Sponsor

Novartis

Generic Drug Name

Vadimezan (ASA404) and docetaxel

Therapeutic Area of Trial

Advanced or recurrent solid tumor

Approved Indication

Investigational

Study Number

CASA404A1102

Title

A safety, tolerability study of intravenous ASA404 administered in combination with docetaxel in Japanese patients with advanced or recurrent solid tumors

Phase of Development

Phase I

Study Start/End Dates

05 Mar 2009 to 15 Dec 2009

Study Design/Methodology

This was an open-label, phase I study of intravenous ASA404 1800 mg/m^2 administered in combination with docetaxel 60 mg/m^2 or 75 mg/m^2 in patients with advanced or recurrent solid tumors. Dose escalation proceeded using "3+3" design principle. Each patient was treated with ASA404 in combination with docetaxel on Day 1 of each cycle. Each cycle was over 21 days. After Cycle 2, no allowance of the administration was permitted before the planned day. Dose escalation decision was to be made based on Cycle 1 data from evaluable patients by incidence of DLT during Cycle 1.

Approximately 12 evaluable patients as dose determining set were evaluated at maximum in this study. A total of 9 patients were enrolled and analyzed.

Centres

Two centers in Japan

Publication

None

Objectives

Primary objective(s)

- To assess the tolerability of ASA404 when administered in combination with docetaxel in Japanese patients with advanced or recurrent solid tumors

Secondary objective(s)

- To characterize the safety profile of ASA404 when administered in combination with docetaxel in Japanese patients
- To characterize the pharmacokinetics profile of ASA404 when administered in combination with docetaxel in Japanese patients
- To assess preliminary evidence of anti tumor activity

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

The starting dose level was ASA404 1800 mg/m^2 + docetaxel 60 mg/m^2 (dose level 1), which was to be escalated to ASA404 1800 mg/m^2 + docetaxel 75 mg/m^2 (dose level 2) or de-escalated to ASA404 1200 mg/m^2 + docetaxel 60 mg/m^2 (dose level -1) as required. Docetaxel administrated by IV infusion of 1 hour followed by ASA404 IV infusion of 20 minutes.

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

None

Criteria for Evaluation

Safety and tolerability

The patient's safety profiles and tolerability were to be individually assessed during Cycle 1.

A DLT was defined as an adverse event (AE) or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications, occurring before Day 21 (include) in Cycle 1, and meeting any of the criteria listed in the following table:

Toxicity	Any of the following criteria (all grades based on CTCAE, v. 3.0)
Hematological toxicity	Grade 4 neutropenia for > 7 consecutive days despite treatment of granulocyte-colony stimulating factor (G-CSF)
	Grade 4 thrombocytopenia ≥ Grade 3 thrombocytopenia required to platelet transfusion
	Febrile neutropenia
Non-hematological toxicity	Grade 4 nausea/vomiting, fatigue, anorexia[*1]
	Grade 3: persistent CNS neurological toxicity[*4]
	≥ Grade 3: other non-hematological toxicity[*1,2,3]

Delay of treatment	When treatment is delayed over 3 weeks in the combination cycle compared to planned date

[*1] Appropriate prophylactic treatment for nausea/vomiting and diarrhea were allowed

[*2] Electrolyte abnormality was to be adapted in case of dose reduction required by the investigator

[*3] Including any Grade 3 or 4 cardiac toxicity (e.g. cardiac dysrhythmia, cardiac ischemia, cardiac failure, etc); any Grade 3 or 4 QTc prolongation (e.g., QTc > 500 msec)

[*4] Including any Grade 3 or 4 ophthalmic toxicity.

Toxicity was to be assessed using the National Cancer Institute (NCI) CTCAE, version 3.0.

Safety was evaluated using assessment of adverse events (AEs) and laboratory test data, electrocardiography, and regular assessments of vital signs and physical condition. Ophthalmic evaluations were also performed by the investigator for all patients in the study.

Pharmacokinetics

Concentrations of total and free ASA404 in plasma and total ASA404 in urine were determined by a validated liquid chromatography-mass spectrometry (LC-MS)/MS method. The Limit of quantification (LOQ) was 0.200 µg/mL and 0.0300 µg/mL for total and free ASA404 in plasma and 0.100 µg/mL for total ASA404 in urine, respectively. Standard PK parameters were calculated by non-compartment methods in Cycle 1.

Efficacy

Tumor responses were evaluated by RECIST criteria, version 1.0 in case of patients who had measurable lesion. Objective response rate (ORR), which was best overall response occurred during the study, was summarized.

Statistical Methods

The statistical analyses of this study were performed when all patients had completed 6 cycles and/or discontinued.

No hypothesis was tested; all analyses were descriptively performed.

Efficacy analysis was performed in the full analysis set (FAS), which consisted of all patients who had received at least one dose of study drug (ASA404).

All safety evaluations were performed in the safety set, which consisted of all patients who had received at least one dose of study drug (ASA404) and had at least one safety evaluation after administration of study drug (ASA404).

The primary variable was the incidence of DLT in Cycle 1. DLTs were summarized by preferred term (PT) using MedDRA, version 12.1 for the dose determining set, which consisted of all patients from the safety set who received the required dose of docetaxel in Cycle 1, and had either completed minimum safety evaluation requirements in Cycle 1 or who had discontinued due to dose limiting toxicity in Cycle 1.

PK analysis was performed in the PK set consisting of all patients from the safety set who provided evaluable PK data. The concentrations (free and total ASA404 concentration in plasma and amount of total ASA404 excreted in urine) were summarized by each time point. Mean and individual plasma concentration-time profiles of free and total ASA404 were displayed graphically.

Concentrations below the LOQ were treated as zero in summary statistics and for calculation of PK parameters.

Study Population

Inclusion criteria:

- Patients aged ≥ 20 years old, with World Health Organization (WHO) Performance Status of 0-1, life expectancy ≥ 12 weeks, with histologically or cytologically confirmed solid tumors whose disease had progressed or recurred after treatment with at least one chemotherapy or hormonal therapy, excluding docetaxel-containing regimens. Progression and recurrence had to be proved by radiological assessment.
- Lab values within the range, as defined below , within 2 weeks of study registration:
  - Absolute neutrophil count (ANC) > 2.0 x 10^9/L
  - Platelets ≥ 100 x 10^9/L
  - Hemoglobin ≥ 9.5 g/dL
  - Serum creatinine ≤ 1.5 x upper limit of normal (ULN)
  - Serum bilirubin ≤ 1.5 x ULN
  - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5 x ULN
  - International Normalized Ratio (INR) ≤ 1.5 x ULN
  - Serum potassium within normal limits (WNL) or correctable with supplements
  - Serum calcium (corrective calculation was performed if serum albumin < 4.0 g/dL) WNL or correctable with supplements
  - Serum magnesium WNL or correctable with supplements

Exclusion criteria:

- Patients having symptomatic central nervous system (CNS) tumor/metastases and requiring treatment (patients who had brain tumor/metastases surgically removed or irradiated were allowed)
- Patients with a history of another primary malignancy that was currently clinically significant or currently required active intervention.
- Radiotherapy / major surgery / other investigational agents / other antineoplastic therapy (including chemo-, hormonal- and immuno therapy) ≤ 4 weeks prior to starting study drug
- Patients who had received prior therapy with ASA404 or other vascular disrupting agents
- Patients with systolic BP > 160 mm Hg and/or diastolic BP > 90 mm Hg
- Patients with fluid retention (pleural effusion, pericardial effusion and/or ascites) to be drained
- Patients with any one of the following:
  - Patients with long QT syndrome
  - Patients with a baseline 12-lead ECG corrected QT interval (QTc) of > 450 msec in males or > 470 msec in females

- Congestive heart failure (CHF)
- Patients with a myocardial infarction within 12 months of study entry
- Unstable or poorly controlled angina pectoris, including Prinzmetal was variant angina pectoris
- History of labile hypertension or poor compliance with anti-hypertensive regimen
- History of a sustained ventricular tachycardia
- Any history of ventricular fibrillation or torsades de pointes (TdP)
- Right bundle branch block (RBBB), complete left bundle branch block (LBBB), bifascicular block (RBBB with either left anterior hemiblock or left posterior hemiblock)
- Bradycardia defined as heart rate (HR) < 50 beats per minute
- Use of a cardiac pacemaker
- Any clinically significant ST segment and/or T wave abnormalities

- Concomitant use of drugs with a risk of prolonging the QT interval
- Known allergy or hypersensitivity to taxane or polysorbate 80
- Peripheral sensory neuropathy with functional impairment

Number of Subjects

Patient disposition (Full analysis set)

Disposition Reasons		ASA404 1800-DTX 60 mg/m^2 N = 3 n (%)	ASA404 1800-DTX 75 mg/m^2 N = 6 n (%)	All patients N = 9 n (%)
Total no. of patients	All treated patients	3 (100.0)	6 (100.0)	9 (100.0)
	Discontinued	3 (100.0)	6 (100.0)	9 (100.0)
Discontinuations	Adverse Event(s)	0 (0.0)	3 (50.0)	3 (33.3)
	Subject withdrew consent	0 (0.0)	1 (16.7)	1 (11.1)
	New cancer therapy	1 (33.3)	0 (0.0)	1 (11.1)
	Disease progression	2 (66.7)	2 (33.3)	4 (44.4)

Demographic and Background Characteristics

Demographic characteristics (FAS)

Demographic Variable	ASA404 1800-DTX 60 mg/m^2 N = 3	ASA404 1800-DTX 75 mg/m^2 N = 6	All patients N = 9
Age (year)			
Mean ± SD	64.3 ± 0.58	62.3 ± 7.50	63.0 ± 6.02
Median	64.0	64.5	64.0
(Minimum – Maximum)	(64.0 – 65.0)	(48.0 – 68.0)	(48.0 – 68.0)
Sex –n (%)			

Female	1 (33.3)	0 (0.0)	1 (11.1)
Male	2 (66.7)	6 (100.0)	8 (88.9)
Race - n (%)			
Oriental	3 (100.0)	6 (100.0)	9 (100.0)
Height (cm)			
Mean ± SD	157.3 ± 11.93	165.9 ± 7.22	163.1 ± 9.31
Median	161.0	163.6	163.2
(Minimum – Maximum)	(144.0 - 167.0)	(160.0 - 180.0)	(144.0 - 180.0)
Weight (kg)			
Mean ± SD	54.1 ± 13.10	66.5 ± 15.08	62.4 ± 14.95
Median	59.0	59.4	59.0
(Minimum – Maximum)	(39.3 - 64.1)	(54.4 - 93.0)	(39.3 - 93.0)
WHO PS - n (%)			
0	1 (33.3)	4 (66.7)	5 (55.6)
1	2 (66.7)	2 (33.3)	4 (44.4)

Primary Objective Result(s)

Dose-limiting toxicities (DLTs)

One patient of the 9 patients had a DLT, Grade 3 febrile neutropenia, during Cycle 1 at the dose level 2 of treatment with ASA404 1800 mg/m^2-docetaxel 75 mg/m^2.

Secondary Objective Result(s)

Safety results

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

Primary SOC PT	ASA404 1800-DTX 60 mg/m^2 N = 3 n (%)	ASA404 1800-DTX 75 mg/m^2 N = 6 n (%)	All patients N = 9 n (%)
Blood and lymphatic system disorders			
Neutropenia	3 (100.0)	6 (100.0)	9 (100.0)
Leukopenia	1 (33.3)	4 (66.7)	5 (55.6)
Anaemia	2 (66.7)	0 (0.0)	2 (22.2)
Febrile neutropenia	1 (33.3)	1 (16.7)	2 (22.2)
Thrombocytopenia	1 (33.3)	1 (16.7)	2 (22.2)
Gastrointestinal disorders			
Constipation	3 (100.0)	4 (66.7)	7 (77.8)
Diarrhoea	2 (66.7)	2 (33.3)	4 (44.4)
Nausea	1 (33.3)	3 (50.0)	4 (44.4)
Stomatitis	1 (33.3)	2 (33.3)	3 (33.3)
Vomiting	1 (33.3)	1 (16.7)	2 (22.2)

General disorders and administration site conditions			
Fatigue	3 (100.0)	6 (100.0)	9 (100.0)
Injection site pain	3 (100.0)	4 (66.7)	7 (77.8)
Feeling abnormal	1 (33.3)	1 (16.7)	2 (22.2)
Feeling hot	1 (33.3)	1 (16.7)	2 (22.2)
Oedema peripheral	0 (0.0)	2 (33.3)	2 (22.2)
Pyrexia	1 (33.3)	1 (16.7)	2 (22.2)
Immune system disorders			
Drug hypersensitivity	1 (33.3)	1 (16.7)	2 (22.2)
Investigations			
Blood alkaline phosphatase increased	0 (0.0)	2 (33.3)	2 (22.2)
Blood lactate dehydrogenase increased	0 (0.0)	2 (33.3)	2 (22.2)
Haemoglobin decreased	0 (0.0)	2 (33.3)	2 (22.2)
Metabolism and nutrition disorders			
Decreased appetite	3 (100.0)	5 (83.3)	8 (88.9)
Musculoskeletal and connective tissue disorders			
Arthralgia	2 (66.7)	3 (50.0)	5 (55.6)
Myalgia	1 (33.3)	3 (50.0)	4 (44.4)
Nervous system disorders			
Dysgeusia	1 (33.3)	3 (50.0)	4 (44.4)
Peripheral sensory neuropathy	1 (33.3)	2 (33.3)	3 (33.3)
Respiratory, thoracic and mediastinal disorders			
Hiccups	0 (0.0)	2 (33.3)	2 (22.2)
Skin and subcutaneous tissue disorders			
Alopecia	3 (100.0)	6 (100.0)	9 (100.0)
Rash	2 (66.7)	4 (66.7)	6 (66.7)
Vascular disorders			
Flushing	2 (66.7)	1 (16.7)	3 (33.3)

AEs are listed in alphabetical order within primary system organ class then descending order within PT level in the All Subjects group.

AEs that occurred more than 20% within PT level in the All patients group are presented.

AEs occurring more than 28 days after the last date of exposure to study treatment are not summarized.

Deaths

No patients died during the treatment with study drug.

Adverse events (CTCAE Grades 3 or 4), regardless of study drug relationship, by preferred term (Safety set)

PT	ASA404 1800-DTX 60 mg/m^2 N = 3 n (%)	ASA404 1800-DTX 75 mg/m^2 N = 6 n (%)	All patients N = 9 n (%)
Any preferred term	3 (100.0)	6 (100.0)	9 (100.0)
Neutropenia	3 (100.0)	6 (100.0)	9 (100.0)

Leukopenia	1 (33.3)	4 (66.7)	5 (55.6)
Febrile neutropenia	1 (33.3)	1 (16.7)	2 (22.2)
Constipation	1 (33.3)	0 (0.0)	1 (11.1)
Hypersensitivity	0 (0.0)	1 (16.7)	1 (11.1)
Hyperuricaemia	1 (33.3)	0 (0.0)	1 (11.1)
Urinary retention	0 (0.0)	1 (16.7)	1 (11.1)

AEs are listed in descending order within PT level in the All patients group.
AEs occurring more than 28 days after the last date of exposure to study treatment are not summarized.

Pharmacokinetic results

Pharmacokinetic parameters of ASA404

PK Parameters	ASA404 1800 - DTX 60 mg/m^2 N = 3		ASA404 1800 - DTX 75 mg/m^2 N = 6	
	Total	**Free**	**Total**	**Free**
C_{max} (µg/mL)	282 ± 1.53	17.6 ± 4.13	280 ± 28.7	14.4 ± 3.97
t_{max} (hr)	0.333 (0.333 – 0.833)	0.333 (0.333 – 0.833)	0.600 (0.317 – 0.833)	0.833 (0.350 – 0.933)
$AUC_{0\text{-}tlast}$ (hr*µg/mL)	1610 ± 129	45.0 ± 3.46	1580 ± 222	37.4 ± 11.1
AUC_{inf} (hr*µg/mL)	1650 ± 126	46.3 ± 2.49	1590 ± 227	38.0 ± 11.3
$AUC_{0\text{-}24h}$ (hr*µg/mL)	1440 ± 108	43.5 ± 2.38	1470 ± 182	36.9 ± 11.1
$t_{1/2}$ (hr)	9.77 ± 3.21	9.08 ± 1.85	7.17 ± 0.747	5.94 ± 2.30
CL (L/hr)	1.69 ± 0.355	59.8 ± 10.1	1.99 ± 0.29	89.0 ± 30.5
V_{ss} (L)	14.1 ± 1.24	310 ± 61.5	12.1 ± 1.54	327 ± 124
V_z (L)	23.2 ± 5.87	775 ± 167	20.4 ± 2.72	736 ± 284
CL_r (L/hr)	0.0465 ± 0.0264	—	0.0666 ± 0.0368 [a)]	—
A_e (mg)	73.7 ± 38.8	—	109 ± 73.8 [a)]	—
f_e (%)	2.56 ± 1.07	—	3.64 ± 2.44 [a)]	—

a) n = 5 ; Data from one patient were excluded from summary statistics since the urine was spilled.

t_{max}: median (range), PK parameters other than t_{max}: mean ± SD.

$AUC_{0\text{-}tlast}$: Area under the plasma concentration-time curve (AUC) from start of ASA404 infusion to the time of the last quantifiable concentration, calculated by a trapezoidal method

$AUC_{0\text{-}24h}$: Area under the plasma concentration-time curve (AUC) from start of ASA404 infusion to the 24 hours after end of ASA404 infusion, calculated by a trapezoidal method

AUC_{inf}: Area under the concentration-time curve from start of ASA404 infusion to infinite time

C_{max} : Maximum plasma concentration from start of ASA404 infusion

t_{max} : Time to reach maximum concentration

$t_{1/2}$: Elimination half-life associated with the terminal slope

CL: Total body clearance of ASA404

V_z: Volume of distribution during terminal phase

V_{ss}: Volume of distribution at steady state

CL_r: Renal clearance

A_e: Amount of ASA404 excreted in urine

f_e: Fractional excretion in urine

Efficacy results

Best overall response (FAS)

Best overall response	ASA404 1800-DTX 60 mg/m^2 N = 3 n (%)	ASA404 1800-DTX 75 mg/m^2 N = 6 n (%)	All patients N = 9 n (%)
Objective Response (CR+PR)	1 (33.3)	0 (0.0)	1 (11.1)
Complete Response (CR)	0 (0.0)	0 (0.0)	0 (0.0)
Partial Response (PR)	1 (33.3)	0 (0.0)	1 (11.1)
Stable Disease (SD)	1 (33.3)	4 (66.7)	5 (55.6)
Progressive Disease (PD)	1 (33.3)	1 (16.7)	2 (22.2)
Unknown (UNK)	0 (0.0)	1 (16.7)	1 (11.1)

Date of Clinical Trial Report

23 Apr 2010 (content final)

Date Inclusion on Novartis Clinical Trial Results Database

2 Apr 2011

Date of Latest Update