Sponsor

Novartis

Generic Drug Name

Patupilone

Therapeutic Area of Trial

Metastatic hormone-refractory prostate cancer

Approved Indication

Patupilone is indicated for treatment of patients with histological or cytological diagnosis of adenocarcinoma of the prostate.

Protocol Number

CEPO906A2229

Title

A randomized multicenter Phase II trial of patupilone (EPO906) plus prednisone versus docetaxel (Taxotere®) plus prednisone in patients with metastatic hormone-refractory prostate cancer

Study Phase

Phase II

Study Start/End Dates

First patient enrolled: 01-Sep-2006; Last patient completed: 26-Sep-2012

Study Design/Methodology

Open-label, active-controlled, randomized, multi-center Phase II study of patupilone plus prednisone and docetaxel plus prednisone in patients with metastatic hormone-refractory prostate cancer (HRPC). The protocol was divided into Stage 1 consisting of two treatment arms and Stage 2 consisting of four treatment arms.

Stage 1 consisted of two study arms. Patients who consented to participate in the study underwent screening evaluations within 14 days prior to the start of study treatment, except computer tomography (CT) or magnetic resonance imaging (MRI) tumor scans, which were permitted within 30 days prior to the start of study treatment. Patients who passed screening and enrolled in the study were randomly assigned (1:1) to receive study treatment with either patupilone (10 mg/m^2 q3w) or docetaxel (75 mg/m^2 q3w). Patients who responded or had stable disease were permitted to continue to receive study treatment until satisfactory response (i.e., complete response (CR), partial response (PR), or stable disease), unacceptable toxicity,

progression of disease, or death, or until the investigator removed the patient from study treatment for any other reason.

At the end of the Stage 1, when all patients were discontinued and no longer in Follow-up period, the Stage 1 data were analyzed and a "Go/No Go" decision to continue the study based on the Simon "optimal" two-stage design was made. Nine or more PSA responders were required in the patupilone group for the study to move into Stage 2.

Stage 2 assessed four treatment arms for anti-tumor response defined by PSA decrease and explored if a reduced dose of patupilone or the higher dose and two different schedules of prednisone could reduce the rate of grade 3 and grade 4 diarrhea. The incidence rate and its 95% confidence interval (CI) for PSA response and for grade 3 or grade 4 diarrhea were recorded for each treatment arm.

Centers

A total of 32 centers in 8 countries were participating: Australia (3), Belgium (1), France (6), Germany (2), Italy (3), Singapore (1), Spain (5), United States (11).

Publication

None

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

- Stage 1 - Arm 1: Patupilone 10 mg/m^2 iv q3w plus prednisone 5 mg po bid
- Stage 1- Arm 2: Docetaxel 75 mg/m^2 iv q3w plus prednisone 5 mg po bid
- Stage 2 - Arm 1: Patupilone 8 mg/m^2 iv q3w plus prednisone 5 mg po bid
- Stage 2 - Arm 2: Patupilone 10 mg/m2 iv q3w plus oral prednisone (or prednisolone) during each cycle with doses ranging from 25 mg po bid on Day 1 to 5 mg po bid on Day 12 until the end of the cycle.
- Stage 2 - Arm 3: Patupilone 10 mg/m2 iv q3w plus oral prednisone (or prednisolone) during each cycle starting with 5 mg po bid on Day 1 to Day 4, followed by 25 mg po bid on Day 5 to Day 12 decreasing to 5 mg po bid on Day 16 until the end of the cycle.
  Patients in Arm 3 who developed diarrhea before Day 5 were started on prednisone 25 mg po bid on the day the diarrhea started.
- Stage 2 - Arm 4: Docetaxel 75 mg/m^2 iv q3w plus prednisone 5 mg po bid

Statistical Methods

Data were summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, and safety observations and measurements. All summary statistics were presented for each arm of Stage 1 and Stage 2.

The primary efficacy endpoint of the study was antitumor response defined by PSA decline in all treatment arms. The primary efficacy variable was the PSA response rate.

PSA response was defined as:

1. At least 50% post-treatment decrease in PSA from baseline, maintained for ≥ 4 weeks AND
2. No clinical evidence of disease progression during this time period (from date of randomization to four weeks after the first 50% post-treatment decrease in PSA).

   An increase in PSA level of ≥ 25% over the baseline value, as determined by two consecutive measurements, constituted clinical evidence of disease progression

AND

3. No radiological evidence of disease progression during this time period (from date of randomization to four weeks after the first 50% post-treatment decrease in PSA), as determined by CT scan evaluation.

PSA results were provided by the central laboratory. Early discontinuation due to AE, death, withdrawal of consent, lost to follow-up, protocol violations, etc. were considered as treatment failures.

This primary objective was analyzed using a cutoff date when all the patients had completed 8 cycles (24 weeks) of study treatment.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

- Patients with histological or cytological diagnosis of adenocarcinoma of the prostate.
- Patients without evidence of PSA progression were required to have clinical or radiological evidence of metastatic disease for which no curative therapy exists and for which systemic chemotherapy is indicated.
- Patients were required to have castrate levels of testosterone (serum testosterone ≤ 50ng/dL) either by being on androgen ablation therapy with a luteinizing hormone-releasing hormone agonist or by prior orchiectomy.
- Patients were required to have documented evidence of disease progression.
- Patients in whom flutamide, nilutamide, megestrol acetate, diethylstilbestrol, aminoglutethimide or ketoconazole had been recently withdrawn were required to demonstrate progression of disease at least four weeks beyond the discontinuation of such agents. Six weeks were required if prior treatment was bicatulamide.
- WHO Performance Status of 0, 1, or 2.
- Adequate hematologic and biochemistry parameters (Hb > 10 g/dL, WBC ≥ 3000/μL, ANC ≥ 1,500/μL, platelet count ≥ 100,000/μL) and adequate hepatic (bilirubin level within normal limits, AST and ALT ≤ 1.5 x the upper normal limit) and renal functions (serum creatinine level ≤ 1.5 the upper limit of normal) within 14 days prior to enrollment.

Exclusion criteria:

- Palliative radiation therapy to centrally located tumors less than four weeks prior to enrollment date.
- Prior strontium chloride (Sr 89) or Samarium (Sm 153) lexidronam pentasodium.
- Unresolved diarrhea of any grade in the last seven days prior to study entry.

Participant Flow

Patient disposition by treatment group during Stage 1 (FAS)

Disposition/Reason	Patupilone 10 mg/m² q3w + Prednisone 5 mg bid N = 36 n (%)	Docetaxel 75 mg/m² q3w + Prednisone 5 mg bid N = 35 n (%)
Randomized	**36 (100)**	**35 (100)**
Treated	35 (97.2)	33 (94.3)
Not treated	1 (2.8)	2 (5.7)
Discontinued	**35 (97.2)**	**33 (94.3)**
Adverse event	18 (50.0)	16 (45.7)
Disease progression	14 (38.9)	13 (37.1)
Death	1 (2.8)	1 (2.9)
Death from other causes	1 (2.8)	1 (2.9)
Subject withdrew consent	1 (2.8)	0
Administrative problems	1 (2.8)	0
Subject condition no longer requires study drug	0	3 (8.6)

FAS: full analysis set

Patient disposition by treatment group during Stage 2 (FAS)

	Patupilone			Docetaxel
Disposition/Reason	8 mg/m² q3w + Prednisone 5 mg bid N = 21 n (%)	10 mg/m² q3w + Prednisone 25 mg bid (day 1 - 8) N = 21 n (%)	10 mg/m² q3w + Prednisone 25 mg bid (day 5 - 12) N = 20 n (%)	75 mg/m² q3w + Prednisone 5 mg bid N = 11 n (%)
Randomized	**21 (100)**	**21 (100)**	**20 (100)**	**11 (100)**
Treated	20 (95.2)	17 (81.0)	20 (100)	11 (100)
Not treated	1 (4.8)	4 (19.0)	0	0
Discontinued	**20 (95.2)**	**17 (81.0)**	**20 (100)**	**11 (100)**
Adverse event	8 (38.1)	6 (28.6)	7 (35.0)	2 (18.2)
Disease progression	8 (38.1)	6 (28.6)	5 (25.0)	5 (45.5)
Administrative problems	2 (9.5)	1 (4.8)	0	0
Subject condition no longer requires study drug	1 (4.8)	3 (14.3)	4 (20.0)	4 (36.4)
Abnormal laboratory value	1 (4.8)	0	0	0
Subject withdrew consent	0	0	3 (15.0)	0
Death	0	1 (4.8)	1 (5.0)	0

Death from other causes	0	1 (4.8)	1 (5.0)	0

FAS: full analysis set

Baseline Characteristics

Demographic characteristics by treatment group during Stage 1 (FAS)

	Patupilone 10mg/m² q3w + Prednisone 5mg bid N = 36 n (%)	Docetaxel 75mg/m² q3w + Prednisone 5mg bid N = 35 n (%)
Age (years) - n	**36**	**35**
Mean (SD)	68.1 (7.40)	67.5 (7.93)
Median (Min, Max)	68.0 (53 – 81)	67.0 (52 – 83)
Age Group - n (%)		
45 - 65 years	13 (36.1)	15 (42.9)
>65 years	23 (63.9)	20 (57.1)
Gender - n (%)		
Male	36 (100.0)	35 (100.0)
Race - n (%)		
Caucasian	32 (88.9)	33 (94.3)
Black	2 (5.6)	0
Asian	1 (2.8)	1 (2.9)
Other	1 (2.8)	1 (2.9)
Weight (kg) - n	**36**	**34**
Mean (SD)	85.7 (13.78)	83.9 (11.40)
Median (Min, Max)	83.5 (58.5 - 114.7)	83.0 (67.3 - 111.0)
Height (cm) - n	**34**	**34**
Mean (SD)	172.4 (8.18)	174.3 (6.27)
Median (Min, Max)	173.5 (143 – 187)	175.0 (162 – 190)

FAS: full analysis set; SD: standard deviation

Demographic characteristics by treatment group during Stage 2 (FAS)

	Patupilone			Docetaxel
	8mg/m² q3w + Prednisone 5mg bid N = 21 n (%)	10mg/m² q3w + Prednisone 25mg bid (day 1 - 8) N = 21 n (%)	10mg/m² q3w + Prednisone 25mg bid (day 5 - 12) N = 20 n (%)	75mg/m² q3w + Prednisone 5mg bid N = 11 n (%)
Age (years) - n	**21**	**21**	**20**	**11**
Mean (SD)	68.9 (6.53)	69.9 (8.14)	67.4 (6.85)	71.1 (7.80)
Median (Min, Max)	66.0 (61 – 82)	71.0 (57 – 82)	68.0 (57 – 82)	71.0 (59 – 82)
Age Group - n (%)				
45 - 65 years	10 (47.6)	6 (28.6)	9 (45.0)	3 (27.3)

>65 years	11 (52.4)	15 (71.4)	11 (55.0)	8 (72.7)
Gender - n (%)				
Male	21 (100.0)	21 (100.0)	20 (100.0)	11 (100.0)
Race - n (%)				
Caucasian	18 (85.7)	19 (90.5)	18 (90.0)	10 (90.9)
Black	3 (14.3)	0	1 (5.0)	0
Asian	0	0	0	0
Other	0	2 (9.5)	1 (5.0)	1 (9.1)
Weight (kg) - n	**20**	**18**	**20**	**11**
Mean (SD)	87.1 (13.45)	86.5 (13.28)	82.0 (15.07)	76.9 (14.01)
Median (Min, Max)	84.0 (72.0 - 120.0)	85.6 (70.0 - 114.5)	82.5 (60.5 - 120.0)	75.0 (56.0 - 98.5)
Height (cm) - n	**20**	**18**	**20**	**11**
Mean (SD)	172.9 (9.00)	171.6 (8.26)	170.0 (6.95)	170.4 (7.23)
Median (Min, Max)	175.0 (152 – 185)	172.5 (160 – 193)	167.0 (160 – 190)	171.0 (161 – 184)

FAS: full analysis set; SD: standard deviation

Outcome measures

Response defined by PSA concentration by treatment group in Stage 1 (FAS)

Disposition/Reason	Patupilone 10 mg/m² q3w + Prednisone 5 mg bid N = 32 n (%)	Docetaxel 75 mg/m² q3w + Prednisone 5 mg bid N = 30 n (%)
PSA response	20 (62.5)	16 (53.3)
95% CI for the proportion of PSA response	(43.69, 78.90)	(34.33, 71.66)

FAS: full analysis set; PSA: prostate specific antigen

Response defined by PSA concentration by treatment group in Stage 2 (FAS)

Disposition/Reason	Patupilone	Docetaxel

	8 mg/m² q3w + Prednisone 5 mg bid N = 17 n (%)	10 mg/m² q3w + Prednisone 25 mg bid (day 1 - 8) N = 14 n (%)	10 mg/m² q3w + Prednisone 25 mg bid (day 5 - 12) N = 16 n (%)	75 mg/m² q3w + Prednisone 5 mg bid N = 11 n (%)
PSA response	9 (52.9)	11 (78.6)	8 (50.0)	8 (72.7)
95% CI for the proportion of PSA response	(27.81, 77.02)	(49.20, 95.34)	(24.65, 75.35)	(39.03, 93.98)

FAS: full analysis set; PSA: prostate specific antigen

Safety Results

Adverse events, by primary system organ class, preferred terms, maximum severity grade and treatment group (Stage 1) (> 10%)

	Patupilone 10 mg/m² q3w + Prednisone 5 mg bid N = 35			Docetaxel 75 mg/m² q3w + Prednisone 5 mg bid N = 33		
	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade
System organ class Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any system organ class	**23 (65.7)**	**1 (2.9)**	**34 (97.1)**	**12 (36.4)**	**11 (33.3)**	**32 (97.0)**
Gastrointestinal disorders	**13 (37.1)**	**0**	**34 (97.1)**	**1 (3.0)**	**0**	**26 (78.8)**
Diarrhoea	11 (31.4)	0	33 (94.3)	0	0	15 (45.5)
Nausea	0	0	18 (51.4)	0	0	17 (51.5)
Constipation	0	0	15 (42.9)	0	0	9 (27.3)
Abdominal pain	1 (2.9)	0	8 (22.9)	0	0	2 (6.1)
Stomatitis	0	0	7 (20.0)	0	0	4 (12.1)
Vomiting	1 (2.9)	0	7 (20.0)	1 (3.0)	0	7 (21.2)
Abdominal pain upper	0	0	4 (11.4)	0	0	1 (3.0)
Dyspepsia	1 (2.9)	0	4 (11.4)	0	0	6 (18.2)
Gastrooesophageal reflux disease	0	0	2 (5.7)	0	0	4 (12.1)

General disorders and administration site conditions	**4 (11.4)**	**0**	**28 (80.0)**	**2 (6.1)**	**1 (3.0)**	**25 (75.8)**
Asthenia	3 (8.6)	0	13 (37.1)	0	0	10 (30.3)
Fatigue	1 (2.9)	0	11 (31.4)	1 (3.0)	1 (3.0)	16 (48.5)
Oedema peripheral	0	0	10 (28.6)	0	0	3 (9.1)
Pyrexia	0	0	5 (14.3)	0	0	4 (12.1)
Nervous system disorders	**4 (11.4)**	**0**	**26 (74.3)**	**5 (15.2)**	**1 (3.0)**	**24 (72.7)**
Neuropathy peripheral	1 (2.9)	0	14 (40.0)	0	0	5 (15.2)
Paraesthesia	1 (2.9)	0	7 (20.0)	1 (3.0)	0	2 (6.1)
Dysgeusia	0	0	6 (17.1)	1 (3.0)	0	12 (36.4)
Peripheral sensory neuropathy	0	0	3 (8.6)	0	0	6 (18.2)
Dizziness	0	0	2 (5.7)	1 (3.0)	0	4 (12.1)
Musculoskeletal and connective tissue disorders	**1 (2.9)**	**0**	**19 (54.3)**	**4 (12.1)**	**0**	**23 (69.7)**
Arthralgia	0	0	7 (20.0)	1 (3.0)	0	9 (27.3)
Back pain	0	0	5 (14.3)	1 (3.0)	0	7 (21.2)
Pain in extremity	0	0	5 (14.3)	0	0	6 (18.2)
Musculoskeletal pain	0	0	1 (2.9)	4 (12.1)	0	5 (15.2)
Myalgia	0	0	1 (2.9)	0	0	5 (15.2)
Infections and infestations	**4 (11.4)**	**0**	**16 (45.7)**	**4 (12.1)**	**2 (6.1)**	**16 (48.5)**
Urinary tract infection	1 (2.9)	0	7 (20.0)	1 (3.0)	0	2 (6.1)
Nasopharyngitis	0	0	2 (5.7)	0	0	4 (12.1)

Metabolism and nutrition disorders	**7 (20.0)**	**0**	**16 (45.7)**	**3 (9.1)**	**0**	**10 (30.3)**
Dehydration	5 (14.3)	0	8 (22.9)	0	0	1 (3.0)
Decreased appetite	0	0	7 (20.0)	1 (3.0)	0	5 (15.2)
Skin and subcutaneous tissue disorders	**0**	**0**	**13 (37.1)**	**0**	**0**	**22 (66.7)**
Alopecia	0	0	5 (14.3)	0	0	16 (48.5)
Nail disorder	0	0	2 (5.7)	0	0	4 (12.1)
Investigations	**2 (5.7)**	**0**	**10 (28.6)**	**1 (3.0)**	**0**	**7 (21.2)**
Weight decreased	0	0	4 (11.4)	0	0	3 (9.1)
Vascular disorders	**0**	**0**	**9 (25.7)**	**2 (6.1)**	**0**	**8 (24.2)**
Hot flush	0	0	4 (11.4)	0	0	2 (6.1)
Psychiatric disorders	**2 (5.7)**	**0**	**8 (22.9)**	**0**	**0**	**5 (15.2)**
Insomnia	0	0	5 (14.3)	0	0	3 (9.1)
Renal and urinary disorders	**2 (5.7)**	**0**	**8 (22.9)**	**2 (6.1)**	**0**	**12 (36.4)**
Dysuria	0	0	1 (2.9)	0	0	4 (12.1)
Respiratory, thoracic and mediastinal disorders	**2 (5.7)**	**0**	**8 (22.9)**	**0**	**5 (15.2)**	**13 (39.4)**
Cough	0	0	1 (2.9)	0	0	4 (12.1)
Dyspnoea	0	0	1 (2.9)	1 (3.0)	0	5 (15.2)
Pulmonary embolism	1 (2.9)	0	1 (2.9)	0	4 (12.1)	4 (12.1)
Cardiac disorders	**1 (2.9)**	**1 (2.9)**	**4 (11.4)**	**2 (6.1)**	**1 (3.0)**	**4 (12.1)**
Blood and lymphatic system disorders	**0**	**0**	**3 (8.6)**	**3 (9.1)**	**8 (24.2)**	**14 (42.4)**

Anaemia	0	0	2 (5.7)	1 (3.0)	0	5 (15.2)
Neutropenia	0	0	1 (2.9)	4 (12.1)	6 (18.2)	10 (30.3)
Injury, poisoning and procedural complications	**0**	**0**	**3 (8.6)**	**2 (6.1)**	**1 (3.0)**	**5 (15.2)**
Eye disorders	**0**	**0**	**1 (2.9)**	**0**	**0**	**5 (15.2)**

Adverse events, by primary system organ class, preferred terms, maximum severity grade and treatment group (Stage 2) (> 10%)

	Patupilone 8 mg/m² q3w + Prednisone 5 mg bid N = 20			**Patupilone 10 mg/m² q3w + Prednisone 25 mg bid (day 1 - 8) N = 17**			**Patupilone 10 mg/m² q3w + Prednisone 25 mg bid (day 5 - 12) N = 20**			**Docetaxel 75 mg/m² q3w + Prednisone 5 mg bid N = 11**		
	Grade 3	**Grade 4**	**Any grade**	**Grade 3**	**Grade 4**	**Any grade**	**Grade 3**	**Grade 4**	**Any grade**	**Grade 3**	**Grade 4**	**Any grade**
System organ class Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any system organ class	**7 (35.0)**	**2 (10.0)**	**20(100.0)**	**11 (64.7)**	**3 (17.6)**	**17(100.0)**	**9 (45.0)**	**5 (25.0)**	**20(100.0)**	**6 (54.5)**	**2 (18.2)**	**11(100.0)**
Gastrointestinal disorders	**2 (10.0)**	**0**	**20(100.0)**	**6 (35.3)**	**1 (5.9)**	**16 (94.1)**	**8 (40.0)**	**0**	**20(100.0)**	**0**	**0**	**9 (81.8)**
Diarrhoea	2 (10.0)	0	17 (85.0)	5 (29.4)	0	15 (88.2)	7 (35.0)	0	20(100.0)	0	0	8 (72.7)
Nausea	0	0	6 (30.0)	2 (11.8)	0	7 (41.2)	0	0	11 (55.0)	0	0	4 (36.4)
Constipation	0	0	6 (30.0)	0	0	3 (17.6)	0	0	5 (25.0)	0	0	1 (9.1)
Abdominal pain	0	0	2 (10.0)	1 (5.9)	0	4 (23.5)	0	0	6 (30.0)	0	0	0
Stomatitis	0	0	2 (10.0)	0	0	1 (5.9)	0	0	0	0	0	3 (27.3)
Vomiting	0	0	4 (20.0)	2 (11.8)	0	9 (52.9)	0	0	8 (40.0)	0	0	0

Abdominal pain upper	0	0	2 (10.0)	0	0	0	0	0	0	0	0	0
Dyspepsia	0	0	1 (5.0)	1 (5.9)	0	2 (11.8)	0	0	2 (10.0)	0	0	0
Gastrooesophageal reflux disease	0	0	2 (10.0)	1 (5.9)	0	2 (11.8)	0	0	2 (10.0)	0	0	1 (9.1)
Oesophagitis	0	0	0	1 (5.9)	0	2 (11.8)	0	0	0	0	0	0
General disorders and administration site conditions	**2 (10.0)**	**0**	**14 (70.0)**	**4 (23.5)**	**0**	**14 (82.4)**	**4 (20.0)**	**1 (5.0)**	**19 (95.0)**	**1 (9.1)**	**0**	**7 (63.6)**
Asthenia	0	0	5 (25.0)	1 (5.9)	0	5 (29.4)	3 (15.0)	0	8 (40.0)	0	0	4 (36.4)
Fatigue	0	0	6 (30.0)	3 (17.6)	0	6 (35.3)	0	0	9 (45.0)	1 (9.1)	0	3 (27.3)
Oedema peripheral	0	0	2 (10.0)	0	0	7 (41.2)	0	0	7 (35.0)	0	0	3 (27.3)
Pyrexia	0	0	3 (15.0)	0	0	1 (5.9)	1 (5.0)	0	5 (25.0)	0	0	4 (36.4)
General physical health deterioration	1 (5.0)	0	1 (5.0)	1 (5.9)	0	2 (11.8)	0	1 (5.0)	1 (5.0)	0	0	0
Nervous system disorders	**2 (10.0)**	**0**	**13 (65.0)**	**4 (23.5)**	**0**	**12 (70.6)**	**3 (15.0)**	**1 (5.0)**	**15 (75.0)**	**1 (9.1)**	**0**	**5 (45.5)**
Neuropathy peripheral	1 (5.0)	0	4 (20.0)	3 (17.6)	0	5 (29.4)	0	0	4 (20.0)	0	0	2 (18.2)
Paraesthesia	0	0	4 (20.0)	0	0	4 (23.5)	0	0	2 (10.0)	0	0	3 (27.3)
Dysgeusia	0	0	1 (5.0)	0	0	1 (5.9)	0	0	2 (10.0)	0	0	2 (18.2)
Peripheral sensory neuropathy	0	0	2 (10.0)	0	0	1 (5.9)	1 (5.0)	0	5 (25.0)	0	0	0
Dizziness	0	0	1 (5.0)	1 (5.9)	0	1 (5.9)	0	0	3 (15.0)	0	0	1 (9.1)
Headache	0	0	3 (15.0)	0	0	1 (5.9)	0	0	4 (20.0)	0	0	0
Syncope	1 (5.0)	0	1 (5.0)	0	0	0	3 (15.0)	0	3 (15.0)	0	0	0
Somnolence	0	0	0	0	0	2 (11.8)	0	0	1 (5.0)	0	0	0

Musculoskeletal and connective tissue disorders	**1 (5.0)**	**1 (5.0)**	**9 (45.0)**	**1 (5.9)**	**0**	**10 (58.8)**	**0**	**0**	**8 (40.0)**	**0**	**0**	**7 (63.6)**
Arthralgia	1 (5.0)	0	2 (10.0)	1 (5.9)	0	4 (23.5)	0	0	1 (5.0)	0	0	0
Back pain	0	0	5 (25.0)	0	0	3 (17.6)	0	0	0	0	0	2 (18.2)
Pain in extremity	1 (5.0)	0	1 (5.0)	0	0	0	0	0	2 (10.0)	0	0	4 (36.4)
Muscle spasms	0	0	1 (5.0)	0	0	0	0	0	3 (15.0)	0	0	2 (18.2)
Muscular weakness	0	0	0	0	0	0	0	0	0	0	0	3 (27.3)
Musculoskeletal pain	0	0	2 (10.0)	0	0	0	0	0	1 (5.0)	0	0	2 (18.2)
Infections and infestations	**1 (5.0)**	**0**	**9 (45.0)**	**3 (17.6)**	**0**	**9 (52.9)**	**2 (10.0)**	**1 (5.0)**	**4 (20.0)**	**2 (18.2)**	**0**	**7 (63.6)**
Urinary tract infection	0	0	5 (25.0)	1 (5.9)	0	4 (23.5)	1 (5.0)	0	1 (5.0)	0	0	2 (18.2)
Bronchitis	0	0	0	0	0	2 (11.8)	0	0	0	0	0	2 (18.2)
Metabolism and nutrition disorders	**2 (10.0)**	**0**	**6 (30.0)**	**1 (5.9)**	**1 (5.9)**	**9 (52.9)**	**6 (30.0)**	**1 (5.0)**	**13 (65.0)**	**0**	**1 (9.1)**	**3 (27.3)**
Decreased appetite	0	0	3 (15.0)	0	0	3 (17.6)	0	0	2 (10.0)	0	0	1 (9.1)
Hypokalaemia	0	0	1 (5.0)	0	0	2 (11.8)	2 (10.0)	0	3 (15.0)	0	0	1 (9.1)
Hyperglycaemia	0	0	1 (5.0)	0	0	0	3 (15.0)	0	4 (20.0)	0	0	0
Hypocalcaemia	1 (5.0)	0	1 (5.0)	0	0	1 (5.9)	1 (5.0)	0	3 (15.0)	0	0	1 (9.1)
Skin and subcutaneous tissue disorders	**0**	**0**	**6 (30.0)**	**0**	**0**	**5 (29.4)**	**0**	**0**	**5 (25.0)**	**0**	**0**	**7 (63.6)**
Alopecia	0	0	1 (5.0)	0	0	2 (11.8)	0	0	0	0	0	5 (45.5)
Nail disorder	0	0	0	0	0	0	0	0	1 (5.0)	0	0	2 (18.2)
Erythema	0	0	0	0	0	2 (11.8)	0	0	0	0	0	0
Penile ulceration	0	0	0	0	0	0	0	0	0	0	0	2 (18.2)

Investigations	**0**	**0**	**2 (10.0)**	**2 (11.8)**	**0**	**7 (41.2)**	**0**	**0**	**4 (20.0)**	**1 (9.1)**	**0**	**3 (27.3)**
Weight decreased	0	0	0	0	0	2 (11.8)	0	0	3 (15.0)	0	0	1 (9.1)
Haemoglobin decreased	0	0	1 (5.0)	0	0	3 (17.6)	0	0	0	0	0	1 (9.1)
Vascular disorders	**0**	**0**	**3 (15.0)**	**2 (11.8)**	**0**	**5 (29.4)**	**1 (5.0)**	**0**	**4 (20.0)**	**0**	**0**	**1 (9.1)**
Hypertension	0	0	2 (10.0)	0	0	2 (11.8)	0	0	2 (10.0)	0	0	1 (9.1)
Psychiatric disorders	**0**	**0**	**2 (10.0)**	**0**	**0**	**4 (23.5)**	**0**	**0**	**4 (20.0)**	**0**	**0**	**0**
Insomnia	0	0	0	0	0	2 (11.8)	0	0	0	0	0	0
Anxiety	0	0	0	0	0	3 (17.6)	0	0	0	0	0	0
Renal and urinary disorders	**0**	**0**	**2 (10.0)**	**0**	**1 (5.9)**	**6 (35.3)**	**0**	**0**	**4 (20.0)**	**0**	**0**	**4 (36.4)**
Haematuria	0	0	1 (5.0)	0	0	2 (11.8)	0	0	0	0	0	1 (9.1)
Pollakiuria	0	0	0	0	0	2 (11.8)	0	0	1 (5.0)	0	0	1 (9.1)
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**6 (30.0)**	**1 (5.9)**	**1 (5.9)**	**6 (35.3)**	**1 (5.0)**	**1 (5.0)**	**4 (20.0)**	**3 (27.3)**	**0**	**5 (45.5)**
Dyspnoea	0	0	3 (15.0)	0	0	0	0	0	2 (10.0)	1 (9.1)	0	3 (27.3)
Epistaxis	0	0	1 (5.0)	0	0	2 (11.8)	0	0	0	0	0	0
Pulmonary embolism	0	0	0	1 (5.9)	1 (5.9)	4 (23.5)	0	1 (5.0)	1 (5.0)	1 (9.1)	0	1 (9.1)
Cardiac disorders	**0**	**0**	**0**	**1 (5.9)**	**0**	**2 (11.8)**	**0**	**0**	**0**	**1 (9.1)**	**0**	**2 (18.2)**
Angina pectoris	0	0	0	0	0	0	0	0	0	1 (9.1)	0	2 (18.2)
Blood and lymphatic system disorders	**1 (5.0)**	**1 (5.0)**	**4 (20.0)**	**1 (5.9)**	**0**	**5 (29.4)**	**0**	**0**	**1 (5.0)**	**2 (18.2)**	**1 (9.1)**	**4 (36.4)**
Anaemia	1 (5.0)	0	4 (20.0)	0	0	2 (11.8)	0	0	1 (5.0)	0	0	1 (9.1)
Neutropenia	0	1 (5.0)	1 (5.0)	1 (5.9)	0	1 (5.9)	0	0	0	0	1 (9.1)	2 (18.2)

Injury, poisoning and procedural complications	**0**	**0**	**2 (10.0)**	**1 (5.9)**	**0**	**3 (17.6)**	**0**	**0**	**0**	**0**	**0**	**0**
Eye disorders	**1 (5.0)**	**0**	**3 (15.0)**	**0**	**0**	**2 (11.8)**	**0**	**0**	**1 (5.0)**	**0**	**0**	**3 (27.3)**
Lacrimation increased	0	0	0	0	0	0	0	0	0	0	0	2 (18.2)

Most frequent serious adverse events by preferred terms and treatment group in Stage 1 (more than or equal 5% in Grade 3 or 4) (Safety set)

	Stage 1					
	Patupilone 10 mg/m² q3w + Prednisone 5 mg bid N = 35 n (%)			**Docetaxel 75 mg/m² q3w + Prednisone 5 mg bid N = 33 n (%)**		
	Grade 3	**Grade 4**	**Any grade**	**Grade 3**	**Grade 4**	**Any grade**
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Patients with SAE (s)	**13 (37.1)**	**1 (2.9)**	**17 (48.6)**	**5 (15.2)**	**8 (24.2)**	**14 (42.4)**
Diarrhoea	5 (14.3)	0	6 (17.1)	0	0	0
Dehydration	4 (11.4)	0	4 (11.4)	0	0	0
Renal failure	1 (2.9)	0	3 (8.6)	0	0	0
Muscular weakness	1 (2.9)	0	2 (5.7)	0	0	0
Urinary retention	1 (2.9)	0	2 (5.7)	0	0	0
Abdominal pain	1 (2.9)	0	1 (2.9)	0	0	0

Abdominal rigidity	1 (2.9)	0	1 (2.9)	0	0	0
Anaemia	0	0	1 (2.9)	1 (3.0)	0	1 (3.0)
Asthenia	1 (2.9)	0	1 (2.9)	0	0	0
Atrial fibrillation	1 (2.9)	0	1 (2.9)	1 (3.0)	1 (3.0)	2 (6.1)
Bone pain	1 (2.9)	0	1 (2.9)	0	0	0
Campylobacter gastroenteritis	1 (2.9)	0	1 (2.9)	0	0	0
Cardiac arrest	0	1 (2.9)	1 (2.9)	0	0	0
Cellulitis	1 (2.9)	0	1 (2.9)	0	0	0
Colitis	1 (2.9)	0	1 (2.9)	0	0	0
Dizziness	0	0	1 (2.9)	1 (3.0)	0	1 (3.0)
Gastroenteritis	1 (2.9)	0	1 (2.9)	0	0	0
Lower respiratory tract infection	1 (2.9)	0	1 (2.9)	0	0	0
Mental status changes	1 (2.9)	0	1 (2.9)	0	0	0
Pulmonary embolism	1 (2.9)	0	1 (2.9)	0	4 (12.1)	4 (12.1)
Pulmonary oedema	1 (2.9)	0	1 (2.9)	0	0	0
Sigmoiditis	1 (2.9)	0	1 (2.9)	0	0	0
Spinal cord compression	1 (2.9)	0	1 (2.9)	0	1 (3.0)	1 (3.0)
Agranulocytosis	0	0	0	0	1 (3.0)	1 (3.0)
Anal abscess	0	0	0	1 (3.0)	0	1 (3.0)
Cardiac failure	0	0	0	1 (3.0)	0	1 (3.0)
Cognitive disorder	0	0	0	1 (3.0)	0	1 (3.0)
Febrile neutropenia	0	0	0	0	1 (3.0)	1 (3.0)
Femoral neck fracture	0	0	0	1 (3.0)	0	1 (3.0)

Groin pain	0	0	0	1 (3.0)	0	1 (3.0)
Hydronephrosis	0	0	0	1 (3.0)	0	1 (3.0)
Hypotension	0	0	0	1 (3.0)	0	1 (3.0)
Hypoxia	0	0	0	0	1 (3.0)	1 (3.0)
Leukopenia	0	0	0	0	1 (3.0)	1 (3.0)
Lung infection	0	0	0	1 (3.0)	0	1 (3.0)
Meningioma	0	0	0	0	0	1 (3.0)
Muscle strain	0	0	0	0	1 (3.0)	1 (3.0)
Musculoskeletal pain	0	0	0	2 (6.1)	0	2 (6.1)
Neutropenia	0	0	0	1 (3.0)	0	1 (3.0)
Pancytopenia	0	0	0	0	1 (3.0)	1 (3.0)
Peripheral embolism	0	0	0	1 (3.0)	0	1 (3.0)
Pneumonia	0	0	0	0	1 (3.0)	1 (3.0)
Respiratory failure	0	0	0	0	1 (3.0)	1 (3.0)
Sepsis	0	0	0	0	1 (3.0)	1 (3.0)
Staphylococcal infection	0	0	0	1 (3.0)	0	1 (3.0)
Urethritis	0	0	0	1 (3.0)	0	1 (3.0)
Urinary tract infection	0	0	0	1 (3.0)	0	1 (3.0)
Urinary tract obstruction	0	0	0	1 (3.0)	0	1 (3.0)

Most frequent serious adverse events by preferred terms and treatment group in Stage 2 (more than or equal 5% in Grade 3 or 4) (Safety set)

	Stage 2

	Patupilone 8 mg/m² q3w + Prednisone 5 mg bid N = 20 n (%)			Patupilone 10 mg/m² q3w + Prednisone 25 mg bid (day 1 - 8) N = 17 n (%)			Patupilone 10 mg/m² q3w + Prednisone 25 mg bid (day 5 - 12) N = 20 n (%)			Docetaxel 75 mg/m² q3w + Prednisone 5 mg bid N = 11 n (%)		
	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with AE (s)	3 (15.0)	2 (10.0)	7 (35.0)	6 (35.3)	3 (17.6)	10 (58.8)	5 (25.0)	5 (25.0)	10 (50.0)	4 (36.4)	1 (9.1)	6 (54.5)
Diarrhoea	0	0	0	3 (17.6)	0	4 (23.5)	5 (25.0)	0	6 (30.0)	0	0	0
Dehydration	0	0	0	1 (5.9)	1 (5.9)	2 (11.8)	1 (5.0)	0	1 (5.0)	0	0	0
Renal failure	0	0	0	0	1 (5.9)	1 (5.9)	0	0	1 (5.0)	0	0	0
Abdominal pain	0	0	0	1 (5.9)	0	1 (5.9)	0	0	1 (5.0)	0	0	0
Bone pain	0	1 (5.0)	1 (5.0)	0	0	0	0	0	0	0	0	0
Colitis	0	0	0	0	0	0	1 (5.0)	0	1 (5.0)	0	0	0
Dizziness	0	0	0	1 (5.9)	0	1 (5.9)	0	0	0	0	0	0
Gastroenteritis	0	0	0	1 (5.9)	0	1 (5.9)	0	0	0	0	0	0
Nausea	0	0	0	2 (11.8)	0	2 (11.8)	0	0	0	0	0	0
Pulmonary embolism	0	0	0	1 (5.9)	1 (5.9)	3 (17.6)	0	1 (5.0)	1 (5.0)	1 (9.1)	0	1 (9.1)
Cough	0	0	0	0	0	0	0	0	1 (5.0)	1 (9.1)	0	1 (9.1)
Cystitis haemorrhagic	0	0	0	1 (5.9)	0	1 (5.9)	0	0	0	0	0	0
Diarrhoea haemorrhagic	0	0	0	0	1 (5.9)	1 (5.9)	0	0	0	0	0	0
Duodenal ulcer haemorrhage	0	0	0	1 (5.9)	0	1 (5.9)	0	0	0	0	0	0
Dyspepsia	0	0	0	1 (5.9)	0	1 (5.9)	0	0	0	0	0	0

Extremity necrosis	0	0	0	1 (5.9)	0	1 (5.9)	0	0	0	0	0	0
Fatigue	0	0	0	1 (5.9)	0	1 (5.9)	0	0	0	0	0	0
Febrile neutropenia	0	0	0	0	0	0	0	0	0	1 (9.1)	0	1 (9.1)
Gastritis erosive	0	0	0	1 (5.9)	0	1 (5.9)	0	0	0	0	0	0
Gastrointestinal haemorrhage	0	0	0	0	0	0	1 (5.0)	0	1 (5.0)	0	0	0
Gastrooesophageal reflux disease	0	0	0	1 (5.9)	0	1 (5.9)	0	0	0	0	0	0
General physical health deterioration	0	0	0	0	0	1 (5.9)	0	1 (5.0)	1 (5.0)	0	0	0
Hepatic neoplasm malignant	1 (5.0)	0	1 (5.0)	0	0	0	0	0	0	0	0	0
Hyperkalaemia	0	0	0	0	1 (5.9)	1 (5.9)	0	0	0	0	0	0
Hyponatraemia	0	0	0	0	0	0	0	1 (5.0)	1 (5.0)	0	0	0
Incoherent	0	0	0	0	0	0	0	1 (5.0)	1 (5.0)	0	0	0
Lethargy	0	0	0	0	0	0	0	0	0	1 (9.1)	0	1 (9.1)
Lobar pneumonia	0	0	0	0	0	0	0	1 (5.0)	1 (5.0)	0	0	0
Localised infection	0	0	0	0	0	0	0	0	0	1 (9.1)	0	1 (9.1)
Lung consolidation	0	0	0	0	0	0	1 (5.0)	0	1 (5.0)	0	0	0
Lung infiltration	0	0	1 (5.0)	0	0	0	1 (5.0)	0	1 (5.0)	0	0	0
Neutropenia	0	1 (5.0)	1 (5.0)	0	0	0	0	0	0	0	1 (9.1)	1 (9.1)
Obstructive uropathy	0	0	0	1 (5.9)	0	1 (5.9)	0	0	0	0	0	0
Oesophagitis	0	0	0	1 (5.9)	0	1 (5.9)	0	0	0	0	0	0
Orthostatic hypotension	0	0	0	1 (5.9)	0	1 (5.9)	0	0	0	0	0	0
Osteomyelitis	0	0	0	0	0	0	0	0	0	1 (9.1)	0	1 (9.1)
Pain	1 (5.0)	0	1 (5.0)	0	0	0	0	0	0	0	0	0

Pneumonia	1 (5.0)	0	1 (5.0)	0	0	0	1 (5.0)	0	1 (5.0)	0	0	0
Pyrexia	0	0	0	0	0	0	1 (5.0)	0	2 (10.0)	0	0	0
Sepsis	0	0	0	0	0	0	1 (5.0)	0	1 (5.0)	0	0	0
Septic shock	0	0	0	0	0	0	1 (5.0)	0	1 (5.0)	0	0	0
Syncope	1 (5.0)	0	1 (5.0)	0	0	0	0	0	0	0	0	0
Urinary tract infection	0	0	0	0	0	0	1 (5.0)	0	1 (5.0)	0	0	0
Vomiting	0	0	1 (5.0)	2 (11.8)	0	3 (17.6)	0	0	2 (10.0)	0	0	0

Deaths by stage and treatment group

	Stage 1		Stage 2			
	Patupilone 10mg/m² q3w + Prednisone 5mg bid	**Docetaxel 75mg/m² q3w + Prednisone 5mg bid**	**Patupilone 8mg/m² q3w + Prednisone 5mg bid**	**Patupilone 10mg/m² q3w + Prednisone 25mg bid (day 1 - 8)**	**Patupilone 10mg/m² q3w + Prednisone 25mg bid (day 5 - 12)**	**Docetaxel 75mg/m² q3w + Prednisone 5mg bid**
	N = 36 n (%)	**N = 35 n (%)**	**N = 21 n (%)**	**N = 21 n (%)**	**N = 20 n (%)**	**N = 11 n (%)**
Deaths	**5 (14)**	**8 (23)**	**4 (19)**	**5 (24)**	**3 (15)**	**0**
Not treated	0	1 (2.9)	0	0	0	0
Treated	5 (14)	7 (20)	4 (19)	5 (24)	3 (15)	0
Deaths leading to discontinuation of treatment or deaths within 28 days of last dose	**2 (5.6)**	**1 (2.9)**	**0**	**1 (4.8)**	**1 (5.0)**	**0**
Deaths from study indication	0	0	0	0	0	0
Deaths from other cause	1 (2.8)	1 (2.9)	0	1 (4.8)	0	0

Missing	1 (2.8)	0	0	0	1 (5.0)	0
Deaths after 28 days of last dose	**3 (8.3)**	**6 (17)**	**4 (19)**	**4 (19)**	**2 (10)**	**0**
Deaths from study indication	3 (8.3)	5 (14)	3 (14)	4 (19)	1 (5.0)	0
Deaths from other cause	0	1 (2.9)	1 (4.8)	0	1 (5.0)	0

Other Relevant Findings

Time to first occurrence of any diarrhea across cycles by treatment group

	Stage 1		Stage 2			
	Patupilone 10 mg/m² q3w + Prednisone 5 mg bid	**Docetaxel 75 mg/m² q3w + Prednisone 5 mg bid**	**Patupilone 8 mg/m² q3w + Prednisone 5 mg bid**	**Patupilone 10 mg/m² q3w + Prednisone 25 mg bid (day 1 - 8)**	**Patupilone 10 mg/m² q3w + Prednisone 25 mg bid (day 5 - 12)**	**Docetaxel 75 mg/m² q3w + Prednisone 5 mg bid**
	N = 35 n (%)	**N = 33 n (%)**	**N = 20 n (%)**	**N = 17 n (%)**	**N = 20 n (%)**	**N = 11 n (%)**
Any diarrhea						
Number of subjects who had diarrhea	33 (94.3)	15 (45.5)	17 (85.0)	15 (88.2)	20 (100)	8 (72.7)
Number of subjects who had no diarrhea	2 (5.7)	18 (54.5)	3 (15.0)	2 (11.8)	0	3 (27.3)
Median time to first diarrhea occurrence (days) and its 95% CI	9.0 (7.0, 12.0)	(90.0, --)	17.0 (9.0, 32.0)	15.0 (2.0, 54.0)	10.0 (6.0, 16.0)	55.0 (2.0, --)
Grades >=3 diarrhea						
Number of subjects who had grade ≥3 diarrhea	11 (31.4)	0	2 (10.0)	5 (29.4)	7 (35.0)	0
Number of subjects who had no grade ≥3 diarrhea	24 (68.6)	33 (100)	18 (90.0)	12 (70.6)	13 (65.0)	11 (100)
Median time to first grade ≥3 diarrhea occurrence (days) and its 95% CI	(80.0, --)	(--, --)	(--, --)	(67.0, --)	(43.0, --)	(--, --)

AE: adverse event; SAE: serious adverse event

Incidence of diarrhea by treatment groups (Safety set)

	Stage 1		Stage 2			
	Patupilone 10 mg/m² q3w + Prednisone 5 mg bid	**Docetaxel 75 mg/m² q3w + Prednisone 5 mg bid**	**Patupilone 8 mg/m² q3w + Prednisone 5 mg bid**	**Patupilone 10 mg/m² q3w + Prednisone 25 mg bid (day 1 - 8)**	**Patupilone 10 mg/m² q3w + Prednisone 25 mg bid (day 5 - 12)**	**Docetaxel 75 mg/m² q3w + Prednisone 5 mg bid**
	N = 35 n (%)	**N = 33 n (%)**	**N = 20 n (%)**	**N = 17 n (%)**	**N = 20 n (%)**	**N = 11 n (%)**
Incidence of Grade3 diarrhea	11 (31.4)	0	2 (10.0)	5 (29.4)	7 (35.0)	0
95% CI for the proportion of subjects with Grade3 diarrhea	(16.85,49.29)	(--,--)	(1.23,31.70)	(10.31,55.96)	(15.39,59.22)	(--,--)
Incidence of Grade4 diarrhea	0	0	0	0	0	0
95% CI for the proportion of subjects with Grade4 diarrhea	(--,--)	(--,--)	(--,--)	(--,--)	(--,--)	(--,--)
Incidence of any grade diarrhea	33 (94.3)	15 (45.5)	17 (85.0)	15 (88.2)	20 (100)	8 (72.7)
95% CI for the proportion of subjects with any grade diarrhea	(80.84,99.30)	(28.11,63.65)	(62.11,96.79)	(63.56,98.54)	(83.16,100.0)	(39.03,93.98)

AE: adverse event; SAE: serious adverse event

Date of Clinical Trial Report Final CSR (28-Feb-2013)
Date Inclusion on Novartis Clinical Trial Results Database 10-Apr-2013
Date of Latest Update