Sponsor

Novartis

Generic Drug Name

Dovitinib

Therapeutic Area of Trial

Advanced solid tumors

Approved Indication

Investigational drug

Protocol Number

CTKI258A1101

Title

A Phase I dose escalating study to evaluate TKI258 administered orally on a 5 days on/2 days off schedule in Japanese patients with advanced solid tumors

Study Phase

Phase I

Study Start/End Dates

Study initiation date: 30-Sep-2008 (first patient first visit)

Study completion date: 15-May-2012 (last patient last visit)

Study Design/Methodology

This was an open label, cohort-type, dose-escalation, Phase-I study to assess the safety and PK profiles as well as the preliminary anti-tumor activity of dovitinib in adult Japanese patients with advanced solid tumors who have progressed despite standard therapy or for whom standard systemic therapy does not exist. Dovitinib was administered on a 5 days on / 2 days off schedule, which started after 2 days of PK run-in and subsequently repeated 3 times up to Day 30, when the next dose or dose-limiting toxicity (DLT) was determined. If recommended, dovitinib treatment was restarted on Day 1 for the next cohort. Dovitinib was administered on the first day of the PK run-in but not on the second day in order to allow assessment of the PK profile up to 48 hours after single-dose dovitinib administration.

Centers

Saitama Medical University International Medical Center (Dr. Sasaki); Osaka Medical College Hospital (Dr. Takiuchi)

Publication

Takiuchi H, Gotoh M, Yoshida M, et al (2012) A phase I study of dovitinib (TKI258) in Japanese patients with advanced solid tumors (abstract). J Clin Oncol;30 (Suppl:abstr 3088)

Test Product (s), Dose(s), and Mode(s) of Administration

Dovitinib capsules at dose strengths of 25 mg and 100 mg were used orally once daily on a 5 days on / 2 days off regimen

Statistical Methods

A two-parameter Bayesian logistic regression model based on the escalation with overdose control (EWOC) principle was used to estimate the MTD. Cohorts were comprised of three patients each. This study had two days of PK run-in period prior to beginning dosing on a schedule of 5 days on/2 days off in a cycle of 28 days. The occurrence of DLT was evaluated during the first 30 days (2 days of PK run-in and the first cycle of 28 days). Posterior distribution of DLT incidence rate was summarized by using Bayesian logistic regression model.

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) were used for continuous variables, while the number and percentage of patients (or events) were calculated for the discrete variables. All data was listed appropriately. No statistical hypothesis testing was conducted.

Demographics and baseline characteristics were summarized using both descriptive statistics and contingency tables. Relevant medical histories and continuing medical conditions were summarized by primary system organ class (SOC) and preferred term (PT). These analyses were performed on the FAS.

No interim analysis was performed.

All adverse events were coded using the MedDRA dictionary (version 15.0) that consisted of the SOC and PT information.

The CTCAE version 3 was used to grade the severity of adverse events. If the CTCAE did not apply to the event in question, an adapted scale was used.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

- Written informed consent was to be obtained prior to any screening procedures.
- Patients with any histologically – or cytologically – confirmed advanced solid tumors which had progressed despite standard therapy or for whom no standard therapy existed (measurable lesion by Response Evaluation Criteria in Solid Tumors (RECIST) was not required).
- Agreement to remain hospitalized during both PK run-in and Cycle 1 (i.e. from the evening before Day 1 of PK run-in to the morning of day 29 of Cycle 1).
- Age ≥ 20 years.
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.
- Life expectancy of at least 3 months.
- Women of childbearing potential had to have a negative pregnancy test at the screening visit. Male and female patients of reproductive potential had to agree to employ an effective method of birth control throughout the study and for up to three months following study drug discontinuation.
- Demonstrated the following hematological/blood chemistry laboratory values within 14 days prior to the first dose of study drug (Day 1 of PK run-in):
    - Absolute neutrophil count (ANC) ≥ 1500/mm^3
    - Hemoglobin ≥ 9.0 g/dL
    - Platelets ≥ 100,000/mm^3
    - Total bilirubin ≤ 1.5 x upper limit of normal (ULN)
    - Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤ 2.5 x ULN
    - Alkaline phosphatase (ALP) ≤ 2.5 x ULN (patients with bone metastases could be eligible with ALP ≤ 5.0 x ULN if ALT and AST were within the normal range and bone metastases were thought to account for elevated ALP)
    - Serum creatinine ≤ 1.5 x ULN

- Serum potassium ≥ lower limit of normal (LLN)
- Serum magnesium ≥ LLN

Exclusion criteria:

- Receipt of any investigational compound within 28 days prior to the first dose of the study drug or failure to recover from the side effects of such prior therapy.
- Receipt of other antineoplastic therapy including chemotherapy, hormone therapy, immunotherapy, radiation therapy within 28 days (42 days for nitrosurea and mitomycin C) prior to the first dose of the study drug. Palliative radiotherapy for local peripheral metastasis and OK-432 for pleurodesis were allowed unless within 14 days.
- Patients with CNS and/or leptomeningeal disease metastases were not allowed on study unless asymptomatic and not receiving corticosteroid therapy.
- Presence or history of thromboembolic or cerebrovascular events within the last 12 months, including transient ischemic attack, cerebrovascular accident, deep vein thrombosis, pulmonary embolism.
- Impaired cardiac function or clinically significant cardiac disease, including any one of the following:
    - Left ventricular ejection fraction <45% on screening echocardiography (ECHO)
    - QTc >480 ms on screening electrocardiogram (ECG)
    - Complete left bundle branch block
    - Bifasicular block (right bundle branch block + left anterior hemiblock)
    - Obligate use of a cardiac pacemaker
    - Ventricular tachyarrhythmia
    - Unstable atrial fibrillation (ventricular response >100 beats per minute (bpm)). Patients with stable atrial fibrillation were eligible, provided they did not meet any of the other cardiac exclusion criteria
    - Presence or history of angina pectoris ≤ 3 months prior to starting study drug
    - Presence or history of acute myocardial infarction (MI) ≤ 3 months prior to starting study drug
    - Other clinically significant heart disease (e.g., congestive heart failure (CHF), uncontrolled hypertension, resting bradycardia (<50 bpm)or history of labile hypertension or history of poor compliance with an anti-hypertensive regimen
- Malabsorption syndrome or uncontrolled gastrointestinal toxicities (nausea, diarrhea, vomiting) with toxicity greater than the Common Terminology Criteria for Adverse Events (CTCAE) Grade 2.
- Patients known to be human immunodeficiency virus-, hepatitis B virus-, or hepatitis C virus-positive

- Patients with the presence of active or suspected acute or chronic uncontrolled infection.
- Patients who have undergone surgery with general anesthesia for any cause within 28 days prior to the first dose of study drug.
- Patients who have been receiving anticoagulant therapy of Warfarin or Heparin.
- Receipt of any hematopoietic colony stimulating factor (e.g. granulocyte colony-stimulating factor) or blood transfusion within 14 days prior to the first dose of study drug.
- Patients who have been administering concomitant medication which may prolong the QTc interval.
- Patients with interstitial pneumonia or pulmonary fibrosis proven on a chest computed tomography (CT) scan.
- Patients with a large volume of ascitic and/or pleural fluid which required drainage.
- Patients with any bone fractures.
- Deemed otherwise unsuitable by the investigator (e.g., patients unwilling to comply with protocol).

Participant Flow

Patient disposition, by treatment sequence (Full Analysis Set)

	100mg N=3 n (%)	200mg N=3 n (%)	300mg N=7 n (%)	400mg N=9 n (%)	500mg N=6 n (%)	Total N=28 n (%)
Discontinued	3 (100)	3 (100)	7 (100)	9 (100)	6 (100)	28 (100)
Cycle 1	0	1 (33.3)	2 (28.6)	3 (33.3)	0	6 (21.4)
Cycle 2	1 (33.3)	0	1 (14.3)	0	1 (16.7)	3 (10.7)
Cycle 3	0	0	2 (28.6)	2 (22.2)	2 (33.3)	6 (21.4)
Cycle 4	1 (33.3)	2 (66.7)	0	1 (11.1)	0	4 (14.3)
Cycle 5	0	0	1 (14.3)	1 (11.1)	0	2 (7.1)
Cycle 6	1 (33.3)	0	0	0	0	1 (3.6)
Cycle 7	0	0	0	0	2 (33.3)	2 (7.1)
Cycle 11	0	0	0	0	1 (16.7)	1 (3.6)
Cycle 15	0	0	1 (14.3)	0	0	1 (3.6)
Cycle 21	0	0	0	1 (11.1)	0	1 (3.6)
Cycle 25	0	0	0	1 (11.1)	0	1 (3.6)

	100mg N=3 n (%)	200mg N=3 n (%)	300mg N=7 n (%)	400mg N=9 n (%)	500mg N=6 n (%)	Total N=28 n (%)
Primary reason for end of treatment						
Adverse event (s)	0	0	1 (14.3)	3 (33.3)	0	4 (14.3)
Disease progression	3 (100)	3 (100)	6 (85.7)	6 (66.7)	6 (100)	24 (85.7)

Baseline Characteristics

Demographics characteristics, and ECOG scores (FAS)

Variable Statistic	100 mg N=3	200 mg N=3	300 mg N=7	400 mg N=9	500 mg N=6	Total N=28
Age (years)						
Mean (SD)	64.0 (7.21)	55.3 (16.56)	58.9 (4.49)	54.4 (14.40)	53.3 (12.93)	56.4 (11.51)
Median (min, max)	66.0 (56, 70)	57.0 (38, 71)	59.0 (53, 67)	59.0 (32, 76)	55.0 (30, 67)	58.5 (30, 76)
Age category - n (%)						
<65	1 (33.3)	2 (66.7)	6 (85.7)	7 (77.8)	5 (83.3)	21 (75.0)
>=65	2 (66.7)	1 (33.3)	1 (14.3)	2 (22.2)	1 (16.7)	7 (25.0)
Sex – n (%)						
Male	2 (66.7)	2 (66.7)	2 (28.6)	6 (66.7)	4 (66.7)	16 (57.1)
Female	1 (33.3)	1 (33.3)	5 (71.4)	3 (33.3)	2 (33.3)	12 (42.9)
Weight (kg)						
Mean	58.9	56.2	55.2	59.7	61.2	58.5
SD	12.27	10.12	6.84	11.80	9.68	9.66
Median (min, max)	65.2 (44.8, 66.8)	60.8 (44.6, 63.2)	54.8 (44.6, 66.8)	59.6 (40.7, 77.9)	63.6 (48.8, 71.5)	59.7 (40.7, 77.9)
Height (cm)						
Mean	161.0	167.7	157.4	164.3	164.7	162.7
SD	8.89	15.50	6.80	9.27	4.55	8.68
Median (min, max)	158.0 (154.0, 171.0)	168.0 (152.0, 183.0)	158.0 (149.0, 169.0)	162.0 (151.0, 178.0)	164.0 (160.0, 170.0)	161.0 (149.0, 183.0)
BSA[a] (m2)						

Variable Statistic	100 mg N=3	200 mg N=3	300 mg N=7	400 mg N=9	500 mg N=6	Total N=28
Mean	1.6	1.6	1.6	1.7	1.7	1.6
SD	0.21	0.21	0.12	0.21	0.15	0.17
Median (min, max)	1.7 (1.4, 1.8)	1.7 (1.4, 1.8)	1.6 (1.4, 1.8)	1.7 (1.3, 2.0)	1.7 (1.5, 1.8)	1.7 (1.3, 2.0)
ECOG PS – n (%)						
0	0	0	2 (28.6)	3 (33.3)	5 (83.3)	10 (35.7)
1	3 (100)	3 (100)	5 (71.4)	6 (66.7)	1 (16.7)	18 (64.3)

[a]: BSA (m2)=234.94 x Weight (kg) $^{0.515}$ x Height (cm) $^{0.422}$ x 0.007184 / 10000

Disease history and baseline characteristics (FAS)

Variable	100 mg N=3 n (%)	200 mg N=3 n (%)	300 mg N=7 n (%)	400 mg N=9 n (%)	500 mg N=6 n (%)	Total N=28 n (%)
Primary site of cancer						
Pancreas	0	0	1 (14.3)	1 (11.1)	0	2 (7.1)
Oesophagus	1 (33.3)	0	0	0	0	1 (3.6)
Stomach	1 (33.3)	0	3 (42.9)	1 (11.1)	1 (16.7)	6 (21.4)
Colon	0	1 (33.3)	1 (14.3)	1 (11.1)	0	3 (10.7)
Rectum	0	0	0	3 (33.3)	2 (33.3)	5 (17.9)
Peritoneum	0	0	0	1 (11.1)	0	1 (3.6)
Ovary	1 (33.3)	0	0	0	0	1 (3.6)
Uterus	0	0	1 (14.3)	0	0	1 (3.6)
Kidneys	0	0	1 (14.3)	0	0	1 (3.6)
CNS: Infratentorial	0	0	0	0	1 (16.7)	1 (3.6)
Other	0	2 (66.7)	0	2 (22.2)	2 (33.3)	6 (21.4)
Tumor Histology/Cytology						
Adenocarcinoma	1 (33.3)	2 (66.7)	4 (57.1)	5 (55.6)	3 (50.0)	15 (53.6)
Endometrioid	1 (33.3)	0	0	0	0	1 (3.6)
Invasive ductal carcinoma	0	0	0	1 (11.1)	0	1 (3.6)
Clear cell adenocarcinoma	0	0	1 (14.3)	0	0	1 (3.6)

Variable	100 mg N=3 n (%)	200 mg N=3 n (%)	300 mg N=7 n (%)	400 mg N=9 n (%)	500 mg N=6 n (%)	Total N=28 n (%)
Squamous cell carcinoma	1 (33.3)	0	0	0	0	1 (3.6)
Sarcoma	0	1 (33.3)	1 (14.3)	0	0	2 (7.1)
Carcinoid	0	0	0	1 (11.1)	0	1 (3.6)
Other	0	0	1 (14.3)	2 (22.2)	3 (50.0)	6 (21.4)
Histologic grade						
Well differential	0	1 (33.3)	2 (28.6)	2 (22.2)	2 (33.3)	7 (25.0)
Moderately differential	1 (33.3)	0	1 (14.3)	2 (22.2)	3 (50.0)	7 (25.0)
Poorly differential	1 (33.3)	0	2 (28.6)	1 (11.1)	0	4 (14.3)
Undifferentiated	0	0	1 (14.3)	0	0	1 (3.6)
Unknown	1 (33.3)	2 (66.7)	1 (14.3)	4 (44.4)	1 (16.7)	9 (32.1)
Type of lesions at baseline						
Target only	1 (33.3)	0	0	1 (11.1)	1 (16.7)	3 (10.7)
Non-target only	0	0	1 (14.3)	1 (11.1)	0	2 (7.1)
Both target and non-target	2 (66.7)	3 (100)	6 (85.7)	7 (77.8)	5 (83.3)	23 (82.1)
Unknown	0	0	0	0	0	0
Stage at initial diagnosis						
Stage 0	0	0	0	1 (11.1)	0	1 (3.6)
Stage I	0	0	0	1 (11.1)	0	1 (3.6)
Stage II	2 (66.7)	0	0	0	1 (16.7)	3 (10.7)
Stage III	0	1 (33.3)	1 (14.3)	3 (33.3)	1 (16.7)	6 (21.4)
Stage IV	1 (33.3)	1 (33.3)	5 (71.4)	4 (44.4)	3 (50.0)	14 (50.0)
Current stage of cancer						
Stage 0	0	0	0	0	0	0
Stage I	0	0	0	0	0	0
Stage II	0	0	0	0	0	0
Stage III	0	0	0	0	0	0
Stage IV	3 (100)	3 (100)	7 (100)	9 (100)	6 (100)	28 (100)

Variable	100 mg N=3 n (%)	200 mg N=3 n (%)	300 mg N=7 n (%)	400 mg N=9 n (%)	500 mg N=6 n (%)	Total N=28 n (%)
Time since first diagnosis category						
-<1 year	0	0	2 (28.6)	2 (22.2)	0	4 (14.3)
->=1 year - <2 years	0	1 (33.3)	0	0	0	1 (3.6)
->=2 years - <5 years	2 (66.7)	2 (66.7)	2 (28.6)	5 (55.6)	4 (66.7)	15 (53.6)
->=5 years	1 (33.3)	0	2 (28.6)	2 (22.2)	2 (33.3)	7 (25.0)
-Unknown	0	0	1 (14.3)	0	0	1 (3.6)
Time since first recurrence/relapse category						
-<1 year	0	0	0	2 (22.2)	0	2 (7.1)
->=1 year - <2 years	1 (33.3)	1 (33.3)	1 (14.3)	1 (11.1)	1 (16.7)	5 (17.9)
->=2 years - <5 years	1 (33.3)	1 (33.3)	1 (14.3)	2 (22.2)	2 (33.3)	7 (25.0)
->=5 years	0	0	0	0	2 (33.3)	2 (7.1)
-Unknown	1 (33.3)	1 (33.3)	5 (71.4)	4 (44.4)	1 (16.7)	12 (42.9)
Time since most recent recurrence/relapse category						
-<1 year	1 (33.3)	2 (66.7)	1 (14.3)	1 (11.1)	1 (16.7)	6 (21.4)
->=1 year - <2 years	0	0	0	2 (22.2)	0	2 (7.1)
->=2 years - <5 years	0	0	0	0	1 (16.7)	1 (3.6)
->=5 years	0	0	0	0	1 (16.7)	1 (3.6)
-Unknown	2 (66.7)	1 (33.3)	6 (85.7)	6 (66.7)	3 (50.0)	18 (64.3)

Outcome measures

Primary Outcome Result(s)

Overall response rate (FAS)

Variable	100 mg N=3 n (%)	200 mg N=3 n (%)	300 mg N=7 n (%)	400 mg N=9 n (%)	500 mg N=6 n (%)	Total N=28 n (%)
Best overall confirmed response						
Complete response (CR)	0	0	0	0	0	0
Partial response (PR)	0	0	0	1 (11.1)	0	1 (3.6)
Stable disease (SD)	2 (66.7)	0	2 (28.6)	3 (33.3)	2 (33.3)	9 (32.1)
Progressive disease (PD)	1 (33.3)	1 (33.3)	5 (71.4)	0	3 (50.0)	10 (35.7)
Unknown (UNK)	0	2 (66.7)	0	5 (55.6)	1 (16.7)	8 (28.6)

Posterior probability distribution of occurrence of DLT (Dose-determining set)

	Posterior probabilities (%) that Pr (DLT) is in interval:						Quantile		
Dose (mg/day)	0-0.16	0.16-0.33	0.33-0.60	0.60-1	Mean	SD	2.5%	50%	97.5%
100	97.5	2.5	0.0	0.0	4.4	4.4	0.1	3.0	15.9
200	90.8	9.2	0.0	0.0	8.2	5.4	0.7	7.3	21.7
300	73.2	26.3	0.4	0.0	12.7	6.1	3.2	11.9	27.0
400	43.9	53.1	3.0	0.0	17.8	7.0	6.3	17.0	33.8
500	22.1	63.9	14.0	0.0	23.2	8.9	8.6	22.2	43.4
600	12.8	55.1	31.0	1.2	28.6	11.6	10.3	27.1	55.0

Secondary Outcome Result(s)

Pharmacokinetics results

Summary of PK parameters of dovitinib for the 100 mg, 200 mg and 300 mg dose groups (PK analysis set)

	100mg			200mg			300 mg		
PK parameters	**PK run-in Day 1**	**Cycle 1 Day 5**	**Cycle 1 Day26**	**PK run-in Day 1**	**Cycle 1 Day 5**	**Cycle 1 Day26**	**PK run-in Day 1**	**Cycle 1 Day 5**	**Cycle 1 Day26**
AUC0-24h (hr*ng/mL)									
n[a]	3	3	3	3	3	3	7	6	6
Mean±SD	1060±9.19	678±142	725±158	2120±614	2440±1400	2260±1060	3620±1290	3820±1310	3760±2120
AUCinf (hr*ng/mL)									
n	*1*	*3*	*3*	*2*	*3*	*3*	*4*	*6*	*6*
Mean±SD	1650	1060±346	1090±341	3880±1930	3930±2660	3540±1860	7190±603	6200±2100	5910±3650
Cmax (ng/mL)									
n	3	3	3	3	3	3	7	6	6
Mean±SD	61.0±3.37	49.0±0.611	54.6±5.02	138±30.2	169±72.4	161±68.6	230±93.6	260±104	275±140
Tmax (hr)									
n	3	3	3	3	3	3	7	6	6
Mean±SD	5.99±1.99	4.66±1.14	3.97±0.0335	4.65±1.17	4.65±1.17	4.00±0.0170	8.55±7.00	3.66±1.97	4.33±2.00
Median	6.00	4.00	3.97	4.00	3.98	4.00	6.00	4.00	4.01
Min-Max	4.00-7.98	4.00-5.97	3.93-4.00	3.95-6.00	3.97-6.00	3.98-4.02	3.95-24.0	0-6.00	1.92-8.05
Gmean[b]	5.76	4.57	3.97	4.56	4.56	4.00	7.05	4.33	3.98
T1/2 (hr)									
n	3	3	3	3	3	3	7	6	6
Mean±SD	16.6±5.27	15.3±5.40	14.2±3.03	16.3±2.97	14.4±2.26	15.7±1.23	18.8±4.63	15.9±2.58	15.5±1.84

[a]: n=Number of patients

[b]: Geometric mean

Summary of PK parameters of dovitinib for the 400mg and 500 mg dose groups (PK analysis set)

	400mg			500mg		
PK parameters	**PK run-in Day 1**	**Cycle 1 Day 5**	**Cycle 1 Day26**	**PK run-in Day 1**	**Cycle 1 Day 5**	**Cycle 1 Day26**
AUC0-24h (hr*ng/mL)						
n[a]	9	9	7	6	5	6
Mean± SD	4520±2030	6690±3230	5690±2500	6100±871	8850±4350	7580±2110
AUCinf (hr*ng/mL)						
n	5	8	6	2	5	5
Mean±SD	7830±4220	11700±8660	8660±5240	10300±3470	17400±13700	11200±3270
Cmax (ng/mL)						
n	9	9	7	6	5	6
Mean±SD	266±116	407±154	355±106	380±93.7	509±136	475±127
Tmax (hr)						
n	9	9	7	6	5	6
Mean±SD	5.77±2.12	5.54±1.65	5.72±1.42	5.67±1.96	5.32±2.96	4.67±1.04
Median	5.98	5.92	6.00	5.03	4.00	4.01
Min-Max	3.97-10.0	3.97-8.00	3.97-8.12	3.98-8.00	3.98-10.6	3.97-6.02
Gmean[b]	5.46	5.33	5.57	5.40	4.86	4.58
T1/2 (hr)						
n	9	9	7	6	5	6
Mean±SD	20.8±11.4	17.1±5.47	17.3±6.43	20.4±5.46	16.1±6.71	15.6±4.50

[a]: n=Number of patients
[b]: Geometric mean

Dose proportionality of PK parameters on PK run-in Day 1 (PK analysis set)

PK parameter (unit)	Intercept estimate	Slope estimate	90% CI for the slope		P-value for lack of fit
			lower limit	upper limit	
Cmax (ng/mL)	-0.69	1.045	0.724	1.366	<0.0001
AUC0-24h (hr*ng/mL)	2.19	1.03	0.704	1.357	<0.0001

A power model analysis was performed with a log-transformed equation; log (parameter)=intercept+slope*log (dose)

Dose proportionality of PK parameters on Cycle 1 day 5 (PK analysis set)

PK parameter (unit)	Intercept estimate	Slope estimate	90% CI for the slope		P-value for lack of fit
			lower limit	upper limit	
Cmax (ng/mL)	-2.62	1.432	1.130	1.717	<0.0001
AUC0-24h (hr*ng/mL)	-0.60	1.546	1.222	1.870	<0.0001

A power model analysis was performed with a log-transformed equation; log (parameter)=intercept+slope*log (dose)

Summary of urinary excretion of dovitinib for PK run-in Day 1 (PK analysis set)

PK Parameter	Initial dose	n	Mean	SD	Med*	Min	Max	Gmean**
Urinary excretion 0-24h (mg)	100 mg	3	0.5	0.19	0.44	0.4	0.8	0.52
	200 mg	3	0.6	0.26	0.67	0.3	0.8	0.52
	300 mg	7	0.7	0.22	0.82	0.3	0.9	0.68
	400 mg	9	1.1	0.73	1.13	0.1	2.3	0.86
	500 mg	6	1	0.5	0.86	0.5	1.9	0.91
Urinary excretion 24-48h (mg)	100 mg	3	0.3	0.17	0.29	0.1	0.5	0.24
	200 mg	3	0.5	0.3	0.62	0.1	0.6	0.35
	300 mg	7	0.5	0.23	0.41	0.2	0.9	0.44
	400 mg	9	0.8	0.73	0.68	0	2.2	0.54
	500 mg	6	0.6	0.35	0.51	0.2	1.1	0.54
Urinary excretion 0-48h (mg)	100 mg	3	0.8	0.35	0.71	0.5	1.2	0.78
	200 mg	3	1	0.55	1.29	0.4	1.4	0.88

PK Parameter	Initial dose	n	Mean	SD	Med*	Min	Max	Gmean**
	300 mg	7	1.2	0.31	1.29	0.7	1.6	1.17
	400 mg	9	2	1.41	1.68	0.2	4.5	1.43
	500 mg	6	1.6	0.41	1.54	1.1	2.3	1.57

*: Med=Median
**: Gmean=Geometric mean

Summary of urinary excretion of dovitinib for Cycle 1 Day 5 (PK analysis set)

PK Parameter	Initial dose	n	Mean	SD	Med*	Min	Max	Gmean**
Urinary excretion 0-24h (mg)	100 mg	3	0.2	0.19	0.18	0.1	0.5	0.2
	200 mg	3	0.8	0.57	0.82	0.2	1.3	0.55
	300 mg	6	0.7	0.38	0.65	0.2	1.3	0.57
	400 mg	9	2.2	2.87	1.11	0.6	9.5	1.47
	500 mg	5	1.6	0.74	1.54	0.6	2.6	1.43

*: Med=Median
**: Gmean=Geometric mean

Summary of urinary excretion of dovitinib for Cycle 1 Day 26 (PK analysis set)

PK parameter	Initial dose	n	Mean	SD	Med*	Min	Max	Gmean**
Urinary excretion 0-24h (mg)	100 mg	3	0.4	0.3	0.36	0.1	0.7	0.29
	200 mg	3	0.7	0.45	0.68	0.2	1.2	0.58
	300 mg	6	1	1.04	0.88	0.1	3	0.6
	400 mg	7	1.3	0.73	1.38	0.4	2.4	1.11
	500 mg	5	1.5	0.49	1.28	1.1	2.2	1.42

*: Med=Median
**: Gmean=Geometric mean

Safety Results

Frequent adverse events regardless of study drug relationship (at least 10%) by primary system organ class and worst grade (Safety set)

	100mg N=3		200mg N=3		300mg N=7		400mg N=9		500mg N=6		Total (%) N=28	
Primary system organ class	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any primary system organ class	3 (100)	1 (33.3)	3 (100)	0	7 (100)	5 (71.4)	9 (100)	6 (66.7)	6 (100)	5 (83.3)	28 (100)	17 (60.7)
Blood and lymphatic system disorders	1 (33.3)	0	2 (66.7)	0	6 (85.7)	4 (57.1)	6 (66.7)	2 (22.2)	4 (66.7)	2 (33.3)	19 (67.9)	8 (28.6)
Cardiac disorders	0	0	1 (33.3)	0	0	0	1 (11.1)	0	1 (16.7)	0	3 (10.7)	0
Gastrointestinal disorders	3 (100)	0	3 (100)	0	6 (85.7)	0	9 (100)	1 (11.1)	6 (100)	1 (16.7)	27 (96.4)	2 (7.1)
General disorders and administration site conditions	3 (100)	1 (33.3)	1 (33.3)	0	6 (85.7)	0	7 (77.8)	0	3 (50.0)	0	20 (71.4)	1 (3.6)
Hepatobiliary disorders	1 (33.3)	1 (33.3)	1 (33.3)	0	1 (14.3)	1 (14.3)	3 (33.3)	2 (22.2)	0	0	6 (21.4)	4 (14.3)
Infections and infestations	0	0	0	0	1 (14.3)	0	2 (22.2)	0	3 (50.0)	0	6 (21.4)	0
Investigations	1 (33.3)	0	2 (66.7)	0	6 (85.7)	1 (14.3)	8 (88.9)	3 (33.3)	5 (83.3)	4 (66.7)	22 (78.6)	8 (28.6)
Metabolism and nutrition disorders	2 (66.7)	1 (33.3)	0	0	6 (85.7)	2 (28.6)	9 (100)	1 (11.1)	5 (83.3)	0	22 (78.6)	4 (14.3)
Musculoskeletal and connective tissue disorders	0	0	0	0	1 (14.3)	0	4 (44.4)	0	2 (33.3)	0	7 (25.0)	0
Neoplasms benign, malignant and unspecified	1 (33.3)	0	1 (33.3)	0	2 (28.6)	1 (14.3)	1 (11.1)	0	1 (16.7)	0	6 (21.4)	1 (3.6)
Nervous system disorders	1 (33.3)	0	1 (33.3)	0	3 (42.9)	0	7 (77.8)	0	4 (66.7)	0	16 (57.1)	0
Renal and urinary disorders	0	0	0	0	1 (14.3)	0	1 (11.1)	0	2 (33.3)	0	4 (14.3)	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1 (14.3)	0	0	0	2 (33.3)	0	3 (10.7)	0
Skin and subcutaneous tissue disorders	2 (66.7)	0	0	0	4 (57.1)	0	4 (44.4)	0	4 (66.7)	0	14 (50.0)	0
Vascular disorders	0	0	1 (33.3)	0	4 (57.1)	1 (14.3)	4 (44.4)	3 (33.3)	1 (16.7)	0	10 (35.7)	4 (14.3)

	100mg N=3		200mg N=3		300mg N=7		400mg N=9		500mg N=6		Total (%) N=28	
Primary system organ class	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**

Only AEs of which occurrence of all grades in Total is at least 10% are presented.
A patient with multiple occurrences of an AE under any group is counted only once in the AE category.
A patient with multiple AEs within a primary system organ class is counted only once in the total row.
Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending order of frequency in the Total column.

Frequent adverse events suspected to study drug relationship (at least 10%) by primary system organ class, preferred term and worst grade (Safety set)

	100mg N=3		200mg N=3		300mg N=7		400mg N=9		500mg N=6		Total N=28	
Primary system organ class	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Preferred term	**n (%)**		**n (%)**		**n (%)**		**n (%)**		**n (%)**		**n (%)**	
Any primary system organ class	3 (100)	0	3 (100)	0	7 (100)	5 (71.4)	9 (100)	6 (66.7)	6 (100)	4 (66.7)	28 (100)	15 (53.6)
Blood and lymphatic system disorders	1 (33.3)	0	2 (66.7)	0	6 (85.7)	4 (57.1)	6 (66.7)	2 (22.2)	4 (66.7)	2 (33.3)	19 (67.9)	8 (28.6)
Lymphopenia	1 (33.3)	0	1 (33.3)	0	5 (71.4)	4 (57.1)	3 (33.3)	1 (11.1)	2 (33.3)	1 (16.7)	12 (42.9)	6 (21.4)
Leukopenia	0	0	1 (33.3)	0	2 (28.6)	0	5 (55.6)	0	0	0	8 (28.6)	0
Neutropenia	0	0	0	0	1 (14.3)	0	3 (33.3)	2 (22.2)	2 (33.3)	2 (33.3)	6 (21.4)	4 (14.3)
Thrombocytopenia	0	0	0	0	1 (14.3)	0	2 (22.2)	0	2 (33.3)	1 (16.7)	5 (17.9)	1 (3.6)
Cardiac disorders	0	0	1 (33.3)	0	0	0	1 (11.1)	0	1 (16.7)	0	3 (10.7)	0
Left ventricular dysfunction	0	0	1 (33.3)	0	0	0	1 (11.1)	0	1 (16.7)	0	3 (10.7)	0

Primary system organ class Preferred term	100mg N=3 All grades n (%)	 Grade 3/4	200mg N=3 All grades n (%)	 Grade 3/4	300mg N=7 All grades n (%)	 Grade 3/4	400mg N=9 All grades n (%)	 Grade 3/4	500mg N=6 All grades n (%)	 Grade 3/4	Total N=28 All grades n (%)	 Grade 3/4
Gastrointestinal disorders	2 (66.7)	0	3 (100)	0	6 (85.7)	0	9 (100)	1 (11.1)	6 (100)	1 (16.7)	26 (92.9)	2 (7.1)
Diarrhoea	2 (66.7)	0	3 (100)	0	5 (71.4)	0	9 (100)	1 (11.1)	5 (83.3)	1 (16.7)	24 (85.7)	2 (7.1)
Nausea	1 (33.3)	0	1 (33.3)	0	6 (85.7)	0	8 (88.9)	1 (11.1)	5 (83.3)	0	21 (75.0)	1 (3.6)
Vomiting	1 (33.3)	0	0	0	5 (71.4)	0	7 (77.8)	1 (11.1)	4 (66.7)	0	17 (60.7)	1 (3.6)
Stomatitis	0	0	0	0	0	0	6 (66.7)	0	1 (16.7)	0	7 (25.0)	0
Dry mouth	0	0	1 (33.3)	0	0	0	2 (22.2)	0	0	0	3 (10.7)	0
Dyspepsia	0	0	0	0	0	0	2 (22.2)	0	1 (16.7)	0	3 (10.7)	0
General disorders and administration site conditions	3 (100)	0	0	0	5 (71.4)	0	7 (77.8)	0	3 (50.0)	0	18 (64.3)	0
Fatigue	3 (100)	0	0	0	4 (57.1)	0	5 (55.6)	0	3 (50.0)	0	15 (53.6)	0
Pyrexia	1 (33.3)	0	0	0	2 (28.6)	0	2 (22.2)	0	2 (33.3)	0	7 (25.0)	0
Oedema peripheral	0	0	0	0	0	0	2 (22.2)	0	1 (16.7)	0	3 (10.7)	0
Hepatobiliary disorders	0	0	0	0	1 (14.3)	1 (14.3)	3 (33.3)	2 (22.2)	0	0	4 (14.3)	3 (10.7)
Hepatic function abnormal	0	0	0	0	1 (14.3)	1 (14.3)	3 (33.3)	2 (22.2)	0	0	4 (14.3)	3 (10.7)
Infections and infestations	0	0	0	0	1 (14.3)	0	2 (22.2)	0	0	0	3 (10.7)	0
Pharyngitis	0	0	0	0	1 (14.3)	0	2 (22.2)	0	0	0	3 (10.7)	0
Investigations	1 (33.3)	0	2 (66.7)	0	6 (85.7)	1 (14.3)	8 (88.9)	3 (33.3)	5 (83.3)	3 (50.0)	22 (78.6)	7 (25.0)
Blood alkaline phosphatase increased	0	0	2 (66.7)	0	4 (57.1)	0	5 (55.6)	0	5 (83.3)	2 (33.3)	16 (57.1)	2 (7.1)

Primary system organ class Preferred term	100mg N=3 All grades n (%)	 Grade 3/4	200mg N=3 All grades n (%)	 Grade 3/4	300mg N=7 All grades n (%)	 Grade 3/4	400mg N=9 All grades n (%)	 Grade 3/4	500mg N=6 All grades n (%)	 Grade 3/4	Total N=28 All grades n (%)	 Grade 3/4
Weight decreased	0	0	0	0	2 (28.6)	0	4 (44.4)	1 (11.1)	3 (50.0)	0	9 (32.1)	1 (3.6)
Aspartate aminotransferase increased	0	0	1 (33.3)	0	0	0	3 (33.3)	0	4 (66.7)	1 (16.7)	8 (28.6)	1 (3.6)
Alanine aminotransferase increased	0	0	1 (33.3)	0	0	0	3 (33.3)	0	3 (50.0)	1 (16.7)	7 (25.0)	1 (3.6)
White blood cell count decreased	0	0	0	0	2 (28.6)	1 (14.3)	3 (33.3)	2 (22.2)	2 (33.3)	1 (16.7)	7 (25.0)	4 (14.3)
Haemoglobin decreased	0	0	0	0	1 (14.3)	1 (14.3)	3 (33.3)	0	2 (33.3)	1 (16.7)	6 (21.4)	2 (7.1)
Blood triglycerides increased	0	0	2 (66.7)	0	1 (14.3)	0	2 (22.2)	0	0	0	5 (17.9)	0
Blood albumin decreased	0	0	1 (33.3)	0	1 (14.3)	0	1 (11.1)	0	1 (16.7)	0	4 (14.3)	0
Blood fibrinogen increased	1 (33.3)	0	0	0	1 (14.3)	0	1 (11.1)	0	1 (16.7)	0	4 (14.3)	0
Neutrophil count decreased	0	0	0	0	2 (28.6)	1 (14.3)	2 (22.2)	1 (11.1)	0	0	4 (14.3)	2 (7.1)
Amylase increased	0	0	0	0	1 (14.3)	0	0	0	2 (33.3)	1 (16.7)	3 (10.7)	1 (3.6)
Blood thyroid stimulating hormone increased	0	0	0	0	1 (14.3)	0	1 (11.1)	0	1 (16.7)	0	3 (10.7)	0
C-reactive protein increased	0	0	0	0	1 (14.3)	0	2 (22.2)	0	0	0	3 (10.7)	0
Gamma-glutamyltransferase increased	0	0	0	0	0	0	0	0	3 (50.0)	1 (16.7)	3 (10.7)	1 (3.6)

	100mg N=3		200mg N=3		300mg N=7		400mg N=9		500mg N=6		Total N=28	
Primary system organ class	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Preferred term	**n (%)**		**n (%)**		**n (%)**		**n (%)**		**n (%)**		**n (%)**	
Lipase increased	0	0	0	0	1 (14.3)	1 (14.3)	1 (11.1)	0	1 (16.7)	0	3 (10.7)	1 (3.6)
Platelet count decreased	0	0	0	0	1 (14.3)	0	2 (22.2)	0	0	0	3 (10.7)	0
Metabolism and nutrition disorders	1 (33.3)	0	0	0	6 (85.7)	1 (14.3)	9 (100)	1 (11.1)	5 (83.3)	0	21 (75.0)	2 (7.1)
Decreased appetite	1 (33.3)	0	0	0	5 (71.4)	1 (14.3)	7 (77.8)	1 (11.1)	5 (83.3)	0	18 (64.3)	2 (7.1)
Hypertriglyceridaemia	0	0	0	0	2 (28.6)	0	4 (44.4)	0	3 (50.0)	0	9 (32.1)	0
Hypoalbuminaemia	0	0	0	0	1 (14.3)	0	3 (33.3)	0	3 (50.0)	0	7 (25.0)	0
Hypocalcaemia	0	0	0	0	1 (14.3)	0	1 (11.1)	0	1 (16.7)	0	3 (10.7)	0
Musculoskeletal and connective tissue disorders	0	0	0	0	0	0	4 (44.4)	0	0	0	4 (14.3)	0
Myalgia	0	0	0	0	0	0	4 (44.4)	0	0	0	4 (14.3)	0
Nervous system disorders	1 (33.3)	0	1 (33.3)	0	2 (28.6)	0	6 (66.7)	0	4 (66.7)	0	14 (50.0)	0
Dysgeusia	1 (33.3)	0	0	0	2 (28.6)	0	2 (22.2)	0	3 (50.0)	0	8 (28.6)	0
Headache	0	0	1 (33.3)	0	0	0	5 (55.6)	0	2 (33.3)	0	8 (28.6)	0
Renal and urinary disorders	0	0	0	0	1 (14.3)	0	1 (11.1)	0	2 (33.3)	0	4 (14.3)	0
Proteinuria	0	0	0	0	1 (14.3)	0	1 (11.1)	0	2 (33.3)	0	4 (14.3)	0
Skin and subcutaneous tissue disorders	2 (66.7)	0	0	0	4 (57.1)	0	4 (44.4)	0	4 (66.7)	0	14 (50.0)	0
Rash	1 (33.3)	0	0	0	3 (42.9)	0	2 (22.2)	0	2 (33.3)	0	8 (28.6)	0
Dry skin	1 (33.3)	0	0	0	0	0	2 (22.2)	0	2 (33.3)	0	5 (17.9)	0
Palmar-plantar erythrodysaesthesia syndrome	0	0	0	0	2 (28.6)	0	2 (22.2)	0	0	0	4 (14.3)	0
Acne	0	0	0	0	0	0	1 (11.1)	0	2 (33.3)	0	3 (10.7)	0

Primary system organ class Preferred term	100mg N=3 All grades n (%)	 Grade 3/4	200mg N=3 All grades n (%)	 Grade 3/4	300mg N=7 All grades n (%)	 Grade 3/4	400mg N=9 All grades n (%)	 Grade 3/4	500mg N=6 All grades n (%)	 Grade 3/4	Total N=28 All grades n (%)	 Grade 3/4
Nail disorder	0	0	0	0	1 (14.3)	0	2 (22.2)	0	0	0	3 (10.7)	0
Vascular disorders	0	0	1 (33.3)	0	4 (57.1)	1 (14.3)	4 (44.4)	3 (33.3)	1 (16.7)	0	10 (35.7)	4 (14.3)
Hypertension	0	0	1 (33.3)	0	4 (57.1)	1 (14.3)	4 (44.4)	3 (33.3)	1 (16.7)	0	10 (35.7)	4 (14.3)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending order of frequency in the Total column.
A patient with multiple occurrences of an AE under any group is counted only once in the AE category.
A patient with multiple severity ratings for an AE while on a treatment is only counted under the maximum rating.

Incidence of SAEs by primary system organ class, preferred term and initial dose (safety set)

Primary system organ class Preferred term	100 mg N=3 n (%)	200 mg N=3 n (%)	300 mg N=7 n (%)	400 mg N=9 n (%)	500 mg N=6 n (%)	Total N=28 n (%)
Any primary system organ class	1 (33.3)	0	3 (42.9)	2 (22.2)	0	6 (21.4)
Gastrointestinal disorders	0	0	1 (14.3)	0	0	1 (3.6)
Nausea	0	0	1 (14.3)	0	0	1 (3.6)
General disorders and administration site conditions	0	0	1 (14.3)	0	0	1 (3.6)
Fatigue	0	0	1 (14.3)	0	0	1 (3.6)
Hepatobiliary disorders	1 (33.3)	0	0	1 (11.1)	0	2 (7.1)
Hepatic function abnormal	1 (33.3)	0	0	1 (11.1)	0	2 (7.1)
Investigations	0	0	0	1 (11.1)	0	1 (3.6)
Neutrophil count decreased	0	0	0	1 (11.1)	0	1 (3.6)
Metabolism and nutrition disorders	0	0	1 (14.3)	0	0	1 (3.6)
Decreased appetite	0	0	1 (14.3)	0	0	1 (3.6)
Dehydration	0	0	1 (14.3)	0	0	1 (3.6)

Primary system organ class Preferred term	100 mg N=3 n (%)	200 mg N=3 n (%)	300 mg N=7 n (%)	400 mg N=9 n (%)	500 mg N=6 n (%)	Total N=28 n (%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0	0	2 (28.6)	0	0	2 (7.1)
Cancer pain	0	0	1 (14.3)	0	0	1 (3.6)
Gastrinoma	0	0	1 (14.3)	0	0	1 (3.6)
Respiratory, thoracic and mediastinal disorders	0	0	1 (14.3)	0	0	1 (3.6)
Dyspnoea	0	0	1 (14.3)	0	0	1 (3.6)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending order of frequency in the Total column.

One patient died in the 28-day follow-up period; the reason for death was disease progression.

Date of Clinical Trial Report

01-Feb-2013