Sponsor

Novartis

Generic Drug Name

Dovitinib

Therapeutic Area of Trial

Locally advanced or metastatic melanoma

Approved Indication

Investigational

Study Number

CTKI258A2105

Title

A phase I/II dose escalating study to evaluate the safety, pharmacokinetics, pharmacodynamics, and efficacy of TKI258 (CHIR-258) in patients with locally advanced or metastatic melanoma

Phase of Development

Phase I/II

Study Start/End Dates

05 Apr 2006 to 28 Sep 2009

Study Design/Methodology

This was an open-label, single-arm, dose-escalating study designed to evaluate the safety, PK, PD, and preliminary efficacy of once daily, orally administered TKI258 in consecutive 28-day cycles in patients with locally advanced or metastatic melanoma that had relapsed or was refractory to standard therapy or for which no curative standard therapy existed.

Before protocol amendment 3, patients were enrolled in groups of 2 and individually assessed for safety and DLT. Dose assignment to receive escalating doses of TKI258 was made according to the continuous reassessment method (CRM). A total of 36 patients were expected to be enrolled. The starting dose was 200 mg orally daily. Following protocol amendment 3, a 2-parameter Bayesian logistic regression model using the Escalation With Overdose Control (EWOC) principle with dosing groups of at least 4 patients was used to guide the dose escalation and MTD determination in the dose escalation segment. Approximately 24 patients were expected to be enrolled in the dose escalation segment (including the patients who entered before protocol amendment 3). Once the MTD was determined, additional patients were enrolled into the dose expansion segment to further evaluate safety, tolerability, and efficacy. The dose

expansion dose level was chosen based on observed toxicities and PK/PD parameters that supported the likelihood of sustained biological activity. A 2-stage multinomial design was used during the dose expansion segment. Twenty patients were to be enrolled in stage 1, and if activity criteria were met, an additional 20 patients were to be enrolled in stage 2. A 2-day PK run-in was implemented in protocol amendment 3 to assist terminal half-life ($T_{1/2}$) estimation of TKI258. Patients who participated in the PK run-in received a single dose of TKI258 on day 1 of the run-in period and had a series of blood samples drawn for PK analysis on both day 1 and day 2. Following the PK run-in, patients received TKI258 on consecutive 28-day cycles via continuous, once daily dosing. Seven dose levels were initially considered in this study: 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, and 800 mg. Some dose levels could be skipped or additional dose levels added during the course of the study. The highest dose evaluated in the study was 500 mg. The MTD was defined to be the highest daily dose of TKI258 given to a minimum of 6 evaluable patients, which met the overdose criteria as described in the protocol. The final recommended dose was based on the MTD estimated by a Bayesian logistic regression model and PK and safety assessments.

Centres

USA (3 centers)

Publication

None

Objectives

Primary objective(s)

For dose escalation:

- To determine the maximum tolerated dose (MTD) based on dose-limiting toxicities (DLT) associated with TKI258
- To determine the pharmacokinetics (PK) of TKI258 administered orally (PO)

For dose expansion:

- To assess tumor response according to Response Evaluation Criteria in Solid Tumors (RECIST) as measured by response rate (RR) and lack of early progressive disease (≤ 2 months) in a multinomial 2-stage design

Secondary objective(s)

For escalation and expansion segments:

- To assess the safety profile of TKI258 in this patient population
- To assess preliminary antitumor activity (dose escalation segment)

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

TKI258 was provided as a capsule in 2 strengths: 25 mg and 100 mg. No patients received the 25 mg capsules. TKI258 was administered orally (at least 1 hour before a meal or at least 2 hours following a meal) during consecutive 28-day cycles via continuous, once daily dosing.

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

Not applicable

Criteria for Evaluation

Safety and tolerability

Safety variables: AEs, laboratory data (including hematology, clinical chemistry, coagulation and urinalyses), and other safety data (ie, LVEF by MUGA/ECHO scans and ECG). The assessment of safety was based primarily on the frequency of AEs and on the number of laboratory values that fell outside of predetermined ranges. Other safety data (ie, ECG, vital signs, and special tests) were considered as appropriate.

Pharmacokinetics

TKI258 blood concentrations and standard PK parameters were assessed

Efficacy

The primary variable for the dose-expansion segment was tumor response according to RECIST and lack of early disease progression (≤ 2 months).

Statistical Methods

The data was summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and PK measurements. Incidence of AEs and serious AEs (SAEs), including those that were dose limiting, were tabulated by dose group, system organ class, preferred term, and worst NCI CTCAE version 3 toxicity grade. Tumor response data during dose escalation was reported by descriptive statistics by dose cohort. A multinomial 2-stage design was used to evaluate efficacy during dose expansion. Standard PK parameters were calculated for TKI258 and summarized descriptively by dose group.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

- Diagnosis of histologically or cytologically documented, locally advanced or metastatic melanoma (American Joint Committee on Cancer stage IIIB, IIIC, or IV) relapsed or refractory to standard therapy or for which no curative standard therapy existed.
- For dose escalation segment patients: at least 1 measurable or nonmeasurable lesion as defined by RECIST; for dose expansion segment patients: at least 1 measurable lesion as defined by RECIST
- Patients had at least 1 measurable liver lesion ≥ 3 cm in diameter to be eligible for DCE-MRI. Patients with no liver involvement were not evaluated by DCE-MRI but were still eligible for study entry.
- Patients had at least 1 measurable lesion ≥ 2 cm in diameter, were able to lie down for ~ 1 hour and had a blood glucose level ≤ 180 mg/dL before [^{18}F] FDG PET imaging. Patients not meeting these criteria were not evaluated by PET imaging but were still eligible for study entry.
- Age at least 18 years
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- All adults of reproductive potential were required to use effective contraception or to be sterile. A negative pregnancy test (serum) within 48 hours before the start of study treatment was required for women of child-bearing potential.
- Required baseline laboratory data included:
  - Absolute neutrophil count (ANC): ≥ 1500/mm^3 (SI units 1.5 x 10^9/L)
  - Platelets: ≥ 75000/mm^3 (SI units 75 x 10^9/L)
  - Hemoglobin: ≥ 8 g/dL (SI units 80 g/L)
  - Serum creatinine: ≤ 1.5 x upper limit of normal (ULN)
  - Bilirubin: ≤ 1.5 x ULN
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT): ≤ 2.5 x ULN;
  - AST and ALT ≤ 5 x ULN in patients with tumor involvement of the liver
  - Amylase, lipase: ≤ ULN
  - Electrolyte levels: ≥ lower limit of normal (LLN) or correctable with supplements (ie,

potassium, total calcium, magnesium, and phosphorus)

- Urine dipstick reading: negative for proteinuria or, if documentation of +1 results for protein on dipstick reading, then total urinary protein ≤ 500 mg and measured creatinine clearance ≥ 50 mL/min/1.73m^2 from a 24-hour urine collection.

Exclusion Criteria:

- Concurrent therapy with any other investigational agent
- Known uncontrolled central nervous system (CNS) metastases
- Impaired cardiac function or clinically significant cardiac disease, including any one of the following:
  - Left ventricular ejection fraction (LVEF) < 45%
  - 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
  - Clinically significant bradycardia (< 50 bpm)
  - QTc > 480 msec on screening electrocardiogram (ECG)
  - Right bundle branch block + left anterior hemiblock (bifasicular block)
  - Angina pectoris ≤ 3 months before starting study drug
  - Acute myocardial infarction (MI) ≤ 3 months before starting study drug
  - Other clinically significant heart disease (eg, congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)
- Concurrent treatment with any of the medications that have a relative risk of prolonging the QT interval or inducing Torsades de Pointes and the treatment cannot be discontinued or switched to a different medication before starting the study drug.
- Received chemotherapy, targeted therapy or monoclonal antibody therapy ≤ 4 weeks before starting study drug (6 weeks in the case of nitrosoureas and mitomycin C) or had not recovered from the side effects of such therapy.
- Received biological therapy or immunotherapy (therapeutic or diagnostic) ≤ 2 weeks before starting study drug or had not recovered from the side effects of such therapy.
- Received an investigational agent (therapeutic or diagnostic) ≤ 4 weeks before starting study drug or had not recovered from the side effects of such therapy.
- Received wide-field radiotherapy ≤ 4 weeks or limited-field radiation for palliation ≤ 2 weeks before starting study drug or had not recovered from side effects of such therapy.
- Received any hematopoietic colony-stimulating factor (eg, granulocyte-colony stimulating factor [G-CSF]) ≤ 2 weeks before starting study drug. Erythropoietin was allowed.
- Had undergone major surgery ≤ 2 weeks before starting study drug or had not recovered from side effects of such surgery.

- Malabsorption syndrome or uncontrolled gastrointestinal toxicities (eg, nausea, diarrhea, vomiting) with toxicity greater than the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade 2.
- Pregnant or breastfeeding women.
- History of another primary malignancy that was clinically significant or required active intervention.
- Chronic anticoagulation therapy with full strength aspirin, coumadin, or heparin (low dose aspirin ≤ 81 mg or low dose coumadin ≤ 1 mg to maintain indwelling venous access device patency was allowed).
- History of thromboembolic or cerebrovascular events within 12 months of study entry,
- History of melena, hematemesis, or hemoptysis within 3 months before study enrollment.
- Known diagnosis of human immunodeficiency virus (HIV) infection
- Severe, acute, or chronic medical or psychiatric condition or laboratory abnormality
- The use of ketoconazole, erythromycin, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's wort, and quinidine was prohibited.
- Patients with any of the following contraindications were excluded from magnetic resonance imaging (MRI) scans:
  - Cardiac pacemaker
  - Ferromagnetic metal implants other than those approved as safe for use in the MRI
  - scanner (eg, some types of aneurysm clips or shrapnel)
  - Claustrophobia
  - Obesity (exceeding the equipment limits)

Number of Subjects

Patient disposition by treatment dose (FAS)

Number (%) of patients	200-300 mg n=4	400 mg n=36	500 mg n=7	All N=47
Completed cycle 1	4 (100.0%)	22 (61.1%)	7 (100.0%)	33 (70.2%)
Main reason for discontinuation, n (%)				
Death	0 (0.0%)	1 (2.8%)	0 (0.0%)	1 (2.1%)
AE(s)	0 (0.0%)	6 (16.7%)	1 (14.3%)	7 (14.9%)
Disease progression	4 (100.0%)	26 (72.2%)	6 (85.7%)	36 (76.6%)
Lost to follow-up	0 (0.0%)	1 (2.8%)	0 (0.0%)	1 (2.1%)
Protocol deviation	0 (0.0%)	1 (2.8%)	0 (0.0%)	1 (2.1%)
Subject withdrew consent	0 (0.0%)	1 (2.8%)	0 (0.0%)	1 (2.1%)

AE-adverse event; FAS-full analysis set.

Demographic and Background Characteristics

Demographic summary by treatment group (FAS)

		200-300 mg n=4	400 mg n=36	500 mg n=7	All N=47
Age (years)	Mean	52.0	55.5	59.7	55.9
	Standard deviation	8.98	14.55	12.89	13.85
Age group, n (%)	< 65 years	3 (75.0%)	25 (69.4%)	4 (57.1%)	32 (68.1%)
	≥ 65 years	1 (25.0%)	11 (30.6%)	3 (42.9%)	15 (31.9%)
Gender, n (%)	Male	2 (50.0%)	19 (52.8%)	4 (57.1%)	25 (53.2%)
	Female	2 (50.0%)	17 (47.2%)	3 (42.9%)	22 (46.8%)
Race, n (%)	Caucasian	4 (100.0%)	36 (100.0%)	7 (100.0%)	47 (100.0%)
Weight (kg)	n	3	32	6	41
	Mean	90.7	88.7	75.1	86.9
	Standard deviation	14.05	21.44	17.01	20.66
Height (cm)	Mean	172.5	172.2	172.4	172.3
	Standard deviation	7.51	10.99	11.94	10.68
Body mass index (kg/m^2)	n	3	32	6	41
	Mean	31.1	29.7	25.8	29.2
	Standard deviation	4.32	5.68	5.15	5.61
ECOG score, n (%)	0	1 (25.0%)	19 (52.8%)	2 (28.6%)	22 (46.8%)
	1	3 (75.0%)	17 (47.2%)	5 (71.4%)	25 (53.2%)

ECOG, Eastern Cooperative Oncology Group.

Primary Objective Result(s)

DLTs by TKI258 dose level in cycle 1 (dose-determining set)

	200-300mg n=4	400 mg n=10	500 mg n=7	All N=21
Experienced DLT, n (%)				
Any DLT event	0 (0%)	3 (30%)	3 (42.9%)	6 (28.6%)
Fatigue grade 3	0 (0%)	2 (20.0%)	1 (14.3%)	3 (14.3%)
Diarrhea grade 3	0 (0%)	0 (0%)	1 (14.3%)	1 (4.8%)
Fatigue grade 4	0 (0%)	0 (0%)	1 (14.3%)	1 (4.8%)
Nausea grade 3	0 (0%)	1 (10.0%)	0 (0.0%)	1 (4.8%)

DLT, dose-limiting toxicity.

Following the recommendation of the Bayesian logistic regression model and clinical review of the safety data, 400 mg was declared as the MTD and the dose expansion portion of the trial opened at that dose and enrolled 20 patients in stage 1.

Pharmacokinetics

PK analysis showed TKI258 exposure increased exponentially with daily dosing with doses ranging from 200 to 500 mg. At doses of 400 mg and below, time-dependent PK resulted in lower or similar exposure at steady state compared to Cycle 1 day 1. At 500 mg, potential inhibitory/saturable metabolism could occur, resulting in a higher exposure, longer $T_{1/2}$, and lower clearance.

Summary of primary PK parameters for TKI258 during PK run-in (PK set)

Dose (mg)	Cycle	Day	Statistics	AUC_{0-inf} (ng/mL*h)	AUC_{0-t} (ng/mL*h)	C_{max} (ng/mL)	T_{max} (h)
400	PK run-in	1	n	30	30	30	30
			Mean (standard deviation)	6295.50 (1845.212)	5286.35 (1519.132)	215.20 (62.141)	
			CV% mean	29.31	28.74	28.88	
			Geo-mean	6031.60	5073.55	207.25	
			CV% geo-mean	30.92	30.23	28.14	
			Median	6095.12	5251.21	200.50	6.03
			[Min; Max]	[3217.77; 10957.75]	[2774.79; 8812.03]	[126.00; 391.00]	[4.00; 24.00]

Note: CV% mean = coefficient of variation (%) = standard deviation/mean*100.

CV% geo-mean = sqrt(exp(variance for log transformed data) -1)*100.

AUC_{0-inf}, area under the curve from time zero to infinity AUC_{0-t}, area under the concentration-time curve from time zero to t; C_{max}, maximum concentration; CV%, coefficient of variation; PK, pharmacokinetics; T_{max}, time to maximum concentration.

Secondary Objective Result(s)

Safety Results

Number of patients with most frequent (≥10%) AEs regardless of study drug relationship by preferred term (safety set)

Preferred term	200-300 mg n=4 n (%)	400 mg n=36 n (%)	500 mg n=7 n (%)	All N=47 N (%)
Any preferred term	4 (100.0)	36 (100.0)	7 (100.0)	47 (100.0)
Diarrhea	3 (75.0)	28 (77.8)	5 (71.4)	36 (76.6)
Fatigue	3 (75.0)	27 (75.0)	6 (85.7)	36 (76.6)
Nausea	2 (50.0)	27 (75.0)	7 (100.0)	36 (76.6)
Vomiting	1 (25.0)	16 (44.4)	5 (71.4)	22 (46.8)
Weight decreased	0 (0.0)	13 (36.1)	4 (57.1)	17 (36.2)
Anorexia	1 (25.0)	13 (36.1)	2 (28.6)	16 (34.0)
Abdominal pain upper	1 (25.0)	11 (30.6)	0 (0.0)	12 (25.5)
Dysgeusia	0 (0.0)	11 (30.6)	1 (14.3)	12 (25.5)
Rash	1 (25.0)	9 (25.0)	2 (28.6)	12 (25.5)
Dyspnea	1 (25.0)	8 (22.2)	2 (28.6)	11 (23.4)
Dehydration	0 (0.0)	8 (22.2)	2 (28.6)	10 (21.3)
Back pain	0 (0.0)	6 (16.7)	3 (42.9)	9 (19.1)
Dizziness	0 (0.0)	8 (22.2)	1 (14.3)	9 (19.1)
Dry mouth	0 (0.0)	6 (16.7)	2 (28.6)	8 (17.0)
Urinary tract infection	1 (25.0)	6 (16.7)	1 (14.3)	8 (17.0)
Constipation	0 (0.0)	4 (11.1)	3 (42.9)	7 (14.9)
Dyspepsia	0 (0.0)	6 (16.7)	1 (14.3)	7 (14.9)
Pyrexia	1 (25.0)	6 (16.7)	0 (0.0)	7 (14.9)
Cough	1 (25.0)	5 (13.9)	0 (0.0)	6 (12.8)
Headache	0 (0.0)	5 (13.9)	1 (14.3)	6 (12.8)
Abdominal pain	0 (0.0)	4 (11.1)	1 (14.3)	5 (10.6)
Hypertriglyceridemia	0 (0.0)	5 (13.9)	0 (0.0)	5 (10.6)
Myalgia	0 (0.0)	3 (8.3)	2 (28.6)	5 (10.6)
Tachycardia	0 (0.0)	4 (11.1)	1 (14.3)	5 (10.6)

AE, adverse event.

Diarrhea, fatigue, and nausea were also the most common AEs assessed by the investigator as suspected to be study drug-related.

Efficacy Results

Based on RECIST criteria, stable disease (≥ 2 months) was observed in 12 of 47 patients (25.5%). No PRs or CRs were observed. The dose expansion segment was completed at the end of stage 1 due to meeting the futility criteria.

Best clinical overall response by treatment (FAS)

	200-300 mg n=4 n (%)	400 mg n=36 n (%)	500 mg n=7 n (%)	All N=47 N (%)
Best overall response				
CR	0	0	0	0
PR	0	0	0	0
SD	1 (25.0)	10 (27.8)	1 (14.3)	12 (25.5)
Progressive disease	3 (75.0)	16 (44.4)	6 (85.7)	25 (53.2)
Unknown	0	1 (2.8)	0	1 (2.1)
Not assessed	0	9 (25.0)	0	9 (19.1)
Overall response (CR or PR)	0	0	0	0
Disease control (CR, PR, or SD)	1 (25.0)	10 (27.8)	1 (14.3)	12 (25.5)
Stable disease (SD) ≥ 2 month	1 (25.0)	10 (27.8)	1 (14.3)	12 (25.5)
Stable disease (SD) ≥ 4 month	1 (25.0)	5 (13.9)	1 (14.3)	7 (14.9)

- Best overall response was calculated based on all overall lesion investigator responses (discontinuation due to PD was also counted as a response).
- 'Unknown' was assigned when the best response could not be classified as CR, PR, SD or disease progression.
- 'Not assessed' was assigned when there was no response assessment for the patient.
-CR, complete response; FAS, full analysis set; PR, partial response; SD, stable disease.

Summary of survival outcome by treatment (FAS)

	200-300 mg n=4	400 mg n=36	500 mg n=7	All N=47
Progression free survival (PFS)				
Number of events, n (%)	4 (100.0)	28 (77.8)	7 (100.0)	39 (83.0)
Median (months)[a]	2.73	2.33	2.04	2.04
Minimum (months)	1.38	0.03	1.15	0.03
Maximum (months)	9.03	11.10	5.75	11.10
95% CI[a]	(1.38, 9.03)	(1.87, 3.71)	(1.15, 4.11)	(1.87, 3.68)
Overall survival				
Number of events, n (%)	4 (100.0)	29 (80.6)	6 (85.7)	39 (83.0)
Median (months)[a]	5.36	8.20	4.40	7.49
Minimum (months)	3.29	1.61	2.79	1.61
Maximum (months)	39.26	19.68	25.40	39.26
95% CI[a]	(3.29, 39.26)	(4.30, 9.56)	(2.79, 9.99)	(4.30, 9.23)

[a]From Kaplan-Meier analysis.
CI, confidence interval; FAS, full analysis set; PFS, progression-free survival.

Serious Adverse Events and Deaths

Number of patients who died or experienced other serious or clinically significant adverse events (safety set)

	200-300 mg n=4	400 mg n=36	500 mg n=7	All N=47
Total number who died, had SAE(s) or clinically significant AE(s)	1 (25.0%)	31 (86.1%)	7 (100.0%)	39 (83.0%)
Death[a]	0 (0.0%)	1 (2.8%)	1 (14.3%)	2 (4.3%)
SAE(s)	**1 (25.0%)**	**16 (44.4%)**	**5 (71.4%)**	**22 (46.8%)**
Clinically significant AE(s)	0 (0.0%)	29 (80.6%)	7 (100.0%)	36 (76.6%)
Discontinuation due to[b]				
Death	0 (0.0%)	1 (2.8%)	0 (0.0%)	1 (2.1%)
SAE	0 (0.0%)	3 (8.3%)	0 (0.0%)	3 (6.4%)
Clinically significant AE	0 (0.0%)	6 (16.7%)	1 (14.3%)	7 (14.9%)

[a]Includes deaths that occurred while patient was receiving study drug or within 28 days after last dose of study drug.

[b]Discontinuation due to SAE(s) and discontinuation due to clinically significant AE(s) are not mutually exclusive and the same patient may be counted in both categories.

AE, adverse event; SAE, serious adverse event.

The cause of death in the 400 mg group was hemorrhage related to metastatic malignant melanoma and in 500 mg group was metastatic malignant melanoma. None of the deaths were suspected to be related to study drug.

SAEs

SAEs related to study medication occurred in 7 patients in the 400 mg group (dehydration, pancreatitis, thrombocytopenia, herpes zoster ophthalmic, diarrhea, eyelid ptosis, acne cystitis, and aortic thrombosis), and 3 patients in the 500 mg group (dehydration, hypertension, peripheral neuropathy). One patient discontinued treatment due to a study drug-related SAE (grade 2 pancreatitis).

Other Relevant Findings None
Date of Clinical Trial Report 23 Mar 2011
Date Inclusion on Novartis Clinical Trial Results Database 9 May 2011
Date of Latest Update