Full Novartis CTRD Results Template

Sponsor

Novartis

Generic Drug Name

Dovitinib

Therapeutic Area of Trial

Breast Cancer

Approved Indication

Investigational

Protocol Number

CTKI258A2202

Title

A multi-center, open label Phase II trial of TKI258 in FGFR1 amplified and non-amplified metastatic HER2 negative breast cancer

Phase of Development

Phase II

Study Start/End Dates

29-Jul-2009 to 02-Mar-2011

Study Design/Methodology

Multicenter, open label, two-stage designed phase II trial to determine the overall response rate (ORR) as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) by a panel of external radiologist (central review) in four groups of patients with metastatic Human Epidermal Growth Factor Receptor 2 negative (HER2–) breast cancer (BC): (Fibroblast Growth Factor Receptor 1 [FGFR1+], Hormones Receptors positive [HR+]) (Group 1), FGFR1+/ HR− (Group 2), FGFR1−/ HR+ (Group 3) and FGFR1−/ HR− (Group 4). Patients were allocated to groups based on their FGFR1 and HR status. A complete treatment cycle was arbitrarily defined as 28 days (4 weeks) for the purposes of scheduling procedures and evaluations. TKI258 was given on days 1-5, 8-12, 15-19, 22-26 (5 days on/2 days off) of each cycle. The first administration of TKI258 was defined as Day 1 of the cycle. The last day of a complete cycle was Day 28. Patients were treated until disease progression.

A two-stage design was used and a total of 20 patients in each group (total 80 patients) were

planned at stage-1. In each group separately, if at least 2 patients met the criteria for the trial (confirmed CR or PR) in stage-1, the trial was to continue to stage-2.

Centres

49 centers in 8 countries: Canada (2 sites), France (4 sites), Italy (6 sites), Spain (3 sites), USA (26 sites), UK (5 sites), Finland (1 site) and Taiwan (2 sites)

Publication

None

Outcome measures

Primary outcome measures(s)

- Overall Response Rate (confirmed complete response (CR) or partial response (PR) defined according to RECIST) as per central radiological assessment

Secondary outcome measures(s)

- Disease control Rate (DCR) according to RECIST
- Progression-Free Survival (PFS)
- Safety and tolerability of TKI258 treatment assessed by frequency and severity of Adverse Events
- Drug plasma concentrations and PK parameters (e.g. Cmax, Tmax, AUC0-t)

The specific key measure(s) or observation(s) will be used to determine the effect of the intervention(s).

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

Daily oral dose of 500 mg of TKI258 for 5 consecutive days, followed by a 2-days rest period

Statistical Methods

Efficacy:

The primary analysis of ORR was performed on primary endpoint analysis set (PEAS) and full analysis set (FAS). Patients with 'Unknown' best overall response were treated as non-responders in the calculation of the ORR in the FAS. Overall response was summarized in terms of counts of patients who had confirmed CR or PR and the associated percentage of patients in FAS and PEAS. The best overall response (BOR) and the ORR (confirmed CR and PR) along with the Clopper-Pearson 95% confidence intervals were summarized for each FGFR1 amplification and HR status group in FAS and PEAS. In each group separately, an initial 20 patients with measurable disease at baseline were to be assessed at the end of stage-1. If at least 2 patients were responders (confirmed CR or PR assessed by the investigator) from stage-1, the study was to continue to enroll additional 20 patients with measurable disease at baseline, in stage-2. The Kaplan-Meier product-limit method was used to estimate the distribution of PFS in each FGFR1 amplification and HR status group. The median, 25^{th} and 75^{th} percentiles along with 95% confidence intervals, were calculated using the method of Brookmeyer and Crowley.

Kaplan-Meier survival curves were also presented. DCR was summarized along with the Clopper-Pearson (95% confidence intervals by FGFR1 amplification and HR status group. All efficacy analyses were performed for central review and local review. A non-protocol planned assessment (adjudication) was also performed by an independent radiologist to adjudicate discrepant efficacy assessments in a blinded fashion. This process included adjudication of disease measurability at baseline, best response and progression status, to either the local assessment or the central assessment. In addition, exploratory efficacy analyses for HR+ patients only by FGF-pathway amplification status were performed.

Safety:
The assessment of safety was mainly based on the frequency of AEs and on the number of laboratory values that fell outside of pre-determined ranges. All safety outputs used the safety set. Although the study safety follow-up was 28 days after last dose, the safety analyses reported assessments collected up to 30 days after study treatment discontinuation. AEs were summarized by presenting the number and percentage of patients having at least one AE, and having at least one AE in each body system/primary system organ class (SOC) and for each preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) coding.

Study Population: Inclusion/Exclusion Criteria and Demographics

Female patients were included in the trial if ≥ 18 years of age and had histological confirmation of adenocarcinoma of the breast, presenting with locally advanced and/or metastatic disease; the primary tumor, metastatic axillary lymph nodes or biopsy of any metastatic tumor tested by Fluorescence/Chromogenic/Silver in situ Hybridization (FISH/CISH/SISH) for FGFR1 amplification before study entry; HER2 and HR (ER/PgR) status of BC was previously determined; HER2− BC; documented disease progression as defined by RECIST at baseline; at least one measurable lesion as defined by RECIST and HR+ disease received at least one prior endocrine therapy in the metastatic setting and received no more than three lines of chemotherapy in the metastatic setting.

Female patients were excluded from the study if they had brain metastases as assessed by radiologic imaging (e.g. CT, MRI) at the baseline screening visit; history of another malignancy within the last five years prior to study entry; received a continuous dosing small molecule therapeutic ≤ 7 days prior to starting study drug or who had not recovered from the side effects of such therapy; received the last administration of biologic therapy (e.g. antibodies) ≤ 6 weeks prior to starting study drug or who had not recovered from the side effects of such therapy; received any other investigational agents/radiotherapy ≤ 4 weeks prior to start of study or undergone major surgery ≤ 4 weeks prior to start of study.

Participant Flow

Disposition Reason	FGFR1+/HR+ N=23 n (%)	FGFR1+/HR- N=2 n (%)	FGFR1-/HR+ N=34 n (%)	FGFR1-/HR- N=22 n (%)	All Patients N=81 n (%)
Patients treated					
End of treatment	23 (100.0)	2 (100.0)	34 (100.0)	22 (100.0)	81 (100.0)
Primary reason for end of treatment					
Adverse event(s)	7 (30.4)	0	8 (23.5)	7 (31.8)	22 (27.2)
Death	0	0	1 (2.9)	2 (9.1)	3 (3.7)
Disease progression	12 (52.2)	2 (100.0)	20 (58.8)	13 (59.1)	47 (58.0)
Subject withdrew consent	4 (17.4)	0	5 (14.7)	0	9 (11.1)
Study evaluation after end of treatment					
Patients no longer being followed for study evaluation	23 (100.0)	2 (100.0)	34 (100.0)	22 (100.0)	81 (100.0)
Primary reason for study evaluation completion					
Administrative problems	0	0	1 (2.9)	1 (4.5)	2 (2.5)
Death	2 (8.7)	0	1 (2.9)	6 (27.3)	9 (11.1)
Disease progression	9 (39.1)	1 (50.0)	12 (35.3)	6 (27.3)	28 (34.6)
F/u phase completed as per protocol.	8 (34.8)	1 (50.0)	14 (41.2)	7 (31.8)	30 (37.0)
New cancer therapy	0	0	0	1 (4.5)	1 (1.2)
Subject withdrew consent	4 (17.4)	0	6 (17.6)	1 (4.5)	11 (13.6)

Baseline Characteristics

Demographic Variable	FGFR1+/HR+ N=23	FGFR1+/HR- N=2	FGFR1-/HR+ N=34	FGFR1-/HR- N=22	All Patients N=81
Age (years)					
n	23	2	34	22	81
Median	56.0	55.5	55.0	59.5	56.0
Min	25.0	51.0	32.0	37.0	25.0
Max	72.0	60.0	78.0	78.0	78.0
Age category (years), n (%)					
≥ 65 years	2 (8.7)	0	10 (29 4)	5 (22.7)	17 (21.0)
WHO performance status, n (%)					
0	13 (56.5)	2 (100.0)	20 (58.8)	15 (68.2)	50 (61.7)
1	10 (43.5)	0	14 (41.2)	6 (27.3)	30 (37.0)
2	0	0	0	1 (4.5)	1 (1.2)
Race, n (%)					
Caucasian	18 (78.3)	2 (100.0)	25 (73.5)	20 (90.9)	65 (80.2)

Other	5 (21.7)	0	9 (26.5)	2 (9.1)	16 (19.8)

Outcome measures

Primary Outcome Result(s) (as per central radiological assessment)

	FGFR1+/HR+ N=20 n (%)	FGFR1+/HR- N=2 n (%)	FGFR1-/HR+ N=28 n (%)	FGFR1-/HR- N=18 n (%)	All Patients N=68 n (%)
Best overall response					
Complete response (CR)	0	0	0	0	0
Partial response (PR)	0	0	0	0	0
Stable disease (SD)	13 (65.0)#	0	13 (46.4)	5 (27.8)	31 (45.6)
Progressive disease (PD)	4 (20.0)	2 (100.0)	8 (28.6)	5 (27.8)	19 (27.9)
Unknown	3 (15.0)	0	7 (25.0)	8 (44.4)	18 (26.5)
Overall response rate (ORR) (CR or PR)	0	0	0	0	0
95% CI for ORR (%)	[0.0, 16.8]	[0.0, 84.2]	[0.0, 12.3]	[0.0, 18.5]	[0.0, 5.3]

- # Two patients achieved unconfirmed PR.
- N: The total number of patients in the treatment group. It is the denominator for percentage (%) calculation.
- n: Number of patients who are at the corresponding category.
- The 95% CI for the frequency distribution of each variable were computed using Clopper-Pearson method.
- Only patients who had measurable disease at baseline per central radiology review are included.

Secondary Outcome Result(s)

Disease Control Rate (DCR) (as per central radiological assessment)

	FGFR1+/HR+ N=20 n (%)	FGFR1+/HR- N=2 n (%)	FGFR1-/HR+ N=28 n (%)	FGFR1-/HR- N=18 n (%)	All Patients N=68 n (%)
Disease control rate (DCR) (CR, PR or SD)	2 (10.0)*	0	0	2 (11.1)¥	4 (5.9)
95% CI for DCR (%)	[1.2, 31.7]	[0.0, 84.2]	[0.0, 12.3]	[1.4, 34.7]	[1.6, 14.4]
Stable disease ≥ 2 months	13 (65.0)	0	13 (46.4)	5 (27.8)	31 (45.6)
Stable disease ≥ 4 months	8 (40.0)	0	8 (28 6)	2 (11.1)	18 (26.5)

* Two patients achieved SD >= 24 weeks after start of TKI258 treatment.
¥ Two patients achieved SD >= 24 weeks after start of TKI258 treatment

- N: The total number of patients in the treatment group. It is the denominator for percentage (%) calculation.
- n: Number of patients who are at the corresponding category.
- The 95% CI for the frequency distribution of each variable were computed using Clopper-Pearson method.
- DCR is defined as CR+PR+SD (SD>=24 weeks after start of TKI258 treatment).
- A 2-week window is applied to SD duration for DCR calculation (SD >= 24 weeks after start of TKI258 treatment), SD >= 2 months and SD >= 4 months.
- Only patients who had measurable disease at baseline per central radiology review are included.

Progression-free survival (PFS) (as per central radiological assessment)

	FGFR1+/HR+ N=23	FGFR1+/HR- N=2	FGFR1-/HR+ N=34	FGFR1-/HR- N=22	All Patients N=81
n (%)	11 (47.8)	2 (100.0)	15 (44.1)	12 (54.5)	40 (49.4)
Median time to censoring (months)	1.79		1.77	0.80	1.77
Percentiles [95% CI] (months)					
75%	4.3 [3.7,5.5]	1.9 [1.7,1.9]	3.8 [3.6,]	6.6 [2.1,9.2]	4.3 [3.7,9.2]
median	3.7 [1.8,5.5]	1.8 [1.7,1.9]	3.6 [1.8,3.8]	2.1 [1.6,6.6]	3.6 [1.9,3.7]
25%	1.8 [0.9,3.7]	1.7 [1.7,1.9]	1.7 [1.2,2.8]	1.7 [0.9,2.1]	1.7 [1.5,1.8]
% Event-free probability estimate [95% C.I]:					
6 months	0.0[,]	0.0[,]	[,]	30.5 [8.8,56.0]	15.9 [5.0,32.3]
12 months	0.0[,]	0.0[,]	[,]	0.0[,]	0.0[,]

- N : Total number of subjects included in the analysis.
- n : Total number of PFS events included in the analysis.
- Greenwood formula is used for CIs of KM estimates.
- % Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point.
- Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

Safety Results

This data can be taken from the NLM ClinicalTrials.gov results record, if available, or from the final CSR.

Note: The AE tables in the NLM ClincalTrials.gov results records differ in the way data is presented due to NLM requirements. NLM has 2 separate AE tables: one is non-serious AEs only; the second is serious AEs only.

Drug-Related Adverse Events by System Organ Class

	FGFR1+/HR+ N=23 n (%)	FGFR1+/HR- N=2 n (%)	FGFR1-/HR+ N=34 n (%)	FGFR1-/HR- N=22 n (%)	All Patients N=81 n (%)
-Any primary system organ class	23 (100.0)	2 (100.0)	33 (97.1)	21 (95.5)	79 (97.5)
Gastrointestinal disorders	22 (95.7)	2 (100.0)	31 (91.2)	19 (86.4)	74 (91.4)
General disorders and administration site conditions	18 (78.3)	2 (100.0)	27 (79.4)	16 (72.7)	63 (77.8)
Nervous system disorders	13 (56.5)	1 (50.0)	13 (38.2)	9 (40.9)	36 (44.4)
Investigations	11 (47.8)	0 (0.0)	15 (44.1)	8 (36.4)	34 (42.0)
Skin and subcutaneous tissue disorders	14 (60.9)	2 (100.0)	12 (35.3)	4 (18.2)	32 (39.5)
Blood and lymphatic system disorders	7 (30.4)	0 (0.0)	6 (17.6)	4 (18.2)	17 (21.0)
Respiratory, thoracic and mediastinal disorders	4 (17.4)	0 (0.0)	7 (20.6)	5 (2.7)	16 (19.8)
Eye disorders	7 (30.4)	0 (0.0)	5 (14.7)	2 (9.1)	14 (17.3)
Musculoskeletal and connective tissue disorders	4 (17.4)	0 (0.0)	7 (20.6)	3 (13.6)	14 (17.3)
Ear and labyrinth disorders	3 (13.0)	0 (0.0)	6 (17.6)	1 (4.5)	10 (12.3)
Hepatobiliary disorders	3 (13.0)	0 (0.0)	6 (17.6)	0 (0.0)	9 (11.1)
Infections and infestations	3 (13.0)	0 (0.0)	2 (5.9)	3 (13.6)	8 (9.9)
Psychiatric disorders	2 (8.7)	0 (0.0)	4 (11.8)	0 (0.0)	6 (7.4)
Cardiac disorders	0 (0.0)	0 (0.0)	2 (5.9)	3 (13.6)	5 (6.2)
Endocrine disorders	1 (4.3)	0 (0.0)	1 (2.9)	0 (0.0)	2 (2.5)
Renal and urinary disorders	0 (0.0)	0 (0.0)	1 (2.9)	1 (4.5)	2 (2.5)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)	1 (1.2)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.2)
Metabolism and nutrition disorders	8 (34.8)	1 (50.0)	16 (47.1)	6 (27.3)	31 (8.3)

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

Preferred Term	FGFR1+/HR+ (N=23)	FGFR1+/HR- (N=2)	FGFR1-/HR+ (N=34)	FGFR1-/HR- (N=22)	All (N=81)
Total	23 (100)	2 (100)	34 (100)	22 (100)	81 (100)
Vomiting	20 (87.0)	1 (50.0)	27 (79.4)	15 (68.2)	63 (77.8)
Diarrhoea	21 (91.3)	2 (100)	24 (70.6)	15 (68.2)	62 (76.5)
Asthenia	14 (60.9)	1 (50.0)	27 (79.4)	13 (59.1)	55 (67.9)
Nausea	15 (65.2)	2 (100)	25 (73.5)	13 (59.1)	55 (67.9)
Decreased appetite	8 (34.8)	1 (50.0)	16 (47.1)	6 (27.3)	31 (38.3)
Headache	11 (47.8)	1 (50.0)	8 (23.5)	7 (31.8)	27 (33.3)
Dry mouth	9 (39.1)	0	10 (29.4)	4 (18.2)	23 (28.4)
Fatigue	9 (39.1)	1 (50.0)	5 (14.7)	6 (27.3)	21 (25.9)
Dyspnoea	4 (17.4)	0	8 (23.5)	7 (31.8)	19 (23.5)
Abdominal pain	6 (26.1)	0	9 (26.5)	2 (9.1)	17 (21.0)

Serious Adverse Events and Deaths (regardless of study drug relationship)

SAEs

Preferred term	FGFR1+/HR+ N=23 n (%)	FGFR1-/HR+ N=34 n (%)	FGFR1-/HR- N=22 n (%)	All Patients N=81 n (%)
Any serious adverse events	9 (39.1)	14 (41.2)	7 (31.8)	30 (37.0)
Asthenia	2 (8.7)	2 (5.9)	1 (4.5)	5 (6.2)
Dyspnoea	1 (4.3)	2 (5.9)	2 (9.1)	5 (6.2)
Blood alkaline phosphatase increased	1 (4.3)	2 (5.9)	0	3 (3.7)
Vomiting	1 (4.3)	2 (5.9)	0	3 (3.7)
Dehydration	1 (4.3)	0	1 (4.5)	2 (2.5)
Gamma-glutamyltransferase increased	1 (4.3)	1 (2.9)	0	2 (2.5)
General physical health deterioration	0	1 (2.9)	1 (4.5)	2 (2.5)
Muscular weakness	0	1 (2.9)	1 (4.5)	2 (2.5)
Pulmonary embolism	2 (8.7)	0	0	2 (2.5)
Pyrexia	1 (4.3)	1 (2.9)	0	2 (2.5)
Renal failure	0	1 (2.9)	1 (4.5)	2 (2.5)

A patient with multiple occurrences of an SAE is counted only once in the SAE category.
Adverse events occurring more than 30 days after the last date of study treatment are not summarized.
2% cuf-off is based on all patient group.
Total rows reflect all patient experiences not just those printed.

Deaths

	FGFR1+/HR+ N=23	FGFR1-/HR+ N=34	FGFR1-/HR- N=22	All Patients N=81

	n (%)	n (%)	n (%)	n (%)
Total number of on- treatment deaths				
Study indication	1 (4.3)	1 (2.9)	1 (4.5)	3 (3.7)
Other	1 (4.3)	0	4 (18.2)	5 (6.2)
Any preferred term/principle cause of death (n)				
Cholestatic liver injury	1	0	0	1
Coma	0	0	1	1
Disease progression	0	0	1	1
Dyspnoea	0	0	1	1
Listeriosis	0	0	1	1
Study indication/Not coded	1	0	0	1
Pleural haemorrhage	0	0	1	1
Respiratory distress	0	1	0	1

No patient died during therapy in the FGFR1-/HR- group
Principal cause of death are presented in descending order of frequency in the all patients group.
AE preferred terms are sorted within principal cause also by descending frequency in the all patients group.
On-treatment deaths are deaths which occurred up to 30 days after the last date of study treatment.

Date of Clinical Trial Report

23 Feb 2012

Date Inclusion on Novartis Clinical Trial Results Database

27 Feb 2012

Date of Latest Update