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Randomized, Open-Label Phase 2 Study Comparing Frontline Dovitinib Versus Sorafenib in Patients With Advanced Hepatocellular Carcinoma

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Angiogenesis inhibition by the vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) inhibitor sorafenib provides survival benefit in hepatocellular carcinoma (HCC); however, angiogenic escape from sorafenib may occur due to angiogenesis-associated fibroblast growth factor receptor (FGFR) pathway activation. In addition to VEGFR and PDGFR, dovitinib inhibits FGFR. Frontline oral dovitinib (500 mg/day, 5 days on, 2 days off; n = 82) versus sorafenib (400 mg twice daily; n = 83) was evaluated in an open-label, randomized phase 2 study of Asian-Pacific patients with advanced HCC. The primary and key secondary endpoints were overall survival (OS) and time to tumor progression (TTP) as determined by a local investigator, respectively. Patients included in the study were ineligible for surgical and/or locoregional therapies or had disease progression after receiving these therapies. The median OS (95% confidence interval [CI]) was 8.0 (6.6-9.1) months for dovitinib and 8.4 (5.4-11.3) months for sorafenib. The median TTP (95% CI) per investigator assessment was 4.1 (2.8-4.2) months and 4.1 (2.8-4.3) months for dovitinib and sorafenib, respectively. Common any-cause adverse events included diarrhea (62%), decreased appetite (43%), nausea (41%), vomiting (41%), fatigue (35%), rash (34%), and pyrexia (30%) for dovitinib and palmar-plantar erythrodysesthesia syndrome (66%) and decreased appetite (31%) for sorafenib. Subgroup analysis revealed a significantly higher median OS for patients in the dovitinib arm who had baseline plasma soluble VEGFR1 (sVEGFR1) and hepatocyte growth factor (HGF) below median levels versus at or above the median levels (median OS [95% CI]: sVEGFR1, 11.2 [9.0-13.8] and 5.7 [4.3-7.0] months, respectively [P = .0002]; HGF, 11.2 [8.9-13.8] and 5.9 [5.0-7.6] months, respectively [P = 0.0002]). *Conclusion:* Dovitinib was well tolerated, but activity was not greater than sorafenib as a frontline systemic therapy for HCC. Based on these data, no subsequent phase 3 study has been planned. (HEPATOLOGY 2016; 00:000–000)

Abbreviations: AE, adverse event; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; HCC, hepatocellular carcinoma; HGF, hepatocyte growth factor; OS, overall survival; PDGFR, platelet-derived growth factor receptor; PK, pharmacokinetics; PPES, palmar-plantar erythrodysesthesia syndrome; RECIST, Response Evaluation Criteria in Solid Tumors; sVEGFR1, soluble vascular endothelial growth factor receptor-1; TKI, tyrosine kinase inhibitor; TTP, time to tumor progression; ULN, upper limit of normal; VEGFR, vascular endothelial growth factor receptor.

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Overexpression of fibroblast growth factor receptors (FGFRs) FGFR1, FGFR2, FGFR3, or FGFR4 and corresponding FGF ligands (FGF2, FGF8, FGF17, or FGF18) has been observed in human hepatocellular carcinoma (HCC) tumors.[1-3] HCC accounts for approximately 80% of primary liver cancer cases, the majority of which are diagnosed at an advanced stage of disease and are not candidates for surgical interventions.[4,5] FGF2, a potent angiogenic factor in HCC, has been shown to augment vascular endothelial growth factor (VEGF)-mediated HCC development and angiogenesis, and perhaps may evade resistance to VEGFR modulating agents.[6-8]

Sorafenib (Nexavar; Whippany, NJ), a multikinase inhibitor of vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR), was the first effective antiangiogenic therapy for advanced HCC and remains the only approved treatment for this disease.[9,10] Although sorafenib was shown to improve overall survival (OS) and radiological time to tumor progression (TTP) in Asian-Pacific patients with advanced HCC (median OS, 6.5 months; median TTP, 2.8 months), better systemic therapy remains an unmet need for patients with HCC in the Asia-Pacific region.

Dovitinib is a potent inhibitor of FGFRs, VEGFRs, and PDGFRβ, with antitumor activity mediated by a dual mechanism of action, including antiproliferative and antiangiogenic effects.[11,12] Preliminary efficacy for dovitinib has been reported in patients with metastatic renal cell carcinoma, metastatic melanoma, breast cancer, multiple myeloma, and acute myeloid leukemia.[12-15] In phase 1 studies in solid tumors, the maximum tolerated dose was determined to be 500 mg/day on a 5 days on, 2 days off schedule.[12,16] Dovitinib activity has been evaluated in multiple preclinical xenograft models in HCC. In the sorafenib-sensitive PLC5 HCC model, dovitinib inhibited tumor growth in a dose-dependent manner.[17] Furthermore, in patient-derived HCC xenograft models, dovitinib demonstrated antitumor activity superior to that of sorafenib and antiangiogenic effects that correlated with FGFR, PDGFRβ, and VEGFR2 signaling pathway activation.[18,19] These data support an investigation of dovitinib in patients with HCC. Here, we present the efficacy and safety results of a phase 2 study of frontline dovitinib versus sorafenib in patients with advanced HCC.

Materials and Methods

STUDY DESIGN AND TREATMENT

This phase 2, open-label, multicenter, randomized study conducted in the Asia-Pacific region evaluated the efficacy and safety of dovitinib compared with sorafenib in patients with advanced HCC. The protocol and all amendments were reviewed by the Independent Ethics Committee or Institutional Review Board for each study site. The study was conducted according to the ethical principles of the Declaration of Helsinki.

Patients were stratified according to Eastern Cooperative Oncology Group performance status (ECOG PS; 0 versus 1) and were randomized 1:1 to receive oral dovitinib at 500 mg/day on a 5 days on, 2 days off schedule or sorafenib at the standard dose, 400 mg continuously twice daily, until disease progression, unacceptable toxicity, death, or discontinuation for any

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reason. Treatment crossover was not planned; however, some patients on the dovitinib arm were given sorafenib as subsequent therapy in countries where sorafenib was clinically available, based on the investigator's judgment. Dose adjustments and interruptions (up to 3 weeks) were allowed for patients unable to tolerate dovitinib or sorafenib study doses. Dovitinib dose reduction for toxicity could not be re-escalated; however, when deemed appropriate by the treating physician, treatment after interruption was resumed on the next day of planned dosing, with every effort made to return to the original 5 days on, 2 days off dosing schedule as soon as possible. Local prescribing information was used to guide sorafenib dose and/or schedule adjustments.

STUDY POPULATION

Patients aged ≥18 years with an ECOG PS of ≤1 and advanced stage B or C HCC according to the American Association for the Study of Liver Diseases guidelines[20] and the Barcelona Clinic Liver Cancer (BCLC) staging classification[21] were eligible for this study. Patients were required to have at least one lesion as assessed by computed tomography or magnetic resonance imaging scans per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients included in the study were either not eligible for surgical and/or locoregional therapies or had disease progression after receiving these therapies. All patients were required to have adequate bone marrow, liver, and renal function, and a current cirrhotic status of Child–Pugh Class A (5-6 points) with no encephalopathy. Patients were excluded from the study if they had received any systemic HCC therapy or sorafenib-based locoregional therapy, received a liver transplant or were awaiting immediate transplantation, or were currently receiving full-dose anticoagulation treatment with therapeutic doses of warfarin or antiplatelet therapy. Patients with clinically significant third space fluid accumulation (i.e., ascites requiring tapping despite use of diuretics, or pleural effusion that either required tapping or is associated with shortness of breath), or impaired cardiac function or clinically significant cardiac diseases were also excluded. Patients were required to stop treatment with any locoregional therapies, radiotherapy (except palliative radiotherapy for bone lesions, within 2 weeks), and major surgery within 4 weeks before study entry. Patients were permitted to receive prophylactic or antiviral treatment as needed, per institutional guidelines. All patients provided written informed consent to participate in the study.

EFFICACY ASSESSMENTS

Tumor response was evaluated locally at investigator sites and centrally by an independent radiologist according to RECIST version 1.1. Criteria for disease progression were also based on RECIST version 1.1. All target and nontarget lesions were assessed by chest, abdomen, and pelvis computed tomography or magnetic resonance imaging scans at baseline and every 6 weeks after the start of dovitinib or sorafenib treatment until radiological progression (see Supporting Information).

SAFETY ASSESSMENTS

Adverse events (AEs) occurring on or after the first dose day through 30 days after the end of treatment were recorded. National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 was used for grading. Hematology, blood chemistry, thyroid and cardiac function, and vital signs were also monitored throughout the study.

PHARMACOKINETICS AND BIOMARKER ASSESSMENTS

Blood samples for full pharmacokinetics (PK) analysis were collected from patients receiving dovitinib on day 1 of week 1 (postdose 1, 3, 6, and 24 hours) and on day 5 of week 2 (predose), week 4 (predose and postdose 1, 3, 6, and 24 hours), and week 6 (predose). Full PK blood sampling was used to estimate dovitinib PK parameters in patients with advanced HCC. A minimum of 18 patients who received dovitinib were enrolled for full PK analysis; the remaining patients in the dovitinib arm participated in sparse PK blood sampling, in which only the postdose 1-hour sample was collected on postdose collection days (day 1 of week 1 and day 5 of week 4).

For plasma pharmacodynamics analysis, blood samples were collected at baseline and predose on day 1 of week 1; day 5 of week 2, 4, and 6; day 1 (±3 days) of week 13; every 12 weeks thereafter; and at the end of treatment. Circulating growth factors, including hepatocyte growth factor (HGF), and soluble receptors, including soluble VEGFR1 (sVEGFR1), were evaluated as core pharmacodynamics biomarkers for FGFR and VEGFR and were measured by way of enzyme-linked immunosorbent or multiplex assays.

STATISTICAL ANALYSIS

The primary endpoint of the study was OS, defined as the time from date of randomization to

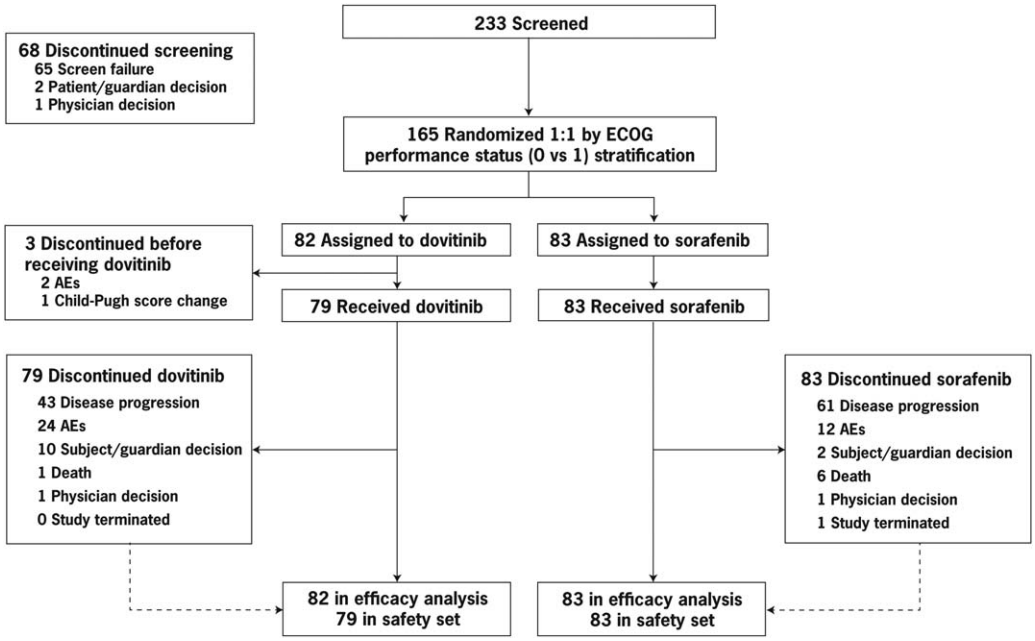

FIG. 1. CONSORT diagram of patient disposition. AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status.

date of death from any cause. If survival status for a patient was unknown at the time of data cutoff, the OS was censored at the last date of contact. Patients who discontinued dovitinib or sorafenib treatment were followed for survival every 6 weeks. Final OS analysis was performed after ≥130 deaths were observed.

The key secondary endpoint was radiologic TTP according to the assessment of a local investigator, which was defined as the time from the date of randomization to the date of first documented radiological disease progression. Patients who did not have a disease progression event were censored on the date of last adequate tumor assessment before the date of data analysis cutoff, start of antineoplastic therapy, or death. Death due to progression without documented radiological disease progression did not represent a disease progression event. Additional secondary endpoints were local investigator-assessed disease control rate (sum of patients with best overall response of complete response, partial response, or stable disease), time to definitive ECOG PS deterioration by ≥1 point (time from the date of randomization to either the date of definitive deterioration of the ECOG PS by ≥1category of the score from baseline or death, whichever came first), and safety.

The study population used for efficacy analyses included all patients who had been randomized. The safety and exploratory PK and biomarker (dovitinib arm only) populations for analysis comprised all patients who received at least one dose of study medication. Descriptive statistics were used to summarize patient demographics, baseline disease characteristics, AEs, PK parameters, and biomarker data, only allowing for an exploratory comparison between the two arms. A Cox proportional hazard model stratified by stratification factor (ECOG PS [0 versus 1]) was used to estimate the hazard ratio and its 95% confidence interval (CI). OS was analyzed using the Kaplan–Meier method, and the median OS along with 95% CIs were determined by treatment group.

Results

PATIENT DEMOGRAPHICS AND DISPOSITION

A total of 165 patients were randomized 1:1 to dovitinib (n = 82) or sorafenib (n = 83), stratified by ECOG PS (Fig. 1). Patient demographics were well balanced between the treatment arms (Table 1). All

TABLE 1. Patient Demographics and Baseline Characteristics

Characteristic	Treatment Arm: Dovitinib (n = 82)	Treatment Arm: Sorafenib (n = 83)
Age, years, median (range)	56 (27-82)	56 (27-83)
Sex, n (%)		
Men	73 (89)	67 (81)
Women	9 (11)	16 (19)
Race, n (%)		
Asian	82 (100)	83 (100)
Ethnicity, n (%)		
East Asian	54 (66)	51 (61)
Japanese	8 (10)	11 (13)
Southeast Asian	19 (23)	20 (24)
South Asian	1 (1)	0 (0)
Other	0 (0)	1 (1)
ECOG PS, n (%)		
0	52 (63)	53 (64)
1	30 (37)	29 (35)
Missing	0 (0)	1 (1)
Histologic grade, n (%)		
Moderately differentiated	14 (17)	13 (16)
Poorly differentiated	5 (6)	11 (13)
Unknown	61 (74)	55 (66)
Well differentiated	2 (2)	4 (5)
BCLC stage at baseline, n (%)		
Stage B	2 (2)	2 (2)
Stage C	80 (98)	81 (98)
Metastatic site of cancer, n (%)		
Adrenal	2 (2.4)	2 (2.4)
Ascites (malignant)	4 (4.9)	2 (2.4)
Bone	7 (8.5)	5 (6.0)
Liver	1 (1.2)	0 (0)
Lung	46 (56.1)	42 (50.6)
Mesenteric lymph nodes	5 (6.1)	9 (10.8)
Other	23 (28.0)	21 (25.3)
Pancreas	1 (1.2)	1 (1.2)
Para-aortic lymph nodes	4 (4.9)	6 (7.2)
Paracardiac lymph nodes	1 (1.2)	0 (0)
Pericardial effusion (malignant)	0 (0)	1 (1.2)
Peritoneum	3 (3.7)	5 (6.0)
Pleura	0 (0)	1 (1.2)
Pleural effusion (malignant)	0 (0)	2 (2.4)
Pulmonary lymph nodes	1 (1.2)	3 (3.6)
Retroperitoneal lymph nodes	1 (1.2)	4 (4.8)
Skin	0 (0)	1 (1.2)
Spleen	1 (1.2)	0 (0)
Supraclavicular lymph nodes	1 (1.2)	0 (0)
Time from primary diagnosis to start of study drug, months, n (%)		
<6	41 (50)	39 (47)
6 to <12	11 (13)	12 (14)
12 to <24	6 (7)	12 (14)
≥24	21 (26)	20 (24)
Missing	3 (4)	0 (0)
Child-Pugh class, n (%)		
A	82 (100)	82 (99)
B	0 (0)	1 (1)

Abbreviations: BCLC, Barcelona Clinic Liver Cancer classification; ECOG PS, Eastern Cooperative Oncology Group performance status.

patients (100%) were Asian-Pacific, with a median age of 56 years (range, 27-83 years), and a majority were men (85%) with an ECOG PS of 0 at baseline (64%). Most patients had BCLC stage C (98%) and Child–Pugh class A (99%) HCC with unknown histological grade (70%). Many patients received prior antineoplastic therapy (56%), including local HCC therapies (56%), surgery (36%), or radiotherapy (7%). Of the local HCC therapies, 35% of patients received antineoplastic medication and 12% received two or more regimens.

All patients discontinued study treatment (Fig. 1), most frequently due to progressive disease (dovitinib, 52%; sorafenib, 73%) or an AE (dovitinib, 29%; sorafenib, 14%). In the dovitinib arm, three patients did not receive the study drug due to AEs (pulmonary embolism [n = 1] and decreased platelets [n = 1]) or change in Child-Pugh score from 6 to 7 at baseline (n = 1) that occurred after study randomization but prior to receiving the first dose. In patients who received at least one dose of the study drug, the median duration of exposure was 2.5 (range, 0.0-11.7) months in the dovitinib arm and 3.2 (range, 0.1-23.5) months in the sorafenib arm. A majority of patients (dovitinib, 72%; sorafenib, 63%) required dose adjustment or interruption for AEs, most commonly including increased bilirubin (14%), aspartate aminotransferase (13%), or alanine aminotransferase (11%), fatigue (11%), and diarrhea (10%) in the dovitinib arm, and palmar-plantar erythrodysesthesia syndrome (PPES; 30%) and increased aspartate aminotransferase (11%) in the sorafenib arm.

EFFICACY

A total of 136 OS events were observed (dovitinib, n = 69; sorafenib, n = 67), with a median follow-up of 113.9 weeks (26.2 months). The median OS (95% CI) was 34.6 (28.6-39.4) weeks (8.0 [6.6-9.1] months) and 36.7 (23.3-49.3) weeks (8.4 [5.4-11.3] months) for dovitinib and sorafenib, respectively, with a hazard ratio (95% CI) of 1.27 (0.90-1.79). Kaplan–Meier curves of the two treatment arms cross between 30 and 36 weeks (6.9 and 8.3 months), with a separation in curves in favor of dovitinib before crossing and in favor of sorafenib after crossing (Fig. 2A). The drop in the Kaplan–Meier plot for the dovitinib arm between 24 and 42 weeks was not due to toxicity; patients who died within 24-42 weeks (5.5-9.7 months) from randomization lived for 6.9-37.1 weeks (1.6-8.5 months) after discontinuing dovitinib (Supporting Table 1).

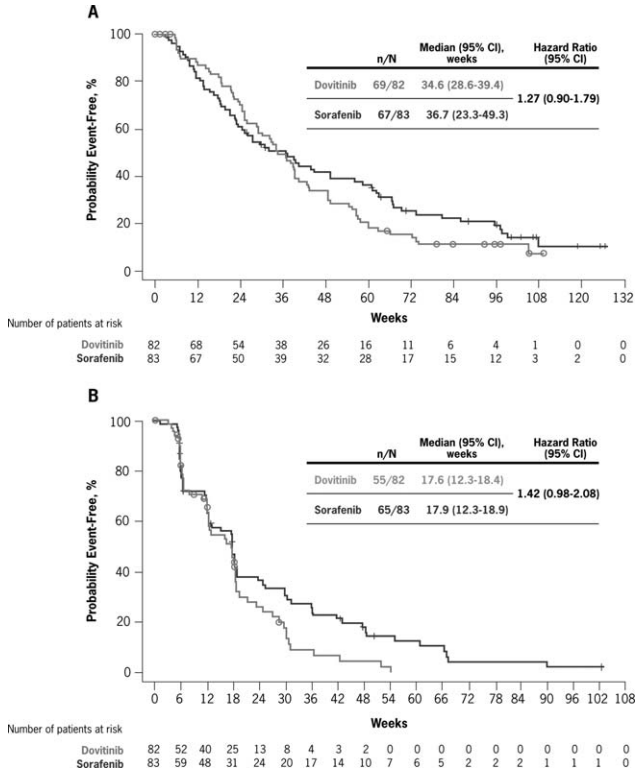

FIG. 2. (A) Overall survival by treatment arm. (B) Time to progression per local investigator assessment by treatment arm. CI, confidence interval; N, number of patients included in the analysis; n, number of events included in the analysis.

The median TTP (95% CI) according to the local investigator's assessment was 17.6 (12.3-18.4) weeks (4.1 [2.8-4.2] months) for dovitinib and 17.9 (12.3-18.9) weeks (4.1 [2.8-4.3] months) for sorafenib (hazard ratio [95% CI], 1.42 [0.98-2.08]). Kaplan–Meier curves for the treatment arms were almost identical until 18 weeks (4.1 months), when the curves separate in favor of sorafenib (Fig. 2B).

The disease control rate according to the local investigator's assessment was lower in the dovitinib arm than the sorafenib arm (57% versus 64%; Table 2). Although the disease control rate was lower for dovitinib than it was for sorafenib, a higher number of patients in the dovitinib arm showed a decrease in best percentage change from baseline in sum of diameters based on RECIST version 1.1 compared with the sorafenib arm (49% versus 41%), and a lower number of patients showed an increase (35% versus 47%) (Supporting Fig. 1). In addition, the number of patients with progressive disease was also lower in the dovitinib arm (21% versus 27%).

Definitive deterioration of ECOG PS was observed in 48% of patients in both treatment arms. The median time to definitive deterioration of ECOG PS (95% CI) was 22.3 (12.6-34.0) weeks (5.1 [2.9-7.8] months) and 21.3 (13.6-not estimable) weeks (4.9 [3.1-not estimable] months) for patients treated with dovitinib and sorafenib, respectively (Supporting Table 2).

SAFETY

All patients experienced at least one AE regardless of study relationship during the study (Table 3). In the dovitinib arm, the most common AEs of any grade, regardless of cause, were diarrhea (62%), decreased appetite (43%), nausea (41%), vomiting (41%), fatigue (35%), rash (34%), and pyrexia (30%). PPES (66%), diarrhea (42%), and decreased appetite (31%) were common in the sorafenib arm. In the dovitinib arm, the most common grade 3/4 AEs, regardless of cause, were increased aspartate aminotransferase (20%), increased alanine aminotransferase (17%), fatigue (14%), hypertension (13%), diarrhea (11%), increased blood bilirubin (11%), and decreased neutrophil count (10%). Common grade 3 and 4 AEs for the sorafenib arm were increased aspartate aminotransferase (24%), PPES (16%), and hypertension (11%).

Serious AEs were experienced by 51% patients in the dovitinib arm and 41% patients in the sorafenib arm (Supporting Table 3), most commonly pyrexia (13% versus 6%). Other serious AEs occurring in 4% of patients were decreased appetite, hepatic encephalopathy, fatigue, and increased blood bilirubin in the dovitinib arm and gastrointestinal hemorrhage in the sorafenib arm. All other serious AEs occurred in ≤2% of patients.

During the study, including up to 30 days after the end of treatment, a total of 18 patients died, five (6%) in the dovitinib arm and 13 (16%) in the sorafenib arm (Supporting Table 4). The most common cause of death was disease progression (dovitinib, n = 4 [5%];

TABLE 2. Best Overall Response by Investigator Assessment

	Dovitinib (n = 82)	Sorafenib (n = 83)
Disease control rate, n (%)	47 (57)	53 (64)
95% CI	46%-68%	53%-74%
Best overall response, n (%)		
Complete response	0 (0)	1 (1)
Partial response	5 (6)	8 (10)
Stable disease	42 (51)	44 (53)
Progressive disease	17 (21)	22 (27)
Unknown	18 (22)	8 (10)

TABLE 3. AEs Regardless of Study Drug Relationship (≥10% Any Grade in Either Treatment Arm)

	Treatment Arm					
	Dovitinib (n = 79)			Sorafenib (n = 83)		
AE	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any	79 (100)	52 (66)	12 (15)	83 (100)	49 (59)	10 (12)
Diarrhea	49 (62)	9 (11)	0 (0)	35 (42)	1 (1)	0 (0)
Decreased appetite	34 (43)	6 (8)	0 (0)	26 (31)	4 (5)	0 (0)
Nausea	32 (41)	4 (5)	0 (0)	16 (19)	0 (0)	0 (0)
Vomiting	32 (41)	1 (1)	0 (0)	10 (12)	1 (1)	0 (0)
Fatigue	28 (35)	11 (14)	0 (0)	13 (16)	2 (2)	0 (0)
Rash	27 (34)	1 (1)	0 (0)	18 (22)	2 (2)	0 (0)
Pyrexia	24 (30)	1 (1)	0 (0)	23 (28)	1 (1)	0 (0)
Increased AST	23 (29)	15 (19)	1 (1)	22 (26)	17 (20)	3 (4)
Increased blood bilirubin	21 (27)	7 (9)	2 (2)	19 (23)	7 (8)	0 (0)
Decreased weight	19 (24)	1 (1)	0 (0)	17 (20)	0 (0)	0 (0)
Hypertension	17 (22)	10 (13)	0 (0)	20 (24)	9 (11)	0 (0)
Increased ALT	17 (22)	13 (16)	1 (1)	17 (20)	8 (10)	0 (0)
Insomnia	17 (22)	0 (0)	0 (0)	9 (11)	0 (0)	0 (0)
Constipation	16 (20)	1 (1)	0 (0)	12 (14)	0 (0)	0 (0)
Peripheral edema	14 (18)	1 (1)	0 (0)	11 (13)	0 (0)	0 (0)
Decreased platelet count	14 (18)	6 (8)	0 (0)	8 (10)	4 (5)	0 (0)
Upper abdominal pain	13 (16)	0 (0)	0 (0)	11 (13)	1 (1)	0 (0)
Stomatitis	13 (16)	1 (1)	0 (0)	11 (13)	0 (0)	0 (0)
Cough	13 (16)	0 (0)	0 (0)	8 (10)	0 (0)	0 (0)
Abdominal pain	12 (15)	3 (4)	0 (0)	17 (20)	3 (4)	0 (0)
Headache	12 (15)	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)
Decreased neutrophil count	12 (15)	8 (10)	0 (0)	2 (2)	0 (0)	0 (0)
PPES	11 (14)	1 (1)	0 (0)	55 (66)	13 (16)	0 (0)
Ascites	10 (13)	2 (2)	0 (0)	9 (11)	4 (5)	0 (0)
Anemia	10 (13)	1 (1)	0 (0)	7 (8)	3 (4)	0 (0)
Hypoalbuminemia	10 (13)	1 (1)	0 (0)	6 (7)	0 (0)	0 (0)
Dizziness	10 (13)	1 (1)	0 (0)	2 (2)	0 (0)	0 (0)
Dyspnea	9 (11)	1 (1)	1 (1)	8 (10)	3 (4)	0 (0)
Thrombocytopenia	9 (11)	4 (5)	1 (1)	2 (2)	1 (1)	0 (0)
Acne	9 (11)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Abdominal distension	8 (10)	0 (0)	0 (0)	9 (11)	1 (1)	0 (0)
Pruritus	8 (10)	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)
Alopecia	1 (1)	0 (0)	0 (0)	19 (23)	0 (0)	0 (0)

Data are presented as n (%).
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPES, palmar-plantar erythrodysesthesia.

sorafenib, n = 12 [14%]). Other causes of death were coronary artery disease (dovitinib only, n = 1) and cerebral hemorrhage (sorafenib only, n = 1).

DOVITINIB PK AND BIOMARKERS

PK analysis of patients with varying degrees of hepatic function and impairment who received dovitinib revealed that exposure was comparable between patients with mild hepatic function impairment and normal hepatic function (Table 4).

Subgroup analysis revealed that higher median OS was achieved by patients in both the dovitinib arm and the sorafenib arm who had baseline plasma sVEGFR1 and HGF below the median levels compared with patients who had baseline plasma sVEGFR1 and HGF at or above the median levels (Fig. 3); however, statistical significance for this association was achieved only with dovitinib (sVEGFR1, $P = 0.0002$; HGF, $P = 0.0002$). The prognostic effect of baseline HGF and sVEGFR1 was not apparent compared with TTP as determined by the local investigator.

Discussion

Currently available treatment options for patients with HCC include the VEGFR and PDGFR inhibitor sorafenib, which has been shown to delay HCC progression through antiangiogenic effects.[9,10] However, clinical benefits observed with sorafenib are usually limited, as angiogenic escape from sorafenib may

TABLE 4. Dovitinib Exposure by Hepatic Function

PK Parameter	Normal Hepatic Function	Mild Hepatic Impairment	Moderate Hepatic Impairment
n, week 1/week 4	19/9	47/14	4/NA
AUC_{last}, h · ng/mL (CV%)			
Week 1, day 1	5291 (29)	5641 (32)	5589 (19)
Week 4, day 5	5986 (42)	6251 (28)	NA
C_{max}, ng/mL (CV%)			
Week 1, day 1	289 (28)	321 (34)	309 (25)
Week 4, day 5	329 (43)	355 (28)	NA
T_{max}, h			
Week 1, day 1	6	6	3
Week 4, day 5	6	6	NA

Values for AUC_{last} and C_{max} are the geometric mean (CV%) and values for T_{max} are the median. Hepatic function definitions: normal = total bilirubin $\leq$ ULN and AST and ALT $\leq$ ULN; mild = total bilirubin $\leq$ ULN and ALT and/or AST > ULN (both below 5× ULN), or 1× ULN < total bilirubin $\leq$ 1.5× ULN and AST and ALT $\leq$ 5× ULN; and moderate = 1.5× ULN < total bilirubin $\leq$ 3× ULN and AST and ALT $\leq$ 5× ULN.
Abbreviations: AUC_{last}, area under the concentration time curve from time zero until the last time point sampled; C_{max}, maximum concentration; CV%, coefficient of variation; NA, not assessed; PK, pharmacokinetics; T_{max}, time to C_{max}; ULN, upper limit of normal.

occur due to FGFR pathway activation.[22] In addition to VEGFR and PDGFR, dovitinib inhibits FGFR[23] and has been hypothesized to provide more effective and sustainable antitumor activity in patients with advanced HCC. However, in this randomized phase 2 study, dovitinib activity was not greater than that of sorafenib as frontline therapy in Asian-Pacific patients with advanced HCC.

In this study, the median OS was similar for dovitinib and sorafenib (34.6 versus 36.7 weeks [8.0 versus 8.4 months]). Similarly, the median TTP as determined by the local investigator did not differ with dovitinib and sorafenib treatment in this study (17.6 versus 17.9 weeks [4.0 versus 4.1 months]). These results are similar to those of studies evaluating other tyrosine kinase inhibitors (TKIs) versus sorafenib, although differences in toxicity and OS have been observed [24].

It is interesting to note that the OS and TTP results in this study are higher than those reported for sorafenib in the phase 3 Asia-Pacific HCC trial (median OS, 6.5 months; median TTP, 2.8 months).[9] Although patient demographics and disease characteristics were similar, overall baseline ECOG PS was more favorable for patients in this study (dovitinib: 0, 63%; 1, 37%; 2, 0%; missing, 0%; sorafenib: 0, 64%; 1, 35%; 2, 0%; missing, 1%) than in the phase 3 Asia-Pacific HCC trial (sorafenib: 0, 25%; 1, 69%; 2, 5%), which may have contributed to the higher activity observed for sorafenib in this study. Similar results were noted in Asian subpopulations in studies of other TKIs versus sorafenib, in which the ECOG PS of 0 (~50%-65%) and median OS (8.5-8.9 months) were comparable to those reported here.[25-27] The effect of ECOG PS on median OS was revealed in some of these TKI versus sorafenib studies, because patients (regardless of region) with ECOG PS 0 had a higher median OS than those with ECOG PS 1.[25,26] For example, in a phase 3 study evaluating linifanib versus sorafenib in HCC, the median OS for ECOG PS 0 compared with ECOG PS 1 was 10.2 versus 8.5 months for sorafenib and 10.2 versus 7.2 months for linifanib[26]; in a phase 3 study of brivanib versus sorafenib, the median OS for ECOG PS 0 compared with ECOG PS 1 was 12.8 versus 6.5 months for sorafenib and 11.6 versus 6.6 months for brivanib.[25] Likewise, ECOG performance status was identified as a prognostic indicator for OS in the SHARP study,[10,28] where risk of death was reduced in patients with ECOG PS 0 (hazard ratio, 0.68 [95% CI, 0.50-0.95]) compared with ECOG PS $\geq$1 (hazard ratio, 0.71 [95% CI, 0.52-0.96]).[10] Therefore, the differences in results between this study and the phase 3 Asia-Pacific HCC trial[9] may be reflective of the difference in patient ECOG PS. However, it should also be noted that in this and more recently reported TKI studies, patients may have tolerated sorafenib better than those in the phase 3 Asia-Pacific HCC trial, because sorafenib AE management has improved greatly in recent years.[29]

The data presented here support the observation from randomized phase 3 studies of sorafenib in patients with HCC, in which median OS and TTP with sorafenib were lower in an Asian-Pacific population compared with a population that was primarily from Europe and North America (OS, 6.5 versus 10.7 months; TTP, 2.8 versus 5.5 months).[9,10] This result may potentially be attributed to differences in

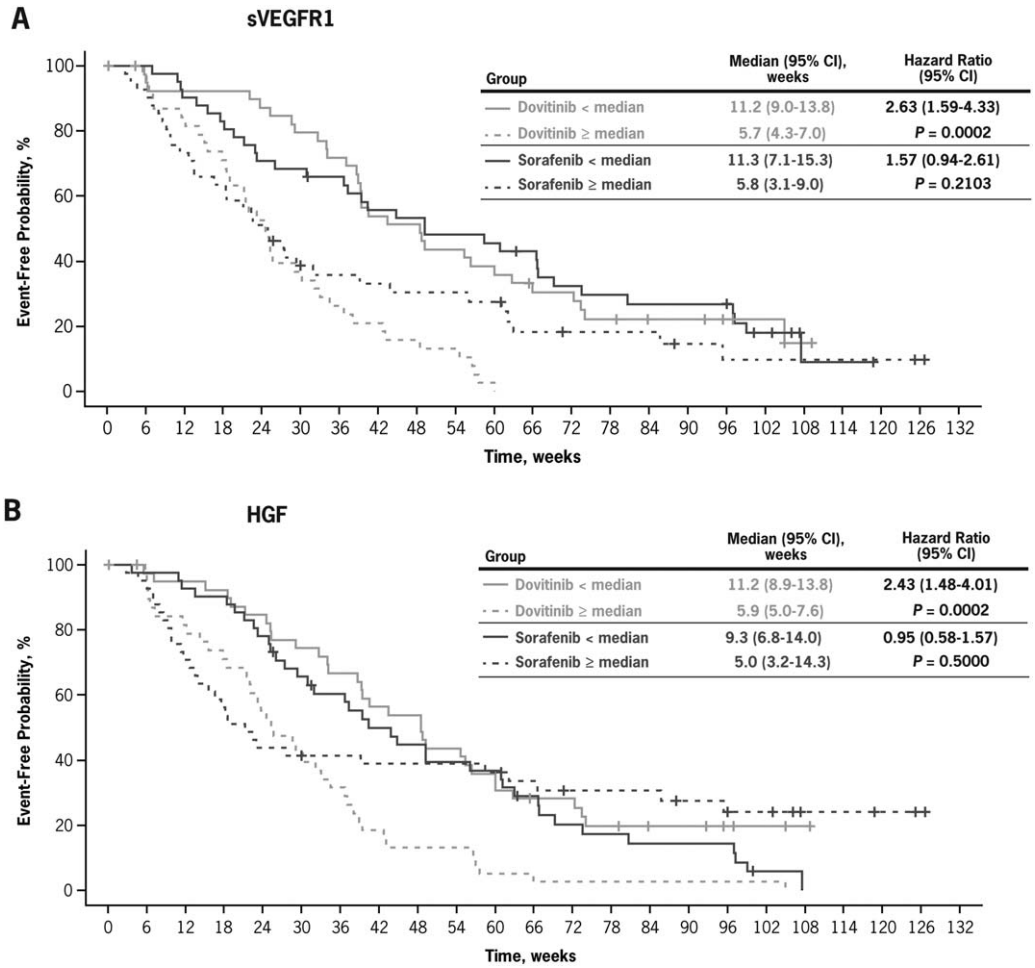

FIG. 3. Overall survival (OS) by baseline plasma levels of (A) soluble vascular endothelial growth factor receptor 1 (sVEGFR1) and (B) hepatocyte growth factor (HGF). The false discovery rate *P* values were adjusted for multiplicity only at the biomarker level within a specific analysis. Therefore, interpretation based on *P* values should be made with caution and in context, considering the point estimates and 95% confidence intervals (CI) of the parameters provided for these biomarker data.

symptomatic disease and extrahepatic metastases at presentation, etiology (e.g., hepatitis B or C infection, alcohol), and varying regional treatment practices.[9,10,30-32] For example, prevalence of hepatitis B infection in this study (dovitinib, 72%; sorafenib 64%) was more similar to that observed in the Asian subpopulation (~65%) than in the non-Asian subpopulation (~20%) in a recently reported study comparing sunitinib versus sorafenib, which may explain why the median OS for sorafenib in this study (8.4 months) was more similar to that observed in the Asian subpopulation (8.8 months) than the non-Asian subpopulation (15.1 months). This is consistent with the association of hepatitis B infection with poor prognosis in patients with advanced HCC, as well as additional subgroup analyses in recently reported TKI versus sorafenib studies demonstrating improved median OS in patients without hepatitis B.[25-27,30] However, although these data indicate that population variations need to be considered when comparing activity between TKI trials, it is important to note that etiology was not found to be a significant predictor of OS in the SHARP trial or the Asia-Pacific study of sorafenib.[9,10] Instead, recent studies have identified tumor stage, Child-Pugh class, and as significant predictors of OS.[33,34]

The results of the AE analysis in this study were consistent with the known safety profile of dovitinib[35-38] and did not identify any new safety concerns associated with the use of dovitinib in patients with

advanced HCC. The most common AEs experienced by patients on dovitinib and sorafenib were diarrhea (62% versus 42%), decreased appetite (43% versus 31%), nausea (41% versus 19%), vomiting (41% versus 12%), fatigue (35% versus 16%), rash (34% versus 22%), pyrexia (30% versus 28%), and PPES (14% versus 66%), respectively. Overall, treatment with dovitinib was shorter and interruptions due to AEs were more frequent, potentially indicating poorer tolerance to this agent; however, this could be attributed partly to the open label design of the study.

Dovitinib exposure in patients with mild hepatic function impairment was comparable to exposure in patients with normal hepatic function. Association of median OS with sVEGFR1 and HGF baseline plasma levels achieved statistical significance for dovitinib.

Pattern of progression has recently been noted as a key parameter in HCC. For example, a recent analysis of patients with advanced HCC treated with sorafenib showed that the emergence of new extrahepatic metastases was an independent predictor of poor prognosis.[39] Although patterns of progression (e.g., intrahepatic versus extrahepatic) and their association with postprogression survival were not assessed in this study, these factors may be worth exploring in future studies evaluating dovitinib in HCC.

In conclusion, though generally well tolerated, dovitinib did not appear to have improved activity over sorafenib in patients with advanced HCC in this study, and OS analyses did not demonstrate any benefit. Based on the data presented, there are no plans for a subsequent phase 3 study.

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REFERENCES

1) Uematsu S, Higashi T, Nouso K, Kariyama K, Nakamura S, Suzuki M, et al. Altered expression of vascular endothelial growth factor, fibroblast growth factor-2 and endostatin in patients with hepatocellular carcinoma. J Gastroenterol Hepatol 2005;20:583-588.
2) Gauglhofer C, Sagmeister S, Schrottmaier W, Fischer C, Rodgarkia-Dara C, Mohr T, et al. Up-regulation of the fibroblast growth factor 8 subfamily in human hepatocellular carcinoma for cell survival and neoangiogenesis. HEPATOLOGY 2011; 53:854-864.
3) Kin M, Sata M, Ueno T, Torimura T, Inuzuka S, Tsuji R, et al. Basic fibroblast growth factor regulates proliferation and motility of human hepatoma cells by an autocrine mechanism. J Hepatol 1997;27:677-687.
4) Madkhali AA, Fadel ZT, Aljiffry MM, Hassanain MM. Surgical treatment for hepatocellular carcinoma. Saudi J Gastroenterol 2015;21:11-17.
5) Thomas MB, Zhu AX. Hepatocellular carcinoma: the need for progress. J Clin Oncol 2005;23:2892-2899.
6) Ribatti D, Vacca A, Nico B, Sansonno D, Dammacco F. Angiogenesis and anti-angiogenesis in hepatocellular carcinoma. Cancer Treat Rev 2006;32:437-444.
7) Yoshiji H, Kuriyama S, Yoshii J, Ikenaka Y, Noguchi R, Hicklin DJ, et al. Synergistic effect of basic fibroblast growth factor and vascular endothelial growth factor in murine hepatocellular carcinoma. HEPATOLOGY 2002;35:834-842.
8) Wang L, Park H, Chhim S, Ding Y, Jiang W, Queen C, et al. A novel monoclonal antibody to fibroblast growth factor 2 effectively inhibits growth of hepatocellular carcinoma xenografts. Mol Cancer Ther 2012;11:864-872.
9) Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34.
10) Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-390.
11) Lopes de Menezes DE, Peng J, Garrett EN, Louie SG, Lee SH, Wiesmann M, et al. CHIR-258: a potent inhibitor of FLT3 kinase in experimental tumor xenograft models of human acute myelogenous leukemia. Clin Cancer Res 2005;11:5281-5291.
12) Angevin E, Lopez-Martin JA, Lin CC, Gschwend JE, Harzstark A, Castellano D, et al. Phase I study of dovitinib (TKI258), an oral FGFR, VEGFR, and PDGFR inhibitor, in advanced or metastatic renal cell carcinoma. Clin Cancer Res 2013;19:1257-1268.
13) Sarker D, Molife R, Evans TR, Hardie M, Marriott C, Butzberger-Zimmerli P, et al. A phase I pharmacokinetic and pharmacodynamic study of TKI258, an oral, multitargeted receptor tyrosine kinase inhibitor in patients with advanced solid tumors. Clin Cancer Res 2008;14:2075-2081.
14) André F, Bachelot T, Campone M, Dalenc F, Perez-Garcia JM, Hurvitz SA, et al. Targeting FGFR with dovitinib (TKI258): preclinical and clinical data in breast cancer. Clin Cancer Res 2013;19:3693-3702.
15) Takiuchi H, Gotoh M, Yoshida M, Kii T, Yamashita K, Sunakawa Y, et al. A phase I study of dovitinib (TKI258) in Japanese patients with advanced solid tumors. ASCO Annual Meeting Abstracts 2012; Abstract 3088.
16) Kim KB, Chesney J, Robinson D, Gardner H, Shi MM, Kirkwood JM. Phase I/II and pharmacodynamic study of dovitinib (TKI258)-an inhibitor of fibroblast growth factor receptors and VEGF receptors-in patients with advanced melanoma. Clin Cancer Res 2011;17:7451-7461.
17) Tai WT, Cheng AL, Shiau CW, Liu CY, Ko CH, Lin MW, et al. Dovitinib induces apoptosis and overcomes sorafenib resistance in hepatocellular carcinoma through SHP-1-mediated inhibition of STAT3. Mol Cancer Ther 2012;11: 452-463.
18) Huynh HT, Chow P, Soo CK, Shi M. Dovitinib (TKI258), a multikinase inhibitor of FGFR, PDGFR, and VEGFR tyrosine

kinases, induces growth suppression in mouse models of human hepatocellular carcinoma (HCC). AACR Annual Meeting 2010; Abstract LB-364.
19) Huynh H, Chow PK, Tai WM, Choo SP, Chung AY, Ong HS, et al. Dovitinib demonstrates antitumor and antimetastatic activities in xenograft models of hepatocellular carcinoma. J Hepatol 2012;56:595-601.
20) Bruix J, Sherman M, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. HEPATOLOGY 2011;53:1020-1022.
21) Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst 2008;100:698-711.
22) Bergers G, Hanahan D. Modes of resistance to anti-angiogenic therapy. Nat Rev Cancer 2008;8:592-603.
23) Lee SH, Lopes de Menezes D, Vora J, Harris A, Ye H, Nordahl L, et al. In vivo target modulation and biological activity of CHIR-258, a multitargeted growth factor receptor kinase inhibitor, in colon cancer models. Clin Cancer Res 2005;11: 3633-3641.
24) Chan SL, Yeo W. Development of systemic therapy for hepatocellular carcinoma at 2013: updates and insights. World J Gastroenterol 2014;20:3135-3145.
25) Johnson PJ, Qin S, Park JW, Poon RT, Raoul JL, Philip PA, et al. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. J Clin Oncol 2013;31:3517-3524.
26) Cainap C, Qin S, Huang WT, Chung IJ, Pan H, Cheng Y, et al. Linifanib versus sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. J Clin Oncol 2015;33:172-179.
27) Cheng AL, Kang YK, Lin DY, Park JW, Kudo M, Qin S, et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. J Clin Oncol 2013;31: 4067-4075.
28) Llovet JM, Pena CE, Lathia CD, Shan M, Meinhardt G, Bruix J; SHARP Investigators Study Group. Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. Clin Cancer Res 2012;18:2290-2300.
29) Bolondi L, Craxi A, Trevisani F, Daniele B, Di Costanzo GG, Fagiuoli S, et al. Refining sorafenib therapy: lessons from clinical practice. Future Oncol 2015;11:449-465.
30) Cantarini MC, Trevisani F, Morselli-Labate AM, Rapaccini G, Farinati F, Del Poggio P, et al. Effect of the etiology of viral cirrhosis on the survival of patients with hepatocellular carcinoma. Am J Gastroenterol 2006;101:91-98.
31) Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362:1907-1917.
32) de Villa V, Lo CM. Liver transplantation for hepatocellular carcinoma in Asia. Oncologist 2007;12:1321-1331.
33) Tsukui Y, Mochizuki H, Hoshino Y, Kawakami S, Kuno T, Fukasawa Y, et al. Factors contributing to the overall survival in patients with hepatocellular carcinoma treated by sorafenib. Hepatogastroenterology 2012;59:2536-2539.
34) Li J, Wang L, Cong N, Shi C, Bu W, Song J, et al. Efficacy of sorafenib for advanced hepatocellular carcinoma and prognostic factors. Hepatogastroenterology 2014;61:954-957.
35) Angevin E, Lopez JA, Pande A, Moldovan C, Shi M, Soria JC, et al. TKI258 (dovitinib lactate) in metastatic renal cell carcinoma (mRCC) patients refractory to approved targeted therapies: a phase I/II dose finding and biomarker study. J Clin Oncol 2009;27(Suppl. 15): Abstract 3563.
36) Kang YK, Yoo C, Ryoo BY, Lee JJ, Tan E, Park I, et al. Phase II study of dovitinib in patients with metastatic and/or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib. Br J Cancer 2013;109:2309-2315.
37) Milowsky MI, Dittrich C, Duran I, Jagdev S, Millard FE, Sweeney CJ, et al. Phase 2 trial of dovitinib in patients with progressive FGFR3-mutated or FGFR3 wild-type advanced urothelial carcinoma. Eur J Cancer 2014;50:3145-3152.
38) Infante JR, Ramanathan RK, George D, Tan E, Quinlan M, Liu A, et al. A randomized, crossover phase 1 study to assess the effects of formulation (capsule vs tablet) and meal consumption on the bioavailability of dovitinib (TKI258). Cancer Chemother Pharmacol 2015;75:729-737.
39) Ogasawara S, Chiba T, Ooka Y, Suzuki E, Kanogawa N, Saito T, et al. Post-progression survival in patients with advanced hepatocellular carcinoma resistant to sorafenib. Invest New Drugs 2016;34:255-260.

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