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Safety, pharmacokinetics and efficacy of donafenib in treating advanced hepatocellular carcinoma: report from a phase 1b trial

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Background: Donafenib is a novel compound similar to sorafenib that functions as a multikinase inhibitor. This phase 1b trial aimed to assess the safety, pharmacokinetics and efficacy of donafenib in treating Chinese patients with advanced hepatocellular carcinoma. *Methods:* From July 2014 to April 2015, 27 eligible advanced hepatocellular carcinoma patients were enrolled in the trial. They were randomly divided into 200 mg and 300 mg bid groups and received these oral doses of donafenib until the appearance of intolerance or disease progression. *Results:* Overall, donafenib was safe and well tolerated in the two groups, and most adverse events were grade 1 or 2. Elevated transaminase (n=19, 70.4 %), hypocalcemia (n=19, 70.4 %), and skin toxicity (n=17, 63.0 %) were the most frequently encountered adverse events. Donafenib exhibited high variability in pharmacokinetic parameters. Areas under the plasma concentration–time curve from 0–12 h increased disproportionally to the dose escalation. The treatment resulted in partial response in two patients and a stable disease status in 17 patients, and the median time to progression was 120 days for both groups. *Conclusion:* The results from this phase 1b trial indicate a favorable safety profile and notable anticancer efficacy of donafenib for treating advanced hepatocellular carcinoma. Comparable or better safety and efficacy were observed for a lower dosage of donafenib compared with sorafenib in the literature.

1. Introduction

Hepatocellular carcinoma (HCC) affects more than 500,000 people each year, as the fifth most prevalent solid tumor worldwide, and it represents the third most common cause for cancer-related deaths because of poor patient prognosis (Kim and Han 2012; Parkin et al. 2005). The most important risk factors for the development of HCC are chronic hepatitis B or C. (Ferlay et al. 2010; Kim et al. 2016). Because of silent symptoms at the early stage and the absence of sensitive detection assays that can be routinely employed among populations at high risk for HCC, most HCC patients are diagnosed at an advanced stage and unable to select the most effective treatment options of resection and liver transplantation. Transarterial chemoembolization (TACE) and ablation are recommended for patients if no vascular invasion and distant metastasis has occurred. Five-year survival rates of 40–70 % and objective response rates of 16–60 % have been reported for ablation therapy and TACE therapy, respectively (Lencioni et al. 2010; Bruix and Sherman 2005).

Sorafenib is the first approved oral drug for the treatment of advanced HCC and has become a standard therapy for unresectable HCC. As a kinase inhibitor with multiple targets, sorafenib can block the RAF/MEK/ERK signal transduction pathway by inhibiting serine/threonine kinase. It can also block tumor angiogenesis by inhibiting vascular endothelial growth factor receptor (VEGFR) and platelet derived growth factor receptor (PDGFR) (Wilhelm et al. 2004; Luo et al. 2017; Hottinger et al. 2014). The Sorafenib HCC Assessment Randomized Protocol (SHARP) trial was a multicenter, double-blind, placebo-controlled phase III clinical trial including 602 patients with advanced HCC. Sorafenib-treated patients showed a significant survival benefit with a median overall survival(OS) of 10.7 months compared to only 7.9 months with placebo ($p<0.001$) (Llovet et al. 2008). Another phase III trial based in the Asia-Pacific (AP) region reported a median OS of 6.5 months with sorafenib compared to 4.2 months with placebo (Cheng et al. 2009).

In the early 1960s, it was suggested that superior stability of the C-D bond, compared with the C-H bond, can be established through introduction of deuterium into drug molecules during the process of development (Elison et al. 1961). The increased stability leads to the lower systematic clearance and prolonged half-life or increased bioavailability, and reduces the dosage required, which is important for reducing adverse events (AEs) through reducing the levels of metabolites in the gastrointestinal tract. In addition, the decreased levels of undesirable metabolites are accompanied by increased levels pharmacologically desirable metabolites (Tung 2010; Shao et al. 2006). However, no deuterium-contained drug listed until AUSTEDO® was approved by the FDA in 2017 for the treatment of Huntington's chorea. Donafenib is a new version of sorafenib that includes deuterium. The donafenib molecular structure is shown in Fig. 1.

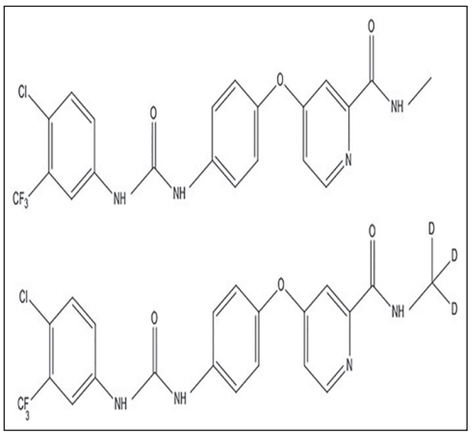

Fig. 1: Chemical formulae of sorafenib and donafenib.

A 10-center study was conducted in China to assess the safety, pharmacokinetics, and preliminary efficacy of donafenib monotherapy in Chinese patients with advanced HCC. Here we report the results of the 1b trial conducted in the First Hospital of Jilin University, Changchun, China.

2. Investigations and results

2.1. Patient demographics and disposition in the screening period

A total of 72 patients with unresectable advanced HCC were screened for selection before enrollment and 27 of them were finally enrolled in the trial and received at least one dose of donafenib. Demographic and disease characteristics are listed in Table 1. Approximately 80 % of patients were male. The median ages were 56 and 54 years and weights were 64.8 and 59.8 kg for the two groups, respectively. Most patients had undergone surgery and received interventional therapy. Generally, the demographics and prior therapies were similar between the two groups.

Table 1: Summary of demographic and disease characteristics

Characteristic	200 mg bid group	300 mg bid group
Total number of treated, n (%)	13 (100)	14 (100)
Female, n (%)	2 (15.4)	3 (21.4)
Age (years), median (range)	56 (44-66)	54 (40-63)
Weight (kg), median(range)	64.8 (52-85.6)	59.8 (42.4-85.6)
Sites of metastasis, n (%)		
Liver	12 (92.3)	10 (71.4)
Lymph gland	4 (30.8)	3 (21.4)
Lung	2 (15.4)	2 (14.3)
Peritoneum	0 (0)	2 (14.3)
Other	1 (7.7)	1 (7.1)
Type of previous therapy, n (%)		
Surgery	5 (38.5)	8 (57.1)
Interventional therapy	3 (23.1)	8 (57.1)
Radiofrequency ablation	2 (15.4)	1 (7.1)
Chemotherapy	2 (15.4)	2 (14.3)
Radiotherapy	2 (15.4)	0 (0)
ECOG PS at screening		
0	7 (53.8)	6 (42.9)
1	6 (46.2)	8 (57.1)

2.2. Safety and tolerability

Overall, donafenib was safe and well tolerated in the two groups. Most AEs were graded at 1 or 2. The most frequently reported treatment-related AEs are listed by grade and dose group in Table 2. Elevated transaminase and hypocalcemia were two of the most frequently observed AEs (both n=19, 70.4 %), followed by hand-foot skin reaction (n=17, 63.0 %), hair loss (n=15, 55.6 %), rash (n=14, 51.9 %), diarrhea, platelet reduction (n=10, 37.0 %) and fatigue (n=9, 33.3 %). There appeared to be a higher incidence and severity of AEs in the 300 mg bid group. For instance, the total incidence of hand-foot skin reaction was 53.9 % in the 200 mg bid group compared with 71.4 % in the 300 mg bid group, and 61.5 %, of patients in the 200 mg bid group experienced elevated transaminase at grade 1 or 2 compared to 78.5 % (one was with grade 3 and 4) in the 300 mg bid group.

Seven of twenty-seven patients experienced drug-related AEs at grade 3 or 4 after the initiation of donafenib treatment, which was subsequently suspended. Six of seven received 300 mg bid. All of them received the prompt treatment for the AEs. The severe AEs were reduced to grade 1 or returned to normal in four patients within 14 days and then donafenib treatment was resumed at the reduced dose per the protocol while the remaining three patients dropped out.

Five patients (18.5 %) experienced serious AEs (SAEs) during the study, but none of these was likely related to donafenib.

2.3. Anticancer efficacy

Twenty-five of 27 patients were evaluable for the anticancer efficacy according to RECIST 1.0. No case of CR was observed. PR was observed in one patient in the 200 mg bid group as well as in one patient in the 300 mg bid group. One was a 47-year-old male patient who had chronic hepatitis B and was treated with a combination of donafenib and the nucleoside analog entecavir during the whole trial period. The other was a 66-year-old female who had chronic hepatitis B and hypertension and was treated with a combination of donafenib and the antihypertensive drug enalapril maleate orally. SD was observed in eight patients (61.5 %) in the 200 mg bid group and nine patients (64.3 %) in the 300 mg bid group. Two patients (15.4 %) in the 200 mg bid group and 4 (28.6 %) in 300 mg bid group had PD. Two patients in the 200 mg bid group prematurely terminated involvement without response evaluation. The efficacy results are listed in Table 3. The median duration of progression free survival (PFS) was 120 days in both groups, and the Kaplan–Meier curves for PFS are shown in Fig. 2.

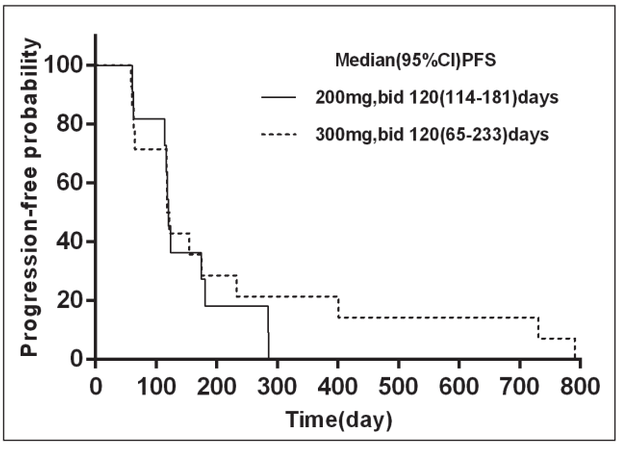

Fig. 2: Kaplan-Meier curves for progression-free survival.

2.4. Pharmacokinetics

The mean donafenib plasma concentration–time profiles of the 200 mg bid and 300 mg bid groups on day 1 and 28 are shown in Fig. 3. Donafenib was moderately absorbed after the first dose on day 1 and day 28. The median T_{max} for both doses was 4.0 h on day 1 and 2.0 and 4.0 h on day 28, respectively. The level of drug exposure seemed to be increased disproportionally to the dose promotion on both days 1 and 28. The $AUC_{0\text{-}12}$ ratio for the 200 mg bid and 300 mg bid groups was 2.17 (90% Cl: 1.38–3.43) on day 1 and then 2.18 (90% Cl: 1.24–3.93) on day 28, exceeding the proportion of dose promotion of 1.5. The $AUC_{0\text{-}12}$ ratios for day 1 and day 28 were 2.96 (90% Cl: 1.51–5.83) in the 200 mg bid group and 2.98 (90% Cl: 2.19–4.13) in the 300 mg group, showing the accumulation in both groups at the stage of continuous administration. The donafenib pharmacokinetic parameters are shown in Table 4. A steady-state plasma concentration of donafenib was reached on day 14, and no further accumulation was detected with subsequent administration.

Table 2: Summary of treatment-related adverse events (NCI CTCAE grades) occurring in > 5 % of patients in the two groups

Group	200 mg bid group (n=13), n (%)				300 mg bid group (n=14), n (%)			
Grade	1	2	3	4	1	2	3	4
Adverse events								
Hand-foot skin reaction	1 (7.7)	6(46.2)	0	0	0	10 (71.4)	0	0
Rash	5 (38.5)	0	0	0	7 (50.0)	2 (14.2)	0	0
Diarrhea	3 (23.1)	1(7.7)	0	0	4 (28.6)	3 (21.4)	0	0
Hair loss	6 (46.2)	1(7.7)	0	0	8 (57.1)	0	0	0
Stomatitis	0	1(7.7)	0	0	0	0	0	0
Mucosal inflammation	0	0	0	0	0	1 (7.1)	0	0
Fatigue	6 (46.2)	0	0	0	3 (21.4)	0	0	0
High blood pressure	0	1(7.7)	0	0	0	1 (7.1)	0	0
Abdominal pain	0	0	0	0	2 (14.3)	0	0	0
Elevated transaminase	7 (53.8)	1(7.7)	0	0	5 (35.7)	4 (28.6)	1 (7.1)	1 (7.1)
Elevated amylase	1 (7.7)	0	0	0	2 (14.3)	0	0	0
Thrombocytopenia	4 (30.8)	1(7.7)	0	0	3 (21.4)	2 (14.3)	0	0
Decreased hemameba	3 (23.1)	0	0	0	0	1 (7.1)	2 (14.3)	0
Decreased neutrophile granulocyte	0	0	0	0	0	3 (21.4)	1 (7.1)	0
Decreased lymphocyte	0	2(15.4)	0	0	2 (14.3)	2 (14.3)	1 (7.1)	0
Hypokalemia	4 (30.8)	0	0	0	2 (14.3)	0	1 (7.1)	0
Hypocalcemia	6 (46.2)	3(23.1)	1(7.7)	0	7 (50.0)	2 (14.3)	0	0
Hyponatremia	2 (15.4)	1(7.7)	0	0	4 (28.6)	0	0	0

Listed are treatment-related adverse events, as defined by the National Cancer Institute Common Terminology Criteria (version 3.0).

Table 3: Therapeutic responses to donafenib

Best overall response, n (%)	200 mg bid group	300 mg bid group	Total
Patients treated (n)	13	14	27
Objective response, n (%)[a]	1 (7.7 %)	1 (7.1 %)	2 (7.4 %)
Disease control, n (%)[c]	9 (69.2 %)	10 (71.4 %)	19 (70.4 %)
Complete response, n (%)	0	0	0
Partial response, n (%)	1 (7.7 %)	1 (7.1 %)	2 (7.4 %)
Stable disease,n (%)[b]	8 (61.5 %)	9 (64.3 %)	17 (63.0 %)
Progressive disease, n (%)	2 (15.4 %)	4 (28.6 %)	6 (22.2 %)
Not evaluated, n (%)	2 (15.4 %)	0	2 (7.4 %)

[a]Objective response: defined as the sum of patients who achieved complete response and partial response.
[b]Stable disease: the patients with best overall response of stable disease for at least 6 weeks after the first dose of donafenib
[c]Disease control included complete response, partial response, and stable disease

3. Discussion

This phase 1b trial was conducted to assess the safety, pharmacokinetics, and efficacy of donafenib, a new version of sorafenib with deuterium incorporated, for treating advanced HCC. A lower systematic clearance and the increased bioavailability from this deuterium-containing drug allowed us to dose donafenib at 200 mg bid and 300 mg bid, about 30–50 % lower than the standard 400 mg dosage of sorafenib, in this 1b trial to investigate if a similar efficacy can be achieved with milder AEs.

Overall, AEs were common, and most donafenib-treated patients experienced drug-related elevated transaminase, hand-foot reaction, hair loss, diarrhea, and hypocalcemia. However, a large proportion of the observed AEs were mild and moderate graded at 1 or 2. AEs were also dose-dependent, as more frequent and more severe AEs appeared in the 300 mg group, leading to the dropout of two patients in comparison to the 200 mg group in which no patient dropped out. Among the AEs, elevated transaminase occurred in 61.5 % and 78.5 % of the treated patients in the two groups, respectively. The

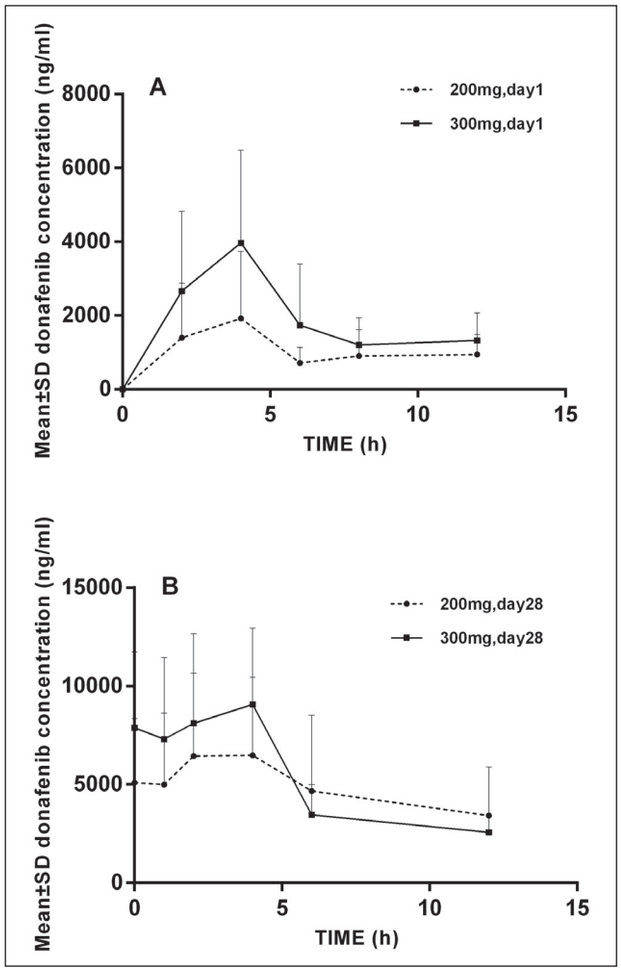

Fig. 3: Mean plasma drug concentration-time curves of donafenib after oral dose of 200 mg bid and 300 mg bid for day 1 (A) and day 28 (B).

pain (20.1 %), and the most commonly reported grade 3 or 4 AEs were hand-foot skin reaction (6.0 %), bilirubin elevation (5.2 %), and thrombocytopenia (4.5 %). Strumberg et al. (2007) summarized the results from four phase I trials (Clark et al. 2005; Awada et al. 2005; Moore et al. 2005; Strumberg et al. 2005). The common AEs among the patients treated with continuous oral sorafenib were fatigue (40 %), anorexia (35 %), diarrhea (34 %), rash/desquamation (27 %), and hand-foot skin reaction (25 %). The commonly reported grade 3 or 4 AEs were hand-foot skin reaction (8.0 %), fatigue (6 %), and diarrhea (4 %), and most occurred with longer treatment duration. Because sorafenib is a favorable treatment option for unresectable advanced HCC patients, it requires compliance to continuous administration of this drug. However, about 20 % of the treated patients were forced to withdraw because of drug-related AEs. There appeared to be lower percentages of AEs at grade 3 or 4 in the 200 mg donafenib group in the current study in comparison to the above-mentioned AE rates caused by sorafenib. Less severe AEs could make donafenib better tolerated than sorafenib.

The anti-cancer efficacy analysis showed that percentages of objective response and SD, as well as median PFS (both 120 days) were comparable in the two dose groups. One case of PR (7.7 %) and eight cases of SD (61.5 %) occurred in the 200 mg bid group, and one cases of PR (7.1 %) and nine cases of SD (64.3 %) in the 300 mg bid group. In the SHARP trial (Llovet et al.2008), seven patients (2 %) achieved PR and 211 patients (71 %) had SD, and HCC progression was delayed by 2.8 months in the placebo group to 5.5 months in the sorafenib treatment groups. In another phase III trial conducted in the Asia/Pacific region (Cheng et al.2009), 150 advanced HCC patients were treated with 400 mg bid sorafenib and 75 patients received placebo. Five patients (3.3 %) achieved PR and 81 patients (54.0 %) achieved SD in the sorafenib treatment group, and the median time to progression was 2.8 months longer than the 1.4 months in placebo group. In a sorafenib phase 1 trial with Japanese HCC patients (Furuse et al. 2008), one patient (4 %) achieved PR and 20 (83 %) SD, and the median time to progression was 4.9 months. Compared with the published efficacy data for sorafenib, both donafenib dose groups in the present study achieved comparable or higher percentages of PR and SD and similar or longer median PFS.

Table 4: Plasma pharmacokinetic parameters after dosing with donafenib 200 mg bid and 300 mg bid on day 1 and 28

	Day 1			Day 28		
Dose	AUC_{0-12} (ng.h/mL) geo mean (CV%)	C_{max} (ng/ml) geo mean (CV%)	T_{max} (h) median (range)	AUC_{0-12} (ng.h/mL) geo mean (CV%)	C_{max} (ng/ml) geo mean (CV%)	T_{max} (h) median (range)
200 mg bid group	9185.6 (95.6)	1488.4 (94.4)	4.0 (2.0-12.0)	27204 (166.4)	5640.1 (57.1)	2.0 (0.0-12.0)
300 mg bid group	19963.7 (61.8)	3737.5 (70.4)	4.0 (2.0-6.0)	59425.4 (38.0)	9526.5 (49.4)	4.0 (0.0-4.0)

AUC_{0-12}, area under the plasma concentration–time curve from 0-12 h; $C_{max,}$ peak plasma concentration; $T_{max,}$ time to peak plasma concentration; CV, coefficient of variation.

elevated transaminase was more severe in the 300 mg group with 28.6 % at grade 2, 7.1 % at grade 3, and 7.1 % at grade 4, compared to only 7.7 % at grade 2 and none at grade 3 or 4 in the 200 mg group. The elevated transaminase raised safety concerns, but appeared to be tolerable if the 200 mg dose was selected.

Diarrhea, weight loss, and hand–foot skin reaction were the most frequent AEs occurring in the sorafenib trials, and grade 3 drug-related AEs consisted of diarrhea (8 %), hand-foot skin reaction (8 %), hypertension (2 %), abdominal pain (2 %), hypophosphatemia (11 %), and thrombocytopenia (4 %), as reported by the SHARP trial (Llovet et al. 2008), in which all eligible patients were randomly assigned in a 1:1 ratio to receive continuous oral treatment with either 400 mg sorafenib (consisting of two 200-mg tablets) twice daily or matching placebo. Kim et al. (2016) reported the real-life experience of sorafenib therapy among treated HCC patients in a Korean population (Lencioni et al. 2014). The common AEs were hand-foot skin reaction (32.2 %), diarrhea (22.8 %), and abdominal

The pharmacokinetic parameters of donafenib determined in this study were highly variable. The plasma concentration–time of donafenib seemed to increase disproportionally with the dose escalation at both days 1 and 28, which differed from the sorafenib pharmacokinetic markers. It appeared that the 300 mg bid donafenib dose achieved a comparable T_{max} and a higher C_{max} at both day 1 and the last day compared with those of 400 mg bid sorafenib (Clark et al. 2005; Moore et al. 2005; Strumberg et al. 2005). In a phase 1 sorafenib trial with Japanese HCC patients (Furuse et al. 2008), the C_{max} and AUC_{0-12} in the 400 mg bid group were obviously lower than those determined in this donafenib trial. Interestingly, we observed dose-dependent AEs, but not dose-dependent anti-cancer efficacy, and we do not know the responsible mechanisms at this time. It appeared that introduction of deuterium into sorafenib may have improved the bioavailability of this drug. Thus, donafenib at 300 mg bid dosing can achieve a similar pharmacokinetic profile to sorafenib at 400 mg bid dosing, while the

pharmacokinetic parameters for 200 mg donafenib were similar to those for 200 mg sorafenib in this trial.

In summary, donafenib was safer at the 200 mg dose, and similar anti-cancer efficacy was observed in both 200 and 300 mg groups. The AEs and efficacy of donafenib determined in this trial were comparable to the reported data for higher sorafenib doses (>400 mg). However, our findings need to be validated in the next phases of trials.

4. Experimental

4.1. Patients

From July 2014 to April 2015, Chinese patients with advanced HCC were screened, and enrolled into the study in the First Hospital of Jilin University, China. Eligible patients with advanced unresectable HCC were 18–70 years old, had a Child-Pugh score of A, at least a 3-month life expectancy, and an Eastern Cooperative Oncology Group (ECOG) performance score 0-2. Additional inclusion criteria included informed consent; at least a measurable lesion; no chemotherapy, radiotherapy, or biotherapy within 4 weeks; and no surgery within 3 months prior to this trial.

The patients who had severe liver cirrhosis, hepatotrophy, portal hypertension, or ascites were excluded. Additional exclusion criteria were those who received liver transplantation; had concurrent digestive diseases that affect drug absorption, distribution, metabolism, or excretion; or HCC progression after treatment with sorafenib; allergic to donafenib or competing drug; brain metastases; HIV, HCV or HDV infection; and any other abnormity considered to affect the evaluation of safety.

The study was approved by the ethics committee of the First Hospital of Jilin University and conducted under the guidelines of the Declaration of Helsinki and the Principles of Good Clinical Practice. Written informed consent was obtained from all patients prior to final enrollment in the study.

4.2. Study design

This was a randomized, open-label, parallel control phase 1b clinical trial conducted in the First Hospital of Jilin University, China (NCT02229071 registered at https://clinicaltrials.gov). Donafenib was supplied in two different unit doses, 200 mg (batch number 201208311/201208312/201208313) and 50 mg (batch number 1405050) by Suzhou Zelgen Biopharmaceuticals Co., Ltd, China.

The primary endpoints were the safety and tolerance of donafenib in the advanced HCC patients. The secondary endpoints were the pharmacokinetics and preliminary efficacy of donafenib. Twenty-seven enrolled HCC subjects were randomly divided into two groups treated with oral donafenib at 200 mg or 300 mg bid. All patients received the treatment until HCC progression or the appearance of intolerance.

4.3. Safety and tolerance analysis

AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 3.0). Dosage adjustments could be applied during the study according to the protocol. Administration would be suspended once the AEs were graded at 3 or 4, and the twice daily dose was reduced to a once-daily dose if the AEs returned to normal or grade 1 within 15 days. If grade 3 or 4 AEs occurred for a second time, the regimen was reduced to alternate-day dose if the AEs returned to normal or grade 1within 15 days. The treatment was terminated if an AE occurred for a third time.

4.4. Efficacy analysis

Tumor assessments were performed at screening and every 8 weeks after the start of the treatment per the Response Evaluation Criteria In Solid Tumors (RECIST) (version 1.0) until progressive disease (PD) was confirmed. Patients with complete response (CR), partial response (PR), and stable disease (SD) were eligible for subsequent doses.

4.5. Combined medications

Combined medications were given if non-hematological toxicity appeared at grade 2 or greater and hematological toxicity at grade 3 or 4. No preventive drugs, metabolism enzymes, or other anti-tumor medications including chemotherapy, thymosin, interferon, and herbal drugs were permitted during the study.

4.6. Pharmacokinetics sampling and analysis

Blood samples (2 ml) for pharmacokinetic analyses were collected on day 1 and 28. Additional pharmacokinetic samples were collected at weeks 2, 8, 12, and 16 before the administration of the morning dose. Pharmacokinetic blood samples were centrifuged at 3,000 rpm for 10 mins at 4 °C and stored at -70 °C. Non-compartmental pharmacokinetics were analyzed using WinNonlin version 6.4 (Pharsight Corporation, Mountain View, CA, USA). The standard non-compartmental methods were utilized to calculate pharmacokinetic parameters including peak plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), area under the plasma concentration–time curve from 0–12 h ($AUC_{0\text{-}12}$), terminal elimination half-life ($t_{1/2}$), clearance (Cl_z/F), apparent volume of distribution after extravascular administration (V_z/F) at the first administration in the morning of day 1, peak plasma concentration at steady state ($C_{max,ss}$), time to peak plasma concentration at the steady state($T_{max,ss}$), terminal elimination half-life at steady state ($t_{1/2,ss}$), area under the plasma concentration–time curve from 0–12h at steady state ($AUC_{0\text{-}12,ss}$), terminal elimination half-life at steady state ($t_{1/2,ss}$), clearance at steady state (Cl_z/F_{ss}), apparent volume of distribution after extravascular administration at steady state (V_z/F_{ss}), and accumulation ratio (R) at the first administration on the morning of day 28.

Author contributions: Jingrui Liu, Xiaojiao Li, Hong Chen, Guiling Chen, Yue Hu, Junqi Niu and Yanhua Ding conducted the clinical trial. Hong Zhang was responsible for data analysis. Jingrui Liu prepared the manuscript. All authors reviewed the results and approved the final version of the manuscript.

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Conflicts of Interest: The authors declare no conflicts of interest.

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