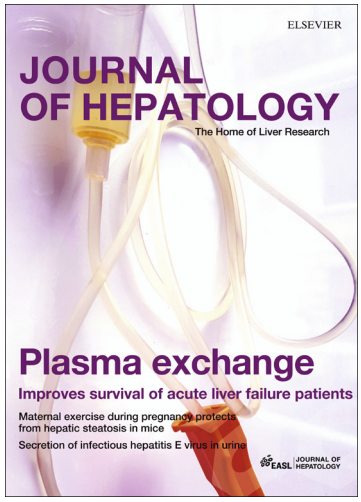

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Objective Response by mRECIST as a Predictor and Potential Surrogate End Point of Overall Survival in Advanced HCC

Authors

Riccardo Lencioni[1]*, Robert Montal[2]*, Ferran Torres[3], Joong-Won Park[4], Thomas Decaens[5], Jean-Luc Raoul[6], Masatoshi Kudo[7], Charissa Chang[8], José Ríos[3], Valerie Boige[9], Eric Assenat[10], Yoon-Koo Kang[11], Ho-Yeong Lim[12], Ian Walters[13], Josep M. Llovet[2,8,14].

**Both authors equally contributed to the study.*

Author affiliations

[1]Department of Interventional Radiology, University of Miami Miller School of Medicine, Sylvester Comprehensive Cancer Center, Miami, FL. [2]Liver Cancer Translational research laboratory, BCLC Group, IDIBAPS, Liver Unit, Hospital Clinic, University of Barcelona, Barcelona, Catalonia, Spain. [3]Medical Statistics Core Facility, IDIBAPS, Hospital Clinic, Barcelona, Spain; Biostatistics Unit, Faculty of Medicine, Autonomous University of Barcelona, Barcelona, Spain. [4]Center for Liver Cancer, National Cancer Center, Goyang, Republic of Korea. [5]Service d'Hepato-gastro-enterologie, Hôpital Henri Mondor, Faculty of Medicine, University of Paris-Est, and INSERM, Creteil, France. [6]Service d'Oncologie Médicale, Institut Paoli Calmette, Marseille, France. [7]Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka, Japan. [8]Liver Cancer Program, Division of Liver Diseases, Ichan School of Medicine at Mount Sinai, New York, NY, USA. [9]Service de Gastro-enterologie, Institut Gustave Roussy, Villejuif, France. [10]Service d'Hépato-gastro-entérologie, Hôpital Saint Eloi, Montpellier Cedex, France. [11]Department of Oncology, Asan Medical Center, Seoul, Republic of Korea. [12]Division of Hematology-Oncology, Samsung Medical Center, Seoul, Republic of Korea. [13]Bristol-Myers Squibb, Wallingford, CT, USA.[14]Institució Catalana de Recerca i Estudis Avançats, Barcelona, Catalonia. Spain.

Corresponding author

Josep M. Llovet, MD

Laboratori de Recerca Translacional en Oncologia Hepàtica;

BCLC-IDIBAPS, Liver Unit, Hospital Clínic;

University of Barcelona.

Carrer Rosselló 153, Barcelona (08036); Catalonia, Spain.

E-mail: jmllovet@clinic.cat;

Tel: +34 93-2279155; Fax: +34 93-3129406.

Keywords

Liver cancer, hepatocellular carcinoma, advanced BCLC, brivanib, mRECIST, objective response, surrogate end point.

Abbreviations

HCC, hepatocellular carcinoma; OS, overall survival; WHO, World Health Organization; RECIST, Response Evaluation Criteria in Solid Tumors; OR, objective response; EASL, European Society for the Study of the Liver; ORR, objective response rate; AASLD, American Association for the Study of Liver Diseases; TTP, time to progression; mRECIST, modified Response Evaluation Criteria in Solid Tumors; VEGFR, vascular endothelial growth factor receptor; FGFR, fibroblast growth factor receptor; BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; CR, complete response; PR, partial response; HR, hazard ratio; CI, confidence interval; AFP, alpha-fetoprotein; PFS, progression-free survival.

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Authors' contributions

Conception and design: RL, RM, FT, IW, JML.

Collection of clinical data: RL, JWP, TD, JLR, MK, CC, VB, EA, YKK, HYL, JML.

Data analysis and interpretation: RL, RM, FT, JR, IW, JML.

Manuscript writing: RL, RM, FT, JR, JML.

Critical review of the manuscript: All authors.

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Abstract

Background & aims. Modification of Response Evaluation Criteria in Solid Tumors (mRECIST) was developed to overcome the limitations of standard RECIST criteria in HCC response assessment by introducing the concept of tumor viability. We aimed to investigate whether objective response (OR) by mRECIST accurately predicts overall survival (OS) in patients with advanced HCC treated by systemic targeted therapies and therefore to preliminary assess OR as a potential surrogate end point of OS.

Methods. We used individual patient data from BRISK-PS randomized phase III trial comparing brivanib vs placebo (OR odds ratio=5.72; OS HR=0.89), the first to prospectively incorporate mRECIST, in order to analyze OR as a predictor of OS in a time-dependent covariate analysis. A total of 334 patients with available imaging scans during follow-up were included, representing 85% of those randomized. Afterwards, we performed a correlation of the survival probability in deciles versus the observed OR to evaluate its suitability as a surrogate end point.

Results. OR was observed in 11.5% and 1.9% of patients treated with brivanib and placebo respectively and was associated with a better survival (median OS 15.0 vs 9.4 months, $p<0.001$). In addition, OR had independent prognostic value (HR=0.48; 95% CI, 0.26-0.91, $p=0.025$) along with known prognostic factors. Finally, OR showed promising results as a potential surrogate of OS in this trial (R=-0.92; 95% CI, -1 – -0.73, $p<0.001$) being an early indicator of the treatment effect (median time to OR was 1.4 months).

Conclusions. OR by mRECIST in advanced HCC predicts OS and thus can be considered as a candidate surrogate end point to be confirmed in future studies.

Introduction

Patients with hepatocellular carcinoma (HCC) are diagnosed when tumors are not eligible for potentially curative therapies in 60% of the cases [1]. In this setting only two treatments have been adopted by guidelines after demonstrating survival advantages in randomized controlled trials. Patients at intermediate stage benefit from chemoembolization and have an estimated median overall survival (OS) of 26 months[2] while at advanced stages sorafenib expands survival from 8 to almost 11 months[3].

The optimal management of HCC requires an early and accurate assessment of tumor response to therapy, particularly for those patients who are experiencing toxicity[1]. Nevertheless, traditionally established response criteria based on size for tumor burden as defined by World Health Organization (WHO) criteria or the Response Evaluation Criteria in Solid Tumors (RECIST) have been challenged in HCC due to the nature of effective treatments. Both chemoembolization and sorafenib often induce direct tumor necrosis without critically affecting tumor size[4]. Moreover, valid radiological criteria are crucial for the optimal development of clinical trials testing new therapies for HCC: although the primary goal is to prolong survival, alternative end points evaluating disease response and progression have been used to assess treatment effectiveness earlier and reduce drug development costs[5].

In addition, controversy remains on what should be an ideal surrogate end point in HCC research. Objective response (OR) was considered an adequate surrogate end point when assessing benefits of loco-regional therapies[2,6] by European Society for the Study of the Liver (EASL) criteria[7]. These criteria were proposed in 2000 by a panel of experts as an amendment of WHO criteria taking into account treatment-induced tumor necrosis and the concept of viable tumor. However, the standardization of RECIST in trials evaluating oncologic therapies led to adopting these criteria for the first time in HCC in the SHARP trial[3]. This landmark trial demonstrated that sorafenib was able to significantly increase OS compared to placebo despite an OR rate (ORR) of just 2%. Subsequently, experts convened

by the American Association for the Study of Liver Diseases (AASLD) developed a set of guidelines that aimed to provide a common conceptual framework for the design of clinical trials in HCC and endorsed time to progression (TTP) as the optimal secondary end point in 2008[5]. At the same time, provided the basis of the modification of RECIST criteria (mRECIST)[8]. These criteria incorporate the concept of viable tumor assessment, defined as the portions of tumor showing arterial enhancement, and thus providing improved sensitivity for clinical assessment. Moreover, mRECIST also incorporates novel concepts in assessing progression with lymph nodes involvement, ascites and development of new lesions[5,8] (Fig. 1). Thus, assessment of response by mRECIST was thereafter endorsed by the EASL clinical practice guidelines of management of HCC[1].

Several studies and one meta-analysis have shown a correlation between OR by mRECIST and survival in patients treated with loco-regional therapies[9–13]. In advanced HCC cases treated with systemic targeted therapies few studies suggest a prognostic value of OR by mRECIST[14–17]; however, their retrospective nature and the absence of a time-dependent multivariate analysis considering immortal time bias limit the level of evidence in this setting.

With the aim to investigate whether OR by mRECIST accurately predict OS in patients with advanced HCC treated by systemic therapies, we performed an individual patient data analysis of BRISK-PS, a phase III trial comparing brivanib and placebo in the second line setting that was the first to prospectively incorporate mRECIST for the assessment of treatment benefit[18].

Patients and Methods

BRISK-PS Trial Design, Treatment and Assessments.

BRISK-PS[18] was a multinational, double-blind, randomized, placebo-controlled, phase III study in which 395 patients were randomly assigned (2:1) to receive brivanib, a dual inhibitor of vascular endothelial growth factor receptor (VEGFR) and fibroblast growth factor receptor (FGFR) signaling pathways, 800mg once per day plus best supportive care (BSC) or

matching placebo plus BSC between February 2009 and June 2011. Patients were eligible if they had documented radiographic or symptomatic progression on/after or were intolerant to sorafenib. Patients were required to have one or more measurable target lesions. Other inclusion criteria included liver function of Child-Pugh Class A or B (a total score ≤ 7) without ascites or encephalopathy an Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 2, and adequate hematologic, hepatic and renal functions. Stratification was done by reason for sorafenib discontinuation (progression versus intolerance), ECOG PS score (0 versus 1-2), distant metastasis and/or macrovascular invasion (yes versus no) and study site. All patients provided written informed consent before enrollment. The study was approved by the institutional review board or ethics committee at each center and complied with provisions of the Good Clinical Practice guidelines and the Declaration of Helsinki and local laws.

The primary end point of OS was defined as the time from random assignment until death as a result of any cause. Secondary end points were TTP and ORR. TTP was defined as the time from random assignment to radiologic disease progression and ORR as the percentage of patients with complete response (CR) or partial response (PR). Tumor measurements were performed every 6 weeks during treatment by contrast-enhanced, computed tomography or magnetic resonance imaging. To define OR, confirmatory assessments were performed ≥ 28 days after the initial demonstration of the response. Assessment was performed by a blinded independent radiologic committee using mRECIST. Results of TTP and ORR were based on central review. Briefly, the study images were subjected to quality control (adherence to image acquisition guidelines and trial protocol) before they were evaluated by two board-certified radiologists with specific expertise in liver imaging. If there was disagreement between the two reviewers in the response assessment at any time point, a third adjudicating radiologist reviewed the case and decided which of the two primary radiologists agrees with. In this regard, a previous study has shown up to 73% of inter-

reader agreement for mRECIST in HCC patients treated with sorafenib and a comparable weighted k coefficient to RECIST[15].

Overall, 226 of 263 brivanib patients (85.9%) and 108 of 132 placebo patients (81.8%) were evaluable for response because of the presence of baseline and at least one on-study scan. Of the 61 patients not evaluable due to discontinuation of treatment before the first radiological assessment, 27 survived less than 6 weeks.

Statistical Analysis.

Analyses were performed using the SPSS v.23 and SAS v.9.4 software packages. A Fisher's exact test was used for comparison of frequency of two categorical variables. Mann-Whitney U test compared one categorical variable with one continuous variable. The hazard ratio (HR) and their associated confidence interval (CI) for OS were computed by Cox proportional hazards models for the aforementioned stratification factors (reason for sorafenib discontinuation, ECOG PS score, distant metastasis and macrovascular invasion), region, age, sex, race, risk factors, baseline analytical factors (albumin, bilirubin and alpha-fetoprotein [AFP]), nodal metastasis and OR. Variables associated with OS (p value < 0.10) in univariate analysis were included in multivariate models. Statistics involving evolutionary events were done by means of time-dependent covariate analysis. Survival curves were performed using Landmark Kaplan-Meier method without a fixed time (patients enter the OR group as soon as they achieved this event); and were compared using the Mantel-Byar test; this method allows to analyze survival from the point where the variable changes[19,20]. The relationship between probability of survival in deciles and log (odds) (i.e. log [p/1-p] where p is the prevalence of the end point) for ORR was evaluated using Pearson correlation coefficient and linear regression; the 95% CI for the R were estimated by bootstrap with 10.000 simulations. The same approach was used to evaluate the association between log HRs for OS and log odds ratios for ORR after dividing the trial into 5 subgroups at random. All statistical tests were two-tailed and the level of the significance was 0.05.

Results

Objective Response by mRECIST as an Independent Prognostic Factor.

At the end of follow up, 233 of the 334 patients with evaluable response had died with a median OS of 10.1 months (95% CI; 8.6 – 11.6) and 9.5 (95% CI; 7.4 – 11.7) for brivanib and placebo groups respectively, without statistically significant differences between treatments (HR=0.88; 95% CI, 0.67 – 1.16, p=0.358) as observed in the whole BRISK-PS population (HR=0.89; 95.8% CI, 0.69 – 1.15, p=0.331).

There was no CR in any of the two arms among patients evaluated. ORR was 11.5% (n=26/226) with brivanib and 1.9% (n=2/108) with placebo. Overall, considering all patients assessed, those patients achieving OR (n=28) had a median OS as per landmark analysis of 15.0 months (95% CI; 13.7 – 16.3), significantly better than the 9.4 (95% CI; 8.2 – 10.6) months of patients without OR (n=306) (HR=0.28; 95%CI 0.14 – 0.54, p<0.001) (Fig. 2A). Specifically, for patients in the brivanib arm, those with OR had better survival (14.3 vs 9.4 months, HR=0.31; 95%CI 0.16 – 0.60, p<0.001) (Fig. 2B).

In order to evaluate OR as a predictor of OS we used a Cox model with OR as a time-dependent variable, since this variable was measured after entry into the study. Multivariate analysis irrespective of treatment identified OR by mRECIST as an independent prognostic factor of OS (HR=0.48; 95% CI, 0.26 – 0.91, p=0.025) along with nodal metastasis, distant metastasis, macrovascular invasion, AFP > 200ng/ml, albumin > median and bilirubin > median (Table 1). OR maintained independent prognostic value in patients treated with brivanib (HR=0.50; 95% CI, 0.25 – 099, p=0.047) (Table 2) indicating that OR by mRECIST captures those patients in which treatment changes the natural history of the disease.

Baseline demographics and disease characteristics that significantly influenced obtaining a higher percentage of OR by mRECIST after treatment with brivanib were: BCLC A/B stage, absence of distant metastasis and the presence of low and high levels of AFP and albumin, respectively (Table 3).

Objective Response by mRECIST as a Surrogate End Point.

To further explore the impact of OR by mRECIST in the assessment of efficacy of a systemic molecular targeted therapy, we performed a Pearson correlation between the raw survival probability of patients in deciles and the logOdds of ORR. This method allows determining the ORR observed in each one of the ten subgroups sorted by worse to better outcome and their association. As shown in Fig. 3, treatment effects on ORR and OS were significantly associated (R=-0.92; 95% CI, -1 – -0.73, p<0.001).

In order to provide additional surrogacy of end points, it is required a proper correlation between the treatment effect on the surrogate outcome (OR by mRECIST) and the treatment effect on the clinical outcome (OS). To attempt this point we split the cases in five random subsgroups of equal size (395/5=79). The association between log HRs for OS and log odds ratios for ORR was high (R=-0.80; 95% CI, -1 – 0.23, p=0.091) (Fig. 4).

Of note, median time to OR was 1.4 months (range 0.7 – 8.4) in the 26 patients that reach a PR with brivanib. This means that the first radiological evaluation, conducted at 6 weeks, detects the majority of patients who respond to treatment and thus, OR could be considered an early surrogate end point.

Discussion

OS remains as the main primary end point in clinical research in oncology and in HCC. However, the field is eager to identify a reliable secondary end point able to recapitulate OS. This need is becoming very relevant for discarding ineffective drugs in phase II trials, and for testing new therapies in phase III, where median survivals of patients with intermediate HCC might exceed 30 months and cross over treatments might dilute the potential benefits during follow-up. OR was considered a reliable surrogate end point for loco-regional therapies in HCC[7], but later studies assessing response by RECIST criteria failed to capture this benefit. At advanced stages of the disease, performance of OR by RECIST was disappointing in capturing benefits of sorafenib therapy[3]. As a consequence of these failures two strategies emerged: a) assess response according to the *hallmarks of HCC* for defining viable tumors (mRECIST criteria)[5,8] and b) endorse TTP as a more adequate surrogate end point, as per SHARP trial results[5].

The present study defines OR as an independent prognostic factor for OS, and as a potentially reliable surrogate end point. First, we established an 11.5% ORR by mRECIST in patients treated with brivanib in the setting of BRISK-PS trial. This figure compares well with data from a phase III trial of brivanib in front-line advanced HCC, where an ORR of 12% in those 577 patients randomized to brivanib arm was reported[21]. Furthermore, in this study ORR for sorafenib was 9%, which is in the range of 9-28% described in several retrospective studies [14–17,22,23]. These figures for sorafenib are far from the 2% ORR described for RECIST[5]. Thus, assessment of mRECIST in patients with advanced HCC treated with anti-angiogenic drugs might be in line with other alternative criteria developed to measure response in other solid tumors. That is the case of Choi criteria for measurement of response in gastrointestinal stromal tumors treated with imatinib[24] or immune-related response criteria for melanomas treated with checkpoint inhibitors[25].

Second, we seek to define if OR was an independent predictor of OS in advanced HCC. For this purpose, we performed a multivariate time-dependent analysis that defined several

variables related to tumoral status (macrovascular invasion, metastases, AFP > 200 ng/mL), liver function (bilirubin, albumin) and treatment response measured by mRECIST as independent predictors for survival. This result is critical, since it represents the first requirement to propose ORR as surrogate end point for OS in advanced HCC. In addition, the level of evidence is high due to the phase III randomized controlled nature of the original study.

Finally, we aimed to explore if ORR could be used as a potential surrogate end point in HCC. Certainly, the way to evaluate therapeutic effectiveness in oncology is based upon a statistically significant and clinically meaningful improvement in OS[26]. In clinical research, surrogate end points are used in order to provide earlier measures of difference in treatment effect than OS[1,27]. In our study, we identified a significant correlation between ORR assessed by mRECIST after brivanib and OS (R=-0.92). Notably, most patients with OR could be identified in the first radiological evaluation conducted at 6 weeks. Moreover, OR overcomes a limitation of other end points that include disease stabilization in their definitions (disease control rate, TTP or progression-free survival [PFS]) since these end points may be influenced by the inherent speed of progression of tumors independently of the effect of the drug[28]. This makes OR by mRECIST a promising surrogate end point to evaluate efficacy (if a treatment is effective for a certain condition) after a phase II trial, and thus to decide its further development.

Thus, if ORR is an independent predictor of survival and a potentially good surrogate of OS, we need to explain how the differences in ORR between brivanib and placebo arms (Odds ratio 5.72; 95% CI, 1.41 – 23.25, p=0.003) were unable to correlate with the lack of survival differences in this trial. The most obvious explanation is that the magnitude of the benefit obtained by a drug certainly depends on the type of ORR benefit (CR vs PR) and the toxicity. The ORR obtained in the trial according to intention to treat for the brivanib arm was 9.9% (26/263), a figure that is suboptimal to impact on the final OS result. Other effective drugs in cancer such as crizotinib, which achieved a 29% absolute increase in ORR

compared to chemotherapy (74% vs 45%) in non-small cell lung cancer[29], or nivolumab, which achieved 40% ORR in melanoma patients, but with a high rate of complete responses[30], are examples defining a threshold for ORR to directly impact in OS benefit. Thereby, to reliably predict differences among treatments, a higher magnitude of the difference in terms of quantity (percentage of OR) and quality (presence of CRs or long-lasting responses) would be necessary. This concept is particularly challenging in the HCC field since, unlike other tumors, the post-progression time is generally longer than TTP and may dilute part of the benefit produced by the drug during treatment[18,31].

The importance of OR as a surrogate end point in cancer trials has been acknowledged in some papers by regulatory agencies and used in breakthrough trials[32]. Indeed, 24 of the 25 FDA accelerated marketing approvals for oncologic indications between 2009 and 2014 were based on ORR[33]. This point is of significance since the last randomized studies conducted in HCC have shown inconsistencies between TTP and OS[34]. In this sense, for instance, the two positive trials showed similar OS rates for sorafenib in front-line and regorafenib in second-line but with clearly distinct TTP figures[3,35]. Thus, TTP is currently re-visited as a surrogate end point in trial design for advanced HCC. In order to provide absolutely robust data to enforce recommendations in guidelines, the definitive evidence will be obtained when several randomized trials following mRECIST assessment will be available, allowing this a meta-analysis approach comparing the Pearson correlation coefficient of ORR, TTP or other surrogate end points with OS[36–40].

In conclusion, these results provide high-level evidence suggesting that radiological response in advanced HCC by mRECIST captures clinically meaningful outcomes in terms of OS and therefore, if confirmed in other future studies at individual and trial-level[36–40], OR can be proposed as a complementary surrogate end point for the efficient development of clinical trials.

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Author names in bold designate shared co-first authorship.

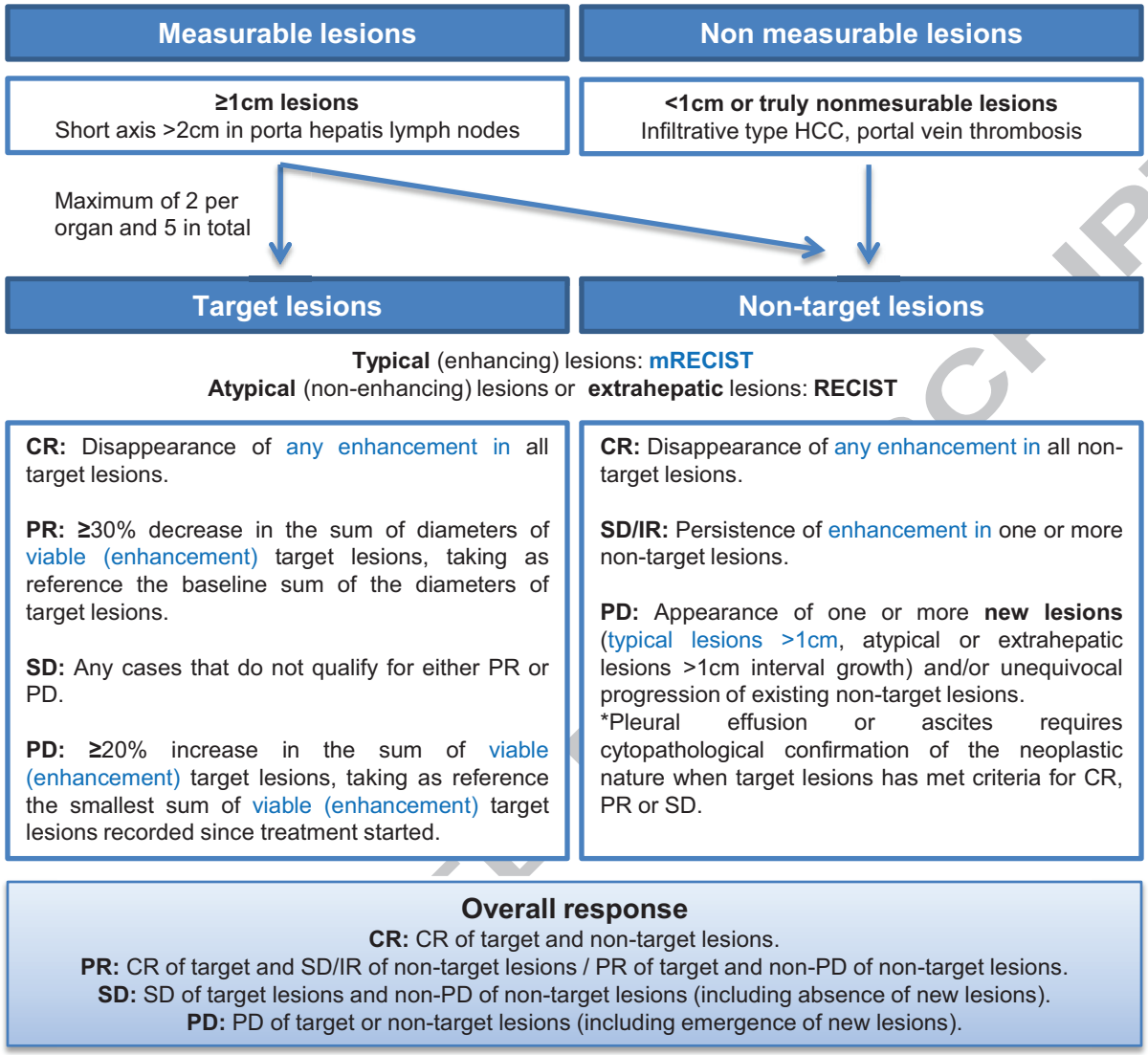
Figure legends

Fig. 1. Response assessment in HCC by mRECIST following the AASLD JNCI Guidelines (adapted from ref 8). CR: Complete response. PR: Partial response. SD: Stable disease. PD: Progressive disease. IR: Incomplete response.

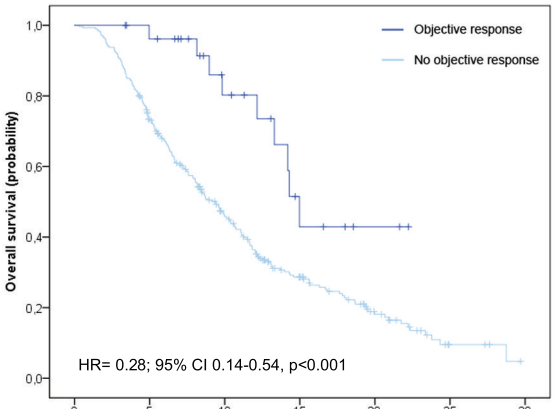
Fig. 2. Landmark Kaplan-Meier curve of OS between patients with response or not by mRECIST in BRISK-PS (A) and in those treated with brivanib (B). *P* value according to Mantel-Byar test.

Fig. 3. Correlation between raw survival probability using deciles and odds of ORR in brivanib patients within BRISK-PS. Each one of the ten subgroups sorted by worse to better outcome has an observed ORR. The central regression line is their association. Internal and external 95% CI bands identify the uncertainty for expected value of the dependent variable and for the individual predicted value, respectively.
Deciles of Survival Probability=-1.293-2.261*logOdds(ORR).

Fig. 4. Correlation between HR for OS and odds ratio for ORR in five random subsamples of patients within BRISK-PS. The central regression line is their association. Internal and external 95% CI bands identify the uncertainty for expected value of the dependent variable and for the individual predicted value, respectively.
ln(HR for OS)=0.621 -1.139*ln(Odds Ratio for ORR).

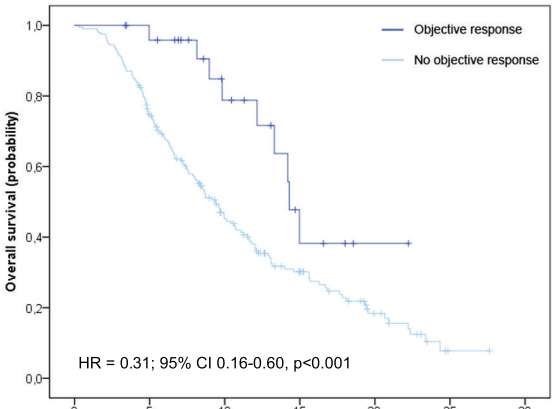


A

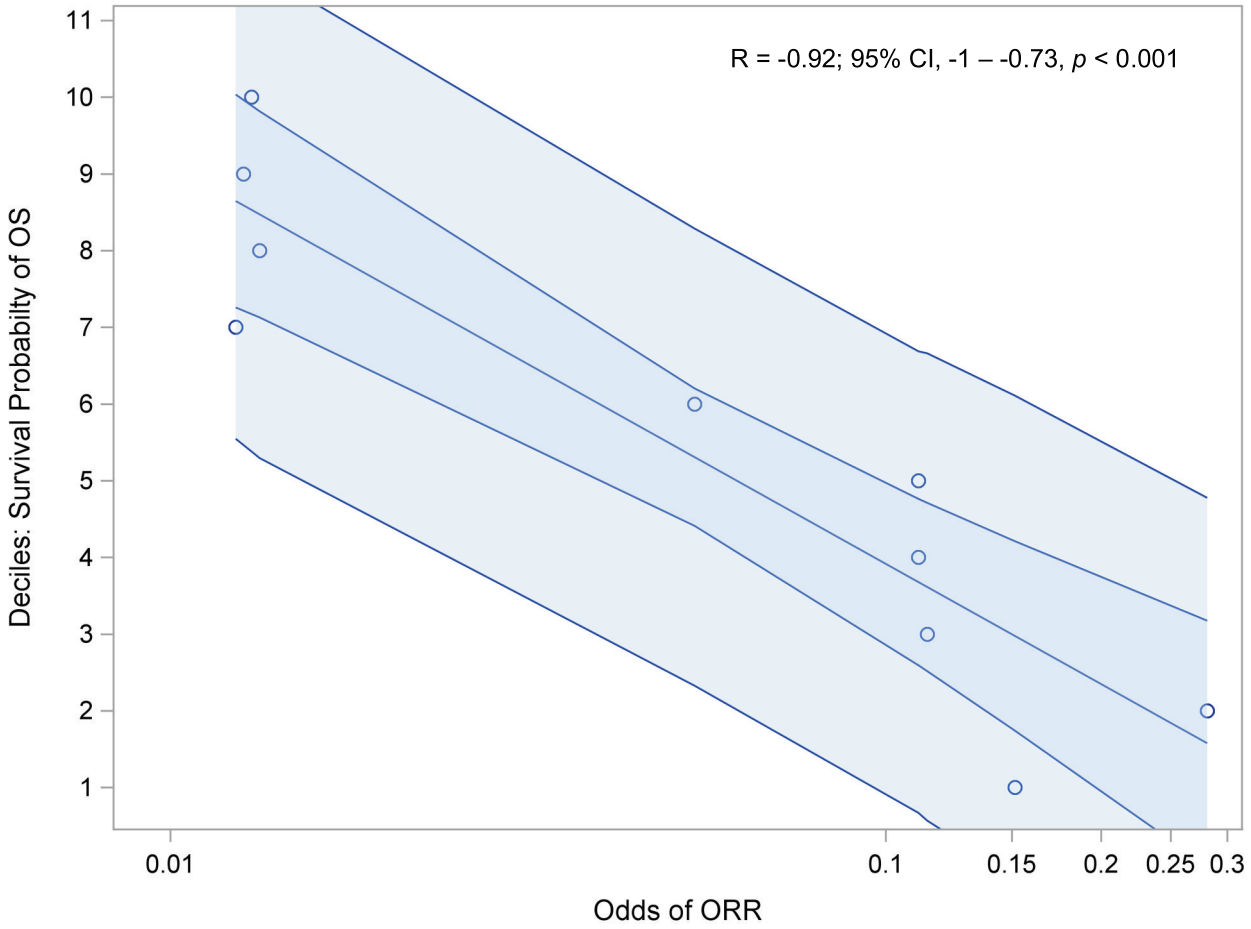


No. at risk						
Objective response	28	25	14	5	2	
No objective response	306	216	115	55	23	4

B



No. at risk						
Objective response	26	23	13	4	1	
No objective response	200	144	72	36	14	1



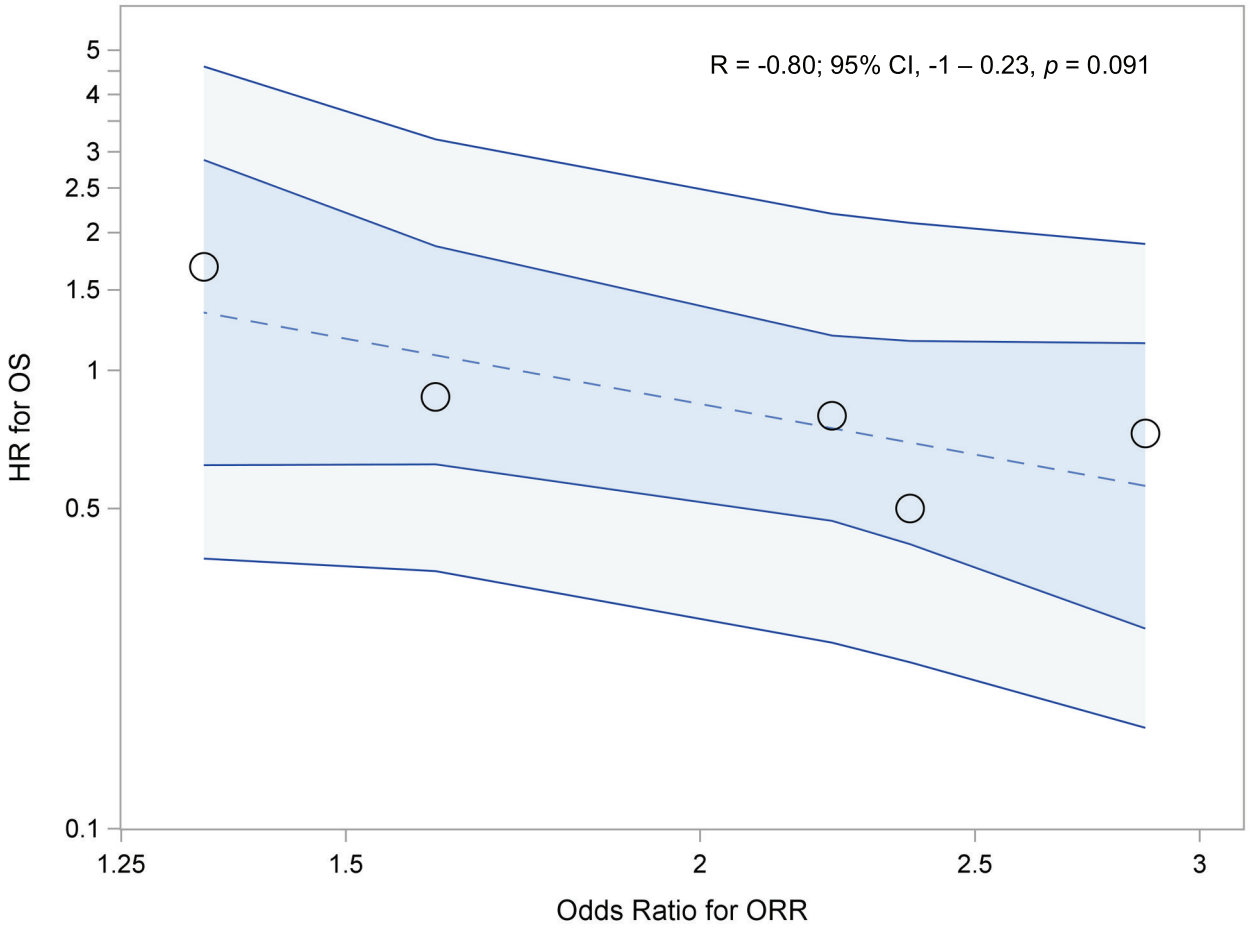


Table 1. Univariate and multivariate time-dependent analysis of OS in BRISK-PS patients who could be assessed for tumor response.

	Univariate analysis		Multivariate analysis	
	HR [95% CI]	***P* value**	**HR [95% CI]**	***P* value**
Distant metastasis	1.27 [0.96 - 1.67]	0.094	1.37 [1.05 - 1.78]	**0.019**
Macrovascular invasion	1.77 [1.33 - 2.34]	< 0.001	1.54 [1.19 - 1.99]	**0.001**
Nodal metastasis	1.52 [1.17 - 1.99]	0.002	1.36 [1.07 - 1.73]	**0.013**
AFP > 200ng/ml	2.02 [1.55 - 2.62]	< 0.001	1.99 [1.56 - 2.54]	**< 0.001**
Albumin > median[1]	0.58 [0.45 - 0.75]	< 0.001	0.65 [0.51 - 0.83]	**0.001**
Bilirubin > median[2]	2.32 [1.78 - 3.03]	< 0.001	2.24 [1.73 - 2.89]	**< 0.001**
OR mRECIST	0.28 [0.14 - 0.54]	< 0.001	0.48 [0.26 - 0.91]	**0.025**

[1] 3.59g/dl, [2] 0.98mg/dl. OR: Objective response.

Variables with p value > 0.10 in univariate analysis were reason for sorafenib discontinuation, ECOG PS score, region, age, sex, race and risk factors.

Table 2. Univariate and multivariate time-dependent analysis of OS in patients treated with brivanib and who could be assessed for tumor response in BRISK-PS.

	Univariate analysis		Multivariate analysis	
	HR [95% CI]	***P* value**	**HR [95% CI]**	***P* value**
Distant metastasis	1.51 [1.06 - 2.16]	0.022	1.35 [0.97 - 1.89]	0.076
Macrovascular invasion	1.85 [1.33 - 2.57]	< 0.001	1.64 [1.20 - 2.24]	**0.002**
Nodal metastasis	1.60 [1.16 - 2.22]	0.005	1.30 [0.96 - 1.77]	0.086
AFP > 200ng/ml	2.16 [1.56 - 2.99]	< 0.001	1.97 [1.44 - 2.69]	**< 0.001**
Albumin > median[1]	0.56 [0.41 - 0.77]	< 0.001	0.58 [0.43 - 0.80]	**0.001**
Bilirubin > median[2]	2.57 [1.85 - 3.57]	< 0.001	2.31 [1.68 - 3.18]	**< 0.001**
OR mRECIST	0.31 [0.16 - 0.60]	< 0.001	0.50 [0.25 - 0.99]	**0.047**

[1] 3.59g/dl, [2] 0.98mg/dl. OR: Objective response.

Variables with p value > 0.10 in univariate analysis were reason for sorafenib discontinuation, ECOG PS score, region, age, sex, race and risk factors.

Table 3. Baseline demographics and disease characteristics in patients with and without objective response by mRECIST after treatment with brivanib.

	OR (n=26)	No OR (n=200)	*P* value
Age (median), years	63 [36–76]	63 [19–85]	0.933
Sex			
Male	23 (88.5)	165 (82.5)	0.583
Female	3 (11.5)	35 (17.5)	
Race			
White	13 (50.0)	84 (42.0)	0.530
Asian	11 (42.3)	103 (51.5)	0.380
Black/Afrincan American	0 (0)	10 (5.0)	0.380
Other	2 (7.7)	3 (1.5)	0.100
Region			
America & Europe	16 (61.5)	110 (55.0)	0.675
Asia	10 (38.5)	90 (45.0)	
Risk factors*			
Alcoholic liver disease	6 (23.1)	20 (10.0)	0.093
Hepatitis B	7 (26.9)	80 (40.0)	0.284
Hepatitis C	7 (26.9)	43 (21.5)	0.615
Other	2 (7.7)	7 (3.5)	0.277
Child-Pugh class			
A	26 (100)	189 (94.5)	0.620
B	0 (0)	11 (5.5)	
ECOG PS score			
0	21 (80.8)	125 (62.5)	0.082
1/2	5 (19.2)	75 (37.5)	
Reason for sorafenib discontinuation			
Progression	21 (80.8)	177 (88.5)	0.337
Intolerance	5 (19.2)	23 (11.5)	
BCLC stage			
A/B	9 (34.6)	18 (9.0)	**0.001**
C	17 (65.4)	182 (91.0)	
Distant metastasis	9 (34.6)	142 (71.0)	**0.001**
Nodal metastasis	7 (26.9)	76 (38.1)	0.387
Macrovascular invasion	8 (30.8)	61 (30.5)	1.000
AFP (median), ng/ml	24 [2–9101]	353 [1–1.2x10^6]	**0.001**
Albumin (median), g/dl	4.0 [3.0–4.4]	3.5 [2.1–5.0]	**0.002**
Bilirubin (median), mg/dl	0.9 [0.4–5.7]	0.98 [0.2 – 15.2]	0.191

OR: Objective response. *54 patients with more than one risk factor were excluded. (%). [range].

Lay Summary

There is a need to identify surrogate end points for overall survival in advanced hepatocellular carcinoma. In the current study, we demonstrate that objective response (OR) is an independent predictor of survival (multivariate time-dependent analysis) of patients randomized to the phase III BRISK study comparing brivanib vs placebo after sorafenib progression. In addition, OR qualifies as a potential surrogate end point for OS in this patient population.

OR by mRECIST as a Predictor and Potential Surrogate End Point of OS in advanced HCC