Sponsor

Novartis

Generic Drug Name

TKI258

Therapeutic Area of Trial

Urothelial carcinoma

Approved Indication

Investigational

Protocol Number

CTKI258A2201

Title

A Phase II, multi-center, non-randomized, open-label study of TKI258 in patients with either fibroblast growth factor receptor 3 (FGFR3) mutated or FGFR3 wild-type advanced urothelial carcinoma

Study Phase

Phase II

Study Start/End Dates

31 Mar 2010 to 04 Apr 2012

In each group, the number of responders failed to meet the criteria for study continuation to stage 2, i.e., at least two responders out of 20 patients from stage 1. Since most patients in the FGFR3 mutated group did not receive >6 months of treatment and meeting the response threshold to proceed to stage 2 was highly unlikely, the study was terminated.

Study Design/Methodology

This was an open-label, multi-center, non-randomized, Phase II study. Simon's two-stage design was conducted in each group (the FGFR3-mutated and FGFR3-wild-type group) independently. Based on the two-stage design, 20 patients were planned to be enrolled for stage 1 and an additional 20 patients for stage 2, if at least two responders were observed at stage 1 (according to pre-specified study design criteria). In this study, all patients were treated with daily oral dose of 500 mg of TKI258 for 5 consecutive days, followed by a 2-day rest period. Patients were continued on study treatment until disease progression occurred or unacceptable toxicity developed.

Centres

20 enrolling centers in eight countries: Austria (1), Italy (1), Germany (2), Spain (5), United Kingdom

(2), Taiwan (1), Canada (1), United States (7)

Publication

None

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

TKI258 was supplied as 100 mg hard gelatin capsules. All patients were treated with daily oral dose of 500 mg of TKI258 for 5 consecutive days, followed by a 2-day rest period in two groups of patients $FGFR3^{MUT}$ and $FGFR3^{WT}$.

Statistical Methods

The full analysis set (FAS) consisted of all patients who received at least one dose of TKI258. All efficacy endpoints were analyzed using FAS.

The primary efficacy variable, overall response rate (ORR) was summarized in terms of counts of patients who had a best overall response of CR or PR and the associated percentage of patients in FAS. The best overall response was derived based on investigator reported lesion responses at different evaluation time points, defined according to RECIST 1.0. Both CR and PR required confirmation at least 4 weeks after its initial observation. The ORR (CR+PR) along with the exact binomial 95% confidence intervals were summarized for each FGFR3 mutation status group in FAS. Waterfall plot was used to display the best percentage change from baseline in the sum of the longest diameter of all target lesions as per local investigator for each patient.

The secondary efficacy variable, ORR was derived as per central radiological review and was summarized using RECIST 1.0 criteria along with the exact binomial 95% confidence intervals for each FGFR3 mutation status group.

The progression free survival (PFS) analysis was performed based on Investigator assessments, and sensitivity analysis was performed using central review assessments on FAS. The Kaplan-Meier estimates of PFS at 2, 4, and 8 months was summarized by FGFR3 mutation status group. The median PFS along with 95% confidence intervals, 25th and 75th percentiles was calculated. Kaplan-Meier plots were also presented by FGFR3 mutation status group.

Overall survival data were listed by FGFR3 mutation status group. DCR was assessed by the local Investigator using RECIST 1.0 and was summarized along with the exact binomial 95% CIs by FGFR3 mutation status group.

The Safety set consisted of all patients who had received at least one dose of TKI258. All safety data were analyzed using the safety set.

Per protocol, sites were required to collect safety data for at least 28 days after the date of last study treatment. The safety summary tables included only assessments collected no later than 30 days after study treatment discontinuation. All safety assessments were listed and those collected later than 30 days after study treatment discontinuation were flagged in the listings. The severity of AEs was assessed according to the CTCAE Version 4.0. Adverse events were summarized by primary system organ class, preferred term, and maximum CTCAE grade for all patients and for each FGFR3 mutation status group.

No formal interim analysis was planned. However, the two-stage sequential design of this study had a decision time point to either stop or initiate stage 2 within each stratum.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

Patients who met the following criteria were eligible:

- Patients with histological confirmation of transitional cell carcinoma (TCC) of the bladder, urethra, ureter, or renal pelvis (locally advanced and/or metastatic)
- Archival tumor tissue available for Novartis designated FGFR3 mutational status analysis
- Patients with progressive disease at baseline: progressive disease defined as new or progressive lesions on cross-sectional imaging
- Patients with at least one measurable site of disease as defined by RECIST 1.0 criteria that has not been previously irradiated
- Previously treated with, at least one but no more than three systemic cytotoxic regimens, with at least one of these regimens including at least one of the following: cisplatin, carboplatin, gemcitabine or taxane, administered in the perioperative or advanced setting and may have been administered sequentially (e.g., first-line treatment followed by second-line treatment at time of progression) or as part of a single regimen
- Age $\geq$ 18 years
- World Health Organization (WHO) Performance Status (PS) $\leq$ 2
- Willing and able to take oral medication, comply with scheduled visits, treatment plan, and laboratory tests
- Signed and witnessed informed consent form obtained prior to any screening procedures
- Required baseline laboratory values:
  - Absolute neutrophil count (ANC) $\geq$ 1500 cells/mm^3 (SI units 1.5 x 10^9/L)
  - Platelets $\geq$ 100,000 cells/mm^3 [SI units 100 x 10^9/L]
  - Hemoglobin $\geq$ 9.0 g/dL [SI units 90 g/L]
  - Aspartate aminotransferase/ serum glutamic oxaloacetic transaminase (AST/SGOT) and alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT) $\leq$3.0 x Upper Limit of Normal [ULN] (with or without liver metastases)

    Note: As per the original protocol, the patients with AST/SGOT and ALT/SGPT $\leq$ 5 x ULN were also to be included if abnormal liver function was due to tumor involvement of the liver but this criteria was later removed after protocol amendment 4.
  - Bilirubin $\leq$ 1.5 x ULN
  - Serum creatinine $\leq$ 1.5 x ULN

    Note: As per the original protocol, the patients with electrolyte values (potassium, sodium, calcium, magnesium, and phosphorus) within normal limits were to be included, but this criterion was later removed after protocol amendment 1.

Exclusion criteria

Patients who met the following criteria were ineligible:

- Patients with known brain metastases or who had signs/symptoms attributable to brain metastases and had not been assessed with radiologic imaging to rule out the presence of brain metastases
- History of another malignancy within the last 3 years prior to study entry, with the exception of adequately treated basal cell carcinoma, squamous cell carcinoma or non-melanomatous skin cancer, excised carcinoma in situ of the cervix, or adenocarcinoma of the prostate that has been surgically treated with a post-treatment PSA that is non-detectable

  Note: This criterion of history of another malignancy was changed from the last 5 years to the last 3 years after protocol amendment 1
- Patients who had received the last administration of chemotherapy, immunotherapy, hormonal therapy, and targeted therapy but excluding: nitrosourea, mitomycin-C, monoclonal antibodies, and radiation ≤ 14 days prior to starting study drug, or who had not recovered from side effects of such therapy
- Patients who had received the last administration of nitrosourea or mitomycin-C ≤ 6 weeks prior to starting study drug, or who have not recovered from the side effects of such therapy
- Patients who received the last administration of an anti-cancer monoclonal antibody ≤ 4 weeks prior to starting study drug, or who had not recovered from the side effects of such therapy

  Note: This criterion of the last administration of an anti-cancer monoclonal antibody was changed from 6 weeks to 4 weeks after protocol amendment 1.
- Patients who had received wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting study drug, or who had not recovered from the side effects of such therapy
- Patients who had undergone major surgery ≤ 2 weeks prior to starting study drug, or who had not recovered from the side effects of such therapy
- Impaired cardiac function or clinically significant cardiac diseases, including:
  - serious uncontrolled ventricular arrhythmias or presence of serious uncontrolled atrial fibrillation
  - clinically significant resting bradycardia
  - left ventricular ejection fraction (LVEF) assessed by 2-D echocardiogram (ECHO) <50% or lower limit of normal (whichever was higher) or multiple gated acquisition scan (MUGA), <45% or lower limit of normal (whichever was higher)

    Note: As per the original protocol, LVEF, assessed by ECHO or MUGA, <45%. This criterion was revised to LVEF assessed by ECHO <50% or lower limit of normal (whichever was higher) or MUGA <45% or lower limit of normal (whichever was higher) after protocol amendment 4.
  - Any of the following within 6 months prior to study entry: myocardial infarction (MI), severe/unstable angina, Coronary Artery Bypass Graft (CABG), Congestive Heart Failure (CHF), Cerebrovascular Accident (CVA), Transient Ischemic Attack (TIA), Pulmonary Embolism (PE)

- Uncontrolled hypertension defined by a systolic blood pressure (SBP) ≥ 160 mm Hg and/or diastolic blood pressure (DBP) ≥ 100 mm Hg, with or without anti-hypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to study entry
- Previous pericarditis; clinically significant pleural effusion in the previous 12 months or current ascites requiring two or more interventions/month
- Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of TKI258
- Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing was not mandatory)
- History of alcoholism, drug addiction, or any psychiatric or psychological condition which would impair study compliance
- Patients who were currently receiving anticoagulation treatment with therapeutic doses of warfarin or have an INR >1.5

  Note: This criterion of INR was added after protocol amendment 1.
- Uncontrolled diarrhea ≥ Common Terminology Criteria for Adverse Events (CTCAE) grade 2
- Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g., active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol
- Pregnant or breast-feeding women
- Cirrhosis, chronic active hepatitis or chronic persistent hepatitis

  Note: The patients with cirrhosis, chronic active hepatitis or chronic persistent hepatitis were added to exclusion criteria after protocol amendment 4.
- Fertile males not willing to use a highly effective method of contraception
- Women of child-bearing potential, who were biologically able to conceive, and not employing two forms of highly effective contraception. Highly effective contraception (e.g., male condom with spermicide, diaphragm with spermicide, intra-uterine device) was to be used by both sexes during the study and was to be continued for 8 weeks after the end of study treatment

  Note: This criterion of duration of contraception usage was changed from one month to 8 weeks after protocol amendment 1.

Participant Flow

Patient disposition by FGFR3 mutation status group (Full Analysis Set)

Disposition Reason	FGFR3-Mutated N=12 n (%)	FGFR3 Wild-Type N=31 n (%)	All Patients N=44 n (%)
Patients treated			
End of treatment	12 (100.0)	31 (100.0)	44 (100.0)
Primary reason for end of treatment			
Abnormal laboratory value(s)	1 (8.3)	0	1 (2.3)
Adverse event(s)	2 (16.7)	10 (32.3)	12 (27.3)
Death	0	4 (12.9)	4 (9.1)
Disease progression	8 (66.7)	13 (41.9)	21 (47.7)
Investigators decision in the patients best interest	0	1 (3.2)	1 (2.3)
Subject withdrew consent	1 (8.3)	3 (9.7)	5 (11.4)
Study evaluation after end of treatment			
Patients no longer being followed for post-treatment follow-up	12 (100.0)	31 (100.0)	44 (100.0)
Primary reason for study evaluation completion			
Death	4 (33.3)	8 (25.8)	12 (27.3)
Disease progression	5 (41.7)	8 (25.8)	14 (31.8)
New cancer therapy	2 (16.7)	1 (3.2)	3 (6.8)
Subject withdrew consent	1 (8.3)	4 (12.9)	5 (11.4)

Note: For study evaluation after end of treatment, only efficacy follow-up is considered as post-treatment follow-up.

One patient with unknown mutation status is included in “All Patients” group.

Baseline Characteristics

Demographics by FGFR3 mutation status group (Full Analysis Set)

Demographic variable	FGFR3-Mutated N=12	FGFR3 Wild-Type N=31	All Patients N=44
Age (years)			
N	12	31	44
Mean	66.0	65.0	65.5
SDEV	8.16	9.17	8.89
Median	67.0	67.0	67.0
Minimum	53.0	46.0	46.0
Maximum	77.0	81.0	81.0

WHO performance status			
0	8 (66.7%)	11 (35.5%)	19 (43.2%)
1	3 (25.0%)	15 (48.4%)	19 (43.2%)
2	1 (8.3%)	5 (16.1%)	6 (13.6%)
Sex			
Female	3 (25.0%)	8 (25.8%)	11 (25.0%)
Male	9 (75.0%)	23 (74.2%)	33 (75.0%)

Note: One patient with unknown mutation status is included in 'All Patients' group.

Disease characteristics at baseline by FGFR3 mutation status group (Full Analysis Set)

	FGFR3-Mutated N=12 n (%)	FGFR3 Wild-Type N=31 n (%)	All Patients N=44 n (%)
Metastatic site of cancer			
Bladder	1 (8.3)	2 (6.5)	3 (6.8)
Bone	1 (8.3)	10 (32.3)	12 (27.3)
Liver	3 (25.0)	10 (32.3)	13 (29.5)
Lung	6 (50.0)	15 (48.4)	21 (47.7)
Lymph Nodes	8 (66.7)	14 (45.2)	23 (52.3)
Other	7 (58.3)	18 (58.1)	26 (59.1)
Pleural/Peritoneum	1 (8.3)	5 (16.1)	6 (13.6)
Number of organs involved			
1	3 (25.0)	7 (22.6)	10 (22.7)
2	4 (33.3)	12 (38.7)	16 (36.4)
≥3	5 (41.7)	12 (38.7)	18 (40.9)
Histologic grade			
Well differentiated	2 (16.7)	2 (6.5)	4 (9.1)
Moderately differentiated	1 (8.3)	1 (3.2)	2 (4.5)
Poorly differentiated	8 (66.7)	24 (77.4)	33 (75.0)
Unknown	1 (8.3)	4 (12.9)	5 (11.4)

Note: One patient with unknown mutation status is included in 'All Patients' group.

Outcome measures

Primary Outcome Result(s)

Analysis of best overall response as per investigator review by FGFR3 mutation status group (FAS*)

	FGFR3-Mutated N=12 n (%)	FGFR3 Wild-Type N=31 n (%)
Best overall response		
Complete Response (CR)	0	0
Partial Response (PR)	0	1 (3.2)
Stable Disease (SD)	5 (41.7)	10 (32.3)
Progressive Disease	5 (41.7)	12 (38.7)
Unknown (UNK)	2 (16.7)	8 (25.8)
Overall Response Rate (ORR)	0	1 (3.2)
95% CI for ORR[1]	[0.0, 26.5]	[0.1, 16.7]
Disease Control Rate (DCR)[#]	3 (25.0)	8 (25.8)
95% CI for DCR[1]	[5.5, 57.2]	[11.9, 44.6]

[#] DCR is defined as the proportion of patients with a best overall response of CR or PR or a response of SD lasting for at least 16 weeks (SD ≥ 16 weeks after start of TKI258 treatment)

1=Exact Binomial 95% confidence interval.

-* FAS * is based on patients assigned a mutation status; one patient with unknown status is not presented.

Secondary Outcome Result(s)

Analysis of best overall response as per central radiology review by FGFR3 mutation status group (FAS*)

	FGFR3-Mutated N=12 n (%)	FGFR3 Wild-Type N=31 n (%)
Best overall response		
Complete Response (CR)	0	0
Partial Response (PR)	1 (8.3)	0
Stable Disease (SD)	3 (25.0)	12 (38.7)
Progressive Disease	6 (50.0)	9 (29.0)
Unknown (UNK)	2 (16.7)	10 (32.3)
Overall Response Rate (ORR)	1 (8.3)	0
95% CI for ORR[1]	[0.2, 38.5]	[0.0, 11.2]
Disease Control Rate (DCR)[#]	2 (16.7)	9 (29.0)
95% CI for DCR[1]	[2.1, 48.4]	[14.2, 48.0]

[#] DCR is defined as the proportion of patients with a best overall response of CR or PR or a response of SD lasting for at least 16 weeks (SD ≥ 16 weeks after start of TKI258 treatment)

1=Exact Binomial 95% confidence interval.

-* FAS * is based on patients assigned a mutation status; one patient with unknown status is not presented.

Analysis of progression free survival as per investigator review using Kaplan-Meier method by FGFR3 mutation status group (FAS*)

	FGFR3-Mutated N=12	FGFR3 Wild-Type N=31
n (%)	10 (83.3)	26 (83.9)
Median PFS (95% CI)	3.0 [1.6,3.6]	1.8 [1.6,3.2]
% PFS probability estimate [95% CI]:		
2 months	63.6 [29.7,84.5]	46.2 [27.2,63.2]
4 months	21.2 [3.3,49.3]	15.4 [4.9,31.3]
8 months	10.6 [0.6,37.3]	5.1 [0.4,20.1]

n : Total number of events included in the analysis

N : Total number of subjects included in the analysis

* FAS * is based on patients assigned a mutation status; one patient with unknown status is not presented.

Safety Results

Most commonly occurring AEs (at least 10%), regardless of study drug relationship by primary system organ class, preferred term, maximum CTCAE grade and FGFR3 mutation status group (Safety Set)

	FGFR3-Mutated N=12			FGFR3 Wild-Type N=31			All Patients N=44		
Primary System Organ Class Preferred Term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Any primary system organ class	12 (100)	5 (41.7)	2 (16.7)	31 (100)	22 (71.0)	5 (16.1)	44 (100)	27 (61.4)	7 (15.9)
Blood And Lymphatic System Disorders	1 (8.3)	1 (8.3)	0	13 (41.9)	4 (12.9)	3 (9.7)	14 (31.8)	5 (11.4)	3 (6.8)
Anaemia	0	0	0	9 (29.0)	2 (6.5)	0	9 (20.5)	2 (4.5)	0
Thrombocytopenia	1 (8.3)	1 (8.3)	0	7 (22.6)	2 (6.5)	1 (3.2)	8 (18.2)	3 (6.8)	1 (2.3)
Gastrointestinal Disorders	11 (91.7)	1 (8.3)	0	27 (87.1)	8 (25.8)	0	39 (88.6)	9 (20.5)	0
Diarrhoea	9 (75.0)	0	0	22 (71.0)	3 (9.7)	0	32 (72.7)	3 (6.8)	0
Nausea	7 (58.3)	0	0	19 (61.3)	1 (3.2)	0	27 (61.4)	1 (2.3)	0
Vomiting	5 (41.7)	0	0	13 (41.9)	1 (3.2)	0	18 (40.9)	1 (2.3)	0
Constipation	3 (25.0)	0	0	7 (22.6)	1 (3.2)	0	11 (25.0)	1 (2.3)	0
Abdominal Pain	3 (25.0)	1 (8.3)	0	6 (19.4)	1 (3.2)	0	9 (20.5)	2 (4.5)	0

Dyspepsia	1 (8.3)	0	0	4 (12.9)	0	0	5 (11.4)	0	0
General Disorders And Administration Site Conditions	10 (83.3)	3 (25.0)	0	29 (93.5)	10 (32.3)	0	40 (90.9)	13 (29.5)	0
Asthenia	5 (41.7)	1 (8.3)	0	16 (51.6)	5 (16.1)	0	22 (50.0)	6 (13.6)	0
Fatigue	4 (33.3)	1 (8.3)	0	14 (45.2)	3 (9.7)	0	18 (40.9)	4 (9.1)	0
Oedema Peripheral	2 (16.7)	0	0	8 (25.8)	0	0	10 (22.7)	0	0
Pyrexia	4 (33.3)	1 (8.3)	0	6 (19.4)	0	0	10 (22.7)	1 (2.3)	0
Infections And Infestations	6 (50.0)	1 (8.3)	0	13 (41.9)	6 (19.4)	1 (3.2)	20 (45.5)	7 (15.9)	1 (2.3)
Urinary Tract Infection	5 (41.7)	1 (8.3)	0	6 (19.4)	3 (9.7)	0	11 (25.0)	4 (9.1)	0
Investigations	4 (33.3)	0	1 (8.3)	15 (48.4)	9 (29.0)	1 (3.2)	19 (43.2)	9 (20.5)	2 (4.5)
Blood Alkaline Phosphatase Increased	0	0	0	10 (32.3)	6 (19.4)	0	10 (22.7)	6 (13.6)	0
Alanine Aminotransferase Increased	1 (8.3)	0	1 (8.3)	7 (22.6)	1 (3.2)	0	8 (18.2)	1 (2.3)	1 (2.3)
Aspartate Aminotransferase Increased	1 (8.3)	0	1 (8.3)	4 (12.9)	1 (3.2)	0	5 (11.4)	1 (2.3)	1 (2.3)
Weight Decreased	1 (8.3)	0	0	4 (12.9)	1 (3.2)	0	5 (11.4)	1 (2.3)	0
Metabolism And Nutrition Disorders	6 (50.0)	1 (8.3)	1 (8.3)	20 (64.5)	9 (29.0)	0	26 (59.1)	10 (22.7)	1 (2.3)
Decreased Appetite	4 (33.3)	0	0	14 (45.2)	1 (3.2)	0	18 (40.9)	1 (2.3)	0
Dehydration	2 (16.7)	0	0	7 (22.6)	4 (12.9)	0	9 (20.5)	4 (9.1)	0
Musculoskeletal And Connective Tissue Disorders	6 (50.0)	1 (8.3)	0	11 (35.5)	3 (9.7)	0	18 (40.9)	4 (9.1)	0
Back Pain	2 (16.7)	0	0	4 (12.9)	0	0	7 (15.9)	0	0
Nervous System Disorders	6 (50.0)	0	0	13 (41.9)	3 (9.7)	0	20 (45.5)	3 (6.8)	0
Dysgeusia	2 (16.7)	0	0	3 (9.7)	0	0	5 (11.4)	0	0
Respiratory, Thoracic And Mediastinal Disorders	4 (33.3)	0	0	13 (41.9)	2 (6.5)	0	18 (40.9)	2 (4.5)	0
Dyspnoea	2 (16.7)	0	0	7 (22.6)	2 (6.5)	0	10 (22.7)	2 (4.5)	0
Cough	3 (25.0)	0	0	4 (12.9)	0	0	7 (15.9)	0	0

Skin And Subcutaneous Tissue Disorders	6 (50.0)	1(8.3)	0	11 (35.5)	1 (3.2)	0	17 (38.6)	2 (4.5)	0
Rash	4 (33.3)	1(8.3)	0	7 (22.6)	1 (3.2)	0	11 (25.0)	2 (4.5)	0
Vascular Disorders	2 (16.7)	1(8.3)	0	8 (25.8)	1 (3.2)	0	10 (22.7)	2 (4.5)	0
Hypertension	1 (8.3)	0	0	5 (16.1)	0	0	6 (13.6)	0	0

Note: One patient with unknown mutation status is included in “All Patients” group.
10% cut-off is based on all grade column under 'All Patients' group of preferred terms

Serious Adverse Events and Deaths

Most commonly occurring serious adverse events (at least 5%), regardless of study drug relationship by primary system organ class, preferred term, maximum CTCAE grade and FGFR3 mutation status group (Safety Set)

	FGFR3-Mutated N=12			FGFR3 Wild-Type N=31			All Patients N=44		
Primary System Organ Class Preferred Term	**All grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**All grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**All grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Any primary system organ class	5 (41.7)	4 (33.3)	0	20 (64.5)	18 (58.1)	2 (6.5)	25 (56.8)	22 (50.0)	2(4.5)
Gastrointestinal Disorders	2 (16.7)	1 (8.3)	0	7 (22.6)	6 (19.4)	0	9 (20.5)	7 (15.9)	0
Diarrhoea	0	0	0	3 (9.7)	1 (3.2)	0	3 (6.8)	1 (2.3)	0
Vomiting	0	0	0	3 (9.7)	1 (3.2)	0	3 (6.8)	1 (2.3)	0
General Disorders And Administration Site Conditions	2 (16.7)	1 (8.3)	0	5 (16.1)	3 (9.7)	0	7 (15.9)	4 (9.1)	0
Asthenia	1 (8.3)	1 (8.3)	0	2 (6.5)	0	0	3 (6.8)	1 (2.3)	0
Infections And Infestations	1 (8.3)	1 (8.3)	0	6 (19.4)	5 (16.1)	1 (3.2)	7 (15.9)	6 (13.6)	1(2.3)
Urinary Tract Infection	1 (8.3)	1 (8.3)	0)	2 (6.5)	2 (6.5)	0	3 (6.8)	3 (6.8)	0
Metabolism And Nutrition Disorders	2 (16.7)	1 (8.3)	0	4 (12.9)	4 (12.9)	0	6 (13.6)	5 (11.4)	0
Dehydration	1 (8.3)	0	0)	4 (12.9)	3 (9.7)	0	5 (11.4)	3 (6.8)	0

One patient with unknown mutation status is included in “All Patients” group.
A 5% cut-off is based on all grade column under “All Patients” group of preferred terms.

On-treatment deaths by primary system organ class, preferred term and FGFR3 mutation status group (Safety Set)

Primary system organ class Preferred term	FGFR3-Mutated N=12 n (%)	FGFR3 Wild-Type N=31 n (%)	All Patients N=44 n (%)
Total number of on-treatment deaths	1 (8.3)	7 (22.6)	8 (18.2)
Study indication	1 (8.3)	5 (16.1)	6 (13.6)
Other	0	2 (6.5)	2 (4.5)
-Any primary system organ class			
-Total	1 (8.3)	7 (22.6)	8 (18.2)
Infections and infestations			
-Total	0	1 (3.2)	1 (2.3)
Sepsis	0	1 (3.2)	1 (2.3)
Neoplasms benign, malignant and unspecified (Incl cysts and polyps)			
-Total	1 (8.3)	6 (19.4)	7 (15.9)
Metastases to central nervous system	0	1 (3.2)	1 (2.3)
Transitional cell carcinoma	1 (8.3)	5 (16.1)	6 (13.6)

- On-treatment deaths are deaths which occurred up to 30 days after the last date of study treatment.
- One patient with unknown mutation status is included in “All Patients” group.

Other Relevant Findings

None

Date of Clinical Trial Report

26-Mar-2013

Date Inclusion on Novartis Clinical Trial Results Database

28-Mar-2013

Date of Latest Update