Sponsor

Novartis

Generic Drug Name

vadimezan

Therapeutic Area of Trial

Non-small cell lung cancer (NSCLC)

Approved Indication

Investigational

Study Number

CASA404A1101

Title

An open-label, phase I trial of intravenous ASA404 administered in combination with paclitaxel and carboplatin in Japanese patients with stage IIIb/IV NSCLC

Phase of Development

Phase I

Study Start/End Dates

24-Apr-2008 to 31-Mar-2009

Study Design/Methodology

This was an open-label, Phase I study of intravenous ASA404 (600, 1200 and 1800 mg/m^2) administered in combination with paclitaxel and carboplatin in stage IIIb/IV NSCLC patients.

Centres

Japan (4 centres)

Publication

None

Objectives

Primary objective(s)

To assess the safety profile and tolerability of ASA404 when administered in combination with paclitaxel and carboplatin in Japanese patients with stage IIIb/IV NSCLC.

Secondary objective(s)

- To characterize the pharmacokinetics profile of ASA404 in Japanese patients.
- To assess pharmacodynamic effects of ASA404 in Japanese patients.
- To assess preliminary evidence of anti-tumor activity.

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

Intravenous ASA404 (dose level 1: 600 mg/m^2, dose level 2: 1200 mg/m^2, dose level 3: 1800 mg/m^2) was administered for six cycles (each cycle was 21 days). Each patient was received paclitaxel (200 mg/m^2) followed by carboplatin (AUC 6) and then followed by ASA404 on Day 1 of each Cycle. Patients could proceed beyond six cycles per investigators discretion in case of responding patients.

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

None

Criteria for Evaluation

Efficacy

Tumor response was assessed in only patient with measurable disease at baseline according to RECIST criteria.

Safety

Safety was evaluated using assessment of adverse events and laboratory data. 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 on the CTC Grade. ECGs, ophthalmic assessments were performed in all of patient.

Pharmacology

Pharmcokinetics (PK): Plasma concentrations of total and free ASA404 were determined, respectively. Urinary excreted unchanged ASA404 were also measured. Standard PK parameters were determined using non-compartmental method on day 1 of cycle 1.

Pharmacodynamics (PD): Plasma was collected for Pharmacodynamic marker of ASA404 (5HIAA) and angiogenesis markers to evaluate the pharmacodynamic effect of ASA404 and whether markers predictive to ASA404 clinical benefit could be defined.

Statistical Methods

The initial dose of ASA404 was 600 mg/m^2. In principle, if probability of DLT incidence on

Cycle 1 was = 1/3, the dose of ASA404 would be escalated to the next dose level. If no DLT was noted in the first three DLT evaluable patients in Cycle 1, the dose of ASA404 study would proceed to the next dose. If DLT was noted in one of the first 3 patients, then the dose level would be expanded by three additional patients. In case of dose level expansion, if DLT was noted in = 2 out of 6 evaluable patients, dose escalation would proceed.

The number of patients evaluated in each ASA404 dose level would be approximately 3 or 6 patients. Intra-patient dose-escalation was not performed. Data was presented primarily in a descriptive fashion with respect to demographic and baseline characteristics, efficacy observation and measurements, safety observation and measurements, and pharmacokinetic and pharmacodynamic measurements.

Dose-determining set included all patients from the safety set who either completed minimum safety evaluation requirements in Cycle 1 or who discontinued due to dose limiting toxicity in Cycle 1. The minimum safety evaluation requirements would have been met if, in Cycle 1, the patient had been treated with study drug and had completed all required safety evaluations. Full analysis set included all patients who had received at least one dose of study drug. Efficacy analysis was performed in this set.

Study Population: Inclusion/Exclusion Criteria and Demographics

The median age was 61 years (range 43 – 71years) and 53.3% of patients were female. 73.3% of patients had PS 1. All patients who enrolled in the study had stage IV lung cancer.

Inclusion criteria

Patients = 20 years of age and life expectancy = 12 weeks with histologically or cytologically confirmed stage IIIb or stage IV NSCLC. Other inclusion criteria included:

- No prior treatment for Stage IIIb/IV non-small cell carcinoma of the lung (Prior neoadjuvant or adjuvant chemotherapy within 6 months was allowed).
- WHO Performance status of 0-1.
- Lab values within the range, as defined below, within 2 weeks of study registration (without the use of growth factors or blood transfusions): Absolute neutrophils count (ANC) > 2.0 x 10^9/L, Platelets = 100 x10^9/L, Hemoglobin = 9.5 g/dL, Serum creatinine = 1.5 x ULN or 1.5 mg/dL, Serum bilirubin = 1.5 x ULN, Aspartate transaminase (AST) and alanine transaminase (ALT) = 2.5 x ULN, PT-INR = 1.5 x ULN, Potassium = LLN or correctable with supplements, Total calcium (corrected for serum albumin) = LLN or correctable with supplements, Magnesium = LLN or correctable with supplements.
- Females of child-bearing potential must have negative serum pregnancy test.

Exclusion criteria

Patients with symptomatic CNS metastasis, second primary cancer (exception of non-melanoma skin cancer or cervical cancer), hemoptysis associated with NSCLC. Other exclusion criteria included:

- Underwent radiotherapy or major surgery or received other investigational agents = 4 weeks or underwent minor surgery = 2 weeks prior to registration and prior exposure to vascular disrupting or targeting agents

- Known allergy or hypersensitivity, peripheral sensory neuropathy with functional impairment (CTC Grade 2 neuropathy regardless of causality), = CTC Grade 2 cardiac arrhythmias (i.e. non urgent medical intervention indicated or more severe) and HBV or HCV positive.

Patient disposition (Full Analysis Set)

Disposition reason	ASA404 600 mg/m^2 N=3	ASA404 1200 mg/m^2 N=6	ASA404 1800 mg/m^2 N=6	All Patients N=15
Total no. of patients				
Treated	3 (100.0%)	6 (100.0%)	6 (100.0%)	15 (100.0%)
Completed treatment	2 (66.7%)	1 (16.7%)	0	3 (20.0%)
Discontinued treatment	1 (33.3%)	5 (83.3%)	6 (100.0%)	12 (80.0%)
Primary reason for treatment discontinuation				
Adverse Event(s)	0	3 (50.0%)	4 (66.7%)	7 (46.7%)
Disease progression	1 (33.3%)	2 (33.3%)	2 (33.3%)	5 (33.3%)

Note: Two patients in ASA404 1200mg/m^2 who discontinued the study due to AE after 6 cycles of treatment were considered as discontinued.

Demographic and Background Characteristics

Demographic	ASA404 600 mg/m^2 N=3	ASA404 1200 mg/m^2 N=6	ASA404 1800 mg/m^2 N=6	All Patients N=15
Age (mean years)	57.3	62.8	60.2	60.7
Sex				
Female	1(33.3%)	5(83.3%)	2(33.3%)	8(53.3%)
Male	2(66.7%)	1(16.7%)	4(66.7%)	7(46.7%)
WHO PS				
0	1(33.3%)	0(0.0%)	3(50.0%)	4(26.7%)
1	2(66.7%)	6(100.0%)	3(50.0%)	11(73.3%)

Efficacy Result(s)

Tumor response was assessed according to RECIST criteria, approximately every 6 weeks. A total of 4 patients achieved objective response (CR: 0%, PR: 26.7%). Overall, 7 patients exhibited stable disease (SD: 46.7%).

Best overall response (Full analysis set)

	ASA404 600 mg/m^2 N=3	ASA404 1200 mg/m^2 N=6	ASA404 1800 mg/m^2 N=6	All Patients N=15
Best overall response	n (%)	n (%)	n (%)	n (%)
Complete Response (CR)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Partial Response (PR)	0(0.0)	3(50.0)	1(16.7)	4(26.7)
Stable Disease (SD)	3(100.0)	2(33.3)	2(33.3)	7(46.7)

Progressive Disease (PD)	0(0.0)	1(16.7)	3(50.0)	4(26.7)
Unknown (UNK)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Objective response (CR+PR)	0(0.0)	3(50.0)	1(16.7)	4(26.7)

Pharmacology Result(s)

Pharmacokinetics (PK):

- AUC of total ASA404 in plasma increased in mostly dose-proportional manner within the dose range investigated, while AUC of free ASA404 increased over dose-proportionally.
- No accumulation was suggested after every 3-week repeated dosing.
- Free fraction of ASA404 in plasma decreased with decline of total ASA404 concentration, indicating saturation of protein binding.
- Urinary excretion of unchanged ASA404 was less than 10% of the administered dose.

Pharmacokinetic parameters of ASA404

	Parameter	ASA404 600 mg/m^2 N=3	ASA404 1200 mg/m^2 N=6	ASA404 1800 mg/m^2 N=6
Total	Tmax (h)	0.317 (0.283, 0.333)	0.308 (0.283, 0.367)	0.325 (0.3, 0.35)
	Cmax (µg/mL)	137 ± 9.50	224 ± 33.8	247 ± 34.1
	AUClast (µg·h/mL)	256 ± 22.7	646 ± 96.7	1030 ± 136
	AUCinf (µg·h/mL)	260 ± 25.9	650 ± 97.2	1040 ± 137
	T1/2 (h)	7.04 ± 1.06	5.86 ± 2.59	4.61 ± 1.07
	CL (L/h)	3.88 ± 0.772	2.87 ± 0.573	2.78 ± 0.554
	ss (L)	14.4 ± 3.12	11.7 ± 3.42	12.9 ± 4.93
Free	Tmax (h)	0.317 (0.283, 0.333)	0.308 (0.283, 0.367)	0.325 (0.3, 0.35)
	Cmax (µg/mL)	3.69 ± 0.744	11.0 ± 4.17	20.2 ± 6.03
	AUClast (µg·h/mL)	5.76 ± 0.958	18.6 ± 3.25	37.2 ± 9.86
	AUCinf (µg·h/mL)	5.87 ± 0.974	18.7 ± 3.25	37.6 ± 9.5
	T1/2 (h)	5.83 ± 0.134	5.68 ± 2.77	5.24 ± 1.92
	CL (L/h)	176 ± 53.7	101 ± 24.6	80.4 ± 28.2
	Vss (L)	517 ± 171	318 ± 81.2	292 ± 227

Pharmacodynamics (PD):

- Induction of 5HIAA was observed after ASA404 infusion at all doses.
- The pattern changes of plasma angiogenesis markers after ASA404 infusion were quite different from anti-angiogenesis compounds.

Safety Results

- DLTs were observed in 2 patients during cycle 1 of ASA404 treatment (Grade 3 febrile neutropenia at the ASA404 1200 mg/m^2 and Grade 3 electrocardiogram QT prolonged at the ASA404 1800 mg/m^2).
- Adverse events occurred in all 15 patients. The most frequently reported AEs by Preferred term (PT) were injection site pain (93.3%), peripheral sensory neuropathy (93.3%), alopecia (93.3%), neutropenia (80.0%), nausea (80.0%), anorexia (80.0%), and arthralgia (80.0%).
- The most frequently reported study-drug related AEs by PT were injection site pain (93.3%). The incidence of other suspected AEs were less than 30%.
- The most frequently reported Grade 3 or 4 AEs by PT were neutropenia (12 patients).

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

	ASA404 600 mg/m^2	ASA404 1200 mg/m^2	ASA404 1800 mg/m^2	All Patients
Primary System Organ Class	**N=3**	**N=6**	**N=6**	**N=15**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any AEs	3(100.0)	6(100.0)	6(100.0)	15(100.0)
Blood and lymphatic system disorders	3(100.0)	6(100.0)	6(100.0)	15(100.0)
Neutropenia	3(100.0)	5(83.3)	4(66.7)	12(80.0)
Anaemia	2(66.7)	4(66.7)	3(50.0)	9(60.0)
Thrombocytopenia	0(0.0)	2(33.3)	2(33.3)	4(26.7)
Lymphopenia	0(0.0)	2(33.3)	1(16.7)	3(20.0)
Gastrointestinal disorders	3(100.0)	5(83.3)	6(100.0)	14(93.3)
Nausea	3(100.0)	5(83.3)	4(66.7)	12(80.0)
Constipation	2(66.7)	2(33.3)	4(66.7)	8(53.3)
Diarrhoea	2(66.7)	2(33.3)	1(16.7)	5(33.3)
Stomatitis	0(0.0)	2(33.3)	2(33.3)	4(26.7)
Vomiting	1(33.3)	2(33.3)	1(16.7)	4(26.7)
General disorders and administration site conditions	3(100.0)	6(100.0)	6(100.0)	15(100.0)
Injection site pain	2(66.7)	6(100.0)	6(100.0)	14(93.3)
Fatigue	2(66.7)	4(66.7)	4(66.7)	10(66.7)
Pyrexia	0(0.0)	1(16.7)	2(33.3)	3(20.0)
Hepatobiliary disorders	1(33.3)	1(16.7)	1(16.7)	3(20.0)
Hepatic function abnormal	0(0.0)	1(16.7)	1(16.7)	2(13.3)
Infections and infestations	1(33.3)	4(66.7)	2(33.3)	7(46.7)
Nasopharyngitis	1(33.3)	2(33.3)	0(0.0)	3(20.0)
Investigations	2(66.7)	5(83.3)	3(50.0)	10(66.7)
Weight decreased	1(33.3)	2(33.3)	1(16.7)	4(26.7)
Alanine Aminotransferase increased	1(33.3)	2(33.3)	0(0.0)	3(20.0)
Electrocardiogram QT prolonged	0(0.0)	1(16.7)	2(33.3)	3(20.0)

Metabolism and nutrition disorders	3(100.0)	5(83.3)	4(66.7)	12(80.0)
Anorexia	3(100.0)	5(83.3)	4(66.7)	12(80.0)
Hypocalcaemia	0(0.0)	1(16.7)	1(16.7)	2(13.3)
Hyponatraemia	0(0.0)	1(16.7)	1(16.7)	2(13.3)
Musculoskeletal and connective tissue disorders	3(100.0)	6(100.0)	5(83.3)	14(93.3)
Arthralgia	3(100.0)	5(83.3)	4(66.7)	12(80.0)
Myalgia	2(66.7)	2(33.3)	4(66.7)	8(53.3)
Back pain	0(0.0)	2(33.3)	0(0.0)	2(13.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0(0.0)	1(16.7)	4(66.7)	5(33.3)
Cancer pain	0(0.0)	0(0.0)	3(50.0)	3(20.0)
Nervous system disorders	3(100.0)	6(100.0)	6(100.0)	15(100.0)
Peripheral sensory neuropathy	3(100.0)	5(83.3)	6(100.0)	14(93.3)
Dysgeusia	1(33.3)	1(16.7)	1(16.7)	3(20.0)
Respiratory, thoracic and mediastinal disorders	2(66.7)	2(33.3)	2(33.3)	6(40.0)
Cough	2(66.7)	1(16.7)	1(16.7)	4(26.7)
Hiccups	1(33.3)	0(0.0)	1(16.7)	2(13.3)
Skin and subcutaneous tissue disorders	2(66.7)	6(100.0)	6(100.0)	14(93.3)
Alopecia	2(66.7)	6(100.0)	6(100.0)	14(93.3)
Rash	0(0.0)	2(33.3)	2(33.3)	4(26.7)
Vascular disorders	0(0.0)	3(50.0)	1(16.7)	4(26.7)
Hot flush	0(0.0)	2(33.3)	1(16.7)	3(20.0)
Hypertension	0(0.0)	1(16.7)	1(16.7)	2(13.3)

Serious Adverse Events and Deaths

- No deaths were reported during the study. One patient died 40 days after the last administration of ASA404 due to acute myocardial infarction.
- A total of 5 SAEs were reported in 5 patients during the study. All of these SAEs (tumor hemorrhage, enterocolitis hemorrhagic, femoral neck fracture, pharyngitis, pneumonia) occurred in one patient each and the events were not clustered in any particular primary system organ class.

Other Relevant Findings

- AEs leading to discontinuation were tuberculosis, enterocolitis hemorrhagic, femoral neck fracture, weight decreased, peripheral sensory neuropathy, and electrocardiogram QT prolonged.
- All of these AEs, except tuberculosis and femoral neck fracture, were suspected to be related to study drugs.
- Electrocardiogram QT prolonged was reported in 2 patients at the ASA404 1800 mg/m^2 and one of these patients had Grade 3 electrocardiogram QT prolonged as DLT, but both events were resolved in short period (1 and 4 days, respectively) without treatment.

Date of Clinical Trial Report 17 Dec 2009
Date Inclusion on Novartis Clinical Trial Results Database 20 June 2010
Date of Latest Update