Sponsor

Novartis

Generic Drug Name

Dovitinib

Therapeutic Area of Trial

Advanced or metastatic renal cell cancer

Approved Indication

Investigational drug

Protocol Number

CTKI258A2107

Title

A phase I/II multi-center, open-label study of TKI258 administered orally on an intermittent schedule in adult patients with advanced or metastatic renal cell cancer

Study Phase

Phase I/II

Study Start/End Dates

30-Jul-2008 to 31-Jul-2012

Study Design/Methodology

This was an open-label, multi-center, phase I/II dose-escalation and dose-expansion study of dovitinib administered orally on a 5 days on/2 days off dosing schedule.

The dose-escalation phase of this study used a two-parameter Bayesian logistic regression model with the Escalation With Overdose Control (EWOC) principle to determine the maximum tolerated dose (MTD) based on the dose-limiting toxicity (DLT) incidence of dovitinib and to characterize the safety, pharmacokinetics, pharmacodynamics, and anti-tumor activity profile of dovitinib in adult patients with metastatic renal cell cancer (RCC) who had progressed despite standard therapy or for whom no standard systemic therapy existed.

The dose-expansion phase used the identified MTD to evaluate safety and preliminary anti-tumor activity on the 5 days on/2 days off schedule in adult patients who had been previously treated with VEGF receptor tyrosine kinase inhibitor (sunitinib and/or sorafenib) and mTOR inhibitor and had measurable, histologically or cytologically confirmed progressive advanced or metastatic RCC with predominant clear cell histology (>50%). Patients previously treated with other therapies (e.g. IL-2, IF-α) were also allowed to be enrolled and treated to determine

the effect of dovitinib in patients who had not been treated with VEGF receptor tyrosine kinase inhibitor and mTOR therapy.

Note: Three patients continued on treatment after the cut-off date for the Phase II clinical study report. Additional data for these three patients was reported in a second, final Phase II clinical study report (data was not presented in tabular format for the final report).

Centers

12 centers in 6 countries: France (2), Germany (2), Spain (1), Taiwan (3), USA (3), and the Netherlands (1)

Publication

Angevin E, Lopez-Martin JA, Lin CC, et al (2013) Phase I study of dovitinib (TKI258), an oral FGFR, VEGFR, and PDGFR inhibitor, in advanced or metastatic renal cell carcinoma. Clin Cancer Res; 19(5):1257-68.

Angevin E, Grünwald A, Ravaud DE (2011) A phase II study of dovitinib (TKI258), an FGFR- and VEGFR-inhibitor, in patients with advanced or metastatic renal cell cancer (mRCC). J of Clin Oncol (ASCO Annual Meeting Proceedings); 29 (15S, May 20 Supplement):4551.

Test Product, Doses, and Modes of Administration

Dovitinib was supplied as 25 mg and 100 mg gelatin capsules. After Amendment 9, 25 mg strength capsules were no longer available as the production was discontinued and no additional supply of 25 mg capsules was provided to the investigational sites. The study treatment was 500 mg dovitinib administered orally on a 5 days on/2 days off schedule.

Statistical Methods

The data was analyzed by Novartis. Any data analysis carried out independently by the Investigator was submitted to Novartis before publication or presentation. The data were summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and PK measurements using appropriate analysis sets.

Populations for analysis:

Full analysis set (FAS): All patients who received at least one dose of study drug.

Per-protocol efficacy set (PPES): All patients who received at least one dose of study drug in the target population (previously treated with VEGF receptor tyrosine kinase inhibitor and an mTOR inhibitor).

Safety set: All patients who received at least one dose of study drug and had at least one valid post-baseline safety assessment.

PK analysis set: All patients who received at least one dose of study drug and at least one concentration measurement above lower limit of quantification.

Dose determining set: All patients from the safety set (from the dose-escalation phase) who met the minimum exposure criterion and had sufficient safety evaluations, or discontinue earlier due to dose-limiting toxicity.

Patients who were screened but never started treatment were listed. Screening failures were not included in any of the summary tables.

Pharmacokinetics characterization in patients of Asian ethnicity: Population PK analysis was employed to characterize dovitinib disposition in patients of Asian ethnicity and to detect ethnic sensitivity of dovitinib pharmacokinetics, if any.

Phase I (dose-escalation component)

Efficacy: The primary variable was the MTD of dovitinib administered on an intermittent schedule (5 days on/2 days off) to patients with advanced or metastatic RCC for whom no standard anticancer therapy exists. Determination of the MTD was based upon the DLT incidence data from Cycle 1. The probability of DLT rate was estimated by a two-parameter Bayesian logistic regression model guided by the EWOC principle.

The efficacy analyses included all data observed in patients from the FAS regardless of whether it was observed on-treatment or after the last date of study treatment.

Safety: The assessment of safety was based mainly on the frequency of AEs, and the number of laboratory values that fell outside of laboratory normal ranges (CTCAE version 3 and MedDRA version 14.0). Other safety data (e.g. vital signs and special tests) were considered as appropriate.

A DLT was defined as an AE or abnormal laboratory value assessed as unrelated to progression of disease, intercurrent illness, or concomitant medications, and occurred during the first 28 days (Cycle 1) following the first dose of dovitinib.

Pharmacokinetics: Descriptive statistics of PK parameters from the standard non-compartmental analysis were provided by dose group at the full PK sampling visits (Cycle 1 Days 1 and 15) and included n, arithmetic mean, geometric mean, median, standard deviation (SD), coefficient of variation CV (%), geometric CV (%), minimum and maximum.

Biomarkers: The biomarker data were addressed in a separate document.

Phase II (dose-expansion component)

Analysis of primary efficacy variables: The primary efficacy endpoint was based on the evaluation of the overall tumor response (complete response (CR), partial response (PR), stable disease (SD), disease progression (PD), unknown, and not assessed) at 8 weeks after start of treatment. The proportion of patients with clinical response (CR or PR at 8 weeks after treatment start) was evaluated. The primary analysis was based on the PPES and central radiological review only. Supportive analyses of the primary efficacy endpoint were based on FAS and central as well as local radiological review.

A multinomial two-stage design (Dent et al 2001) was used to evaluate the response rate and lack of early PD. Best overall response (BOR) at 8 weeks, clinical response, and no clinical benefit (NCB) were summarized descriptively using the PPES and the FAS.

Analysis of secondary efficacy variables: Secondary efficacy endpoints were progression-free survival (PFS) and overall survival (OS). A standard Kaplan-Meier survival analysis was performed using SAS PROC LIFETEST from which the median survival (PFS or OS) and 95% CI for the median was generated and reported using the FAS.

Additional analyses of tumor response and PFS were planned to be performed by prior therapy groups (or subsets of the FAS) such as VEGFR TKI and mTOR inhibitors.

Safety: The assessment of safety was based mainly on the frequency of AEs, and the number of laboratory values that fell outside of laboratory normal ranges. Other safety data (e.g. vital signs and special tests) were considered as appropriate. Safety analyses were performed for the safety set.

Pharmacokinetics: Descriptive statistics of PK parameters from the standard non-compartmental analysis were provided by dose group at the full PK sampling visits (Cycle 1 Days 1 and 15) and included n, arithmetic mean, geometric mean, median, standard deviation (SD), coefficient of variation CV (%), geometric CV (%), minimum and maximum.

The concentration-time profile was presented using descriptive statistics and plotting mean (with SD) concentrations at each time point, by dose group. The aforementioned presentations used the PK set.

All patient level concentration and PK parameter data were listed using PK set. Exploratory population PK modeling could be performed as appropriate. The PK parameters were determined in blood using non-compartmental methods.

Pharmacodynamics: Summary statistics were provided as appropriate and the relationship between dose and PD biomarker response was assessed.

Biomarkers: Summary statistics were provided as tables and longitudinal plots to evaluate the concentrations of circulating growth factors and soluble receptors (e.g. bFGF, VEGF, PlGF, sVEGFR1 and 2) during the study treatment period. Additional analyses of biomarker data will be described in a separate biomarker report.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

Prior therapy with any prior anti-cancer agent (i.e. IL-2, interferon, etc.) was permitted as long as it was administered 14 days (6 weeks for nitrosoureas or mitomycin C, and 4 weeks for any investigational agents and bevacizumab) prior to first administration of dovitinib (Cycle 1 Day 1). The only exception was made for palliative radiotherapy for symptomatic bone metastases. Patients must have recovered from adverse events (AEs) (to grade 1 or less toxicity according to the common terminology criteria for adverse events (CTCAE version 3.0) due to the prior anti-cancer agents (with the exception of the gastrointestinal toxicities mentioned in the exclusion criteria).

- Patients with measurable histologically or cytologically confirmed progressive metastatic RCC with predominant clear cell histology (>50%)
- Age at least 18 years
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

- Required baseline laboratory data included:
- Absolute neutrophil count ≥ 1500/mm^3 (International System (SI) units: 1.5×10^9/L)
- Platelets ≥ 75000/mm^3 (SI units: 75×10^9/L)
- Hemoglobin ≥ 8.0 g/dL (SI units: 80 g/L)
- Serum creatinine ≤ 1.5×upper limit of normal (ULN)
- Bilirubin ≤ 1.5×ULN
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5×ULN (with or without liver metastases)
- Electrolyte levels:
  - Potassium <lower limit of normal (LLN) 3.0 mmol/L or >ULN 5.5 mmol/L
  - Sodium <LLN 130 mmol/L or >ULN 150 mmol/L
- Urine dipstick reading: Negative for proteinuria or, if documentation of ≤ +2 results for protein on dipstick reading, then total urinary protein ≤ 500 mg and measured creatinine clearance ≥ 50 mL/min from a 24-hour urine collection
- Life expectancy ≥ 12 weeks
- Signed and witnessed informed consent form obtained prior to any screening procedures
- Patients must have been previously treated with VEGF receptor TKI (sunitinib and/or sorafenib) and an mTOR inhibitor. However, patients previously treated with other therapies (e.g. IL-2, IF-α) were also allowed to be enrolled and treated to determine the effect of dovitinib in patients who had not been treated with VEGF receptor TKI and mTOR therapy
- Patients of Asian ethnicity who failed standard treatment or for whom no standard treatment exists
- Patients with at least one measurable lesion at baseline as per the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, either on physical exam or as determined by computed tomography (CT) scan or magnetic resonance imaging (MRI)

Exclusion criteria

- Concurrent therapy with any other investigational agent within 28 days prior to baseline
- Women of child-bearing potential, who were biologically able to conceive, not employing two forms of highly effective contraception. Highly effective contraception (e.g. male condom with spermicide, diaphragm with spermicide, intra-uterine device) must have been used by both sexes during the study and must have continued for 8 weeks after the end-of-study (EOS) treatment. Oral, implantable, or injectable contraceptives may be affected by cytochrome P (CYP) 450 interactions, and were therefore not considered effective for this study. Women of child-bearing potential, defined as sexually mature women who had not undergone a hysterectomy or who had not been naturally postmenopausal for at least 12 consecutive months (i.e. who have had menses any time in the preceding 12 consecutive months), must have had a negative serum pregnancy test ≤ 72 hours prior to starting dovitinib

- Clinically significant cardiac disease (New York Heart Association, Class III or IV) or impaired cardiac function or clinically significant cardiac diseases, including any one of the following:
  - Left ventricular ejection fraction (LVEF) assessed by 2-echocardiogram (ECHO) <50% or LLN (whichever is higher) or multiple gated acquisition scan (MUGA) <45% or LLN (whichever is higher)
  - Complete left bundle branch block
  - Obligate use of a cardiac pacemaker

  Congenital long QT syndrome
  - History or presence of ventricular tachyarrhythmia
  - Presence of unstable atrial fibrillation (ventricular response >100 bpm). Patients with stable atrial fibrillation were eligible, provided they did not meet any of the other cardiac exclusion criteria
  - Clinically significant resting bradycardia (<50 bpm)
  - Uncontrolled hypertension (systolic blood pressure ≥ 150 mmHg and/or diastolic blood pressure ≥ 100 mmHg, with or without anti-hypertensive medication).
  - QTc >480 ms on screening electrocardiogram (ECG)
  - Right bundle branch block + left anterior hemiblock (bifasicular block)
  - Angina pectoris ≤ 3 months prior to starting study drug
  - Acute myocardial infarction ≤ 3 months prior to starting study drug
  - Other clinically significant heart disease (e.g., congestive heart failure, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)
- Uncontrolled infection
- Diabetes mellitus (insulin dependent or independent disease requiring chronic medication) with signs of clinically significant peripheral vascular disease
- Previous pericarditis; clinically significant pleural effusion in the previous 12 months or current ascites requiring two or more interventions/month
- Known pre-existing clinically significant disorder of the hypothalamic-pituitary axis, adrenal or thyroid glands
- Prior acute or chronic pancreatitis of any etiology
- Acute and chronic liver disease and all chronic liver impairment
- Malabsorption syndrome or uncontrolled gastrointestinal toxicities (nausea, diarrhea, or vomiting) with toxicity greater than National Cancer Institute CTCAE grade 2
- Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for this study
- Treatment with any of the medications that have a potential risk of prolonging the QT interval or inducing torsades de pointes and the treatment cannot be discontinued or switched to a different medication prior to starting study drug

- Use of ketoconazole, erythromycin, carbamazepine, phenobarbital, rifampin, phenytoin, and quinidine 2 weeks prior to baseline
- Major surgery ≤ 28 days prior to starting study drug or who have not recovered from side effects of such therapy
- Known diagnosis of HIV infection (HIV testing was not mandatory)
- History of another primary malignancy that was currently clinically significant or currently required active intervention
- Patients with brain metastases as assessed by radiologic imaging (e.g. CT and MRI)
- Alcohol or substance abuse disorder

Participant Flow

Phase I (dose-escalation component): Patient disposition by treatment (FAS)

Disposition reason	Dovitinib 500 mg N=15 n (%)	Dovitinib 600 mg N=5 n (%)
Patients treated		
End of treatment	15 (100)	5 (100)
Primary reason for end of treatment		
Disease progression	11 (73.3)	2 (40.0)
Adverse events	4 (26.7)	2 (40.0)
Subject withdrew consent	0	1 (20.0)

Phase II (dose-expansion component): Patient disposition by treatment (FAS)

Disposition reason		Dovitinib 500mg N=67 (%)
Patients treated	End of treatment	64 (95.5)
	Treatment ongoing*	3 (4.5)
Primary reason for end of treatment	Disease progression	41 (61.2)
	Adverse events	17 (25.4)
	Protocol deviation	2 (3.0)
	Subject withdrew consent	2 (3.0)
	Death	1 (1.5)
	Lost to follow-up	1 (1.5)

*The data for the three ongoing patients were reported in the final Phase II clinical study report as follows: The primary reasons for end of treatment for the three ongoing patients were disease progression for two patients and withdrew consent for one patient.

Baseline Characteristics:

Phase I (dose-escalation component): Demographics by treatment (FAS)

Demographic variable		Dovitinib 500 mg N=15	Dovitinib 600 mg N=5	All patients N=20
Age (years)	n	15	5	20
	Mean (SD)	54.8 (11.30)	52.2 (12.38)	54.2 (11.30)
	Median	55.0	56.0	55.5

	Range	29.0-71.0	36.0-66.0	29.0-71.0
Age category (years), n (%)	<65	12 (80.0)	4 (80.0)	16 (80.0)
	≥ 65	3 (20.0)	1 (20.0)	4 (20.0)
Sex, n (%)	Male	11 (73.3)	5 (100.0)	16 (80.0)
	Female	4 (26.7)	0	4 (20.0)
Race, n (%)	Caucasian	12 (80.0)	4 (80.0)	16 (80.0)
	Asian	3 (20.0)	0	3 (15.0)
	Other	0	1 (20.0)	1 (5.0)
Weight (kg)	n	15	5	20
	Mean (SD)	77.5 (15.62)	95.4 (17.87)	81.9 (17.62)
	Median	75.6	96.0	78.2
	Range	59.0-113.0	77.0-119.0	59.0-119.0
Body surface area (m^2)	n	15	5	20
	Mean (SD)	1.9 (0.22)	2.2 (0.21)	2.0 (0.24)
	Median	1.9	2.2	2.0
	Range	1.6-2.4	1.9-2.4	1.6-2.4
Height (cm)	n	15	5	20
	Mean (SD)	171.5 (7.38)	175.2 (5.12)	172.5 (6.95)
	Median	170.0	175.0	171.0
	Range	161.0-192.0	169.0-183.0	161.0-192.0
Body mass index (kg/m^2)	n	15	5	20
	Mean (SD)	26.4 (5.72)	31.1 (5.61)	27.6 (5.92)
	Median	25.3	31.3	25.8
	Range	20.5-39.7	24.9-39.8	20.5-39.8
ECOG Score, n (%)	0	3 (20.0)	4 (80.0)	7 (35.0)
	1	12 (80.0)	1 (20.0)	13 (65.0)

Phase II (dose-expansion component): Demographics by treatment (FAS)

Demographic variable		**Dovitinib 500mg N=67**
Age (years)	N	67
	Mean (SD)	60.1 (9.22)
	Median	59.0
	Min-Max	28.0-81.0
Age category (years) - n (%)	<65	45 (67.2)
	≥ 65	22 (32.8)
Sex - n (%)	Male	46 (68.7)
	Female	21 (31.3)
Race - n (%)	Asian	12 (17.9)
	Caucasian	52 (77.6)
	Other	3 (4.5)
Weight (kg)	N	67
	Mean (SD)	74.1 (14.50)
	Median	72.9
	Min - Max	46.2-115.2
Height (cm)	N	67
	Mean (SD)	168.9 (9.23)

Demographic variable		Dovitinib 500mg N=67
Body mass index (kg/m^2)	Median	168.0
	Min - Max	150.0-189.0
	n	67
	Mean (SD)	25.9 (4.50)
	Median	25.0
	Min - Max	17.2-40.3
ECOG Score - n (%)	0	28 (41.8)
	1	39 (58.2)

Outcome measures

Primary Outcome Results

Phase I (dose-escalation component): Dose-limiting toxicities in Cycle 1 (Dose-determining set)

Dose-limiting toxicity event	Dovitinib 500 mg N=15 n (%)	Dovitinib 600 mg N=4 n (%)
Any dose-limiting toxicity event	**1 (6.7)**	**2 (50.0)**
Sinus bradycardia	1 (6.7)	0
Hypertensive crisis grade 4	0	1 (25.0)
Asthenia grade 3 with nausea and vomiting grade 2	0	1 (25.0)

Phase II (dose-expansion component): Summary of overall response at 8 weeks per central and local review by treatment (PPES)

	Central review		Local review	
	Dovitinib 500mg N=55 (%)	90% CI*	Dovitinib 500mg N=55 (%)	90% CI*
Best overall response (BOR) at 8 weeks				
Complete response (CR)	0		0	
Partial response (PR)	1 (1.8)		2 (3.6)	
Stable disease (SD)	28 (50.9)		32 (58.2)	
Disease progression (PD)	14 (25.5)		9 (16.4)	
Unknown	1 (1.8)		2 (3.6)	
Not assessed	11 (20.0)		10 (18.2)	
Overall response at 8 weeks - (CR or PR)	1 (1.8)	[0.1 - 8.3]	2 (3.6)	[0.6 - 11.0]
Disease control at 8 weeks - (CR, PR or SD)	29 (52.7)	[40.9 - 64.4]	34 (61.8)	[49.8 - 72.8]
No clinical benefit (NCB) at 8 weeks	26 (47.3)	[35.6 - 59.1]	21 (38.2)	[27.2 - 50.2]
Unconfirmed PR or CR at 8 weeks	0		2 (3.6)	

BOR was based on central and local review of disease status using RECIST criteria
*90% CI was based on Clopper Pearson (exact) method
NCB: Patients without response (CR or PR) at 8 weeks post treatment and no SD for at least 8 weeks of treatment start

Summary of overall response per central review (PPES)

	Dovitinib 500mg N=55 (%)	90% CI*
BOR		
CR	0	
PR	2 (3.6)	
SD	29 (52.7)	
PD	16 (29.1)	
Unknown	1 (1.8)	
Not assessed	7 (12.7)	
Overall response - (CR or PR)	2 (3.6)	[0.6 - 11.0]
Disease control - (CR, PR or SD)	31 (56.4)	[44.4 - 67.8]
≥ 2 months	31 (56.4)	
≥ 4 months	28 (50.9)	
No clinical benefit (NCB)	24 (43.6)	[32.2 - 55.6]
Unconfirmed PR or CR	2 (3.6)	

BOR was based on central review of disease status using RECIST criteria
*90% CI was based on Clopper Pearson (exact) method
A window of 2 weeks was applied to the duration of disease control for disease control ≥ 2 months and disease control ≥ 4 months
NCB: No response (CR or PR) or no SD after start of treatment.

Data from the three patients who continued on treatment were reported in the final Phase II clinical study report as follows: The three ongoing patients discontinued shortly after the previous cut-off date: two due to disease progression and one due to withdrawal of consent.

Secondary Outcome Results

Phase I (dose-escalation component)

Summary of overall response per central review by treatment (FAS)

	Dovitinib 500 mg N=15 n (%)	Dovitinib 600 mg N=5 n (%)
Best overall response (BOR)		
Complete response (CR)	0	0
Partial response (PR)	2 (13.3)	0
Stable disease (SD)	9 (60.0)	3 (60.0)
Progressive disease (PD)	3 (20.0)	0
Unknown	0	2 (40.0)
Not assessed	1 (6.7)	0
Overall response (CR or PR)	2 (13.3)	0
Disease control (CR, PR, or SD)	11 (73.3)	3 (60.0)
SD ≥ 2 months	11 (73.3)	3 (60.0)
SD ≥ 4 months	9 (60.0)	2 (40.0)
No clinical benefit (NCB)	4 (26.7)	2 (40.0)
No. of patients who had unconfirmed PR or CR	0	0

	Dovitinib 500 mg N=15 n (%)	Dovitinib 600 mg N=5 n (%)

NCB: patients without CR, PR, and SD
BOR was based on central review of disease status using RECIST criteria
A window of 2 weeks was applied to the duration of SD≥ 2 months and SD≥ 4 months

Summary of primary PK parameters for dovitinib for Cycle 1 by treatment group and day (PK set)

		Dovitinib 500 mg			Dovitinib 600 mg		
Day	Statistics	$AUC_{0\text{-last}}$ (h.ng/mL)	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-last}}$ (h.ng/mL)	C_{max} (ng/mL)	T_{max} (h)
1	n	15	15	15	5	5	5
	Mean (SD)	5952.413 (1544.6066)	340.000 (97.1810)		5630.925 (1318.0016)	329.600 (98.9662)	
	CV% mean	25.95	28.58		23.41	30.03	
	Geo-mean	5752.593	325.914		5504.231	318.668	
	CV% geo-mean	28.27	31.75		24.48	29.21	
	Median	6128.583	359.000	6.033	5953.500	332.000	6.000
	[Min; Max]	[3309.00; 8590.17]	[180.00; 483.00]	[3.00; 24.17]	[3921.00; 7424.50]	[230.00; 487.00]	[6.00; 6.00]
15	n	11	11	11	2	2	2
	Mean (SD)	4411.000 (1921.0451)	303.455 (136.7043)		4448.545 (688.0691)	313.500 (70.0036)	
	CV% mean	43.55	45.05		15.47	22.33	
	Geo-mean	4025.241	277.615		4421.859	309.567	
	CV% geo-mean	49.28	46.96		15.62	22.81	
	Median	4008.817	254.000	6.000	4448.545	313.500	4.542
	[Min; Max]	[1443.52; 8300.07]	[112.00; 570.00]	[2.92; 6.58]	[3962.01; 4935.08]	[264.00; 363.00]	[3.00; 6.08]

Note: CV%=coefficient of variation (%)=(SD/mean)*100
CV% geo-mean=sqrt (exp (variance for log transformed data)-1)*100

Summary of secondary PK parameters for dovitinib for Cycle 1 by treatment group and day (PK set)

Day	Statistics	Dovitinib 500 mg $T_{1/2}$ (h)	Dovitinib 600 mg $T_{1/2}$ (h)
1	n	3	0
	Mean (SD)	23.673 (5.5846)	
	CV% mean	23.59	
	Geo-mean	23.200	
	CV% geo-mean	25.50	
	Median	25.053	

Day	Statistics	Dovitinib 500 mg $T_{1/2}$ (h)	Dovitinib 600 mg $T_{1/2}$ (h)
	[Min; Max]	[17.53; 28.44]	
15	n	5	1
	Mean (SD)	10.480 (2.3178)	13.555
	CV% mean	22.12	
	Geo-mean	10.264	13.555
	CV% geo-mean	23.53	
	Median	11.025	13.555
	[Min; Max]	[7.54; 12.62]	[13.55; 13.55]

Note: CV%=coefficient of variation (%)=(SD/mean)*100
CV% geo-mean=sqrt (exp (variance for log transformed data)-1)*100

Phase II (dose-expansion component)*

***Note:** The results for the tables in this section were based on the DBL on 30-Mar-2012. The tables were not regenerated at the final DBL. Therefore, these tables do not include data for the ongoing patients past the DBL.

Summary of progression-free survival per central review by treatment (FAS)

		Dovitinib 500mg N=67
n (%)		42 (62.7%)
Percentiles (95% CI) (months)	25%	1.9 [1.8,3.0]
	Median	3.7 [3.0,5.6]
	75%	9.1 [5.5,17.9]
% Event-free probability estimate [95% CI]:	3 months	63.0 [49.0,74.1]
	6 months	33.2 [20.5,46.5]
	9 months	27.7 [15.6,41.2]

Percentiles with 95% CIs were calculated from PROC LIFETEST output using the Brookmeyer and Crowley method (Brookmeyer and Crowley 1982)
% Event-free probability estimate was the estimated probability that a patient remained event-free up to the specified time point and was obtained from the Kaplan-Meier survival estimates; Greenwood formula was used for CIs of Kaplan-Meier estimates
n: Total number of progression free survival (PFS) events included in the analysis; N: Total number of subjects included in the analysis

Summary of overall survival (FAS)

		Dovitinib 500mg N=67
n (%)		45 (67.2)
Percentiles [95% CI] (months)	25%	6.3 [3.9, 7.9]
	Median	11.8 [7.9, 17.4]
	75%	21.1 [17.4,]
% Event-free probability estimate [95% CI]:	6 months	76.2 [63.6, 84.9]
	12 months	46.9 [33.8, 58.9]
	18 months	36.0 [23.9, 48.2]

	Dovitinib 500mg N=67

Percentiles with 95% CIs were calculated from PROC LIFETEST output using the Brookmeyer and Crowley (1982) method
% Event-free probability estimate was the estimated probability that a patient remained event-free up to the specified time point and was obtained from the Kaplan-Meier survival estimates; Greenwood formula was used for CIs of Kaplan-Meier estimates
n: Total number of overall survival (OS) events included in the analysis; N: Total number of subjects included in the analysis

Summary of primary PK parameters for dovitinib for Cycle 1 by day (PK set)

Treatment	Day	Statistics	AUC(0-last) (ng.h/mL)	Cmax (ng/mL)	Tmax (h)
Dovitinib	1	N	65	65	65
		Mean (SD)	5576.38 (1922.129)	326.34 (124.210)	
		CV% mean	34.47	38.06	
		Geo-mean	5250.14	305.71	
		CV% geo-mean	37.13	37.60	
		Median	5323.50	306.00	6.08
		Min; Max	1741.6; 12157.0	95.8; 817.0	2.8; 24.0
	15	N	56	56	56
		Mean (SD)	3933.25 (1643.232)	263.52 (103.705)	
		CV% mean	41.78	39.35	
		Geo-mean	3666.07	246.74	
		CV% geo-mean	38.43	37.26	
		Median	3886.79	247.00	6.00
		Min; Max	1601.5; 12085.9	117.0; 704.0	2.9; 23.9

CV% = coefficient of variation (%) = (SD/mean)*100
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100

Summary of secondary PK parameters for dovitinib for Cycle 1 by day (PK set)

Treatment	Day	Statistics	T1/2 (h)
Dovitinib	1	n	9
		Mean (SD)	25.38 (8.841)
		CV% mean	34.84
		Geo-mean	24.17
		CV% geo-mean	33.40
		Median	23.93
		Min; Max	15.1; 44.4
	15	n	11
		Mean (SD)	11.55 (3.283)
		CV% mean	28.43
		Geo-mean	11.18
		CV% geo-mean	26.30
		Median	10.63
		Min; Max	7.8; 19.5

CV% = coefficient of variation (%) = (SD/mean)*100
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100

Safety Results

Adverse Events by System Organ Class

Phase I (dose-escalation component)

Adverse events irrespective of causality, with at least 10% incidence of any grade events in either group, by system organ class and maximum CTCAE and treatment (Safety set)

	Dovitinib 500 mg N=15 n (%)			Dovitinib 600 mg N=5 n (%)		
System organ class (SOC)	**Any grade**	**grade 3**	**grade 4**	**Any grade**	**grade 3**	**grade 4**
Any primary system organ class	15 (100.0)	8 (53.3)	1 (6.7)	5 (100.0)	3 (60.0)	1 (20.0)
Gastrointestinal disorders	14 (93.3)	2 (13.3)	0	5 (100.0)	0	0
General disorders and administration site conditions	12 (80.0)	3 (20.0)	0	5 (100.0)	2 (40.0)	0
Musculoskeletal and connective tissue disorders	10 (66.7)	2 (13.3)	0	3 (60.0)	1 (20.0)	0
Nervous system disorders	10 (66.7)	1 (6.7)	0	3 (60.0)	1 (20.0)	0
Respiratory, thoracic and mediastinal disorders	10 (66.7)	0	0	3 (60.0)	0	0
Metabolism and nutrition disorders	9 (60.0)	1 (6.7)	0	3 (60.0)	0	0
Skin and subcutaneous tissue disorders	8 (53.3)	1 (6.7)	0	3 (60.0)	0	0
Infections and infestations	7 (46.7)	2 (13.3)	0	2 (40.0)	0	0
Vascular disorders	7 (46.7)	1 (6.7)	0	3 (60.0)	0	1 (20.0)
Investigations	6 (40.0)	0	0	2 (40.0)	0	0
Blood and lymphatic system disorders	5 (33.3)	3 (20.0)	0	0	0	0
Eye disorders	5 (33.3)	1 (6.7)	0	0	0	0
Injury, poisoning and procedural complications	3 (20.0)	1 (6.7)	1 (6.7)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (20.0)	1 (6.7)	0	0	0	0
Psychiatric disorders	3 (20.0)	0	0	1 (20.0)	0	0
Endocrine disorders	2 (13.3)	0	0	0	0	0
Hepatobiliary disorders	2 (13.3)	0	0	0	0	0
Renal and urinary disorders	2 (13.3)	0	0	0	0	0

SOCs were sorted by descending frequency of any grade in the dovitinib 500 mg group
A patient with multiple AEs within a SOC was counted only once
AEs occurring more than 28 days after the last date of study treatment were not summarized

Phase II (dose-expansion component)

Adverse events irrespective of causality with at least 10% incidence of any grade events by system organ class and maximum CTCAE grade (Safety set)

	Dovitinib 500mg (N=67)				
Primary System Organ Class (SOC)	**Any grade n (%)**	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Any primary SOC	**67 (100.0)**	**0**	**12 (17.9)**	**42 (62.7)**	**13 (19.4)**
Gastrointestinal disorders	63 (94.0)	21 (31.3)	25 (37.3)	17 (25.4)	0
General disorders and administration site conditions	58 (86.6)	15 (22.4)	22 (32.8)	18 (26.9)	3 (4.5)
Metabolism and nutrition disorders	49 (73.1)	10 (14.9)	18 (26.9)	14 (20.9)	7 (10.4)
Respiratory, thoracic and mediastinal disorders	43 (64.2)	18 (26.9)	12 (17.9)	11 (16.4)	2 (3.0)
Musculoskeletal and connective tissue disorders	41 (61.2)	13 (19.4)	21 (31.3)	7 (10.4)	0
Nervous system disorders	37 (55.2)	17 (25.4)	11 (16.4)	9 (13.4)	0
Skin and subcutaneous tissue disorders	36 (53.7)	28 (41.8)	7 (10.4)	1 (1.5)	0
Investigations	32 (47.8)	10 (14.9)	9 (13.4)	12 (17.9)	1 (1.5)
Vascular disorders	27 (40.3)	4 (6.0)	12 (17.9)	10 (14.9)	1 (1.5)
Eye disorders	23 (34.3)	19 (28.4)	3 (4.5)	1 (1.5)	0
Infections and infestations	21 (31.3)	9 (13.4)	7 (10.4)	3 (4.5)	2 (3.0)
Psychiatric disorders	17 (25.4)	10 (14.9)	5 (7.5)	2 (3.0)	0
Blood and lymphatic system disorders	16 (23.9)	3 (4.5)	10 (14.9)	3 (4.5)	0
Renal and urinary disorders	14 (20.9)	7 (10.4)	5 (7.5)	2 (3.0)	0
Cardiac disorders	13 (19.4)	4 (6.0)	5 (7.5)	4 (6.0)	0
Ear and labyrinth disorders	8 (11.9)	6 (9.0)	2 (3.0)	0	0

SOCs were sorted by descending frequency of any grade
A patient with multiple AEs within a SOC was counted only once
AEs occurring more than 28 days after the last date of study treatment were not summarized

Data from the three patients who continued on treatment were reported in the final Phase II clinical study report as follows: One patient had no new grade 1, 2, 3, or 4 AEs since the cut-off date 30-Mar-2012. AEs that started before the cut-off date and were ongoing included: seven grade 1 AEs (dry mouth (suspected), polyneuropathy (suspected), reduced visual acuity (not suspected), breast pain (suspected), vitamin D deficiency (suspected), fatigue (suspected), and arrhythmia (not suspected) and two grade 3 AEs (hypertriglyceridemia (suspected) and pulmonary embolism (not suspected)).

One patient had no new grade 3 or 4 AEs after the cut-off date (30-Mar-2012). Ongoing grade 1 AEs included: dry eye (suspected), hypertriglyceridemia (suspected), skin papilloma (not suspected), hypertension (suspected), skin discoloration (suspected), and increased blood creatinine (not suspected). One ongoing grade 2 AE hypoalbuminemia (suspected) was reported. Newly reported AEs after the cut-off date were: grade 1 increased blood creatine phosphokinase (suspected), grade 1 cough (not suspected), and grade 2 nausea (suspected) and grade 1 ongoing increased blood creatinine (not suspected).

One patient had no new grade 3 or 4 AEs since the cut-off date 30-Mar-2012. AEs ongoing since before the cut-off date were: grade 1 face oedema (suspected) and grade 3 hypertension (suspected). The patient had grade 3 hypertriglyceridemia from 05-Mar-2012 to 01-Apr-2012 and grade 2 hypertriglyceridemia from 02-Apr-2012 (continuing), which were suspected to be study-drug related. Additional grade 2 AEs since 30-Mar-2012 were as follows: increased lactate dehydrogenase (not suspected), blurred vision (suspected), left sciatica (not suspected), and arthralgia (not suspected). Grade 1 AEs since 30-Mar-2012 included: thrombocytopenia (suspected), increased lactate dehydrogenase (not suspected), hypophosphatemia (not suspected), thrombocytopenia (suspected), increased lactate dehydrogenase (not suspected), increased troponin (suspected), glaucoma (ongoing, suspected), cough (not suspected), increased low density lipoprotein (not suspected), dermal cyst (not suspected), infected dermal cyst (not suspected), central obesity (ongoing, suspected), rash (ongoing, suspected), increased low density lipoprotein (ongoing, suspected), and thrombocytopenia (ongoing, suspected).

Most Frequently Reported AEs Overall by Preferred Term n (%)

Phase I (dose-escalation component)

Adverse events irrespective of causality with at least 10% incidence of any grade events in either group by preferred term and maximum CTCAE grade (Safety set)

	Dovitinib 500 mg N=15 n (%)			Dovitinib 600 mg N=5 n (%)		
Preferred term	**Any grade**	**grade 3**	**grade 4**	**Any grade**	**grade 3**	**grade 4**
Any preferred term	15 (100.0)	8 (53.3)	1 (6.7)	5 (100.0)	3 (60.0)	1 (20.0)
Diarrhoea	11 (73.3)	0	0	3 (60.0)	0	0
Nausea	11 (73.3)	1 (6.7)	0	5 (100.0)	0	0
Vomiting	10 (66.7)	0	0	4 (80.0)	0	0
Decreased appetite	7 (46.7)	1 (6.7)	0	2 (40.0)	0	0
Asthenia	6 (40.0)	2 (13.3)	0	4 (80.0)	1 (20.0)	0
Constipation	5 (33.3)	0	0	0	0	0
Cough	5 (33.3)	0	0	3 (60.0)	0	0
Weight decreased	5 (33.3)	0	0	1 (20.0)	0	0
Dry skin	4 (26.7)	0	0	1 (20.0)	0	0
Dyspnoea	4 (26.7)	0	0	1 (20.0)	0	0
Hypertension	4 (26.7)	0	0	1 (20.0)	1 (20.0)	0
Musculoskeletal pain	4 (26.7)	0	0	0	0	0
Pain in extremity	4 (26.7)	0	0	0	0	0
Urinary tract infection	4 (26.7)	0	0	0	0	0
Anaemia	3 (20.0)	1 (6.7)	0	0	0	0
Conjunctivitis	3 (20.0)	0	0	0	0	0
Dizziness	3 (20.0)	0	0	0	0	0
Headache	3 (20.0)	0	0	3 (60.0)	1 (20.0)	0
Hypotension	3 (20.0)	0	0	0	0	0
Myalgia	3 (20.0)	0	0	1 (20.0)	0	0
Neutropenia	3 (20.0)	2 (13.3)	0	0	0	0

	Dovitinib 500 mg N=15 n (%)			Dovitinib 600 mg N=5 n (%)		
Preferred term	**Any grade**	**grade 3**	**grade 4**	**Any grade**	**grade 3**	**grade 4**
Non-cardiac chest pain	3 (20.0)	0	0	2 (40.0)	1 (20.0)	0
Oedema peripheral	3 (20.0)	0	0	0	0	0
Pyrexia	3 (20.0)	0	0	3 (60.0)	0	0
Rash	3 (20.0)	1 (6.7)	0	2 (40.0)	0	0
Rhinitis	3 (20.0)	0	0	1 (20.0)	0	0
Tumour pain	3 (20.0)	1 (6.7)	0	0	0	0
Abdominal pain	2 (13.3)	0	0	1 (20.0)	0	0
Anxiety	2 (13.3)	0	0	0	0	0
Arthralgia	2 (13.3)	0	0	1 (20.0)	0	0
Dysphagia	2 (13.3)	1 (6.7)	0	0	0	0
Fall	2 (13.3)	1 (6.7)	0	0	0	0
Fatigue	2 (13.3)	0	0	0	0	0
Folliculitis	2 (13.3)	0	0	0	0	0
Hyperglycaemia	2 (13.3)	1 (6.7)	0	1 (20.0)	0	0
Hypertriglyceridaemia	2 (13.3)	0	0	1 (20.0)	0	0
Hypothyroidism	2 (13.3)	0	0	0	0	0
Lacrimation increased	2 (13.3)	0	0	0	0	0
Musculoskeletal chest pain	2 (13.3)	1 (6.7)	0	0	0	0
Palmar-plantar erythrodysaesthesia syndrome	2 (13.3)	1 (6.7)	0	0	0	0
Paraesthesia	2 (13.3)	0	0	0	0	0
Productive cough	2 (13.3)	0	0	0	0	0
Rash maculo-papular	2 (13.3)	0	0	0	0	0
Stomatitis	2 (13.3)	1 (6.7)	0	0	0	0
Dysaesthesia	1 (6.7)	0	0	1 (20.0)	0	0
Dysgeusia	1 (6.7)	0	0	1 (20.0)	0	0
Gastrooesophageal reflux disease	1 (6.7)	0	0	1 (20.0)	0	0
Insomnia	1 (6.7)	0	0	1 (20.0)	0	0
Phlebitis	1 (6.7)	1 (6.7)	0	1 (20.0)	0	0
Back pain	0	0	0	1 (20.0)	1 (20.0)	0
Blood triglycerides increased	0	0	0	1 (20.0)	0	0
Dyspnoea exertional	0	0	0	1 (20.0)	0	0
Haemoptysis	0	0	0	1 (20.0)	0	0
Haemorrhoids	0	0	0	1 (20.0)	0	0
Hyperaesthesia	0	0	0	1 (20.0)	0	0
Hyperkeratosis	0	0	0	1 (20.0)	0	0
Hypertensive crisis	0	0	0	1 (20.0)	0	1 (20.0)
Loss of consciousness	0	0	0	1 (20.0)	0	0
Lung disorder	0	0	0	1 (20.0)	0	0
Nasopharyngitis	0	0	0	1 (20.0)	0	0
Raynaud's phenomenon	0	0	0	1 (20.0)	0	0
Sinusitis	0	0	0	1 (20.0)	0	0

	Dovitinib 500 mg N=15 n (%)			Dovitinib 600 mg N=5 n (%)		
Preferred term	**Any grade**	**grade 3**	**grade 4**	**Any grade**	**grade 3**	**grade 4**

Preferred terms were sorted by descending frequency of any grade in the 500 mg group.
AEs occurring more than 28 days after the last date of study treatment are not summarized.

Phase II (dose-expansion component)

Adverse events irrespective of causality with at least 10% incidence of any grade events in either group by preferred term and maximum CTCAE grade (Safety set)

	Dovitinib 500 mg (N=67)				
Preferred term	**Any grade n (%)**	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Total	**67 (100)**	**0**	**12 (17.9)**	**42 (62.7)**	**13 (19.4)**
Diarrhoea	46 (68.7)	28 (41.8)	11 (16.4)	7 (10.4)	0
Nausea	45 (67.2)	29 (43.3)	10 (14.9)	6 (9.0)	0
Vomiting	42 (62.7)	27 (40.3)	10 (14.9)	5 (7.5)	0
Decreased appetite	33 (49.3)	14 (20.9)	13 (19.4)	6 (9.0)	0
Fatigue	24 (35.8)	9 (13.4)	7 (10.4)	8 (11.9)	0
Dyspnoea	23 (34.3)	9 (13.4)	9 (13.4)	4 (6.0)	1 (1.5)
Asthenia	21 (31.3)	3 (4.5)	10 (14.9)	8 (11.9)	0
Stomatitis	19 (28.4)	10 (14.9)	7 (10.4)	2 (3.0)	0
Hypertension	17 (25.4)	2 (3.0)	8 (11.9)	7 (10.4)	0
Constipation	16 (23.9)	13 (19.4)	3 (4.5)	0	0
Cough	16 (23.9)	8 (11.9)	7 (10.4)	1 (1.5)	0
Dysgeusia	16 (23.9)	11 (16.4)	4 (6.0)	1 (1.5)	0
Headache	15 (22.4)	13 (19.4)	2 (3.0)	0	0
Hypertriglyceridaemia	14 (20.9)	4 (6.0)	2 (3.0)	3 (4.5)	5 (7.5)
Non-cardiac chest pain	14 (20.9)	7 (10.4)	5 (7.5)	2 (3.0)	0
Oedema peripheral	14 (20.9)	9 (13.4)	5 (7.5)	0	0
Pyrexia	14 (20.9)	9 (13.4)	3 (4.5)	2 (3.0)	0
Rash	14 (20.9)	11 (16.4)	3 (4.5)	0	0
Weight decreased	13 (19.4)	8 (11.9)	5 (7.5)	0	0
Anaemia	12 (17.9)	3 (4.5)	8 (11.9)	1 (1.5)	0
Pain in extremity	12 (17.9)	9 (13.4)	2 (3.0)	1 (1.5)	0
Abdominal pain	11 (16.4)	9 (13.4)	0	2 (3.0)	0
Back pain	11 (16.4)	5 (7.5)	5 (7.5)	1 (1.5)	0
Myalgia	11 (16.4)	7 (10.4)	4 (6.0)	0	0
Abdominal pain upper	10 (14.9)	9 (13.4)	1 (1.5)	0	0
Arthralgia	10 (14.9)	6 (9.0)	3 (4.5)	1 (1.5)	0
Dry skin	9 (13.4)	9 (13.4)	0	0	0
Hypoalbuminaemia	9 (13.4)	2 (3.0)	5 (7.5)	2 (3.0)	0
GGT increased	8 (11.9)	1 (1.5)	0	7 (10.4)	0
General physical health deterioration	8 (11.9)	2 (3.0)	4 (6.0)	2 (3.0)	0
Anxiety	7 (10.4)	5 (7.5)	2 (3.0)	0	0
Dry eye	7 (10.4)	7 (10.4)	0	0	0
Dyspnoea exertional	7 (10.4)	5 (7.5)	1 (1.5)	1 (1.5)	0

Preferred term	Dovitinib 500 mg (N=67) Any grade n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Hypotension	7 (10.4)	3 (4.5)	3 (4.5)	0	1 (1.5)
Insomnia	7 (10.4)	5 (7.5)	1 (1.5)	1 (1.5)	0
Pulmonary embolism	7 (10.4)	0	2 (3.0)	4 (6.0)	1 (1.5)
Vision blurred	7 (10.4)	6 (9.0)	1 (1.5)	0	0

Preferred terms were sorted by descending frequency of any grade
AEs occurring more than 28 days after the last date of study treatment were not summarized

Serious Adverse Events and Deaths

Phase I (dose-escalation component)

One patient died of pneumonia four days after the last treatment with 500 mg dovitinib.

Serious adverse events, irrespective of causality, with at least 2% incidence in either group by preferred term, maximum CTCAE grade and treatment (Safety set)

Preferred term	Dovitinib 500 mg N=15 n (%) Any grade	grade 3	grade 4	Dovitinib 600 mg N=5 n (%) Any grade	grade 3	grade 4
Any preferred term	5 (33.3)	3 (20.0)	1 (6.7)	3 (60.0)	1 (20.0)	1 (20.0)
Device dislocation	1 (6.7)	1 (6.7)	0	0	0	0
Fall	1 (6.7)	1 (6.7)	0	0	0	0
Herpes oesophagitis	1 (6.7)	1 (6.7)	0	0	0	0
Joint dislocation postoperative	1 (6.7)	0	1 (6.7)	0	0	0
Lower limb fracture	1 (6.7)	1 (6.7)	0	0	0	0
Pathological fracture	1 (6.7)	1 (6.7)	0	0	0	0
Phlebitis	1 (6.7)	1 (6.7)	0	0	0	0
Pneumonia	1 (6.7)	1 (6.7)	0	0	0	0
Sinus bradycardia	1 (6.7)	0	0	0	0	0
Headache	0	0	0	1 (20.0)	1 (20.0)	0
Hypertensive crisis	0	0	0	1 (20.0)	0	1 (20.0)
Non-cardiac chest pain	0	0	0	1 (20.0)	1 (20.0)	0
Pyrexia	0	0	0	1 (20.0)	0	0

Preferred terms were sorted by descending frequency of any grade in the dovitinib 500 mg group.
A patient with multiple occurrences of an SAE was counted only once in the SAE category.
SAE events occurring more than 28 days after the last date of study treatment were not summarized.

Adverse events leading to study drug discontinuation, regardless of study drug relationship, with at least 2% incidence in either group by preferred term and treatment (Safety set)

Preferred term	Dovitinib 500 mg N=15 n (%)	Dovitinib 600 mg N=5 n (%)
Any preferred term	**4 (26.7)**	**2 (40.0)**

Preferred term	Dovitinib 500 mg N=15 n (%)	Dovitinib 600 mg N=5 n (%)
General physical health deterioration	1 (6.7)	0
Nausea	1 (6.7)	1 (20.0)
Rash	1 (6.7)	0
Sinus bradycardia	1 (6.7)	0
Vomiting	1 (6.7)	1 (20.0)
Asthenia	0	1 (20.0)
Hypertension	0	1 (20.0)
Hypertensive crisis	0	1 (20.0)

Preferred terms are sorted by descending frequency in the dovitinib 500 mg group
A patient with multiple occurrences of an AE was counted only once in the AE category
AEs occurring more than 28 days after the last date of study treatment were not summarized

Phase II (dose-expansion component)

On-treatment deaths by primary system organ class and preferred term (Safety set)

Primary SOC preferred term		Dovitinib 500mg N=67 n (%)
Any primary SOC	**Total**	**3 (4.5)**
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Total	2 (3.0)
	Metastatic RCC	2 (3.0)
Respiratory, thoracic and mediastinal disorders	Total	1 (1.5)
	Dyspnoea	1 (1.5)

Primary SOCs were presented alphabetically; preferred terms were sorted within primary SOC alphabetically
Only deaths occurring during treatment or within 28 days of the last date of study treatment were reported

Data from the three patients who continued on treatment were reported in the final Phase II clinical study report as follows: No new deaths, other SAEs, or other significant AEs were reported after the 30-Mar-2012 cut-off date.

Serious adverse events irrespective of causality with at least 2% incidence by preferred term and maximum CTCAE grade (Safety set)

	Dovitinib 500mg (N=67)				
Preferred Term	Any grade n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Total	**46 (68.7)**	**0**	**3 (4.5)**	**34 (50.7)**	**9 (13.4)**
Dyspnoea	7 (10.4)	1 (1.5)	1 (1.5)	4 (6.0)	1 (1.5)
Nausea	6 (9.0)	0	2 (3.0)	4 (6.0)	0
Pulmonary embolism	5 (7.5)	0	1 (1.5)	3 (4.5)	1 (1.5)
Decreased appetite	4 (6.0)	0	1 (1.5)	3 (4.5)	0
Diarrhoea	4 (6.0)	0	1 (1.5)	3 (4.5)	0
Vomiting	4 (6.0)	0	0	4 (6.0)	0
Fatigue	3 (4.5)	0	0	3 (4.5)	0

Preferred Term	Dovitinib 500mg (N=67) Any grade n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Non-cardiac chest pain	3 (4.5)	1 (1.5)	0	2 (3.0)	0
Pneumonia	3 (4.5)	0	1 (1.5)	0	2 (3.0)
Troponin T increased	3 (4.5)	0	1 (1.5)	1 (1.5)	1 (1.5)
Abdominal pain	2 (3.0)	0	0	2 (3.0)	0
Asthenia	2 (3.0)	0	0	2 (3.0)	0
Brain oedema	2 (3.0)	0	0	2 (3.0)	0
Dizziness	2 (3.0)	0	1 (1.5)	1 (1.5)	0
General physical health deterioration	2 (3.0)	0	0	2 (3.0)	0
Hemiparesis	2 (3.0)	0	0	2 (3.0)	0
Hypercalcaemia	2 (3.0)	0	0	1 (1.5)	1 (1.5)
Hypertriglyceridaemia	2 (3.0)	0	0	0	2 (3.0)
Hypotension	2 (3.0)	1 (1.5)	0	0	1 (1.5)
Monoparesis	2 (3.0)	0	0	2 (3.0)	0
Musculoskeletal pain	2 (3.0)	1 (1.5)	1 (1.5)	0	0
Pain	2 (3.0)	1 (1.5)	0	0	1 (1.5)
Pathological fracture	2 (3.0)	0	0	2 (3.0)	0
Performance status decreased	2 (3.0)	0	0	0	2 (3.0)
Pyrexia	2 (3.0)	0	1 (1.5)	1 (1.5)	0

Preferred terms were sorted by descending frequency of any grade; A patient with multiple occurrences of an SAE was counted only once in the SAE category; SAEs occurring more than 28 days after the last date of study treatment were not summarized.

Adverse events leading to study drug discontinuation, irrespective of causality, with at least 2% incidence by preferred term (Safety set)

SOC Preferred term	Dovitinib 500mg N=67 n (%)
Any primary SOC total	17 (25.4)
Cardiac disorders total	2 (3.0)
Angina pectoris	1 (1.5)
Coronary artery disease	1 (1.5)
Gastrointestinal disorders total	4 (6.0)
Diarrhoea	2 (3.0)
Aphagia	1 (1.5)
Intestinal obstruction	1 (1.5)
General disorders and administration site conditions total	2 (3.0)
Fatigue	1 (1.5)
Performance status decreased	1 (1.5)
Investigations total	1 (1.5)
GGT increased	1 (1.5)
Metabolism and nutrition disorders total	4 (6.0)

SOC Preferred term	Dovitinib 500mg N=67 n (%)
Hypertriglyceridaemia	2 (3.0)
Decreased appetite	1 (1.5)
Hyperuricaemia	1 (1.5)
Nervous system disorders total	3 (4.5)
Hemiparesis	2 (3.0)
Cerebral haemorrhage	1 (1.5)
Cerebrovascular accident	1 (1.5)
Convulsion	1 (1.5)
Embolic cerebral infarction	1 (1.5)
Psychiatric disorders total	1 (1.5)
Confusional state	1 (1.5)
Respiratory, thoracic and mediastinal disorders total	2 (3.0)
Pulmonary embolism	2 (3.0)
Vascular disorders total	1 (1.5)
Phlebitis	1 (1.5)

Other Relevant Findings

No other relevant findings were reported.

Date of Clinical Trial Report

17 Jun 2013

Date Inclusion on Novartis Clinical Trial Results Database

16 Jul 2013

Date of Latest Update