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ORIGINAL RESEARCH ARTICLE

A Phase I Study to Investigate the Safety, Tolerability and Pharmacokinetics of Napabucasin Combined with Sorafenib in Japanese Patients with Unresectable Hepatocellular Carcinoma

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Abstract

Background and Objective For patients with advanced hepatocellular carcinoma (HCC), the standard of care for many years has been sorafenib. Preliminary data have suggested that the combination of the NAD(P)H:quinone oxidoreductase 1 bioactivatable agent napabucasin plus sorafenib may improve clinical outcomes in patients with HCC. In this phase I, multicenter, uncontrolled, open-label study, we evaluated napabucasin (480 mg/day) plus sorafenib (800 mg/day) in Japanese patients with unresectable HCC.

Methods Adults with unresectable HCC and an Eastern Cooperative Oncology Group performance status of 0 or 1 were enrolled in a 3 + 3 trial design. The occurrence of dose-limiting toxicities was assessed through 29 days from the start of napabucasin administration. Additional endpoints included safety, pharmacokinetics, and preliminary antitumor efficacy.

Results In the six patients who initiated treatment with napabucasin, no dose-limiting toxicities occurred. The most frequently reported adverse events were diarrhea (83.3%) and palmar-plantar erythrodysesthesia syndrome (66.7%), all of which were grade 1 or 2. The pharmacokinetic results for napabucasin were consistent with prior publications. The best overall response (per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) was stable disease in four patients. Using Kaplan–Meier methodology, the 6-month progression-free survival rate was 16.7% per RECIST 1.1 and 20.0% per modified RECIST for HCC. The 12-month overall survival rate was 50.0%.

Conclusions These findings confirm the viability of napabucasin plus sorafenib treatment, and there were no safety or tolerability concerns in Japanese patients with unresectable HCC.

Clinical Trial Registration ClinicalTrials.gov identifier NCT02358395, registered on 9 February 2015.

Key Points

We evaluated the safety, tolerability, pharmacokinetics, and preliminary clinical efficacy of napabucasin (480 mg/day) plus sorafenib (800 mg/day) in Japanese patients with unresectable hepatocellular carcinoma (HCC).

No dose-limiting toxicities occurred, and the safety profile was manageable. Four of six patients had stable disease, and two patients had stable disease lasting ≥ 12 weeks.

This therapeutic combination appears to be viable for the treatment of advanced HCC, with no tolerability concerns, and further clinical investigation may be warranted.

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1 Introduction

Globally, liver cancer is the fifth most common type of cancer, with almost 1 million new cases in 2020, and is the third most common cause of cancer-related death [1]. In Japan, liver cancer was reported to be responsible for 26,000 deaths in 2018; the mortality rate due to liver cancer has shown a slight decrease in the past decade but remains the fifth most common cause of cancer-related death in Japan [2]. Among patients with primary liver cancer in Japan, hepatocellular carcinoma (HCC) is the most common type, comprising >93% of cases [3]. The major risk factors for developing HCC include cirrhosis and infection with hepatitis B or C virus [4].

Current treatment options for HCC vary according to the disease stage and degree of underlying hepatic impairment, and include resection, local ablation, chemotherapy, chemoembolization, and liver transplantation [5]. However, although earlier diagnosis and the development of new treatments have improved survival rates [6], disease recurrence is common (reportedly 68% at 5 years) [7] and the prognosis of patients with advanced disease remains unsatisfactory.

For almost a decade, the oral multikinase inhibitor sorafenib was the standard of care for patients with advanced HCC, based on the placebo-controlled, phase III SHARP trial [8]. More recently, systemic therapy options for patients with unresectable HCC have expanded to include single-agent lenvatinib and the combination of atezolizumab plus bevacizumab [9].

As an oral NAD(P)H:quinone oxidoreductase 1 bioactivatable agent generating reactive oxygen species (ROS), napabucasin is hypothesized to affect multiple oncogenic cellular pathways, including signal transducer and activator of transcription 3 (STAT3), ultimately resulting in cancer cell death [10]. Preliminary data have suggested antitumor activity and acceptable toxicity profiles with napabucasin combinations in patients with metastatic colorectal cancer, including a phase I/II study of napabucasin plus pembrolizumab [11] and a phase I study of napabucasin plus chemotherapy and bevacizumab [12]. However, several phase III clinical trials in solid tumors were suspended due to futility or they failed to meet their primary endpoint [13–17].

STAT3 is a known therapeutic target for HCC [18]. In vitro, napabucasin was shown to reduce the viability of HCC cells by inducing apoptosis and cell cycle arrest [19], suggesting the potential utility of napabucasin in the management of HCC. A phase Ib study (103HCC) of napabucasin plus sorafenib was in progress in the US when this study was devised [20], and a subsequent phase II analysis planned. The present study was conducted in Japanese patients with unresectable HCC to evaluate the safety, tolerability and pharmacokinetics (PK) of napabucasin plus sorafenib. The preliminary efficacy of this treatment combination in Japanese patients was also evaluated.

2 Methods

2.1 Patients

Patients aged ≥ 20 years with unresectable HCC confirmed by histology or imaging, no prior systemic chemotherapy for HCC, Eastern Cooperative Oncology Group performance status of 0 or 1, and Child–Pugh class A were eligible for enrollment. Additional inclusion criteria were life expectancy ≥ 3 months, adequate major organ function, and use of appropriate contraception.

Exclusion criteria were prior receipt of systemic chemotherapy for HCC; receipt (within 28 days before enrollment in this study) of radiotherapy (except palliative local irradiation for pain control or symptomatic relief), hormonal therapy, immunotherapy, thermotherapy, surgical therapy, local therapy (e.g., radiofrequency ablation, percutaneous transhepatic ethanol injection therapy, microwave coagulation therapy), transcatheter arterial embolization, transcatheter arterial chemoembolization, or other antitumor treatment; presence of brain metastasis requiring treatment or being symptomatic; active multiple primary cancers at the time of enrollment; positive pregnancy test at baseline; previous treatment with napabucasin or receipt of any other investigational treatment within 4 weeks of study start; prior hypersensitivity to sorafenib or its excipients; or any other clinically significant medical condition or concomitant treatment that might confound the study outcomes or endanger the patient, making them inappropriate for participation in the opinion of the investigator.

2.2 Study Design and Treatment

This was a phase I, multicenter, uncontrolled, open-label study in patients with unresectable HCC. The study was conducted at four Japanese medical institutions between 19 March 2015 and 28 August 2017.

The study design is shown in Online Resource 1. Napabucasin was initiated within 7 days after enrollment in this study (defined as day 1), and sorafenib was initiated on day 2. A standard 3 + 3 design was used to assess the occurrence of dose-limiting toxicities (DLTs) through 29 days from the start of napabucasin administration. Three patients were treated initially. If DLTs occurred in two or

more patients, enrolment was to be terminated. If DLTs occurred in one patient, three additional patients were to be enrolled, for a total of six patients. If no DLTs occurred, then only three patients would be enrolled in this cohort. Patients were required to be hospitalized from day 1 to the morning of day 4, and from day 29 to the end of day 30. Following completion of the DLT evaluation stage, an additional three patients were enrolled in an expansion cohort to further evaluate the safety and efficacy of napabucasin. No hospitalization was mandated for this expansion cohort. Napabucasin was to be continued for patients in both cohorts until the cessation of clinical benefit, per the opinion of the investigator. The follow-up observation period was defined as the period between the last dose of napabucasin until the final examination visit; this visit occurred 28 days later or prior to the start of subsequent treatment if that treatment was initiated earlier than 28 days after discontinuation of napabucasin.

The daily dose of napabucasin was 480 mg. On day 1, napabucasin was administered orally as a single dose before breakfast to patients in a fasted state. Subsequently, 240 mg was administered twice daily (morning and evening); sorafenib was administered orally at a dose of 400 mg twice daily. Each dose of sorafenib was taken ≥ 2 h after a dose of napabucasin.

2.3 Endpoints

A DLT was defined as any of the following adverse events (AEs) that occurred during the DLT evaluation period with a definite, probable or possible causal relationship to napabucasin: any grade 4 or 5 event; all-grade febrile neutropenia; grade ≥ 3 thrombocytopenia requiring platelet transfusion; grade ≥ 3 non-hematologic events, with the exception of nausea, vomiting, anorexia, diarrhea, malaise, and electrolyte abnormality that, within 7 days of onset, improved to grade ≤ 2 or resolved after appropriate treatment, or changes in liver enzymes; or any other clinically significant event, in the opinion of the investigator. DLTs were to be referred to the Data and Safety Monitoring Board for an opinion on trial continuation. AEs were classified according to the Medical Dictionary for Regulatory Activities version 17.1, and severity was categorized using the Common Terminology Criteria for Adverse Events version 4.03.

Safety endpoints for the overall population included the occurrence of AEs, adverse drug reactions (ADRs), and measurement of vital signs, body weight, laboratory test values, and 12-lead electrocardiogram (ECG).

PK blood sampling was conducted in the DLT cohort. Blood samples for napabucasin analysis (3 mL) were collected on day 1 (prior to napabucasin dosing, and 2, 4, 6, 8, 10, and 12 h post-dose) and on day 2 (prior to napabucasin dosing). Samples for analysis of napabucasin (3 mL) and sorafenib (3 mL) were collected on day 29 (prior to napabucasin dosing [napabucasin sampling only], and at 2, 4, 6, 8, 10, and 12 h post-dose) and on day 30 (prior to napabucasin dosing). Plasma was extracted, transported to a central laboratory on dry ice, and stored at − 70°C. Plasma concentrations of napabucasin and sorafenib were determined using high performance liquid chromatography coupled with tandem mass spectrometry, as previously reported [21]. PK parameters measured included the maximum and minimum observed plasma concentrations (C_{max} and C_{min}); the area under the plasma concentration-time curve from either time zero to 12 h (AUC_{12}), time zero to 24 h (AUC_{24}) or from time zero to infinity (AUC_{∞}); time to C_{max} (t_{max}); the elimination rate constant (λ_z); the elimination half-life ($t_{½}$); and mean residence time.

Efficacy endpoints included tumor response (complete response [CR], partial response [PR], stable disease [SD], or progressive disease [PD]), progression-free survival (PFS), and overall survival (OS). Response was based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. PFS was defined as the time from first administration of napabucasin to documented PD or death, and OS was defined as the time from first administration of napabucasin to death. Responses were also evaluated according to the modified (m)RECIST assessment for HCC [22].

2.4 Statistical Methods

The planned sample size was three to six patients in the DLT cohort (with the final number dependent on whether DLTs occurred or not) and a further three to six in the expansion cohort for further safety evaluation. The DLT evaluation population consisted of patients in the DLT cohort who received the investigational drug and had either a ≥ 70% napabucasin compliance rate or onset of a DLT during the DLT evaluation period. The safety analysis population consisted of all patients who received napabucasin; the PK population included all napabucasin-treated patients with at least one available post-dose plasma concentration measurement; and the efficacy analysis population included all napabucasin-treated patients (intention-to-treat [ITT] group).

Data were summarized using frequency (n, %) or mean, standard deviation, median, range, and coefficient of variation. Baseline values were based on data obtained during screening or within 28 days before enrollment for 12-lead ECG and imaging). Missing data were not imputed. For patients without PD or death, PFS and OS were censored at the last assessment for tumor response. Calculations were conducted using SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

3 Results

3.1 Patients

Overall, six patients initiated treatment with napabucasin and none were excluded from the analysis populations. Thus, the DLT and PK populations included three patients and the safety analysis and ITT populations included six patients.

Baseline demographic and clinical characteristics are shown in Table 1. Patients were all Asian, predominantly male (5/6 [83.3%]), with a median age of 72.0 years. The majority (4/6 [66.7%]) had stage IV disease and half (3/6 [50.0%]) had a history of hepatitis C infection. The median disease duration was 6.1 years, and 5/6 (83.3%) had undergone prior transarterial chemoembolization.

3.2 Safety and Tolerability

All three patients in the DLT evaluation cohort reported AEs but no DLTs occurred. Three serious AEs occurred in two patients in the DLT cohort, of whom one died. One patient developed necrotizing fasciitis (grade 3) and bacterial meningitis (fatal) outside of the DLT assessment period. Given the patient's background of compensatory hepatic cirrhosis, both AEs were assessed by the investigator as unlikely to be treatment-related. A second patient initially developed grade 2 pyrexia on day 11 that subsequently necessitated hospitalization, resulting in classification as a serious AE. This event was judged possibly related to study treatment and resolved on day 23 after interruption of both napabucasin and sorafenib; pyrexia was not observed after restarting napabucasin treatment. The Data and Safety Monitoring Board recommended expanding the study to include three additional patients (the expansion cohort); no serious AEs occurred in that cohort.

In the safety analysis population ($N = 6$), a total of 52 AEs occurred in six patients; of these, 19 ADRs occurred in five patients (Table 2). The most frequently reported AEs were diarrhea (5/6 patients [83.3%]) and palmar-plantar erythrodysesthesia (PPE) syndrome (4/6 patients [66.7%]). All these events were grade 1 or 2. The only grade ≥ 3 AE occurring in more than one patient was lipase increased, and these events were not judged to be causally related to napabucasin. The most frequent ADRs were diarrhea (4/6 [66.7%]), hypoalbuminemia (2/6 [33.3%]), and decreased appetite (2/6 [33.3%]).

During the study, the only AEs resulting in napabucasin and sorafenib treatment discontinuation occurred in the patient who died (necrotizing fasciitis and meningitis bacterial). Two events of pyrexia occurring in two patients resulted in napabucasin interruption; no AEs leading to napabucasin dose reduction occurred. AEs leading to sorafenib interruption occurred in three patients—pyrexia in two patients, and PPE syndrome and hypertension in one patient. Eight AEs resulting in sorafenib dose reduction occurred in four patients—PPE syndrome, white

Table 1 Patient baseline demographic and clinical characteristics (safety analysis population)

	Patients [$N = 6$]
Male sex	5 (83.3)
Age, years [median (range)]	72.0 (63, 80)
≥ 65	4 (66.7)
Weight, kg [median (range)]	62.9 (51.0, 73.7)
ECOG performance status	
0	5 (83.3)
1	1 (16.7)
Disease stage	
IIIA	2 (33.3)
IVA	1 (16.7)
IVB	3 (50.0)
Disease duration, years [median (range)]	6.1 (0.0, 12.1)
Disease status	
New onset	0
Relapse	6 (100)
Presence of vascular invasion	3 (50.0)
Number of extrahepatic metastatic sites	
0	4 (66.7)
1	2 (33.3)
Chronic liver disease[a]	
Hepatitis B	2 (33.3)
Hepatitis C	3 (50.0)
Hepatitis alcoholic	0
NASH/NAFLD	0
Other	3 (50.0)
Child–Pugh class	
A (5–6 points)	6 (100)
B (7–9 points)	0
C (10–15 points)	0
Prior treatment[a]	
Surgery	4 (66.7)
Local therapy	4 (66.7)
Radiofrequency ablation	4 (66.7)
TACE	5 (83.3)
Radiotherapy	1 (16.7)
Systemic medication	0

Data are expressed as *n* (%) unless otherwise specified. All patients were Asian—none were Hispanic or Latino; all had Child–Pugh Class A disease (per the inclusion requirements)

ECOG Eastern Cooperative Oncology Group, *NAFLD* non-alcoholic fatty liver disease, *NASH* non-alcoholic steatohepatitis, *TACE* transarterial chemoembolization

[a]Patients could be included in multiple categories

Table 2 Summary of AEs and ADRs (safety analysis population)

Outcome	AE		ADR	
Patients reporting ≥ 1 event	6 (100)		5 (83.3)	
Patients reporting ≥ 1 serious event	2 (33.3)		1 (16.7)	
Patients with events leading to death	1 (16.7)		0	
Patients with events leading to napabucasin dose modification				
Withdrawn	1 (16.7)		0	
Interrupted	2 (33.3)		1 (16.7)	
Reduced	0		0	
Patients with events leading to sorafenib dose modification				
Withdrawn	1 (16.7)		0	
Interrupted	3 (50.0)		1 (16.7)	
Reduced	4 (66.7)		3 (50.0)	
Events occurring in ≥ 2 patients	Grade 1–2	Grade ≥ 3	Grade 1–2	Grade ≥ 3
Diarrhea	5 (83.3)	0	4 (66.7)	0
PPE syndrome	4 (66.7)	0	0	0
Lipase increased	0	2 (33.3)	0	0
Decreased appetite	2 (33.3)	0	2 (33.3)	0
Hypoalbuminemia	2 (33.3)	0	2 (33.3)	0
Pyrexia	2 (33.3)	0	1 (16.7)	0
Constipation	2 (33.3)	0	0	0
Dysgeusia	2 (33.3)	0	0	0
Proteinuria	2 (33.3)	0	0	0
Amylase increased	1 (16.7)	1 (16.7)	0	0
Hypertension	1 (16.7)	1 (16.7)	0	0

Data are expressed as *n* (%). AEs were classified according to the Medical Dictionary for Regulatory Activities version 17.1, and severity was categorized using the Common Terminology Criteria for Adverse Events version 4.03

ADRs adverse drug reactions, *AEs* adverse events, *PPE* palmar-plantar erythrodysesthesia

blood cell count decreased, platelet count decreased, and aspartate aminotransferase increased all occurring in one patient, and diarrhea, nausea and neutrophil count decreased in one patient each.

No clinically problematic changes were observed in systolic blood pressure, diastolic blood pressure, pulse rate, body temperature, weight, and 12-lead ECG.

3.3 Pharmacokinetics

Summary statistics for plasma napabucasin PK parameters ($n = 3$) are shown in Table 3. The mean plasma napabucasin concentration reached a maximum of 425 ng/mL by 6 h after the initial dose (day 1) and subsequently decreased to 20 ng/mL by day 2 (24 h after the initial dose). After repeated napabucasin administration, the predose concentration on day 29 was 295 ng/mL, reaching a maximum of 580 ng/mL by 6 h postdose and decreasing to 334 ng/mL by 12 h postdose (Online Resource 2).

After repeated administration of napabucasin with concomitant sorafenib, C_{max} and AUC_{12} of napabucasin increased, compared with those on day 1 after single-dose napabucasin administration. However, t_{max} of napabucasin did not show any notable change (Table 3). As two patients did not receive sorafenib on days 26–28, only one patient had available PK data for sorafenib on day 29. As such, no conclusions could be drawn regarding sorafenib PK parameters in these patients, and the effects of sorafenib on the PK of napabucasin will require additional clarification.

3.4 Efficacy Outcomes

In the ITT population ($N = 6$), the best overall response was SD in four patients and PD in two patients (per RECIST 1.1), resulting in a disease control rate of 66.7% (4/6 patients). In the determination according to mRECIST for HCC (Table 4), one patient was not evaluable due to a lack of liver lesions. One patient had an overall response of PD due

Table 3 PK parameters of plasma napabucasin (PK population)

	C_{max} [ng/mL]	AUC_{12} [ng·h/mL]	AUC_{24} [ng·h/mL]	AUC_{∞} [ng·h/mL]	t_{max} [h]	$t_{½}$ λz [h]	λz [h]	MRT [h]	C_{min} [ng/mL]
Day 1 (n = 3)									
Mean (SD)	440.7 (168.5)	3436.7 (1236.4)	4281.0 (1255.6)	4519.9 (909.5)	4.6 (1.0)	5.4 (4.4)	0.2 (0.1)	9.4 (4.2)	–
Median (min, max)	456.0 (265, 601)	3739.0 (2077, 4494)	4702.3 (2869, 5272)	4728.2 (3524, 5307)	4.0 (4.0, 5.8)	3.0 (2.8, 10.5)	0.2 (0.1, 0.3)	7.3 (6.7, 14.2)	–
CV%	38.2	36.0	29.3	20.1	22.5	81.3	55.6	44.4	–
Geometric mean (geometric CV%)	417.2 (43.5)	3268.0 (42.0)	4143.1 (33.2)	4455.3 (21.3)	4.5 (21.7)	4.4 (86.8)	0.2 (86.8)	8.8 (43.0)	–
Day 29 (n = 3)									
Mean (SD)	643.3 (207.9)	5801.7 (1420.7)	8411.2 (2188.7)	9866.5 (2734.3)	4.0 (2.0)	8.3 (1.0)	0.1 (0.0)	13.2 (1.5)	291.3 (92.9)
Median (min, max)	578.0 (476, 876)	6041.4 (4276, 7087)	9082.8 (5965, 10,185)	11,053.7 (6739, 11,806)	3.9 (2.1, 6.0)	8.5 (7.2, 9.2)	0.1 (0.1, 0.1)	13.3 (11.8, 14.6)	306.0 (192, 376)
CV%	32.3	24.5	26.0	27.7	49.3	12.4	12.9	10.9	31.9
Geometric mean (geometric CV%)	622.3 (31.9)	5678.5 (26.3)	8202.5 (28.7)	9581.1 (31.4)	3.65 (57.3)	8.22 (12.7)	0.08 (12.7)	13.19 (11.1)	280.6 (35.5)

AUC_{12} area under the plasma concentration–time curve from time zero to 12 h, *AUC_{24}* area under the plasma concentration–time curve from time zero to 24 h, *AUC_{∞}* area under the plasma concentration-time curve from time zero to infinity, *C_{max}* maximum observed plasma concentration, *C_{min}* minimum observed plasma concentration, *CV* coefficient of variation, *λz* elimination rate constant, *MRT* mean residence time, *max* maximum, *min* minimum, *PK* pharmacokinetic, *SD* standard deviation, *$t_{½}$* elimination half-life, *t_{max}* time to C_{max}

to the appearance of a new lesion (peritoneal dissemination), but nonetheless demonstrated a reduction of > 50% in the original target lesion on day 114.

Two patients had disease control lasting ≥ 12 weeks. By the end of the study, PFS events (according to RECIST 1.1 or mRECIST for HCC) had occurred in all six patients, and five patients had died. The median PFS, calculated using Kaplan–Meier methodology, was 3.2 months (per RECIST 1.1) and 3.8 months (per mRECIST for HCC), and the 6-month PFS rate was 16.7 and 20.0%, respectively. The median OS was 12.6 months and the 12-month OS rate was 50.0%.

4 Discussion

In this open-label, uncontrolled trial, the tolerability and safety of napabucasin (480 mg/day) in combination with sorafenib (800 mg/day) in Japanese patients with HCC were investigated. Although no DLTs occurred during the DLT assessment period, the observation of serious AEs resulting in death resulted in the addition of an expansion cohort to confirm the safety and tolerability. The death was deemed to be due to hepatic cirrhosis and unlikely to be treatment-related, and was investigated and evaluated by the Data and Safety Monitoring Board prior to making the decision to proceed with additional patient enrolment. No serious AEs occurred in the expansion cohort.

Overall, the AEs occurring in this study were not significantly different from those reported during napabucasin [17, 23] and sorafenib [8] monotherapy. In both healthy volunteers and patients with advanced solid tumors, the most common AE associated with administration of single-agent napabucasin 480 mg/day was grade 1/2 diarrhea (healthy volunteers, 4/7 individuals [57.1%] and 9/17 individuals [52.9%] [24]; solid tumors, 1/3 patients [33.3%] [23]).

The PK results for napabucasin were also consistent with prior publications. In this analysis, after repeated administration, napabucasin exposure increased compared with day 1, although t_{max} was not notably different. Similar results have been reported with the 480 mg/day dose in both healthy volunteers [24] and patients with advanced solid tumors [23]. Due to a lack of sorafenib PK data, the impact of sorafenib on the PK of napabucasin could not be definitively evaluated. However, no DLTs occurred in the DLT cohort, and

Table 4 Efficacy outcomes (intention-to-treat analysis population)

	RECIST 1.1 [$n = 6$]	mRECIST for hepatocellular carcinoma [$n = 6$]
Response [n (%)]		
Complete response	0	0
Partial response	0	0
Stable disease	4 (66.7)	4 (66.7)
Progressive disease	2 (33.3)	1 (16.7)
Not evaluated	0	1 (16.7)[a]
Disease control rate [n (%)]	4 (66.7)	4 (66.7)
Disease control for ≥ 12 weeks	2 (33.3)	2 (33.3)
Median PFS, months	3.2	3.8
6-month PFS rate, %	16.7	20.0
Median OS, months	12.6	–
12-month OS rate, %	50.0	–

mRECIST modifed RECIST, *PFS* progression-free survival, *OS* overall survival, *RECIST* Response Evaluation Criteria in Solid Tumors

[a]Due to a lack of liver lesions

although DLTs were not assessed in the expansion cohort, no AEs that would have met the criteria for DLTs occurred in that cohort either; thus, it was considered that no significant safety and tolerability issues were associated with this treatment combination.

The interpretation of the efficacy data was limited by the small number of patients. In this analysis, the best overall response was SD in 4/6 patients, for a disease control rate of 66.7%. In addition to the small sample size, this analysis was limited by the inclusion of only Japanese patients, which reduced the generalizability of the data. Moreover, we must consider the results in the current clinical context: in the time since this study was initiated, several other studies of napabucasin in various cancer types have reported disappointing results [13–17], leading to a halt in clinical development. However, interest in elevating ROS levels [25, 26] and modulation of downstream pathways (such as STAT3 [27, 28]) remains high, and it now appears that treatment should be closely tailored to the specific tumor type and oncogenic environment for optimal benefits [29, 30].

Given the manageable safety profile, larger-scale studies to revisit and further investigate the clinical efficacy of napabucasin in HCC may have been warranted; however, development of this particular drug was terminated by the manufacturer. Nonetheless, clinical assessment of combination therapies for HCC remains a key focus of research in this field, with multiple human trials involving a range of drug classes currently in progress. Ongoing drug development may also identify additional candidates capable of modulating ROS levels and/or the STAT3 pathway for future evaluation.

5 Conclusions

The results of this phase I analysis suggest that concomitant treatment with napabucasin and sorafenib is viable, without safety or tolerability concerns, for Japanese patients with unresectable HCC.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40268-023-00416-8.

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Declarations

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Conflict of interest Takuji Okusaka has received grants and personal fees from AstraZeneca K.K., Chugai Pharmaceutical Co., Ltd, Sumitomo Dainippon Pharma Co., Ltd, Eisai Co., Ltd and Incyte Biosciences Japan GK; received grants from EP-CRSU Co., Ltd, Linical Co., Ltd, MSD K.K., and Syneos Healthfrom; and received personal fees from Bristol-Myers Squibb Company, Daiichi Sankyo Co., Ltd, Eli Lilly Japan K.K., Fujifilm Toyama Chemical Co., Ltd, Johnson & Johnson K.K., Mundipharma K.K., Nihon Servier Co., Ltd, Nippon Shinyaku Co., Ltd, Ono Pharmaceutical Co., Ltd, Pfizer Japan Inc., Taiho Pharmaceutical Co. Ltd, Teijin Pharma Ltd, and Yakult Honsha Co., Ltd. Shuichi Iino and Rie Kageyama are employees of Sumitomo Pharma Co., Ltd. Manabu Morimoto, Yuichiro Eguchi, and Shinichiro Nakamura have no conflicts of interest to declare.

Ethics approval This study was conducted in accordance with Good Clinical Practice ordinance, the ethical principles that have their origins in the Declaration of Helsinki, and all relevant national and international regulatory requirements. The protocol and all other study docu-

mentation were approved by the Institutional Review Board of each study center before enrollment of any patients into the study.

Consent to participate All patients provided written informed consent for study participation.

Consent for publication Not applicable.

Availability of data and material The research data underlying this study are subject to restrictions and cannot be shared.

Author contributions Takuji Okusaka, Manabu Morimoto, Yuichiro Eguchi, Shinichiro Nakamura, Shuichi Iino, and Rie Kageyama contributed to the study design and conduct, and to data collection. Data analysis was performed by Shuichi Iino and Rie Kageyama, and all authors contributed to data interpretation. All authors substantively reviewed each manuscript draft and approved the final version.

Code availability Not applicable.

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