**Name of journal: *World Journal of Hepatology***

**ESPS Manuscript NO: 25575**

**Manuscript type: Minireviews**

**How to assess the efficacy or failure of targeted therapy: deciding when to stop sorafenib in hepatocellular carcinoma**

Raoul JL *et al*. When to stop sorafenib in HCC

**Jean-Luc Raoul, Xavier Adhoute, Marine Gilabert, Julien Edeline**

**Jean-Luc Raoul, Marine Gilabert,** Department of Medical Oncology, Paoli-Calmettes Institute, 13273 Marseille, France

**Xavier Adhoute,** Department of Hepatology, Hopital Saint-Joseph, 26 Bd Louvain, 13008 Marseille, France

**Julien Edeline,** Department of Medical Oncology, Centre E Marquis, Bd de la Bataille Frandres-Dunkerque, 35043 Rennes Cedex, France

**Author contributions:** Raoul JL, Adhoute X, Gilabert M, and Edeline J wrote the paper and approved its content.

**Conflict-of-interest statement:** Raoul JL has received consultancy fees from Bayer, Taiho, and BTG; Adhoute X has received consultancy fees from Bayer; Gilabert M and Edeline J have no potential conflicts of interest to disclose.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Correspondence to: Dr. Jean-Luc Raoul, Professor,** Department of Medical Oncology, Paoli-Calmettes Institute, BP 156, 13273 Marseille, France. raouljl@ipc.unicancer.fr

**Telephone:** +33-4-91223679

**Fax:** +33-4-91223670

**Received:** March 15, 2016

**Peer-review started:** March 18, 2016

**First decision:** April 18, 2016

**Revised:** Sptember 20, 2016

**Accepted:** November 1, 2016

**Article in press:**

**Published online:**

**Abstract**

Sorafenib is thus far the only systemic treatment for hepatocellular carcinoma (HCC) based on the results of two randomized controlled trials performed in Western and in Eastern countries, despite a poor response rate (from 2% to 3.3%) following conventional evaluation criteria. It is now recognized that the criteria (European Association of the Study of the Liver criteria, modified response evaluation criteria in solid tumors) based on contrast enhanced techniques (computed tomography scan, magnetic resonance imaging) aimed to assess the evolution of the viable part of the tumor (hypervascularized on arterial phase) are of major interest to determine the efficacy of sorafenib and of most antiangiogenic drugs in patients with HCC. The role of alpha-fetoprotein serum levels remains unclear. In 2016, in accordance with the SHARP and the Asia-Pacific trials, sorafenib must be stopped when tolerance is poor despite dose adaptation or in cases of radiological and symptomatic progression. This approach will be different in cases of available second-line therapy trials. Some recent data (in renal cell carcinoma) revealed that despite progression in patients who received sorafenib, this drug can still decrease tumor progression compared to drug cessation. Then, before deciding to continue sorafenib post-progression or shift to another drug, knowing other parameters of post-progression survival (Child-Pugh class, Barcelona Clinic Liver Cancer, alpha-fetoprotein, post-progression patterns in particular, the development of extrahepatic metastases and of portal vein thrombosis) will be of major importance.

**Key words:** Hepatocellular carcinoma; tumor evaluation; sorafenib; response evaluation criteria in solid tumors; modified response evaluation criteria in solid tumors

**© The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** The response rate of sorafenib in hepatocellular carcinoma is low using standard parameters and is better assessed using new criteria based on tumor vascularization (European Association of the Study of the Liver criteria, modified response evaluation criteria in solid tumors). In case of minor progression, if sorafenib is well tolerated, knowing the predictors of post-progression survival will be of value in deciding whether to continue or stop sorafenib.

Raoul JL, Adhoute X, Gilabert M, Edeline J. How to assess the efficacy or failure of targeted therapy: deciding when to stop sorafenib in hepatocellular carcinoma. *World J Hepatol* 2016; In press

**INTRODUCTION**

In the majority of solid tumors, assessing the efficacy or failure of a systemic treatment is based on the tumor size, which is measured either bidimensionally using the World Health Organization criteria (WHO) criteria or unidimensionally using response evaluation criteria in solid tumors (RECIST). The response rate is used as a surrogate marker of drug efficacy in clinical trials, and in clinical practice, the evolution of tumor size is a major parameter to decide whether to stop or continue treatment. In a palliative setting, a treatment is continued as long as the disease is controlled (stable disease or response) and the regimen is tolerated. This approach is less simple with targeted therapies. In gastrointestinal stromal tumors, the efficacy of imatinib was associated with modifications in tumor content and not always with a decrease in tumor size. That finding leads researchers to propose new response criteria[1] not only based on tumor size but also based on combining size and density shown on computed tomography (CT) scans. The efficacy of bevacizumab that is associated with chemotherapy is also underestimated under the standard criteria. In a large series, Chun *et al*[2] demonstrated that CT scan-based morphologic criteria correlated better with the histological response than the response by RECIST in patients with liver metastases of colorectal cancer treated with bevacizumab-containing chemotherapy. In hepatocellular carcinoma (HCC), despite a low and disappointing response rate (2%) using conventional criteria in a phase II trial[3], sorafenib is thus far the only systemic treatment[4,5] that has been demonstrated to improve overall survival. In this era of great expectations regarding new drugs, we would like to briefly review these response evaluation criteria used in patients with HCC and the determination of when to continue or stop sorafenib treatment.

**Conventional criteria for evaluating tumor response: WHO and RECIST**

The WHO criteria for defining a response to treatment are based on bidimensionally measured lesions (*i.e.*, the product of the greatest tumor diameter and the greatest perpendicular distance summed over all measured tumors). The RECIST guidelines were published in 2000, with the major change being that the RECIST 1.0 uses unidimensional measurements of the sum of the longest diameters of the tumors. All unmeasurable lesions are considered to be “non-target” lesions, and lymph nodes are not distinguished from extranodal lesions. Progression is defined by an increase of at least 20% of the sum of the longest diameter and the appearance of new lesions or the progression of a non-target lesion. In 14 studies, the application of the WHO criteria and RECIST to the same patients with a large range of cancers has shown similar results[6]. A few years later, the RECIST 1.1 criteria were published[7], which better defined the minimal target size and reduced the number of allowed target lesions to 2 per organ and to a total of 5. It was also stated that a lymph node was considered as a target only if the short axis was larger than 15 mm. Ascites, pleural effusion, and lymph nodes from 10 mm to 14 mm on the short axis were considered as non-measurable lesions. Progression of non-target lesions was, by definition, considered to be a sign of disease progression. In a comparison of RECIST 1.0 with RECIST 1.1 in patients with lung cancer treated by erlotinib, the latter group demonstrated a slightly better performance[8].

However, all these criteria were subject to failure in HCC. Ascites or pleural effusions are usually related to the underlying liver cirrhosis, lymph nodes are frequent and may be large in the case of viral hepatitis, and the appearance of non/malignant small liver nodules is common. Moreover, most non-surgical treatments target tumor vascularization (chemo-embolization, radio-embolization, antiangiogenic drugs), and efficacy might be poorly reflected by size only.

**New criteria specifically dedicated to HCC**

Thus, new, more appropriate criteria were required to assess treatment efficacy in patients with HCC. European Association of the Study of the Liver (EASL) criteria were introduced during the EASL conference in Barcelona in 2000. They were based on bidimensional WHO criteria and the targeting of viable tumors, which were defined as those that showed contrast material-enhancing areas in the arterial phase of a dynamic CT scan[9]. These criteria were later adapted to RECIST[10]; in addition to this new definition of target lesions, non-target lesions were revisited, and new hepatic nodules were considered as evidence of progression only if they had typical imaging and a longest diameter of at least 10 mm. Cytopathological confirmation of the neoplastic nature of any effusion that appeared or worsened was required. These new parameters, named modified RECIST (mRECIST), were considered to be a better tool for assessing HCC tumors[11]. Several Japanese authors proposed response evaluation criteria in cancer of the liver (RECICL), based on the bidirectional measurement of tumors showing arterial enhancement and considering non-hypervascularized tumors[12]. In a series of 156 patients receiving sorafenib for more than 30 d, response rates and the evaluation of overall survival by mRECIST and RECICL were similar. Recently, mRECIST was prospectively validated[13] in a phase 3 study (brivanib in second-line treatment). In this study comparing 395 patients who progressed after sorafenib was administered or were intolerant (brivanib to placebo; 2:1 ratio), tumor assessment every 6 weeks by contrast-enhanced CT or MRI was performed by a central review using mRECIST. A partial response was achieved in 8% of patients who received brivanib and 2% of patients who received placebo; the median overall survival was 16.4 mo for mRECIST responders and 8.3 months for non-responders, and mRECIST evaluation had a prognostic value in multiparametric analysis.

Another way to evaluate tumor vascularization is contrast-enhanced ultrasound. In a short series of 19 patients (16 who received sorafenib and 3 who received sunitinib), this technique seemed effective at distinguishing progressors from non-progressors at 1 mo[14]. In a prospective series of 37 patients treated with sorafenib and explored by contrast-enhanced ultrasound before treatment and on days 7, 14 and 28, Sugimoto *et al*[15] found that this technique was not only predictive of tumor response (tumor vascularization) but also of major adverse events (liver parenchyma vascularization). Additional data are still necessary to validate these results.

The impact of alpha-fetoprotein (AFP) evaluation is unclear. In a series of 72 patients who had an elevated baseline AFP and were treated with different antiangiogenic drugs (thalidomide, bevacizumab), a decline of > 20% from the baseline AFP level within the first 4 wk (early AFP response) was associated with a higher response rate and a longer PFS and OS[16]. In contrast, in patients who received brivanib[17], a longer survival rate was not associated with either an early AFP response (*i.e.*, a decrease by more than 20% from baseline within the first 4 wk) or an AFP response (*i.e.*, an AFP decrease by more than 50% from baseline). In a Japanese retrospective study[18], the best way to assess prognosis was a combination of mRECIST and AFP ratio (AFP under treatment/AFP before treatment), but this ratio (< or > 1) was only associated with survival at 8 weeks.

**Comparison of these response evaluation criteria in HCC cases**

After transarterial chemoembolization (TACE) and percutaneous ablation in 55 patients, Forner *et al*[19] demonstrated that RECIST missed all complete responses (including patients treated by curative options) and underestimated the extent of tissue necrosis. The authors concluded that RECIST should not be used and that dynamic imaging techniques and evaluations must become the standard for assessing treatment efficacy. In a series of 143 patients with HCC who underwent TACE, a comparison of various response criteria showed that volumetric functional imaging is better correlated with outcome than other parameters and that AFP serum levels[20] and new 3D-imaging approaches are of great value in differentiating the responders from the non-responders to TACE[21] and can be used early to predict outcome after initial TACE. Shim *et al*[22] compared WHO, RECIST, EASL and mRECIST in a cohort of 332 patients with intermediate HCC treated by TACE. They concluded that the enhancement models (EASL guidelines and mRECIST) were the best independent predictors of overall survival after chemoembolization. Similarly, the same results were found in an English series of 83 patients[23]. Thus, measuring the viable part of the tumor seems to be the best option after loco-regional treatment of HCC.

In the seminal SHARP[4] and AP[5] trials, the response rates using RECIST were 2% and 3.3% for patients who received sorafenib and 1% and 1.3% for those who received placebo, respectively; however, the overall survival analysis was clearly in favor of sorafenib, showing a discrepancy between the response rate by RECIST and outcome, with sorafenib efficacy being related to an increase in the time to progression. Many retrospective series have analyzed tumor responses using different criteria for patients receiving sorafenib. Their common features were that the evaluation of the viable part of the tumor based on arterial enhancement provided better results than the usual parameters and showed a real response rate and, thus, should be used for assessing treatment efficacy. Edeline *et al*[24], in a series of 53 patients, determined that 1 out of 10 patients considered as PD by RECIST was scored as SD using mRECIST. Forty-two patients evaluated as stable by RECIST were reassessed as complete response in 1 case, partial response in 10 cases, SD in 29 cases and PD in 2 cases using mRECIST. Then, the objective response rate of 1.9% by RECIST increased to 22.6% with mRECIST. The mRECIST result was associated with outcome, as those initially considered as SD by RECIST but as responders (*n* = 11), stable (*n* = 29) or progressive (*n* = 2) by mRECIST had different median overall survival rates of 17.1 mo, 9.7 mo and 3.7 mo, respectively. However, there was no difference between these two criteria regarding the median time to progression. Another retrospective study[25] compared RECIST 1.1 with vascularization-based criteria (Choi criteria, EASL criteria, and mRECIST). The response rates were 3%, 51%, 28% and 28%, respectively, in a cohort of 64 patients treated using sorafenib. The tumor response following RECIST 1.1 did not correlate well with the overall survival rate, whereas other criteria were more appropriate to identify responders with longer survival rates. In two phase II trials (101 patients) evaluating brivanib, an independent review compared the outcomes between the WHO criteria and mRECIST[17]. The response rates were higher with mRECIST *vs* WHO in both cohorts, and PD assessed by mRECIST, was associated with a poorer overall survival rate than when assessed using the WHO criteria.

Thus, these vascularization-based criteria are better than size-only criteria to categorize responders. However, the essential problem exists: how do we define when sorafenib treatment is no longer effective? Progression can be related to an increase in tumor size (or of its viable part) and also to the appearance of new liver nodules (considering vascularization, size, and evolution), effusion and ascites (cytology required), and lymph nodes (size and vascularization). These parameters are listed in a recent paper from the BCLC[26]. However, is progression a strict criterion to stop sorafenib treatment?

**In 2016, when to stop sorafenib?**

In the SHARP trial, treatment was continued until both radiological and symptomatic progression or unacceptable toxicity occurred. In our experience, many patients seem to clinically benefit from the drug despite progression; in clinical practice, progression is not always a clear indication to stop sorafenib, particularly if there is no second-line trial available. In patients with poor prognostic factors at progression (worsening of performance status or of Child-Pugh status), cessation of the drug is recommended. In contrast, if the patients are candidates for second-line therapies, then inclusion is the best option if available. In other cases, we can postulate that sorafenib may retain some efficacy in certain instances despite tumor progression and that cessation of the drug might lead to an acceleration of tumor growth. In metastatic renal cell cancer, some data show that, at progression, the tumor growth rate is lower than before initiation of the treatment using sorafenib and lower than will be observed after cessation of the drug. More interestingly, in renal cell carcinoma, this persistent activity beyond progression with an apparent flare-up effect after drug discontinuation of the drug was observed only with sorafenib and not with everolimus[27]. Then, even after progression, this treatment can participate in slowing down the disease. However, continuing sorafenib treatment after progression can be of interest only for patients who have a reasonable life expectancy and an excellent tolerance of the drug. Analysis of post-progression survival (Table 1) showed that, in addition to performance status, Child-Pugh score, and macrovascular invasion at progression, some other parameters are valuable. These include AFP, time to progression (correlation between time to progression using sorafenib and post-progression survival)[28], and pattern of progression[29]. Post-progression survival is significantly worse for patients who developed new extrahepatic lesions compared to patients with intra- or extra-hepatic growth or new intrahepatic lesions. These data in a Spanish cohort were later confirmed in Asian patients[30,31]. Thus, continuing sorafenib is a possibility if second-line trials are unavailable or if the patient cannot be included. This is particularly relevant for patients who had mild intrahepatic progression, who had a good PS with no worsening in BCLC or the Child-Pugh scores, and who had progressed very slowly (Figure. 1).

**Conclusion**

contrast-enhanced imaging techniques using mRECIST criteria are the best objective approach to appreciate the efficacy of vascularization targeting agents, particularly sorafenib. The value of AFP serum levels is not clear and not sufficient to impact therapeutic decisions. The enrollment of progressing patients in second-line trials is the best option. If this is not possible, then sorafenib must be discontinued if patients have poor prognostic factors or poor tolerance. In contrast, if patients do not have worsening PS or Child-Pugh classification or if macrovascular invasion occurs, then sorafenib can be pursued; however, we must consider the important prognostic values of the progression pattern.

**REFERENCES**

1 **Choi H**. Critical issues in response evaluation on computed tomography: lessons from the gastrointestinal stromal tumor model. *Curr Oncol Rep* 2005; **7**: 307-311 [PMID: 15946591 DOI: 10.1007/s11912-005-0055-4]

2 **Chun YS**, Vauthey JN, Boonsirikamchai P, Maru DM, Kopetz S, Palavecino M, Curley SA, Abdalla EK, Kaur H, Charnsangavej C, Loyer EM. Association of computed tomography morphologic criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases. *JAMA* 2009; **302**: 2338-2344 [PMID: 19952320 DOI: 10.1001/jama.2009.1755]

3 **Abou-Alfa GK**, Schwartz L, Ricci S, Amadori D, Santoro A, Figer A, De Greve J, Douillard JY, Lathia C, Schwartz B, Taylor I, Moscovici M, Saltz LB. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2006; **24**: 4293-4300 [PMID: 16908937 DOI: 10.1200/JCO.2005.01.3441]

4 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]

5 **Cheng AL**, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25-34 [PMID: 19095497 DOI: 10.1016/S1470-2045(08)70285-7]

6 **Therasse P**, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**: 205-216 [PMID: 10655437 DOI: 10.1093/jnci/92.3.205]

7 **Eisenhauer EA**, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228-247 [PMID: 19097774 DOI: 10.1016/j.ejca.2008.10.026]

8 **Nishino M**, Jackman DM, Hatabu H, Yeap BY, Cioffredi LA, Yap JT, Jänne PA, Johnson BE, Van den Abbeele AD. New Response Evaluation Criteria in Solid Tumors (RECIST) guidelines for advanced non-small cell lung cancer: comparison with original RECIST and impact on assessment of tumor response to targeted therapy. *AJR Am J Roentgenol* 2010; **195**: W221-W228 [PMID: 20729419 DOI: 10.2214/AJR.09.3928]

9 **Bruix J**, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodés J. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001; **35**: 421-430 [PMID: 11592607 DOI: 10.1016/S0168-8278(01)00130-1]

10 **Llovet JM**, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, Sherman M, Schwartz M, Lotze M, Talwalkar J, Gores GJ. Design and endpoints of clinical trials in hepatocellular carcinoma. *J Natl Cancer Inst* 2008; **100**: 698-711 [PMID: 18477802 DOI: 10.1093/jnci/djn134]

11 **Lencioni R**, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010; **30**: 52-60 [PMID: 20175033 DOI: 10.1055/s-0030-1247132]

12 **Arizumi T**, Ueshima K, Takeda H, Osaki Y, Takita M, Inoue T, Kitai S, Yada N, Hagiwara S, Minami Y, Sakurai T, Nishida N, Kudo M. Comparison of systems for assessment of post-therapeutic response to sorafenib for hepatocellular carcinoma. *J Gastroenterol* 2014; **49**: 1578-1587 [PMID: 24499826 DOI: 10.1007/s00535-014-0936-0]

13 **Lencioni R**, Park JW, Torres F, et al. Objective response by mRECIST predicts survival in hepatocellular carcinoma: a multivariate, time-rependent analysis from the phase 3 BRISK-PS study. ILCA 2015

14 **Frampas E**, Lassau N, Zappa M, Vullierme MP, Koscielny S, Vilgrain V. Advanced Hepatocellular Carcinoma: early evaluation of response to targeted therapy and prognostic value of Perfusion CT and Dynamic Contrast Enhanced-Ultrasound. Preliminary results. *Eur J Radiol* 2013; **82**: e205-e211 [PMID: 23273822 DOI: 10.1016/j.ejrad.2012.12.004]

15 **Sugimoto K**, Moriyasu F, Saito K, Rognin N, Kamiyama N, Furuichi Y, Imai Y. Hepatocellular carcinoma treated with sorafenib: early detection of treatment response and major adverse events by contrast-enhanced US. *Liver Int* 2013; **33**: 605-615 [PMID: 23305331 DOI: 10.1111/liv.12098]

16 **Shao YY**, Lin ZZ, Hsu C, Shen YC, Hsu CH, Cheng AL. Early alpha-fetoprotein response predicts treatment efficacy of antiangiogenic systemic therapy in patients with advanced hepatocellular carcinoma. *Cancer* 2010; **116**: 4590-4596 [PMID: 20572033 DOI: 10.1002/cncr.25257]

17 **Raoul JL**, Park JW, Kang YK, Finn RS, Kim JS, Yeo W, Polite BN, Chao Y, Walters I, Baudelet C, Lencioni R. Using Modified RECIST and Alpha-Fetoprotein Levels to Assess Treatment Benefit in Hepatocellular Carcinoma. *Liver Cancer* 2014; **3**: 439-450 [PMID: 26280005 DOI: 10.1159/000343872]

18 **Kawaoka T**, Aikata H, Murakami E, Nakahara T, Naeshiro N, Tanaka M, Honda Y, Miyaki D, Nagaoki Y, Takaki S, Hiramatsu A, Waki K, Takahashi S, Chayama K. Evaluation of the mRECIST and α-fetoprotein ratio for stratification of the prognosis of advanced-hepatocellular-carcinoma patients treated with sorafenib. *Oncology* 2012; **83**: 192-200 [PMID: 22890083 DOI: 10.1159/000341347]

19 **Forner A**, Ayuso C, Varela M, Rimola J, Hessheimer AJ, de Lope CR, Reig M, Bianchi L, Llovet JM, Bruix J. Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma: are response evaluation criteria in solid tumors reliable? *Cancer* 2009; **115**: 616-623 [PMID: 19117042 DOI: 10.1002/cncr.24050]

20 **Bonekamp S**, Halappa VG, Geschwind JF, Li Z, Corona-Villalobos CP, Reyes D, Bhagat N, Cosgrove DP, Pawlik TM, Mezey E, Eng J, Kamel IR. Unresectable hepatocellular carcinoma: MR imaging after intraarterial therapy. Part II. Response stratification using volumetric functional criteria after intraarterial therapy. *Radiology* 2013; **268**: 431-439 [PMID: 23616632 DOI: 10.1148/radiol.13121637]

21 **Tacher V**, Lin M, Duran R, Yarmohammadi H, Lee H, Chapiro J, Chao M, Wang Z, Frangakis C, Sohn JH, Maltenfort MG, Pawlik T, Geschwind JF. Comparison of Existing Response Criteria in Patients with Hepatocellular Carcinoma Treated with Transarterial Chemoembolization Using a 3D Quantitative Approach. *Radiology* 2016; **278**: 275-284 [PMID: 26131913 DOI: 10.1148/radiol.2015142951]

22 **Shim JH**, Lee HC, Kim SO, Shin YM, Kim KM, Lim YS, Suh DJ. Which response criteria best help predict survival of patients with hepatocellular carcinoma following chemoembolization? A validation study of old and new models. *Radiology* 2012; **262**: 708-718 [PMID: 22187634 DOI: 10.1148/radiol.11110282]

23 **Gillmore R**, Stuart S, Kirkwood A, Hameeduddin A, Woodward N, Burroughs AK, Meyer T. EASL and mRECIST responses are independent prognostic factors for survival in hepatocellular cancer patients treated with transarterial embolization. *J Hepatol* 2011; **55**: 1309-1316 [PMID: 21703196 DOI: 10.1016/j.jhep.2011.03.007]

24 **Edeline J**, Boucher E, Rolland Y, Vauléon E, Pracht M, Perrin C, Le Roux C, Raoul JL. Comparison of tumor response by Response Evaluation Criteria in Solid Tumors (RECIST) and modified RECIST in patients treated with sorafenib for hepatocellular carcinoma. *Cancer* 2012; **118**: 147-156 [PMID: 21713764 DOI: 10.1002/cncr.26255]

25 **Ronot M**, Bouattour M, Wassermann J, Bruno O, Dreyer C, Larroque B, Castera L, Vilgrain V, Belghiti J, Raymond E, Faivre S. Alternative Response Criteria (Choi, European association for the study of the liver, and modified Response Evaluation Criteria in Solid Tumors [RECIST]) Versus RECIST 1.1 in patients with advanced hepatocellular carcinoma treated with sorafenib. *Oncologist* 2014; **19**: 394-402 [PMID: 24652387 DOI: 10.1634/theoncologist.2013-0114]

26 **Reig M**, Darnell A, Forner A, Rimola J, Ayuso C, Bruix J. Systemic therapy for hepatocellular carcinoma: the issue of treatment stage migration and registration of progression using the BCLC-refined RECIST. *Semin Liver Dis* 2014; **34**: 444-455 [PMID: 25369306 DOI: 10.1055/s-0034-1394143]

27 **Ferté C**, Koscielny S, Albiges L, Rocher L, Soria JC, Iacovelli R, Loriot Y, Fizazi K, Escudier B. Tumor growth rate provides useful information to evaluate sorafenib and everolimus treatment in metastatic renal cell carcinoma patients: an integrated analysis of the TARGET and RECORD phase 3 trial data. *Eur Urol* 2014; **65**: 713-720 [PMID: 23993162 DOI: 10.1016/j.eururo.2013.08.010]

28 **Shao YY**, Wu CH, Lu LC, Chan SY, Ma YY, Yen FC, Hsu CH, Cheng AL. Prognosis of patients with advanced hepatocellular carcinoma who failed first-line systemic therapy. *J Hepatol* 2014; **60**: 313-318 [PMID: 24036008 DOI: 10.1016/j.jhep.2013.08.027]

29 **Reig M**, Rimola J, Torres F, Darnell A, Rodriguez-Lope C, Forner A, Llarch N, Ríos J, Ayuso C, Bruix J. Postprogression survival of patients with advanced hepatocellular carcinoma: rationale for second-line trial design. *Hepatology* 2013; **58**: 2023-2031 [PMID: 23787822 DOI: 10.1002/hep.26586]

30 **Lee IC**, Chen YT, Chao Y, Huo TI, Li CP, Su CW, Lin HC, Lee FY, Huang YH. Determinants of survival after sorafenib failure in patients with BCLC-C hepatocellular carcinoma in real-world practice. *Medicine (Baltimore)* 2015; **94**: e688 [PMID: 25860213 DOI: 10.1097/MD.0000000000000688]

31 **Ogasawara S**, Chiba T, Ooka Y, Suzuki E, Kanogawa N, Saito T, Motoyama T, Tawada A, Kanai F, Yokosuka O. Post-progression survival in patients with advanced hepatocellular carcinoma resistant to sorafenib. *Invest New Drugs* 2016; **34**: 255-260 [PMID: 26769245 DOI: 10.1007/s10637-016-0323-1]

**P-Reviewer:** Bayraktar Y, Guo RP, Gwak GY, **S-Editor:** Gong ZM

**L-Editor:** **E-Editor:**

**Table 1 Parameters of post-progression survival for patients receiving sorafenib**

|  |
| --- |
| Parameters of post-progression survival for patients receiving sorafenib |
| Performance status |
| Child-Pugh class |
| BCLC class |
| CLIP score |
| Macroscopic venous invasion |
| AFP serum level |
| TTP on sorafenib |
| Pattern of progression |

BCLC: Barcelona Clinic Liver Cancer staging classification; CLIP: Cancer of the Liver Italian Program; AFP: alpha-fetoprotein; TTP: time to progression.



**Figure 1 Proposed algorithm for deciding to continue or stop sorafenib in patients with hepatocellular carcinoma.** ce CT scan: contrast-enhanced computed tomography scan; ce MRI: contrast-enhanced magnetic resonance imaging; DC: disease controlled; PD: progressive disease; BSC: best supportive care.