Sponsor

Novartis

Generic Drug Name

Vadimezan

Therapeutic Area of Trial

Non-small-cell lung cancer (NSCLC)

Approved Indication

Investigational

Study Number

CASA404A2302

Title

A phase III, randomized, double-blind, placebo-controlled, multi-center study of Vadimezan in combination with docetaxel in second-line treatment of patients with locally advanced or metastatic (stage III b/IV) non-small-cell lung cancer (NSCLC)

Phase of Development

Phase III

Study Start/End Dates

19 Dec 2008 to 20 Dec 2010

Study Design/Methodology

This was a prospective, global, multi-center, double-blind, placebo-controlled, randomized Phase III trial. Patients were randomized in a 1:1 ratio into one of the following two treatment arms ASA404 1800 mg/m^2 plus docetaxel 75 mg/m^2 or to placebo plus docetaxel 75 mg/m^2. Randomization was stratified by: World health Organization (WHO) performance status 0-1 versus 2; histology (squamous versus non-squamous); prior treatment with a paclitaxel-based regimen, if any, in the first-line setting.

Centres

218 centres in 23 countries: Argentina (5), Belgium (8), Brazil (13), Canada (10), China (9), Egypt (2), Germany (21), Hungary (7), Italy (12), Japan (15), Lebanon (1), Luxembourg (1), Mexico (1), Netherlands (3), New Zealand (4), Poland (4), South Africa (3)Spain (4), Switzerland (2), Thailand (3), Turkey (4), UK (8), USA (78)

Publication:

None.

Objectives

Primary objective(s)

To compare the Overall survival (OS) between the Vadimezan plus docetaxel group and the placebo plus docetaxel group.

Secondary objective(s)

Key secondary objective:

To compare Progression-free Survival (PFS) and the Overall Response Rate (ORR) per Response Evaluation Criteria in Solid Tumors(RECIST) assessed by the investigator between patients receiving Vadimezan or placebo in combination with docetaxel.

Other secondary objectives:

- To assess Time to Response (Complete Response [CR] or Partial Response [PR]) and Duration of Response per RECIST assessed by the investigator between patients receiving Vadimezan or placebo in combination with docetaxel.
- To assess safety of Vadimezan in combination with docetaxel.
- To determine population pharmacokinetics (PK) and factors influencing systemic exposure to Vadimezan.
- To assess physical functioning and global health status quality of life (QoL) as measured by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 in patients receiving Vadimezan or placebo in combination with docetaxel.

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

20-minute IV infusion of Vadimezan 1800 mg/m^2 + docetaxel 75 mg/m^2

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

20-minute IV infusion of placebo + docetaxel 75 mg/m^2.

Criteria for Evaluation

Primary variables

Primary end point:

Overall survival (OS) is defined as the 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 cutoff for the final analysis.

Secondary variables

Key secondary end point:

1) Progression Free Survival (PFS) is defined as the time from the date of randomization to the date of event defined as documented progression per RECIST or death due to any cause, whichever occurs first. 2) Overall Response Rate (ORR) was calculated by CT scan, MRI or clinical exam (for skin lesions only) following RECIST criteria.

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.

Other

An ophthalmic sub-study, performed at baseline and at the end of treatment, assessed patients' visual acuity, color vision, and central vision.

Statistical Methods

Efficacy analyses were based on the full analysis set while safety analyses were based on the safety set. The primary objective was phrased in terms of the null hypothesis that OS distribution of the two groups was equivalent. The alternative hypothesis was that OS was prolonged in either treatment group. In accordance with the stratified randomization scheme used in the study, a stratified log-rank test was used to test this hypothesis. A Kaplan-Meier survival plot for each treatment group and hazard ratio (HR) of the treatment effect along with its 95% confidence interval (CI) using a Cox proportional hazard model was provided for all patients as well as subgroups defined using randomization stratification factors. The Kaplan-Meier curves of the OS function displayed the number of patients at risk at equidistant time points. Median OS for each treatment group was obtained along with 95% CIs; 25% and 75% percentiles were also given. Kaplan-Meier estimates at 3, 6, 9, 12 months along with their 95% CIs were summarized.

The key secondary efficacy variables were PFS and ORR. A patient who had not progressed or died at the date of the analysis cut-off or when he/she received any further anti-cancer therapy had his/her PFS censored at the time of the last tumor assessment before the cut-off date or the anti-cancer therapy date whichever occurred first. Overall response rate would be analyzed using Cochran-Mantel-Haenszel test based on strata at randomization. The ORR (CR or PR) along with 95% CIs would be summarized by treatment group for all patients as well as subgroups defined using randomization stratification factors.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

- Histologically confirmed non-small-cell carcinoma of the lung of all histologies. (Histological or cytological specimens were collected via surgical biopsy, brushing, washing or core needle aspiration of a defined lesion. Sputum cytology was not acceptable.)
- Patients who had progressed while on or following a first-line chemotherapy regimen for Stage IIIb disease (malignant pleural effusion or pericardial effusion that had been confirmed cytologically) or Stage IV disease. Patients who had received bevacizumab and/or EGFR inhibitors in the first-line setting were eligible.
- Age ≥ 18 years old.
- WHO Performance Status 0-2.
- Central or local laboratory values within the range, as defined below, within 2 weeks of randomization:
  - Absolute neutrophils 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)
  - Serum bilirubin ≤ 1.5 x ULN
  - Alkaline phosphatase ≤ 2.5 x ULN
  - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5 x ULN (≤ 5 x ULN if liver metastases)
  - International Normalized Ratio (INR) or Prothrombin Time (PT) < 1.5 x ULN
  - Electrolyte values (sodium, potassium, calcium, magnesium) within > 1 x lower limit of normal (LLN) and < 1 x ULN. Patients with corrected electrolyte values were eligible
  - Females of child-bearing potential were to have negative serum pregnancy test (confirmation of negative urine pregnancy test within 72 hours prior to initial dosing). Any female presenting with a positive or borderline pregnancy test might undergo a gynecological exam and ultrasound to rule out pregnancy and if found to be negative might be included in the trial.
- Life expectancy ≥ 12 weeks.
- Written informed consent was obtained

Exclusion Criteria:

- Patients with central nervous system (CNS) metastases (patients having any clinical signs of CNS metastases were to have a computerized tomography scan (CT) or an Magnetic Resonance Imaging (MRI) of the brain performed to rule out CNS metastases in order to be eligible for study participation. Patients who have had brain metastases surgically removed or irradiated with no residual disease confirmed by imaging were allowed).
- Patients with a concurrent malignancy, or history of prior malignancy within the past three years, except for basal cell or squamous cell skin cancer, carcinoma in situ of the cervix, treated early stage (T1a) prostate cancer or treated early stage ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) breast cancer.
- Radiotherapy ≤ 2 weeks prior to randomization**.** Patients must have recovered from all acute radiotherapy-related toxicities.
- Major surgery was to be completed 4 weeks prior to starting study treatment. Major surgery is defined at the investigator's discretion. Insertion of a vascular access device is not considered major or minor surgery. Patients must have recovered from all acute major surgery-related complications.
- Treatment with all prior anticancer therapies ≤ 3 weeks prior to randomization (≤ 6 weeks for bevacizumab, mitomycin, and nitrosoureas).
- Concurrent use of other investigational agents and patients who had received investigational agents ≤ 4 weeks prior to randomization
- Prior treatment with docetaxel for NSCLC in the locally advanced or metastatic first-line setting
- Prior treatment with Vascular disrupting agents (VDAs) or tumor - VDAs
- Any medical condition resulting in ≥ Common Terminology Criteria (CTC) Grade 2 dyspnea
- Patients with systolic blood pressure (BP) > 160 mm Hg and/or diastolic BP > 90 mm Hg while on medication for hypertension
- 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 electrocardiogram (ECG) QTcF of > 450 msec for men or > 470 msec for women using the Fridericia [QTcF formula] measurement determined per central ECG evaluation report
  - Congestive heart failure (NY Heart Association class III or IV)
  - Patients with a myocardial infarction within 12 months of starting study treatment or with implanted cardiac pacemaker
  - Unstable or poorly controlled angina pectoris, including Prinzmetal variant angina pectoris
  - History of poorly-controlled hypertension or poor compliance with anti-hypertensive regimen
  - History of a sustained ventricular tachycardia
  - Presence of atrial tachyarrhythmia (e.g., atrial fibrillation, atrial flutter, multifocal atrial

tachycardia, supraventricular tachycardia) if not effectively rate-controlled
    - History of ventricular fibrillation or Torsades de Pointes
    - Right bundle branch block and either left anterior hemiblock-or left posterior hemiblock (bifasicular block)
    - Bradycardia defined as heart rate < 50 beats per minute
    - [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 left ventricular ejection fraction (LVEF) ≤ 40%]
    - Any clinically significant cardiac abnormality as assessed by the investigator
- Patients who were currently receiving treatment with any medications that had the potential to prolong QT interval or are known to have a risk of causing Torsades de Pointeswhich could not be either safely discontinued or switched to a different medication prior to starting study drug administration were discussed with and approved by the Novartis Global Clinical team prior to randomization.
- Known allergy or hypersensitivity to docetaxel or drugs formulated with polysorbate 80.
- Peripheral sensory neuropathy with functional impairment (CTC Grade 2 neuropathy, regardless of causality)
- Pregnant or breast feeding females
    - 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).
- 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 including an intrauterine device (IUD), oral or depot contraceptive or the barrier method plus spermicide).
    - Oral, implantable, or injectable contraceptives may be affected by cytochrome P450 interactions while taking docetaxel and therefore were not considered effective contraceptive methods for this study when used as a single agent. Therefore, it was highly recommended that a concomitant barrier method be used with oral, implantable, or injectable contraceptives. The investigator should counsel the patient accordingly. Women of childbearing potential must have a negative pregnancy test (serum or urine) 72 hours prior to administration of study treatment. For a list of substrates of human liver microsomal P450 enzymes, visit website (http://medicine.iupui.edu/flockhart)
- Concurrent severe and/or uncontrolled medical disease (i.e. uncontrolled diabetes, chronic renal disease, chronic liver disease, confirmed diagnosis of human immunodeficiency virus infection or active uncontrolled infection).
- Significant neurologic or psychiatric disorder which could compromise participation in the study.
- Patient unwilling or unable to comply with the protocol.
- Patients receiving full-dose therapeutic oral or parenteral anticoagulation were ineligible. Patients receiving thrombolytic therapy within 10 days of starting study treatment were also

ineligible.

Number of Subjects

Patient disposition (Full analysis set):

Disposition Reason	Vadimezan + Doc N=460 n (%)	Placebo + Doc N=460 n (%)	All patients N=920 n (%)
Patients screened			1196
Patient randomized			
Treated	438 (95.2)	441 (95.9)	879 (95.5)
Untreated	22 (4.8)	19 (4.1)	41 (4.5)
Primary reason for treatment discontinued			
Abnormal test procedure result(s)	1 (0.2)	1 (0.2)	2 (0.2)
Administrative problems	85 (18.5)	88 (19.1)	173 (18.8)
Adverse Event(s)	64 (13.9)	52 (11.3)	116 (12.6)
Death	32 (7.0)	18 (3.9)	50 (5.4)
Disease progression	236 (51.3)	240 (52.2)	476 (51.7)
Lost to follow-up	1 (0.2)	2 (0.4)	3 (0.3)
Protocol deviation	1 (0.2)	2 (0.4)	3 (0.3)
Subject withdrew consent	16 (3.5)	27 (5.9)	43 (4.7)
Treatment duration completed as per protocol	2 (0.4)	11 (2.4)	13 (1.4)
Reason for not being treated			
Abnormal laboratory value(s)	2 (0.4)	1 (0.2)	3 (0.3)
Abnormal test procedure result(s)	3 (0.7)	1 (0.2)	4 (0.4)
Administrative problems	5 (1.1)	2 (0.4)	7 (0.8)
Adverse Event(s)	2 (0.4)	4 (0.9)	6 (0.7)
Disease progression	1 (0.2)	0	1 (0.1)
Protocol deviation	4 (0.9)	6 (1.3)	10 (1.1)
Subject withdrew consent	2 (0.4)	3 (0.7)	5 (0.5)
Missing	3 (0.7)	2 (0.4)	5 (0.5)

Doc=Docetaxel

Demographic and Background Characteristics

Demographic summary (Full analysis set):

Demographic variable	Vadimezan + Doc N=460	Placebo + Doc N=460	All patients N=920
Age (Years)			
n	460	460	920
Mean (SD)	60.5 (9.89)	60.2 (10.03)	60.3 (9.96)
Median	61.0	61.0	61.0
Minimum, Maximum	33.0, 82.0	23.0, 83.0	23.0, 83.0
Age - n (%)			
<65	285 (62.0)	292 (63.5)	577 (62.7)

≥65	175 (38.0)	168 (36.5)	343 (37.3)
Sex - n (%)			
Female	159 (34.6)	171 (37.2)	330 (35.9)
Male	301 (65.4)	289 (62.8)	590 (64.1)
Race - n (%)			
Caucasian	340 (73.9)	339 (73.7)	679 (73.8)
Black	12 (2.6)	9 (2.0)	21 (2.3)
Asian	80 (17.4)	88 (19.1)	168 (18.3)
Native American	1 (0.2)	1 (0.2)	2 (0.2)
Pacific Islander	2 (0.4)	1 (0.2)	3 (0.3)
Other	24 (5.2)	22 (4.8)	46 (5.0)
Missing	1 (0.2)	0	1 (0.1)
Ethnicity - n (%)			
Hispanic/Latino	67 (14.6)	67 (14.6)	134 (14.6)
Chinese	27 (5.9)	37 (8.0)	64 (7.0)
Indian (Indian subcontinent)	2 (0.4)	1 (0.2)	3 (0.3)
Japanese	31 (6.7)	22 (4.8)	53 (5.8)
Mixed Ethnicity	6 (1.3)	2 (0.4)	8 (0.9)
Other	298 (64.8)	296 (64.3)	594 (64.6)
Missing	29 (6.3)	35 (7.6)	64 (7.0)
Body surface area (m^2)			
n	453	451	904
Mean (SD)	1.8 (0.25)	1.8 (0.22)	1.8 (0.23)
Median	1.8	1.8	1.8
Minimum, Maximum	1.0, 2.7	1.1, 2.5	1.0, 2.7
WHO performance status - n (%)			
0	173 (37.6)	154 (33.5)	327 (35.5)
1	258 (56.1)	277 (60.2)	535 (58.2)
2	27 (5.9)	28 (6.1)	55 (6.0)
Missing	2 (0.4)	1 (0.2)	3 (0.3)

DOC=Docetaxel; SD=Standard deviation; WHO=World Health Organization

Primary Objective Result(s)

Time from last alive date to data cut-off date (Full Analysis Set):

Time from last alive date to data cut-off date	Vadimezan + Doc N=261 n (%)	Placebo + Doc N=278 n (%)	All patients N=539 n (%)
>12 weeks to ≤18 weeks	3 (1.1)	2 (0.7)	5 (0.9)
>18 weeks to ≤24 weeks	56 (21.5)	62 (22.3)	118 (21.9)
>24 weeks	202 (77.4)	214 (77.0)	416 (77.2)

Data cut-off date is 16-May-2011.

Time from last alive date to data cut-off date = data cut-off date - last date that a patient was known to be alive.

Doc=Docetaxel

Analysis of Overall Survival using Cox regression model and Kaplan-Meier method (Full analysis set):

	Vadimezan + Doc N=460	Placebo + Doc N=460	p-value [1]	Hazard ratio [2] 95%[CI] Vadimezan + Doc/ Placebo + Doc
No. of events - n (%)	**199 (43.3)**	**181 (39.3)**	**0.929**	**1.17 [0.95,1.43]**
No. censored - n (%)	**261 (56.7)**	**279 (60.7)**		
Kaplan-Meier estimates [95% CI] at:				
3 months	83.1 [79.6; 86.6]	86.3 [83.1; 89.6]		
6 months	62.3 [57.3; 67.3]	67.7 [62.9; 72.6]		
9 months	46.5 [40.5; 52.5]	51.3 [45.3; 57.2]		
12 months	36.7 [29.8; 43.6]	41.4 [34.4; 48.5]		
25th percentile for [95% CI] (months)	3.84 [3.48; 4.57]	4.67 [4.14; 5.59]		
Median [95% CI] (months)	8.57 [7.59; 10.02]	9.59 [7.95; 11.60]		
75th percentile for [95% CI] (months)	18.56 [13.50; NA]	15.84 [14.23; 19.58]		

[1] P-value is obtained from the one-sided Stratified Log-Rank test.

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

Doc=Docetaxel

Overall survival for non-squamous NSCLC patients using Cox regression model and Kaplan-Meier method:

	Vadimezan + Doc N=460	Placebo + Doc N=460	Hazard ratio [1] 95%[CI] Vadimezan + Doc/ Placebo + Doc

No. of events - n (%)	**136 (41.1)**	**126 (38.0)**	**1.15 [0.90,1.47]**
No. censored - n (%)	**195 (58.9)**	**206 (62.0)**	
Kaplan-Meier estimates [95% CI] at:			
3 months	84.8 [80.8; 88.7]	87.3 [83.6; 91.0]	
6 months	65.4 [59.6; 71.1]	68.9 [63.3; 74.5]	
9 months	50.4 [43.5; 57.4]	53.2 [46.3; 60.2]	
12 months	40.0 [31.7; 48.4]	43.4 [34.9; 51.9]	
25th percentile for [95% CI] (months)	4.14 [3.52; 4.96]	4.83 [4.27; 5.82]	
Median [95% CI] (months)	9.03 [7.92; 11.10]	10.97 [8.02; 13.31]	
75th percentile for [95% CI] (months)	18.56 [14.00; NA]	15.84 [14.62; 19.58]	

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

Doc=Docetaxel

Overall survival for squamous NSCLC patients using Cox regression model and Kaplan-Meier method:

	Vadimezan + Doc N=129	**Placebo + Doc N=128**	**Hazard ratio [1] [95% CI] Vadimezan +Doc / Placebo+Doc**
No. of events - n (%)	**63 (48.8)**	**55 (43.0)**	**1.21 [0.84, 1.75]**
No. censored - n (%)	**66 (51.2)**	**73 (57.0)**	
Kaplan-Meier estimates [95% CI] at:			
3 months	78.9 [71.5; 86.2]	83.8 [77.1; 90.5]	
6 months	54.3 [44.4; 64.2]	64.7 [55.3; 74.1]	
9 months	35.9 [24.4; 47.5]	46.2 [34.6; 57.8]	
12 months	27.9 [15.7; 40.0]	36.1 [23.5; 48.7]	
25th percentile for [95% CI] (months)	3.48 [2.69; 4.47]	4.21 [3.22; 5.85]	
Median [95% CI] (months)	7.33 [5.52; 8.57]	8.31 [6.77; 10.38]	
75th percentile for [95% CI] (months)	12.06 [8.77; NA]	14.23 [10.38; NA]	

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

Doc=Docetaxel

Secondary Objective Result(s)

Progression-free survival based on investigator assessment using a Cox regression model and Kaplan-Meier method (Full analysis set):

	Vadimezan + Doc N=460	Placebo + Doc N=460	p-value [1]	Hazard ratio [2] [95% CI] Vadimezan +Doc / Placebo+Doc
No. of events – n (%)	284 (61.7)	287 (62.4)	0.824	1.08 [0.92,1.28]
Progression	236 (51.3)	245 (53.3)		
Death	48 (10.4)	42 (9.1)		
No. censored - n (%)	176 (38.3)	173 (37.6)		
Kaplan-Meier estimates [95% CI] at:				
3 months	51.9 [46.9; 57.0]	53.2 [48.1; 58.3]		
6 months	24.0 [18.9; 29.1]	23.3 [18.3; 28.4]		
9 months	9.0 [4.4; 13.6]	12.4 [7.8; 17.0]		
12 months	5.6 [0.9; 10.4]	6.0 [2.0; 10.0]		
25th percentile for [95% CI] (months)	**1.41 [1.38; 1.48]**	**1.45 [1.41; 1.61]**		
Median [95% CI] (months)	**3.29 [2.83; 4.11]**	**3.61 [2.89; 4.17]**		
75th percentile for [95% CI] (months)	**5.95 [5.52; 6.90]**	**5.72 [5.55; 6.67]**		

[1] P-value is obtained from the one-sided Stratified Log-Rank test.

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

Doc=Docetaxel

Best overall response as per investigator assessment (Full analysis set):

Best overall response	**Vadimezan + Doc N=460 n (%)**	**Placebo + Doc N=460 n (%)**	**P-value[1]**
Complete response (CR)	0	1 (0.2)	
Partial response (PR)	31 (6.7)	33 (7.2)	
Stable disease (SD)	183 (39.8)	185 (40.2)	
Progressive disease (PD)	132 (28.7)	135 (29.3)	
Unknown	113 (24.6)	105 (22.8)	
Objective response rate ORR (CR or PR)	31 (6.7)	34 (7.4)	0.7970
95% CI for ORR	[4.6, 9.4]	[5.2, 10.2]	

[1] P-value is obtained from Exact Cochran-Mantel-Haenszel test; test is stratified by histology, WHO PS and prior treatment.

The 95% CI for the proportion of overall response is computed using the Clopper-Pearson method.

Doc=Docetaxel

Treatment cycles with combination study treatment administered (Safety set):

	Vadimezan + Doc N=438	Placebo + Doc N=441
Treatment Cycles		
1	438 (100)	441 (100)
2	384 (87.7)	399 (90.5)
3	262 (59.8)	280 (63.5)
4	221 (50.5)	239 (54.2)
5	161 (36.8)	172 (39.0)
6	131 (29.9)	146 (33.1)
Total number of cycles on treatment		
N	438	441
Mean (SD)	3.6 (1.86)	3.8 (1.84)
Median	4.0	4.0
Min, Max	1.0, 6.0	1.0, 6.0

Only cycles with combinational study treatment administered are counted
Doc=Docetaxel

Treatment cycles with study drug alone (Vadimezan or placebo) administered (Safety set):

	Vadimezan + Doc N=438	Placebo + Doc N=441
Treatment Cycles		
1	108 (24.7)	119 (27.0)
2	87 (19.9)	96 (21.8)
3	56 (12.8)	54 (12.2)
4	40 (9.1)	44 (10.0)
5	30 (6.8)	30 (6.8)
6	25 (5.7)	27 (6.1)
7	9 (2.1)	20 (4.5)
8	5 (1.1)	15 (3.4)
9	2 (0.5)	12 (2.7)
10	2 (0.5)	9 (2.0)
11	1 (0.2)	5 (1.1)
12	1 (0.2)	5 (1.1)
13	1 (0.2)	3 (0.7)
14	1 (0.2)	2 (0.5)
15	1 (0.2)	2 (0.5)
16	1 (0.2)	2 (0.5)
17	0	1 (0.2)
Total number of cycles on treatment		
N	108	119
Mean (SD)	3.4 (2.42)	3.7 (3.24)
Median	3.0	2.0

Min, Max	1.0, 16.0	1.0, 17.0

Only maintenance cycles with Vadimezan /Placebo administered alone are counted.
DOC=Docetaxel

PK analysis:

No PK analysis was performed.

Quality of life (QOL):

Physical function decreased over time in both treatment arms. However, no differences were observed between the treatment arms for global health status or QoL.

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 group, by system organ class, maximum Common Terminology Criteria for Adverse Events(CTCAE) grade (Safety Set):

	Vadimezan + Doc N=438			Placebo + Doc N=441		
System organ class	**All grades**	**Grade 3**	**Grade 4**	**All grades**	**Grade 3**	**Grade 4**
-Any system organ class	430 (98.2)	152 (34.7)	200 (45.7)	429 (97.3)	135 (30.6)	209 (47.4)
General disorders and administration site conditions	322 (73.5)	55 (12.6)	7 (1.6)	295 (66.9)	50 (11.3)	14 (3.2)
Blood and lymphatic system disorders	283 (64.6)	80 (18.3)	147 (33.6)	285 (64.6)	76 (17.2)	153 (34.7)
Gastrointestinal disorders	266 (60.7)	36 (8.2)	4 (0.9)	277 (62.8)	23 (5.2)	3 (0.7)
Respiratory, thoracic and mediastinal disorders	243 (55.5)	48 (11.0)	19 (4.3)	225 (51.0)	51 (11.6)	14 (3.2)
Skin and subcutaneous tissue disorders	201 (45.9)	11 (2.5)	0	184 (41.7)	5 (1.1)	1 (0.2)
Metabolism and nutrition disorders	183 (41.8)	36 (8.2)	4 (0.9)	165 (37.4)	26 (5.9)	5 (1.1)
Nervous system disorders	182 (41.6)	19 (4.3)	6 (1.4)	168 (38.1)	18 (4.1)	4 (0.9)
Musculoskeletal and connective tissue disorders	171 (39.0)	23 (5.3)	3 (0.7)	168 (38.1)	15 (3.4)	3 (0.7)
Infections and infestations	150 (34.2)	31 (7.1)	14 (3.2)	146 (33.1)	27 (6.1)	13 (2.9)
Investigations	128 (29.2)	18 (4.1)	30 (6.8)	114 (25.9)	19 (4.3)	23 (5.2)
Vascular disorders	92 (21.0)	14 (3.2)	3 (0.7)	56 (12.7)	5 (1.1)	3 (0.7)
Psychiatric disorders	82 (18.7)	8 (1.8)	0	78 (17.7)	9 (2.0)	1 (0.2)
Eye disorders	78 (17.8)	4 (0.9)	0	59 (13.4)	0	0
Cardiac disorders	61 (13.9)	8 (1.8)	8 (1.8)	47 (10.7)	8 (1.8)	6 (1.4)
Immune system disorders	43 (9.8)	9 (2.1)	1 (0.2)	17 (3.9)	3 (0.7)	2 (0.5)
Renal and urinary disorders	31 (7.1)	2 (0.5)	1 (0.2)	25 (5.7)	2 (0.5)	1 (0.2)
Ear and labyrinth disorders	28 (6.4)	2 (0.5)	1 (0.2)	16 (3.6)	2 (0.5)	0
Injury, poisoning and procedural complications	23 (5.3)	6 (1.4)	2 (0.5)	21 (4.8)	5 (1.1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	20 (4.6)	8 (1.8)	0	27 (6.1)	6 (1.4)	5 (1.1)

System organ classes are sorted by descending frequency of all grades in the Vadimezan group.

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.

DOC=Docetaxel

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

Adverse events, regardless of study drug relationship, with at least 5% incidence of any grade events in either group, by preferred term, maximum CTCAE grade (Safety Set):

	Vadimezan + Doc N=438			Placebo + Doc N=441		
Preferred term	**All grades**	**Grade 3**	**Grade 4**	**All grades**	**Grade 3**	**Grade 4**
Neutropenia	213 (48.6)	57 (13.0)	133 (30.4)	228 (51.7)	64(14.5)	142(32.2)
Fatigue	175 (40.0)	27 (6.2)	1 (0.2)	173 (39.2)	28(6.3)	2(0.5)
Alopecia	136 (31.1)	3 (0.7)	0	122 (27.7)	3(0.7)	0
Decreased appetite	117 (26.7)	7 (1.6)	0	107 (24.3)	9(2.0)	0
Dyspnoea	115 (26.3)	28 (6.4)	7 (1.6)	107 (24.3)	36(8.2)	6(1.4)
Nausea	115 (26.3)	6 (1.4)	1 (0.2)	134 (30.4)	6(1.4)	0
Diarrhoea	112 (25.6)	9 (2.1)	0	94(21.3)	7(1.6)	0
Anaemia	101 (23.1)	14 (3.2)	2 (0.5)	82 (18.6)	5(1.1)	0
Cough	93 (21.2)	3 (0.7)	0	79 (17.9)	6(1.4)	0
Pyrexia	74 (16.9)	3 (0.7)	0	70 (15.9)	1(0.2)	1(0.2)

Preferred terms are sorted by descending frequency of all grades in the Vadimezan group.

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

Doc=Docetaxel

Serious Adverse Events and Deaths

Summary of patients with at least 1 adverse event in any category:

	Vadimezan + Doc N= 438 n (%)	Placebo + Doc N= 441 n (%)
Adverse events	**430 (98.2)**	**429 (97.3)**
Grade 3-4 AE	352 (80.4)	344 (78.0)
with suspected relationship to study treatment	192 (43.8)	183 (41.5)
All deaths	**193 (44.1)**	**177 (40.1)**
On-treatment death[1]	35 (8.0)	24 (5.4)
Serious adverse events	**164 (37.4)**	**139 (31.5)**
with suspected relationship to study treatment	60 (13.7)	56 (12.7)
Other clinically significant adverse events[2]	**325 (74.2)**	**286 (64.9)**
with suspected relationship to study treatment	237 (54.1)	199 (45.1)
Adverse events leading to discontinuation	**66 (15.1)**	**49 (11.1)**
Serious adverse events	30 (6.8)	31 (7.0)
Other clinically significant AEs	37 (8.4)	18 (4.1)

[1] On-treatment deaths are deaths which occurred up to 28 days after last date of study treatment

[2] The groupings consist of AEs for which there is a specific clinical interest in connection with Vadimezan or AEs which are similar in nature.

Categories are not mutually exclusive

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

Doc=Docetaxel

Date of Clinical Trial Report

15-Nov-2011

Date Inclusion on Novartis Clinical Trial Results Database

10-Jan-2012

Date of Latest Update