Sponsor

Novartis

Generic Drug Name

Dovitinib

Therapeutic Area of Trial

Relapsed or refractory multiple myeloma

Approved Indication

Investigational drug

Protocol Number

CTKI258A2204

Title

A Phase II, multi-center, non-randomized, open-label study of TKI258 in patients with relapsed or refractory multiple myeloma, who are with or without t(4;14) translocation

Study Phase

Phase II

Study Start/End Dates

10-May-2010 (first patient first visit) to 12-Feb-2013 (last patient last visit)

The study was terminated early for the following reasons:

- Stage 1 efficacy evaluation in the t(4;14) negative group did not meet the success criteria as three or more responders were not observed among the first 20 patients in that group. Thus, as per protocol, stage 2 patient enrollment was not opened and further enrollment in the t(4;14) negative group was closed in September 2011.
- Enrollment in the t(4;14) positive group was closed by the Sponsor on 29-Dec-2011 due to lack of efficacy observed to date and slow rate of enrollment. At that time, only thirteen patients had been enrolled to the t(4;14) positive group.

Study Design/Methodology

This was a multi-center, open label, two-stage, phase II trial of dovitinib administered at a dose of 500 mg/day, on a 5 days on/2 days off dosing schedule in patients with relapsed or refractory multiple myeloma, as defined by the International Myeloma Working Group (IMWG) criteria.

The study used a two-stage design for both patient groups. Each group planned to enroll 20 patients in the first stage and an additional 20 patients in the second stage, if the pre-determined response criteria were met during the first stage. For the 20 patients enrolled in

each group during Stage 1, response was required in 3 or more patients to proceed to Stage 2 enrollment.

Patients received treatment until disease progression (PD) or unacceptable toxicities occurred, or until the Investigator or patient decided to discontinue.

As an exploratory objective, when reaching PD on dovitinib monotherapy, a patient had the option to continue on a dexamethasone supplemented dovitinib regimen. The M-protein levels at the first PD were considered as the new baseline, and the patient was allowed to continue until further progression, unacceptable toxicity, or patient/Investigator's decision to discontinue.

Centers

22 centers in 7 countries: Australia (2), Turkey (2), Germany (3), Netherlands (3), Canada (2), France (1), and USA (9).

Publication

None

Test Product, Doses, and Modes of Administration

All patients received a single daily oral dose of 500 mg dovitinib on a 5 days on/2 days off schedule in 28-day cycles.

Low dose dexamethasone (40 mg tablet on Days 1, 8, 15, and 22 of each cycle) was added to the dovitinib regimen after a patient had developed PD on dovitinib monotherapy.

Statistical Methods

The data was analyzed by Novartis Oncology Biometrics and Data Management. The data from all centers that participated in this study were used in the final safety and efficacy analysis. A separate analysis was performed for t(4;14) positive and t(4;14) negative groups.

Data from all centers were used, unless otherwise stated. Continuous data were summarized using descriptive statistics such as mean, standard deviation (SD), median, and range. Categorical data were summarized using contingency tables with frequencies and percentages.

Efficacy analyses were performed for both t(4;14) positive and t(4;14) negative groups. Safety analyses were done for all patients as well as for each t(4;14) group.

Patients were classified in one of the study groups according to the baseline t(4;14) status determined by the laboratory designated by the sponsor. Patients whose baseline t(4;14) status could not be determined were classified as "non-interpretable" and they were not included in the primary and secondary efficacy analysis, but were included in all other analyses.

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

Patients were excluded from the analysis populations defined above based on protocol deviations entered in the database and/or on specific subject classification rules.

Full analysis set (FAS): The FAS consisted of all patients who received at least one dose of dovitinib. All baseline demographic and disease characteristics, and primary and secondary efficacy endpoints were analyzed using the FAS.

Safety set: The safety set consisted of all patients who received at least one dose of dovitinib. All safety data was analyzed using the safety set.

Per-Protocol (PP) set: The PP set consisted of all patients from the FAS without any major protocol deviation who were evaluable for efficacy.

The pharmacokinetic (PK) set: The PK set consisted of all patients who received at least one dose of dovitinib and had at least one post dose concentration measurement of dovitinib.

The FAS was used for all baseline and demographic summaries and listings.

Demographic and other baseline characteristics were summarized by means of contingency tables for each t(4;14) group and quantitative data were summarized by appropriate descriptive statistics (mean, SD, median, minimum, and maximum).

Summary statistics were tabulated for the diagnosis and extent of cancer, according to the data collected on the eCRF.

Medical history and ongoing conditions, including cancer related conditions and symptoms were summarized and listed. Prior anti-neoplastic therapies were also summarized and listed.

All data collected at baseline, including source of patient referral, child bearing potential, and pregnancy test results were listed for each t(4;14) group.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

Male and female patients aged 18 or older meeting the following key inclusion criteria

1. Cytopathologically or histologically confirmed diagnosis of multiple myeloma previously requiring systemic treatment
2. Evidence of relapsed or refractory disease (detailed definition provided in the protocol post-text supplement-1)
3. Have received at least 2 prior treatment regimens for multiple myeloma including chemotherapy, autologous transplantation, immunotherapy, or other investigational agents. Pre-planned induction followed by transplant and maintenance was considered as one regimen
4. Presence of measurable disease as defined by at least one of the following:
    - Serum M-protein ≥ 1g/dL
    - Urine M-protein ≥ 200 mg/24 hours by protein electrophoresis

Exclusion Criteria:

1. Patients with non-secretory or oligosecretory multiple myeloma
2. Patients with symptomatic amyloidosis, or with plasma cell leukemia
3. Patients who had received allogeneic stem cell transplantation and who showed evidence of active graft versus host disease that required immunosuppressive therapy

Other inclusion/exclusion criteria defined in the study protocol were also applicable.

Participant Flow: Patient disposition by t(4;14) status (Full Analysis Set)

Disposition Reason	Positive N=13 n (%)	Negative N=26 n (%)	Non-interpretable N=4 n (%)	All patients N=43 n (%)
End of treatment (EOT) (dovitinib monotherapy)	13 (100.0)	26 (100.0)	4 (100.0)	43 (100.0)
EOT (dovitinib plus dexamethasone)	3 (23.1)	3 (11.5)	0	6 (14.0)
Primary reason for EOT (dovitinib monotherapy)				
Disease progression	7 (53.8)	20 (76.9)	0	27 (62.8)
Adverse event(s)	4 (30.8)	3 (11.5)	3 (75.0)	10 (23.3)
Subject withdrew consent	2 (15.4)	3 (11.5)	1 (25.0)	6 (14.0)
Primary reason for EOT (dovitinib plus dexamethasone)				
Disease progression	2 (15.4)	3 (11.5)	0	5 (11.6)
Adverse event(s)	1 (7.7)	0	0	1 (2.3)
Study evaluation after EOT				
Primary reason for study evaluation completion				
Disease progression	5 (38.5)	19 (73.1)	2 (50.0)	26 (60.5)
Subject withdrew consent	2 (15.4)	4 (15.4)	1 (25.0)	7 (16.3)
Death	4 (30.8)	2 (7.7)	0	6 (14.0)
New cancer therapy	1 (7.7)	1 (3.8)	1 (25.0)	3 (7.0)
Administrative problems	1 (7.7)	0	0	1 (2.3)

Baseline Characteristics: Demographics by t(4;14) status (Full Analysis Set)

Demographic	Variable	Positive N=13	Negative N=26	Non-interpretable N=4	All patients N=43
Age (years)	N	13	26	4	43
	Mean (SD)	60.5 (5.91)	63.0 (13.16)	54.0 (12.11)	61.4 (11.42)
	Median	61.0	67.0	55.0	63.0
	Min; Max	47.0; 69.0	29.0; 84.0	40.0; 66.0	29.0; 84.0
Sex, n (%)	Female	6 (46.2)	10 (38.5)	4 (100.0)	20 (46.5)
	Male	7 (53.8)	16 (61.5)	0	23 (53.5)
Race, n (%)	Caucasian	12 (92.3)	23 (88.5)	4 (100.0)	39 (90.7)
	Black	1 (7.7)	2 (7.7)	0	3 (7.0)
	Asian	0	1 (3.8)	0	1 (2.3)
Ethnicity, n (%)	Other	12 (92.3)	24 (92.3)	4 (100.0)	40 (93.0)
	Mixed Ethnicity	1 (7.7)	1 (3.8)	0	2 (4.7)
	Hispanic/Latino	0	1 (3.8)	0	1 (2.3)
WHO performance status n (%)	0	4 (30.8)	9 (34.6)	0	13 (30.2)
	1	8 (61.5)	15 (57.7)	2 (50.0)	25 (58.1)
	2	1 (7.7)	2 (7.7)	2 (50.0)	5 (11.6)

Outcome measures

Primary Outcome Results: Analysis of overall response by t(4;14) status by local review—dovitinib monotherapy (Full Analysis Set)

Extended overall response	Positive N=13 n (%)	Negative N=26 n (%)	Non-interpretable N=4 n (%)	All patients N=43 n (%)
Complete response (CR)	0	0	0	0
Very good partial response (VGPR)	0	0	0	0
Partial response (PR)	0	0	0	0
Minor response (MR)	0	0	0	0
Stable disease (SD)	8 (61.5)	9 (34.6)	3 (75.0)	20 (46.5)
Progressive disease (PD)	4 (30.8)	13 (50.0)	1 (25.0)	18 (41.9)
Not determined	1 (7.7)	4 (15.4)	0	5 (11.6)
Extended overall response rate (EORR)*	0	0	0	0
95% CI for EORR (%)	[0, 24.7]	[0, 13.2]	[0, 60.2]	[0, 8.2]
Overall response rate (ORR)**	0	0	0	0
95% CI for ORR (%)	[0, 24.7]	[0, 13.2]	[0, 60.2]	[0, 8.2]

*Extended ORR was defined as the proportion of patients with a best overall response of CR, VGPR, PR, or MR
**ORR was defined as the proportion of patients with a best overall response of CR, VGPR, or PR

Secondary Outcome Results

Analysis of progression-free survival per local investigator assessment using Kaplan-Meier method by t(4;14) status (Full Analysis Set)

	Positive N=13	Negative N=26
n (%)	8 (61.5)	20 (76.9)
Median progression-free survival (95% CI) months	2.6 [0.9,3.9]	0.9 [0.8,1.7]

n: Total number of events included in the analysis
N: Total number of patients included in the analysis

Dovitinib monotherapy trough plasma concentration by t(4;14) status (Pharmacokinetic Set)

		Patient group by t(4;14) status			
Visit Name	Statistics	Positive N=8	Negative N=15	Non-interpretable N=2	All patients N=25
Cycle 1 Day 26	n	6	13	2	21
	Mean (SD)	113.07 (73.160)	80.18 (65.462)	222.50 (146.371)	103.13 (82.324)
	CV%	64.7	81.6	65.8	79.8
	Geometric mean	94.60	62.32	196.96	79.25
	Geometric CV%	73.2	126.3	81.3	113.3
	Median	87.95	57.40	222.50	77.60
	Min-Max	46.0-222.0	0.0-210.0	119.0-326.0	0.0-326.0
Cycle 2 Day 26	n	3	5		8

Visit Name	Statistics	Patient group by t(4;14) status: Positive N=8	Negative N=15	Non-interpretable N=2	All patients N=25
	Mean (SD)	29.83 (27.308)	79.12 (33.982)		60.64 (39.033)
	CV%	91.5	42.9		64.4
	Geometric mean	22.46	71.30		46.24
	Geometric CV%	114.6	60.2		108.0
	Median	18.40	99.90		59.75
	Min-Max	10.1-61.0	29.2-108.0		10.1-108.0

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

Safety Results

Adverse events irrespective of causality with at least 10% incidence of any grade events by system organ class, maximum CTCAE grade and t(4;14) status—dovitinib monotherapy (Safety set)

	Positive N=13		Negative N=26		Non-interpretable N=4		All patients N=43	
Primary SOC	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)
Any primary SOC	**13 (100.0)**	**11 (84.6)**	**26 (100.0)**	**19 (73.1)**	**4 (100.0)**	**4 (100.0)**	**43 (100.0)**	**34 (79.1)**
Gastrointestinal disorders	12 (92.3)	5 (38.5)	24 (92.3)	9 (34.6)	4 (100.0)	0	40 (93.0)	14 (32.6)
General disorders and administration site conditions	7 (53.9)	3 (23.1)	16 (61.5)	5 (19.2)	2 (50.0)	1 (25.0)	25 (58.1)	9 (20.9)
Metabolism and nutrition disorders	5 (38.5)	4 (30.8)	15 (57.7)	9 (34.6)	2 (50.0)	1 (25.0)	22 (51.2)	14 (32.6)
Blood and lymphatic system disorders	7 (53.9)	5 (38.5)	11 (42.3)	9 (34.6)	2 (50.0)	2 (50.0)	20 (46.5)	16 (37.2)
Investigations	4 (30.8)	3 (23.1)	13 (50.0)	6 (23.1)	2 (50.0)	1 (25.0)	19 (44.2)	10 (23.3)
Musculoskeletal and connective tissue disorders	3 (23.1)	1 (7.7)	12 (46.2)	3 (11.5)	3 (75.0)	1 (25.0)	18 (41.9)	5 (11.6)
Nervous system disorders	6 (46.2)	1 (7.7)	9 (34.6)	2 (7.7)	1 (25.0)	0	16 (37.2)	3 (7.0)
Infections and infestations	4 (30.8)	3 (23.1)	8 (30.8)	4 (15.4)	3 (75.0)	2 (50.0)	15 (34.9)	9 (20.9)
Respiratory, thoracic and mediastinal disorders	4 (30.8)	1 (7.7)	7 (26.9)	2 (7.7)	1 (25.0)	0	12 (27.9)	3 (7.0)
Skin and subcutaneous tissue disorders	3 (23.1)	1 (7.7)	7 (26.9)	2 (7.7)	0	0	10 (23.3)	3 (7.0)
Vascular disorders	1 (7.7)	0	6 (23.1)	1 (3.9)	1 (25.0)	1 (25.0)	8 (18.6)	2 (4.7)
Psychiatric disorders	1 (7.7)	0	6 (23.1)	0	1 (25.0)	0	8 (18.6)	0

Eye disorders	1 (7.7)	0	4 (15.4)	0	2 (50.0)	0	7 (16.3)	0
Renal and urinary disorders	1 (7.7)	1 (7.7)	4 (15.4)	2 (7.7)	0	0	5 (11.6)	3 (7.0)

SOC: System organ class
A patient with multiple occurrences of an adverse event (AE) under one treatment was counted only once.
A patient with multiple AEs within a primary SOC was counted only once in the total row
AEs occurring more than 30 days after the last date of study treatment were not summarized
The event with maximum severity was counted for patients who experienced multiple episodes of an event
AEs were graded according to the CTCAE V4.0 unless specified otherwise in the study report and analysis plan

Adverse events irrespective of causality with at least 10% incidence for all patients by preferred term, maximum CTCAE grade and t(4;14) status—dovitinib monotherapy (Safety set)

	Positive N=13		Negative N=26		Non-interpretable N=4		All patients N=43	
Preferred Term	**Any grade n (%)**	**Grade 3/4 n (%)**	**Any grade n (%)**	**Grade 3/4 n (%)**	**Any grade n (%)**	**Grade 3/4 n (%)**	**Any grade n (%)**	**Grade 3/4 n (%)**
Total	13 (100.0)	11 (84.6)	26 (100.0)	19 (73.1)	4 (100.0)	4 (100.0)	43 (100.0)	34 (79.1)
Nausea	10 (76.9)	1 (7.7)	15 (57.7)	2 (7.7)	4 (100.0)	0	29 (67.4)	3 (7.0)
Diarrhoea	7 (53.9)	3 (23.1)	18 (69.2)	7 (26.9)	3 (75.0)	0	28 (65.1)	10 (23.3)
Vomiting	7 (53.9)	1 (7.7)	13 (50.0)	3 (11.5)	3 (75.0)	0	23 (53.5)	4 (9.3)
Fatigue	5 (38.5)	3 (23.1)	14 (53.9)	5 (19.2)	1 (25.0)	0	20 (46.5)	8 (18.6)
Thrombocytopenia	5 (38.5)	4 (30.8)	6 (23.1)	5 (19.2)	2 (50.0)	2 (50.0)	13 (30.2)	11 (25.6)
Anaemia	6 (46.2)	4 (30.8)	5 (19.2)	4 (15.4)	1 (25.0)	0	12 (27.9)	8 (18.6)
Decreased appetite	2 (15.4)	1 (7.7)	7 (26.9)	1 (3.9)	0	0	9 (20.9)	2 (4.7)
Dehydration	2 (15.4)	1 (7.7)	7 (26.9)	5 (19.2)	0	0	9 (20.9)	6 (14.0)
Pyrexia	2 (15.4)	0	4 (15.4)	0	2 (50.0)	1 (25.0)	8 (18.6)	1 (2.3)
Back Pain	1 (7.7)	0	5 (19.2)	1 (3.9)	1 (25.0)	0	7 (16.3)	1 (2.3)
Urinary tract infection	2 (15.4)	1 (7.7)	4 (15.4)	1 (3.9)	1 (25.0)	1 (25.0)	7 (16.3)	3 (7.0)
Headache	2 (15.4)	0	4 (15.4)	0	0	0	6 (14.0)	0
Neutropenia	3 (23.1)	3 (23.1)	3 (11.5)	2 (7.7)	0	0	6 (14.0)	5 (11.6)
Constipation	2 (15.4)	0	1 (3.9)	0	2 (50.0)	0	5 (11.6)	0
Dyspepsia	1 (7.7)	0	2 (7.7)	0	2 (50.0)	0	5 (11.6)	0
GGT increased	1 (7.7)	1 (7.7)	4 (15.4)	2 (7.7)	0	0	5 (11.6)	3 (7.0)

Preferred terms were sorted by descending frequency of 'all grades' in the specific treatment group
A patient with multiple occurrences of an AE under one treatment was counted only once in the AE category for that treatment
AEs occurring more than 30 days after the last date of study treatment were not summarized
The event with maximum severity was counted for patients who experienced multiple episodes of an event
AEs were graded according to the CTCAE V4.0 unless specified otherwise in the study report and analysis plan

Deaths on treatment by primary system organ class and preferred term—dovitinib monotherapy (Safety set)

Primary SOC Principal cause of death	Positive N=13 n (%)	Negative N=26 n (%)	All patients N=43 n (%)
Any primary SOC class	**2 (15.4)**	**2 (7.7)**	**4 (9.3)**
Cardiac disorders total	0	1 (3.8)	1 (2.3)
Cardio-respiratory arrest	0	1 (3.8)	1 (2.3)
Neoplasms benign, malignant and unspecified (Incl. cysts and polyps) total	2 (15.4)	1 (3.8)	3 (7.0)
Multiple myeloma	2 (15.4)	1 (3.8)	3 (7.0)

Primary SOCs are presented alphabetically; preferred terms were sorted within primary SOC
Only deaths occurring during treatment or within 30 days of the last date of study treatment were reported

Serious adverse events (at least 5%) irrespective of causality by preferred term—dovitinib monotherapy (Safety set)

	Positive N=13		Negative N=26		Non-interpretable N=4		All patients N=43	
Preferred Term	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)
Total	**4 (30.8)**	**4 (30.8)**	**11 (42.3)**	**11 (42.3)**	**4 (100.0)**	**4 (100.0)**	**19 (44.2)**	**19 (44.2)**
Dehydration	1 (7.7)	1 (7.7)	3 (11.5)	3 (11.5)	0	0	4 (9.3)	4 (9.3)
Diarrhoea	0	0	3 (11.5)	3 (11.5)	1 (25.0)	0	4 (9.3)	3 (7.0)
Renal failure acute	1 (7.7)	1 (7.7)	2 (7.7)	1 (3.9)	0	0	3 (7.0)	2 (4.7)
Vomiting	0	0	2 (7.7)	2 (7.7)	1 (25.0)	0	3 (7.0)	2 (4.7)
Confusional state	1 (7.7)	0	1 (3.9)	0	0	0	2 (4.7)	0
Fatigue	1 (7.7)	1 (7.7)	1 (3.9)	1 (3.9)	0	0	2 (4.7)	2 (4.7)
Febrile neutropenia	2 (15.4)	2 (15.4)	0	0	0	0	2 (4.7)	2 (4.7)
Hypercalcaemia	1 (7.7)	1 (7.7)	0	0	1 (25.0)	1 (25.0)	2 (4.7)	2 (4.7)
Nausea	0	0	1 (3.9)	1 (3.9)	1 (25.0)	0	2 (4.7)	1 (2.3)
Pneumonia	1 (7.7)	1 (7.7)	1 (3.9)	1 (3.9)	0	0	2 (4.7)	2 (4.7)
Sepsis	0	0	1 (3.9)	1 (3.9)	1 (25.0)	1 (25.0)	2 (4.7)	2 (4.7)
Thrombocytopenia	0	0	2 (7.7)	2 (7.7)	0	0	2 (4.7)	2 (4.7)

A patient with multiple occurrences of an serious adverse events (SAEs) was counted only once in the SAE category
AEs occurring more than 30 days after the last date of study treatment were not summarized
AEs were graded according to the CTCAE V4.0 unless specified otherwise in the study report and analysis plan

Adverse events leading to discontinuation irrespective of causality by preferred term—dovitinib monotherapy (Safety set)

	Positive N=13		Negative N=26		Non-interpretable N=4		All patients N=43	
Preferred Term	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)
Total	4 (30.8)	4 (30.8)	4 (15.4)	3 (11.5)	3 (75.0)	2 (50.0)	11 (25.6)	9 (20.9)
Diarrhoea	2 (15.4)	2 (15.4)	3 (11.5)	2 (7.7)	0	0	5 (11.6)	4 (9.3)
Vomiting	1 (7.7)	1 (7.7)	1 (3.9)	1 (3.9)	1 (25.0)	0	3 (7.0)	2 (4.7)
Fatigue	1 (7.7)	1 (7.7)	1 (3.9)	1 (3.9)	0	0	2 (4.7)	2 (4.7)
Bone marrow failure	0	0	1 (3.9)	1 (3.9)	0	0	1 (2.3)	1 (2.3)
Hepatic enzyme increased	0	0	0	0	1 (25.0)	1 (25.0)	1 (2.3)	1 (2.3)
Rash	0	0	1 (3.9)	1 (3.9)	0	0	1 (2.3)	1 (2.3)
Rash maculo-papular	0	0	1 (3.9)	1 (3.9)	0	0	1 (2.3)	1 (2.3)
Renal failure acute	1 (7.7)	1 (7.7)	0	0	0	0	1 (2.3)	1 (2.3)
Thrombocytopenia	0	0	0	0	1 (25.0)	1 (25.0)	1 (2.3)	1 (2.3)

Preferred terms were sorted by descending frequency
A patient with multiple occurrences of an AE was counted only once in the AE category
AEs occurring more than 30 days after the last date of study treatment were not summarized
AEs were graded according to the CTCAE V4.0

Other Relevant Findings

None

Date of Clinical Trial Report

24-May-2013

Date Inclusion on Novartis Clinical Trial Results Database

10-Jul-2013

Date of Latest Update