Phase I study of nintedanib in Japanese patients with advanced hepatocellular carcinoma and liver impairment

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This phase I, dose-escalation study evaluated the safety, preliminary efficacy and pharmacokinetics of nintedanib, a triple angiokinase inhibitor, in Japanese patients with advanced hepatocellular carcinoma and mild/moderate liver impairment. Thirty patients with unresectable hepatocellular carcinoma were enrolled to groups, depending on whether liver impairment was mild (group I, aspartate aminotransferase and alanine aminotransferase $\leq 2\times$ upper limit of normal and Child–Pugh score 5 [$n = 14$] or 6 [$n = 2$]) or moderate (group II, Child–Pugh score 5–6 and aspartate aminotransferase or alanine aminotransferase $>2\times$ to $\leq 5\times$ upper limit of normal [$n = 7$] or Child–Pugh score 7 [$n = 7$]); 22 patients had prior sorafenib treatment. Nintedanib was given twice daily in 28-day cycles until disease progression or unacceptable adverse events, starting at 150 mg (group I) or 100 mg (group II) and escalating to 200 mg. The primary objective was to define the maximum tolerated dose based on occurrence of dose-limiting toxicities during cycle 1 (grade ≥ 3 non-hematological and grade 4 hematological adverse events). No dose-limiting toxicities were reported during cycle 1 and the maximum tolerated dose for both groups was 200 mg twice daily. The most frequent adverse events were gastrointestinal (diarrhea, nausea, vomiting, and decreased appetite). No patients discontinued nintedanib due to adverse events; 31% of group I and 21% of group II had dose reductions. Median time to progression was 2.8 months (95% confidence interval, 1.05–5.52) for group I and 3.2 months (95% confidence interval, 0.95–6.70) for group II. Nintedanib showed a manageable safety profile and efficacy signals, including in patients previously treated with sorafenib. Clinical trial registration NCT01594125; 1199.120 (ClinicalTrials.gov).

Hepatocellular carcinoma is the third leading cause of cancer-related deaths worldwide.[1] The prevalence of HCC is highest in Asia, largely due to high infection rates with HBV and HCV.[2] Among the Asian countries, Japan is unique in that HCV infection is much more prevalent than HBV infection in HCC patients (65% vs. 15%), with few co-infected cases (2%).[3] Since peaking in 2004, there has been a fall in the total number of deaths in Japan from HCC;[2] however, HCC remains a major clinical problem. In 2012, there were an estimated 36 168 new cases and 32 518 deaths in Japan due to liver cancer,[4] of which HCC would have accounted for the majority of primary cases.[5] Hepatocellular carcinoma is a hypervascular tumor that is often resistant to chemotherapy, and treatment is complicated by the potential for liver failure.[6,7] The efficacy of angiokinase inhibitors has been reported in patients with advanced HCC by sorafenib, an inhibitor of VEGFRs, PDGFR-β, Raf-1, and B-Raf.[8,9] Sorafenib is a recommended first-line treatment of advanced HCC;[10] however, the benefit is transient and disease progression occurs in all patients, suggesting a continued need for new agents

and/or combination therapies for patients with advanced HCC.[11]

Nintedanib is an oral, triple angiokinase inhibitor that targets elements of three pro-angiogenic pathways: VEGFR 1–3, PDGFR-α and -β, and FGFR 1–3, as well as RET, Flt-3, and Src.[12] Nintedanib in combination with docetaxel has been approved in the European Union and other countries for the treatment of patients with advanced or metastatic non-small-cell lung cancer tumors of adenocarcinoma histology after first-line chemotherapy, and nintedanib monotherapy has been approved for the treatment of patients with idiopathic pulmonary fibrosis in the USA, European Union, and Japan.

Nintedanib monotherapy has shown promising efficacy and a manageable safety profile versus sorafenib in phase I/II studies of Asian (NCT00987935; 1199.39)[13] and European patients (NCT01004003; 1199.37) with advanced HCC.[14] Evaluation of nintedanib in phase I studies in patients with advanced solid tumors found elevated liver enzymes to be the primary DLT.[15,16] Increased levels of liver enzymes, including AST and ALT, are indicators of liver damage.[17] Moreover, HCC is

often accompanied by underlying liver disease, such as cirrhosis or chronic hepatitis, which can impair liver function.[18] This is routinely measured using Child–Pugh scores, considered to be a prognostic factor for patient survival, with class C representing the worst prognosis rates.[17,19–21] Thus, patients in the European and Asian studies with nintedanib were stratified by the extent of liver damage and liver function, as measured by the level of AST and ALT, and Child–Pugh score.[22,23] The studies in both Asian and European patients indicated a MTD for nintedanib of 200 mg b.i.d. in patients with mild and moderate liver impairment.[22,23] Results from both studies showed comparable efficacy for nintedanib and sorafenib, with similar TTP and overall survival, but a different safety profile. In both studies, mean dose intensity was higher in the nintedanib arm compared with the sorafenib arm.

This phase I dose-escalation study (NCT01594125; 1199.120) aimed to define the MTD of nintedanib in Japanese patients with advanced HCC and mild or moderate liver impairment.

Materials and Methods

Patients. Patients with histologically or cytologically confirmed HCC not amenable to curative surgery or locoregional therapy (including radiofrequency ablation, percutaneous ethanol injection, and transcatheter arterial chemoembolization) were eligible for the study. Other inclusion criteria included: (i) age ≥20 years; Eastern Cooperative Oncology Group performance status score of 0 or 1; (ii) Child–Pugh score ≤7; and (iii) life expectancy >3 months as assessed by the investigator. Exclusion criteria included: (i) more than one line of prior systemic therapy for metastatic/unresectable HCC (prior sorafenib therapy was permitted in the expansion cohort); (ii) fibrolamellar HCC; (iii) inadequate organ function (including total bilirubin >1.5× ULN, AST and ALT >5× ULN, hepatic encephalopathy grade ≥2 according to Child–Pugh criteria, proteinuria of Common Terminology Criteria for Adverse Events grade ≥2); (iv) treatment with anticancer agents (including investigational drugs and locoregional therapies) or major surgery within 4 weeks before study treatment; (v) known inherited disposition to bleeding or thrombosis, history of major thrombotic (except portal vein thrombosis), or clinically relevant major bleeding in the 6 months prior to study treatment; and (vi) significant cardiovascular disease.

Study design. This was a multicenter (five sites in Japan), open-label, dose-escalating phase I study (Fig. 1). Patients were enrolled to one of two groups according to their baseline liver function: (i) group I included patients with mild liver impairment (AST and ALT ≤2× ULN and Child–Pugh score 5–6); and (ii) group II included patients with moderate liver impairment (AST or ALT >2× to ≤5× ULN or Child–Pugh score 7). Both groups were recruited in parallel.

Patients received continuous oral nintedanib twice daily in 28-day cycles if there were no treatment interruptions or gaps between cycles. In the dose-escalation period, the starting nintedanib dose in group I was 150 mg b.i.d. (three to nine patients), with a further dose level of 200 mg b.i.d. allowed (three to nine patients). The starting nintedanib dose in group II was 100 mg b.i.d. (three to nine patients), with dose escalation to 150 and 200 mg b.i.d. allowed (three to nine patients at each level). The 200 mg b.i.d. dose was given as two 100-mg capsules twice daily, each dose approximately 12 h apart. Dose escalation took place if the incidence of DLTs in cycle 1 was <33.3% (0/3, 1/6, or 2/9). The MTD was defined as the highest dose level at which 0/3, 1/6, or 2/9 patients experienced a DLT.

Once the MTD for nintedanib was determined, an expansion cohort of 12 additional patients was treated at the determined MTD. The purpose of the expansion cohort was to expand the safety and PK database. In a protocol amendment, the expansion cohort also included six patients treated in group I who had been treated with sorafenib as prior therapy for ≥14 days before discontinuing due to radiographic or symptomatic progression or intolerance.

Patients were allowed to continue treatment until they met discontinuation criteria, which included radiologically documented disease progression (including new clinical lesion, new or unequivocally increased viable lesion in previously irradiated area, or a ≥20% increase from lowest on-treatment value in the sum of the longest diameter of target lesions) and unacceptable toxicities. End-of-treatment examinations were carried out within 7 days of study treatment discontinuation, with follow-up for AEs undertaken 28 days (+4 days) after the end-of-treatment visit. If a patient discontinued for reasons other than disease progression, follow-up for disease progression was undertaken every 8 weeks. Treatment beyond progression was allowed if the patient continued to have clinical or symptomatic benefit from treatment according to the judgment of the investigator.
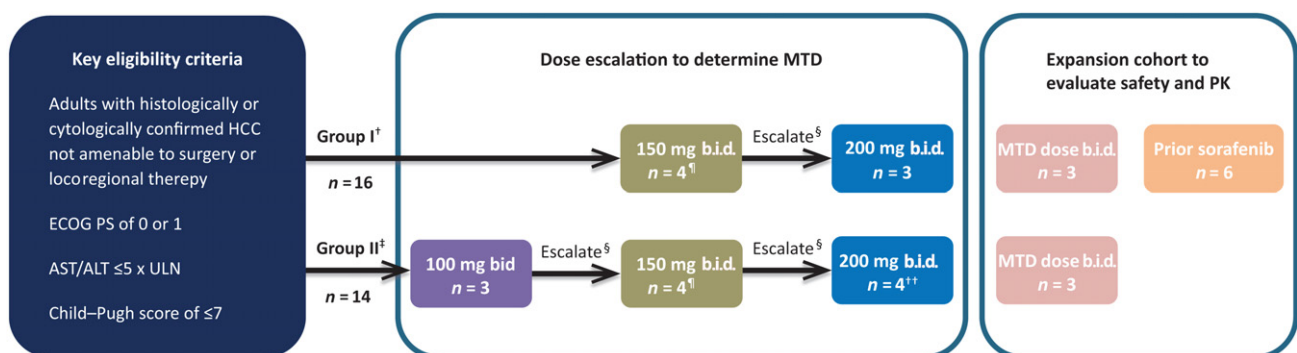

Fig. 1. Design of the phase I study of nintedanib in Japanese patients with advanced hepatocellular carcinoma (HCC) and liver impairment. [†]Group I included patients with mild liver impairment (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤2× upper limit of normal [ULN] and Child–Pugh score 5–6). [‡]Group II included patients with moderate liver impairment (AST or ALT >2× to ≤5× ULN, or Child–Pugh score 7). [§]Dose escalation took place if incidence of dose-limiting toxicities in cycle 1 was ≤33.3% (0/3, 1/6, or 2/9). [¶]Replacement of one patient due to withdrawal of informed consent during cycle 1. [††]Replacement of one patient due to discontinuation of trial treatment for >7 days. ECOG PS, Eastern Cooperative Oncology Group performance status; MTD, maximum tolerated dose; PK, pharmacokinetics.

The study was carried out in accordance with institutional guidelines, Japanese Good Clinical Practice, and the Declaration of Helsinki. All patients provided written informed consent before undergoing any procedure related to this study. Nintedanib was supplied by Nippon Boehringer Ingelheim Co. Ltd (Tokyo, Japan) as 50-, 100-, and 150-mg capsules.

Patient assessments. All analyses of this trial were descriptive; therefore, no statistical model was adopted in the trial and no hypothesis was tested. The baseline evaluation included medical history (Eastern Cooperative Oncology Group performance status, Child–Pugh score, etiology of underlying liver disease [including HBV surface antigen, anti-HBV surface antibody, anti-HBV core antibody, serum HBV-DNA, and anti-HCV antibody assessments], macrovascular invasion, extrahepatic spread, and prior systemic therapy including sorafenib treatment). Baseline assessments were made during the screening period, up to a maximum of 14 days before first dose of study treatment.

Dose-limiting toxicities were defined as the following drug-related AEs: (i) grade 4 non-febrile neutropenia lasting for ≥8 days; (ii) grade 4 febrile neutropenia or thrombocytopenia of any duration; (iii) non-hematological toxicities grade ≥3, except for alopecia, transient electrolyte abnormalities resolving spontaneously with appropriate treatment within 3 days, or gastrointestinal toxicities (vomiting, nausea, or diarrhea) with no adequate supportive care; and (iv) according to liver function tests (AST, ALT, ALP elevation >5× ULN, or total bilirubin >3× ULN if baseline liver enzymes are within the normal range, or AST, ALT, or ALP >baseline value + 4× ULN if the baseline value is elevated). Isolated elevation of γ-glutamyltransferase without DLT definition of AST/ALT/ALP was not considered to be a DLT.

During the observation period, the incidence and severity of AEs was assessed and graded according to Common Terminology Criteria for Adverse Events version 3.0. Safety and efficacy analyses were carried out for the treated set, defined as patients who received at least one dose of nintedanib.

Patients in the treated set who had evaluable parameters for at least one PK end-point were included in the PK set and used for PK analysis. Blood samples were collected for PK evaluation before and 1, 2, 3, 4, 6, 8, 10, and 24 h after drug treatment on day 15 of cycle 1. Additional samples were collected before and 2 h after drug treatment on days 1 and 15 of cycle 2. Twenty-four-hour urine sampling for PK evaluation was undertaken on day 15 of cycle 1. Plasma and urine samples were stored at −20°C or below until analysis by liquid chromatography/tandem mass spectrometry. Pharmacokinetic parameters were calculated with non-compartmental analysis using Phoenix WinNonlin (Certara, Princeton, NJ, USA).

Objective tumor response was evaluated by investigator assessment according to the Response Evaluation Criteria in Solid Tumors version 1.0. Other efficacy end-points were TTP by investigator assessment (defined as the duration from start of treatment to disease progression [Response Evaluation Criteria in Solid Tumors version 1.0] or death due to HCC), and response by AFP.

Assessment of response by AFP followed modified published criteria[24] and may be predictive of radiological response. Response by AFP is defined as a decline of 20% or more in AFP levels between the baseline value and the AFP value after three cycles (12 weeks) of therapy. If patients only received two cycles of therapy, the AFP value after two cycles (8 weeks) was used for the analysis. Patients who received fewer than two cycles of treatment were omitted from the analysis. Only patients with AFP elevation (>20 μg/L) at baseline and post-baseline AFP assessment after two or three cycles were evaluated for AFP response.

Results

Patients. From May 2012 to October 2014, 30 patients were entered in the study (16 patients in group I and 14 patients in group II) (Table 1). Most patients were male (81.3% in group I and 57.1% in group II); the main etiology of HCC in group I was HBV infection (37.5%) and in group II it was HCV infection (64.3%). Twenty-two patients (73%) had prior sorafenib treatment (group I, *n* = 13; group II, *n* = 9). Prior sorafenib treatment was discontinued in 19 patients for disease progression and in three patients for intolerance.

Safety and tolerability. The median duration of nintedanib treatment was 113.5 days (range, 39–280 days) for group I and 127.0 days (range, 50–253 days) for group II. Mean dose intensity was 91.7% (SD 13.2%) in group I and 93.2% (SD 14.1%) in group II.

No patient experienced a DLT during the MTD period (cycle 1) in either group I (dose escalation levels, 150 mg b.i.d., 200 mg b.i.d.) or group II (dose escalation levels, 100 mg b.i.d., 150 mg b.i.d., 200 mg b.i.d.). Therefore, nintedanib 200 mg b.i.d. was deemed to be the MTD for both groups.

An expansion cohort consisting of nine patients in group I and three patients in group II received nintedanib 200 mg b.i.d. Including the expansion cohort, of the 19 patients treated with nintedanib at the 200-mg b.i.d. dose level (12 in group I, seven in group II), three patients (two in group I, one in group II) experienced a DLT. A DLT of grade 3 drug-induced liver injury was reported in one patient in each group, and one patient in group I had a DLT of grade 3 diarrhea. All three patients were in the expansion cohort; however, the percentage of DLTs in this cohort was still lower than the 33.3% cut-off used to determine dose escalation during the dose-escalation period. All patients experienced at least one AE (Table 2).

Dose reduction of nintedanib due to AEs was required by five patients (31.3%) in group I and three patients (21.4%) in group II. All the patients in group I who had dose reductions were on the 200-mg dose. In group II, one patient from each dose (dose escalation levels, 100 mg b.i.d., 150 mg b.i.d., 200 mg b.i.d.) had a dose reduction. No patients discontinued nintedanib due to AEs.

Serious AEs (all requiring hospitalization) were reported in four patients (25.0%) in group I and six patients (42.9%) in group II. In group I, serious AEs that were considered to be drug-related by the investigator were grade 3 immune thrombocytopenic purpura and grade 3 hyponatremia. In group II, serious AEs that were considered to be drug-related were grade 2 gastroenteritis, grade 3 drug-induced liver injury, and grade 2 pyrexia.

No drug-related fatal AEs were reported. Two patients in group II had a fatal AE within 28 days of completion of study treatment: one malignant neoplasm progression in the nintedanib 150 mg b.i.d. cohort, and one tumor embolism in a patient treated with nintedanib at 200 mg b.i.d. Neither fatal AE was considered to be drug-related by the investigator.

The most frequent AEs of any grade, occurring in more than 30% patients in either group, were diarrhea (group I, 50.0%; group II, 42.9%), nausea (group I, 43.8%; group II, 35.7%), vomiting (group I, 37.5%; group II, 21.4%), decreased appetite (group I, 37.5%; group II, 50.0%), increased AST (group I, 25.0%; group II, 35.7%), fatigue (group I, 18.8%; group II, 35.7%), hypoalbuminemia (group I, 12.5%; group II, 42.9%),

Table 1. Demographics and baseline characteristics of Japanese patients with advanced hepatocellular carcinoma in a phase I study of nintedanib, grouped according to liver impairment

	Group I (mild liver impairment)			Group II (moderate liver impairment)			
	150 mg b.i.d. (n = 4)	200 mg b.i.d. (n = 12)	All patients (n = 16)	100 mg b.i.d. (n = 3)	150 mg b.i.d. (n = 4)	200 mg b.i.d. (n = 7)	All patients (n = 14)
Male, n (%)	2 (50.0)	11 (91.7)	13 (81.3)	0 (0.0)	2 (50.0)	6 (85.7)	8 (57.1)
Mean age, years (range)	67.0 (46–80)	63.1 (43–77)	64.1 (43–80)	73.3 (72–76)	66.5 (60–75)	67.4 (62–74)	68.4 (60–76)
ECOG PS, n (%)							
0	3 (75.0)	7 (58.3)	10 (62.5)	2 (66.7)	2 (50.0)	5 (71.4)	9 (64.3)
1	1 (25.0)	5 (41.7)	6 (37.5)	1 (33.3)	2 (50.0)	2 (28.6)	5 (35.7)
Etiology of liver disease							
Alcohol related	1 (25.0)	1 (8.3)	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
HBV related	1 (25.0)	5 (41.7)	6 (37.5)	0 (0.0)	1 (25.0)	3 (42.9)	4 (28.6)
HCV related	0 (0.0)	3 (25.0)	3 (18.8)	3 (100.0)	2 (50.0)	4 (57.1)	9 (64.3)
HBV + HCV related	1 (25.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	3 (25.0)	3 (18.8)	0 (0.0)	1 (25.0)	0 (0.0)	1 (7.1)
Other	1 (25.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Child–Pugh score, n (%)							
5	4 (100.0)	10 (83.3)	14 (87.5)	0 (0.0)	1 (25.0)	1 (14.3)	2 (14.3)
6	0 (0.0)	2 (16.7)	2 (12.5)	3 (100.0)	1 (25.0)	1 (14.3)	5 (35.7)
7	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	5 (71.4)	7 (50.0)
Macrovascular invasion, n (%)	1 (25.0)	4 (33.3)	5 (31.3)	0 (0.0)	3 (75.0)	4 (57.1)	7 (50.0)
Extrahepatic spread, n (%)	3 (75.0)	8 (66.7)	11 (68.8)	0 (0.0)	3 (75.0)	4 (57.1)	7 (50.0)
Prior sorafenib treatment, n (%)	2 (50.0)	11 (91.7)	13 (81.3)	1 (33.3)	2 (50.0)	6 (85.7)	9 (64.3)

ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus.

Table 2. Summary of adverse events (AEs) (on-treatment period) in phase I study of nintedanib in Japanese patients with advanced hepatocellular carcinoma, grouped according to liver impairment

	Group I (mild liver impairment)			Group II (moderate liver impairment)			
	150 mg b.i.d. (n = 4)	200 mg b.i.d. (n = 12)	All patients (n = 16)	100 mg b.i.d. (n = 3)	150 mg b.i.d. (n = 4)	200 mg b.i.d. (n = 7)	All patients (n = 14)
Any AE	4 (100.0)	12 (100.0)	16 (100.0)	3 (100.0)	4 (100.0)	7 (100.0)	14 (100.0)
Investigator-defined drug-related AE	3 (75.0)	11 (91.7)	14 (87.5)	3 (100.0)	4 (100.0)	5 (71.4)	12 (85.7)
Other significant AEs[†]	0 (0.0)	5 (41.7)	5 (31.3)	1 (33.3)	1 (25.0)	1 (14.3)	3 (21.4)
AEs leading to nintedanib dose reduction	0 (0.0)	5 (41.7)	5 (31.3)	1 (33.3)	1 (25.0)	1 (14.3)	3 (21.4)
AEs leading to nintedanib discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Significant AEs (pre-specified events)[‡]	0 (0.0)	2 (16.7)	2 (12.5)	0 (0.0)	1 (25.0)	1 (14.3)	2 (14.3)
Serious AEs	0 (0.0)	4 (33.3)	4 (25.0)	1 (33.3)	2 (50.0)	3 (42.9)	6 (42.9)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (14.3)	2 (14.3)
Immediately life-threatening	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	1 (7.1)
Required hospitalization	0 (0.0)	4 (33.3)	4 (25.0)	1 (33.3)	2 (50.0)	3 (42.9)	6 (42.9)
Prolonged hospitalization	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	1 (7.1)

[†]Adverse events (including serious AEs) leading to dose reduction or permanent discontinuation of nintedanib. [‡]Adverse events (including serious AEs) with a dose-limiting toxicity or pregnancy occurring during the treatment phase. Data are presented as n (%). Percentages are calculated using total number of patients per treatment as the denominator. A patient may be counted in more than one seriousness criterion.

and ascites (group I, 6.3%; group II, 50.0%) (Table 3). The AE profile of nintedanib was similar in the 22 patients previously treated with sorafenib compared with all patients (data not shown). There was a relatively low incidence of AEs commonly associated with VEGF/VEGFR inhibitors, such as bleeding (group I, 12.5%; group II, 14.3%), hypertension (group I, 12.5%; group II, 21.4%), and thromboembolic events (group I, 0.0%; group II, 7.1%). Hand–foot skin reaction was reported in one patient in group I and no patients in group II.

Adverse events at grade ≥3 were reported in seven patients (43.8%) in group I and 11 patients (78.6%) in group II. The most frequent grade ≥3 AEs, occurring in more than one patient in either group, were increased AST, neutropenia, increased ALT, malignant neoplasm progression, hyperuricemia, lymphopenia, and decreased platelet count. Few grade ≥3 hematological or hepatobiliary AEs were reported. At grade ≥3, bleeding was reported by one patient (6.3%) in group I and no patients in group II, hypertension was not

Table 3. Most frequent adverse events (AEs) during the on-treatment period in a phase I study of nintedanib in Japanese patients with advanced hepatocellular carcinoma and liver impairment, by preferred term

	Group I (mild liver impairment) n = 16		Group II (moderate liver impairment) n = 14	
	All grades	Grade ≥3	All grades	Grade ≥3
Any AE	16 (100)	7 (43.8)	14 (100)	11 (78.6)
Diarrhea	8 (50.0)	1 (6.3)	6 (42.9)	0 (0.0)
Nausea	7 (43.8)	0 (0.0)	5 (35.7)	0 (0.0)
Vomiting	6 (37.5)	0 (0.0)	3 (21.4)	0 (0.0)
Decreased appetite	6 (37.5)	0 (0.0)	7 (50.0)	0 (0.0)
Increased AST	4 (25.0)	0 (0.0)	5 (35.7)	3 (21.4)
Malaise	4 (25.0)	0 (0.0)	3 (21.4)	0 (0.0)
Abdominal pain[†]	4 (25.0)	0 (0.0)	2 (14.3)	0 (0.0)
Fatigue	3 (18.8)	1 (6.3)	5 (35.7)	0 (0.0)
Hypoalbuminemia	2 (12.5)	0 (0.0)	6 (42.9)	1 (7.1)
Pyrexia	2 (12.5)	0 (0.0)	4 (28.6)	0 (0.0)
Neutropenia	2 (12.5)	0 (0.0)	3 (21.4)	2 (14.3)
Decreased platelet count	2 (12.5)	2 (12.5)	1 (7.1)	0 (0.0)
Ascites	1 (6.3)	0 (0.0)	7 (50.0)	1 (7.1)
Increased ALT	1 (6.3)	0 (0.0)	4 (28.6)	2 (14.3)
Malignant neoplasm progression	1 (6.3)	0 (0.0)	4 (28.6)	2 (14.3)
Increased blood bilirubin	1 (6.3)	0 (0.0)	4 (28.6)	0 (0.0)
Hyperuricemia	1 (6.3)	0 (0.0)	3 (21.4)	2 (14.3)
Lymphopenia	NR	NR	2 (14.3)	2 (14.3)

[†]Upper abdominal pain for group II; abdominal pain as a preferred term was not reported. Only AEs occurring at any grade in ≥4 patients or at grade ≥3 in ≥2 patients in either group are listed. ALT, alanine aminotransferase; AST, aspartate aminotransferase; NR, not reported.

reported by any patients in this study, and thromboembolic events were reported in no patients in group I and one patient (7.1%) in group II.

Pharmacokinetic analysis. Plasma and urine samples of 29 patients were included in the PK analysis: 15 patients in group I (150 mg, n = 3; 200 mg, n = 12), and 14 patients in group II (100 mg, n = 3; 150 mg, n = 4; 200 mg, n = 7). Plasma concentrations of nintedanib reached their maximum 3–4 h after multiple oral dose administration at steady state (Fig. 2). Thereafter, plasma concentrations of nintedanib declined, displaying at least biphasic disposition kinetics.

On the basis of interindividual variability in parameters, exposure to nintedanib generally increased with increasing doses over the tested dose range (Table 4). A numerically slightly higher exposure to nintedanib was observed for group II *versus* group I (26% increase in $AUC_{\tau,ss,norm}$). However, the range of individual values overlapped substantially. Two patients in group I (200 mg b.i.d. cohort) showed high exposure to nintedanib ($AUC_{\tau,ss}$ 6170 and 5700 ng·h/mL, respectively), the cause of which was unknown. Renal elimination of nintedanib was low; 0.49–0.66% of the administered dose was recovered in the urine over 24 hours after dosing at steady state.

The effect of hepatic impairment on nintedanib PK parameters was examined using Child–Pugh criteria for categorization (data not shown). Exposure to nintedanib was slightly higher (37% increase in $AUC_{\tau,ss,norm}$) in patients with Child–Pugh score 7 than those with Child–Pugh score 5 or 6. There was no clear correlation between nintedanib exposure ($AUC_{\tau,ss,norm}$) and AST or ALT levels (days 1–22 of cycle 1).

Efficacy. At the time of analysis, 15 of 16 patients in group I and all 14 patients in group II had progressed. Overall, median TTP was 2.8 months (95% CI, 1.05–5.52) for group I and 3.2 months (95% CI, 0.95–6.70) for group II. Among patients treated at the MTD of 200 mg b.i.d., median TTP was 2.8 months (95% CI, 1.05–5.52) for group I and 2.8 months (95% CI, 0.95–5.62) for group II. For patients who had prior sorafenib treatment, median TTP was 2.8 months (95% CI 1.05–5.68) for group I and 2.8 months (95% CI, 0.95–6.70) for group II (Fig. 3). Similar results were observed for the subset of patients treated at the MTD.

There were no complete or partial responses. Stable disease was reported in 12 patients in group I (75.0%; 10 treated at the MTD) and in 11 patients in group II (78.6%; all treated at the MTD). Response by AFP (Fig. 4) was evaluable in nine patients (56.3%) in group I, three of whom achieved the response criterion of a decline from baseline of >20% in AFP levels. Similarly, nine patients in group II (64.3%) were evaluable, with three patients showing a response by AFP. Figure 4
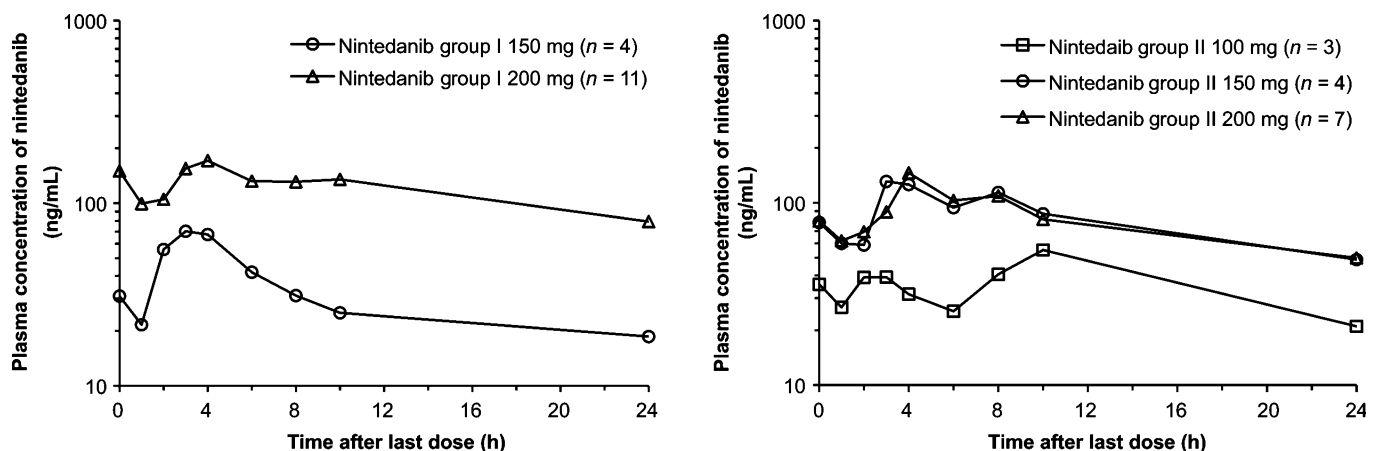

Fig. 2. Arithmetic mean plasma concentration–time profiles of nintedanib after multiple doses b.i.d. to Japanese patients with hepatocellular carcinoma (semi-log scale). Left panel, group I with mild liver impairment (aspartate aminotransferase and alanine aminotransferase ≤2× upper limit of normal and Child–Pugh score 5 or 6). Right panel, group II with moderate liver impairment (Child–Pugh score 5–6 and aspartate aminotransferase or alanine aminotransferase >2× to ≤5× ULN or Child–Pugh score 7).

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Table 4. Key pharmacokinetic parameters of nintedanib after multiple oral administration in a phase I study in Japanese patients with advanced hepatocellular carcinoma, grouped according to liver impairment

	Group I (mild liver impairment)		Group II (moderate liver impairment)		
	150 mg b.i.d. (n = 4)	200 mg b.i.d. (n = 11)	100 mg b.i.d. (n = 3)	150 mg b.i.d. (n = 4)	200 mg b.i.d. (n = 7)
$AUC_{\tau,ss}$ (ng·h/mL), gMean (gCV%)	445 (46.4)	912 (128.0)	354 (128.0)	970 (77.5)	1060 (39.4)
$C_{max,ss}$ (ng/mL), gMean (gCV%)	75.8 (52.2)	127 (113.0)	55.7 (129.0)	143 (85.7)	142 (42.5)
$t_{1/2,ss}$ (h), gMean (gCV%)	23.6 (66.8)[†]	16.6 (35.3)[‡]	41.6 (36.5)[§]	14.6 (19.5)[†]	17.7 (55.0)
$t_{max,ss}$ (h), median (range)	3.48 (1.98–4.08)	4.00 (0–10.0)	3.00 (2.00–9.82)	4.08 (3.00–8.15)	4.00 (3.78–6.00)

[†]n = 3. [‡]n = 9. [§]n = 2. $AUC_{\tau,ss}$, area under the curve over a dosing interval at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; gCV, geometric coefficient of variation; gMean, geometric mean; $t_{1/2,ss}$, half-life at steady state; $t_{max,ss}$, time to maximum plasma concentration at steady state.
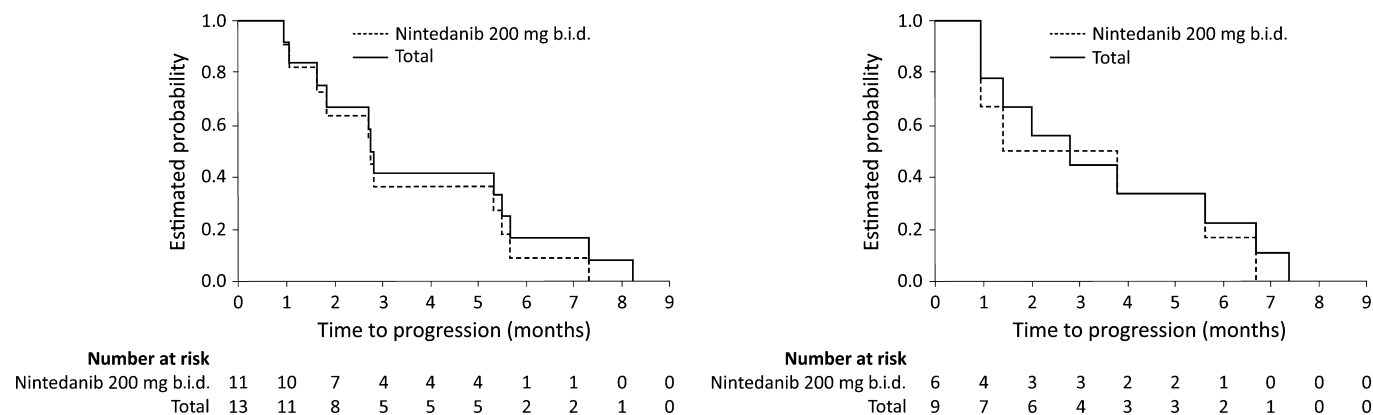

Fig. 3. Time to progression in Japanese patients with hepatocellular carcinoma and liver impairment treated with nintedanib, who had received prior sorafenib treatment. Left panel, group I with mild liver impairment (aspartate aminotransferase and alanine aminotransferase ≤2× upper limit of normal and Child–Pugh score 5 or 6). Right panel, group II with moderate liver impairment (Child–Pugh score 5–6 and aspartate aminotransferase or alanine aminotransferase >2× to ≤5× ULN or Child–Pugh score 7).

also shows a computed tomography image of tumor necrosis after 1 month of nintedanib treatment.

Discussion

The primary objective of this trial was to evaluate the MTD of nintedanib in two groups of Japanese patients with HCC on the basis of their liver function, grouped using the same criteria as other phase I trials evaluating nintedanib in Asian and European patients with HCC.[22,23] Although not stratified into groups as they were here, similar inclusion criteria were also used in the phase III SHARP trial that evaluated sorafenib *versus* placebo in advanced HCC; patients had AST/ALT levels ≤5, and were Child–Pugh A, although a small number of Child–Pugh B patients were also enrolled.[8]

No patient experienced a DLT during cycle 1 or during the dose-escalation period; therefore, the dosage of nintedanib 200 mg b.i.d. was deemed to be the MTD for both groups. The tolerability of the MTD was confirmed with data from all patients treated at 200 mg b.i.d. (including the expansion cohort), with the number of patients experiencing a DLT being only two out of 12 for group I and one out of seven for group II. The MTD analysis in the present study is consistent with the MTD previously observed for other Asian and European patients with HCC,[13,14] and may be applied for further potential studies of nintedanib in Japanese patients with advanced HCC that is not amenable to curative surgery or locoregional therapy. However, given the low number of patients with a

Child–Pugh score of 7, no firm conclusion can be drawn as to the safety in patients with Child–Pugh B (score 7–9). Across the whole observation period, nintedanib displayed a manageable safety profile irrespective of prior sorafenib treatment. The most frequently reported AEs were gastrointestinal, and there were no unexpected AEs; the safety profile in both groups was similar to that reported for nintedanib monotherapy in previous trials in HCC and other types of cancer.[13–16] Adverse events that are associated with some antiangiogenic agents include bleeding, hypertension, and thromboembolic events.[25] Previous studies of nintedanib monotherapy and combination therapy have shown that nintedanib is not generally associated with these AEs, particularly at grade ≥3.[13,14,26,27] This is confirmed in this study, with no grade ≥3 hypertension events experienced, and grade ≥3 bleeding and thromboembolic events reported in one patient each. Phase II and III trials in multiple tumor types have confirmed that nintedanib treatment is not associated with HFSR.[26,28–30] However, HFSR is common during treatment with sorafenib,[8] and it has been suggested that the presence of skin toxicity, including HFSR, may be a surrogate biomarker for sorafenib clinical efficacy.[31,32] Hand–foot skin reaction can be severe, necessitating dose reductions or treatment discontinuation, and is thus a treatment concern.[8,31] There is speculation that sorafenib-related HFSR may be due to the combined inhibition of several receptors,[33] specifically VEGFR, PDGFR, c-KIT, and Flt-3.[34] This may explain why HFSR is not associated with nintedanib treatment; the specific targets of nintedanib differ
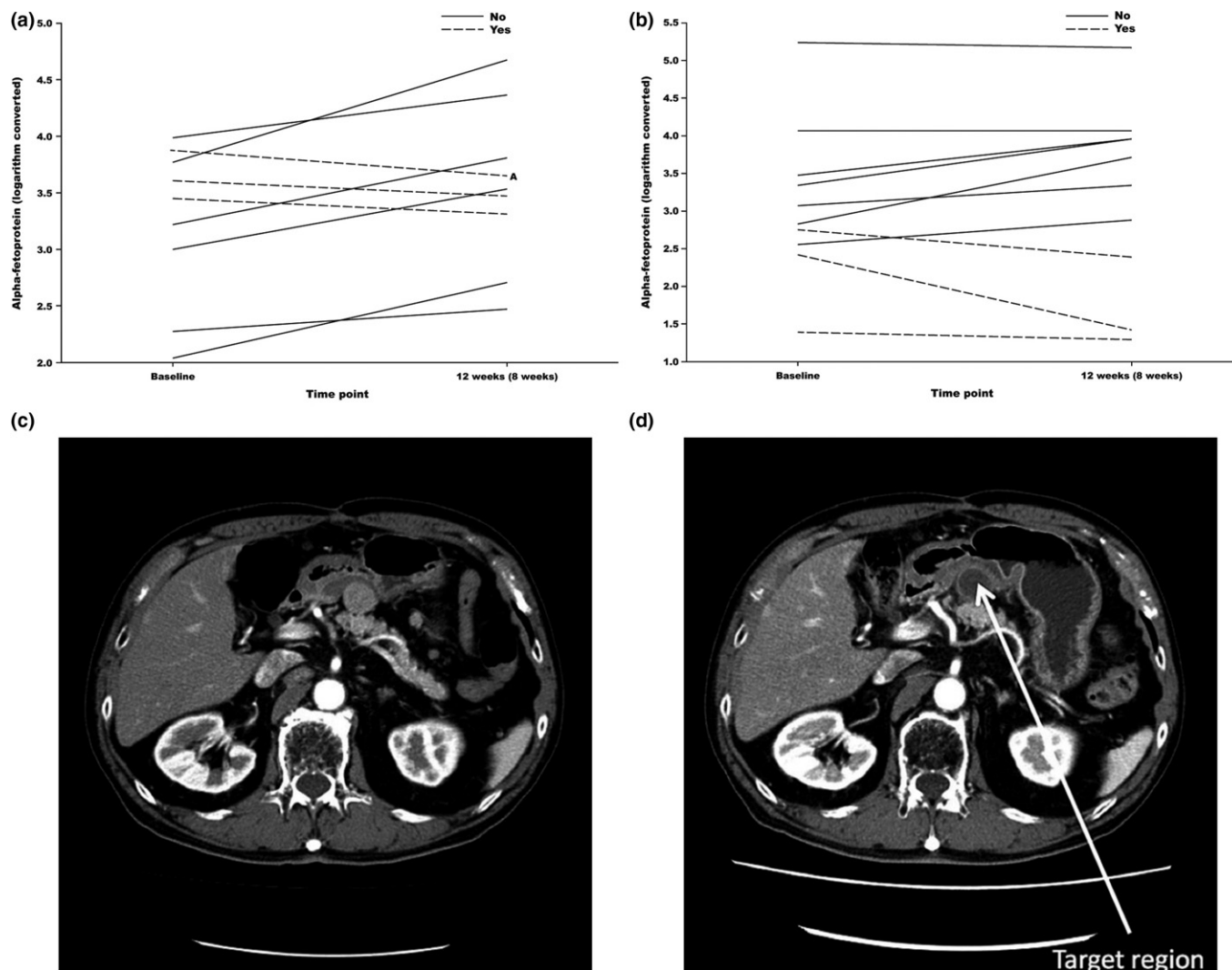
Fig. 4. (a, b) Alpha-fetoprotein levels in Japanese patients with hepatocellular carcinoma and liver impairment, prior to and following 12 weeks of treatment with nintedanib. Patients were grouped according to liver impairment. Individual patients' responses (yes or no) are shown in group I (mild liver impairment) (a) and group II (moderate liver impairment) (b). (c, d) Computed tomography images of tumor necrosis with nintedanib treatment, from an 80-year-old patient with multiple hepatocellular carcinoma tumors after transcatheter arterial chemoembolization and sorafenib that had progressed in 2 months. This patient is indicated by an 'A' on graph (a). Metastatic lesions in the lymph node (c) showed tumor necrosis (d) after 1 month of nintedanib treatment.

from sorafenib, thus low rates of HFSR seen with nintedanib likely reflect differences in the mechanisms of action between nintedanib and sorafenib.

Nintedanib undergoes extensive intestinal and/or hepatic first-pass metabolism by esterases and subsequent glucuronidation, forming the carboxylate derivative BIBF 1202 and BIBF 1202 glucuronide, respectively, as the predominant metabolites.[35,36] Pharmacokinetic analysis showed that plasma concentration profiles of nintedanib were of similar shape for the two different liver function groups, and were consistent with a previous trial in Japanese patients with advanced solid tumors.[16] Given that the half-life of nintedanib in the 150 and 200 mg b.i.d. dose cohorts was similar to the values obtained from other trials,[15,16] the first-pass metabolism and hence the bioavailability of nintedanib might be influenced by liver impairment and by the elimination of nintedanib only to a minor extent. Median time to maximum plasma concentration at steady state values for both groups were also

comparable with those previously reported for nintedanib monotherapy.[15,16,36] The geometric mean values for the maximum plasma concentration at steady state and $AUC_{\tau,ss}$ of nintedanib increased with increasing doses over the tested dose range, with moderate to high interpatient variability observed.

Overall, nintedanib showed signs of efficacy in this phase I study. The TTP reported in groups I and II were similar to the TTP reported in Asian patients with HCC with no prior sorafenib therapy (2.8 months by central independent review).[13] As would be expected due to differences in risk factors and etiologies between patient populations, the TTP was lower than the TTP reported in European patients (5.5 months by central independent review).[14] The patient group in the study reported here had been predominantly pretreated with sorafenib (73.3%), and comparable TTP in the first- and second-line settings support a potential role for nintedanib in Japanese patients with HCC who are refractory to or intolerant of sorafenib. Stable disease was reported for >75% of patients in each group.

In conclusion, the triple angiokinase inhibitor nintedanib had a manageable safety profile in Japanese patients with advanced HCC and mild to moderate liver impairment, with the MTD established as 200 mg b.i.d.

Abbreviations

AE	adverse event
AFP	α-fetoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
$AUC_{\tau,ss,norm}$	dose-normalized area under the curve at steady state
DLT	dose-limiting toxicity
FGFR	fibroblast growth factor receptor
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HFSR	hand–foot skin reaction
MTD	maximum tolerated dose
PDGFR	platelet-derived growth factor receptor
PK	pharmacokinetic
SD	standard deviation
TTP	time to progression
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

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