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

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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

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Abstract

Background & aims. The Modified Response Evaluation Criteria in Solid Tumors (mRECIST) was developed to overcome the limitations of standard RECIST criteria in response assessment of hepatocellular carcinoma (HCC). We aimed to investigate whether objective response by mRECIST accurately predicted overall survival (OS) in patients with advanced HCC treated with systemic targeted therapies and also to preliminarily assess this end-point as a potential surrogate of OS.

Methods. Individual patient data from the BRISK-PS randomized phase III trial comparing brivanib *vs.* placebo (the first to prospectively incorporate mRECIST) were used to analyze objective response as a predictor of OS in a time-dependent covariate analysis. Patients with available imaging scans during follow-up were included (n = 334; 85% of those randomized). Moreover, a correlation of the survival probability in deciles *vs.* the observed objective response was performed to evaluate its suitability as a surrogate end-point.

Results. Objective response 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, objective response had an independent prognostic value (HR = 0.48; 95% confidence interval [CI], 0.26–0.91, p = 0.025) along with known prognostic factors. Finally, objective response showed promising results as a surrogate of OS in this trial (R = −0.92; 95% CI, −1 to −0.73, p <0.001). It was an early indicator of the treatment effect (median time to objective response was 1.4 months).

Conclusions. Objective response by mRECIST in advanced HCC predicts OS and thus can be considered as a candidate surrogate end-point. Further studies are needed to support this finding.

Introduction

In 60% of cases, patients with hepatocellular carcinoma (HCC) are diagnosed when tumors are no longer eligible for potentially curative therapies [1]. In this setting, only two treatments have been included in guidelines after demonstrating survival advantages in randomized controlled trials. Patients at an intermediate stage benefit from chemoembolization and have an estimated median overall survival (OS) of 26 months [2], while at advanced stages, sorafenib extends 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 experience 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 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 to WHO criteria, considering treatment-induced tumor necrosis and the concept of viable tumor assessment. 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 objective response 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, this 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 node 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 objective response 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 objective response 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.

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]. The aim was to investigate whether objective response by mRECIST could accurately predict OS in patients with advanced HCC treated by systemic therapies.

Patients and Methods

BRISK-PS Trial Design, Treatment and Assessments.

BRISK-PS [18] was a multinational, double-blind, randomized, placebo-controlled, phase III study carried out between February 2009 and June 2011. Three hundred and ninety-five patients were randomly assigned (2:1) to receive brivanib, a dual inhibitor of vascular endothelial growth factor receptor and fibroblast growth factor receptor signaling pathways, 800 mg once per day or matching placebo plus best supportive care (BSC). 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 $\leqslant$7) without ascites or encephalopathy an Eastern Cooperative Oncology Group performance status (ECOG PS) $\leqslant$2, and adequate hematologic, hepatic and renal functions. Stratification was carried out according to reason for sorafenib discontinuation (progression *vs.* intolerance), ECOG PS score (0 *vs.* 1–2), distant metastasis and/or macrovascular invasion (yes *vs.* 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 assignmentuntil 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 objective response, confirmatory assessments were performed $\geqslant$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 should be agreed with. In this regard, a previous study showed 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 hazard 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 objective response. 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 objective response group as soon as they achieved this event); and were compared using the Mantel-Byar test; this method allowed analysis of survival from the point

where the variable changed [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's 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 five subgroups at random. All statistical tests were two-tailed and the threshold level of 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. There were no 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 either 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 objective response (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 objective response (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 objective response 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 objective response as a predictor of OS we used a Cox model with objective response as a time-dependent variable, since this variable was measured after entry into the study. Multivariate analysis irrespective of treatment identified objective response 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 >200 ng/ml, albumin > median and bilirubin > median (Table 1). Objective response maintained independent prognostic value in patients treated with brivanib (HR = 0.50; 95% CI, 0.25–099, $p = 0.047$) (Table 2), indicating that objective response 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 objective response 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 objective response 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 log odds ratios of ORR. This method allowed the determination of 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 to −0.73, p <0.001).

In order to provide additional surrogacy of end-points, a proper correlation between the treatment effect on the surrogate outcome (objective response by mRECIST) and the treatment effect on the clinical outcome (OS) is required. To attempt this, we split the cases in five random subgroups 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 to 0.23, p = 0.091) (Fig. 4).

Of note, median time to objective response was 1.4 months (range: 0.7–8.4) in the 26 patients that reached a PR with brivanib. This means that the first radiological evaluation, conducted at 6 weeks, detects the majority of patients responding to treatment and thus, objective response 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, there is a need to identify a reliable secondary end-point able to recapitulate OS. This will allow ineffective drugs in phase II trials to be discarded, and enable 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. Objective response was previously considered a reliable surrogate end-point for loco-regional therapies in HCC [7], but studies assessing response by RECIST criteria failed to capture this benefit. At advanced stages of the disease, performance of objective response 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], b) endorse TTP as a more adequate surrogate end-point, as per the SHARP trial results [5].

The present study defines objective response 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 within 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. This is the case for Choi criteria, for the 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 sought to define if objective response 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. 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 objective response could be identified in the first radiological evaluation conducted at 6 weeks. Moreover, objective response 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 objective response 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. Therefore, to reliably predict differences among treatments, a higher magnitude of the difference in terms of quantity (percentage of objective response) 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 objective response 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],

objective response can be proposed as a complementary surrogate end-point for the efficient development of clinical trials.

References

[1] EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908–43.

[2] Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002;359:1734–9.

[3] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc J-F, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–90.

[4] Jiang T, Zhu AX, Sahani D V., Thomas MB, Zhu AX, Jemal A, et al. Established and novel imaging biomarkers for assessing response to therapy in hepatocellular carcinoma. J Hepatol 2013;58:169–77.

[5] Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst 2008;100:698–711.

[6] Sala M, Llovet JM, Vilana R, Bianchi L, Solé M, Ayuso C, et al. Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. Hepatology 2004;40:1352–60.

[7] Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001;35:421–30.

[8] Lencioni R, Llovet J. Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma. Semin Liver Dis 2010;30:052–60.

[9] Vincenzi B, Di Maio M, Silletta M, D'Onofrio L, Spoto C, Piccirillo MC, et al. Prognostic Relevance of Objective Response According to EASL Criteria and mRECIST Criteria in Hepatocellular Carcinoma Patients Treated with Loco-Regional Therapies: A Literature-Based Meta-Analysis. PLoS One 2015;10:e0133488.

[10] Gillmore R, Stuart S, Kirkwood A, Hameeduddin A, Woodward N, Burroughs AK, et al. EASL and mRECIST responses are independent prognostic factors for survival in hepatocellular cancer patients treated with transarterial embolization. J Hepatol 2011;55:1309–16.

[11] Prajapati HJ, Spivey JR, Hanish SI, El-rayes BF, Kauh JS, Chen Z, et al. mRECIST and EASL responses at early time point by contrast-enhanced dynamic MRI predict survival in patients with unresectable hepatocellular carcinoma (HCC) treated by doxorubicin drug-eluting beads transarterial chemoembolization (DEB TACE). Ann Oncol 2013;24:965–73.

[12] Jung ES, Kim JHJS, Yoon EL, Lee HJ, Lee SJ, Suh SJ, et al. Comparison of the methods for tumor response assessment in patients with hepatocellular carcinoma undergoing transarterial chemoembolization. J Hepatol 2013;58:1181–7.

[13] Kim BK, Kim SU, Kim KA, Chung YE, Kim M, Park M, et al. Complete response at first chemoembolization is still the most robust predictor for favorable outcome in hepatocellular carcinoma. J Hepatol 2015;62:4–10.

[14] Edeline J, Boucher E, Rolland Y, Vauléon E, Pracht M, Perrin C, et al. 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;118:147–56.

[15] Ronot M, Bouattour M, Wassermann J, Bruno O, Dreyer C, Larroque B, et al. 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.

[16] Takada J, Hidaka H, Nakazawa T, Kondo M, Numata K, Tanaka K, et al. Modified response evaluation criteria in solid tumors is superior to response evaluation criteria in solid tumors for assessment of responses to sorafenib in patients with advanced hepatocellular carcinoma. BMC Res Notes 2015;8:609.

[17] Ogasawara S, Kanai F, Ooka Y, Motoyama T, Suzuki E, Tawada A, et al. Initial response to sorafenib by using enhancement criteria in patients with hepatocellular carcinoma. Hepatol Int 2013;7:703–13.

[18] Llovet JM, Decaens T, Raoul JL, Boucher E, Kudo M, Chang C, et al. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. J Clin Oncol 2013;31:3509–16.

[19] Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response. J Clin Oncol 1983;1:710–9.

[20] Memon K, Kulik L, Lewandowski RJ, Wang E, Riaz A, Ryu RK, et al. Radiographic response to locoregional therapy in hepatocellular carcinoma predicts patient survival times. Gastroenterology 2011;141:526–35, 535.e1–2.

[21] Johnson PJ, Qin S, Park JW, Poon RT, Raoul JL, Philip P a, et al. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. J Clin Oncol 2013;31:3517–24.

[22] Kawaoka T, Aikata H, Murakami E, Nakahara T, Naeshiro N, Tanaka M, et al. 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.

[23] Spira D, Fenchel M, Lauer UM, Claussen CD, Gregor M, Bitzer M, et al. Comparison of different tumor response criteria in patients with hepatocellular carcinoma after systemic therapy with the multikinase inhibitor sorafenib. Acad Radiol 2011;18:89–96.

[24] Choi H, Charnsangavej C, Faria SC, Macapinlac HA, Burgess MA, Patel SR, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with

imatinib mesylate: proposal of new computed tomography response criteria. J Clin Oncol 2007;25:1753–9.

[25] Hodi FS, Hwu W-J, Kefford R, Weber JS, Daud A, Hamid O, et al. Evaluation of Immune-Related Response Criteria and RECIST v1.1 in Patients With Advanced Melanoma Treated With Pembrolizumab. J Clin Oncol 2016;34:1510–7.

[26] Booth CM, Tannock I. Reflections on medical oncology: 25 years of clinical trials--where have we come and where are we going? J Clin Oncol 2008;26:6–8.

[27] Wilson MK, Karakasis K, Oza AM. Outcomes and endpoints in trials of cancer treatment: the past, present, and future. Lancet Oncol 2015;16:e32–42.

[28] Le Tourneau C, Paoletti X, Coquan E, Sablin MP, Zoubir M, Tannock IF. Critical evaluation of disease stabilization as a measure of activity of systemic therapy: Lessons from trials with arms in which patients do not receive active treatment. J Clin Oncol 2014;32:260–3.

[29] **Solomon BJ, Mok T**, Kim D-W, Wu Y-L, Nakagawa K, Mekhail T, et al. First-Line Crizotinib versus Chemotherapy in ALK -Positive Lung Cancer. N Engl J Med 2014;371:2167–77.

[30] Robert C, Long G V., Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015;372:320–30.

[31] Zhu AX, Park JO, Ryoo B-Y, Yen C-J, Poon R, Pastorelli D, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol 2015:859–70.

[32] Johnson JR, Williams G, Pazdur R. End points and United States Food and Drug Administration approval of oncology drugs. J Clin Oncol 2003;21:1404–11.

[33] Kim C, Prasad V. Strength of Validation for Surrogate End Points Used in the US Food and Drug Administration's Approval of Oncology Drugs. Mayo Clin Proc 2016;91:713–25.

[34] Llovet JM, Hernandez-Gea V. Hepatocellular carcinoma: reasons for phase III failure and novel perspectives on trial design. Clin Cancer Res 2014;20:2072–9.

[35] Bruix J, Finn RS, Kudo M, Llovet JM, Qin S, Le Berre M-A, et al. RESORCE: An ongoing randomized, double-blind, phase III trial of regorafenib (REG) in patients with hepatocellular carcinoma (HCC) progressing on sorafenib (SOR). ASCO Meet Abstr 2014;32:TPS4156.

[36] Zhao F. Surrogate End Points and Their Validation in Oncology Clinical Trials. J Clin Oncol 2016;34:1436–7.

[37] Buyse M, Molenberghs G. Criteria for the validation of surrogate endpoints in randomized experiments. Biometrics 1998;54:1014–29.

[38] Blumenthal GM, Karuri SW, Zhang H, Zhang L, Khozin S, Kazandjian D, et al. Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non-small-cell lung cancer: US Food and Drug Administration trial-level and patient-level analyses. J Clin Oncol 2015;33:1008–14.

[39] Tang P a., Bentzen SM, Chen EX, Siu LL. Surrogate End Points for Median Overall Survival in Metastatic Colorectal Cancer: Literature-Based Analysis From 39 Randomized Controlled Trials of First-Line Chemotherapy. J Clin Oncol 2007;25:4562–8.

[40] Zer a., Prince RM, Amir E, Abdul Razak A. Evolution of Randomized Trials in Advanced/Metastatic Soft Tissue Sarcoma: Endpoint Selection, Surrogacy, and Quality of Reporting. J Clin Oncol 2016:1–8.

Author names in bold designate shared co-first authorship.

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].

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).

Fig. 1

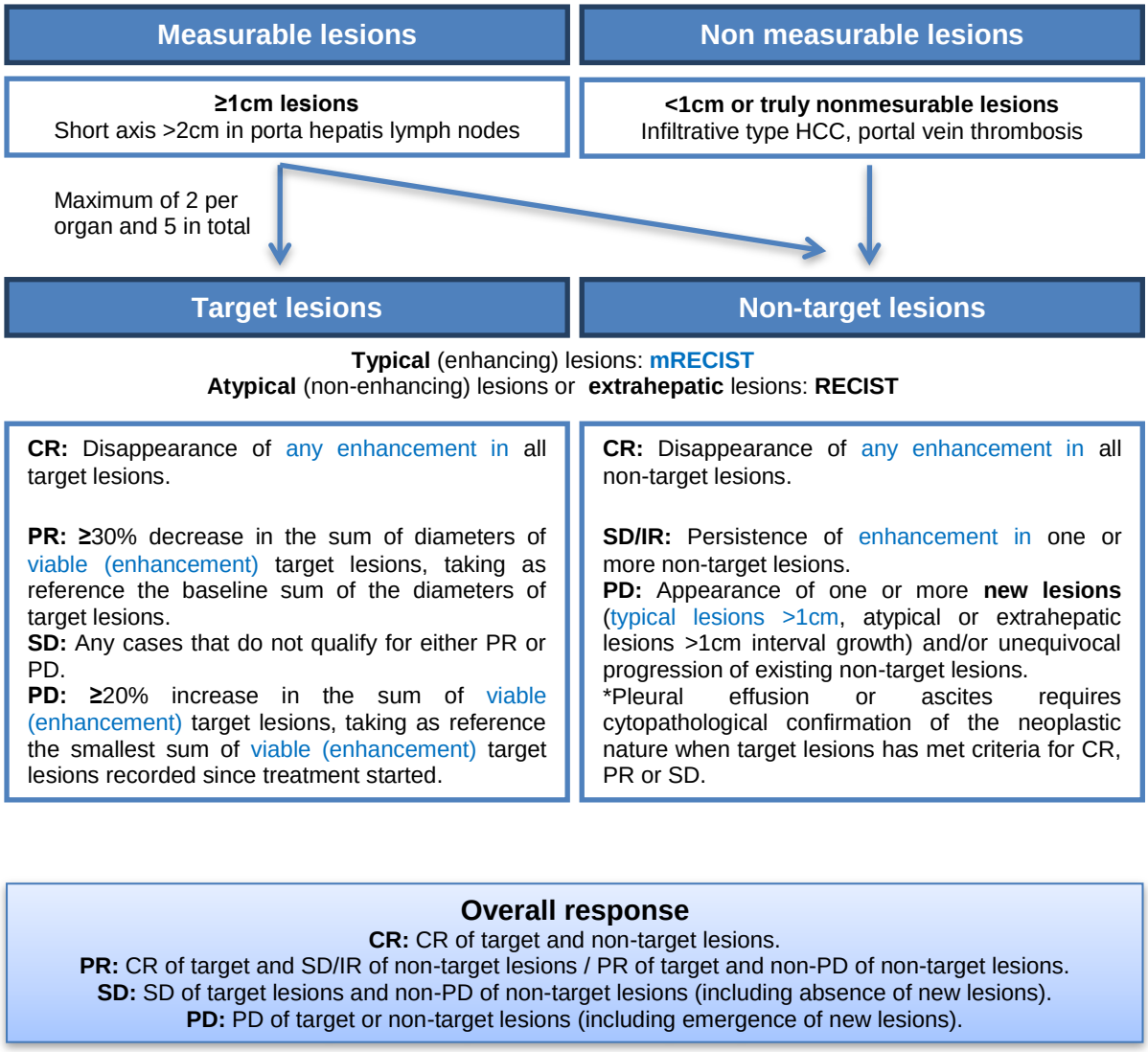
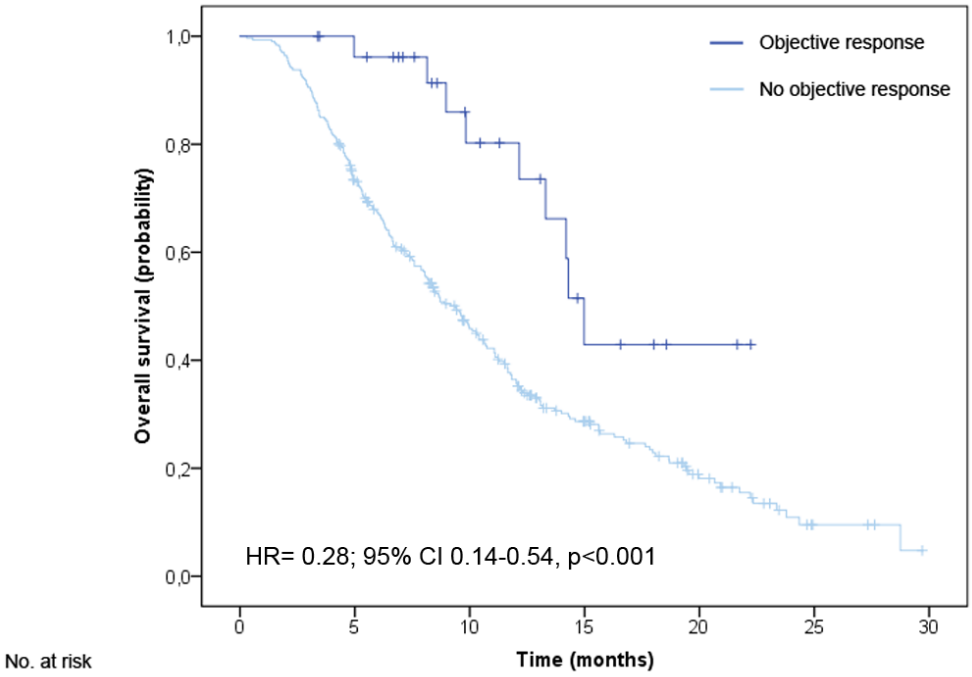

Measurable lesions
Non measurable lesions
≥1cm lesions
Short axis >2cm in porta hepatis lymph nodes
<1cm or truly nonmesurable lesions
Infiltrative type HCC, portal vein thrombosis
Maximum of 2 per organ and 5 in total
Target lesions
Non-target lesions
Typical (enhancing) lesions: mRECIST
Atypical (non-enhancing) lesions or extrahepatic lesions: RECIST
CR: Disappearance of any enhancement in all target lesions.
PR: ≥30% decrease in the sum of diameters of viable (enhancement) target lesions, taking as reference the baseline sum of the diameters of target lesions.
SD: Any cases that do not qualify for either PR or PD.
PD: ≥20% increase in the sum of viable (enhancement) target lesions, taking as reference the smallest sum of viable (enhancement) target lesions recorded since treatment started.
CR: Disappearance of any enhancement in all non-target lesions.
SD/IR: Persistence of enhancement in one or more non-target lesions.
PD: Appearance of one or more new lesions (typical lesions >1cm, atypical or extrahepatic lesions >1cm interval growth) and/or unequivocal progression of existing non-target lesions.
*Pleural effusion or ascites requires cytopathological confirmation of the neoplastic nature when target lesions has met criteria for CR, PR or SD.
Overall response
CR: CR of target and non-target lesions.
PR: CR of target and SD/IR of non-target lesions / PR of target and non-PD of non-target lesions.
SD: SD of target lesions and non-PD of non-target lesions (including absence of new lesions).
PD: PD of target or non-target lesions (including emergence of new lesions).

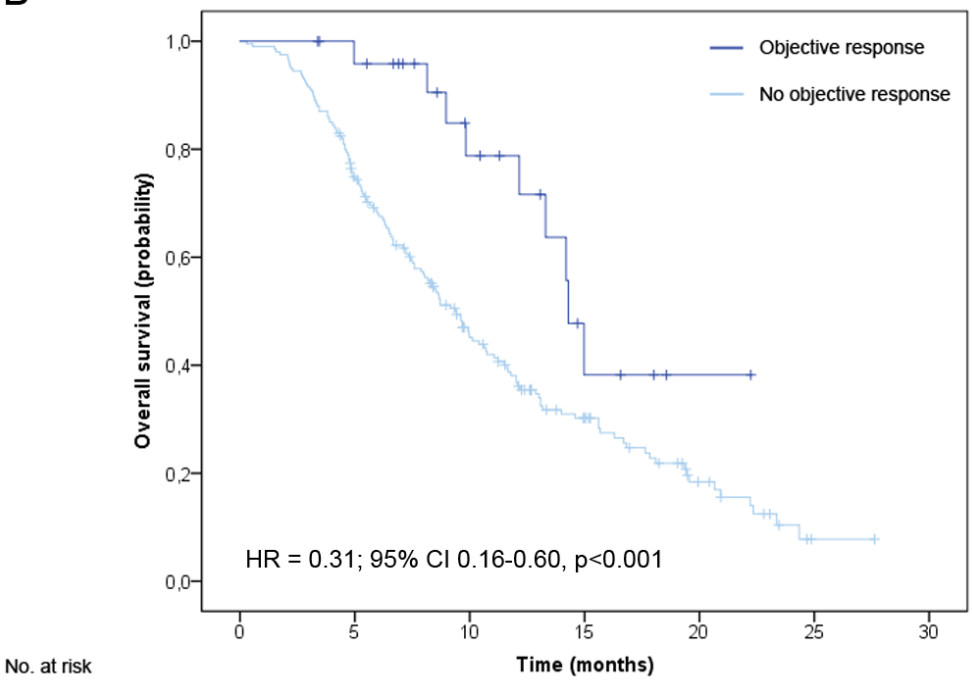
Fig. 2

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

Fig. 3

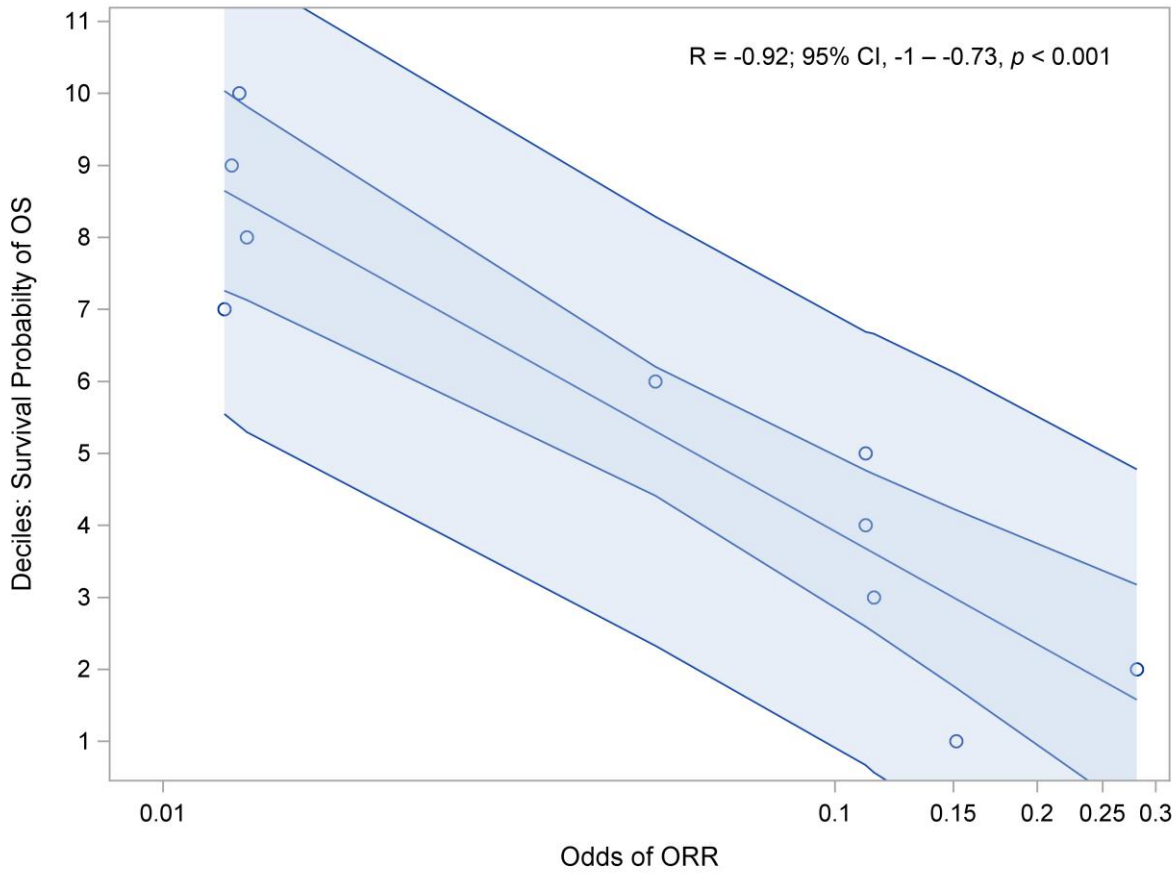
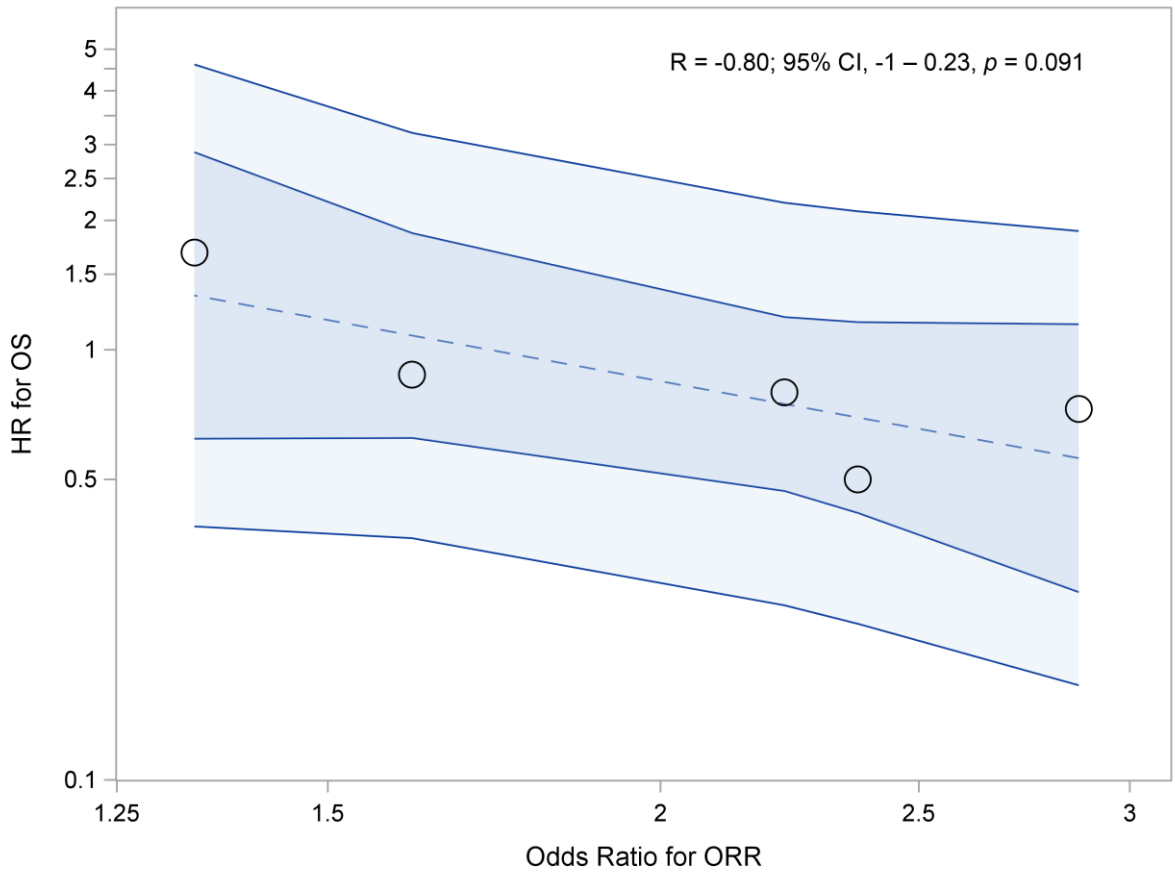

R = -0.92; 95% CI, -1 – -0.73, p < 0.001
Deciles: Survival Probability of OS
11
10
9
8
7
6
5
4
3
2
1
0.01
0.1
0.15
0.2
0.25
0.3
Odds of ORR

Fig. 4


R = -0.80; 95% CI, -1 – 0.23, p = 0.091
HR for OS
5
4
3
2.5
2
1.5
1
0.5
0.1
1.25
1.5
2
2.5
3
Odds Ratio for ORR