 <sup>a</sup>	–	–	3.1	1.5
HR (95% CI)	0.64 (0.55–0.75)				0.46 (0.37–0.56)	
p value	p<0.0001				p<0.0001	
<b>TTP per RECIST v1.1</b> Median, months	7.4 <sup>a</sup>	3.7 <sup>a</sup>	–	–	3.9	1.5
HR (95% CI)	0.61 (0.51–0.72)				0.41 (0.34–0.51)	
p value	p<0.0001				p<0.0001	
<b>TTP per mRECIST</b> Median, months	7.4 <sup>a</sup>	3.7 <sup>a</sup>	–	–	3.2	1.5
HR (95% CI)	0.60 (0.51–0.71)				0.44 (0.36–0.55)	
p value	p<0.0001				p<0.0001	
<b>OS</b> Median, months	13.6	12.3	19.2	13.4	10.6	7.8
HR (95% CI)	0.92 (0.79–1.06)		0.66 (0.52–0.85)		0.63 (0.50–0.79)	
p value	–		p<0.001		p<0.0001	

**Notes:** <sup>a</sup>Assessed by masked independent imaging review. <sup>b</sup>Assessed in 48 evaluable patients (regorafenib: n=40; placebo: n=8). Data from.<sup>5–7</sup>

**Abbreviations:** ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria for Solid Tumors version 1.1; 95% CI, 95% confidence interval; CR, complete response; PR, partial response; SD, stable disease; DCR, disease control rate; mRECIST, modified RECIST; DOR, duration of response; PFS, progression-free survival; HR, hazard ratio; TTP, time-to-progression; OS, overall survival; p, p value; NE, not evaluable.



nevertheless, the surrogate value of ORR for OS was only modest either per RECIST v1.1 or mRECIST, according to a recent meta-analysis.<sup>77</sup> Hence, ORR could not be recommended as a primary endpoint in phase 3 trials for advanced HCC so far, but its use should be limited to proof-of-concept early phase studies. As a matter of fact, in most landmark phase 3 trials for advanced HCC, a large contribution to the net survival benefit was provided by the substantial proportion of patients achieving a durable SD.<sup>3,4,7-9</sup> Therefore, DCR will eventually be a more informative outcome in this setting. Furthermore, with the approval of novel therapeutics with distinct mechanisms of action, such as ICIs, which are capable to induce delayed long-lasting responses, the evaluation of the estimated rates of responders at certain time cut-offs are additional parameters that deserve specific investigation in the HCC field.<sup>78</sup>

Tumor progression acts as a surrogate of survival with variable impact according to the pattern of disease progression. Indeed, the different radiological progression patterns, which include new extrahepatic lesion and/or vascular invasion (NEH), new intrahepatic lesion, extrahepatic growth, or intrahepatic growth, demonstrated to harbor distinctive prognostic connotations.<sup>47</sup> As opposed to intrahepatic progression or growth of pre-existent extrahepatic lesions, NEH was independently correlated with inferior outcomes. In fact, it was associated with poorer OS and post-progression survival (PPS), and patterns of progression on first-line sorafenib maintained a concordant prognostic significance in trials of second-line regorafenib and tivantinib.<sup>7,28,47</sup> Additionally, even in the second-line setting, the pattern of progression retained a prognostic implication with the development of NEH for patients on ramucirumab/placebo foreshadowing the worst survival, according to an exploratory analysis of the REACH and REACH-2 trials.<sup>48</sup> Therefore, to avoid potential imbalances across treatment arms, the significance of each pattern requires prospective validation to endorse a structured stratification in clinical trials.<sup>47</sup>

Survival in patients with HCC is a composite outcome due to the competing risk of liver cirrhosis.<sup>79</sup> The degree of liver impairment and its consequences might drive the overall prognosis even further than the tumor burden, affect treatment tolerability and quality of life,<sup>80-82</sup> and confound tumor assessments, as some cirrhosis-induced morphological alterations of the liver could be misread as tumor progression.<sup>46</sup> This clearly adds significant complexity to the assessment and monitoring of treatment response in patients with HCC. Several functional scores have been proposed to recapitulate the degree of functional liver impairment and the relative risk of fatal liver decompensation in cirrhotic patients.<sup>83-85</sup> Although acknowledging some limitations (inclusion of subjective clinical variables, choice of laboratory parameters with non-uniform normal ranges, and omission of other relevant indicators of liver dysfunction), the most widely used both in HCC trials and in routine clinical practice is the Child-Pugh score.

In clinical trials, the restriction of treatment allocation to patients with a well-preserved liver function (Child-Pugh A) aims at minimizing the risk that liver failure could bewilder trial results. However, since in clinical practice treatment is often offered to patients outside the eligibility criteria of clinical trials, understanding the value of therapeutic interventions in patients with a mild liver derangement (Child-Pugh B) remains a crucial yet controversial topic.<sup>86,87</sup> In this subset of patients, MKIs and ICIs alone (nivolumab) or in combinations (atezolizumab plus bevacizumab) showed an overall comparable safety and tolerability.<sup>9,46,80,88-93</sup> However, the survival outcomes were remarkably shorter than in patients with preserved liver function. Therefore, in this context, where the survival metrics are highly impacted by the natural course of the underlying liver disease, recapitulating the efficacy of a certain treatment intervention in terms of tumor response might help distinguish the reasons behind treatment failure (tumor progression or liver decompensation) and possibly identify a subgroup of patients who is more likely to derive greater benefit from active treatment.

## Assessment of Drug Activity by Baseline AFP and AFP Response

In patients with advanced HCC, the prognostic value of elevated baseline AFP levels and AFP response has been thoroughly investigated for first-line agents (sorafenib, lenvatinib, and atezolizumab plus bevacizumab),<sup>5,65-68,94</sup> and further-line therapies (regorafenib, cabozantinib, and ramucirumab).<sup>8,9,69-71,80,95</sup>

According to a retrospective analysis, AFP response (defined as a >20% decrease of AFP levels from baseline to week 8) was significantly associated with longer OS (13.3 months versus 8.2 months,  $p = 0.022$ ) in a group of 85 patients treated with sorafenib, and this survival difference remained significant even when more stringent criteria were applied to define AFP responders ( $\geq 50\%$  decrease from baseline levels to week 8).<sup>65</sup> Interestingly, AFP response more accurately predicted a survival benefit as compared to the image-based assessment of disease control, demonstrating better surrogacy for OS than the radiologic response criteria.

In the REFLECT trial, patients with baseline AFP levels <200 ng/mL achieved a longer median OS (19.5 months with lenvatinib and 16.3 months with sorafenib, HR 0.91, 95% CI, 0.74–1.12) than those with AFP levels  $\geq$ 200 ng/mL (10.4 months with lenvatinib and 8.2 months with sorafenib, HR 0.78, 95% CI, 0.63–0.98) irrespective of the treatment arm, even though they were not prospectively stratified by AFP values.<sup>5</sup> Furthermore, in patients receiving lenvatinib outside the landmark clinical trial, AFP response (defined as  $\geq$ 40% decrease of AFP levels at week 4 among patients with baseline AFP levels  $\geq$ 10 ng/mL) was the only significant predictor of objective response and a subsequent retrospective study highlighted the association between early AFP response (defined as >20% decrease in AFP levels from baseline to week 4) and higher ORR, DCR, and PFS in a small cohort of Asian patients with HBV-related unresectable HCC.<sup>66,67</sup>

Also with atezolizumab plus bevacizumab, AFP response (defined as  $\geq$ 75% decrease or  $\leq$ 10% increase of AFP levels from baseline to week 6) significantly correlated with better PFS per RECIST v1.1 and OS in a post hoc analysis performed on the data from the phase 1b trial and then validated with the phase 3 data.<sup>68</sup> Of note, an association with tumor response was documented, with the majority of CRs/PRs being observed in patients who achieved a  $\geq$ 75% decrease in AFP levels and the majority of disease control cases being reported in patients who experienced  $\leq$ 10% increase in AFP levels either per RECIST v1.1 or mRECIST. Additional AFP response cut-offs were tested (20% and 50% decrease from baseline). However, the  $\geq$ 75% decrease threshold better correlated with tumor objective response, while the 20% decrease cut-off better discriminated between disease control and primary progression. On the contrary, an increase in AFP levels was an early predictor of treatment failure both in the IMbrave150 trial and in a subsequent retrospective analysis.<sup>68,94</sup> However, 5 of the 43 patients who experienced a >10% increase in AFP at week 6 receiving the combination within the IMbrave150 trial still achieved an objective response at a later time point.<sup>68</sup>

Data from the RESORCE study suggested that AFP response (defined as a decrease of  $\geq$ 20% in AFP levels from baseline to week 8) was associated with improved OS (13.8 versus 9.8 months; HR 0.72, 95% CI, 0.48–1.07) in 168 patients receiving regorafenib.<sup>70</sup> Interestingly, these data were consistent with those acquired in a larger cohort of 232 patients obtained pooling the two treatment arms of the study, regorafenib and matched placebo. Furthermore, baseline AFP levels  $\geq$ 400 ng/mL and the increase of AFP levels were predictors of poor survival and shorter TTP, but AFP fluctuations were not predictive of treatment benefit.<sup>95</sup>

In a secondary analysis of the CELESTIAL trial,<sup>8</sup> patients with baseline AFP levels <400 ng/mL had a median OS of 13.9 months with cabozantinib versus 10.3 months with placebo (HR 0.81, 95% CI, 0.62–1.04). On the other hand, patients with baseline AFP levels  $\geq$ 400 ng/mL experienced a median OS of 8.5 months with cabozantinib versus 5.2 months with placebo (HR 0.71, 95% CI, 0.54–0.94). AFP response (defined as  $\geq$ 20% decrease from baseline to week 8) occurred in 50% of the evaluable patients in the cabozantinib group versus 13% in the placebo group and was associated with improved OS, TTP, and PFS as compared to those with no AFP response. In the cabozantinib arm, median OS for patients with an AFP response ( $n = 117$ ) and without an AFP response ( $n = 119$ ) was 16.1 months and 9.1 months (HR 0.61, 95% CI, 0.45–0.84), whereas median PFS in the same subgroups was 7.3 months and 4.0 months (HR 0.55, 95% CI, 0.41–0.74).<sup>71</sup>

In a pooled analysis of REACH and REACH-2 studies,<sup>9,80</sup> median OS was longer in patients with AFP 400–1000 ng/mL compared to patients with AFP >1000 ng/mL. Patients receiving ramucirumab were more likely to experience an AFP response (defined as a decrease of  $\geq$ 20% of AFP levels from baseline with serial AFP measurements every 6 weeks) as compared with patients treated with placebo, and AFP responders had significantly longer median OS than non-responders (13.6 versus 5.6 months, HR 0.451, 95% CI, 0.354–0.574;  $p < 0.0001$ ). Interestingly, regardless of the treatment received, no differences were observed in OS among patients experiencing an AFP response (13.6 versus 12.1 months, HR 0.963, 95% CI, 0.52–1.77, for ramucirumab compared to placebo, respectively). Furthermore, AFP kinetics were consistently associated with radiographic tumor response (AFP decrease) or progression (AFP increase).<sup>69</sup>

In addition, an early AFP response (defined as  $\geq$ 10% decrease in AFP levels from baseline to week 4) significantly predicted better OS (24.7 months versus 5.6 months,  $p = 0.014$ ), ORR (63.6% versus 10.2%,  $p < 0.001$ ), and DCR (81.8% versus 14.3%,  $p < 0.001$ ) in a mixed cohort of naïve and pretreated Asian patients receiving ICIs either as monotherapy or in combinations according to a retrospective analysis.<sup>96</sup> Similarly, a real-world analysis of nivolumab showed that AFP response ( $\geq$ 50% decrease from baseline levels to week 4 [class I] followed by a further  $\geq$ 10% decline from baseline at week 12 [class II]) was significantly associated with OS, PFS, and ORR, irrespective of the line of treatment.<sup>97</sup> Of note, baseline AFP levels were independent predictors of survival but no significant correlation was shown with ORR according to a cut-off of 400 ng/mL.<sup>97,98</sup> However, further validation is requested to draw meaningful conclusions in this subset of patients. Survival outcomes by AFP response are summarized in Table 3.

**Table 3** Survival Outcomes by AFP Response in Clinical Trials for Advanced HCC

	AFP Response
<b>Sorafenib</b> <sup>a,65</sup>	>20% decrease from baseline to week 8
<b>Median OS, months<sup>b</sup></b>	13.3 versus 8.2
HR (95% CI)	–
p value	p=0.022
<b>Lenvatinib</b> <sup>66</sup>	≥40% decrease from baseline to week 4
<b>Median OS, months<sup>b</sup></b>	NR <sup>c</sup> versus 12.7
HR (95% CI)	–
p value	p = 0.077
<b>Atezolizumab + bevacizumab</b> <sup>a,68</sup>	≥75% decrease from baseline to week 6
<b>Median OS, months<sup>b</sup></b>	NE versus 14.2
HR (95% CI)	0.36 (0.20–0.66)
p value	p<0.001
<b>Atezolizumab + bevacizumab</b> <sup>a,68</sup>	≤10% increase from baseline to week 6
<b>Median OS, months<sup>b</sup></b>	23.7 versus 10.6
HR (95% CI)	0.45 (0.29–0.70)
p value	p<0.001
<b>Ramucirumab</b> <sup>a,69</sup>	≥20% decrease from baseline to week 6
<b>Median OS, months<sup>b</sup></b>	13.6 versus 5.6
HR (95% CI)	0.45 (0.35–0.57)
p value	p<0.0001
<b>Regorafenib</b> <sup>a,70</sup>	≥20% decrease from baseline to week 8
<b>Median OS (in the regorafenib arm), months<sup>b</sup></b>	13.8 versus 9.8
HR (95% CI)	0.72 (0.48–1.07)
p value	–
<b>Median OS (in the regorafenib + placebo arm), months<sup>b</sup></b>	13.8 versus 8.9
HR (95% CI)	0.57 (0.40–0.82)
p value	–
<b>Cabozantinib</b> <sup>a,71</sup>	≥20% decrease from baseline to week 8
<b>Median OS (in the cabozantinib arm), months<sup>b</sup></b>	16.1 versus 9.1
HR (95% CI)	0.61 (0.45–0.84)
p value	–
<b>Nivolumab</b> <sup>97</sup>	≥50% decrease from baseline to week 4 (class I)
<b>Median OS, months<sup>d</sup></b>	17.1 versus 14.7
HR (95% CI)	–
p value	p=0.338
<b>Nivolumab</b> <sup>97</sup>	±50% decrease from baseline to week 4 + ≥ 10% decline from baseline at week 12 (class II)
<b>Median OS, months<sup>d</sup></b>	NR versus 7.7
HR (95% CI)	–
p value	p<0.001

**Notes:** <sup>a</sup>Data from pivotal clinical trials. <sup>b</sup>Median OS is reported for responders versus non-responders. <sup>c</sup>Median survival time was not reached due to the short follow-up of the study. <sup>d</sup>Compared to AFP non-responders defined as ±50% decrease in AFP levels from baseline to week 4 not followed by ≥ 10% decline from baseline at week 12 (class III) and rapid ≥ 50% increase in AFP levels from baseline at week 4 (class IV). Data from.<sup>65,66,68–71,97</sup>

**Abbreviations:** AFP, alpha-fetoprotein; OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval; NR, not reached; NE, not estimated.

Although the thresholds and timing of the assessments were highly heterogeneous, there is evidence that on-treatment AFP dynamic changes reflect well treatment response. Therefore, the inclusion of serial AFP measurements within the response assessment will be helpful to better characterize the role of AFP kinetics as a surrogate endpoint for OS in future clinical trials.

Another important consideration is that AFP kinetics may be dependent upon the therapeutic mechanism of action. Available data mostly concern patients receiving anti-angiogenic agents. The role of AFP in monitoring treatment response to ICIs remains less clear, with preliminary reports mainly limited to the atezolizumab–bevacizumab combination.<sup>68,94</sup>

Although an AFP decline suggests improved outcomes, increased AFP levels, in the absence of radiological confirmation, cannot be considered as an indicator of resistance to treatment and cannot determine treatment discontinuation. Hopefully, future investigations should prospectively evaluate AFP kinetics in large, randomized studies, as already done with other tumor types such as prostate cancer where the kinetics of prostate-specific antigen can inform further treatment decisions.<sup>99</sup>

## Conclusions

The baseline identification of tumor burden and the assessment of tumor response (or progression) to anticancer treatments is a crucial step to gauge the activity of a novel drug and estimate patients' prognosis. However, in HCC, the common radiological framework adopted for solid tumors can be flawed by the concomitance of cirrhosis-related liver alterations and the inability to capture the biological tumor modifications other than shrinkage. Indeed, a scarce alignment was observed between the reported response rates per RECIST and the survival benefit obtained in many pivotal trials with targeted agents.<sup>3,4,7–9</sup> Restricting the measurement to the “viable tumor”, mRECIST led to higher ORRs, particularly improving the identification of patients with CRs.<sup>5–7,16</sup> This is particularly true for patients on antiangiogenics, a class of agents expected to induce those radiological changes interpreted as tumor response per mRECIST. However, for ICIs alone, albeit lacking a comparison in larger clinical trials, tumor response has been observed in a similar proportion of patients irrespective of the radiological criteria adopted.<sup>16</sup> Moving forward, despite the flourishing of clinical trials with ICIs in HCC, outcomes by iRECIST are still largely underreported,<sup>12</sup> therefore, their use remains investigational. With the multiplied number of treatments available and the consequent substantial survival prolongation, early biomarkers of response have become increasingly needed as OS is affected by further lines of therapy and requires a longer time to be assessed.<sup>40</sup> However, determinants of survival in HCC include both tumor progression (and its patterns) and end-stage chronic liver disease.<sup>86,87</sup> Thus, OS alone could possibly miss the efficacy of a certain intervention because of the competing risk of dying of liver decompensation in an unselected population. On the other hand, PFS and ORR are imperfect surrogates for OS in advanced HCC and would require additional investigation as novel agents become available.<sup>26,40,73–77</sup> Of note, ORR is greater affected by the response criteria adopted, PFS might appear a better surrogate endpoint for OS, being supported by more consistent data.<sup>5–7,16</sup> Further guidance might be provided by serum biomarkers. With this respect, baseline AFP levels and AFP response showed an association with patients' prognosis, although a sizeable proportion of patients remains not evaluable according to such parameters. In retrospective analyses with MKIs, ramucirumab, and ICIs alone or in combinations, the on-treatment decrease of AFP levels repeatedly predicted radiologic tumor response and better survival outcomes, supporting a prospective evaluation of the AFP dynamic changes as a surrogate biomarker of survival.<sup>65–71,94–97</sup> Further circulating biomarkers, including MKIs targets, their ligands, and other plasma proteins, mainly with a role in inflammation/HCC pathogenesis were found to be prognostic and sometimes predictive in retrospective analyses of the SHARP, REFLECT, RESORCE, and CELESTIAL trials.<sup>95,100–102</sup> However, they were not evaluated as biomarkers of response, and the non-homogenous significance across different studies and treatment arms, the lack of established cut-offs and uniform protocols for their measurement, and the rather intricate process required for their analysis limit further validation and make their use not yet feasible in clinical practice.

Future areas of research involve the appraisal of some novel imaging technologies for which RECIST do not apply – such as perfusion and diffusion MRI and metabolic imaging – with the hope to clarify their role in the assessment and on-treatment monitoring of tumor response in the setting of advanced HCC.<sup>103,104</sup> For instance, positron emission tomography (PET) with 18F-fluorodeoxyglucose is being increasingly evaluated to estimate patients' prognosis and measure treatment response to the

currently available front-line treatment options in advanced HCC with preliminary intriguing results.<sup>105–108</sup> Additional information might be eventually offered by the implementation of radiomics, an emergent research area fostering models that can predict clinical outcomes from high-throughput imaging data, and radiogenomics, a related field of research that tries to correlate the imaging characteristics with the genetic profiles, under investigation, particularly in earlier disease stages.<sup>109,110</sup> With this respect, the ongoing trials delivering ICIs in the neoadjuvant and perioperative setting will eventually represent a valuable connection to help integrate the mechanisms of tumor response at a biological level with the radiologic modifications observed.<sup>111–113</sup> Furthermore, the search for accurate serum biomarkers has a prominent role in the HCC research agenda, as shown by the growing relevance that liquid biopsy is gaining in this setting.<sup>114,115</sup> An emerging body of literature suggests that circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) might not only predict a higher risk of recurrence/progression but also correlate with tumor response to systemic therapy. Elevated levels of CTCs and ctDNA correlated with increased tumor burden and vascular invasion, and increased levels of ctDNA during systemic therapy have been associated with tumor progression and increased AFP levels.<sup>115</sup> Moreover, some mutational signatures predicted response/resistance to MKIs, and PD-L1 positive CTCs were linked with response to anti-PD-(L)1 agents in a small series of patients.<sup>115,116</sup> Although pending a thorough validation in larger prospective studies, longitudinal monitoring of ctDNA levels during the course of systemic treatment appears a useful tool to timely identify treatment response or resistance while providing further insights into the underlying biological mechanisms. Forthcoming the era of precision medicine, developing non-invasive, imaging- and serum-based metrics capable of revealing the phenotypic signatures of HCC will hopefully provide tailored guidance for informed treatment choices and insightful hints for the evaluation and monitoring of tumor response.

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