Sponsor

Novartis

Generic Drug Name

Patupilone

Therapeutic Area of Trial

Advanced solid tumors

Approved Indication

Investigational

Study Number

CEPO906A2121

Title

An open-label, phase I study to evaluate the safety, tolerability, and pharmacokinetics of patupilone in patients with advanced solid tumors and varying degrees of hepatic function.

Phase of Development

Phase I

Study Start/End Dates

04 Jan 2006 to 27 Jul 2010

Study Design/Methodology

Open-label, multi-center, phase I study to determine the PK profile of patupilone, and the MTD in patients with advanced solid tumors with varying degrees of hepatic function: normal function, mild dysfunction, and moderate dysfunction. Sequential treatment of patients with mild and moderate hepatic impairment was scheduled in this dose-finding, non-randomized trial. Patients were stratified based on hepatic function.

Patupilone was administered as a 20 minute i.v infusion at 5.0, 7.5, or 10.0 mg/m^2 once every three weeks (q3w) for 2 cycles.

Pharmacokinetic and safety evaluation occurred at various time points in Cycles 1 and 2 (core phase). Patients who completed 2 cycles with stable or responding disease were allowed to receive additional cycles until disease progression provided they tolerated the treatment (extension phase).

Centres

Four centers in USA.

Publication

None

Objectives

Primary objectives

- To assess the effect of hepatic impairment on the pharmacokinetics of patupilone and its metabolite CGP 85217.
- To determine the MTD of patupilone in patients with hepatic impairment, categorized by liver function tests (LFT) (total bilirubin and Serum glutamic oxaloacetic transaminase / aspartate aminotransferase (SGOT/AST).

Secondary objective(s)

- To correlate the level of hepatic dysfunction (i.e., LFT, Child-Pugh Classification, as available) to observed toxicity and PK of patupilone.
- To evaluate the safety and tolerability of patupilone in patients with hepatic impairment.
- To evaluate the preliminary anti-tumor activity of patupilone in patients with hepatic impairment.

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

Patupilone 5, 7.5 and 10 mg/m^2 administered intravenously over a period of 20 minutes.

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

None

Criteria for Evaluation

Primary variables

Blood PK of patupilone and its metabolite CGP 85217 were evaluated in patients after patupilone administration.

- PK sampling was performed at the following time points on Day 1 of Cycle 1 and 2
  - Pre-infusion: Immediately prior to infusion of patupilone
  - Post-infusion: Immediately after infusion of patupilone ends, 1 h, 2 h, 4 h, and 8 h
- PK sampling was performed at the following time points on the following days: patupilone infusion 24 h, 72 h, 168 h, 336 h, 504 h

Secondary variables

Efficacy was evaluated as a function of tumor response (best overall response) in patients who received at least one dose of study medication and had a baseline tumor assessment that was based on the Novartis RECIST guidelines.

Safety and tolerability

Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. This included the regular monitoring of hematology, blood chemistry and urine and regular assessments of vital signs, physical condition and body weight, along with a neurological exam.

Statistical Methods

For the MTD determination of mild and moderate liver impairment patients groups, a standard "3+3"design for dose escalation was used. ANOVA including dose, cycle, hepatic function (Total bilirubin, AST/SGOT; CPC) and dose by hepatic function interaction term as fixed factors and subject as a random factor was used to analyze the log-transformed PK parameters (parent and its metabolite CGP 85217).

Study Population: Inclusion/Exclusion Criteria and Demographics

***Inclusion criteria*:**

- Age ≥18 years
- WHO Performance Status 0, 1 or 2
- life expectancy ≥ 3 months
- histologically documented advanced solid tumor progressed after systemic therapy or when standard systemic therapy does not exist
- measurable disease defined by modified RECIST criteria or evaluable disease
- ANC ≥ 1.5 x 10^9/L; Hb ≥ 10.0 g/dL; Platelet count ≥ 100 x 10^9/L

- Serum creatinine < 1.5 x ULN
- Normal hepatic function, mild or moderate hepatic impairment
- patients negative serum pregnancy test at screening.

***Exclusion criteria*:**

- Severe and/or uncontrolled medical disease
- diagnosis of HIV infection
- presence of any other active or suspected acute or chronic uncontrolled infection
- severe cardiac insufficiency (NYHA III or IV), with uncontrolled and/or unstable cardiac or coronary artery disease; history of another malignancy within 5 years prior to study entry
- evidence of progressive liver disease (within the previous 2 weeks)
- positive HBsAg, Hepatitis C test or any positive immunoprofile result
- symptoms or history of Stage II or worse degree of encephalopathy within 3 months prior to study entry
- presence of unstable ascites in the previous 2 weeks and/or requiring > 2 ascitic taps within 2 weeks; colostomy; concurrent alcohol abuse
- prior administration of epothilone
- chemotherapy, biologics, immunotherapy, vaccine, cytokine therapy within 3 weeks (6 weeks for nitrosoureas or mitomycin-C) prior to study entry
- radiation therapy or surgery within 3 weeks prior to study entry
- symptomatic brain metastases or leptomeningeal disease
- peripheral neuropathy > grade 1; grade 3 neuropathy in the past 6 months; prolonged grade 2 neuropathy (≥ 8 weeks duration) in the past
- unresolved diarrhea of any grade, within the last 7 days before treatment; patients receiving known diarrheogenic agents had to have stopped treatment with these agents within 7 days prior to enrollment in the study
- patients receiving hematopoietic growth factors except erythropoietin
- patients taking Coumadin® or other agents containing warfarin, with the exception of low dose Coumadin® (1 mg or less daily) administered prophylactically for maintenance of in-dwelling lines or ports
- pregnant or breast-feeding

Number of Subjects

Patient disposition – core phase (safety set)

Disposition	Normal	Mild Dysfunction				Moder-ate dys-function	All
	10 mg/m² N=10 N(%)	5 mg/m² N=8 N(%)	7.5mg/m² N= 3 N(%)	10 mg/m² N=6 N(%)	Total N=17 N(%)	5 mg/m² N=9 N (%)	N=36 N (%)
Completed core	8 (80.0)	6 (75.0)	2 (66.7)	4 (66.7)	12 (70.6)	6 (66.7)	26 (72.2)
Entered extension	4 (40.0)	4 (50.0)	1 (33.3)	2 (33.3)	7 (41.2)	3 (33.3)	14 (38.9)
Discontinued after core	4 (40.0)	2 (25.0)	1 (33.3)	2 (33.3)	5 (29.4)	3 (33.3)	12 (33.3)
AE	2 (20.0)	0	0	1 (16.7)	1 (5.9)	0	3 (8.3)
Patient with-drew consent	0	0	0	1 (16.7)	1 (5.9)	0	1 (2.8)
Death	1 (10.0)	0	0	0	0	0	1 (2.8)
Discontinued in core	2 (20.0)	2 (25.0)	1 (33.3)	2 (33.3)	5 (29.4)	3 (33.3)	10 (27.8)
AE	0	0	0	1 (16.7)	1 (5.9)	0	1 (2.8)
Patient with-drew consent	0	0	0	1 (16.7)	1 (5.9)	0	1 (2.8)
Death	2 (20.0)	1 (12.5)	0	0	1 (5.9)	0	3 (8.3)
Principal cause of death							
Other	2 (20.0)	1 (12.5)	0	0	1 (5.9)	0	3 (8.3)
Disease pro-gression	0	1 (12.5)	1 (33.3)	0	2 (11.8)	3 (33.3)	5 (13.9)

Note: -Patients are considered to have completed the core phase if they received at least two doses of study medication and provided PK data for Cycle 1.

-^ Denotes patients who completed core but did not enter extension.

Patient disposition – extension phase (safety set patients who entered the extension phase)

Disposition	Normal	Mild Dysfunction				Moderate Dysfunc-tion	All Patients
	10.0mg/m² N=4 n (%)	5.0mg/m² N=4 n (%)	7.5mg/m² N=1 n (%)	10.0mg/m² N=2 n (%)	Total N=7 n (%)	5.0mg/m² N=3 n (%)	N=14 n (%)
Completed core phase and entered extension phase	**4 (100)**	**4 (100)**	**1 (100)**	**2 (100)**	**7 (100)**	**3 (100)**	**14 (100)**
Discontinued	**4 (100)**	**4 (100)**	**1 (100)**	**2 (100)**	**7 (100)**	**3 (100)**	**14 (100)**

Adverse events(s)	2 (50.0)	0	0	1 (50.0)	1 (14.3)	1 (33.3)	4 (28.6)
Patient withdrew consent	1 (25.0)	0	0	0	0	0	1 (7.1)
Disease progression	1 (25.0)	4 (100.0)	1 (100.0)	1 (50.0)	6 (85.7)	2 (66.7)	9 (64.3)

Demographic and Background Characteristics

Demographic and other baseline characteristics (Safety set)

Disposition	Normal	Mild Dysfunction				Moderate dysfunc-tion	All
	10 mg/m² N=10 N(%)	5 mg/m² N=8 N(%)	7.5mg/m² N= 3 N(%)	10 mg/m² N=6 N(%)	Total N=17 N(%)	5 mg/m² N=9 N (%)	N=36 N (%)
Age (years)							
n	10	8	3	6	17	9	36
Mean	62.7	57.9	65.7	47.2	55.5	54.9	57.3
SD	8.06	17.49	6.81	11.69	15.18	6.25	11.94
Range	53-77	36-79	58-71	34-61	34-79	46-65	34-79
Sex							
Male	6 (60.0)	7 (87.5)	1 (33.3)	4 (66.7)	12 (70.6)	3 (33.3)	21 (58.3)
Female	4 (40.0)	1 (12.5)	2 (66.7)	2 (33.3)	5 (29.4)	6 (66.7)	15 (41.7)
Race							
Caucasian	8 (80.0)	5 (62.5)	3 (100.0)	4 (66.7)	12 (70.6)	8 (88.9)	28 (77.8)
Black	0	1 (12.5)	0	0	1 (5.9)	0	1 (2.8)
Asian	1 (10.0)	1 (12.5)	0	0	1 (5.9)	0	2 (5.6)
Other	1 (10.0)	1 (12.5)	0	2 (33.3)	3 (17.6)	1 (11.1)	5 (13.9)
Ethnicity							
Hispanic/latino	2 (20.0)	1 (12.5)	0	1 (16.7)	2 (11.8)	2 (22.2)	6 (16.7)
Chinese	0	1 (12.5)	0	0	1 (5.9)	0	1 (2.8)
Mixed ethnicity	1 (10.0)	0	0	1 (16.7)	1 (5.9)	0	2 (5.6)
Other	6 (60.0)	6 (75.0)	3 (100.0)	4 (66.7)	13 (76.5)	7 (77.8)	26 (72.2)
Missing	1 (10.0)	0	0	0	0	0	1 (2.8)
Height (cm)							
n	10	8	3	6	17	9	36
Mean	169.5	173.8	167.0	174.7	172.9	166.1	170.3
SD	9.07	6.84	8.72	11.88	9.06	9.60	9.36
Range	157-185	163-185	157-173	159-188	157-188	158-183	157-188
Weight (kg)							
n	10	8	3	6	17	9	36
Mean	71.54	72.25	71.43	75.10	73.11	71.38	72.24
SD	16.644	24.522	5.133	13.373	18.018	14.124	16.308
Range	46.3-96.5	56.0-126.4	66.0-76.2	58.3-93.8	56.0-126.4	52.3-93.0	46.3-126.4
Child Bearing Potential							
Able to bear children	0	0	0	0	0	1 (16.7)	1 (6.7)
Post meno-pausal	4 (100.0)	1 (100.0)	1 (50.0)	1 (50.0)	3 (60.0)	4 (66.7)	11 (73.3)
Sterile- of child bearing age	0	0	1 (50.0)	1 (50.0)	2 (40.0)	1 (16.7)	3 (20.0)
Note: -Age is calculated from birth date to day of first dose.							

-For 'Child Bearing Potential' the percentage is based on the number of female patients in the corresponding liver function and dose group.

Liver function classification based on Child-Pugh classification (CPC) score and liver function test (Safety set)

CPC Scores	Liver Function Tests (Total Bilirubin and SGOT/AST)			
	Normal N=10 N(%)	Mild N=17 N(%)	Moderate N=9 N (%)	Total N=36 N(%)
Mild (N=19)	7 (70.0)	11 (64.7)	1 (11.1)	19 (52.8)
Moderate (N=13)	3 (30.0)	3 (17.6)	7 (77.8)	13 (36.1)
Severe (N=1)	0	0	1 (11.1)	1 (2.8)
Missing (N=3)	0	3 (17.6)	0	3 (8.3)
Total (N=36)	**10 (100.0)**	**17 (100.0)**	**9 (100.0)**	**36 (100.0)**

Normal: Total bilirubin≤ULN; Mild liver dysfunction: Total bilirubin≤ 1.5× ULN; Moderate liver dysfunction: Total bilirubin> 1.5 to 3× ULN

Primary Objective Result(s)

Summary of patupilone and CGP 85217 primary PK parameters (PK set)

Analyte Cycle Parameter (unit)	Normal	Mild Dysfunction				Moderate Dysfunction
	10.0 mg/m² N=10	5.0 mg/m² N=5	7.5 mg/m² N=5	10.0mg/m² N=5	Total N=13	5.0 mg/m² N=8
Patupilone Cycle 1						
AUC(0-tz) (ng/mL.h)	1585.332 (29.120)	679.190 (99.039)	1663.718 (33.850)	1857.942 (28.924)	1229.911 (81.907)	1522.049 (23.608)
AUC(0-inf) (ng/mL.h)	1633.538 (26.657)	1046.028 (28.309)	1809.867 (33.461)	2127.848 (37.977)	1612.754 (46.535)	1740.072 (28.928)
C_{max} (ng/mL)	82.982 (41.965)	59.810 (56.517)	36.504 (99.469)	113.895 (103.880)	68.372 (97.229)	52.337 (57.073)
Cycle 2 AUC(0-tz) (ng/mL.h)	2024.697 (47.0650)	861.463 (16.0530)	2000.178 (42.2320)	2834.660 (47.6440)	1763.713 (71.4730)	1883.122 (46.8750)
C_{max} (ng/mL)	110.131 (61.9270)	100.414 (61.0430)	72.911 (80.1860)	104.450 (86.0430)	95.172 (67.1480)	65.313 (127.3200)
CGP 85217 Cycle 1						
AUC(0-tz) (ng/mL.h)	821.860 (123.6690)	471.152 (20.4210)	861.847 (103.6460)	174.443 (81.9410)	343.628 (126.3670)	196.350 (96.0400)
C_{max} (ng/mL)	3.655 (91.8780)	1.255 (28.5380)	2.512 (83.5180)	2.895 (45.8670)	2.347 (61.8800)	1.120 (47.8490)
Cycle 2						
AUC(0-tz) (ng/mL.h)	395.936 (218.4220)	439.633	322.691 (391.9890)	123.773 (57.4360)	195.059 (124.9880)	142.821 (285.0080)
C_{max} (ng/mL)	3.407 (105.5560)	1.470	1.616 (49.5380)	2.165 (16.8260)	1.884 (29.1450)	1.062 (60.6160)

Note: Values are geometric mean (CV%).

Summary of patupilone and CGP 85217 secondary PK parameters (PK set)

Analyte Cycle Parameter (unit)	Normal	Mild Dysfunction				Moderate Dysfunction
	10.0 mg/m² N=10	5.0 mg/m² N=5	7.5 mg/m² N=5	10.0mg/m² N=5	Total N=13	5.0 mg/m² N=8
Patupilone Cycle 1						
t1/2 (h)	122.924 (40.761)	94.181 (139.017)	139.352 (6.793)	162.269 (42.917)	127.087 (78.507)	157.433 (37.032)
CL (L/h/m^2)	6.117 (25.834)	4.743 (25.608)	4.044 (31.622)	4.658 (37.558)	4.523 (30.196)	2.815 (28.870)
Vss (L/m^2)	885.224 (53.975)	761.310 (40.747)	764.902 (35.156)	926.495 (21.023)	827.192 (30.478)	582.312 (33.951)
Cycle 2						
R	1.344 (24.667)	0.936 (37.865)	1.104 (1.108)	1.458 (28.306)	1.183 (33.445)	1.268 (22.100)
t1/2 (h)	120.037 (43.729)	181.699 (14.788)	139.857 (63.704)	148.567 (14.101)	159.183 (29.452)	189.243 (22.996)
CL (L/h/m^2)	4.907 (45.900)	5.669 (14.987)	3.703 (40.557)	3.485 (46.337)	4.154 (40.591)	2.611 (44.984)
Vss (L/m^2)	484.324	771.646	342.002	474.412	518.791	464.350
	(67.776)	(9.376)	(135.558)	(41.810)	(59.090)	(27.615)
CGP 85217 Cycle 1						
t1/2 (h)	144.863 (10.695)	355.856 (81.407)	354.438 (46.018)	220.479	327.911 (49.145)	115.200 (47.872)
MR-AUC (0-tz)	0.4330 (166.115)	0.3883 (13.203)	0.5004 (95.693)	0.0907 (100.858)	0.2025 (150.547)	0.1275 (63.509)
MR-C_{max}	0.0467 (171.133)	0.0203 (4.231)	0.0665 (17.297)	0.0246 (109.785)	0.0319 (92.847)	0.0262 (53.466)
Cycle 2						
R	1.836 (92.131)	0.809	0.527 (94.687)	0.753 (72.799)	0.687 (65.057)	1.415 (34.953)
t1/2 (h)	85.893 (61.575)	289.301	-	146.710 (135.785)	173.853 (111.912)	615.931 (55.164)
MR- AUC (0-tz)	0.2312 (153.778)	0.4309	0.1558 (199.406)	0.0422 (89.063)	0.0854 (180.458)	0.0794 (152.445)
MR-C_{max}	0.0333 (146.731)	0.0180	0.0214 (23.950)	0.0200 (75.067)	0.0201 (51.613)	0.0245 (112.155)

Note: -Values are geometric mean (CV%).
R= Drug accumulation by AUC 0-504h Cycle 2 / AUC0-504h Cycle 1.
MR = Metabolic ratio. The primary PK parameter ratio of CGP 85217-to-patupilone will be multiplied with 0.966, which is calculated as the molecular weight of patupilone (508 g/mole) divided by the molecular weight of CGP 85217 (526 g/mole).

Summary of statistical analysis of dose-normalized patupilone and CGP 85217 primary PK parameters (PK set)

PK Parameter (unit)	Hepatic Function	n	Adjusted Geo-mean	Comparison(s)	Treatment Comparison 90% CI		
					Geo-Mean Ratio	Lower	Upper
Patupilone							
AUC(0-inf) (ng/mL.h)	Normal	9	157.617				
	Mild	12	224.603	Mild: Normal	1.42	1.17	1.74
	Moderate	7	362.304	Moderate: Normal	2.30	1.83	2.88
AUC(0-tz) (ng/mL.h)	Normal	10	150.712				
	Mild	13	221.175	Mild: Normal	1.47	1.06	2.04
	Moderate	8	292.235	Moderate: Normal	1.94	1.34	2.81
C_{max} (ng/mL)	Normal	10	9.097				
	Mild	13	10.991	Mild: Normal	1.21	0.78	1.87
	Moderate	8	11.308	Moderate: Normal	1.24	0.76	2.03
CGP 85217							
AUC(0-tz) (ng/mL.h)	Normal	7	55.355				
	Mild	10	30.575	Mild: Normal	0.55	0.22	1.40
	Moderate	6	30.795	Moderate: Normal	0.56	0.20	1.51
C_{max} (ng/mL)	Normal	7	0.316				
	Mild	10	0.296	Mild: Normal	0.94	0.61	1.45
	Moderate	6	0.186	Moderate: Normal	0.59	0.35	0.99

n* = number of patients with non-missing values.

-Geo-mean = geometric mean. Adjusted Geo-mean, Geo-mean ratio, and 90% CI were determined from either a mixed effect model or a fixed effect model (C_{max} for CGP 85217), and back-transformed from log scale.

-The model on log transformed dose-normalized PK parameters included hepatic function as a fixed effect and patient as a random effect. For patupilone, age was also included in the model for AUC(0-inf) and albumin, SGOT and age were included for AUC(0-tz) (after backward selection; see SAP for details). For CGP 85217, age, SGOT and plasma protein binding fraction were included in the model for AUC(0-tz) and albumin was included for C_{max}. Analysis of AUC(0-inf) was based on cycle 1 data only.

Summary of dose limiting toxicities (DLT) (MTD determining set)

DLT	Normal	Mild Dysfunction				Moderate Dysfunction	All Patients
	10 mg/m² N=10 n (%)	5 mg/m² N=8 n (%)	7.5 mg/m² N=3 n (%)	10 mg/m² N=6 n (%)	Total N=7 n (%)	5 mg/m² N=8 n (%)	N=35 n (%)

Any DLT	0	1 (12.5)	0	1 (16.7)	2 (11.8)	0	2 (5.7)
Diarrhea, grade 3	0	0	0	1 (16.7)	1 (5.9)	0	1 (2.9)
Sudden Death	0	1 (12.5)	0	0	1 (5.9)	0	1 (2.9)

Secondary Objective Result(s)

Best overall response at study completion

Best Overall Response	Normal	Mild Dysfunction			Moderate Dysfunction	All Patients
	10.0 mg/m² N=8 N (%)	5.0 mg/m² N=7 N (%)	7.5 mg/m² N=3 N (%)	10.0 mg/m² N=6 N (%)	5.0 mg/m² N=9 N (%)	N=33 N (%)
PR	0	0	0	2 (33.3)	0	2 (6.1)
SD	3 (37.5)	3 (42.9)	0	0	2 (22.2)	8 (24.2)
PD	2 (25.0)	2 (28.6)	3 (100.0)	1 (16.7)	5 (55.6)	13 (39.4)
Unknown	3 (37.5)	2 (28.6)	0	3 (50.0)	2 (22.2)	10 (30.3)
ORR : CR or PR [95% CI]	0	0	0	2 (33.3) [4.33,77.72]	0	2 (6.1) [0.74,20.23]
DCR: CR or PR or SD [95% CI]	3 (37.5) [8.52,75.51]	3 (42.9) [9.90,81.59]	0	2 (33.3) [4.33,77.72]	2 (22.2) [2.81,60.01]	10 (30.3) [15.59,48.71]

PR= Partial response; SD= Stable disease; PD= Progressive disease; CR= Complete response

Safety Results

Adverse Events by System Organ Class

Primary System Organ Class	Normal	Mild Dysfunction				Moderate Dysfunction	All Patients
	10.0 mg/m² N=10 N(%)	5.0 mg/m² N=8 N(%)	7.5 mg/m² N=3 N(%)	10.0 mg/m² N=6 N(%)	Total N=17 N(%)	5.0 mg/m² N=9 N(%)	N=36 N(%)
Any primary system organ class	10 (100.0)	8 (100.0)	3 (100.0)	6 (100.0)	17 (100.0)	9 (100.0)	36 (100.0)
Blood and lymphatic system disorders	3 (30.0)	0	1 (33.3)	1 (16.7)	2 (11.8)	2 (22.2)	7 (19.4)
Gastrointestinal disorders	9 (90.0)	7 (87.5)	3 (100.0)	6 (100.0)	16 (94.1)	8 (88.9)	33 (91.7)
General disorders and administration site conditions	9 (90.0)	6 (75.0)	3 (100.0)	3 (50.0)	12 (70.6)	5 (55.6)	26 (72.2)
Nervous system disorders	5 (50.0)	1 (12.5)	2 (66.7)	3 (50.0)	6 (35.3)	3 (33.3)	14 (38.9)

Adverse events, suspected to be study drug related (preferred term occurring in at least 10% of the patients)

Preferred term	Normal	Mild Dysfunction				Moderate Dysfunction	All Patients
	10.0 mg/m² N=10 N(%)	5.0 mg/m² N=8 N(%)	7.5 mg/m² N=3 N(%)	10.0 mg/m² N=6 N(%)	Total N=17 N(%)	5.0 mg/m² N=9 N(%)	N=36 N(%)
Abdominal pain	3 (30.0)	0	0	1 (16.7)	1 (5.9)	0	4 (11.1)
Diarrhea	7 (70.0)	4 (50.0)	3 (100.0)	5 (83.3)	12 (70.6)	4 (44.4)	23 (63.9)
Nausea	4 (40.0)	1 (12.5)	1 (33.3)	3 (50.0)	5 (29.4)	0	9 (25.0)
Vomiting	3 (30.0)	0	1 (33.3)	3 (50.0)	4 (23.5)	0	7 (19.4)
Fatigue	5 (50.0)	1 (12.5)	2 (66.7)	2 (33.3)	5 (29.4)	2 (22.2)	12 (33.3)
Dehydration	1 (10.0)	0	0	2 (33.3)	2 (11.8)	1 (11.1)	4 (11.1)
Neuropathy peripheral	4 (40.0)	0	0	3 (50.0)	3 (17.6)	0	7 (19.4)

Serious Adverse Events and Deaths

Serious or Significant Events	Normal	Mild Dysfunction				Moderate Dysfunction	All Patients
	10.0 mg/m² N=10 N(%)	5.0 mg/m² N=8 N(%)	7.5 mg/m² N=3 N(%)	10.0 mg/m² N=6 N(%)	Total N=17 N(%)	5.0 mg/m² N=9 N(%)	N=36 N(%)

All deaths	3(30.0)	2 (25.0)	0	0	2 (11.8)	1 (11.1)	6 (16.7)
On treatment deaths*	3 (30.0)	2 (25.0)	0	0	2 (11.8)	1 (11.1)	6 (16.7)
All SAEs	7 (70.0)	2 (25.0)	0	4 (66.7)	6 (35.3)	6 (66.7)	19 (52.8)
Study-drug-related SAEs	4 (40.0)	1 (12.5)	0	3 (50.0)	4 (23.5)	1 (11.1)	9 (25.0)
AEs causing study drug discontinua-tion	5 (50.0)	1 (12.5)	0	3 (50.0)	4 (23.5)	1 (11.1)	10 (27.8)
AEs causing dose adjustment or dose delay	4 (40.0)	2 (25.0)	0	2 (33.3)	4 (23.5)	3 (33.3)	11 (30.6)
Note: * Includes deaths up to 28 days after last dose of study drug.							

Other Relevant Findings

None

Date of Clinical Trial Report

18 Aug 2011

Date Inclusion on Novartis Clinical Trial Results Database

9 Jan 2012

Date of Latest Update