



mRECIST for HCC: Performance and novel refinements

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Summary

In 2010, modified RECIST (mRECIST) criteria were proposed as a way of adapting the RECIST criteria to the particularities of hepatocellular carcinoma (HCC). We intended to overcome some limitations of RECIST in measuring tumour shrinkage with local and systemic therapies, and also to refine the assessment of progression that could be misinterpreted with conventional RECIST 1.1, due to clinical events related to the natural progression of chronic liver disease (development of ascites, enlargement of lymph nodes, etc.). mRECIST has served its purpose since being adopted or included in clinical practice guidelines (European, American and Asian) for the management of HCC; it has also been instrumental for assessing response and time-to-event endpoints in several phase II and III investigations. Nowadays, mRECIST has become the standard tool for measurement of radiological endpoints at early/intermediate stages of HCC. At advanced stages, guidelines recommend both methods. mRECIST has been proven to capture higher objective response rates in tumours treated with molecular therapies and those responses have shown to be independently associated with better survival. With the advent of novel treatment approaches (*i.e.* immunotherapy) and combination therapies there is a need to further refine and clarify some concepts around the performance of mRECIST. Similarly, changes in the landscape of standard of care at advanced stages of the disease are pointing towards progression-free survival as a potential primary endpoint in some phase III investigations, as effective therapies applied beyond progression might mask overall survival results. Strict recommendations for adopting this endpoint have been reported. Overall, we review the performance of mRECIST during the last decade, incorporating novel clarifications and refinements in light of emerging challenges in the study and management of HCC.

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Introduction

Hepatocellular carcinoma (HCC) is a major cause of cancer-related mortality worldwide.^{1–3} Nowadays, almost all patients with HCC in the West receive either potentially curative therapies (*i.e.* resection, liver transplantation and local ablation) for early tumours,^{1,2} transarterial chemoembolisation (TACE) for intermediate stages, or any of the effective drugs approved for advanced tumours, such as sorafenib or lenvatinib in front-line and regorafenib, cabozantinib or ramucirumab in second-line^{1,2,4} (Fig. 1). Life expectancy has improved substantially, with median survival times of more than 5 years for early stages, around 30 months for intermediate cases and already surpassing the 1-year threshold in advanced cases.^{1,2} Novel drugs and combinations are flooding the research arena and addressing unmet medical needs. The main clinical trials are currently exploring agents in the adjuvant setting, combinations with TACE at intermediate stages and combinations of systemic agents (*i.e.* TKI plus checkpoint inhibitors) at advanced stages.^{2,4} All these research activities require precise endpoints and tools for measuring clinical benefit.

Overall survival remains the primary endpoint in oncology and HCC research.^{1,4} It has driven clinical research in HCC for more than 40 years and has

been the gold-standard for measuring benefits at all stages of the disease. Nonetheless, the emergence of several effective drugs in advanced HCC has highlighted the need for alternative endpoints that enable researchers to capture clinical benefits before they are diluted by sequential treatments beyond progression.⁴ Thus, progression-free survival (PFS), time-to-progression (TTP) and objective response rate (ORR) are now emerging as tools to identify strong early signals of efficacy that can lead to accelerated regulatory approval (particularly ORR and PFS)^{5,6} and test the benefit of interventions prior to administering additional sequential drugs, which might otherwise mask the actual benefit of the tested drug. In this context, a recent investigation analysing 21 reported phase III studies^{7–27} in advanced HCC proposed PFS (with restrictive hazard ratio [HR] criteria ≤ 0.6) as a surrogate endpoint for survival, and thus as a potential primary endpoint in advanced HCC trial design.⁴ How we are measuring all those radiology-based endpoints is therefore critical for capturing real clinical benefits.

In 2010, we developed the mRECIST (modified Response Evaluation Criteria in Solid Tumours) for HCC.²⁸ This guideline followed the recommendation posed by the original RECIST publication to

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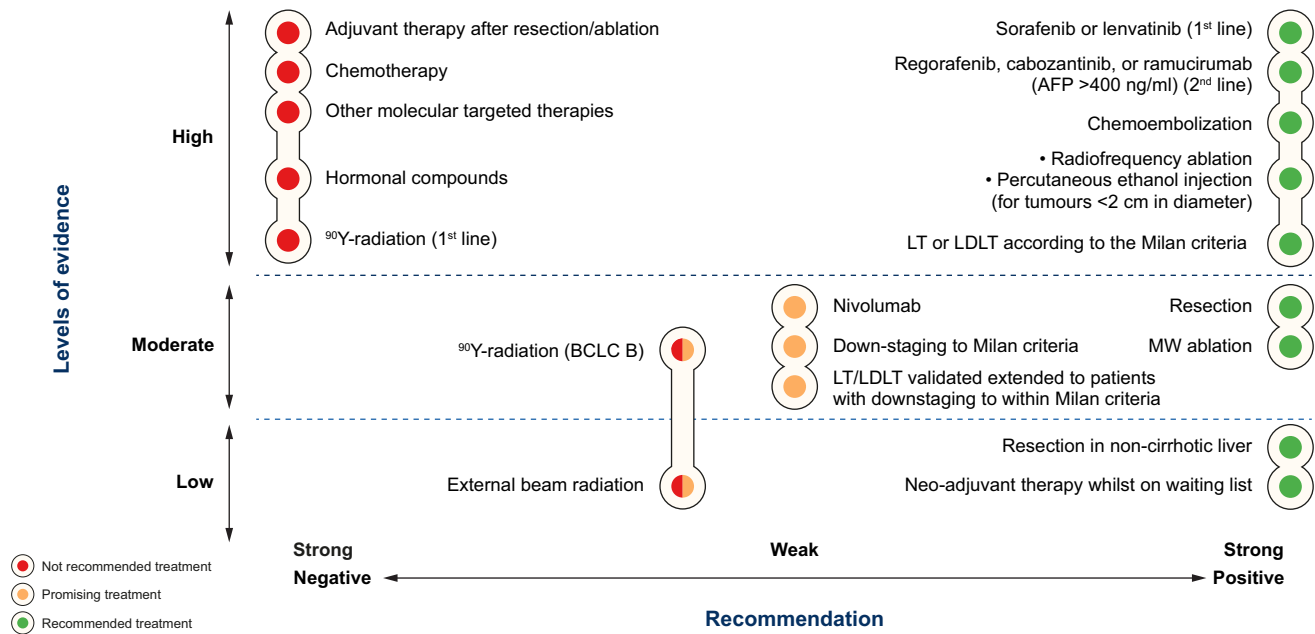


Fig. 1. Representation of EASL Guidelines: recommendations for treatment according to levels of evidence and strength of recommendation (adaptation of the GRADE system). Adapted from EASL Guidelines. J Hep 2018.¹ In green, recommended treatments based on level 1–2 evidence. In orange, treatments with promising results based on phase II data. In red, treatments not recommended because of negative clinical trial investigations. AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; LDLT, living donor liver transplantation; LT, orthotopic liver transplantation; MW, microwave.

encourage amendments for tumours presenting unique complexities and for the evaluation of anti-cancer therapies other than cytotoxic drugs.²⁹ In fact, both these issues are highly relevant in the setting of HCC:

- **Lack of tumour shrinkage with effective therapies:** effective treatments in HCC, including some locoregional therapies and systemic targeted agents,^{1,30–34} often fail to induce sizeable tumour shrinkage despite the reported improvement in survival, frustrating attempts to capture tumour response with standard RECIST metrics.^{7,8,13,22,24,25,34,35} Failures of RECIST assessments were paramount when evaluating responses to radiofrequency or chemoembolisation treatments.³⁵
- **Coexistence of cancer and cirrhosis:** HCC and cirrhosis coexist in more than 80% of cases creating unique complexities for imaging assessment. Pathogenic and haemodynamic changes inherent to cirrhosis may mimic or conceal intrahepatic tumours³⁰. In addition, extrahepatic manifestations of chronic liver disease – such as lymph node enlargement at the porta hepatis or the development of ascites – may be major causes of misinterpretation and have been assumed to represent evidence of tumour progression by conventional RECIST assessment.

The proposed mRECIST criteria for HCC were conceived to address the drawbacks of standard RECIST. The absence of shrinkage was overcome by introducing the concept of “viable tumour” in the measurement of intrahepatic HCC lesions.²⁸ This modification – originating from previous guidelines^{36,37} – was made to enable the detection

of objective responses in patients who develop substantial treatment-related intratumoural necrosis in the absence of major changes in tumour diameter. Similarly, we addressed the confounding factors related to cirrhosis by introducing specific RECIST amendments for the assessment of lymph nodes, ascites, portal vein thrombosis, and newly detected hepatic nodules. These recommendations were made with the primary intent of preventing overreporting of progressive disease (PD).

Over the past 10 years, mRECIST has been used extensively in HCC clinical research³⁸ and in major phase II–III trials of intermediate^{39–41} and advanced HCC^{10,13,18,19,22}. Similarly, EASL, ESMO and AASLD guidelines recommend assessment of ORR, PFS and TTP by mRECIST in trials targeting early/intermediate HCC cases^{1,32–34,42} and both mRECIST and RECIST in advanced cases^{1,34,42}. Thus, mRECIST has served its purpose.

In the present article, we aimed to review the performance of mRECIST for the assessment of tumour response in patients receiving locoregional or systemic treatments since its seminal publication. In addition, we will address some of the questions that have been raised following the publication of mRECIST criteria, by providing more detailed information on the proper use of this tool. Finally, we will detail a selection of refinements, particularly relating to response assessment with novel therapies.

Overview of trial design and endpoints in HCC

Trial design in HCC has been evolving, with new challenges emerging as novel therapies become

Key point

Over the last decade, mRECIST has been widely used in clinical research and in major phase II/III trials of HCC.

standard of care. Although there might be distinct approaches to trial design in HCC, there is consensus on the basic principles that have recently been reported in guidelines and critical appraisal papers^{1,4,37,42}. The key points are summarized below:

- **Selection of the target population:** clinical trials should consider the Barcelona Clinic Liver Cancer staging system, Child-Pugh class and Eastern Cooperative Oncology Group (ECOG) performance status for selection of the target population. In principle, for advanced stages of the disease almost all randomised controlled trials (RCTs) include patients with well-preserved liver function (Child-Pugh A) and good performance status (ECOG 0 and 1).
- **Control arm:** The control arm of randomised phase II and III studies should be the standard of care established according to guidelines. Thus, for early cases testing local ablation therapies, the control arm should be radiofrequency ablation; for intermediate HCC, chemoembolization⁴³; for advanced HCC in front-line, either sorafenib or lenvatinib are accepted^{7,13}; for second-line therapies, regorafenib (in patients tolerant to sorafenib),²² cabozantinib²⁴ or ramucirumab (in patients with alpha-fetoprotein [AFP] ≥ 400 ng/ml)²⁵. When no standard of care is available (adjuvant trials, third-line setting) a placebo-control arm is recommended. Double-blinded trials are recommended to prevent selection and allocation biases.
- **Stratification for prognostic factors prior to randomisation:** stratification is critical for balanced comparisons in randomised studies. For early HCC, region and high risk of recurrence factors are critical. Regarding the latter, both size ($>/ < 3$ cm in single tumours) and multinodularity have been considered. If pathological data are available, high risk patients have been defined as those with microvascular invasion, poor differentiation degree and/or satellites. In intermediate HCC, region and high AFP (either > 200 or 400 ng/ml) are recommended. For advanced HCC the recommendation is as follows: region, macrovascular invasion, extrahepatic spread, AFP > 400 ng/ml and ECOG 0 vs. 1–2. In case sorafenib is used for the control arm, aetiology (HCV vs. others) should be considered.⁴⁴
- **End points:**
 - **Overall survival:** For primary treatments (locoregional or systemic) the primary endpoint should be OS, while for adjuvant therapies after resection/ablation it should be recurrence-free survival (RFS) or time to recurrence (TTR). All regular FDA and EMA drug approvals in advanced HCC were based upon improvements in OS.
 - **Surrogate endpoints:** OS has some limitations as a sole endpoint in cancer research: it might require a long follow-up to capture adequate numbers (i.e. median OS for TACE is 26–30 months)^{39,40} and can be affected by sequen-

tial therapies. Thus, surrogate endpoints that are more practical for trial execution are needed. However, they are subject to interpretation by investigators and data on surrogates of OS are lacking in most instances.

- Early and intermediate HCC: ORR by mRECIST correlates with OS in patients treated with TACE.⁴¹ Clinical guidelines recommend complete response (for thermal ablation) and ORR by mRECIST (for TACE) as primary endpoints for phase II investigations.^{1,34,42}
- Advanced HCC: there are no optimal surrogate endpoints able to recapitulate OS in HCC, and thus clinical practice guidelines do not recommend ORR, TTP and PFS as primary endpoints in phase III investigations.^{1,42} ORR was an independent predictor of OS in 3 phase II and III trials,^{45–47} but it is still considered a suboptimal primary endpoint for phase III investigations. Nonetheless, ORRs of 16–18% have led to accelerated FDA approval for nivolumab and pembrolizumab in advanced HCC in second-line.^{48,49} PFS was formerly discarded as a primary endpoint for phase III investigations due to the concept of competing risk of survival (competing between death due to tumour progression and due to the natural history of cirrhosis).³⁷ However, this competing risk drawback has been reduced by the universal selection of Child-Pugh A patients for these investigations, thus reducing the 1-year risk of death due to decompensation to $< 5\%$. In fact, a recent meta-analysis of 21 RCTs suggests that there is a correlation between PFS and OS ($r = 0.84$) and that a HR for PFS ≤ 0.6 correlated with significant clinical benefits in terms of OS.⁴ Regarding ORR, use of both RECIST1.1 and mRECIST are proposed for the assessment of response in HCC treated with systemic therapy, whereas changes in serum biomarker levels (i.e. AFP levels) are not supported.¹
- **Magnitude of benefit:** In HCC, there is no consensus on what absolute survival benefit (or the magnitude of benefit in OS according to HR) can be defined as clinically relevant. Reported thresholds of OS with HR < 0.8 are sound for capturing the benefit of patients in advanced HCC trials.^{4,50}
- **Description of baseline and outcome characteristics:** The baseline description of patient characteristics and outcomes should follow previously reported guidelines.³⁷

Performance of mRECIST

mRECIST has been widely used by investigators/guidelines to assess radiological endpoints (ORR, TTP and PFS) in early and intermediate HCC treated with local ablation or TACE.⁵¹ Conversely, its use is currently competing with RECIST for the assessment of these endpoints in advanced HCC.¹ Overall, mRECIST ORR is always higher than

RECIST, both in the assessment of local and systemic therapies (both methods were reported for sorafenib, lenvatinib, brivanib, regorafenib and nintedanib; **Table 1**).^{4,13,22,48,51} Conversely median PFS and TTP endpoints are similar with both tools in the few cases where they have been reported (lenvatinib, sorafenib and regorafenib phase III trials).^{13,22} This is counterintuitive considering the paramount differences between both methods when measuring progression due to development of ascites and new lesions. We herein provide a short overview of the performance of this tool throughout the last decade (**Table 1**) and analyse reasons for similar outcomes with RECIST and mRECIST for time-to-event endpoints.

Assessment of objective response

Objective response in locoregional therapies

Overall median ORRs (measured by mRECIST) with TACE and with Y-90 radioembolisation have been reported to range from 40–80%, depending on whether treatment was applied to patients with early-stage or intermediate-stage disease.^{39,40,51–53} In 2 RCTs assessing combination therapies (TACE plus systemic agents) ORRs according to mRECIST were 41–42% for TACE, 55% for TACE-sorafenib and 48% for TACE-brivanib.^{39,40} Regarding surrogacy, several clinical investigations have shown that ORR (measured by mRECIST) predicts survival in patients treated with locoregional therapies.⁴¹ A meta-analysis including 7 trials and 1357 patients reported a HR for OS (responders vs. non-responders) of 0.39 (95% CI 0.26–0.61; $p < 0.0001$).⁴¹ This performance was similar to the former EASL criteria. Assessment of response based on RECIST for locoregional therapies has barely been reported in recent phase II–III investigations due to previous failures.³⁵

Objective response in systemic therapies

mRECIST criteria have been used in 5 phase III trials testing targeted therapies and in several other phase II investigations^{10,13,18,19,22,47,48} (**Table 1**). In the setting of phase III studies, ORR was 9–17% with sorafenib,^{10,13,18} 24% with lenvatinib,¹³ 10–12% with brivanib^{10,19} and 11% with regorafenib.²² In all studies, mRECIST ORR was superior to RECIST ORR (**Table 1**). Similarly, in single phase II studies, patients on nivolumab achieved an ORR of 19% by mRECIST (vs. 14% for RECIST),⁴⁸ while those on combination treatments with lenvatinib plus pembrolizumab,⁵⁴ or atezolizumab plus bevacizumab (n = 67) achieved ORRs of 42% or 34%,⁵⁵ both by mRECIST, respectively. Of note, most of the drugs approved by the FDA under the accelerated programme reported ORRs exceeding 30%.⁵⁶

The association between tumour response and improved OS in patients with HCC at advanced stages has been shown in at least 3 studies specifically addressing whether mRECIST ORR was an independent predictor of survival.^{45–47} Median

survival for responders vs. non-responders to lenvatinib or sorafenib was 22.4 months vs. 11.4 months (HR 0.61, $p < 0.001$);⁴⁶ to brivanib was 14.3 months vs. 9.4 months (HR 0.31; $p < 0.001$);⁴⁵ to nintedanib or sorafenib was 16.7 months vs. 10.9 months (HR 0.54; $p = 0.012$)⁴⁷ (**Table 1**). This data complement what was already known in patients treated with locoregional therapies at early and intermediate stages.^{41,47,57–61} As observed for other solid tumours treated with efficacious targeted therapies,^{62,63} the reported response rates are still sub-optimal for estimating the maximum number of responses needed to impact OS at the trial level.

The advent of immunotherapy has required modifications to the basic structure of the RECIST model in melanoma and other solid tumours treated with immunotherapies.^{64–68} Two features have been identified: A) response to immunotherapy may take longer than for other agents and B) response can be preceded by tumour flare or ‘pseudo-progression’, defined as an increase in the size of existing lesions or the appearance of new lesions, followed by a response.⁶⁴ Differentiating pseudo-progression from true progression is a challenging issue with important implications: while early discontinuation of an effective drug is not desirable, continued long-term treatment with a non-effective drug past true progression might delay the initiation of potentially effective therapies. In order to prevent misinterpretations, immune-related response criteria have been developed,^{67,68} including the concept of ‘confirmation of progression’ by a second scan obtained at least 4 weeks after PD has been registered.^{67–69}

Limited information is available concerning the use of immune-related criteria in the setting of HCC. None of the phase II studies, including ~400 patients, testing checkpoint inhibitors described tumour flares or pseudo-progression in HCC.^{48,49} In a phase II study of 104 patients who received pembrolizumab monotherapy in second line after sorafenib, the use of immune-related RECIST (irRECIST) did not affect response rate or time to response compared to mRECIST; however median PFS was 7.0 months (95% CI 4.9–8.0) when assessed by irRECIST vs. 3.2 months (95% CI 2.2–4.1) when registered according to mRECIST.⁴⁹ In a recent phase IIb study⁷⁰ investigating a vaccinia virus-based oncolytic immunotherapy – pexastimogene devacirepvec – in advanced HCC, changes to mRECIST were implemented because the tested treatment induces a flare response with swelling and oedema.⁷¹ These changes included the concept of confirmation at 4 weeks, either based on a further increase in size or additional signs of progression such as the emergence of new lesions.⁷⁰ Overall, in order to address assessment of response to checkpoint inhibitors or immunotherapies in HCC, we recommend evaluation by CT/MRI at 8–12 weeks after treatment, as opposed to the classic 6–8 weeks for tyrosine kinase inhibi-

Key point

Overall the response rates obtained with mRECIST are always higher than those obtained by RECIST, both when assessing local and systemic therapies.

Table 1. Assessment of objective response by mRECIST for locoregional and systemic therapies in the setting of phase II and III investigations.

Trial	Arms	n	ORR-mRECIST	ORR-RECIST	Median OS	ORR predicts survival	OS responders vs. non responders (HR; p value)
TACE							
BRISK-TA	TACE + brivanib	249	48%	n.a.	26.4		
	TACE + placebo	253	42%	n.a.	26.1		
SPACE	TACE + sorafenib	154	55%	n.a.	NR		
	TACE + placebo	153	41%	n.a.	NR		
Meta-analysis (7 studies)	TACE	1,357	62%	n.a.		Yes	0.38 (p < 0.0001)
First-line							
BRISK-FL* (10)	Brivanib	577	12%	n.a.	9.5		
	Sorafenib	578	8.80%	n.a.	9.9		
REFLECT* (13)	Lenvatinib	478	24.10%	18.80%	13.6	Yes	22.4 months vs. 11.4 months (0.61; p < 0.001)
SILIUS* (18)	Sorafenib	476	9.20%	6.50%	12.3		
	Sorafenib + HAIC	103	36.30%	n.a.	11.8		
BRISK-PS* (19)	Sorafenib	103	17.50%	n.a.	11.5		
	Brivanib	263	10%	n.a.	9.4	Yes	14.3 months vs. 9.4 months (0.31; p < 0.001)
	Placebo	132	1.50%	n.a.	8.2		
Second-line							
RESORCE* (22)	Regorafenib	379	11%	7%	10.6		
	Placebo	194	4.10%	3%	7.8		
Phase II	Nivolumab	145	19%	14%		Yes	NR vs. 13.4 months
Phase II	Pembrolizumab	104	15%	17%*			
Phase II	Nintedanib	180	15.60%	4.40%		Yes	16.7 months vs. 10.9 months (0.54; p = 0.012)

HAIC, hepatic arterial infusion chemotherapy; HR, hazard ratio; n.a., not applicable; NR, not reached; ORR, objective response rate; OS, overall survival; TACE, transarterial chemoembolisation.

* Both RECIST and irRECIST.

tors. This window was used in phase II studies testing nivolumab (12 weeks)⁴⁸ and pembrolizumab (9 weeks)⁴⁹ and is similar to that applied to Y-90 radioembolisation in 2 RCTs (12 weeks).^{14,15}

Assessment of time-to-event end points: PFS and TTP

The main time-to-event endpoints in oncology are PFS and TTP, both incorporating radiological tumour progression in their assessment. Differences in the assessment of progression between mRECIST²⁸ versus RECIST⁷² in HCC are based on: A) an increase of at least 20% in the sum of diameters of active target lesions (viable tumour) for mRECIST, as opposed to a 20% increase in the sum of diameters of target lesions (RECIST); B) for non-target lesions, mRECIST defines progression more conservatively, since i) lymph nodes should have at least a 20 mm short axis (as opposed to 15 mm for RECIST), ii) ascites and pleural effusions are not progression, except if there is cytological confirmation of malignancy; C) in terms of new lesions, progression refers to either new lesions >1 cm with hallmark HCC enhancement, or an interval increase in size of at least 1 cm for mRECIST (as opposed to RECIST that defines progression as any new lesion of 1 cm in diameter). Thus, overall mRECIST is considered a more conservative tool aimed at preventing the overreporting of progression.²⁸

PFS is a composite endpoint of 2 variables, death and radiological progression, whereas TTP

only considers the event of radiological tumour progression. Two phase III studies have assessed PFS and TTP by using both tools (mRECIST and RECIST).^{13,22} It is remarkable how similar or even identical the results are. Median PFS for lenvatinib was 7.3 and for sorafenib 3.6 months, regardless of the tool used.¹³ Similarly, PFS was almost identical for regorafenib (3.1–3.4 months) and identical for placebo 1.5 months with both methods.²² Even TTP for lenvatinib was identical regardless of the method used (median 7.4 months) and the same occurred with sorafenib (median 3.7 months).¹³ It is certainly difficult to explain these similarities, rather than pointing to the fact that some radiological charters already assume changes proposed by mRECIST (size of lymph nodes, presences of ascites, criteria to define a new HCC) even when assessing PFS/TTP by RECIST criteria. Nonetheless, this concept would require specific research for clarification.

PFS and TTP have a correlation with overall survival at the trial level, with $R^2 = 0.71$ and $R = 0.83$, respectively.⁴ However, a recent meta-analysis of 21 RCTs of phase III studies observed that significant differences for PFS and TTP did not unquestionably impact survival. In fact, only 3 out of 7 RCTs showing significant differences in PFS ultimately showed differences in OS.^{22,24,25} All cases with a positive correlation reported HR for PFS ≤ 0.6 (with 95% below 0.8). In addition, using mathematic modelling, this study extrapolated an estimated HR for PFS (sorafenib vs. placebo) in the SHARP trial⁷ of 0.6⁴ (Fig. 2). As a result, it

Key point

The use of optimised and consistent image acquisition protocols is crucial for the proper application of mRECIST and the accurate assessment of response.

was concluded that a conservative minimum surrogate threshold effect of HR ≤ 0.6 for PFS is highly predictive of a significant improvement in OS, whereas HR ranging from 0.6 to 0.7 is considered an uncertain surrogate.⁴ This information is important for the design of new trials where PFS is becoming the primary endpoint of phase III investigations for systemic therapies or combination strategies.

Finally, a brief consideration regarding the type of progression. Recent data suggest that at least 2 types of progression should be considered:^{73,74} occurrence of a new extrahepatic lesion and/or vascular invasion compared to progression due to growth of existing intrahepatic/extrahepatic lesions or the development of a new intrahepatic lesion. Better post-progression survival has been reported for the latter cases.^{73,74}

mRECIST clarifications and refinements

In this article, we will provide clarification and additional recommendations concerning the use of mRECIST in HCC response assessment by addressing, in particular, the following points: A) technical guidelines for image acquisition and contrast administration in CT and MRI; B) definition of typical and atypical intrahepatic lesions; C) selection, measurement, and assessment of target and non-target lesions; D) combination of viable tumour diameter measurements (for intrahepatic lesions with typical features) and overall tumour diameter measurements (for intrahepatic lesions with atypical features and extrahepatic lesions) for global patient assessment; E) differentiation of tumour necrosis and viable tumour with reduced arterial perfusion. A summary of key concepts is provided in Table 2.

Image acquisition guidelines

The use of optimised and consistent image acquisition protocols is key for proper application of mRECIST. Patients can be followed with either CT or MRI. Each modality has advantages and disadvantages, and mRECIST does not recommend one modality over another. However, it is recommended that the same imaging modality be used throughout the study. Ultrasound – including contrast-enhanced ultrasound – is not recommended for the general use of mRECIST, although this modality provides useful information on tumour response achieved in individual lesions, especially after local ablation therapies.⁷⁵ PET/CT is not accepted for treatment assessment in guidelines.^{1,31–34,37}

Obtaining a pre-contrast scan is useful but not mandatory for CT. Conversely, establishing the intrinsic T1 intensity of tumour lesions at baseline is recommended in MRI, in order to infer subsequent contrast enhancement or perform subtraction imaging.⁷⁶ The administration of intravenous contrast is recommended for all CT or MRI studies if not medically contraindicated.

In contrast-enhanced studies, it is crucial to time the contrast administration so that high-quality arterial-phase imaging is obtained on the first run, and high-quality portal venous-phase imaging is obtained on the second run. An arterial phase that is acquired too early (*i.e.*, when the hepatic arterial branches are fully enhanced but the portal vein is not yet enhanced) may be inadequate since the degree of enhancement of HCC is usually higher in the late arterial phase (*i.e.*, when the hepatic arterial branches are fully enhanced, the portal vein is also enhanced, but the hepatic veins are not yet enhanced).⁷⁶ Delayed imaging acquired 2 min to 5 min after injection may be useful, but it is not mandatory and should be done only if it is part of clinical practice. In MRI studies, when using a hepatobiliary contrast agent instead of an extracellular contrast agent, the hepatobiliary phase acquired about 20 min after injection of gadoxetate disodium may be used to aid lesion detection and diagnostic confidence.

We emphasise here that proper background expertise and skills are required for accurate and consistent application of mRECIST. Image interpretation should be performed by qualified radiolo-

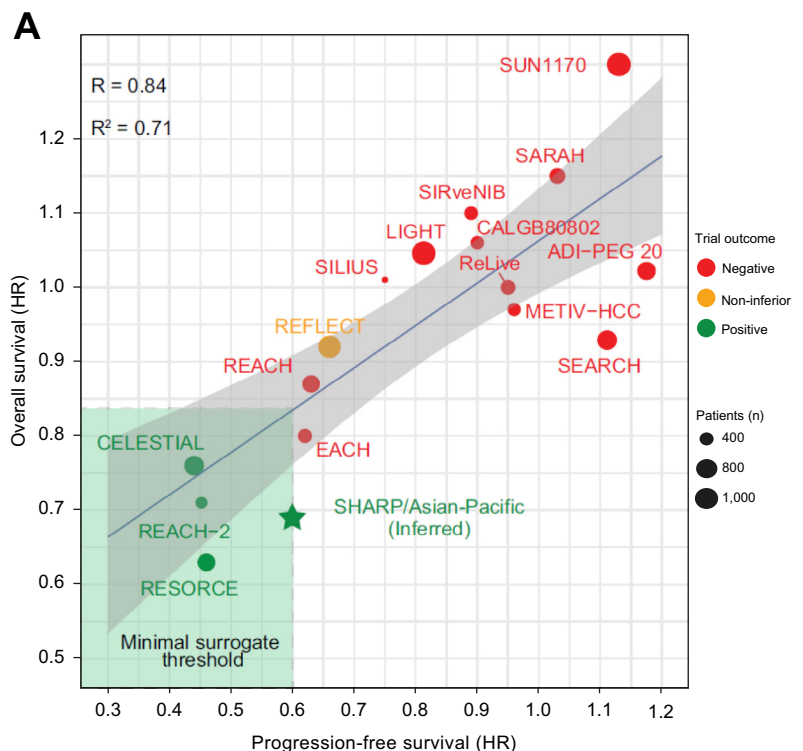


Fig. 2. Correlation between progression-free survival and overall survival (adapted from Llovet JM et al., J Hep 2019).⁴ Trial level correlation between endpoints. R and R2 refers to the weighted Pearson coefficient between the HR of PFS and the HR of TTP. Each dot represents one of the phase III clinical trials conducted on advanced HCC. Size of the dot is proportional to the total number of patients enrolled in the trial. Trials are coloured based on whether the final result was positive, negative or non-inferior for the primary endpoint (OS). X and Y axis depict the value of the HR for the surrogate TTP and PFS, respectively. Gray shaded areas represent the upper and lower limits of the 95% CIs for the regression. HCC, hepatocellular carcinoma; HR, hazard ratio; mRECIST, modified RECIST; OS, overall survival; PFS, progression-free survival; TTP, time-to-progression.

Table 2. Overall response assessment in mRECIST.*

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	NN	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes/no	PD
Any	PD	Yes/no	PD
Any	Any	Yes	PD

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NN, non CR, non PD.

*Adapted from Lencioni *et al.*, *Semin Liver Dis*: 2010;30:52–60.728.

gists with specific training. In clinical trials, the use of a blinded independent central review is recommended to provide more verifiable and uniform reader training, to ensure quality control of the images and the interpretations, and to decrease variability in image interpretations, leading to a more precise estimate of treatment effect.⁷⁷

Assessment of tumour lesions at baseline (Box 1)

Selection of target lesions

In principle, mRECIST can be applied by measuring up to a maximum of 2 target lesions per organ and 5 target lesions in total, following the schema of the 1.1 version of standard RECIST⁷² or up to a maximum of 5 target lesions per organ and 10 target lesions in total, following the schema of the original version of standard RECIST.²⁹ The available data do not show specific advantages of one method over another.^{51,78,79} Therefore, we recommend evaluations following the recent 1.1 version and, thus, include a maximum of 2 target lesions per organ and 5 target lesions in total. Other lesions (or sites of disease) should be identified

as non-target lesions and should also be recorded at baseline.

Tumour lesions selected as target lesions for mRECIST are required to be representative of the involved organs, to measure ≥ 1 cm in the longest diameter with CT or MRI, and to appear suitable for accurate and repeat measurements. Concerning the selection of intrahepatic target lesions, every effort should be made in order to include in this group the dominant tumour mass (if any), as long as it is considered suitable for accurate and repeat measurements. In addition, in the process of target lesion selection, mRECIST recommends that intrahepatic lesions with typical imaging features are prioritised over intrahepatic lesions with atypical features. In fact, for typical intrahepatic lesions, mRECIST allows one to measure the longest viable tumour diameter instead of the overall tumour diameter, like standard RECIST. However, this modification is neither applicable to intrahepatic lesions with atypical features nor to extrahepatic lesions. Thus, at the patient level, mRECIST assessment is a combination of viable tumour diameter measurements (intrahepatic lesions with typical features) and overall tumour diameter measurements (intrahepatic lesions with atypical features and extrahepatic lesions).

Definition of typical intrahepatic lesion

For the purpose of target lesion selection at baseline, mRECIST defines an intrahepatic HCC lesion that shows intratumoural (*i.e.*, non-rim-like) arterial enhancement on contrast-enhanced CT or MRI as “typical”. This is considered as the hallmark of HCC.^{1,31–34,37} Additional imaging characteristics of HCC, such as non-peripheral washout in the portal venous or the delayed phase, or the presence of a capsule, are not required to classify an

Box 1. Basic concepts and key points for baseline mRECIST assessment in HCC.

Assessment of tumour lesions at baseline

Target lesions

Selection of target lesions:

- Identify intrahepatic tumour lesions ≥ 1 cm in longest diameter that show intratumoural arterial enhancement and appear suitable for accurate and repeat measurement. Select up to 2 lesions with these characteristics as typical intrahepatic target lesions.
- If 2 typical intrahepatic target lesions have been identified, move to the next point. Otherwise, identify intrahepatic tumour lesions ≥ 1 cm in longest diameter, that appear suitable for accurate and repeat measurement but do not depict intratumoural enhancement. Lesions with these characteristics can be selected as atypical intrahepatic target lesions, taking into account that the maximum overall number of intrahepatic target lesions (typical lesions plus atypical lesions) shall not exceed 2.
- Identify extrahepatic tumour lesions ≥ 1 cm in longest diameter, that appear suitable for accurate and repeat measurement. Up to 2 lesions per organ with these characteristics can be selected, taking into account that the maximum overall number of target lesions (intrahepatic plus extrahepatic) shall not exceed 5.
- When selecting lymph nodes as extrahepatic target lesions, the short axis must measure at least 1.5 cm, except for porta hepatis lymph nodes that should measure ≥ 2 cm.

Measurement of target lesions:

- Measure the longest viable tumour diameter of typical intrahepatic target lesions, avoiding major areas of internal necrosis.
- Measure the longest overall tumour diameter of atypical intrahepatic target lesions and non-nodal extrahepatic target lesions.
- Measure the short axis diameter of nodal target lesions.
- Calculate the baseline sum of diameters of target lesions.

CR, complete response; HCC, hepatocellular carcinoma; PD, progressive disease.

intrahepatic lesion as typical. In fact, the presence of intratumoural enhancement is used in mRECIST to enable detection and delineation of viable tumour tissue in order to capture any subsequent necrosis induced by the treatment, rather than for diagnostic purposes. The assumption is that the diagnosis of HCC has already been established before the patient has been scheduled to receive anticancer treatment. Individual intrahepatic nodules of equivocal malignancy are an exception to this general rule, for which the same strict criteria used to diagnose a newly detected intrahepatic lesion as unequivocal HCC are recommended.

Definition of atypical intrahepatic lesion

Atypical intrahepatic lesions are defined in mRECIST as non-enhancing lesions, *i.e.*, lesions that do not show the intratumoural arterial enhancement pattern described above. These atypical HCC features may be observed in very well differentiated tumours with immature neovascularity, steatotic and scirrhous tumours, and poorly differentiated tumours with infiltrative appearance.⁸⁰ The definition of atypical lesions includes HCC tumours with rim-like arterial enhancement, in which neovascularity is concentrated mainly in the tumour periphery and frequently occurs in conjunction with central ischaemia and/or necrosis.⁷⁶

It is important to note that, in a non-negligible percentage of cases, the absence of intratumoural enhancement is not related to the atypical vascular pattern of the tumour, but rather to a mistiming of the arterial phase.⁷⁶ An arterial phase that is acquired too early – before the start of enhancement in the portal vein – may be inadequate, as tumour lesions may not be enhanced or fully enhanced yet.⁷⁶ Radiologists interpreting the imaging study should decide whether viable tumour tissue can be identified and delineated after a comprehensive review of all the available scans: if the answer is positive, the viable tumour diameter can be captured according to mRECIST recommendations. Otherwise, if the measurement of the viable tumour component appears to be potentially inaccurate and/or inconsistent, then the overall tumour diameter should be registered, as for extrahepatic lesions. Atypical intrahepatic lesions, in which the mRECIST viable tumour concept cannot be applied, can only be selected as target lesions if the number of typical intrahepatic lesions is not adequate.

Intrahepatic lesions treated with prior locoregional therapy

Intrahepatic HCC lesions treated with prior locoregional therapies may or may not be suitable to be selected as target lesions, depending on the imaging features. If, after locoregional therapy, residual or recurrent tumour can be detected as a well-

delineated enhancing area that has a longest diameter of at least 1 cm, then the lesion can be considered as typical and measured according to the mRECIST concept of viable tumour. In this regard, it has been shown that in patients who received prior TACE with lipiodol, dense iodised oil deposits observed within the tumour on CT scans should be assumed to represent necrosis rather than viable neoplastic tissue, and therefore should be excluded from the measurement of the longest viable tumour diameter.^{81,82} In contrast, when residual or recurrent viable tumour and necrotic phenomena induced by the prior intervention coexist and are irregularly mixed, identification and delineation of the viable tumour component may be inaccurate and/or inconsistent, and therefore these lesions should not be selected as target lesions for mRECIST. Finally, intrahepatic nodules that show imaging features consistent with complete response induced by prior locoregional treatments should neither be included in the target lesion group nor in the non-target lesion group, since they no longer represent detectable active tumour.

Special considerations for lymph nodes

Lymph nodes should be measured in the short axis, since it is a more reproducible measurement and, when enlarged, is highly predictive of malignancy.⁸³ Standard RECIST version 1.1 recommends that lymph nodes with a short axis of at least 1.5 cm are considered measurable and assessable as target lesions.⁸³ In patients with chronic liver disease, however, enlarged abdominal lymph nodes due to benign nodal hyperplasia are found on imaging in about 50% of cases.⁸⁵ The most common location of benign enlarged nodes is around the porta hepatis, including the portocaval space and the gastrohepatic ligament.⁸⁴ Their short axis is usually smaller than 2 cm⁸⁴. The mRECIST guideline states that lymph nodes detected at the porta hepatis can only be considered as malignant if their short axis is at least 2 cm²⁸. Lymph nodes in other anatomic locations will follow the recommendations issued by standard RECIST 1.1 and will be considered measurable target lesions if their short axis is at least 1.5 cm⁸³.

Selection of target lesions: key points

- Identify intrahepatic tumour lesions ≥ 1 cm in longest diameter that show intratumoural arterial enhancement and appear suitable for accurate and repeat measurement. Select up to 2 lesions with these characteristics as typical intrahepatic target lesions.
- If 2 typical intrahepatic target lesions have been identified, move to the next point. Otherwise, identify intrahepatic tumour lesions with a longest diameter ≥ 1 cm that appear suitable for accurate and repeat measurement but do not depict intratumoural enhancement. Lesions

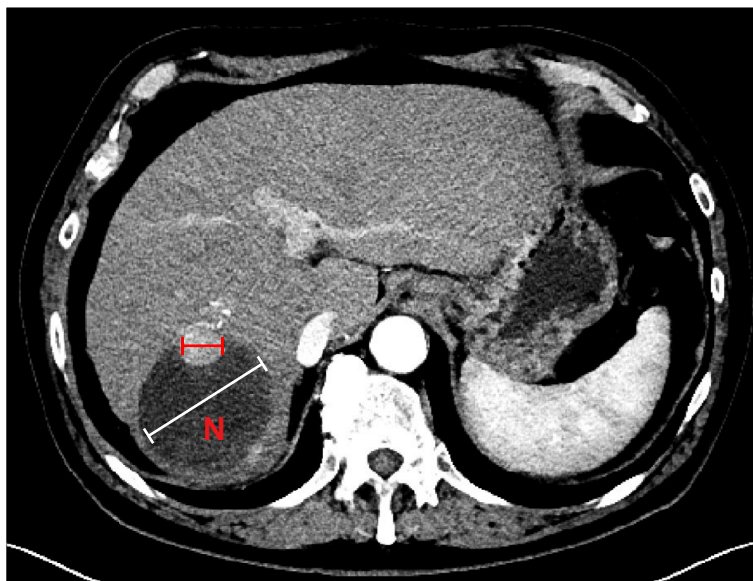


Fig. 3. Measurement of the longest tumour diameter in a target hepatic lesion: mRECIST vs. standard RECIST. Arterial-phase CT scan obtained after systemic targeted therapy. According to standard RECIST, the overall longest diameter of the tumour is captured (white arrow), regardless of the presence of a large area of intratumoural treatment-induced necrosis ("N"). In contrast, mRECIST measurement (red arrow) only includes the longest diameter of the viable portion of the tumour, as recognized by contrast enhancement. mRECIST, modified RECIST.

with these characteristics can be selected as atypical intrahepatic target lesions, taking into account that the maximum overall number of intrahepatic target lesions (typical lesions plus atypical lesions) shall not exceed 2.

- Identify extrahepatic tumour lesions with a longest diameter ≥ 1 cm, that appear suitable for accurate and repeat measurement. Up to 2 lesions per organ can be selected with these characteristics, taking into account that the maximum overall number of target lesions (intrahepatic plus extrahepatic) shall not exceed 5.
- When selecting lymph nodes as extrahepatic target lesions, the short axis must measure at least 1.5 cm, with the exception of porta hepatis lymph nodes that should measure ≥ 2 cm.

Measurement of target lesions

According to standard RECIST 1.1, the baseline sum of diameters of the target lesions, to which subsequent measurements will be compared for the determination of response, is obtained by calculating the sum of the longest diameters of non-nodal target lesions and the short axis diameters of nodal target lesions.⁷²

The mRECIST guideline has introduced the concept of viable tumour to take into account the mechanisms of action of treatments other than cytotoxic drugs, that can induce tumour necrosis without leading to substantial shrinkage.²⁸ According to mRECIST, it is the longest diameter

of the viable portion of the tumour – not the longest overall tumour diameter – that must be measured and used for subsequent comparisons. Viable tumour is defined as tumour showing enhancement in the arterial phase of contrast-enhanced CT or MRI²⁸ (Fig. 3). Therefore, when capturing the baseline measurement of longest diameter, areas of internal tumour necrosis (either spontaneous necrosis or necrosis induced by prior treatments) should be avoided. The following recommendations should be followed for the determination of the longest viable tumour diameter of the target lesions: i) the longest diameter of the viable portion of the tumour may or may not be located at the same anatomical level of the longest overall lesion diameter: a thorough evaluation of CT or MRI scans is required; ii) measurement of the longest viable tumour diameter should not include any major intervening areas of necrosis and iii) measurement of the longest viable tumour diameter should be preferentially obtained on arterial-phase images, in which the contrast between enhancing viable tumour tissue and non-enhancing necrotic tissue is usually the highest. However, radiologists can use portal venous-phase images for measurements if, in individual patients, the viable tumour component appears to be better delineated in these scans.

As discussed above, the measurement of the longest viable tumour diameter should only be used for typical intrahepatic target lesions. In contrast, for atypical intrahepatic target lesions, as well as for extrahepatic target lesions, the longest overall tumour diameter (irrespective of the presence of internal areas of necrosis) should be measured. For nodal lesions selected as target lesions, the short axis diameter – defined as the widest dimension perpendicular to the long axis – should be measured.

Therefore, the baseline sum of diameters of the target lesions will be the sum of the longest viable tumour diameter of typical intrahepatic target lesions, plus the sum of the longest overall tumour diameter of atypical intrahepatic target lesions and non-nodal extrahepatic target lesions, plus the sum of the short axis diameters of nodal target lesions.

Measurement of target lesions: key points

- Measure the longest viable tumour diameter of typical intrahepatic target lesions, avoiding major areas of internal necrosis.
- Measure the longest overall tumour diameter of atypical intrahepatic target lesions and non-nodal extrahepatic target lesions.
- Measure the short axis diameter of nodal target lesions.
- Calculate the baseline sum of diameters of target lesions.

Key point

mRECIST incorporates the concept of viable tumour, which is an important consideration as new treatments may induce tumour necrosis without leading to tumour shrinkage.

Assessment of non-target lesions

Tumour lesions (or sites of disease) that have not been selected as target lesions should be identified as non-target lesions and should also be recorded at baseline. These may include typical intrahepatic lesions, as well as atypical intrahepatic lesions and extrahepatic lesions. It is especially recommended to include in this group the dominant intrahepatic tumour mass (if any) in all individuals in whom that lesion was considered unsuitable for accurate and repeat measurements, for instance because of its infiltrative appearance with ill-defined borders, and therefore not already included in the target lesion group. In addition, reporting any extrahepatic tumour manifestations in the non-target lesions group that have not already been captured in the target lesions group is recommended. Measurements of non-target lesions are not required, but the presence or absence of each should be noted throughout follow-up. The following recommendations should be followed in the baseline assessment of non-target lesions: A) The presence of malignant portal vein thrombosis should always be noted and considered as a non-target lesion due to the difficulty in performing consistent repeat measurements of the malignant thrombus. In addition, accurate measurement of the malignant thrombus may be impaired by the possible presence of a bland component of the thrombosis, that may progress or regress over time,⁸⁵ B) Ascites and

pleural effusion should not be considered as tumour lesions – and therefore should not be selected as non-target lesions – unless associated with unequivocal neoplastic peritoneal or pleural nodules or when cytological confirmation of their malignant nature is available. In fact, benign ascites and pleural effusion occur commonly in patients with cirrhosis,¹ and C) lymph nodes detected at the porta hepatis can be considered as malignant only if their short axis is at least 2 cm. This cut-off value of course applies to both target and non-target lesions.

Assessment of tumour response (Box 2)

Overall patient response at a given post-baseline timepoint is the result of the combined assessment of response in target lesions and non-target lesions. In addition, overall patient response is dependent on the presence or absence of new tumour lesions. In order to prevent tumour progression being reported prior to the completion of a given locoregional therapy, it is recommended that response be assessed by mRECIST once the treatment of all lesions has been completed.

Target lesion response

According to standard RECIST 1.1, complete response (CR) is the disappearance of all target lesions (including all lymph node short axis diam-

Box 2. Basic concepts and key points for mRECIST response assessment in HCC.

Assessment of tumour response

Target lesions

- Measure the longest viable tumour diameter of typical intrahepatic target lesions, considering that the longest viable tumour diameter may or may not be located in the same scan plane in which the baseline longest viable tumour diameter was measured
- In presence of multiple intratumoural areas of enhancing viable tumour surrounded by areas of necrosis within the same typical intrahepatic target lesion, only the longest viable tumour diameter should be captured, by avoiding the inclusion of any major intervening areas of necrosis.
- Carefully distinguish areas of tumour necrosis from areas of reduced arterial perfusion caused by changes in local haemodynamics. A change from hypervascularity to hypovascularity does not represent tumour necrosis. Only tumours or tumour areas that show complete absence of contrast enhancement can be assumed to represent necrotic tissue and therefore be excluded from the measurement of the longest viable tumour diameter in mRECIST. Subtraction imaging or quantitative determinations of contrast uptake using regions of interest can be used to support the assessment.
- Measure the longest overall tumour diameter for atypical intrahepatic target lesions and non-nodal extrahepatic target lesions, and the short axis diameter for nodal target lesions.
- Calculate the sum of diameters of target lesions.

Non-target lesions

- Tumour necrosis should be considered when assessing response of typical intrahepatic non-target lesions.
- Complete disappearance of enhancement inside malignant portal vein thrombus should be considered equivalent to CR.
- Ascites or pleural effusion that appear or worsen during treatment should not be assumed to represent PD, unless associated with the emergence or the unequivocal progression of neoplastic peritoneal or pleural nodules or when cytological confirmation of their malignant nature is available.

New HCC lesions

- By definition, a new liver lesion has no corresponding lesion on the baseline imaging.
- A new liver lesion ≥ 1 cm that shows non-rim-like hypervascularisation in the arterial phase with non-peripheral washout in the portal venous or the delayed phase meets the criteria for unequivocal new lesion and declares PD.
- Any new liver lesion < 1 cm or any new liver lesion of any size that fails to show the enhancement pattern described above should be considered as equivocal and can only be diagnosed as HCC by evidence of either a change in enhancement pattern (when ≥ 1 cm) or an interval growth ≥ 1 cm in subsequent scans.
- If an equivocal new lesion is later determined to be unequivocal, the timepoint of progression will be the timepoint that the lesion was first noted as equivocal.

CR, complete response; HCC, hepatocellular carcinoma; PD, progressive disease.

eters regressed to normal, *i.e.*, short axis that shrinks to <1 cm); partial response (PR) is at least a 30% decrease in the sum of the pertinent diameters of the target lesions, taking as reference the baseline sum of diameters; PD is at least a 20% increase in the sum of diameters of the target lesions, taking as reference the nadir (smallest sum of diameters recorded since baseline; including a minimum of 5 mm absolute increase); stable disease (SD) is neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

The mRECIST for HCC has introduced the following amendments to standard RECIST 1.1 in the definition of tumour response for typical intrahepatic target lesions: CR is the disappearance of any intratumoural arterial enhancement in all target lesions; PR is at least a 30% decrease in the sum

of the longest viable tumour diameters of target lesions, taking as reference the baseline sum of the longest viable tumour diameters of target lesions; PD is at least a 20% increase in the sum of the longest viable tumour diameters, taking as reference the nadir sum of diameters of target lesions recorded since treatment started; and SD is any case that shows neither sufficient decrease to qualify for PR nor sufficient increase to qualify for PD.

When measuring the longest viable tumour diameter of typical intrahepatic target lesions, the recommendations provided above for baseline assessment also apply to measurements obtained at any post-baseline timepoints. In addition, the following recommendations should be followed (Figs. 4 and 5): A) The longest viable tumour diam-

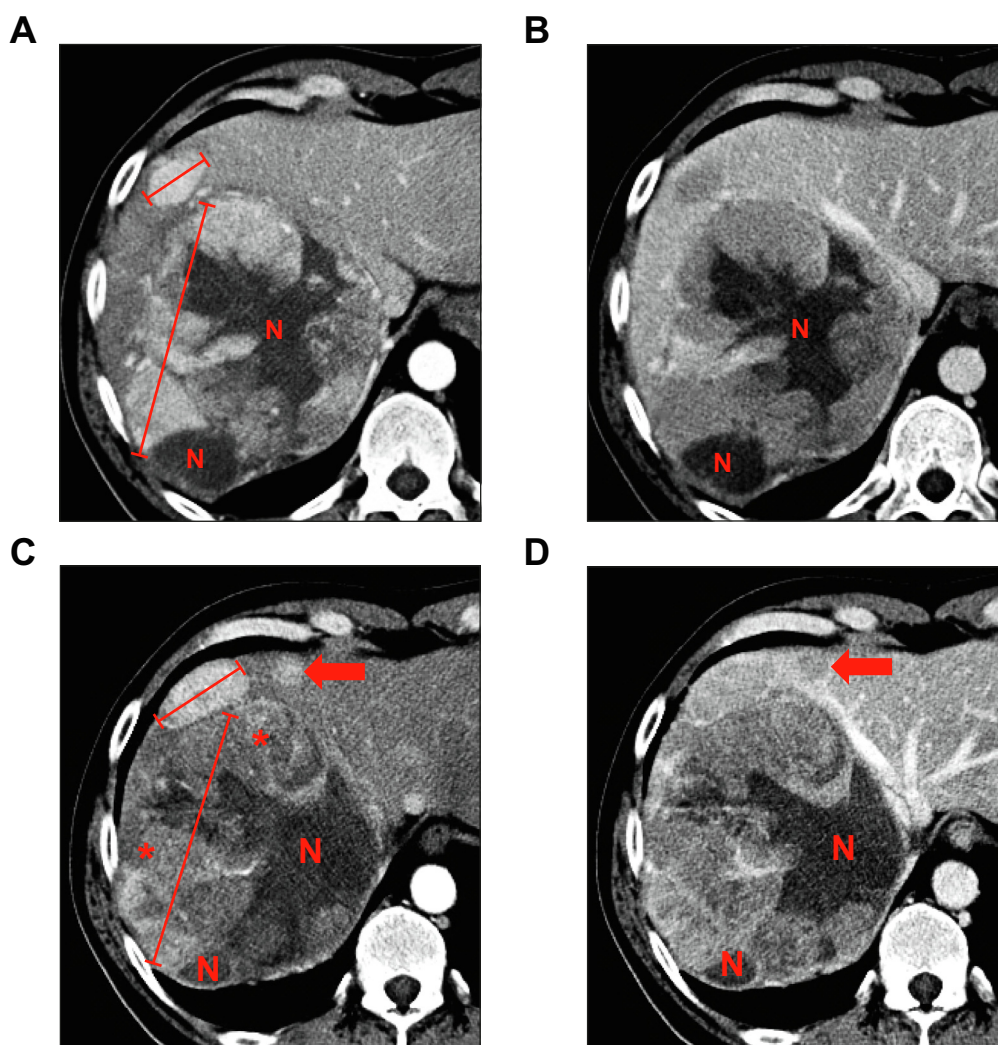


Fig. 4. Differentiation between spontaneous tumour necrosis and viable tumour with reduced arterial perfusion. Baseline (A) arterial phase and (B) portal venous phase CT scans: 2 lesions with typical vascular pattern are selected as mRECIST target lesions and the longest viable tumour diameters are measured in the (A) arterial-phase scan by avoiding the inclusion of major intervening areas of spontaneous necrosis (“N”). In the (C) arterial phase and (D) portal venous phase CT scans obtained after treatment with systemic targeted therapy, the viable portion of the larger tumour shows reduced arterial perfusion (* in C) with respect to baseline; however, it still shows unequivocal contrast uptake (the level of arterial enhancement is similar to that of liver parenchyma) and can be distinguished from the non-enhancing areas of necrosis (“N”). (C) The longest viable tumour diameter of both lesions is measured. Note also the appearance of an unequivocal 1 cm new lesion (arrows in C and D). mRECIST, modified RECIST.

eter may or may not be located at the same anatomical level in which the longest viable tumour diameter was measured at baseline: a thorough evaluation of CT or MRI scans is required; B) In the presence of multiple intratumoural areas of enhancing viable tumour surrounded by areas of necrosis within the same target lesion, only the longest viable tumour diameter should be captured, by avoiding the inclusion of any major intervening areas of necrosis, and C) Reduced arterial perfusion, either involving the whole tumour mass or circumscribed to intratumoural areas, must be distinguished from necrosis. Changes from hypervascularity to

hypovascularity observed in post-baseline CT or MRI scans compared to baseline may be due to the use of a different contrast injection protocol or to changes in local haemodynamics (*i.e.*, caused by the administration of antiangiogenic drugs).⁸⁶ The mRECIST guideline defines response as the disappearance of any intratumoural arterial enhancement.²⁸ Only tumours or tumour areas that show complete absence of contrast uptake can be assumed to represent necrotic tissue and, as such, be excluded from the measurement of the longest viable tumour diameter. As in clinical radiology practice, subtraction imaging or quantitative determinations of contrast uptake obtained

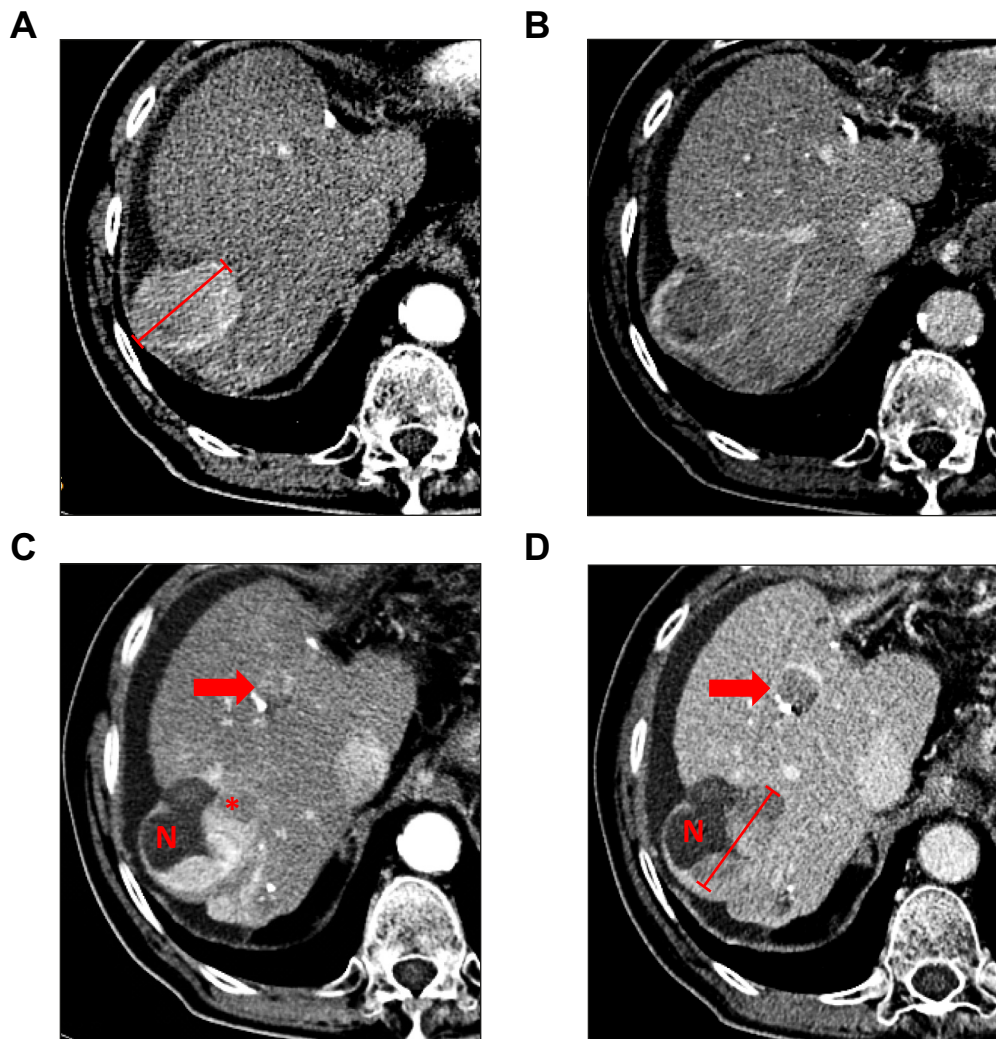


Fig. 5. Differentiation between treatment-induced tumour necrosis and viable tumour with reduced arterial perfusion. Baseline (A) arterial phase and (B) portal venous phase CT scans. The tumour shows typical vascular profile, with arterial enhancement and portal venous washout. The longest viable tumour diameter is measured in the arterial phase, in which the tumour is better delineated (A). In the (C) arterial phase and (D) portal venous phase CT scans obtained after treatment with systemic targeted therapy, the tumour shows an area of treatment-induced necrosis (“N”) that fails to show any contrast enhancement. The area of necrosis can be distinguished from the area indicated by the asterisk, that, despite the reduced arterial perfusion compared to baseline, still shows unequivocal contrast uptake, consistent with viable tumour (C). The longest viable tumour diameter is obtained in the portal venous phase, in which viable tumour is better delineated, and includes the area of reduced perfusion (C). Note also the appearance of an unequivocal new lesion with typical vascular pattern (arrows in C and D).

by comparing relevant regions of interest measurements on pre-contrast and post-contrast scans can be used, whenever considered appropriate, to support the assessment.

It is important to remember that the concept of “viable tumour” measurement by mRECIST can only be applied to lesions classified as typical intrahepatic target lesions at baseline. Any atypical intrahepatic target lesion or extrahepatic target lesion will be measured following standard RECIST metrics, *i.e.*, by capturing the longest overall diameter. Thus, the following definitions should be used for the determination of overall target lesion response at a given post-baseline timepoint:

- Complete response = disappearance of any intratumoural arterial enhancement in all typical intrahepatic target lesions AND disappearance of all atypical intrahepatic target lesions and extrahepatic target lesions. Nodal lesions with short axis diameters regressed to <1 cm are considered normal.
- Partial response = at least a 30% decrease in the sum of diameters of the target lesions (including viable tumour diameters for typical intrahepatic target lesions and short axis diameters for nodal lesions), taking as reference the baseline sum of the longest diameters.
- Progressive disease = at least a 20% increase AND an absolute increase of at least 5 mm in the sum of diameters of the target lesions (including viable tumour diameters for typical intrahepatic target lesions and short axis diameters for nodal lesions), taking as reference the nadir sum of diameters recorded since baseline.
- Stable disease = neither sufficient decrease to qualify for PR nor sufficient increase to qualify for PD.
- Not evaluable = at least 1 target lesion is not evaluable and the change in the sum of diameters of the measurable target lesions does not meet the criteria for PD.

It is important to acknowledge that the longest viable diameter of typical intrahepatic target lesions or the longest overall diameter of atypical intrahepatic target lesions or extrahepatic target lesions may become too small to be accurately measured. In this case, the default value for such “too small to measure” lesions is 5 mm. Under the same rationale, a minimum absolute increase of 5 mm in the sum of diameters of the target lesions has been included – in addition to the 20% increase – as a requirement to declare PD. If a typical intrahepatic target lesion fails to show any intratumoural arterial enhancement or an atypical intrahepatic target lesion or an extrahepatic target lesion completely resolves or disappears, 0 mm should be recorded. Lymph nodes that shrink to <1 cm short axis are also considered normal.

Key point

mRECIST has already proven to be a hugely useful tool for the assessment of response in early/intermediate HCC, while its relevance in advanced HCC is likely to continue growing.

Individual lesions that are identified at baseline but not measurable or assessable at follow-up timepoints should be assessed as “not evaluable”. This could be because they are not imaged or the imaging is technically inadequate to measure/assess the lesion(s), because of inconsistent timing of post-contrast scanning for example. If at least 1 target lesion is not evaluable at a timepoint, then the target lesion response for that timepoint should be considered not evaluable unless the change in the sum of diameters of the measurable target lesions meets the criteria for PD; then PD should be recorded.

Target lesions response: key points

- Measure the longest viable tumour diameter of typical intrahepatic target lesions, considering that the longest viable tumour diameter may not be located in the same scan plane in which the baseline longest viable tumour diameter was measured.
- In presence of multiple intratumoural areas of enhancing viable tumour surrounded by areas of necrosis within the same typical intrahepatic target lesion, only the longest viable tumour diameter should be captured, by avoiding the inclusion of any major intervening areas of necrosis.
- Carefully distinguish areas of tumour necrosis from areas of reduced arterial perfusion caused by changes in local haemodynamics. A change from hypervascularity to hypovascularity does not represent tumour necrosis. Only tumours or tumour areas that show a complete absence of contrast enhancement can be assumed to represent necrotic tissue and therefore be excluded from the measurement of the longest viable tumour diameter in mRECIST. Subtraction imaging or quantitative determinations of contrast uptake using regions of interest can support the assessment.
- Measure the longest overall tumour diameter for atypical intrahepatic target lesions and non-nodal extrahepatic target lesions, and the short axis diameter for nodal target lesions.
- Calculate the sum of diameters of target lesions.

Non-target lesion response

Standard RECIST criteria for the determination of non-target lesion responses include: CR, disappearance of all non-target lesions; non-CR–non-PD, persistence of ≥ 1 non-target lesions; and PD, unequivocal progression of non-target lesions. According to mRECIST, tumour necrosis should be considered when assessing responses to typical intrahepatic lesions: the disappearance of ANY intratumoural arterial enhancement in such non-target lesions should be considered equivalent to CR, while the persistence of areas of intratumoural arterial enhancement should be considered equivalent to non-CR–non-PD. Recommendations for the assessment of non-target lesions at baseline were reported above.

Specific recommendations have been issued by mRECIST concerning portal vein thrombosis, ascites and pleural effusion that appear or worsen with respect to baseline. In individuals with portal vein thrombosis, complete disappearance of enhancement inside the malignant thrombus should be considered equivalent to CR. Ascites or pleural effusion that appear (or worsen) during treatment should not be assumed to represent PD if the measurable tumour has met criteria for CR, PR, or SD, unless associated with the emergence (or the unequivocal progression) of peritoneal or pleural nodules or when cytological confirmation of their malignant nature is available. In fact, ascites and pleural effusion can appear (or worsen) at any post-baseline timepoint regardless of tumour progression, because of hepatic decompensation caused by either the natural evolution of chronic liver disease, or treatment.

Assessment of non-target lesion responses includes individual non-target lesion assessment, as well as an overall assessment of non-target disease at each timepoint. The following definitions should be used for the determination of overall non-target lesion responses at a given post-baseline timepoint:

- Complete response = disappearance of any intratumoural arterial enhancement in all typical intrahepatic non-target lesions **AND** disappearance of all atypical intrahepatic non-target lesions and extrahepatic non-target lesions (including all nodal lesions regressing to normal size).
- Non-CR–non-PD = persistence of intratumoural arterial enhancement in ≥ 1 typical intrahepatic non-target lesions **OR** persistence of atypical intrahepatic non-target lesions or extrahepatic non-target lesions (including any nodal lesions not regressing to normal size).
- Progressive disease = unequivocal progression of typical intrahepatic non-target lesions **OR** unequivocal progression of atypical intrahepatic non-target lesions or extrahepatic non-target lesions.
- Not evaluable = ≥ 1 non-target lesion is not evaluable and the assessable non-target lesions do not meet the criteria for PD.

Non-target lesions response: key points

- Tumour necrosis should be considered when assessing the response of typical intrahepatic non-target lesions.
- Complete disappearance of enhancement inside malignant portal vein thrombus should be considered equivalent to CR.
- Ascites or pleural effusion that appear or worsen during treatment should not be assumed to represent PD, unless associated with the emergence or the unequivocal progression of

neoplastic peritoneal or pleural nodules, or when cytological confirmation of their malignant nature is available.

New HCC lesions (Box 2)

In standard RECIST, the appearance of ≥ 1 new lesion(s) indicates progression, irrespective of the response of target and non-target lesions. This concept has been endorsed by the mRECIST guideline. However, mRECIST states that the characterisation of a newly detected focal liver lesion as a true HCC is a challenging issue in the setting of chronic liver disease, since pathologic changes inherent to the cirrhotic process – such as the development of large regenerative nodules and dysplastic nodules – may be indistinguishable from a small tumour.⁸⁷ Moreover, the clear-cut separation of the hepatic phases of liver enhancement routinely achieved by state-of-the-art CT or MRI creates additional problems in a cirrhotic liver, mostly related to the presence of perfusion abnormalities resulting in areas of abnormal liver enhancement. In most cases, such perfusion abnormalities are detected as arterially hyper-enhancing areas caused by a selective impairment of the portal venous feeding. Such perfusion abnormalities may ultimately mimic or conceal focal liver lesions, and thus, they represent an additional major source of interpretation errors.^{1,31–34,37,87}

The mRECIST guideline provides strict recommendations for the classification of newly detected focal liver lesions, based on the well-established criteria endorsed by several scientific societies and organisations for the diagnosis of HCC in cirrhosis:⁷⁶ A) A new liver lesion can be classified as HCC – and therefore considered as unequivocal evidence of progression – when its longest diameter is ≥ 1 cm and the nodule shows non-rim-like hypervascularisation in the arterial phase with non-peripheral washout in the portal venous or the delayed phase; B) Any new liver lesion < 1 cm or any new liver lesion of any size that fails to show the enhancement pattern described above should be considered as equivocal, unless associated with unequivocal evidence of malignancy such as vascular invasion, and C) Equivocal lesions can be diagnosed as HCC by evidence of either a change in enhancement pattern (when ≥ 1 cm) or an interval growth ≥ 1 cm in subsequent scans (Fig. 6).

To prevent artificial prolongation of time-to-progression, the mRECIST guideline states that any individual radiological event can be adjudicated in retrospect as progression at the time it was first detected by imaging techniques, even if strict criteria were fulfilled only on subsequent radiological testing.

For extrahepatic lesions, standard RECIST criteria will be applied: any lesion that is detected at a given post-baseline timepoint and has no corre-

Key point

mRECIST incorporates specific recommendations for the assessment of response in patients with portal vein thrombosis, ascites and pleural effusion.

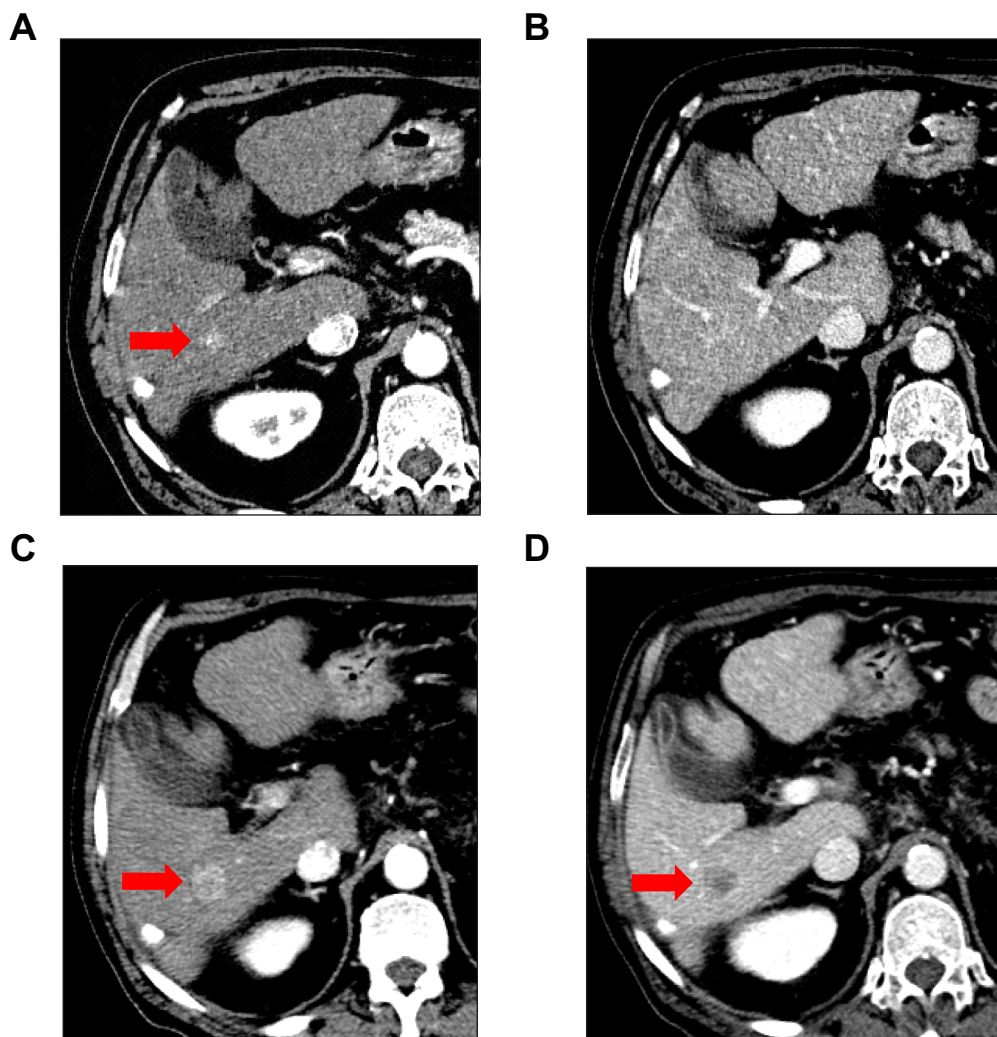


Fig. 6. Equivocal new lesion determined to be unequivocal at subsequent time point. (A) Arterial phase and (B) portal venous phase CT scans obtained at post-baseline time point 2. A new lesion is detected (arrow in A). However, the lesion is smaller than 1 cm and shows (A) arterial hypervascularization without (B) venous washout. The new lesion must be considered equivocal. (C) Arterial phase and (D) portal venous phase CT scans obtained at post-baseline timepoint 3: the lesion is now larger than 1 cm and shows (C) arterial hypervascularisation with (D) portal venous washout. Thus, it meets the criteria for unequivocal diagnosis of HCC, and can be considered as evidence of progressive disease. However, the time point of progression will be time point 2, the time point that the lesion was first noted as equivocal. HCC, hepatocellular carcinoma.

sponding lesion on baseline imaging is unequivocally malignant and will be considered as evidence of disease progression.

New lesions: key points

- By definition, a new liver lesion has no corresponding lesion on baseline imaging.
- A new liver lesion ≥ 1 cm that shows non-rim-like hypervascularisation in the arterial phase with non-peripheral washout in the portal venous or the delayed phase should be considered an unequivocal new lesion, indicating PD.
- Any new liver lesion < 1 cm or any new liver lesion of any size that fails to show the enhancement pattern described above should be considered as equivocal and can only be diagnosed as HCC by evidence

of either a change in enhancement pattern (when ≥ 1 cm) or an interval growth ≥ 1 cm in subsequent scans.

- If an equivocal new lesion is later determined to be unequivocal, the time point of progression will be the time point that the lesion was first noted as equivocal.

Overall response assessment by mRECIST

Overall patient response at a given time point is a result of the combined assessment of the 3 categories of target lesions, non-target lesions, and new lesions. It is important to remember that evidence of progression in any of these categories indicates overall disease progression, irrespective of the assessment recorded for the other categories. However, it is important that the specific

category or categories that declared progression are clearly noted. While overall disease progression may be captured by isolated progression of non-target lesions, it has to be acknowledged that this is exceptional, and that unequivocal findings are required to confirm PD based on such a qualitative assessment. Disease progression caused by the emergence of new lesions is not rare in the setting of HCC. However, only new lesions that meet the reported criteria should be considered as unequivocal and therefore trigger PD. Overreporting of equivocal nodules as new HCC have a major impact on overall response assessment. The possible combinations of tumour responses in target and non-target lesions with or without the appearance of new lesions are reported in [Table 2](#). Of note, mRECIST has shown good to excellent inter-observer agreement, with kappa values that are similar or higher with respect to those reported for standard RECIST in the same series.^{88,89}

Conclusions and future prospects

The implementation of mRECIST in clinical practice guidelines (recently also adopted by Korean Guidelines⁹⁰), clinical trials and clinical practice has surpassed any expectation when the seminal paper was published.²⁸ Herein, we have pointed to the fact that assessment of radiological response and progression will be critical for the novel era of trial design in HCC. With the advent of combination regimens and several drug approvals, it has been apparent that benefits obtained in certain lines of therapy can be overridden by subsequent treatments. Thus, objective responses and time-to-event endpoints warrant more attention in future phase III investigations, even as primary endpoints. mRECIST is already the standard tool for measuring radiological endpoints at early and intermediate stages of HCC, and evidence is growing regarding its relevance in advanced HCC. In fact, a recent meta-analysis pointed to a clear correlation between PFS and OS, defining a PFS threshold for capturing a true survival benefit. In addition, ORR assessed by mRECIST was demonstrated to be an independent predictor of survival in 3 phase II and III investigations. In this review, we have also refined some concepts and practicalities regarding clinical/research management of mRECIST, and propose

that a 12-week time point should be adopted for the assessment of response to specific therapies, *i.e.* immunotherapies and radioembolisation. We encourage further comparisons of mRECIST to RECIST in advanced stages of HCC, in order to clarify the respective benefits of each method.

Abbreviations

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CR, complete response; HCC, hepatocellular carcinoma; HAIC, hepatic arterial infusion chemotherapy; HR, hazard ratio; IR, incomplete response; LDLT, living donor liver transplantation; LT, orthotopic liver transplantation; mRECIST, modified RECIST; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RFA, radiofrequency ablation; RFS, recurrence-free survival; SD, stable disease; TACE, transarterial chemoembolisation; TTP, time-to-progression; TTR, time to recurrence.

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Conflict of interest

JML is receiving research support from Bayer HealthCare Pharmaceuticals, Eisai Inc, Bristol-Myers Squibb and Ipsen, and consulting fees from Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb, Eisai Inc, Celsion Corporation, Eli Lilly, Exelixis, Merck, Ipsen, Glycotest, Navigant, Leerink Swann LLC, Midatech Ltd, Fortress Biotech, Sprink Pharmaceuticals, Nucleix and Can-Fite and Roche. RL has nothing to declare with respect to this manuscript.

Please refer to the accompanying [ICMJE disclosure](#) forms for further details.

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