Sponsor

Novartis

Generic Drug Name

ASA404 / Vadimezan

Therapeutic Area of Trial

Non-small cell lung cancer.

Approved Indication

Investigational

Study Number

CASA404A2301

Title

A Phase III, randomized, double-blind, placebo-controlled, multi-center study of ASA404 in combination with paclitaxel and carboplatin as first-line treatment for locally advanced or metastatic (stage IIIb/IV) non-small cell lung cancer (NSCLC).

Phase of Development

Phase III

Study Start/End Dates

08-Apr-2008 to 20- May-2010

Study Design/Methodology

This was a prospective, global, multicenter, double-blind, placebo-controlled, randomized Phase III study. Patients were randomized in a 1:1 ratio into two treatment arms: ASA404 1800 mg/m^2 plus paclitaxel 200 mg/m^2 and carboplatin AUC 6.0 (ASA404 arm) or Placebo plus paclitaxel 200 mg/m^2 and carboplatin AUC 6.0 (placebo arm). Randomization was stratified by gender and NSCLC histology (squamous NSCLC versus non-squamous NSCLC).

All patients began study treatment within 7 days from randomization and continued for 6 treatment cycles (each cycle was 21 days). Patients who completed 6 cycles of study treatment without progressive disease (PD) as confirmed by RECIST continued to receive blinded study drug, either ASA404 or placebo as maintenance treatment until PD. Patients who did not complete 6 cycles were not eligible to continue on maintenance treatment. Study treatment continued until disease progression, unacceptable toxicity or consent was withdrawn. Tumor assessments were performed every 6 weeks in patients who discontinued study treatment, until PD. Patients were followed every 6 weeks for survival following every treatment completion, discontinuation, or documented PD until either death or the data cut-off date (01-Jun-2010). No

treatment-arm cross-over was allowed during this study.

Centres

A total of 222 centers in 25 countries: Argentina (5 sites), Belgium (4 sites), Brazil (5 sites), Canada (7 sites), China (3 sites), Czech Republic (3 sites), France (10 sites), Germany (15 sites), Greece (1 site), Hong Kong (1 site), Hungary (4 sites), Israel (1 site), Italy (9 sites), Japan (32 sites), Korea (7 sites), Netherlands (6 sites), New Zealand (4 sites), Poland (4 sites), Singapore (2 sites), Spain (10 sites), Sweden (1 site), Taiwan (7 sites), Turkey (6 sites), UK (6 sites), US (69 sites)

Publication

None

Objectives

Primary objective

The primary objective was to compare the overall survival (OS) of patients receiving ASA404 or placebo in combination with paclitaxel and carboplatin for first-line treatment of Stage IIIb/IV NSCLC.

Key Secondary objectives

- To compare the OS of patients with non-squamous NSCLC receiving ASA404 or placebo in combination with paclitaxel and carboplatin.
- To compare the OS of patients with squamous NSCLC receiving ASA404 or placebo in combination with paclitaxel and carboplatin.

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

ASA404 was administered at a dose of 1800 mg/m^2 calculated based on body surface area as a 50 mL intravenous (IV) infusion over a period of 20 minutes following the administration of paclitaxel and carboplatin on Day 1 of every treatment cycle. Prior to the IV infusion, ASA404 was diluted using 5% glucose (dextrose) in an infusion bag covered with amber colored cover and tubing, as ASA404 is light sensitive.

ASA404 was administered for 6 cycles (each cycle was 21 days). Patients who completed 6 cycles of study treatment without disease progression (PD) as confirmed per RECIST continued to receive blinded study drug, either ASA404 or placebo as maintenance treatment until PD.

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

All patients received a 50 mL IV infusion of placebo over a period of 20 minutes following the administration of paclitaxel and carboplatin on Day 1 of every treatment cycle. The placebo used was a commercially available infusion bag filled with glucose (dextrose) solution, which was also covered with amber colored cover and tubing identical to the ASA404 infusion bag. All patients received a 3-hour IV infusion of commercially available paclitaxel 200 mg/m^2 as the first treatment and a 30-minute IV infusion of commercially available carboplatin AUC 6.0 as the second treatment on Day 1 of every treatment cycle.

Criteria for Evaluation

Efficacy

Primary endpoint:

The primary endpoint of this study was OS of all patients with NSCLC. OS was calculated as time from the date of randomization to the date of death due to any cause, or the last date the patient was known to be alive (censored observation) at the date of the data cut-off.

Secondary endpoints:

- Key secondary endpoints were OS of patients with non-squamous NSCLC and OS of patients with squamous NSCLC.
- The other secondary efficacy variables were to compare progression free survival (PFS), patient reported outcomes (PRO) and overall response rate (ORR) between two treatment groups.
- Included ORR defined as the proportion of patients with CR or PR; PFS defined as the time from the date of randomization to the date of an event defined as documented progression per RECIST or death due to any cause, whichever occurs first; PROs (physical function scale and global health status/QoL scale).

Safety and tolerability

Safety assessments consisted of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs), with their severity and relationship to study drug, and regular monitoring of hematology, blood chemistry, urine, vital signs, physical condition, and body weight. Adverse events are assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

There were some special safety assessments which consisted of:

- ECG: All patients received ECG assessments. In addition, a sub-study of patients underwent frequent ECG testing with corresponding pharmacokinetic (PK) sampling at selected sites.
- Ophthalmic: A substudy of patients underwent an ophthalmic evaluation at Baseline Visit and End of Treatment Visit to assess visual disturbances.

Pharmacology

Pharmacokinetic testing was performed immediately following the ECG assessment. A sub-study of 150 patients and subset of Japanese patients (maximum 20, approximately 10 patients per arm) at designated sites also had blood drawn for PK assessments. For PK analyses, PK parameters (AUClast, AUC∞, λz, t1/2, Tmax, Cmax) and ASA404 concentrations were summarized.

Pharmacodynamic biomarkers

The plasma levels of the pharmacodynamic biomarker of ASA404, 5-hydroxy indoleacetic acid (5-HIAA) were measured to assess the pharmacodynamic effect of ASA404.

Statistical Methods

Analyses of primary and all secondary efficacy endpoints was based on the Full Analysis set (FAS) defined according to the Intention to Treat (ITT) principle as all patients to whom study treatment was assigned. Safety analysis was performed for the safety analysis population.

In each treatment arm, the Kaplan-Meier estimate of the OS function was estimated and displayed. Median OS for each treatment arm was obtained along with 95% CI. The hazard ratio (HR) of the treatment effect was estimated from a stratified Cox proportional hazard model using randomization strata, and was presented with 95% CI. The statistical basis for a claim of efficacy was the statistically significant difference between the treatment arms at 5% overall significance level in favor of ASA404 treatment arm.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Histologically confirmed non-small cell carcinoma of the lung.
- Newly diagnosed Stage IIIb/IV disease
- No prior systemic antineoplastic treatment for Stage IIIb/IV non-small cell carcinoma of the lung
- Age ≥ 18 years old.
- WHO Performance Status of 0-1.
- Measurable or non-measurable disease per RECIST criteria.
- Lab values within the range, as defined below, within 2 weeks of randomization:
  - Absolute neutrophil count (ANC) > 2.0 x 10^9/L
  - Platelets ≥ 100 x10^9/L
  - Hemoglobin ≥ 10 g/dL
  - Serum creatinine ≤ 1.5 x upper limit of normal (ULN) (≤ 120 µmol/L)
  - Serum bilirubin ≤ 1.5 x ULN (≤ 25 µmol/L)
  - Aspartate aminotransaminase (AST) and alanine aminotransaminase (ALT) ≤ 2.5 x ULN (≤ 5 x ULN if liver metastases)
  - International Normalized Ratio (INR) or Prothrombin Time (PT) ≤ 1.5 x IULN
  - Electrolyte values (potassium, calcium, magnesium) within ≥ 1 x LLN and ≤ 1 x ULN.

Patients with corrected electrolyte values are eligible

- Females of child-bearing potential must have negative serum pregnancy test
- Life expectancy ≥ 12 weeks.
- Written informed consent obtained according to local guidelines.

Exclusion criteria

- Patients having central nervous system (CNS) metastases.
- Patients with a history of another primary malignancy ≤ 5 years, with the exception of non-melanoma skin cancer or cervical cancer in situ.
- Radiotherapy ≤ 2 weeks prior to randomization
- Major surgery ≤ 4 weeks prior to randomization or minor surgery ≤ 2 weeks prior to randomization.
- Concurrent use of other investigational agents and patients who had received investigational agents ≤ 4 weeks prior to randomization.
- Prior exposure to tumor-vascular disrupting agents or other vascular targeting agents.
- Pleural effusion causing ≥ common terminology criteria (CTC) Grade 2 dyspnea.
- Patients with systolic blood pressure (BP) > 160 mm Hg and/or diastolic BP > 90 mm Hg.
- Patients with recent hemoptysis associated with NSCLC (> 1 teaspoon in a single episode within 4 weeks).
- Patients with any one of the following:
  - Patients with long QT syndrome
  - Patients with a baseline 12-lead ECG QTc of > 450 ms per central evaluation
  - Congestive heart failure (NY Heart Association class III or IV)
  - Patients with a myocardial infarction within 12 months of study entry
  - Unstable or poorly controlled angina pectoris, including Prinzmetal 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
  - Right bundle branch block and left anterior hemiblock (bifasicular block)
  - Bradycardia defined as heart rate <50 beats per minute (bpm)
  - For China only: Patients older than 70 years with evidence of myocardial ischemia by coronary artery angiography or cardiac radionucleotide imaging examination
  - For China only: Patients with LVEF ≤ 40%
- Concomitant use of drugs with a risk of causing Torsades de Pointes.
- 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 (CTC Grade 2 neuropathy, re-

gardless of causality).

- Pregnant or breast feeding females.
- 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. [Note: In Korea, women of childbearing potential were excluded].
- Concurrent severe and/or uncontrolled medical disease (i.e. uncontrolled diabetes, chronic renal disease, chronic liver disease, confirmed diagnosis of HIV infection or active uncontrolled infection).
- Significant neurologic or psychiatric disorder which compromised participation in the study.
- Patient unwilling or unable to comply with the protocol.

Demographics

A total of 1299 patients were enrolled into this study, 649 patients to the ASA404 arm and 650 patients to the placebo arm. For the sub study, a total of 171 patients were enrolled 81 to the ASA404 arm and 90 to the placebo arm.

Number of Subjects

Patient disposition by treatment (Full analysis Set)

	ASA404 + PC N=649 n (%)	Placebo + PC N=650 n (%)	All patients N=1299 n (%)
Patients randomized			
Treated	628 (96.8)	626 (96.3)	1254 (96.5)
Untreated	21 (3.2)	24 (3.7)	45 (3.5)
Patients treated			
Treatment Discontinued	628 (96.8)	626 (96.3)	1254 (96.5)
Primary reason for treatment discontinued			
Abnormal laboratory value(s)	8 (1.2)	6 (0.9)	14 (1.1)
Abnormal test procedure result(s)	4 (0.6)	0 (0.0)	4 (0.3)
Administrative problems	49 (7.6)	55 (8.5)	104 (8.0)
Adverse Event(s)	155 (23.9)	137 (21.1)	292 (22.5)
Death	23 (3.5)	21 (3.2)	44 (3.4)
Disease progression	333 (51.3)	332 (51.1)	665 (51.2)
Lost to follow-up	2 (0.3)	1 (0.2)	3 (0.2)
Protocol deviation	10 (1.5)	15 (2.3)	25 (1.9)
Subject withdrew consent	31 (4.8)	38 (5.8)	69 (5.3)
Treatment duration completed as per protocol	13 (2.0)	21 (3.2)	34 (2.6)
Primary reason for not being treated			
Abnormal laboratory value(s)	2 (0.3)	4 (0.6)	6 (0.5)
Abnormal test procedure result(s)	3 (0.5)	1 (0.2)	4 (0.3)
Administrative problems	1 (0.2)	0 (0.0)	1 (0.1)
Adverse Event(s)	3 (0.5)	2 (0.3)	5 (0.4)
Death	1 (0.2)	0 (0.0)	1 (0.1)
Disease progression	0 (0.0)	2 (0.3)	2 (0.2)
Protocol deviation	7 (1.1)	11 (1.7)	18 (1.4)
Subject withdrew consent	4 (0.6)	4 (0.6)	8 (0.6)
PC= Paclitaxel and carboplatin, which is defined as standard therapy in this study.			

Demographic and Background Characteristics

Demographic summary by treatment (Full Analysis Set)

	ASA404 + PC N=649	Placebo + PC N=650	All patients N=1299
Age (Years)			
n	649	650	1299
Mean	60.8	60.0	60.4
SD	9.15	9.67	9.42
Median	62.0	61.0	61.0
Minimum	29.0	23.0	23.0
Maximum	87.0	85.0	87.0
Age category (n, %)			
< 65	401 (61.8)	433 (66.6)	834 (64.2)
≥ 65	248 (38.2)	217 (33.4)	465 (35.8)
Sex (n, %)			
Female	246 (37.9)	245 (37.7)	491 (37.8)
Male	403 (62.1)	405 (62.3)	808 (62.2)
Race (n, %)			
Caucasian	464 (71.5)	465 (71.5)	929 (71.5)
Black	11 (1.7)	8 (1.2)	19 (1.5)
Asian	162 (25.0)	164 (25.2)	326 (25.1)
Native American	2 (0.3)	5 (0.8)	7 (0.5)
Pacific Islander	1 (0.2)	0 (0.0)	1 (0.1)
Other	9 (1.4)	8 (1.2)	17 (1.3)
Ethnicity (n, %)			
Hispanic/Latino	41 (6.3)	29 (4.5)	70 (5.4)
Chinese	51 (7.9)	61 (9.4)	112 (8.6)
Indian (Indian subcontinent)	3 (0.5)	1 (0.2)	4 (0.3)
Japanese	70 (10.8)	69 (10.6)	139 (10.7)
Mixed Ethnicity	2 (0.3)	7 (1.1)	9 (0.7)
Other	448 (69.0)	453 (69.7)	901 (69.4)
Missing	34 (5.2)	30 (4.6)	64 (4.9)
WHO PS (n, %)			
0	266 (41.0)	258 (39.7)	524 (40.3)
1	381 (58.7)	384 (59.1)	765 (58.9)
Missing	2 (0.3)	8 (1.2)	10 (0.8)
Body surface area (m^2)			
n	637	641	1278

Mean	1.8	1.8	1.8
SD	0.23	0.23	0.23
Median	1.8	1.8	1.8
Minimum	1.1	1.1	1.1
Maximum	2.5	2.7	2.7
PC= Paclitaxel and carboplatin, PS= Performance status			

Primary Objective Results

There was no significant difference in OS between the ASA404 and the placebo treatment arms with 13.44 months and 12.71 months respectively, HR=1.01 (95% CI: 0.85, 1.19), one-sided p-value=0.535.

Analysis of Overall Survival for all patients (Full Analysis Set)

	ASA404 + PC N=649	**Placebo + PC N=650**	**P-value[1]**	**Hazard Ratio [2] [95% CI]**
No. of events	266 (41.0%)	266 (40.9%)	0.535	1.01 [0.85,1.19]
No. censored	383 (59.0%)	384 (59.1%)		
Kaplan-Meier estimates [95% CI] at:				
3 months	90.3 [88.0;92.6]	92.2 [90.1;94.3]		
6 months	76.7 [73.4;80.0]	79.0 [75.7;82.2]		
9 months	60.8 [56.7;64.9]	65.2 [61.2;69.1]		
12 months	52.7 [48.0;57.4]	51.6 [46.6;56.6]		
25th percentile [95% CI] (months)	6.51 [5.75;6.93]	6.97 [6.11;7.52]		
Median [95% CI] (months)	13.44 [11.43;16.62]	12.71 [11.33;14.42]		
75th percentile [95% CI] (months)	20.80 [18.73;NA]	19.32 [16.62;NA]		
PC= Paclitaxel and carboplatin [1] P-value is obtained from the one-sided Stratified Log-Rank test. [2] Hazard ratio is obtained from Stratified Cox model.				

Secondary Objective Results

Analysis of Overall Survival for non-squamous NSCLC patients (Full Analysis Set)

	ASA404 + PC N=501	**Placebo + PC N=500**	**Hazard ratio [1] [95% CI]**
No. of events	191 (38.1%)	196 (39.2%)	0.98 [0.80,1.19]
No. censored	310 (61.9%)	304 (60.8%)	
Kaplan-Meier estimates [95% CI] at:			

3 months	90.3 [87.7;92.9]	93.4 [91.2;95.6]	
6 months	77.7 [74.0;81.4]	79.5 [75.8;83.1]	
9 months	64.1 [59.6;68.7]	66.9 [62.5;71.3]	
12 months	56.7 [51.5;61.9]	53.7 [48.1;59.4]	
25th percentile [95% CI] (months)	6.57 [5.82;7.56]	7.10 [6.34;7.89]	
Median [95% CI] (months)	15.05 [13.37;20.80]	13.50 [11.66;15.28]	
75th percentile [95% CI] (months)	20.80 [18.73;NA]	19.32 [16.62;NA]	

PC= Paclitaxel and carboplatin

[1] Hazard ratio is obtained from Stratified Cox model.

Analysis of Overall Survival for squamous NSCLC patients (Full Analysis Set)

	ASA404 + PC N=148	**Placebo + PC N=150**	**Hazard ratio [1] [95% CI]**
No. of events	75 (50.7%)	70 (46.7%)	1.10 [0.79,1.52]
No. censored	73 (49.3%)	80 (53.3%)	
Kaplan-Meier estimates [95% CI] at:			
3 months	90.4 [85.6;95.2]	88.2 [83.0;93.5]	
6 months	73.3 [66.1;80.6]	77.3 [70.4;84.3]	
9 months	49.0 [39.8;58.2]	59.4 [50.8;68.0]	
12 months	38.4 [28.3;48.6]	43.7 [32.9;54.6]	
25th percentile [95% CI] (months)	5.85 [5.29;7.03]	6.24 [4.83;7.52]	
Median [95% CI] (months)	8.94 [8.28;11.93]	10.74 [9.03;14.16]	
75th percentile [95% CI] (months)	NA [12.39;NA]	14.82 [14.16;15.97]	

PC= Paclitaxel and carboplatin

[1] Hazard ratio is obtained from Stratified Cox model.

Safety Results

Adverse Events by System Organ Class

Adverse events, regardless of study drug relationship, with at least 5% incidence of any grade events in either arm, by system organ class, maximum grade and treatment (Safety Set)

	ASA404 + PC N=629 n (%)			Placebo + PC N= 625 n (%)		
System organ class	**All grades**	**Grade 3**	**Grade 4**	**All grades**	**Grade 3**	**Grade 4**
Any system organ class	622 (98.9)	274 (43.6)	233 (37.0)	614 (98.2)	303 (48.5)	187 (29.9)
Gastrointestinal disorders	445 (70.7)	52 (8.3)	5 (0.8)	433 (69.3)	35 (5.6)	3 (0.5)
Blood and lymphatic system disorders	433 (68.8)	175 (27.8)	179 (28.5)	402 (64.3)	174 (27.8)	132 (21.1)
General disorders and administration site conditions	430 (68.4)	50 (7.9)	6 (1.0)	421 (67.4)	54 (8.6)	8 (1.3)
Nervous system disorders	414 (65.8)	43 (6.8)	10 (1.6)	425 (68.0)	44 (7.0)	8 (1.3)
Musculoskeletal and connective tissue disorders	382 (60.7)	48 (7.6)	2 (0.3)	373 (59.7)	48 (7.7)	6 (1.0)
Skin and subcutaneous tissue disorders	367 (58.3)	16 (2.5)	3 (0.5)	368 (58.9)	12 (1.9)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	317 (50.4)	59 (9.4)	18 (2.9)	312 (49.9)	47 (7.5)	23 (3.7)
Metabolism and nutrition disorders	261 (41.5)	37 (5.9)	6 (1.0)	253 (40.5)	33 (5.3)	4 (0.6)
Infections and infestations	193 (30.7)	44 (7.0)	9 (1.4)	190 (30.4)	45 (7.2)	7 (1.1)
Investigations	177 (28.1)	35 (5.6)	12 (1.9)	182 (29.1)	34 (5.4)	9 (1.4)
Psychiatric disorders	154 (24.5)	10 (1.6)	0 (0.0)	177 (28.3)	6 (1.0)	2 (0.3)
Vascular disorders	141 (22.4)	23 (3.7)	6 (1.0)	95 (15.2)	12 (1.9)	4 (0.6)
Eye disorders	124 (19.7)	7 (1.1)	0 (0.0)	51 (8.2)	1 (0.2)	1 (0.2)
Cardiac disorders	73 (11.6)	8 (1.3)	9 (1.4)	59 (9.4)	11 (1.8)	3 (0.5)
Injury, poisoning and procedural complications	46 (7.3)	3 (0.5)	0 (0.0)	44 (7.0)	5 (0.8)	0 (0.0)
Ear and labyrinth disorders	39 (6.2)	0 (0.0)	0 (0.0)	32 (5.1)	2 (0.3)	0 (0.0)
Renal and urinary disorders	37 (5.9)	4 (0.6)	1 (0.2)	50 (8.0)	5 (0.8)	2 (0.3)
Immune system disorders	32 (5.1)	3 (0.5)	4 (0.6)	24 (3.8)	7 (1.1)	2 (0.3)

PC= Paclitaxel and carboplatin

System organ classes are sorted by descending frequency of all grades in the ASA404A+PC arm.

A patient with multiple adverse events within a system organ class is counted only once.

Adverse events occurring more than 28 days after the last date of study treatment are not summarized.

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

Preferred term	ASA404 + PC N=629 n (%)			Placebo + PC N= 625 n (%)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Neutropenia	357 (56.8)	158 (25.1)	167 (26.6)	317 (50.7)	148 (23.7)	119 (19.0)
Alopecia	297 (47.2)	10 (1.6)	3 (0.5)	303 (48.5)	6 (1.0)	0 (0.0)
Nausea	250 (39.7)	14 (2.2)	1 (0.2)	251 (40.2)	13 (2.1)	0 (0.0)
Fatigue	224 (35.6)	22 (3.5)	1 (0.2)	219 (35.0)	21 (3.4)	0 (0.0)
Decreased appetite	195 (31.0)	13 (2.1)	0 (0.0)	166 (26.6)	12 (1.9)	0 (0.0)
Constipation	166 (26.4)	7 (1.1)	1 (0.2)	161 (25.8)	5 (0.8)	0 (0.0)
Anemia	155 (24.6)	29 (4.6)	5 (0.8)	156 (25.0)	28 (4.5)	2 (0.3)
Diarrhea	154 (24.5)	15 (2.4)	1 (0.2)	128 (20.5)	6 (1.0)	1 (0.2)
Arthralgia	153 (24.3)	7 (1.1)	0 (0.0)	146 (23.4)	13 (2.1)	2 (0.3)
Dyspnea	131 (20.8)	32 (5.1)	5 (0.8)	131 (21.0)	26 (4.2)	4 (0.6)
Myalgia	131 (20.8)	5 (0.8)	0 (0.0)	12 (20.3)	10 (1.6)	0 (0.0)
Vomiting	131 (20.8)	9 (1.4)	0 (0.0)	146 (23.4)	13 (2.1)	0 (0.0)

PC= Paclitaxel and carboplatin

Preferred terms are sorted by descending frequency of all grades in the ASA40A+PC arm.

Adverse events occurring more than 28 days after last date of study treatment are not summarized.

Serious Adverse Events and Deaths

Serious Adverse Events

The overall incidence of SAEs was comparable between the ASA404 and placebo treatment arms (37.0% and 32.5%, respectively). The most frequently reported SAEs in the ASA404 arm were dyspnea, pneumonia, and febrile neutropenia; while those in the placebo arm were pyrexia, pneumonia, and dyspnea.

Serious adverse events, regardless of study drug relationship, with at least 2% incidence in either arm by preferred term (Safety Set)

Preferred term	ASA404 + PC N=629 n (%)	Placebo + PC N=625 n (%)

Any primary system organ class	233 (37.0)	203 (32.5)
Dyspnea	27 (4.3)	15 (2.4)
Pneumonia	26 (4.1)	17 (2.7)
Anemia	15 (2.4)	7 (1.1)
Febrile neutropenia	13 (2.1)	15 (2.4)
Pleural effusion	10 (1.6)	13 (2.1)
Pyrexia	10 (1.6)	19 (3.0)
Vomiting	5 (0.8)	13 (2.1)

PC= Paclitaxel and carboplatin
Preferred terms are sorted by descending frequency in the ASA40A+PC arm.
A patient with multiple occurrences of an SAE is counted only once in the SAE category.
Adverse events occurring more than 28 days after last date of study treatment are not summarized.

Deaths

The ASA404 and placebo treatment arms had similar incidence of all deaths (260 deaths in each arm) and on-treatment deaths (28 and 25 deaths, respectively). Of the on-treatment deaths, 11 patients in the ASA404 arm and 16 patients in the placebo arm died due to disease progression.

Number of patients who died, had SAE, other clinically significant AE, AE leading to discontinuation and Grade 3-4 AE (Safety Set)

	ASA404 + PC N= 629 n (%)	**Placebo + PC N= 625 n (%)**
All deaths	260 (41.3)	260 (41.6)
On-treatment death	28 (4.5)	25 (4.0)
Serious adverse events (SAEs), regardless of relationship to study treatment	233 (37.0)	203 (32.5)
Serious adverse events (SAEs), with suspected relationship to study treatment	54 (8.6)	36 (5.8)
Other clinically significant adverse events, regardless of relationship to study treatment	467 (74.2)	442 (70.7)
Other clinically significant adverse events, with suspected relationship to study treatment	340 (54.1)	290 (46.4)
Adverse events leading to discontinuation	152 (24.2)	132 (21.1)
Serious adverse events	40 (6.4)	34 (5.4)
Other clinically significant AEs	116 (18.4)	102 (16.3)
Grade 3-4 AE regardless of relationship to study treatment	507 (80.6)	490 (78.4)
Grade 3-4 AE with suspected relationship to study treatment	247 (39.3)	209 (33.4)

PC= Paclitaxel and carboplatin
Categories are not mutually exclusive
On-treatment deaths are deaths which occurred up to 28 days after last date of study treatment
Adverse events occurring more than 28 days after last date of study treatment are not summarized.

On-treatment deaths by preferred term and treatment (Safety Set)

Principle cause of death	**ASA404 + PC N=629 n (%)**	**Placebo + PC N=625 n (%)**
Total number of on-treatment deaths	28 (4.5)	25 (4.0)
Other	17 (2.7)	9 (1.4)
Study indication	11 (1.7)	16 (2.6)
Any preferred term/ principal cause of death	17 (2.7)	9 (1.4)
Sepsis	3 (0.5)	0 (0.0)
Acute respiratory failure	1 (0.2)	1 (0.2)
Cachexia	1 (0.2)	0 (0.0)
Cardio-respiratory arrest	1 (0.2)	0 (0.0)
Cerebrovascular accident	1 (0.2)	1 (0.2)
Chronic obstructive pulmonary disease	1 (0.2)	0 (0.0)
Circulatory collapse	1 (0.2)	0 (0.0)
General physical health deterioration	1 (0.2)	0 (0.0)
Idiopathic pulmonary fibrosis	1 (0.2)	0 (0.0)
Ileus	1 (0.2)	0 (0.0)
Myocardial infarction	1 (0.2)	0 (0.0)
Pneumonia	1 (0.2)	1 (0.2)
Pneumonia aspiration	1 (0.2)	0 (0.0)
Septic shock	1 (0.2)	1 (0.2)
Sudden death	1 (0.2)	1 (0.2)
Cardiopulmonary failure	0 (0.0)	2 (0.3)
Death	0 (0.0)	1 (0.2)
Multi-organ failure	0 (0.0)	1 (0.2)

PC= Paclitaxel and carboplatin.
Principal cause of death is presented in descending order of frequency in the ASA404 treatment arm; AE preferred terms are sorted within principal cause also by descending frequency in the ASA404 arm.
On-treatment deaths are deaths which occurred up to 28 days after last date of study treatment.
If death is due to study indication, MedDRA coding is not applicable.

Other Relevant Findings None
Date of Clinical Trial Report 09-Dec-2010.
Date Inclusion on Novartis Clinical Trial Results Database 14 Jun 2011
Date of Latest Update