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Editorial

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Objective Response to Systemic Therapy Is a Strong Predictor of Overall Survival in Patients with Unresectable Hepatocellular Carcinoma

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Introduction

Some factors identified before systemic therapy for unresectable hepatocellular carcinoma (HCC) can be used to estimate prognosis to a certain extent. Such prognostic factor is essential to estimate whether a patient will survive long term once systemic therapy is initiated. In other words, knowledge of surrogate markers of overall survival (OS) in individual patients after the start of treatment is crucial.

The European Association for the Study of the Liver (EASL) clinical practice guidelines, published in the *Journal of Hepatology* in 2018 [1], cite seven clinical trials on locoregional therapy, each of which shows that responders (according to the mRECIST criteria) have a better prognosis than nonresponders. A meta-analysis of these seven trials showed that responders survive longer than nonresponders (hazard ratio [HR], 0.39; $p < 0.001$) [2]. Thus, EASL clinical practice guidelines recommend that there is high level of evidence that patients who respond to locoregional therapy have a better prognosis than those who do not.

The EASL clinical practice guidelines also describe the objective response (OR) to systemic therapy. Database analyses of two clinical trials showed that responders to systemic therapy have a better prognosis than nonresponders [3, 4]; however, EASL states that additional data are still needed to fully support a correlation between OR and OS [1].

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Guarantee-Time Bias on Responder Analysis in Systemic Therapy

There were several intensive arguments from biomedical statisticians associated with usual analysis of "response and OS" to systemic therapy. In 1983, Anderson et al. [5] stated that such usual responder analyses have a guarantee-time bias (GTB) (immortal-time bias) that favors the responder,

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often resulting in misinterpretations such as "response to systemic therapy contributes to survival." Anderson et al. [6] also introduced two statistical methods that remove this bias: landmark analysis and the Mantel-Byer test. Anderson, Weiss [7], and Simon [8] proposed that the *Journal of Clinical Oncology* (JCO) should not publish articles that include data on survival according to tumor response analyzed by the usual method. Dr. Josep Bertino, then Editor-in-Chief of the JCO, agreed with these suggestions and stated that "Authors should not compare survival of responders and nonresponders without discussing the limitations of such a comparison." [9, 10]. In 2013, JCO published a paper by Giobbie-Hurder et al. [11], entitled "Challenges of Guarantee-Time Bias," which introduced three statistical methods that can be used to remove GTB: (1) landmark analysis; (2) multivariate analysis using a Cox regression model with OR as a time-dependent covariate; and (3) inverse probability waiting. In addition, Simon and Makuch et al. [8] suggested a method for estimating the survival probability of responders and nonresponders that combined ideas based on the landmark and time-dependent covariate approaches.

Adequate Responder Analysis after Removing GTB

Two papers cited in the EASL guidelines (by Lencioni [3] and Meyer [4]) were published in 2017. The authors conducted multivariate analysis of individual patient data from the BRISK-PS trial [12] comparing brivanib with a placebo as a second-line treatment after sorafenib to demonstrate that an OR based on the mRECIST criteria predicts OS [3]. The ORR was 11.5% for brivanib and 1.9% for placebo. Moreover, the median OS for responders was 15.0 months, whereas that for nonresponders was 9.4 months ($p < 0.001$). Furthermore, OR was an independent prognostic factor (HR, 0.48; 95% confidence interval [CI]: 0.26–0.91; $p = 0.025$) by multivariate analysis. These results suggest that OR according to mRECIST is an independent predictor of OS. This is the first paper to use multivariate analysis with response as a time-dependent covariate, which removes GTB, to clarify the relationship between OR and OS during systemic therapy for HCC [3]. Meyer et al. [4] also combined European and Asian cohort databases from phase II clinical trials of patients treated with nintedanib or sorafenib [13, 14] and analyzed the response according to RECIST v1.0 and mRECIST. The authors also conducted multivariate Cox regression analysis using OR as a time-dependent covariate to eliminate GTB. The results demonstrate that OR according to mRECIST and RECIST v1.0 correlates with prognosis after systemic therapy [4]. They also noted that the HRs and p values were better for mRECIST and RECIST than for extrahepatic metastases or vascular invasion [4]. Furthermore, in the SILIUS trial [15], Kudo et al. [16] reported that the OR to sorafenib, as assessed by mRECIST, was predictive of OS. The authors performed (1) landmark analysis, (2) the Mantel-Byer test, and (3) multivariate analysis with OR as a time-dependent covariate, and the results showed that response to sorafenib was the strongest predictor than other factors such as performance status and AFP. In the sorafenib + hepatic arterial infusion chemotherapy arm of the SILIUS trial, OR was also the strongest predictor of the outcome (stronger than AFP). Combined analysis of the overall SILIUS study (sorafenib arm + sorafenib plus hepatic arterial infusion chemotherapy arm) revealed that OR was the strongest predictor of OS, with an HR of 0.37 (95% CI, 0.24–0.57; $p < 0.0001$); indeed, OR was associated more strongly with OS than AFP [16]. Kudo et al. [17] also analyzed the REFLECT study database and showed that OR correlated well with OS [17, 18]; to do this, they used all available statistical methods to eliminate GTB: (1) the Mantel-Byer test, (2) Simon-Makuch estimate, (3) landmark analysis, and (4) multivariate analysis with OR as a time-dependent covariate. The results showed that the OR to sorafenib or lenvatinib was the strongest predictor of OS (HR, 0.55; 95% CI, 0.44–0.68; $p < 0.0001$) [18]. Analysis of lenvatinib and sorafenib separately also showed that OR was a good predictor of prognosis [18]. Furthermore, an analysis of the IMbrave150 trial [19] by Ducreux et al. [20] revealed that OR was the strongest predictor of OS after both landmark analysis and multivariate Cox regression model analysis with OR as a time-dependent covariate (Table 1). In addition, Lim et al. [21] performed multivariate and landmark analyses of IMbrave150 and real-world data to eliminate GTB and showed clearly that the OR to Atezo/Bev correlated with OS.

A Meta-Analysis of Five Trials

Since much data comparing responders and nonresponders to systemic therapy for HCC have now been assessed using appropriate statistical methods, a meta-analysis of the five publications mentioned above, all of which performed adequate responder analyses without

Table 1. Studies included in the meta-analysis assessing the correlation of OR and OS

RCT	Study assessing the relation of OR and OS	Treatment evaluated, *N*	Best response, %	OS (95% CI) (responder vs. non-responder), months	HR (95% CI), *p* value	Statistical method to remove GTB
Llovet et al. *J Clin Oncol* [12] (2013) BRISK-PS (phase III)	Lencioni et al. *J Hepatol* [3] (2017)	Brivanib (263)	CR 0 (0) PR 26 (10) SD 135 (51) PD 49 (19)	15.0 (NA-NA) vs. 9.4 (NA-NA)	0.50 (0.25–0.99), 0.047	• Landmark analysis • Multivariate Cox regression analysis with OR as a time-dependent covariate
Palmer et al. *Br J Cancer* [13] (2018) Europe (phase II) Yen et al. *Liver Cancer* [14] (2018) Asia (phase II)	Meyar et al. *Liver Int* [4] (2017)	Nintedanib (125) Sorafenib (63)	NE 53 (20) CR 2 (1) PR 26 (14) SD 123 (65) PD 29 (15) NE 8 (4)	16.7 (10.7–28.4)s vs. 10.9 (6.2–18.2)	0.54 (0.34–0.88), 0.0122	• Multivariate Cox regression analysis with OR as a time-dependent covariate
Kudo et al. *Lancet Gastroenterol Hepatol* [15] (2018) SILIUS (phase III)	Kudo et al. *Liver Cancer* [16] (2019)	Sorafenib (103)	CR 2 (2) PR 16 (16) SP 57 (55) PD 21 (20) NE 7 (7)	27.2 (16.0–NR) vs. 8.9 (6.5–12.6)	0.32 (0.17–0.62), $p < 0.0001$	• Landmark analysis • Multivariate Cox regression analysis with OR as a time-dependent covariate • Mantel-Bayer test
Finn et al. *N Eng J Med* [19] (2020) IMbrave150 (phase III)	Ducreux et al. *ASCO* [20] (2021)	Atezolizumab + Bevacizumab (336)	CR, PR } 118 (35) SD 121 (36) PD 66 (20) NE 31 (9)	NR (26.2–NR) vs. NA	0.22 (0.15–0.32), $p < 0.001$	• Landmark analysis • Multivariate Cox regression analysis with OR as a time-dependent covariate
Kudo et al. *Lancet* (2018) [17] REFLECT (phase III)	Kudo et al. *J Hepatol* [18] (2023)	Lenvatinib (478) Sorafenib (476)	CR 8 (1) PR 151 (16) SD 490 (51) PD 218 (23) NE 87 (9)	21.6 (18.6–24.5) vs. 11.9 (10.7–12.8)	0.61 (0.49–0.76), $p < 0.001$	• Landmark analysis • Multivariate Cox regression analysis with OR as a time-dependent covariate • Mantel-Bayer test • Simon-Makuch estimate

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OR, objective response; OS, overall survival; HR, hazard ratio; NE, not evaluable; NR, not reached; NA, not available; GTB, guarantee-time bias.

GTB using information from the databases of the five clinical trials, was performed [22]. The results clearly showed that patients who respond to systemic therapy have better OS than those who do not (HR, 0.44; 95% CI, 0.27–0.70; $p = 0.0006$); thus, a meta-analysis of the highest and robust level of evidence demonstrated that the OR to systemic therapy is predictive of OS in HCC [22] (Fig. 1). Thus, in the near future, it is expected that clinical practice guidelines, including the EASL, will make a general statement that "OR to systemic therapy for HCC is a strong predictor of OS."

Can ORR Be a Surrogate Endpoint of Clinical Trials?

We showed that OR per mRECIST is an independent predictive and prognostic factor for OS in patients with advanced HCC treated with systemic therapies. However, in trial levels, ORR showed weak correlation with OS (correlation coefficient = 0.677, 95% CI, 0.655–0.697, $p = 0.022$) [22]. This low correlation coefficient may be due to the frequency or grade of adverse events in these phase 3 clinical trials. These facts suggest that the impact of ORR as an endpoint at the current level (20–30% ORR in the phase 3

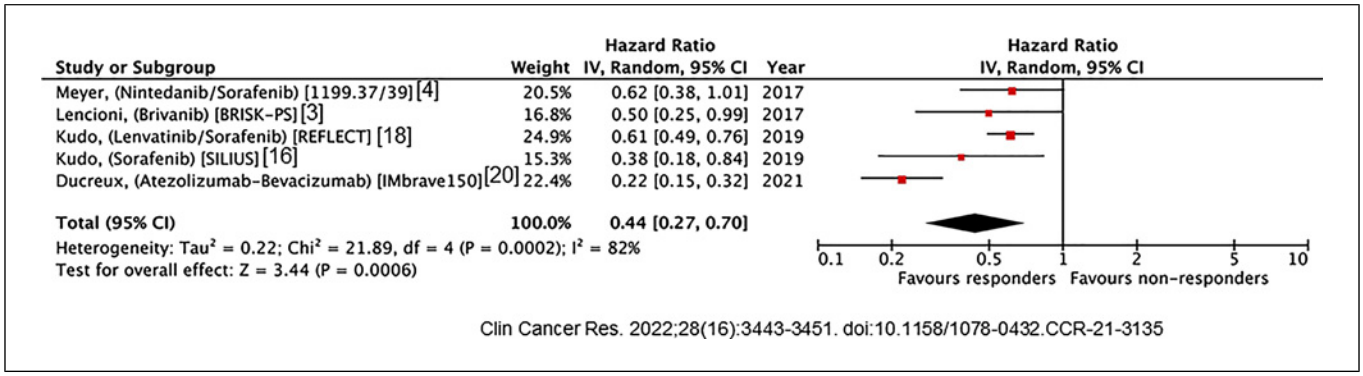

Fig. 1. A meta-analysis of the five independent studies to evaluate the impact of OR according to mRECIST in the OS forest plot for OS in responders versus nonresponders according to mRECIST criteria. HRs for each trial are represented by red squares; the size of the square represents the weight of the trial in the meta-analysis, and the horizontal line crossing the square represents the 95% CI. The diamond represents the estimated overall effect based on the meta-analysis of all trials. Inverse variance and random-effects methods were used to calculate HRs, 95% CIs, *p* values, and the test for overall effect; these calculations were two-sided (modified from ref #19 with permission).

clinical trials) does not suffice to propose a surrogate endpoint of OS in the phase 3 clinical trials evaluating systemic therapies for advanced HCC. However, since OR by mRECIST is an independent predictor of OS, it can be proposed as an efficacy endpoint in early-phase proof-of-concept single-arm clinical trials assessing novel systemic therapies in HCC to shorten the duration of early-phase clinical trials [22, 23].

Conclusion

It should be generally accepted that the OR to systemic therapy is a strong predictor of OS in individual HCC patients based on the additional studies and meta-analysis; however, it is still too early to make ORR a primary endpoint of phase 3 clinical trials [22, 23].

Conflict of Interest Statement

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Author Contributions

Masatoshi Kudo conceived, wrote, and approved the final manuscript.

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