Sponsor

Novartis

Generic Drug Name

Patupilone

Therapeutic Area of Trial

Advanced solid tumors

Approved Indication

Investigational

Study Number

CEPO906A2105

Title

A phase Ib, multicenter, open-label, dose-finding study of patupilone administered intravenously every 3 weeks in combination with carboplatin AUC 6 in adult patients with advanced solid tumors

Phase of Development

Ib

Study Start/End Dates

28-Aug-2006 to 19-Aug-2010

Study Design/Methodology

This was an open label, multicenter, Phase Ib dose-escalation study of patupilone administered every three weeks (q3w) in combination with a fixed dose of carboplatin (AUC 6) to determine the dose limiting toxicity (DLTs) and the maximum tolerated dose (MTD) when administered to patients with advanced cancer tumors who had progressed despite standard therapy or for whom no standard therapy existed or whom might have benefitted from a treatment with carboplatin.

One cycle was defined as a 3-week (21-day) period of time. Day 1 of each cycle was defined as the day of the administration of the study drugs (both or any of them).

The study consisted in two parts.

Part 1: dose escalation: The MTD of patupilone when combined with carboplatin was deter-

mined using a 2-parameter Bayesian logistic regression model with overdose control.

Part 2: cohort expansion: Once the MTD of patupilone in combination with carboplatin had been established, the next patients entered in the study participated to the part 2. Twenty four patients were planned to be allocated to one of the 2 cohorts by randomization:

In Cohort A (n = 12), patients were planned to receive patupilone alone in Cycle 1 followed by patupilone/carboplatin in subsequent cycles

In Cohort B (n = 12), patients were planned to receive carboplatin alone in Cycle 1 followed by patupilone/carboplatin combination in subsequent cycles.

Cohorts A and B were to assess the existence of a drug to drug interaction (DDI) between patupilone and carboplatin.

Centres

France (2), United States (5)

Publication

None

Objectives

Primary objective(s)

- To determine the MTD and DLT of patupilone in combination with carboplatin (AUC 6) when administered intravenously q3w to adult patients with advanced solid tumors who had progressed despite standard therapy or for whom no standard therapy existed or who might have benefitted from treatment with carboplatin.

Secondary objective(s)

- To determine the safety of patupilone combined with carboplatin
- To evaluate the overall response rate (complete response [CR] + partial response [PR]) according to the Response Evaluation Criteria in Solid Tumor (RECIST) of patupilone combined with carboplatin
- To evaluate the time to progression (TTP), duration of overall response, duration of stable disease and time to overall response of patupilone combined with carboplatin administrated to a population of patients with advanced solid tumors
- To characterize the pharmacokinetic profile of patupilone combined with carboplatin
- To characterize the pharmacokinetic profile of carboplatin combined with patupilone
- To investigate the relationship between pharmacokinetics of patupilone and clinical outcome

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

Patupilone was supplied as 10 mg/4mL clear, colorless concentrate for solution for injection in individual 10 mL glass vials.

Carboplatin was supplied as a sterile, pyrogen-free, 10 mg/ml aqueous solution

In Part 1 of the study the dose levels of patupilone were to be escalated (planned range: 4.8 mg/m^2 to 10 mg/m^2 based on body surface area).

In Part 2, the dose of patupilone was administered according to the MTD determined in part 1.

Patupilone was administered as a single i.v infusion over a period of 20 minutes once q3w. Carboplatin was administered throughout the study at a fixed dose of AUC 6 (determined with the Calvert formula) as a single i.v infusion over a period of 60 minutes once q3w immediately after the completion of the administration of patupilone.

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

Not applicable

Criteria for Evaluation

Safety: Safety assessments included monitoring and recording of all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of hematology, blood chemistry and regular assessments of vital signs, physical condition and body weight.

Efficacy: The best overall response was evaluated as a function of tumor response only in patients with at least one measurable lesion according to the RECIST guidelines.

The secondary efficacy variables included time to progression (TTP), duration of overall response, duration of stable disease, and time to overall response.

Pharmacology

Pre-dose blood samples (2 mL each) for determination of patupilone concentration in blood were collected prior to dosing in all dosing Cycles of Part 1, starting from Cycle 2. Pre-dose blood samples (2 mL each) for determination of patupilone concentration in blood will be collected prior to dosing in all dosing Cycles, starting from Cycle 2, for both cohorts of Part 2.

Blood samples for determination of patupilone blood levels were collected immediately prior to and at the end of infusion, and at 1, 2, 4, 8, 24, 72, 168, 336, and 504 (immediately prior to Cycle 2 dose administration) hours during Cycle 1 and Cycle 2. Blood samples for determination of carboplatin plasma levels were collected at pre-dose, immediately at the end of the infusion, and at 0.5, 1, 1.5, 2, 3, 4, 5, 8, 10, and 24 hours post initiation of infusion during Cycle 1 and Cycle 2.

Blood concentrations of patupilone were determined by a LC-MS/MS method and plasma concentrations of carboplatin were determined by an ICP/ MS method.

Statistical Methods

A 2-parameter Bayesian logistic regression model with overdose control was used during the dose escalation phase for dose level selection and determination of the MTD.

The best overall response was summarized for Part 1 by dose level and Part 2 by cohorts based on the Full Analysis set. Estimates for overall response rate (CR/ PR) and the disease control rate (CR/ PR/ SD) along with 95% CI based on the exact binomial method were reported.

Safety analysis was presented in summary tables separately by dose levels for Part 1 and by cohorts for Part 2. The assessment of safety was based primarily on the frequency of AEs and laboratory abnormalities. Other safety data (e.g., vital signs, ECG) were considered as appropriate. All safety evaluations were performed based on the Safety Set.

The PK parameters of patupilone ($AUC_{0\text{-}tz}$, $AUC_{0\text{-}\infty}$, C_{max} , C_{min} , CL , $t_{½}$, and V_{ss};) and PK parameters of carboplatin ($AUC_{0\text{-}24h}$, $AUC_{0\text{-}tz}$, $AUC_{0\text{-}\infty}$, C_{max} , CL , $t_{½}$, V_{ss} , $Ae_{0\text{-}24h}$ and CL_r) were determined using non-compartmental methods in blood and plasma respectively.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

- Histologically or cytologically confirmed advanced solid tumors which had progressed despite standard therapy, or for which no standard therapy existed, or who might have benefitted from treatment with carboplatin
- A minimum of 4 weeks since the last treatment with chemotherapy
- World health organization (WHO) performance status 0 to 1
- Age ≥ 18
- Adequate hematological parameters:
  - Absolute neutrophil Count (ANC) ≥ 1.5 x 10^9/L
  - Hb ≥ 10.0 g/dL; (red blood cell transfusions and repeat evaluations for study entry are allowed; hemoglobin should be stable for 2 weeks after transfusion before first dose of study treatment)
  - PLT ≥ 100,000/mm^3 (non-transfused)
- No major impairment of renal or hepatic function, as defined by the following laboratory parameters:
  - total bilirubin ≤ 1.5 x upper limit of normal (ULN) (regardless of liver involvement)
  - Alanine aminotransferase/aspartate aminotransferase (AST/ALT) ≤ 2.5 x ULN
  - Alkaline phosphatases ≤ 5.0 x ULN
  - Albumin ≥ 2.5 g/dL
  - Creatinine clearance ≥ 60mL/min
- Negative serum pregnancy test at screening (Not applicable to patients who were surgically sterilized or who were postmenopausal)
- Women of child bearing potential were required to use effective contraception (i.e. double barrier method intrauterine device plus condom, spermicidal gel plus condom)
- Written informed consent obtained

Exclusion criteria:

- Major surgery less than 4 weeks prior to study entry and who did not recover fully from surgery for any cause
- Prior chemotherapy within 4 weeks before start of study or planned to receive other chemotherapy agents while participating in the study. Patients must have recovered from prior treatment-related toxicity
- Prior administration of an epothilone
- Hypersensitivity to carboplatin. Carboplatin-resistant patients were not recommended to enter the trial (patients who experienced disease progression during administration or within 6 months after completion of a carboplatin-based therapy)
- Previous radiotherapy within 4 weeks before start of study (except for palliative therapy of distant metastases in extremities, but such lesions could not be used as target lesions), or where radiotherapy was being planned while participating in the study. Patients must have recovered from prior treatment-related toxicity
- Received radiotherapy to ≥25% of the bone marrow
- Unresolved bowel obstruction

- Any peripheral neuropathy > Common Toxicity Criteria (CTC) Grade 1
- Unresolved diarrhea of any Grade within last 7 days prior to start of treatment
- Symptomatic brain metastases and/or lepto-meningeal disease
- Colostomy
- Underlying medical disease(s) that were not controlled (e.g. uncontrolled non-insulin dependant diabetes mellitus)
- Received any investigational compound within the past 28 days or who were planning to receive other investigational drugs while participating in the study
- Presence of an active or suspected acute or chronic uncontrolled infection, including human immune deficiency virus (HIV), abscess or fistulae
- Severe cardiac insufficiency (NYHA III or IV); uncontrolled and/or unstable cardiac or coronary artery disease
- History of another malignancy within 5 years prior to study entry that required active treatment at the time of inclusion in the study
- Receiving haematopoietic growth factors (except erythropoietin)
- Concomitant administration of warfarin or other agents containing warfarin, with the exception of low dose warfarin (1 mg or less daily) administered prophylactically for maintenance of in-dwelling lines or ports. Wash-out period from therapeutic warfarin use should be ≥ 7 days
- Concomitant administration of any drug/agent known to cause, or increase the severity of, diarrhea. Patients should have ceased treatment with any such agents at least 7 days prior to start of study treatment
- A history of noncompliance to medical regimens or inability or unwillingness to return to the study center for scheduled visits, including tumor assessments and blood draws
- Pregnancy, breast-feeding, or unwillingness to use an acceptable method of contraception (i.e. barrier contraception) while receiving, and up to 3 months after cessation of study treatment
- Presence of another nonmalignant disease which in the opinion of the investigator was incompatible with the protocol

Number of Subjects

Patient disposition by dose level- n (%) of patients (Full Analysis Set) Part 1

Disposition/Reason	4.8 mg/m² + AUC 6 N = 6 n (%)	6.4 mg/m² + AUC 6 N = 3 n (%)	7.0 mg/m² + AUC 6 N = 7 n (%)	7.5 mg/m² + AUC 6 N = 9 n (%)	All doses + AUC 6 N = 25 n (%)
Randomized	6 (100)	3 (100)	7 (100)	9 (100)	25 (100)
Not treated	0	0	0	0	0
Treated	6 (100)	3 (100)	7 (100)	9 (100)	25 (100)
Discontinued	6 (100)	3 (100)	7 (100)	9 (100)	25 (100)
Adverse event	0	0	2 (28.6)	2 (22.2)	4 (16.0)
Abnormal laboratory value	0	0	0	0	0
Abnormal test procedure results	0	0	0	0	0
Subject condition no longer requires study drug	0	0	0	0	0
Protocol violations	0	0	0	0	0
Subject withdrew consent	1 (16.7)	0	1 (14.3)	1 (11.1)	3 (12.0)
Lost to follow-up	0	0	0	0	0
Administrative problems	0	1 (33.3)	0	1 (11.1)	2 (8.0)
Death	1 (16.7)	0	0	0	1 (4.0)
Death from study indication	1 (16.7)	0	0	0	1 (4.0)
Death from other causes	0	0	0	0	0
New cancer therapy	0	0	0	0	0
Disease progression	4 (66.7)	2 (66.7)	4 (57.1)	5 (55.6)	15 (60.0)
Treatment duration completed as per protocol	0	0	0	0	0
On treatment	0	0	0	0	0

Patient disposition by cohort- n (%) of patients (Full Analysis Set) Part 2

Disposition/Reason	Cohort A 7 mg/m² + AUC 6 N = 20 n (%)	Cohort B 7 mg/m² + AUC 6 N = 17 n (%)	Total N = 37 n (%)
Randomized	20 (100)	17 (100)	37 (100)
Not treated	0	0	0
Treated	20 (100)	17 (100)	37 (100)
Discontinued	20 (100)	17 (100)	37 (100)
Adverse event	6 (30.0)	4 (23.5)	10 (27.0)
Abnormal laboratory value	0	0	0
Abnormal test procedure results	0	0	0
Subject condition no longer requires study drug	0	0	0
Protocol violations	0	0	0

Subject withdrew consent	1 (5.0)	1 (5.9)	2 (5.4)
Lost to follow-up	0	0	0
Administrative problems	0	0	0
Death	1 (5.0)	1 (5.9)	2 (5.4)
Death from study indication	1 (5.0)	0	1 (2.7)
Death from other causes	0	1 (5.9)	1 (2.7)
New cancer therapy	0	0	0
Disease progression	12 (60.0)	11 (64.7)	23 (62.2)
Treatment duration completed as per protocol	0	0	0
On treatment	0	0	0

Demographic and Background Characteristics

Demographic summary by dose level (Full analysis set) Part 1

	4.8 mg/m² + AUC 6 N=6	6.4 mg/m² + AUC 6 N=3	7.0 mg/m² + AUC 6 N=7	7.5 mg/m² + AUC 6 N=9	All doses + AUC 6 N=25
Age (years)					
n	6	3	7	9	25
Mean	58.3	57.0	61.6	50.7	56.3
SD	16.55	10.15	6.75	11.19	11.83
Median	64.0	59.0	60.0	54.0	57.0
Range	36.0-77.0	46.0-66.0	54.0-71.0	31.0-65.0	31.0-77.0
Age group - n (%)					
< 45 years	2 (33.3)	0	0	3 (33.3)	5 (20.0)
45-65 years	1 (16.7)	2 (66.7)	4 (57.1)	6 (66.7)	13 (52.0)
> 65 years	3 (50.0)	1 (33.3)	3 (42.9)	0	7 (28.0)
Gender - n (%)					
Female	3 (50.0)	1 (33.3)	3 (42.9)	4 (44.4)	11 (44.0)
Male	3 (50.0)	2 (66.7)	4 (57.1)	5 (55.6)	14 (56.0)
Race - n (%)					
Caucasian	4 (66.7)	3 (100.0)	5 (71.4)	7 (77.8)	19 (76.0)
Black	2 (33.3)	0	1 (14.3)	2 (22.2)	5 (20.0)
Asian	0	0	0	0	0
Native American	0	0	1 (14.3)	0	1 (4.0)
Pacific Islander	0	0	0	0	0
Other	0	0	0	0	0
Weight (kg)					
n	6	3	7	9	25
Mean	70.5	63.7	74.2	85.8	76.2
SD	15.75	0.52	15.62	33.74	23.57
Median	66.5	64.0	73.2	73.0	69.0
Range	53.0-99.4	63.1-64.0	52.7-91.0	56.6-167.9	52.7-167.9
Height (cm)					
n	6	3	7	9	25
Mean	170.2	172.7	167.6	171.1	170.1
SD	13.67	5.77	14.06	9.12	11.04
Median	169.5	176.0	175.0	169.0	172.0
Range	150.0-188.0	166.0-176.0	148.0-182.0	160.0-189.0	148.0-189.0

Demographic summary by cohort (Full analysis set) Part 2

	Cohort A 7 mg/m² + AUC 6 N=20	Cohort B 7 mg/m² + AUC 6 N=17	Total N=37

Age (years)			
n	20	17	37
Mean	59.9	62.2	60.9
SD	12.13	10.82	11.45
Median	59.5	64.0	62.0
Range	36.0-79.0	42.0-77.0	36.0-79.0
Age group - n (%)			
< 45 years	3 (15.0)	1 (5.9)	4 (10.8)
45-65 years	10 (50.0)	9 (52.9)	19 (51.4)
> 65 years	7 (35.0)	7 (41.2)	14 (37.8)
Gender - n (%)			
Female	9 (45.0)	6 (35.3)	15 (40.5)
Male	11 (55.0)	11 (64.7)	22 (59.5)
Race - n (%)			
Caucasian	17 (85.0)	15 (88.2)	32 (86.5)
Black	2 (10.0)	2 (11.8)	4 (10.8)
Asian	1 (5.0)	0	1 (2.7)
Native American	0	0	0
Pacific Islander	0	0	0
Other	0	0	0
Weight (kg)			
n	20	17	37
Mean	80.6	78.7	79.7
SD	15.75	15.87	15.62
Median	79.8	75.7	79.5
Range	53.0-108.0	55.0-103.9	53.0-108.0
Height (cm)			
n	20	17	37
Mean	172.1	169.0	170.6
SD	8.83	9.20	9.01
Median	171.0	170.0	171.0
Range	157.0-189.0	152.0-186.0	152.0-189.0

Primary Objective Result(s)

Dose limiting toxicities - n (%) of patients by dose level (MTD determining analysis set) Part 1

Patients with dose limiting toxicity	**4.8 mg/m² + AUC 6 N=6 n (%)**	**6.4 mg/m² + AUC 6 N=3 n (%)**	**7.0 mg/m² + AUC 6 N=6 n (%)**	**7.5 mg/m² + AUC 6 N=9 n (%)**	**All doses + AUC 6 N=24 n (%)**
Patients with DLT (any type)	0	0	0	3 (33.3)	3 (12.5)
Patients with grade 4 thrombopenia	0	0	0	2 (22.2)	2 (8.3)
Patients with grade 2 neutropenia*	0	0	0	1 (11.1)	1 (4.2)

Patients with grade 4 anemia	0	0	0	1 (11.1)	1 (4.2)

*Note: Grade 2 neutropenia lasting for more than 28 days

The MTD and recommended dose for patupilone in Part 2 of the study was established at patupilone 7 mg/m^2.

Secondary Objective Result(s)

Best overall response by dose level (RECIST, Full analysis set) Part 1

	4.8 mg/m² + AUC 6 N = 6	**6.4 mg/m² + AUC 6 N = 3**	**7.0 mg/m² + AUC 6 N = 7**	**7.5 mg/m² + AUC 6 N = 9**	**All doses + AUC 6 N = 25**
Best overall response	n (%)	n (%)	n (%)	n (%)	n (%)
Complete Response (CR)	0	0	0	0	0
Partial Response (PR)	0	0	1 (14.3)	0	1 (4.0)
Stable Disease (SD)	2 (33.3)	1 (33.3)	5 (71.4)	4 (44.4)	12 (48.0)
Progressive Disease (PD)	2 (33.3)	2 (66.7)	0	4 (44.4)	8 (32.0)
Unknown	2 (33.3)	0	1 (14.3)	1 (11.1)	4 (16.0)
Best overall response (CR, PR)	0	0	1 (14.3)	0	1 (4.0)
95% CI for the response rate	(-- , --)	(-- , --)	(0.36, 57.87)	(-- , --)	(0.10, 20.35)
Disease control (CR,PR, SD) and the disease control rate	2 (33.3)	1 (33.3)	6 (85.7)	4 (44.4)	13 (52.0)
95% CI for the disease control rate	(4.33, 77.72)	(0.84, 90.57)	(42.13, 99.64)	(13.70, 78.80)	(31.31, 72.20)

Note: Best overall response is based on local investigator's opinion using RECIST criteria. The 95% CI for the response rate is from the exact binomial method (Clopper & Pearson 1934).

Best overall response by cohort (RECIST, Full analysis set) Part 2

	COHORT A 7 mg/m² + AUC N = 20	**COHORT B 7 mg/m² + AUC N = 17**	**Total N = 37**
Best overall response	**n (%)**	**n (%)**	**n (%)**
Complete Response (CR)	0	0	0
Partial Response (PR)	1 (5.0)	0	1 (2.7)
Stable Disease (SD)	6 (30.0)	9 (52.9)	15 (40.5)
Progressive Disease (PD)	8 (40.0)	4 (23.5)	12 (32.4)
Unknown	5 (25.0)	4 (23.5)	9 (24.3)
Best overall response (CR, PR)	1 (5.0)	0	1 (2.7)
95% CI for the response rate	(0.13, 24.87)	(-- , --)	(0.07, 14.16)
Disease control (CR,PR, SD) and the disease control rate	7 (35.0)	9 (52.9)	16 (43.2)
95% CI for the disease control rate	(15.39, 59.22)	(27.81, 77.02)	(27.10, 60.51)

Note: Best overall response is based on local investigator's opinion using RECIST criteria. The 95% CI for the response rate is from the exact binomial method (Clopper & Pearson 1934).

Summary of primary PK parameters for patupilone by cycle – Part II, Cohort A (PK set)

Cycle	Statistics	$AUC_{(0\text{-}inf)}$ (h.ng/mL)	$AUC_{(0\text{-}tz)}$ (h.ng/mL)	C_{max} (ng/mL)
1	n	12	14	14
	Mean (SD)	1262.073 (629.1580)	1243.426 (623.4182)	92.400 (84.0953)
	CV% mean	49.85	50.14	91.01
	Geo-mean	1144.754	1119.199	70.545
	CV% geo-mean	46.78	49.15	79.68
	Median	1056.858	971.960	52.200
	[Min; Max]	[675.01; 2451.69]	[644.81; 2690.37]	[28.40; 302.00]
2	n	9	13	13
	Mean (SD)	1240.820 (675.9273)	1229.300 (640.5324)	90.654 (57.7236)
	CV% mean	54.47	52.11	63.67
	Geo-mean	1110.282	1079.282	74.914
	CV% geo-mean	51.08	57.88	73.20
	Median	942.924	1011.665	61.000
	[Min; Max]	[608.02; 2674.81]	[445.00; 2172.13]	[25.60; 215.00]

Note: CV% mean = coefficient of variation (%) = sd/mean*100.
CV% geo-mean = sqrt(exp(variance for log transformed data)-1)*100.
Cohort A: patupilone in cycle 1 and patupilone + carboplatin afterwards

Summary of secondary PK parameters for patupilone by cycle – Part II, Cohort A (PK set)

Cycle	Statistics	C_{min} (ng/mL)	$T_{1/2}$ (h)	CL ($L/h/m^2$)	V_{ss} (L/m^2)
1	n	13	13	12	12
	Mean (SD)	1.119 (1.0832)	123.979 (33.6675)	6.635 (2.5544)	821.569 (276.8635)
	CV% mean	96.81	27.16	38.50	33.70
	Geo-mean	0.786	119.580	6.115	765.547
	CV% geo-mean	102.50	29.06	46.78	45.54
	Median	0.645	121.097	6.632	832.834
	[Min; Max]	[0.23; 3.85]	[68.59; 177.95]	[2.86; 10.37]	[238.11; 1238.44]
2	n	10	12	9	9
	Mean (SD)	1.571 (2.6637)	96.052 (40.5256)	6.916 (2.8818)	796.173 (345.7251)
	CV% mean	169.58	42.19	41.67	43.42
	Geo-mean	0.761	88.636	6.305	678.202
	CV% geo-mean	156.68	43.69	51.08	84.17
	Median	0.535	87.272	7.424	851.460
	[Min; Max]	[0.19; 8.95]	[49.10; 163.30]	[2.62; 11.51]	[111.13; 1282.43]

Note: CV% mean = coefficient of variation (%) = sd/mean*100.
CV% geo-mean = sqrt(exp(variance for log transformed data)-1)*100.
Cohort A: patupilone in cycle 1 and patupilone + carboplatin afterwards

Summary of primary PK parameters for carboplatin by cycle – Part II, Cohort B (PK set)

Cycle	Statistics	$AUC_{(0\text{-}inf)}$ (min.mg/mL)	$AUC_{(0\text{-}tz)}$ (min.mg/mL)	$AUC_{(0\text{-}24)}$ (min.mg/mL)	C_{max} (ng/mL)
1	n	13	13	13	13

	Mean (SD)	10.695 (2.3887)	8.396 (1.7231)	8.406 (1.7453)	35453.846 (16343.2767)
	CV% mean	22.34	20.52	20.76	46.10
	Geo-mean	10.456	8.231	8.237	32801.087
	CV% geo-mean	22.27	21.15	21.37	40.41
	Median	9.964	8.161	8.172	29000.000
	[Min; Max]	[7.47; 14.88]	[5.41; 11.07]	[5.41; 10.94]	[22500.00; 77600.00]
2	n	7	7	7	7
	Mean (SD)	11.477 (3.0825)	8.455 (1.7301)	8.485 (1.7317)	35885.714 (9677.5390)
	CV% mean	26.86	20.46	20.41	26.97
	Geo-mean	11.142	8.314	8.345	34836.324
	CV% geo-mean	26.56	19.66	19.55	26.41
	Median	11.504	8.252	8.240	30100.000
	[Min; Max]	[7.73; 17.05]	[6.68; 11.60]	[6.68; 11.66]	[26900.00; 49700.00]

Note: CV% mean = coefficient of variation (%) = sd/mean*100.
CV% geo-mean = sqrt(exp(variance for log transformed data)-1)*100.
Cohort B: carboplatin in cycle 1 and patupilone + carboplatin afterwards

Summary of secondary PK parameters for carboplatin by cycle – Part II, Cohort B (PK set)

Cycle	Statistics	CL ($L/h/m^2$)	$T_{1/2}$ (h)	V_{ss} (L/m^2)
1	n	13	11	13
	Mean (SD)	4.102 (1.3110)	15.095 (2.4938)	55.234 (18.6013)
	CV% mean	31.96	16.52	33.68
	Geo-mean	3.891	14.913	52.675
	CV% geo-mean	36.18	16.36	32.39
	Median	4.204	14.571	53.122
	[Min; Max]	[1.93; 6.12]	[11.58; 19.57]	[30.72; 102.44]
2	n	7	6	7
	Mean (SD)	3.953 (1.5591)	17.354 (3.2327)	60.450 (8.6165)
	CV% mean	39.44	18.63	14.25
	Geo-mean	3.754	17.070	59.901
	CV% geo-mean	33.56	20.79	14.84
	Median	3.597	18.378	63.228
	[Min; Max]	[2.71; 7.33]	[11.79; 20.70]	[48.98; 71.83]

Note: CV% mean = coefficient of variation (%) = sd/mean*100.
CV% geo-mean = sqrt(exp(variance for log transformed data)-1)*100.
Cohort B: carboplatin in cycle 1 and patupilone + carboplatin afterwards

Safety Results

Adverse events by primary system organ class, preferred term, maximum severity grade and dose level -- n (%) of all patients (>10%) (Safety set) Part 1

	4.8 mg/m^2 + AUC 6	6.4 mg/m^2 + AUC 6		7.0 mg/m^2 + AUC 6		7.5 mg/m^2 + AUC 6		All doses + AUC 6	
	N = 6	N = 3		N = 7		N = 9		N= 25	
	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade
Primary system organ class Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any Primary system organ class	6 (100)	6 (100)	1 (33)	3 (100)	5 (71.4)	7 (100)	6 (66.7)	9 (100)	18 (72)	25 (100)
Gastrointestinal disorders	3 (50)	6 (100)	1 (33)	3 (100)	4 (57.1)	7 (100)	1 (11.1)	7 (77.8)	9 (36)	23 (92)
Diarrhea	2 (33.3)	4 (66.7)	0	3 (100)	2 (28.6)	7 (100)	1 (11.1)	6 (66.7)	5 (20)	20 (80)
Nausea	1 (16.7)	5 (83.3)	0	2 (66.7)	0	6 (85.7)	0	5 (55.6)	1 (4)	18 (72)
Constipation	1 (16.7)	3 (50.0)	0	1 (33.3)	0	5 (71.4)	0	3 (33.3)	1 (4)	12 (48)
Abdominal pain	1 (16.7)	3 (50.0)	0	0	0	5 (71.4)	0	3 (33.3)	1 (4)	11 (44)
Vomiting	1 (16.7)	3 (50.0)	0	1 (33.3)	0	2 (38.6)	0	3 (33.3)	1 (4)	9 (36)
Flatulence	0	1 (16.7)	0	0	0	2 (28.6)	0	0	0	3 (12)
Blood and lymphatic system disorders	3 (50)	4 (66.7)	0	3 (100)	3 (42.9)	7 (100)	4 (44.4)	8 (88.9)	10 (40)	22 (88)
Anemia	0	3 (50)	0	2 (66.7)	1 (14.3)	7 (100)	2 (22.2)	7 (77.8)	3 (12)	19 (76)
Neutropenia	1 (16.7)	2 (33.3)	0	1 (33.3)	1 (14.3)	4 (57.1)	2 (22.2)	3 (33.3)	4 (16)	10 (40)
Thrombocytopenia	2 (33.3)	2 (33.3)	0	0	2 (28.6)	2 (86.6)	4 (44.4)	5 (55.6)	8 (32)	9 (36)
Leukopenia	0	0	0	1 (33.3)	0	2 (28.6)	1 (11.1)	3 (33.3)	1 (4)	6 (24)
Lymphopenia	0	0	0	0	0	2 (28.6)	0	1 (11.1)	0	3 (12)
General disorders and administration site	2 (33.3)	3 (50)	1 (33.3)	2 (66.7)	2 (28.6)	6 (85.7)	2 (22.2)	6 (66.7)	7 (28)	17 (68)

conditions										
Asthenia	1 (16.7)	2 (33.3)	1 (33.3)	2 (66.7)	0	3 (42.9)	0	3 (33.3)	2 (8)	10 (40)
Fatigue	1 (16.7)	1 (16.7)	0	0	2 (28.6)	4 (57.1)	1 (11.1)	2 (22.2)	4 (16)	7 (28)
Pyrexia	1 (16.7)	2 (33.3)	0	1 (33.3)	0	3 (42.9)	0	1 (11.1)	1 (4)	7 (28)
Edema periph-eral	0	2 (33.3)	0	1 (33.3)	0	1 (14.3)	0	1 (11.1)	0	5 (20)
Metabolism and nutrition disorders	3 (50)	4 (66.7)	1 (33.3)	2 (66.7)	4 (57.1)	6 (85.7)	1 (11.1)	5 (55.6)	9 (36)	17 (68)
De-creased appetite	2 (33.3)	4 (66.7)	0	2 (66.7)	2 (28.6)	3 (42.9)	0	1 (11.1)	4 (16)	10 (40)
Dehydra-tion	1 (16.7)	2 (33.3)	0	0	2 (28.6)	4 (57.1)	0	1 (11.1)	3 (12)	7 (28)
Hypo-mag-nesemia	0	1 (16.7)	1 (33.3)	1 (33.3)	0	2 (28.6)	1 (11.1)	3 (33.3)	2 (8)	7 (28)
Hypoka-lemia	1 (16.7)	1 (16.7)	1 (33.3)	1 (33.3)	1 (14.3)	2 (28.6)	0	1 (11.1)	3 (12)	5 (20)
Nervous system dis-orders	1 (16.7)	2 (33.3)	0	2 (66.7)	2 (28.6)	6 (85.7)	2 (22.20	4 (44.4)	5 (20)	14 (56)
Dyses-thesia	0	1 (16.7)	0	1 (33.3)	0	1 (14.3)	0	0	0	3 (12)
Dysgeu-sia	0	0	0	1 (33.3)	0	1 (14.3)	0	1 (11.1)	0	3 (12)
Head-ache	0	0	0	0	0	1 (14.3)	0	2 (22.2)	0	3 (12)
Investiga-tions	0	3 (50.0)	0	1 (33.3)	0	4 (57.1)	0	3 (33.3)	0	11 (44)
Weight de-creased	0	2 (33.3)	0	1 (33.3)	0	2 (28.6)	0	2 (22.2)	0	7 (28)
Neutro-phil count de-creased	0	1 (16.7)	0	0	0	2 (28.6)	0	0	0	3 (12)
Psychiat-ric disor-ders	0	2 (33.3)	0	1 (33.3)	0	3 (42.9)	0	3 (33.3)	0	9 (36)
Anxiety	0	0	0	1 (33.3)	0	1 (14.3)	0	3 (33.3)	0	5 (20)
Insomnia	0	1 (16.7)	0	1 (33.3)	0	2 (28.6)	0	1 (11.1)	0	5 (20)
Respiratory, thoracic and mediastinal disorders	1 (16.7)	3 (50.0)	0	0	1 (14.3)	2 (28.6)	0	4 (44.4)	2 (8)	9 (36)
Dyspnea	0	2 (33.3)	0	0	0	2 (28.6)	0	2 (22.2)	0	6 (24)

Cough	0	1 (16.7)	0	0	0	1 (14.3)	0	3 (33.3)	0	5 (20)
Infections and infestations	2 (33.3)	2 (33.3)	0	1 (33.3)	1 (14.3)	3 (42.9)	0	1 (11.1)	3 (12)	7 (28)
Urinary tract infection	0	1 (16.7)	0	1 (33.3)	1 (14.3)	2 (28.6)	0	0	1 (4)	4 (16)
Renal and urinary disorders	0	1 (16.7)	0	2 (66.7)	2 (28.6)	2 (28.6)	0	1 (11.1)	2 (8)	6 (24)
Hematuria	0	0	0	2 (66.7)	0	1 (14.3)	0	0	0	3 (12)
Eye and labyrinth disorders	0	0	0	1 (33.3)	0	2 (28.6)	0	0	0	3 (12)
Vertigo	0	0	0	1 (33.3)	0	2 (28.6)	0	0	0	3 (12)

Adverse events by primary system organ class, preferred term, maximum severity grade and cohort -- n (%) of all patients (>10%) (Safety set) Part 2

	Cohort A 7 mg/m^2 + AUC 6 N = 20		Cohort B 7 mg/m^2 + AUC 6 N = 17		Total 7.0 mg/m^2 + AUC 6 N = 37	
Primary system organ class Preferred Term	**Grade 3/4 n (%)**	**Any Grade n (%)**	**Grade 3/4 n (%)**	**Any Grade n (%)**	**Grade 3/4 n (%)**	**Any Grade n (%)**
Any Primary system organ class	16 (80.0)	20 (100.0)	14 (82.4)	17 (100)	30 (81.1)	37 (100)
Gastrointestinal disorders	6 (30.0)	19 (95.0)	6 (35.3)	16 (94.1)	12 (32.4)	35 (94.6)
Diarrhea	5 (25.0)	15 (75.0)	4 (23.5)	13 (76.5)	9 (24.3)	28 (75.7)
Nausea	1 (5.0)	9 (45.0)	1 (5.9)	6 (35.3)	2 (5.4)	15 (40.5)
Constipation	0	8 (40.0)	0	7 (41.2)	0	15 (40.5)
Abdominal pain	0	5 (25.0)	1 (5.9)	5 (29.4)	1 (2.7)	10 (27.0)
Vomiting	1 (5.0)	5 (25.0)	1 (5.9)	2 (11.8)	2 (5.4)	7 (18.9)
Flatulence	0	5 (25.0)	0	1 (5.9)	0	6 (16.2)
General disorders and administration site conditions	1 (5.0)	16 (80.0)	4 (23.5)	13 (76.5)	5 (13.5)	29 (78.4)
Fatigue	0	9 (45.0)	2 (11.8)	6 (35.3)	2 (5.4)	15 (40.5)
Asthenia	1 (5.0)	5 (25.0)	0	8 (47.1)	1 (2.7)	13 (35.1)
Edema peripheral	0	2 (10.0)	1 (5.9)	3 (17.6)	1 (2.7)	5 (13.5)
Pyrexia	0	2 (10.0)	1 (5.9)	3 (17.6)	1 (2.7)	5 (13.5)
Blood and lymphatic system disorders	8 (40.0)	9 (45.0)	9 (52.9)	12 (70.6)	17 (45.9)	21 (56.8)
Thrombocytopenia	5 (25.0)	7 (35.0)	7 (41.2)	11 (64.7)	12 (32.4)	18 (48.6)

Anemia	4 (20.0)	7 (35.0)	4 (23.5)	8(47.1)	8 (21.6)	15 (40.5)
Neutropenia	6 (30.0)	6 (30.0)	3 (17.6)	6 (35.3)	9 (24.3)	12 (32.4)
Metabolism and nutrition disorders	4 (20.0)	9 (45.0)	4 (23.5)	-52.9	8 (21.6)	18 (48.6)
Dehydration	2 (10.0)	6 (30.0)	1 (5.9)	2 (11.8)	3 (8.1)	8 (21.6)
Decreased appetite	0	3 (15.0)	0	4 (23.5)	0	7 (18.9)
Hypomagnesemia	0	2 (10.0)	0	3 (17.6)	0	5 (13.5)
Hypokalemia	1 (5.0)	2 (10.0)	2 (11.8)	2 (11.8)	3 (8.1)	4 (10.8)
Musculoskeletal and connective tissue disorders	2 (10.0)	10 (50.0)	2 (11.8)	8 (47.1)	4 (10.8)	18 (48.6)
Bach pain	1 (5.0)	3 (15.0)	1 (5.9)	3 (17.6)	2 (5.4)	6 (16.2)
Arthralgia	0	2 (10.0)	0	2 (11.8)	0	4 (10.8)
Musculoskeletal pain	1 (5.0)	2 (10.0)	0	2 (11.8)	1 (2.7)	4 (10.8)
Respiratory, thoracic and mediastinal disorders	2 (10.0)	10 (50.0)	1 (5.9)	8 (47.1)	3 (8.1)	18 (48.6)
Dyspnea	1 (5.0)	4 (20.0)	1 (5.9)	5 (29.4)	2 (5.4)	9 (24.3)
Cough	0	5 (25.0)	0	2 (11.8)	0	7 (18.9)
Nervous system disorders	2 (10.0)	11 (55.0)	1 (5.9)	6 (35.3)	3 (8.1)	17 (45.9)
Dizziness	0	4 (20.0)	0	1 (5.9)	0	5 (13.5)
Headache	0	1 (5)	0	3 (17.6)	0	4 (10.8)
Investigations	2 (10.0)	8 (40.0)	1 (5.9)	2 (11.8)	3 (8.1)	10 (27.0)
Weight decreased	1 (5.0)	4 (20.0)	0	1 (5.9)	1 (2.7)	5 (13.5)
Psychiatric disorders	1 (5.0)	6 (30.0)	1 (5.9)	3 (17.6)	2 (5.4)	9 (24.3)
Anxiety	0	3 (15.0)	0	1 (5.9)	0	4 (10.8)
Vascular disorders	1 (5.0)	7 (35.0)	2 (11.8)	2 (11.8)	3 (8.1)	9 (24.3)
Hypotension	0	4 (20.0)	1 (5.9)	1 (5.9)	1 (2.7)	5 (13.5)

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

Part 1: Gastrointestinal disorders (92%), and blood and lymphatic system disorders (88%) were the most commonly reported AEs: the most frequent were diarrhea (80%), anemia (76%) and nausea (72%).

Part 2: Gastrointestinal disorders (94.6%) was most commonly reported AEs, with the most frequent reported AE was diarrhea (64.9%).

Serious Adverse Events and Deaths

Deaths, other serious or grade 3/4 adverse events or related discontinuations by dose level – n (%) of patients (Safety set) Part 1

	4.8 mg/m² + AUC 6 N=6 n (%)	6.4 mg/m² + AUC 6 N=3 n (%)	7.0 mg/m² + AUC 6 N=7 n (%)	7.5 mg/m² + AUC 6 N=9 n (%)	All doses + AUC 6 N=25 n (%)
Patients with AE(s)	6 (100.0)	3 (100.0)	7 (100.0)	9 (100.0)	25 (100.0)
Serious or significant events					
Deaths	1 (16.7)	0	0	1 (11.1)	2 (8.0)
SAE(s)	4 (66.7)	1 (33.3)	3 (42.9)	6 (66.7)	14 (56.0)
Grade 3/4 AE(s)	6 (100.0)	1 (33.3)	5 (71.4)	6 (66.7)	18 (72.0)
Discontinued due to SAE(s)	0	0	1 (14.3)	1 (11.1)	2 (8.0)
Discontinued due to Grade 3/4 AE(s)	0	0	2 (28.6)	1 (11.1)	3 (12.0)

Deaths, other serious or grade 3/4 adverse events or related discontinuations by cohort – n (%) of patients (Safety set) Part 2

	Cohort A 7 mg/m² + AUC 6 N=20 n (%)	Cohort B 7 mg/m² + AUC 6 N=17 n (%)	Total N=37 n (%)
Patients with AE(s)	19 (95.0)	17 (100.0)	36 (97.3)
Serious or significant events			
Deaths	2 (10.0)	0	2 (5.4)
SAE(s)	7 (35.0)	7 (41.2)	14 (37.8)
Grade 3/4 AE(s)	16 (80.0)	14 (82.4)	30 (81.1)
Discontinued due to SAE(s)	1 (5.0)	1 (5.9)	2 (5.4)
Discontinued due to Grade 3/4 AE(s)	3 (15.0)	2 (11.8)	5 (13.5)

Most frequent serious adverse events (i.e. > 10%) by preferred term and dose level - n (%) of patients (Safety set) Part 1

	4.8 mg/m² + AUC 6 N = 6	6.4 mg/m² + AUC 6 N = 3	7.0 mg/m² + AUC 6 N = 7	7.5 mg/m² + AUC 6 N = 9	All doses + AUC 6 N = 25
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)
Any Preferred Term	4 (66.7)	1 (33.3)	3 (42.9)	6 (66.7)	14 (56.0)
Diarrhea	1 (16.7)	0	1 (14.3)	2 (22.2)	4 (16.0)
Thrombocytopenia	0	0	0	4 (44.4)	4 (16.0)
Dehydration	0	0	3 (42.9)	0	3 (12.0)
Neutropenia	1 (16.7)	0	0	2 (22.2)	3 (12.0)
Anemia	0	0	0	2 (22.2)	2 (8.0)
Fatigue	0	0	1 (14.3)	1 (11.1)	2 (8.0)
Urinary tract infection	1 (16.7)	0	1 (14.3)	0	2 (8.0)
Vomiting	0	0	1 (14.3)	1 (11.1)	2 (8.0)
Abdominal pain	1 (16.7)	0	0	0	1 (4.0)
Acute myocardial infarction	0	0	1 (14.3)	0	1 (4.0)
Cecitis	0	0	1 (14.3)	0	1 (4.0)
Cerebral hemorrhage	0	0	0	1 (11.1)	1 (4.0)
Colonic obstruction	0	0	1 (14.3)	0	1 (4.0)
Decreased appetite	0	0	1 (14.3)	0	1 (4.0)
Dizziness	0	0	1 (14.3)	0	1 (4.0)
Electrocardiogram QT prolonged	0	1 (33.3)	0	0	1 (4.0)
Epilepsy	0	0	0	1 (11.1)	1 (4.0)
Fecaluria	0	1 (33.3)	0	0	1 (4.0)
Gastrointestinal fistula	0	1 (33.3)	0	0	1 (4.0)
Haematochezia	0	0	1 (14.3)	0	1 (4.0)
Hypocalcaemia	0	1 (33.3)	0	0	1 (4.0)
Hypokalemia	0	1 (33.3)	0	0	1 (4.0)
Hypomagnesaemia	0	1 (33.3)	0	0	1 (4.0)
Hypotension	1 (16.7)	0	0	0	1 (4.0)
Hypovolemia	1 (16.7)	0	0	0	1 (4.0)
Metastases to central nervous system	0	0	0	1 (11.1)	1 (4.0)
Nausea	0	0	1 (14.3)	0	1 (4.0)
Non-cardiac chest pain	0	0	1 (14.3)	0	1 (4.0)
Pneumonia	1 (16.7)	0	0	0	1 (4.0)
Pulmonary embolism	0	0	1 (14.3)	0	1 (4.0)
Pyrexia	1 (16.7)	0	0	0	1 (4.0)
Renal failure acute	0	0	1 (14.3)	0	1 (4.0)
Respiratory distress	1 (16.7)	0	0	0	1 (4.0)
Sepsis	1 (16.7)	0	0	0	1 (4.0)
Tachycardia	0	0	0	1 (11.1)	1 (4.0)

Most frequent serious adverse events (i.e. > 10%) by preferred term and cohort - n (%) of patients (Safety set) Part 2

	Cohort A N = 20	Cohort B N = 17	Total N = 37
	n (%)	n (%)	n (%)
Any	7(35.0)	7(41.2)	14(37.8)
Diarrhea	1(5.0)	4(23.5)	5(13.5)

Other Relevant Findings

None

Date of Clinical Trial Report

17 Aug 2011

Date Inclusion on Novartis Clinical Trial Results Database

14 Feb 2012

Date of Latest Update