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Objective Response by mRECIST is an Independent Prognostic Factor for overall Survival in Hepatocellular Carcinoma in SILIUS Trial

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Abstract

Background

In SILIUS (NCT01214343), combination of sorafenib and hepatic arterial infusion chemotherapy did not significantly improve overall survival in patients with advanced hepatocellular carcinoma (HCC) compared with sorafenib alone. In this study, we explored the relationship between objective response by mRECIST and overall survival (OS) in the sorafenib group, in the combination group and in all patients in the SILIUS trial.

Methods

Association between objective response and OS in patients treated with sorafenib (n=103), combination (n=102) and all patients (n=205) were analyzed. The median OS of responders was compared with that of non-responders. Landmark analyses were performed according to objective response at several fixed time points, as sensitivity analyses, and the effect on OS was evaluated by Cox regression analysis with objective response as a time-dependent covariate, with other prognostic factors was performed.

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Results

In the sorafenib group, OS of responders (n = 18) was significantly better than that of non-responders (n = 78) ($p < 0.0001$), where median OS was 27.2 (95% CI, 16.0–not reached) months for responders and 8.9 (95% CI, 6.5–12.6) months for non-responders. HRs from landmark analyses at 4, 6, and 8 months were 0.45 (p=0.0330), 0.37 (p=0.0053), and 0.36 (p=0.0083), respectively. Objective response was an independent predictor of OS based on unstratified Cox regression analyses. In the all patients and the combination group, similar results were obtained.

Conclusion

In the SILIUS trial, objective response was an independent prognostic factor for OS in patients with HCC.

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I. Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer deaths globally[1,2]. In Japan, more than 60% of HCC cases are detected early enough to be eligible for hepatectomy or ablation[3]. However, globally, most cases are diagnosed as advanced HCCs that are no longer resectable[4,5]. Currently, sorafenib and lenvatinib[6] are the first-line systemic agents approved worldwide for the treatment of advanced HCC.

Sorafenib is a multi-kinase inhibitor for which survival benefit was proven in the phase III SHARP trial[7] and the phase III Asia Pacific trial[8]. Lenvatinib is also a multi-kinase inhibitor, with a particularly strong inhibitory effect on VEGFR1-3, FGFR1-4, PDGFRα, RET, and KIT, and blocks angiogenesis and tumor growth[9-12].

The two major regimens used for hepatic arterial infusion chemotherapy (HAIC) are low-dose cisplatin plus 5-fluorouracil (5FU), and 5FU plus a systemic interferon, both of which are widely used in Japan, South Korea, and Taiwan[13]. Several retrospective comparative cohort studies have demonstrated a survival benefit of HAIC over no treatment in advanced HCC patients with vascular invasion or multiple liver lesions[14-20]. Furthermore, the

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Liver Cancer Study Group of Japan conducted a propensity score-matched analysis of data from a nationwide follow-up study and demonstrated a survival benefit of HAIC over best supportive care in 476 HCC patients[21]. In addition, phase I/II prospective studies also suggested the favorable results of HAIC in advanced HCC[22,23].

However, HAIC has not yet been tested in a prospective randomized phase III clinical trial, and thus it is not globally regarded as standard of care. Meanwhile, Kudo et al. conducted the prospective, controlled phase III SILIUS trial, which compared OS between sorafenib alone and sorafenib plus HAIC (5FU and cisplatin)[24]. The authors found that addition of HAIC to sorafenib did not significantly improve OS (the primary endpoint) in patients with advanced HCC. However, subgroup analysis revealed a better objective response rate (ORR) in the sorafenib plus HAIC group (36% in intention-to-treat [ITT] cohort) than in the sorafenib alone group (18% in ITT cohort) in ITT analysis. Also, time to progression (TTP) was significantly better in the sorafenib plus HAIC group than in the sorafenib alone group, demonstrating that sorafenib plus HAIC had a stronger antitumor effect than that of sorafenib alone. Furthermore, stratification by portal vein invasion (Vp0, Vp1-3, or Vp4, denoting no, first-to-third branch, or

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main portal vein invasion, respectively) revealed that sorafenib plus HAIC tended to result in a greater survival benefit compared with sorafenib alone specifically in Vp4 patients[24].

In the SILIUS trial, modified Response Evaluation Criteria in Solid Tumors (mRECIST) was used to assess ORR, and the ORR to sorafenib plus HAIC was significantly better than the ORR to sorafenib alone. It is well known that OR to transarterial chemoembolization (TACE), ablation, or molecular targeted therapy does not correlate with OS if OR is assessed using the standard RECIST1.1. To address this issue, Lencioni et al. developed the mRECIST to assess the response to treatment for HCC[25,26]. The mRECIST regards necrotic tissue as an effect of treatment, and distinguishes necrotic tissue from residual viable tumor tissue by size measurement on dynamic contrast-enhanced computed tomography (CT) or magnetic resonance imaging. A meta-analysis of seven studies showed that OR to TACE and ablation, as assessed by mRECIST, correlated well with OS[27], and subsequently the European Association for the Study of the Liver (EASL) used this in its guidelines as evidence that OR to locoregional therapy is a prognostic factor for OS[2]. Similarly, OR to molecular targeted therapy, as assessed by mRECIST, was an independent prognostic

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factor as well as a predictive factor, based on retrospective analyses of two previous clinical trials[26,28]. Nevertheless, as stated in the EASL guidelines, additional data are needed to confirm the relationship between OR to systemic therapy and OS[2] since from a statistical point of view the usual methods of comparing responders with non-responders were wrong due to guarantee-time bias or immortal time bias, leading to biased estimates of the survival distributions, invalid statistical tests, and misleading conclusions.[29,30].

In addition, J Clin Oncol decided that no longer publish articles that include survival by tumor response based on simple responder analysis. An editorial accompanying the letter by the then-editor of the *Journal of Clinical Oncology*, Joseph Bertino, MD, indicated that “authors should not compare survival of responders and non-responders without discussing the limitations of such a comparison”[31]. Therefore, usual method of responder analysis has been regarded to be a highly biased method and has been recommended not to perform to identify objective response (OR) as an independent predictor or prognostic factor of cancer treatment by almost all biostatical specialists or oncologists. Actually, Simon R indicated in the guideline that it should not publish comparisons of survival by tumor response in clinical trials because of the

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enormous biases[32]. In 2013, Giobbie-Hurder A, et al published the statistical methodology paper that there are several analytical methodologies that can remove the “Guarantee-time bias or immortal bias”; 1. Landmark analysis at the several fixed time points, 2. Cox regression analysis using OR as a time dependent covariate, 3. Inverse probability weighing and 4. Use of Mantel-Byar test instead of log rank test[33,34]. In this article, the relationship between OR and OS in sorafenib and sorafenib plus HAIC was examined using the phase 3 clinical trial data base of SILIUS study to determine whether OR evaluated by mRECIST is a predictive and prognostic factor for OS in HCC. As stated earlier, usual method of responder analysiswas not used. In stead, we followed Giobbie-Hurder’s statistical methods, which are currently becoming acceptable statistical methods to exclude the potential Guarantee-time bias. In this article, we used Mantel-Byar test for overall responder analysis and performed landmark analysis at 3 fixed points (4, 6 and 8 months). Also, we performed Cox regression multivariate analysis using OR as a time-dependent covariate and used a weighted Kaplan-Meier estimate.

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Patients and Methods

I. SILIUS trial design and assessments

The SILIUS study[24] is a phase III multicenter, open-label, prospective, randomized controlled trial of patients with unresectable HCC. A total of 205 patients were assigned in a 1:1 ratio to sorafenib alone (n = 102) or sorafenib plus HAIC (n = 103). The starting dose of sorafenib was 800 mg/day. In the sorafenib plus HAIC group, cisplatin was administered at 20 mg/m^2 per day on days 1 and 8, and fluorouracil was administered at a dose of 330 mg/m^2 per day on days 1–5 and 8–12 of every 28 day cycle, followed by 2 weeks off treatment. The first treatment cycle was started within 28 days of randomization. Sorafenib was continued until patients progressed, as assessed by mRECIST, or their general health worsened. Key inclusion criteria were as follows: age ≥ 20 years; advanced HCC untreatable by hepatectomy, local ablation, or TACE; life expectancy ≥ 12 weeks; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; Child-Pugh score ≤ 7; and adequate bone marrow, liver, and renal function. The key exclusion criterion was the presence of another previous or current malignancy. Stratification factors were institution, the presence or absence of an extrahepatic metastasis, and macroscopic vascular invasion (Vp0, Vp1-3, or Vp4). All patients provided written informed consent. The study protocol, amendments of the protocol, and the informed consent were approved by the ethics committees or Institutional Review Boards of individual participating institutions (ethic approval ID： Kindai University Faculty of Medicine Ethics Committee Approval code number 22-065). This clinical trial was conducted in compliance with the Declaration of Helsinki and the Good Clinical Practice Guidelines. The primary endpoint was OS, defined as the length of time from randomization to death from any cause. Secondary endpoints were progression-free survival, TTP, ORR, and safety. CT was performed every 8 weeks to assess the treatment effect.

Overall, 96 of 103 patients in the sorafenib group (93.3%) and 82 of 102 patients in the sorafenib plus HAIC group (80.4%) were evaluable for response with a baseline and at least one on-study scan. In this study, unlike in the

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original report[24], patients in whom objective response was not evaluable were excluded from subanalysis.

II. Statistical analysis

Analyses were performed using the SAS 9.4 software packages.

This post-hoc retrospective study compared investigator-assessed OR by mRECIST to OS in the total study population, in the sorafenib alone group, and in the sorafenib plus HAIC group. Responders were defined as those who had a CR or PR, and non-responders as those who had SD or progressive disease (PD). The difference of investigator-assessed OR between the two groups was evaluated by Fisher's exact test. OS in responders and non-responders in the sorafenib alone group and in the sorafenib plus HAIC group was estimated by the Kaplan-Meier method. In the total patient population, the OS was estimated by the weighted Kaplan-Meier method with treatment (sorafenib alone or sorafenib plus HAIC) as the weight. In the sorafenib alone and the sorafenib plus HAIC groups, the unweighted Kaplan-Meier method was used. The Mantel-Byar test was used to assess statistical significance. Landmark analysis of OS in each group by OR status was conducted at 4, 6,

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and 8 months after the initiation of therapy. The log-rank test was used for the inference associated to the landmark analysis. HRs and the 95% CIs were calculated from Cox models with all variables assessed as time-fixed covariates except OR, which was analyzed as a time-dependent covariate. Significant factors identified by univariable analysis were tested in multivariable analyses. A multivariable Cox regression model with OR as a time-dependent covariate was used to explore prognostic factors of OS.

Results

Efficacy

At the end of follow-up, 165 of the 205 patients had died, with a median OS of 11.5 months (95% CI, 8.2–14.8) in patients treated with sorafenib alone and 11.8 months (95% CI, 9.1–14.5) in those treated with sorafenib plus HAIC [HR, 1.009 (95% CI, 0.743–1.371); p = 0.955]. In the total patient population, 30.9% of patients (55/178) were responders, and the remaining 69.1% (123/178) were non-responders. In the sorafenib alone group, 18.8% of patients (18/96) were responders and the remaining 81.2% (78/96) were non-responders. In the sorafenib plus HAIC group, 45.1% of patients (37/82) were

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responders and the remaining 54.9% (45/82) were non-responders. Baseline and clinical characteristics of responders and non-responders are shown in Table 1.

Objective response as an independent prognostic factor

1) Total SILIUS patient population

In all patients, the median OS was 25.7 months (95% CI, 17.3–33.4) in responders and 9.3 months (95% CI, 6.9–11.4) in non-responders. The HR was 0.31 (95% CI, 0.20–0.46; $p < 0.0001$). ORR assessed by mRECIST was 30.9% (55/178; 95% CI, 24.2–38.3) in the SILIUS population. The ORR was significantly higher in the sorafenib plus HAIC group than in the sorafenib alone group; investigator-assessed ORR by mRECIST was 45.1% (95% CI, 34.1–56.5) in the sorafenib plus HAIC group and 18.8% (95% CI, 11.5–28.0) in the sorafenib alone group ($p=0.0001$, Fisher's exact test). Kaplan-Meier estimates in responders and in non-responders are shown in Figure 1.

Landmark analyses at 4, 6, and 8 months showed an overall OS benefit in responders compared with non-responders. Landmark analysis at 4 months after randomization revealed that OS was significantly longer in patients with

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OR than in those without OR [HR, 0.54 (95% CI, 0.34–0.87); p = 0.0106]. The same was true at 6 months [HR, 0.41 (95% CI, 0.26–0.66); p = 0.0003] and 8 months [HR, 0.36 (95% CI, 0.22–0.58); p < 0.0001] (Figure 2).

Multivariable Cox regression analysis revealed that OR assessed by mRECIST was an independent prognostic factor [HR, 0.37 (95% CI, 0.24–0.57); p < 0.0001]. Other prognostic factors identified were ECOG PS [HR, 1.88 (95% CI, 1.15–3.08); p = 0.0122] and alpha fetoprotein (AFP) level [HR, 1.84 (95% CI, 1.31–2.60); p = 0.0005] (Table 2).

2) Sorafenib alone group

The median OS was 27.2 months [95% CI, 16.0–not reached (NR)] in responders and 8.9 months (95% CI, 6.5–12.6) in non-responders in the sorafenib alone group. The HR was 0.32 (95% CI, 0.17–0.62; p < 0.0001). ORR assessed by mRECIST was 18.8% (18/96; 95% CI, 11.5–28.0). Kaplan-Meier estimates in responders and in non-responders in all SILIUS trial patients are shown in Figure 3.

Landmark analyses at each time point showed an overall OS benefit in responders compared with non-responders. Landmark analysis at 4 months after randomization revealed that OS was significantly longer in patients with

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OR than in those without OR [HR, 0.45 (95% CI, 0.21–0.96); p = 0.0330]. This was also the case at 6 months [HR, 0.37 (95% CI, 0.18–0.76); p = 0.0053] and at 8 months [HR, 0.36 (95% CI, 0.17–0.79); p < 0.0083] (Figure 4).

Multivariable Cox regression analysis revealed that OR assessed by mRECIST was an independent prognostic factor [HR, 0.38 (95% CI, 0.18–0.84); p = 0.0164]. AFP level was also identified as an independent prognostic factor [HR, 1.70 (95% CI, 1.02–2.83); p = 0.0406] (Table 3).

3) Sorafenib plus HAIC group

The median OS was 23.0 months (95% CI, 16.9–31.2) in responders and 9.9 months (95% CI, 5.3–11.8) in non-responders in the sorafenib plus HAIC group. The HR was 0.28 (95% CI, 0.16–0.49; p < 0.0001). ORR assessed by mRECIST was 45.1% (18/96; 95% CI, 11.5–28.0). Kaplan-Meier estimates in responders and in non-responders in the sorafenib plus HAIC group are shown in Supplementary Figure 1.

Landmark analyses at 4, 6, and 8 months showed an overall OS benefit in responders compared with non-responders. Landmark analyses at 4 months after randomization revealed that OS was not significantly longer in

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patients with OR than in those without OR [HR, 0.74; 95% CI, 0.42–1.28; p = 0.2752]. However, the median OS was significantly better in patients with OR than in those without OR at 6 months [HR, 0.54; 95% CI, 0.29–0.99; p = 0.0439] and at 8 months [HR, 0.36; 95% CI, 0.22–0.58; p < 0.0001] (Supplementary Fig. 2).

Multivariable Cox regression analysis revealed that OR assessed by mRECIST was an independent prognostic factor [HR, 0.32 (95% CI, 0.18–0.59); p = 0.0003]. APF level was also a significant prognostic factor [HR 2.46 (95% CI, 1.33–4.55), p = 0.0043] (Table 4).

Discussion

This retrospective study analyzed data from the SILIUS study to determine the association between investigator-assessed OR by mRECIST and OS, and showed that OR by mRECIST was an independent prognostic factor in patients receiving sorafenib alone, in patients receiving sorafenib plus HAIC, and in the total study population. OS was significantly better in patients with a CR or PR by mRECIST than in those with SD or PD. This secondary study used

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landmark analyses, which are a common method to eliminate a guarantee-time bias (lead-time bias)[29,30,33]. Responder analysis was performed at three time points (4, 6, and 8 months); that is, survival at a certain time point was evaluated in relation to the best response by that time point in patients who were still participating in the study at that time. Patients who died before a landmark time point were excluded.

Another established method that eliminates guarantee-time bias (lead-time bias) is to use a multivariable Cox regression model with OR as a time-dependent covariate[29,30,33]. This approach adjusts for possible confounding factors, thereby enabling assessment of the effect of tumor response on survival. This statistical method also takes into account time-dependent changes in response status.

The important findings of this study are that OR status at 4 months was a strong predictor and prognostic factor for survival in SOR alone group, and that OR status at 6 months and 8 months were also significant prognostic factors for OS in both SOR alone and SOR plus HAIC groups. This implies that survival can be predicted based on OR assessed by mRECIST at a relatively early stage after randomization in systemic therapy.

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Multivariable Cox regression analyses in this study also identified PS and AFP levels as independent predictive factors for prognosis in the SILIUS patient population, which is in good agreement with the findings of several previous studies. Landmark analyses and multivariable Cox regression analyses of patients that received sorafenib alone or sorafenib plus HAIC showed similar results, confirming that OR by mRECIST is an independent prognostic factor. The relationship between OR by mRECIST and OS shown in this study is consistent with previously reported results from prospective trials[24,28,35]. In one such study, a time-dependent multivariable analysis of data from the phase III BRISK-PS trial clearly showed that OR by mRECIST is an independent predictor of prognosis, and multivariable analyses confirmed that OR is an independent prognostic factor of OS[26]. In a different study, an analysis of pooled data from two phase II trials comparing nintedanib to sorafenib revealed a good relationship between OR assessed by mRECIST and OS[28]. OR by mRECIST was also an independent prognostic factor of OS in the REFLECT trial regardless of treatment (lenvatinib or sorafenib) [32].

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The present study also confirmed that OR to systemic therapy, sorafenib, assessed by mRECIST is a predictive and prognostic factor for OS[36]. We note that this would not guarantee that the OR is a surrogate endpoint of OS [37]

III. Conclusions

This study clearly demonstrates that OR assessed by mRECIST is a predictive and prognostic factor for OS irrespective of the therapy given. These findings also suggest that therapies that result in a high ORR may provide a survival benefit in more patients. Consistent with findings from three previous prospective studies, this study showed that OR by mRECIST in systemic therapy is a predictive and a prognostic factor of OS. To provide further evidence of this relationship, more data must be accumulated and ultimately subjected to meta-analysis.

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Table 1

Patient Characteristics of Responders and Non Responders in SILIUS Trial

Characteristics		All Cohort		Sorafenib Alone Group		Sorafenib Plus HAIC Group	
		Responders (n=55)	Non responders (n=123)	Responders (n=18)	Non responders (n=78)	Responders (n=37)	Non responders (n=45)
Median Age, years(range)							
	≥65	35(64%)	82(67%)	14(78%)	54(69%)	21(57%)	28(62%)
	<65	20(36%)	41(33%)	4(22%)	24(31%)	16(43%)	17(38%)
Sex, n(%)							
	Male	47(85%)	108(88%)	15(83%)	67(86%)	32(86%)	41(91%)
	Female	8(15%)	15(12%)	3(17%)	11(14%)	5(14%)	4(9%)
Performance status, n(%)							
	0	50(91%)	107(87%)	17(94%)	69(88%)	33(89%)	38(84%)
	1	5(9%)	16(13%)	1(6%)	9(12%)	4(11%)	7(16%)
Etiology HBV, n(%)							
	Yes	14(25%)	28(23%)	4(22%)	15(19%)	10(27%)	13(29%)
	No	40(73%)	94(76%)	13(72%)	62(79%)	27(73%)	32(71%)
	indeterminate	1(2%)	1(1%)	1(6%)	1(1%)	0(0%)	0(0%)
Etiology HCV, n(%)							
	Yes	26(47%)	54(44%)	9(50%)	34(44%)	17(46%)	20(44%)
	No	28(51%)	67(54%)	8(44%)	43(55%)	20(54%)	24(53%)
	indeterminate	1(2%)	2(2%)	1(6%)	1(1%)	0(0%)	1(2%)
ALBI Grade, n(%)							
	1	24(44%)	40(33%)	9(50%)	28(36%)	15(41%)	12(27%)
	2	31(56%)	82(67%)	9(50%)	50(64%)	22(59%)	32(71%)
	3	0(0%)	1(1%)	0(0%)	0(0%)	0(0%)	1(2%)
Albumin, n(%)							
	≥3.7 g/dl	34(62%)	62(50%)	10(56%)	43(55%)	24(65%)	19(42%)
	<3.7 g/dl	21(38%)	61(50%)	8(44%)	35(45%)	13(35%)	26(58%)
Bilirubin, n (%)							
	<0.8 mg/dl	33(60%)	53(43%)	15(83%)	30(38%)	18(49%)	23(51%)
	≥0.8 mg/dl	22(40%)	70(57%)	3(17%)	48(62%)	19(51%)	22(49%)
Macroscopic portal vein invasion, n (%)							
	Vp0	23(42%)	49(40%)	7(39%)	30(38%)	16(43%)	19(42%)
	Vp1-4	32(58%)	74(60%)	11(61%)	48(62%)	21(57%)	26(58%)
Extrahepatic spread, n (%)							
	Yes	15(27%)	31(25%)	5(28%)	19(24%)	10(27%)	12(27%)
	No	40(73%)	92(75%)	13(72%)	59(76%)	27(73%)	33(73%)
Baseline serum AFP, n (%)							
	<400 ng/ml	30(55%)	63(51%)	11(61%)	41(53%)	19(51%)	22(49%)
	≥400 ng/ml	23(42%)	60(49%)	7(39%)	37(47%)	16(43%)	23(51%)
	Missing	2(4%)	0(0%)	0(0%)	0(0%)	2(5%)	0(0%)
Baseline serum DCP, n (%)							
	<2050 mAU/ml	27(49%)	61(50%)	9(50%)	42(54%)	18(49%)	19(42%)
	>2050 mAU/ml	25(45%)	62(50%)	8(44%)	36(46%)	17(46%)	26(58%)
	Missing	3(5%)	0(0%)	1(6%)	0(0%)	2(5%)	0(0%)
mRECIST BOR, n (%)							
	Complete response	10(18%)	0(0%)	2(11%)	0(0%)	8(22%)	0(0%)
	Partial response	45(82%)	0(0%)	16(89%)	0(0%)	29(78%)	0(0%)
	Stable disease	0(0%)	86(70%)	0(0%)	57(73%)	0(0%)	29(64%)
	Progressive disease	0(0%)	37(30%)	0(0%)	21(27%)	0(0%)	16(36%)
Treatment							
	Sorafenib + HAIC	37(67%)	45(37%)				
	Sorafenib	18(33%)	78(63%)				

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Table 2

Univariable and Multivariable Analysis of Factors Associated with OS (Overall SILIUS)

	Univariable Analysis			Multivariable Analysis		
Parameter	HR [95% CI]		*p* Value	HR [95% CI]		*p* Value
Treatment (SOR+HAIC vs SOR)	0.88	[0.63–1.23]	0.4521			
Response (CR+PR vs SD+PD)	0.39	[0.26–0.58]	<0.0001	0.37	[0.24–0.57]	<0.0001
Age (≥65 vs <65)	1.25	[0.87–1.78]	0.2245			
Sex (Male vs Female)	0.76	[0.47–1.22]	0.2575			
PS (1 vs 0)	2.17	[1.34–3.51]	0.0015	1.88	[1.15–3.08]	0.0122
Vp(Vp1-4 vs Vp0)	0.88	[0.63–1.22]	0.4384			
Extrahepatic spread (yes vs no)	1.03	[0.70–1.51]	0.8981			
HBV (yes vs no)	1.15	[0.78–1.71]	0.4753			
HCV (yes vs no)	0.93	[0.66–1.30]	0.6741			
Albumin (≥3.6 mg/dl vs <3.6 mg/dl)	0.80	[0.58–1.12]	0.1976			
Bilirubin(≥0.8 mg/dl vs <0.8 mg/dl)	1.57	[1.12–2.21]	0.0086	1.34	[0.95–1.89]	0.0995
ALBI grade (Grade2 vs Grade1)	1.26	[0.88–1.79]	0.2019			
AFP(≥400 ng/ml vs <400 ng/ml)	1.68	[1.20–2.36]	0.0024	1.84	[1.31–2.60]	0.0005
DCP (≥2050 mAU/ml vs <2050 mAU/ml)	1.05	[0.75–1.47]	0.7610			

All covariates were time-fixed except for response which was time-dependent

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Table 3

Univariable and Multivariable Analysis of Factors Associated with OS (Sorafenib Alone Group)

	Univariable Analysis			Multivariable Analysis		
Parameter	HR [95% CI]		*p* Value	HR [95% CI]		*p* Value
Response (CR+PR vs SD+PD)	0.37	[0.19–0.71]	0.0029	0.38	[0.18–0.84]	0.0164
Age (≥65 vs <65)	0.94	[0.57–1.53]	0.7936			
Sex (Male vs Female)	1.06	[0.56–2.01]	0.8550			
PS (1 vs 0)	1.95	[1.00–3.80]	0.0509	1.88	[0.91–3.88]	0.0880
Vp(Vp1-4 vs Vp0)	0.90	[0.57–1.42]	0.6502			
Extrahepatic spread (yes vs no)	1.14	[0.68–1.92]	0.6205			
HBV (yes vs no)	1.77	[1.01–3.10]	0.0472	1.39	[0.71–2.72]	0.3381
HCV (yes vs no)	0.68	[0.43–1.08]	0.0997	0.86	[0.50–1.49]	0.5989
Albumin (≥3.6 mg/dl vs <3.6 mg/dl)	1.10	[0.70–1.74]	0.6839			
Bilirubin(≥0.8 mg/dl vs <0.8 mg/dl)	1.94	[1.21–3.09]	0.0055	1.35	[0.80–2.26]	0.2608
ALBI grade (Grade2 vs Grade1)	0.92	[0.58–1.45]	0.7071			
AFP(≥400 ng/ml vs <400 ng/ml)	1.48	[0.94–2.33]	0.0884	1.70	[1.02–2.83]	0.0406
DCP(≥2050 mAU/ml vs <2050 mAU/ml)	1.04	[0.67–1.64]	0.8500			

All covariates were time-fixed except for response which was time-dependent

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Table4

Univariable and Multivariable Analysis of Factors Associated with OS (Sorafenib plus HAIC Group)

	Univariable Analysis			Multivariable Analysis		
Parameter	HR [95% CI]		*p* Value	HR [95% CI]		*p* Value
Response (CR+PR vs SD+PD)	0.36	[0.21–0.64]	0.0004	0.32	[0.18–0.59]	0.0003
Age (≥65 vs <65)	1.63	[0.97–2.73]	0.0651	1.70	[0.94–3.08]	0.0788
Sex (Male vs Female)	0.43	[0.21–0.89]	0.0231	0.67	[0.28–1.61]	0.3730
PS (1 vs 0)	2.66	[1.31–5.37]	0.0066	1.54	[0.65–3.69]	0.3284
Vp(Vp1-4 vs Vp0)	0.87	[0.53–1.42]	0.5777			
Extrahepatic spread (yes vs no)	0.94	[0.53–1.66]	0.8213			
HBV (yes vs no)	0.87	[0.50–1.52]	0.6276			
HCV (yes vs no)	1.30	[0.79–2.13]	0.2981			
Albumin (≥3.6 mg/dl vs <3.6 mg/dl)	0.55	[0.33–0.90]	0.0169	0.98	[0.48–1.98]	0.9446
Bilirubin(≥0.8 mg/dl vs <0.8 mg/dl)	1.22	[0.74–2.00]	0.4348			
ALBI grade (Grade2 vs Grade1)	1.95	[1.11–3.45]	0.0208	1.66	[0.78–3.53]	0.1855
AFP(≥400 ng/ml vs <400 ng/ml)	2.06	[1.24–3.45]	0.0056	2.46	[1.33–4.55]	0.0043
DCP (≥2050 mAU/ml vs <2050 mAU/ml)	1.11	[0.67–1.84]	0.6824			

All covariates were time-fixed except for response which was time-dependent