after single oral dose at 100 mg/kg in mice was 6971 ng/mL.

Novel drugs are expected to extend the overall survival time in patients with HCC. Therefore, PR and CR, which are commonly used to evaluate solid tumors, are important indicators of the response to treatment. The disease control rate is also commonly used to evaluate the tumor response. Earlier Phase 3 trials of sorafenib (the SHARP trial[19] and the Asian-Pacific trial[20]) used the disease control rate as a secondary endpoint and the overall survival time as a primary endpoint. In these trials, although the proportions of patients with PR or better outcomes were low (≤5% of patients had tumor regression effects of PR or better; ≥50% of patients had SD), administration of sorafenib extended the time to progression and the overall survival time compared with a placebo. Because the SD control rate may help extend the overall survival time in patients, a SD control rate is often used in addition to PR and CR in studies of HCC therapies. Therefore, in this study, we assessed the SD control rate as well as CR and PR to assess the efficacy of OPB-31121.

In this study, none of the patients had a CR or PR, but reduced tumor sizes were observed in three patients (two patients in the 50-mg dose cohort, and one patient in the 100-mg dose cohort) and six patients maintained SD for ≥8 consecutive weeks. These results suggested the possibility that OPB-31121 has antitumor activity from lower doses, and disease control effect contributing to prolonged survival. Furthermore, although there were no apparent reductions in tumor size, the SD control rate was 42.9% in the 200-mg dose cohort, suggesting that a dose of

200 mg/day is an optimal starting dose for future studies examining the efficacy of OPB-31121.

The present PK results revealed the accumulation of OPB-31121 and its major active metabolite in terms of their plasma concentrations. The results also showed that the exposure to the major active metabolite was greater than that of OPB-31121. However, it was difficult to determine the PK characteristics of OPB-31121 and its metabolites because of the high inter-patient variability and small number of patients in the highest dose cohort (i.e. 400 mg/day). The present results showed that the mean C_{max} of OPB-31121 at 200 mg was two-times higher than its IC_{50} for inhibiting tumor proliferation of HepG2 cells and other liver cancer cell lines. However, the C_{max} for the 200-mg dose was about 1/500 of the C_{max} that showed tumor regression in mice subcutaneously inoculated with a human liver cancer cell line *in vivo*. The reasons for the low absorption or concentration of OPB-31121 in human blood were considered to be due to the metabolization of OPB-31121 by CYP3A4 and 2C9 in small intestine and liver, and the organ distribution is larger than in blood. In the preclinical PK studies, the concentration of OPB-31121 in the liver was greater than its plasma concentrations in rats and monkeys *in vivo* (in rats, the concentrations were compared in terms of the radioactivity of OPB-31121 and its metabolites). The liver-to-plasma concentration ratio was 1.9 (at 2 h after a single oral dose at 1 mg/kg) in rats and 69.5 (at 8 h after 7 days of repeated administration at 30 mg/kg) in monkeys. Because the PK characteristics of OPB-31121 were comparable between the preclinical studies in monkeys and the Phase 1 trial in humans, the

liver concentrations of OPB-31121 in humans were expected to be high. Furthermore, the result of *in vitro* study has shown that the solubility of OPB-31121 is particularly poor at pH around neutral. Therefore, there was a possibility that the absorption of OPB-31121 in blood was low due to poor solubility caused by gastric pH in each patient.

In conclusion, the PK analyses conducted here suggest that OPB-31121 is not easily absorbed and its plasma concentration in the patients did not reach the concentration at which antiproliferative activities were expected based on prior results. Although OPB-31121 was suggested to be effective based on results from some cases where long SD for more than 8 weeks duration and reduction in the size of viable target lesions were observed after treatment, it was not sufficiently potent to suppress the progression of advanced HCC. Overall, while OPB-31121 was safe and well tolerated in patients with advanced HCC at doses of 50–200 mg/day, peripheral nervous system-related toxicities were observed that could negatively affect long-term administration of OPB-31121. Based on these findings, it was deemed difficult to continue the clinical development of OPB-31121 for treating advanced HCC. However, regarding the relationship between inhibition of STAT 3 activation and clinical antitumor activity, JAK inhibitor which targets the Janus kinase family, interfering the JAK-STAT signaling pathway has shown to be clinically effective against a kind of hematological malignancy[21]. STAT3 activation has also been observed in various solid tumors including HCC by several studies[9-14, 22]. Therefore, STAT3 inhibitor is expected to be a promising treatment

option against HCC. Further investigation is expected in the agent with favorable profile in this

category.

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Table 1. Patient characteristics

Variable	Value
n	23
Age (years), median (range)	65.0 (46–79)
Sex, n (%)	
Male	20 (87.0)
Female	3 (13.0)
ECOG PS, n (%)	
0	16 (69.6)
1	7 (30.4)
2	0 (0.0)
Child–Pugh class, n (%)	
A	22 (95.7)
B	1 (4.3)
Tests for infectious diseases, n (%)[†]	22
HBV positive	6 (27.3)

HCV positive	6 (27.3)
HBC/HCV negative	10 (45.5)

Stage of primary disease, *n* (%)

I	0 (0.0)
II	1 (4.3)
III	4 (17.4)
IVA	0 (0.0)
IVB	18 (78.3)

Intrahepatic tumor size, *n* (%)

≤2 cm	6 (26)
>2 to ≤5 cm	6 (26)
>5 cm	11 (48)

Distant metastasis, *n* (%)

No	5 (21.7)
Yes	18 (78.3)

Portal vein tumor thrombus, *n* (%)

No	18 (78.3)
Yes	5 (21.7)
Previous therapy for HCC, *n* (%)	
Liver resection	15 (65.2)
Radiotherapy	1 (4.3)
RFA	5 (21.7)
TACE	15 (65.2)
Chemotherapy	23 (100.0)
Number of regimens, median (range)	2 (1–5)
Sorafenib	22 (95.7)

[†]The number of patients differs from that of the safety population.

ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization.

Table 2 Incidence of potential adverse drug reactions in >10% of patients

Dose level Adverse event	50 mg %	100 mg %	200 mg %	400 mg %	All patient %
Blood and lymphatic system disorders	14.3	0.0	14.3	60.0	21.7
Leukopenia	0.0	0.0	0.0	60.0	13.0
Gastrointestinal disorders	71.5	100.0	100.0	100.0	91.3
Nausea	57.2	100.0	100.0	100.0	87.0
Vomiting	57.1	75.0	100.0	100.0	82.6
Diarrhea	28.6	100.0	85.8	80.0	69.6
General disorders and administration site conditions	71.4	25.0	71.4	60.0	60.9
Fatigue/malaise	71.4	25.0	57.2	40.0	52.2
Investigations	42.9	50.0	57.2	40.0	47.8
Neutrophil count decreased	14.3	25.0	14.3	0.0	13.0
Platelet count decreased	14.3	25.0	14.3	0.0	13.0
Metabolism and nutrition disorders	28.6	50.0	42.9	100.0	52.2
Anorexia	14.3	50.0	42.9	100.0	47.8

Nervous system disorders	14.3	25.0	57.2	40.0	34.8
Peripheral sensory neuropathy	0.0	0.0	57.2	40.0	26.1
Respiratory, thoracic and mediastinal disorders	0.0	25.0	14.3	20.0	13.0

Table 3 Best overall responses

Dose level	*n*	CR	PR	SD†	PD	Not evaluable	Disease control rate‡
50 mg	7	0	0	2 (28.6)	4 (57.1)	1 (14.3)	(28.6)
100 mg	4	0	0	1 (25.0)	2 (50.0)	1 (25.0)	(25.0)
200 mg	7	0	0	3 (42.9)	2 (28.6)	2 (28.6)	(42.9)
400 mg	5	0	0	0	1 (20.0)	4 (80.0)	0
All patients	23	0	0	6 (26.1)	9 (39.1)	8 (34.8)	(26.1)

Values are shown as the n (%), except the disease control rate (%).

†SD for ≥8 consecutive weeks.

‡CR + PR + SD for ≥8 consecutive weeks.

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Table 4 Time to disease progression (days)

	50 mg	100 mg	200 mg	400 mg	All patients
25th percentile	32.0	33.0	59.0	35.0	35.0
Median	60.0	61.0	89.0	—	61.0
75th percentile	102.0	86.0	114.0	—	102.0

Table 5 Pharmacokinetics of OPB-31121 after a single oral dose

Dose level	n	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	$t_{1/2,z}$ (h)
50 mg	6	2.5 ± 1.3	36.0 ± 16.4	64.8 ± 53.1
100 mg	4	11.7 ± 13.4	99.4 ± 120.0	25.4 ± 13.7
200 mg	7	15.1 ± 9.3	$156.0 \pm 10.7.0$	34.8 ± 34.8
400 mg	4	19.0 ± 12.2	437.0 ± 358.0	31.9 ± 18.9

Values are presented as the mean ± standard deviation.

AUC_{inf}, area under the plasma concentration–time curve from time 0 to the last sampling time; C_{max}, maximum plasma drug concentration; $t_{1/2,z}$, terminal half-life.
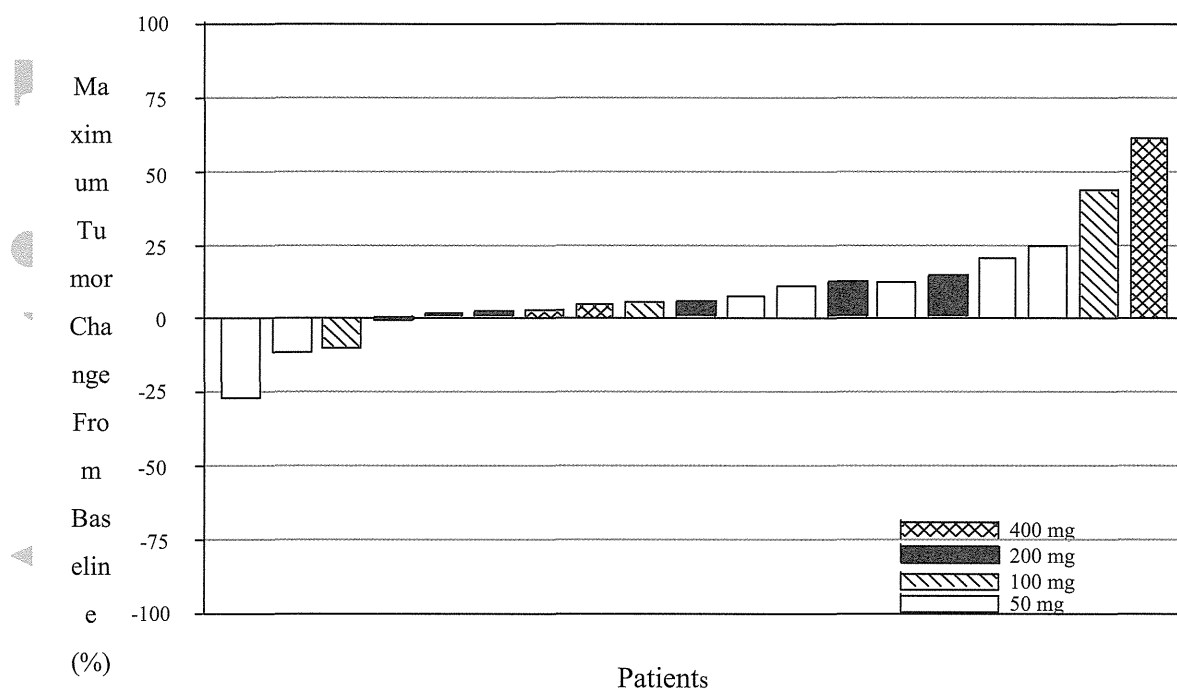
Fig. 1. Waterfall plot of the maximum change in size of the viable (contrast enhancement in the arterial phase) target lesions. Maximum change in tumor size from baseline (%) = (sum of the longest diameters at screening − minimum sum of longest diameters)/(sum of the longest diameters at screening) × 100. Reductions in the maximum tumor size before and after treatment with OPB-31121 are shown as negative values.
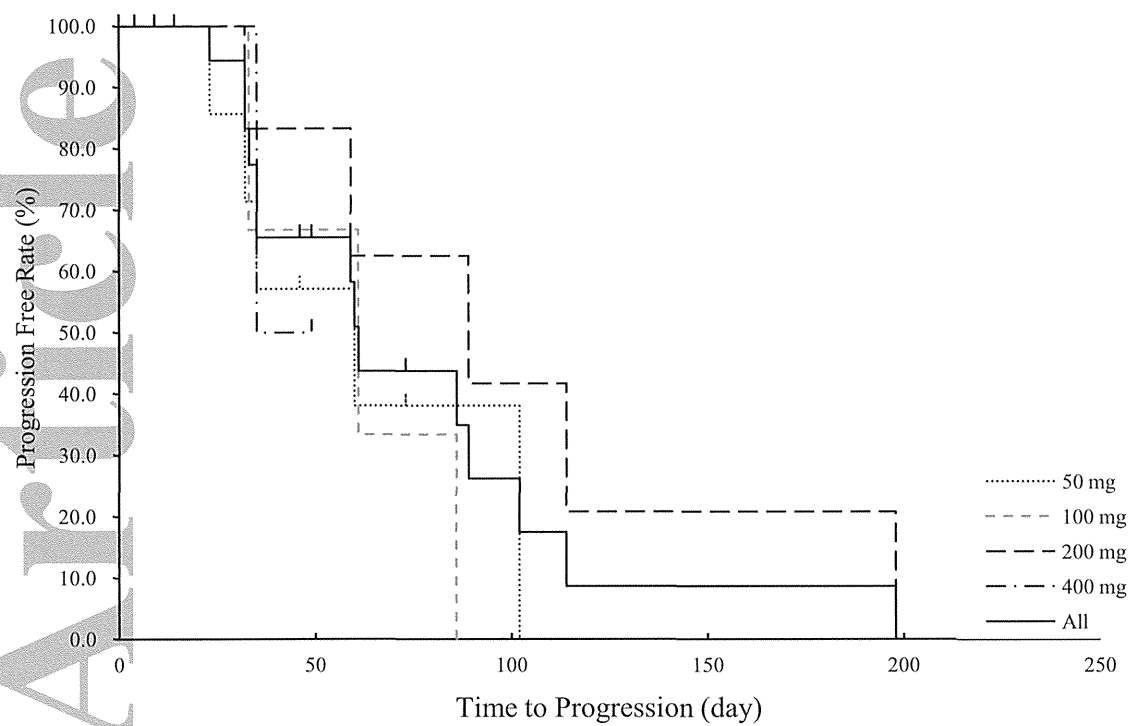
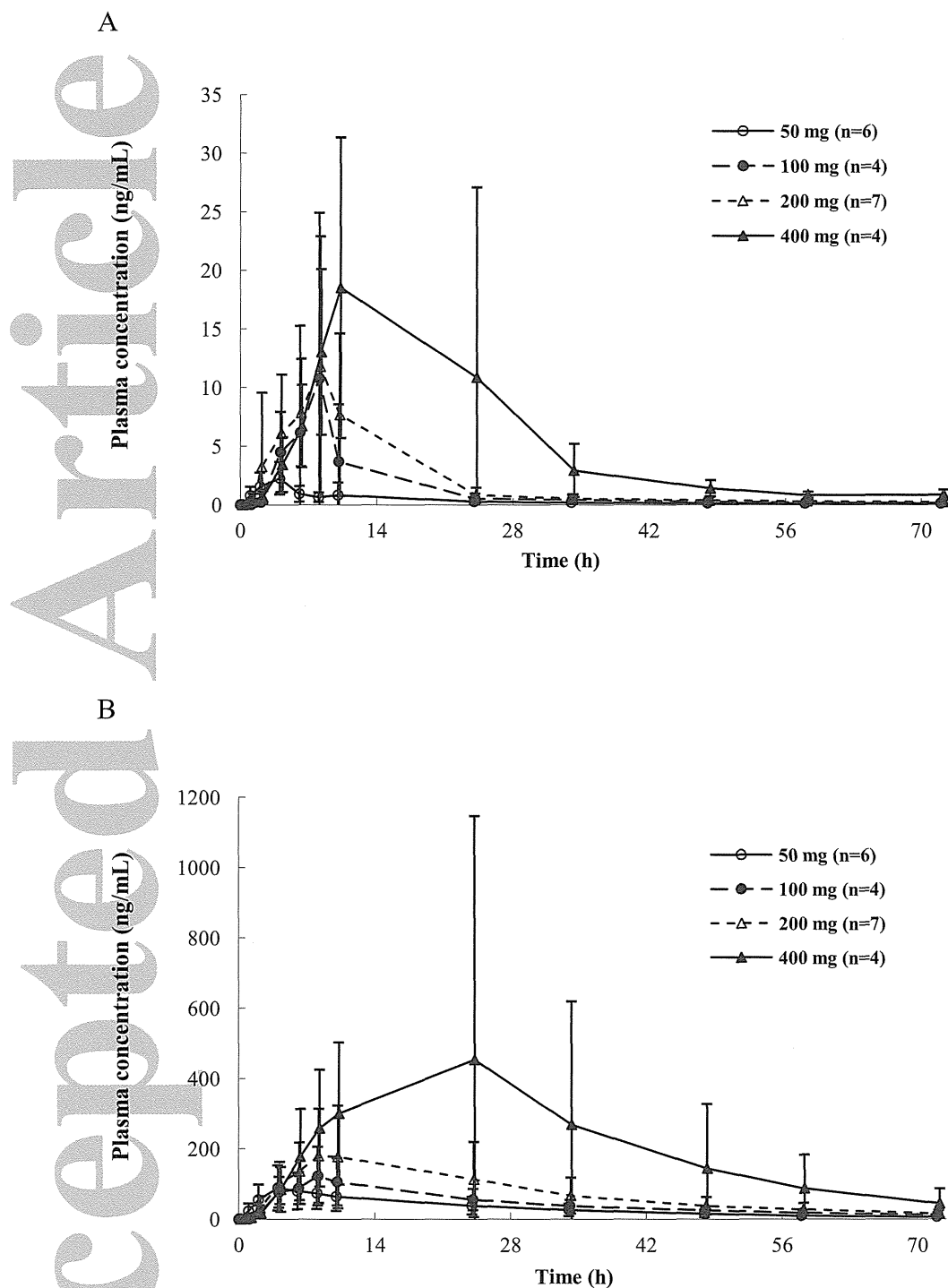Fig. 2. Kaplan–Meier plot of time to disease progression.

A

B

Fig. 3. Time-courses of the plasma concentrations of OPB-31121 (A) and its major metabolite (B) after a single oral dose of OPB-31121. Plasma concentrations below the lower limit of quantification were defined as 0 ng/mL. Values are presented as the mean ± standard deviation.

Hepatology Research

Original Article

Characteristics of 18 patients with hepatocellular carcinoma who obtained a complete response after treatment with sorafenib

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Aim: Sorafenib, a multi-targeted tyrosine kinase inhibitor, is a first-line systemic treatment for advanced hepatocellular carcinoma (HCC). However, possible predictors of the efficacy of sorafenib treatment in HCC patients remain unclear.

Methods: We conducted a nationwide survey to examine the situation of patients with HCC treated with sorafenib who obtained a complete response (CR) according to the modified response evaluation criteria in solid tumors (mRECIST). The investigation was intended to collect clinical information regarding CR patients and to compare this data with an interim report examining all-patient surveillance for sorafenib use in Japan, which was released in May 2012.

Results: Among the 3047 patients who were treated at institutions belonging to the Liver Cancer Study Group of Japan, 18 patients (0.6%) obtained a CR. Significant factors in the CR group were a female sex, a low bodyweight (<59 kg), an early clinical stage and a small initial dose of sorafenib ($P < 0.05$). Furthermore, specific adverse events (palmar–plantar erythrodysesthesia syndrome, hypertension, diarrhea, alopecia, fatigue, nausea and anorexia) were frequently observed in the CR group ($P < 0.05$).

Conclusion: This study identified the characteristics of CR patients during sorafenib treatment. The evaluation of patients receiving sorafenib, including the investigation of biomarkers, warrants further exploration in future clinical studies to identify a population in which sorafenib treatment is remarkably effective.

Key words: adverse drug event, complete response, data collection, hepatocellular carcinoma, population characteristics, sorafenib

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is the sixth most common cancer and the third most common cause of cancer-related death worldwide.[1] Although potentially curative therapies including liver transplantation, resection and local ablation are avail-able for HCC patients diagnosed at early stages, an advanced stage of HCC has a poor prognosis because of liver dysfunction and a lack of effective treatments.[2-4] The recent development of molecular-targeted therapies has begun to change strategies for treating HCC. Sorafenib was the first molecular-targeted agent to demonstrate a significant survival benefit in HCC patients. Sorafenib is an oral multiple tyrosine kinase inhibitor that exerts its therapeutic benefit by inhibiting Raf kinases (CRAF, BRAF and V600 BRAF), platelet-derived growth factor receptor, Flt-3, c-KIT, and the kinase activities of vascular endothelial growth factor receptor (VEGFR)-2 and VEGFR-3.[5] The efficacy and safety of sorafenib were assessed in the SHARP study[6] and also in the Asia–Pacific study.[7] Specific populations in which efficacy can be expected have not yet been elucidated, and possible biomarkers for predicting prognosis

remain unclear even though it is widely known that epidermal growth factor receptor (EGFR) mutations often occur in lung cancer,[8] K-ras mutations often occur in colorectal cancer,[9] and HER2 mutations occur in breast[10] and gastric cancer[11] clinically. Recent studies have reported that an early response of tumor markers such as α-fetoprotein and des-γ-carboxyprothrombin may predict the treatment efficacy of sorafenib in advanced HCC patients.[12,13] Other studies have reported that serum or plasma components of proliferative and angiogenic signals or molecules related to angiogenesis pathways may provide sensitive indicators of the response to treatment with sorafenib and drug-related adverse events.[14] Although sorafenib rarely induces a complete response (CR), some patients have shown remarkable tumor shrinkage and/or absolute tumor necrosis. However, which patients are likely to exhibit a remarkable response and how sorafenib affects such patients remain unknown. Therefore, in the present study, we conducted a nationwide survey to examine the situation of patients treated with sorafenib who showed a CR according to the modified response evaluation criteria in solid tumor (mRECIST)[2,15] at institutions belonging to the Liver Cancer Study Group of Japan.

METHODS

THE FOLLOWING INFORMATION regarding the actual use of sorafenib in patients with non-resectable HCC was collected or confirmed: the number of patients with a CR, the circumstances under which adverse drug reactions occurred during administration, and factors that may have affected safety and efficacy. The results were compared with the second interim report of an all-patient surveillance for sorafenib in Japan, which was released by Bayer Yakuhin (Osaka, Japan) in May 2012.[16] In 2011, we asked 483 institutions belonging to the Liver Cancer Study Group of Japan to complete the first survey, which included the number of patients with HCC who were treated with sorafenib after its approval for use in patients with HCC in Japan and the number of patients who obtained a CR according to the mRECIST. Furthermore, we conducted a second survey regarding only the CR patients. The attending physicians at the participating institutions were asked to complete the data collection instrument. The results are shown in the tables, with the data categorized into CR patients in this nationwide survey, defined as the CR group, and all the patients in the second interim report of Bayer Yakuhin, defined as the

control group. We compared the CR group with the control group for each survey item.

For the statistical analysis, the Wilcoxon rank sum test was used to compare the continuous data, and Fisher's exact test was used to compare each categorical data. For these exploratory analyses, a P-value less than 0.05 was considered significant. All the statistical analyses were performed using SPSS statistical software version 19 (SPSS, Chicago, IL, USA). The cut-off values for age and bodyweight were set at 70 years and 60 kg, respectively, referring to the median of age and bodyweight in the interim report (i.e. the control group). The adverse events were estimated using version 4.0 of the National Cancer Institute's Common Terminology Criteria for Adverse Events. This multicenter observational study in a Japanese population was conducted according to the ethical guidelines for epidemiological research issued by the Ministry of Health, Labor and Welfare, according to which it is not mandatory to obtain informed consent from the subjects in such studies. In such a case, information on the research should be open to the public. According to the guidelines, we released information about the research by 31 December 2012. This study was approved by the ethical committee of the National Cancer Center in accordance with the ethical guidelines for epidemiological research.

RESULTS

OF THE INSTITUTIONS to which a data collection instrument was sent, 57% (277/483) responded, while 43% (206/483) did not respond. In this survey, 18 of the 3047 patients with HCC for whom data was collected from the cooperating hospitals attained a CR during sorafenib treatment (CR rate, 0.6%; non-CR rate, 99.4%). Detailed information on all 18 patients with a CR was collected from the affiliated institutions. When these details were compared with data from an interim report on the efficacy and safety of sorafenib, the following findings were obtained.

The background characteristics showed that the CR group ($n = 18$) consisted of nine females (50%) and nine males (50%), while the control group consisted of 205 females (20%) and 840 males (80%). Females were statistically more prevalent than males in the CR group, and a significant difference in sex was observed between the two groups ($P < 0.01$). As Table 1 indicates, the CR group tended to have more older patients than younger patients, but the age distribution did not differ significantly between the CR and control groups when a cut-off value of 70 years was used ($P = 0.06$). The