Sponsor

Novartis

Generic Drug Name

Vadimezan (ASA404)

Therapeutic Area of Trial

Advanced cancer

Approved Indication

Investigational

Study Number

CASA404A2112

Title

A multi-center, open-label, dose-escalation study in patients with advanced cancer to determine the effect of the ASA404 infusion rate and co-administration with the paclitaxel plus carboplatin regimen or docetaxel on the pharmacokinetics of free and total ASA404.

Phase of Development

Phase I

Study Start/End Dates

Study initiation date: 13 Oct 2009 (first patient first visit)

Early termination date: 07 Nov 2010

Study completion date: 01 Dec 2010 (last patient last visit)

Study Design/Methodology

This was a multi-center, open-label, dose-escalation study to determine the effect of the ASA404 infusion rate and co-administering ASA404 with the paclitaxel + carboplatin chemotherapy regimen or docetaxel on the pharmacokinetics (PK) of the free and total ASA404.

The study consisted of two phases, a core phase and an extension phase. Cycles 1 to 3 comprised the core phase and cycles 4 to 12 in extension phase. Cycle 1 was 7-14 days in duration, while all other cycles were 21 days in length.

Treatment arm 1:

- ASA404 (1800 or 2400 mg/m^2) + paclitaxel (200 mg/m^2) + carboplatin (AUC 6)

Treatment arm 2:

- ASA404 (1200, 1800,or 2400 mg/m^2) + docetaxel (75 mg/m^2)

Centers

4 sites in Belgium

Publication

None

Objectives

Primary objective(s)

- To determine the effect of infusion rate on the pharmacokinetics of ASA404 and the QTcF interval in the presence of chemotherapy at each dose level within each treatment arm.
- To determine the effect of infusion rate on the pharmacokinetics of ASA404 and QTcF interval in absence of chemotherapy at each dose level within each treatment arm.
- To determine the effect of co-administering taxane-based chemotherapy (paclitaxel + carboplatin regimen or docetaxel) on the pharmacokinetics of ASA404 administered over 20 minute or 60 minute intravenous infusion at each dose level within each treatment arm.

Secondary objective(s)

- To assess the safety of ASA404 administered at different infusion rates with and without taxanes.

Test Products, Doses, and Mode of Administration

ASA404 1200 mg/m^2 and 1800 mg/m^2 were administered over 20-minute or 60 minute intravenous infusion.

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

Paclitaxel (200 mg/m^2) + Carboplatin (AUC 6)

Docetaxel (75 mg/m^2)

Criteria for Evaluation

Primary variables

Plasma concentrations of free and total ASA404 were measured in all patients during the core phase using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantification (LLOQ) of approximately 100 ng/mL for the total ASA404 and 2.00 ng/mL for the free ASA404 concentrations in human plasma samples. Plasma protein binding of ASA404 was determined in all patients prior to study drug administration.

The criteria used when evaluating ECGs for QTcF prolongation are presented below

National Cancer Institute Prolonged QTc Clinical Terminology Criteria for Adverse Events

QTc Prolongation Grade	Definition
I	QTc > 450-470 msec
II	QTc > 470-500 msec or > 60 msec above cycle baseline
III	QTc > 500 msec
IV	QTc > 500 msec; life-threatening signs or symptoms (i.e., arrhythmia, CHF, hypotension, shock, syncope, TdP)
V	Death

Secondary variables

Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of hematology, blood chemistry, electrocardiogram (ECG), urinalysis, and regular assessments of vital signs, physical condition and body weight. The assessment of safety was based mainly on the frequency of adverse events and on the number of abnormal laboratory values that were new or worsening based upon the common terminology criteria for adverse events (CTCAE v3.0).

Safety and tolerability

Described as Secondary variables

Pharmacology

Not applicable

Others

Biomarker Studies: Due to premature study termination, biomarkers including pharmacogenetic markers (genotypes) were not assayed. Therefore, no analyses of biomarkers were conduct-

ed and no data was reported.

Statistical Methods

The primary variables were related to PK of free and total ASA404. Due to premature study termination, the PK parameters for free or total ASA404 were not calculated and no statistical analyses were reported. Descriptive statistics for raw QTcF and QTcF change from baseline were tabulated by time point, ASA404 dose level, treatment regimen (with or without chemotherapy), and infusion rate. Triplicate ECGs were taken at Day 1 of Cycle 1 prior to ASA404 infusion. The baseline value was defined as the average of the pre-drug ECGs performed on Day 1 of Cycle 1.

All adverse events (AEs) recorded during the study were listed by assigned treatment arm and ASA404 dose level. The incidence (number and percentage) of all the treatment emergent adverse events (TEAEs) were tabulated by system organ class, preferred term, ASA404 dose level and infusion rate. All laboratory values were converted into SI units and classified by severity grades using CTCAE version 3.0. Individual data listings by assigned treatment arm and ASA404 dose level was provided for the vital sign parameters with the values below/above the normal range flagged. Individual data listings by assigned treatment arm and ASA404 dose level were provided for the ECG parameters with out-of-range and notable values flagged.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Patients with histologically-proven and radiologically-confirmed solid tumors for whom treatment with an investigational agent in combination with the paclitaxel + carboplatin chemotherapy regimen or docetaxel was appropriate.
- Age ≥ 18 years.
- WHO Performance Status (PS) of 0 to 2.
- Laboratory values within the range, as defined below, within 2 weeks of starting study drug:
  - Absolute neutrophil count (ANC) ≥ 2.0 x 109/L
  - Platelets ≥ 100 x 109/L
  - Hemoglobin ≥ 10 g/dL
  - Creatinine clearance according to Cockcroft-Gault formula ≥ 60 mL/minute for patients receiving ASA404 1200 mg/m^2 in Arm 2 and 1800 mg/m^2 in Arm 1; ≥ 80 mL/minute for patients receiving ASA404 1800 mg/m^2 and 2400 mg/m^2 in Arm 2 and 2400 mg/m^2 in Arm 1.
  - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5 x upper limit of normal (ULN) (≤ 5 x ULN if liver metastases).
  - Alkaline phosphatase (ALP) ≤ 2.5 x ULN; Patients with known bone metastases were included with ALP ≤ 4.0 x ULN if ALT and AST were within the inclusion criteria for this study.
  - Prothrombin time (PT) ≤ 1.5 x ULN
  - Partial thromboplastin time (PTT) ≤ 1.5 x ULN

  - Electrolyte values (potassium, calcium, magnesium) within the normal range. Patients with corrected electrolyte values were eligible.
  - Total bilirubin ≤ 1.5 X ULN
  - Urinalysis (no evidence of proteinuria [≥+2 or > 100 mg/dL] and hematuria [≥+1 blood] on urine dipstick)
- A minimum of 4 weeks had elapsed since the last drug administration of other cancer therapies (e.g., endocrine therapy, immunotherapy, chemotherapy, etc) and 6 weeks for nitrosoureas and mitomycin C.
- Females of child-bearing potential had a negative serum pregnancy test at screening (confirmation of negative serum or urine pregnancy test within 72 hours prior to initial start of study drug on Day 1).
- Patients had recovered from all acute radiotherapy-related toxicities.
- Written informed consent was obtained prior to any non-standard of care screening procedures being performed.

Exclusion criteria

- Patients having central nervous system (CNS) metastases. Patients having any clinical signs of CNS metastases were to have a CT or MRI of the brain performed to rule out CNS metastases in order to be eligible for study participation.
- Patients with leptomeningeal metastatic disease.
- Known history of seizures requiring anti-convulsant therapy
- Major surgery ≤ 4 weeks prior to starting study treatment. Major surgery was defined as any invasive operative procedure in which extensive resection was performed (e.g., a body cavity is entered, organs are removed, mesenchymal barrier is opened, an extensive orthopedic procedure is involved, or normal anatomy is significantly altered). Patients recovered from all acute surgery-related complications.
- Patients who have not recovered from all acute minor surgery-related complications. Minor surgery was defined as any invasive operative procedure in which only skin or mucous membranes and connective tissue were resected (e.g., vascular cut down for catheter placement, implanting pumps in subcutaneous tissue, biopsies, placement of probes or catheters requiring the entry into a body cavity, tooth extractions, and gingival grafts). Insertion of a vascular access device was allowed.
- Concurrent use of other investigational agents and patients who had received investigational agents within 4 weeks (or longer if required by local regulation) prior to starting study drug. Concurrent use of any homeopathic or naturopathic medicines.
- Prior exposure to vascular disrupting agents (VDA). Prior use of anti-angiogenesis agents such as VEGF receptor inhibitors was allowed.
- Patients with systolic blood pressure (BP) < 100 mmHg or > 160 mmHg and/or diastolic BP < 60 mmHg or > 90 mmHg.
- Patients with any one of the following:
  - Long QT syndrome
  - Any family history of unexplained sudden death

- Screening 12-lead ECG QTcF of > 450 msec for males or > 470 for females (using the Fridericia formula) as per central ECG evaluation report
- Myocardial infarction within 12 months of starting study drug
- Unstable or poorly controlled angina pectoris, including Prinzmetal variant angina pectoris
- History of a sustained ventricular tachycardia
- History of ventricular fibrillation or Torsades de pointes (TdP)
- Right bundle branch block (RBBB), complete left bundle branch block (LBBB), bifascicular block (right bundle branch block with either left anterior hemiblock or left posterior hemiblock)
- Bradycardia defined as heart rate <50 beats per minute
- Use of a cardiac pacemaker or defibrillator
- Congestive heart failure
- History of labile hypertension or poor compliance with anti-hypertensive regimen
- Any clinically significant ST segment and/or T wave abnormalities
- History of atrial tachyarrhythmia (e.g., atrial fibrillation, atrial flutter, multifocal atrial tachycardia, supraventricular tachycardia)

- Administration of drugs that are known to prolong QT interval or cause TdP, within 14 days (or 5 half-lives, if longer) prior to starting study drug.
- Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test (> 5 mIU/mL).
- Concurrent severe and/or uncontrolled medical disease (e.g., uncontrolled diabetes, chronic renal or liver disease, confirmed diagnosis of Human Immunodeficiency Virus (HIV) infection, or active uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with protocol.
- History of clinically significant gastrointestinal bleeding within 3 weeks of starting study treatment.
- Significant neurologic or psychiatric disorder which could compromise participation in the study.
- Administration of CYP1A2 and CYP3A4/5 substrates, inducers and inhibitors within 14 days (or 5 half-lives, if longer) prior to starting study drug.
- Administration of UGT1A9 and UGT2B7 inducers and inhibitors within 7 days prior to starting study drug and during the core phase of the study.
- Consumption of grapefruit, grapefruit juice, star fruit, star fruit juice or caffeinated beverages within 48 hours of starting study drug. Consumption was not allowed during the core phase of the study and was permitted during the extension phase.
- Donation or loss of 400 mL or more of blood within 4 weeks prior to starting study drug.
- Women of child bearing potential or sexually active males, unwilling or unable to use the required highly effective method(s) of contraception for both sexes while receiving treatment and for at least 6 months after the discontinuation of study treatment. Adequate forms

of contraception include intrauterine device (IUD), oral or depot contraceptive the barrier method + spermicide.

- Concomitant use of full-dose therapeutic, oral or parenteral, anticoagulation. Patients receiving thrombolytic therapy within 10 days of starting are also ineligible. Patients may receive prophylactic anticoagulation therapy for port clot prophylaxis.
- Patient unwilling or unable to comply with the protocol.

If patient was to be treated with paclitaxel:

- Known allergy or hypersensitivity to platinum-containing drugs, taxanes, other drugs formulated in Cremophor EL (polyoxyethylated castor oil) or any known excipients of these drugs.
- Peripheral sensory neuropathy with functional impairment (CTCAE ≥ grade 2 neuropathy, regardless of causality).
- Oral, implantable, or injectable contraceptives may be affected by cytochrome P450 interactions while taking paclitaxel and therefore were not considered effective contraceptive methods for this study when used as a single agent. Patients taking oral, implantable, or injectable contraceptives who were not willing or otherwise unable to use a concomitant barrier method were excluded.

If patient was to be treated with docetaxel:

- Known allergy or hypersensitivity to drugs formulated with polysorbate 80 or any known excipients of docetaxel.

Number of Subjects

Out of the planned multiple doses of ASA404, in treatment arm 1 patients were administered ASA404 1800 mg/m^2 and in treatment arm 2 patients were administered ASA404 1200 and 1800 mg/m^2.

Patient disposition by treatment arm and dose level (Full analysis set)

Disposition	**Treatment Arm 1 1800 mg/m^2 N=8 n (%)**	**Treatment Arm 2 1200 mg/m^2 N=9 n (%)**	**Treatment Arm 2 1800 mg/m^2 N=9 n (%)**	**All Patients N=26 n (%)**
Enrolled	8 (100.0)	9 (100.0)	9 (100.0)	26 (100.0)
Discontinued	5 (62.5)	1 (11.1)	9 (100.0)	15 (57.7)
Adverse event(s)	3 (37.5)	1 (11.1)	2 (22.2)	6 (23.1)
Abnormal laboratory value(s)	0	0	0	0
Abnormal test procedure result(s)	0	0	0	0
Patient withdrew consent	0	0	0	0
Lost to follow-up	0	0	0	0
Administrative problems	1 (12.5)	0	7 (77.8)	8 (30.8)
Death	0	0	0	0
Disease progression	2 (25.0)	8 (88.9)	0	10 (38.5)
Treatment duration completed as per protocol	1 (12.5)	0	0	1 (3.8)
Protocol deviation	1 (12.5)	0	0	1 (3.8)
Entered Extension Phase	4 (50.0)	7 (77.8)	5 (55.6)	16 (61.5)

Demographic and Background Characteristics

Demographics and other baseline characteristics by treatment arm and dose level (Full analysis set)

Demographic Variable	**Treatment Arm 1 1800 mg/m^2 (N=8)**	**Treatment Arm 2 1200 mg/m^2 (N=9)**	**Treatment Arm 2 1800 mg/m^2 (N=9)**	**All Patients (N=26)**
Age (years)				
Mean (SD)	53.8 (14.28)	52.4 (15.15)	58.2 (9.2)	54.8 (12.81)
Median (Min-max)	54 (26-73)	50 (23-74)	60 (42-70)	55.5 (23-74)
Sex, n(%)				
Male	3 (37.5)	7 (77.8)	5 (55.6)	15 (57.7)
Female	5 (62.5)	2 (22.2)	4 (44.4)	11 (42.3)
Race, n(%)				
Caucasian	7 (87.5)	8 (88.9)	9 (100.0)	24 (92.3)
Asian	0	1 (11.1)	0	1 (3.8)
Other	1 (12.5)	0	0	1 (3.8)
Ethnicity, n(%)				

Other	8 (100.0)	9 (100.0)	9 (100.0)	26 (100.0)
Weight (kg)				
Mean (SD)	70.31 (15.492)	62.71 (11.308)	72.04 (13.462)	68.28 (13.553)
Median (Min-max)	66.2 (53-102.3)	64.8 (42.7-81)	75 (42-89.1)	67.7 (42-102.3)
Height (cm)				
Mean	164.8 (4.53)	168.2 (4.18)	175 (6.3)	169.5 (6.54)
Median	164.5 (157-172)	169 (162-175)	173 (167-185)	169 (157-185)
BMI (kg/m^2)				
Mean	25.85 (5.048)	22.13 (3.764)	23.47 (3.979)	23.74 (4.372)
Median (Min-max)	24.65 (19.5-35.8)	22.7 (15.5-28)	24.4 (14.4-28)	24 (14.4-35.8)
BSA (m^2)				
Mean (SD)	1.8 (0.185)	1.72 (0.179)	1.88 (0.205)	1.8 (0.194)
Median (Min-max)	1.75 (1.6-2.2)	1.7 (1.4-2)	1.9 (1.4-2.1)	1.8 (1.4-2.2)
Note: The baseline weight (kg) and baseline height (cm) were defined as the last non-missing assessment of weight and height before the first study drug administration. BMI (kg/m^2) = weight (kg) / height (m)^2. BMI is calculated using the baseline weight and baseline height. BSA (m^2) = sqrt([height (cm) x weight (kg)]/ 3600).				

Primary Objective Results

The PK parameters of free and total ASA404 was the primary endpoints in this trial; however due to premature study termination, these were not calculated and no statistical analyses were reported.

Secondary objective Results

Safety and tolerability

Adverse events, regardless of study drug relationship, by primary system organ class and treatment (Safety set)

Primary System Organ Class **Preferred Term**	**1200 mg/m^2 20 min iv N=5 n (%)**	**1200 mg/m^2 60 min iv N=4 n (%)**	**1800 mg/m^2 20 min iv N=10 n (%)**	**1800 mg/m^2 60 min iv N=7 n (%)**	**Total N=26 n (%)**
Any Primary system organ class	5 (100.0)	4 (100.0)	10 (100.0)	7 (100.0)	26 (100.0)
Blood and lymphatic system disorders	2 (40.0)	3 (75.0)	7 (70.0)	3 (42.9)	15 (57.7)
Cardiac disorders	0	1 (25.0)	3 (30.0)	0	4 (15.4)
Ear and labyrinth disorders	0	0	1 (10.0)	1 (14.3)	2 (7.7)
Eye disorders	0	0	1 (10.0)	2 (28.6)	3 (11.5)
Gastrointestinal disorders	5 (100.0)	1 (25.0)	7 (70.0)	5 (71.4)	18 (69.2)
General disorders and administration site conditions	3 (60.0)	3 (75.0)	6 (60.0)	6 (85.7)	18 (69.2)
Hepatobiliary disorders	1 (20.0)	0	0	0	1 (3.8)
Immune system disorders	0	0	0	1 (14.3)	1 (3.8)
Infections and infestations	1 (20.0)	1 (25.0)	6 (60.0)	1 (14.3)	9 (34.6)
Injury, poisoning and procedural complications	0	0	0	1 (14.3)	1 (3.8)

Investigations	1 (20.0)	2 (50.0)	2 (20.0)	1 (14.3)	6 (23.1)
Metabolism and nutrition disorders	2 (40.0)	2 (50.0)	8 (80.0)	2 (28.6)	14 (53.8)
Musculoskeletal and connective tissue disorders	2 (40.0)	1 (25.0)	4 (40.0)	4 (57.1)	11 (42.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (20.0)	0	0	0	1 (3.8)
Nervous system disorders	2 (40.0)	1 (25.0)	5 (50.0)	4 (57.1)	12 (46.2)
Psychiatric disorders	1 (20.0)	1 (25.0)	4 (40.0)	1 (14.3)	7 (26.9)
Renal and urinary disorders	2 (40.0)	0	1 (10.0)	1 (14.3)	4 (15.4)
Reproductive system and breast disorders	0	0	1 (10.0)	0	1 (3.8)
Respiratory, thoracic and mediastinal disorders	0	3 (75.0)	5 (50.0)	2 (28.6)	10 (38.5)
Skin and subcutaneous tissue disorders	2 (40.0)	2 (50.0)	5 (50.0)	2 (28.6)	11 (42.3)
Vascular disorders	1 (20.0)	0	3 (30.0)	1 (14.3)	5 (19.2)

Primary system organ classes are presented alphabetically; Preferred terms are sorted within primary system organ class by descending order of frequencies, as reported in the Total column.

Treatment labels reflect administration with and without chemotherapy.

A patient with multiple occurrences of an AE under one cycle or under the Total column is counted only once in the AE category for that cycle or for the Total column.

A patient with multiple adverse events within a primary system organ class is counted only once in the Total row.

A TEAE may be counted in more than one cycle if multiple start dates were recorded for that TEAE, hence the sum across cycles may exceed the total column.

Adverse events (at least 15% incidence in any group), regardless of study drug relationship, by preferred term and treatment (Safety set)

Preferred term	**1200 mg/m^2 20 min i.v. N=5 n (%)**	**1200 mg/m^2 60 min i.v. N=4 n (%)**	**1800 mg/m^2 20 min i.v. N=10 n (%)**	**1800 mg/m^2 60 min i.v. N=7 n (%)**	**Total N=26 n (%)**
Any preferred term	5 (100.0)	4 (100.0)	10 (100.0)	7 (100.0)	26 (100.0)
Fatigue	2 (40.0)	2 (50.0)	3 (30.0)	5 (71.4)	12 (46.2)
Neutropenia	1 (20.0)	2 (50.0)	6 (60.0)	2 (28.6)	11 (42.3)
Diarrhoea	2 (40.0)	0	4 (40.0)	3 (42.9)	9 (34.6)
Nausea	2 (40.0)	0	4 (40.0)	3 (42.9)	9 (34.6)
Alopecia	0	2 (50.0)	4 (40.0)	2 (28.6)	8 (30.8)
Decreased appetite	2 (40.0)	0	4 (40.0)	2 (28.6)	8 (30.8)
Asthenia	1 (20.0)	0	4 (40.0)	2 (28.6)	7 (26.9)
Cough	0	2 (50.0)	3 (30.0)	2 (28.6)	7 (26.9)
Anaemia	2 (40.0)	0	3 (30.0)	1 (14.3)	6 (23.1)
Febrile neutropenia	1 (20.0)	1 (25.0)	3 (30.0)	0	5 (19.2)
Hypomagnesaemia	0	1 (25.0)	4 (40.0)	0	5 (19.2)
Myalgia	0	1 (25.0)	2 (20.0)	2 (28.6)	5 (19.2)
Vomiting	1 (20.0)	0	3 (30.0)	1 (14.3)	5 (19.2)
Constipation	2 (40.0)	0	1 (10.0)	1 (14.3)	4 (15.4)

Dizziness	1 (20.0)	0	1 (10.0)	2 (28.6)	4 (15.4)
Hypokalaemia	0	0	4 (40.0)	0	4 (15.4)
Insomnia	0	1 (25.0)	2 (20.0)	1 (14.3)	4 (15.4)
Pain in extremity	1 (20.0)	0	1 (10.0)	2 (28.6)	4 (15.4)
Paraesthesia	1 (20.0)	1 (25.0)	1 (10.0)	1 (14.3)	4 (15.4)
Abdominal pain	0	0	3 (30.0)	0	3 (11.5)
Back pain	1 (20.0)	0	2 (20.0)	0	3 (11.5)
Dysgeusia	0	1 (25.0)	1 (10.0)	1 (14.3)	3 (11.5)
Dyspepsia	1 (20.0)	0	1 (10.0)	1 (14.3)	3 (11.5)
General physical health deterioration	0	1 (25.0)	1 (10.0)	1 (14.3)	3 (11.5)
Hypotension	1 (20.0)	0	2 (20.0)	0	3 (11.5)
Nasopharyngitis	0	1 (25.0)	1 (10.0)	1 (14.3)	3 (11.5)
Pyrexia	0	1 (25.0)	1 (10.0)	1 (14.3)	3 (11.5)
Stomatitis	0	0	1 (10.0)	2 (28.6)	3 (11.5)
Anxiety	1 (20.0)	0	1 (10.0)	0	2 (7.7)
Dyspnoea	0	1 (25.0)	0	1 (14.3)	2 (7.7)
Dysuria	1 (20.0)	0	1 (10.0)	0	2 (7.7)
Electrocardiogram qt prolonged	0	1 (25.0)	1 (10.0)	0	2 (7.7)
Hot flush	1 (20.0)	0	0	1 (14.3)	2 (7.7)
Hypocalcaemia	0	1 (25.0)	1 (10.0)	0	2 (7.7)
Nail discolouration	0	1 (25.0)	1 (10.0)	0	2 (7.7)
Oedema peripheral	1 (20.0)	1 (25.0)	0	0	2 (7.7)
Rhinorrhoea	0	1 (25.0)	0	1 (14.3)	2 (7.7)
Sepsis	0	0	2 (20.0)	0	2 (7.7)
Tachycardia	0	0	2 (20.0)	0	2 (7.7)
Thrombocytopenia	1 (20.0)	0	1 (10.0)	0	2 (7.7)
Urinary tract infection	1 (20.0)	0	1 (10.0)	0	2 (7.7)
Abdominal pain upper	0	1 (25.0)	0	0	1 (3.8)
Alanine aminotransfer-ase increased	1 (20.0)	0	0	0	1 (3.8)
Albuminuria	1 (20.0)	0	0	0	1 (3.8)
Blood alkaline phos-phatase increased	1 (20.0)	0	0	0	1 (3.8)
Bone pain	1 (20.0)	0	0	0	1 (3.8)
Chest discomfort	0	1 (25.0)	0	0	1 (3.8)
Cold sweat	1 (20.0)	0	0	0	1 (3.8)
Cystitis	1 (20.0)	0	0	0	1 (3.8)
Face oedema	1 (20.0)	0	0	0	1 (3.8)
Gastritis	0	1 (25.0)	0	0	1 (3.8)
Haemoptysis	0	1 (25.0)	0	0	1 (3.8)
Haemorrhoids	1 (20.0)	0	0	0	1 (3.8)
Herpes virus infection	1 (20.0)	0	0	0	1 (3.8)
Hyperbilirubinaemia	1 (20.0)	0	0	0	1 (3.8)
Hypertension	0	0	1 (10.0)	0	1 (3.8)
Lymphopenia	1 (20.0)	0	0	0	1 (3.8)

Rash	1 (20.0)	0	0	0	1 (3.8)
Supraventricular tachy-cardia	0	1 (25.0)	0	0	1 (3.8)
Tumour pain	1 (20.0)	0	0	0	1 (3.8)
Weight decreased	0	1 (25.0)	0	0	1 (3.8)
Weight increased	0	1 (25.0)	0	0	1 (3.8)

- Preferred terms are sorted by descending order of frequencies, as reported in the total column
- Treatment labels reflect administration with or without chemotherapy.
- A patient with multiple occurrences of an AE under one cycle or under the Total column is counted only once in the AE category for that cycle or for the total column.
- A TEAE may be counted in more than one cycle if multiple start dates were recorded for that TEAE, hence the sum across cycles may exceed the total column.

Serious Adverse Events and Deaths

Deaths, other serious adverse events and other significant adverse events

Deaths

There were four patient deaths and all of these deaths were due to disease progression. Of these, one patient death occurred after the 30 day follow-up period.

Serious adverse events, regardless of study drug relationship by primary system organ class, preferred term and treatment (Safety set)

Primary System Organ Class **Preferred Term**	**Treatment Arm 1** **1800 mg/m^2** **(N=8)**	**Treatment Arm 2** **1200 mg/m^2** **(N=9)**	**Treatment Arm 2** **1800 mg/m^2** **(N=9)**	**All Patients** **(N=26)**
Any Primary system organ class				
Total	5 (62.50)	3 (33.3)	4 (44.44)	12 (46.15)
Blood and lymphatic system disorders				
-Total	1 (12.50)	2 (22.22)	2 (22.22)	5 (19.23)
Febrile neutropenia	1 (12.50)	2 (22.22)	2 (22.22)	5 (19.23)
General disorder and administrative conditions				
-Total	1 (12.50)	1 (11.11)	3 (33.33)	5 (19.23)
General physical health deterioration	1 (12.50)	1 (11.11)	1 (11.11)	3 (11.54)
Chest discomfort	0	1 (11.11)	0	1 (3.85)
Pain	0	0	1 (11.11)	1 (3.85)
Pyrexia	0	0	1 (11.11)	1 (3.85)
Hypothermia	0	0	1 (11.11)	1 (3.85)
Asthenia	0	0	1 (11.11)	1 (3.85)
Gastrointestinal disorders				
-Total	1 (12.50)	0	1 (11.11)	2 (7.69)

Small intestinal obstruction	1 (12.50)	0		1 (3.85)
Vomiting	0	0	1 (11.11)	1 (3.85)
Respiratory, thoracic and mediastinal disorders				
-Total	0	1 (11.11)	1 (11.11)	2 (7.69)
Cachexia	0	0	1 (11.11)	1 (3.85)
Dyspnoea	0	1 (11.11)	0	1 (3.85)
Haemoptysis	0	1 (11.11)	0	1 (3.85)
Cardiac disorders		0		
-Total	0	1 (11.11)	1 (11.11)	2 (7.69)
Atrial flutter	0	0	1 (11.11)	1 (3.85)
Sinus tachycardia	0	0	1 (11.11)	1 (3.85)
Supraventricular tachycardia	0	1 (11.11)	0	1 (3.85)
Immune system disorder				
-Total	1 (12.50)	0	0	1 (3.85)
Drug Hypersensitivity	1 (12.50)	0	0	1 (3.85)
Infections and infestations			0	
-Total	0	0	2 (22.22)	2 (7.69)
Eshcherichia sepsis	0	0	1 (11.11)	1 (3.85)
Pneumonia	0	0	1 (11.11)	1 (3.85)
Sepsis	0	0	1 (11.11)	1 (3.85)
Metabolism and nutrition disorders				
-Total	0	1 (11.11)	0	1 (3.85)
Decreased Appetite	0	1 (11.11)	0	1 (3.85)
Ear and labyrinth disorders				
-Total	1 (12.50)	0	0	1 (3.85)
Vertigo	1 (12.50)	0	0	1 (3.85)

- Primary system organ classes and preferred terms within primary system organ class are sorted in descending frequency, over all treatment regimens.
- A patient with multiple occurrences of an SAE is counted only once in the SAE category.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

Incidence of AEs leading to discontinuation of study treatment (Safety set)

Primary system organ class **Preferred term**	**Treatment Arm 1** **1800 mg/m^2** **N=8** **n (%)**	**Treatment Arm 2** **1200 mg/m^2** **N=9** **n (%)**	**Treatment Arm 2** **1800 mg/m^2** **N=9** **n (%)**	**All Patients** **N=26** **n (%)**
Patients with any AE leading to discontinuation				
-Total	3 (37.50)	1 (11.1)	2 (22.2)	6 (23.08)
Investigations				

-Total	1 (12.50)	0	1 (11.11)	2 (7.69)
Platelet count	1 (12.50)	0	0	1 (3.85)
Electrocardiogram QT prolonged	0	0	1 (11.11)	1 (3.85)
General disorder and administration site conditions				
-Total	1 (12.50)	0	0	1 (3.85)
Fatigue	1 (12.50)	0	0	1 (3.85)
Nervous system disorders				
-Total	1 (12.50)	0	0	1 (3.85)
Neuropathy peripheral	1 (12.50)	0	0	1 (3.85)
Ear and Labyrinth disorders				
-Total	1 (12.50)	0	0	1 (3.85)
Vertigo	1 (12.50)	0	0	1 (3.85)
Gastrointestinal disorder				
-Total	1 (12.50)	0	0	1 (3.85)
Small intestinal obstruction	1 (12.50)	0	0	1 (3.85)
Immune system disorders				
-Total	1 (12.50)	0	0	1 (3.85)
Drug hypersensitivity	1 (12.50)	0	0	1 (3.85)
General disorder and administration site conditions				
-Total	0	1 (11.11)	0	1 (3.85)
Oedema	0	1 (11.11)	0	1 (3.85)
Vascular disorders				
-Total	0	1 (11.11)	0	1 (3.85)
Hot flush	0	1 (11.11)	0	1 (3.85)
Cardiac disorders				
-Total	0	0	1 (11.11)	1 (3.85)
Atrial flutter	0	0	1 (11.11)	1 (3.85)

- Primary system organ classes and preferred terms within primary system organ class are sorted in descending frequency, over all treatment regimens.
- A patient with multiple occurrences of an AE is counted only once in the AE category.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

Safety Results

Adverse Events by System Organ Class

Described under secondary objective results.

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

Described under secondary objective results.

Serious Adverse Events and Deaths

There were four patient deaths and all of these deaths were due to disease progression. Of these, one patient death occurred after the 30 day follow-up period.

Other Relevant Findings

Biomarker assessments

Due to premature study termination, biomarkers including pharmacogenetic markers (genotypes) were not assayed. Therefore, no analyses of biomarkers were conducted and no data were reported.

Date of Clinical Trial Report

20 Dec 2011

Date Inclusion on Novartis Clinical Trial Results Database

27-Feb-2012

Date of Latest Update