Sponsor

Novartis

Generic Drug Name

Everolimus

Therapeutic Area of Trial

Small-Cell Lung Cancer (SCLC)

Approved Indications

- Advanced neuroendocrine tumors of gastrointestinal, lung or pancreatic origin.
- Advanced renal cell carcinoma.
- Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS)
- For the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving an allogeneic renal or cardiac transplant. In kidney and heart transplantation, everolimus should be used in combination with ciclosporin for microemulsion and corticosteroids.
- For the prophylaxis of organ rejection in patients receiving a hepatic transplant. In liver transplantation, everolimus should be used in combination with tacrolimus and corticosteroids.

Study Number

CRAD001C2116

Title

A phase Ib study investigating the combination of Everolimus with cisplatin and etoposide (EP) in patients with extensive-stage small-cell lung cancer (ED-SCLC) not previously treated with chemotherapy.

Phase of Development

Phase I

Study Start/End Dates

26 Apr 2007 to 24 Nov 2010

Study Design/Methodology

This was an open-label, multi-center, dose-escalation Phase 1b study of everolimus in combination with cisplatin/etoposide (EP) in patients with ED-SCLC not previously treated with systemic chemotherapy. The study was designed as a Bayesian sequential dose-escalation scheme based on a time-to-event model of the rate of dose-limiting toxicities (DLTs) estimating the

probability that patients experience a DLT within their first cycle of treatment ("End-of-Cycle 1 DLT rate"). The study was divided into 2 treatment stages; core stage and extension stage.

Core treatment stage: The study investigated 2 different dosing schedules of everolimus (i.e., daily and weekly treatment arms) in combination with the standard 21-day cyclic administration of EP. Up to four individual dose levels of everolimus in both the daily and weekly arms were planned to be explored. Patients could receive a maximum of 6 cycles of chemotherapy during the core treatment stage. One cycle was defined as the interval between 2 consecutive administrations of chemotherapy regimens (with a default of 21 days i.e. 3-weekly administration) and Day 1 of each cycle was defined as the initiation of chemotherapy. As part of Amendment 3, as excessive hematologic toxicity was reported in both the treatment arms, dose escalation with primary prophylactic use of granulocyte colony-stimulating factor (G-CSF) from cycle 1 was initiated. The feasibility of a dose level / regimen was based solely on data generated while patients were in the core treatment stage.

Extension treatment stage: Following completion of the core treatment stage of the study (or early discontinuation of chemotherapy), a patient could continue to receive everolimus until progressive disease or unacceptable toxicity occurred.

Centres

8 centers in 3 countries: France (1), United Kingdom (2), United States (5)

Publication

None.

Objectives

Primary objective(s)

To explore the feasible dose levels/regimens of everolimus combined with a standard EP regimen in patients with (ED-SCLC) not previously treated with systemic chemotherapy, as based on the evaluation of safety.

Secondary objective(s)

- To assess the ability to deliver the standard EP treatment when administered in combination with everolimus.
- To assess the pharmacokinetics (PK) of everolimus in ED-SCLC patients treated with everolimus in combination with EP and to estimate the PK interaction between everolimus, cisplatin and etoposide.
- To assess the clinical efficacy of combined administration of different everolimus dose levels/regimens with standard EP treatment based on the evaluation of overall tumor response according to Response Evaluation Criteria in Solid Tumors (RECIST).

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

- Everolimus was supplied by Novartis as tablets in 3 different dosage strengths, 2.5, 5 and 10 mg. The tablet (or tablets as appropriate for the dose) was taken orally with a glass of water at the same time of the day, approximately one hour before the ingestion of food, or 2

hours after the last meal. Everolimus dosing began on Day 2 of Cycle 1.

- Cisplatin (75 mg/m^2) as a 60-minute continuous intravenous (i.v.) infusion after standard pre-hydration and administration of anti-emetics on Day 1 of each cycle.
- Etoposide (100 mg/m^2) as a 60 minute i.v. infusion 30 minutes after cisplatin on Day 1, or directly after everolimus dosing on Days 2 and 3 (if everolimus given on those days)

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

Not applicable.

Criteria for Evaluation

Primary variables

- The primary variable used in the time-to-event model was time-to-DLT, defined as the time from date of treatment start to the date of the (first) DLT. The primary endpoint was expressed in terms of the probability of the End-of-Cycle 1 DLT rate falling within prespecified intervals and was estimated via a Bayesian time-to-event model.

Secondary variables

- Descriptive statistics for RDI of everolimus and for each combination partner were presented by regimen, schedule and dose level. In addition, the number of patients who received particular RDI categories, 0%-<50%, 50%-<70%, 70%-<90%, 90%-<110%, >=110% as well as the number of patients achieving RDI <80% and >=80% were summarized.
- Evaluation of overall objective tumor response rate according to RECIST.
- PK parameters such as $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}tau}$ and C_{max} were determined using non-compartmental analysis methods. PK parameters derived from the PK profile of treatment drugs when administered alone and in combination was used to estimate the extent of drug interaction.

Safety and tolerability

Safety assessments consisted of collecting all AEs, including all DLTs, and serious adverse events (SAEs), with their severity and relationship to study drug. They also included pulmonary function, hematology, HBV testing, hepatitis C (HCV) testing, coagulation, blood chemistry, Electrocardiogram (ECG), urine testing, vital signs, physical condition, body weight/height, and World Health Organization (WHO) performance status.

Other

An estimation of progression free survival (PFS) was provided at the end of the study as an exploratory analysis.

Statistical Methods

To address the primary objective of the study, a Bayesian time-to-event model of the rate of DLT was used for the dose escalation process. Dose escalation decision-making was made based on the distribution of the probability of the End-of-Cycle 1 DLT rate as derived from the model.

Data from all centers that participated in this protocol were used; if a patient discontinued study treatment his/her data were still analyzed. The analysis described in this document refers to core outputs, except for the efficacy analysis which combined all data collected in core and extension treatment stages of the study. All summaries were provided split by regimen (Non-GCSF or G-CSF), schedule (Daily or Weekly) and everolimus dose level. Unless otherwise stated, continuous data were summarized using descriptive statistics such as mean, standard deviation, median and range; and categorical data were summarized using contingency tables with frequency and percentages.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

Patients with histologically or cytologically confirmed diagnosis of ED-SCLC with

- Age ≥ 18 years,
- WHO Performance Status Grade ≤ 1,
- Adequate bone marrow function (absolute Neutrophil Count [ANC] ≥ 1.5 x 10^9/L,
- Platelets ≥ 100 x 10^9/L,
- Hemoglobin (Hb) ≥ 9g/dL),
- Adequate liver function (serum aspartate aminotransferase [AST]) and alanine aminotransferase [ALT] ≤ 2.5 upper limit of normal [ULN] or ≤ 5 if hepatic metastases are present,
- Total bilirubin ≤ 1.5 x ULN)
- Adequate renal function (serum creatinine ≤ 1.5 x ULN)

Exclusion Criteria:

- Patients who had received prior systemic chemotherapy for ED-SCLC or any prior therapy for limited stage SCLC,
- Patients who had received any investigational drug within 5 half-lives, 4 weeks for antibodies prior to first study treatment,
- Patients who had received field radiation therapy to ≥ 25 % of the bone marrow within 4 weeks,
- Patients who had received limited radiation therapy for palliation (including cranial irradiation for brain metastases) within 2 weeks prior to first study treatment,
- Patients who had taken drugs known to be strong inhibitors or inducers of isoenzyme CYP3A or everolimus (or other mTOR inhibitors).
- Patients who had been receiving chronic treatment with steroids or another immunosuppressive agent and with a history of another primary malignancy within the last 5 years still requiring treatment (with the exception of inactive basal or squamous cell carcinoma of the

skin or cervical cancer in situ).

- Patients who had not recovered from the side effects of any major surgery (defined as requiring general anesthesia),
- Patients who might require major surgery during the course of the study,
- Patients who had not recovered from the side effects of any prior therapies,
- Patients who had symptomatic, leptomeningeal or uncontrolled brain metastases (including patients who continued to require glucocorticoids or intrathecal chemotherapy for brain or leptomeningeal metastases) or who had any severe and/or uncontrolled medical conditions.

Number of Subjects

Patient disposition (Full Analysis Set)

Non-G-CSF patients:

	Daily			Weekly		
	Everolimus 2.5mg + EP N=4	Everolimus 5mg + EP N=6	All QD patients N=10	Everolimus 20mg + EP N=5	Everolimus 30mg + EP N=13	All QW patients N=18
Enrolled	**4 (100.0)**	**6 (100.0)**	**10 (100.0)**	**5 (100.0)**	**13 (100.0)**	**18 (100.0)**
Completed 6 cycles	**2 (50.0)**	**1 (16.7)**	**3 (30.0)**	**3 (60.0)**	**7 (53.8)**	**10 (55.6)**
Entered extension treatment stage*	**2 (100.0)**	**1 (100.0)**	**3 (100.0)**	**3 (100.0)**	**6 (85.7)**	**9 (90.0)**
Discontinued	**2 (50.0)**	**5 (83.3)**	**7 (70.0)**	**2 (40.0)**	**6 (46.2)**	**8 (44.4)**
Adverse Event(s)	2 (50.0)	2 (33.3)	4 (40.0)	1 (20.0)	1 (7.7)	2 (11.1)
Abnormal laboratory value(s)	0	1 (16.7)	1 (10.0)	0	0	0
Abnormal test procedure result(s)	0	0	0	0	0	0
Subject withdrew consent	0	1 (16.7)	1 (10.0)	0	0	0
Lost to follow-up	0	0	0	0	0	0
Administrative problems	0	0	0	0	0	0
Death	0	0	0	0	0	0
New cancer therapy	0	0	0	0	0	0
Disease progression	0	1 (16. 7)	1 (10.0)	1 (20.0)	5 (38.5)	6 (33.3)
Entered extension treatment stage #	**0**	**0**	**0**	**0**	**1 (16.7)**	**1 (12.5)**

*Percentage of patients entering extension who completed 6 cycles in core treatment stage.

#Percentage of patients who entered extension having discontinued core treatment stage.

G-CSF patients:

	Everolimus 2.5mg + EP N=7 n (%)	Everolimus 5mg + EP N=5 n (%)	All QD patients N=12 n (%)
Enrolled	**7 (100.0)**	**5 (100.0)**	**12 (100.0)**

Completed 6 cycles	**3 (42.9)**	**3 (60.0)**	**6 (50.0)**	
Entered extension treatment stage*	**3 (100.0)**	**3 (100.0)**	**6 (100.0)**	
Discontinued	**4 (57.1)**	**2 (40.0)**	**6 (50.0)**	
Adverse Event(s)	2 (28.6)	0	2 (16.7)	
Abnormal laboratory value(s)	0	0	0	
Abnormal test procedure result(s)	0	0	0	
Subject withdrew consent	0	0	0	
Lost to follow-up	0	0	0	
Administrative problems	0	0	0	
Death	1 (14.3)	0	1 (8.3)	
New cancer therapy	0	0	0	
Disease progression	1 (14.3)	2 (40.0)	3 (25.0)	
Entered extension treatment stage#	**1 (25.0)**	**0**	**1 (16.7)**	

*Percentage of patients entering extension who completed 6 cycles in core treatment stage.
#Percentage of patients who entered extension having discontinued core treatment stage.

Demographic and Background Characteristics (Full Analysis Set)

Non-G-CSF patients:

	Daily			Weekly		
	Everolimus 2.5mg+EP N=4 n (%)	**Everolimus 5mg + EP N=6 n (%)**	**All QD patients N=10 n (%)**	**Everolimus 20mg +EP N=5 n (%)**	**Everolimus 30mg +EP N=13 n (%)**	**All QW patients N=18 n (%)**
Sex - n (%)						
Female	2 (50.0)	3 (50.0)	5 (50.0)	1 (20.0)	3 (23.1)	4 (22.2)
Male	2 (50.0)	3 (50.0)	5 (50.0)	4 (80.0)	10 (76.9)	14 (77.8)
Baseline age - n (%)						
< 65	4 (100.0)	4 (66.7)	8 (80.0)	5 (100.0)	11 (84.6)	16 (88.9)
>= 65	0	2 (33.3)	2 (20.0)	0	2 (15.4)	2 (11.1)
Age (Year)						
n	4	6	10	5	13	18
Mean	50.5	60.0	56.2	57.8	57.2	57.3
SD	8.23	12.41	11.50	3.96	6.30	5.64
Median	51.0	62.5	60.0	58.0	56.0	57.0
Range	40 - 60	36 - 70	36 - 70	53 - 63	45 - 67	45 - 67
WHO PS - n (%) [1]						
0	2 (50.0)	2 (33.3)	4 (40.0)	2 (40.0)	5 (38.5)	7 (38.9)
1	2 (50.0)	4 (66.7)	6 (60.0)	3 (60.0)	7 (53.8)	10 (55.6)
2	0	0	0	0	1 (7.7)	1 (5.6)

[1] Key: 0=Fully active, able to carry out normal activity without restriction, 1=Restricted in physical strenuous activity but ambulatory and able to carry work of a light or sedentary nature e.g. light housework, office work, 2=Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours, 3=Capable of only limited self-care, confined to bed or chair more than 50% of waking hours, 4=Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.

G-CSF patients:

	Everolimus 2.5mg + EP N=7 n (%)	**Everolimus 5mg + EP N=5 n (%)**	**All QD patients N=12 n (%)**

Sex - n (%)			
Female	4 (57.1)	1 (20.0)	5 (41.7)
Male	3 (42.9)	4 (80.0)	7 (58.3)
Baseline age - n (%)			
< 65	6 (85.7)	3 (60.0)	9 (75.0)
≥ 65	1 (14.3)	2 (40.0)	3 (25.0)
Age (Year)			
N	7	5	12
M an	58.9	59.2	59.0
SD	7.82	12.64	9.56
Median	61.0	57.0	61.0
Range	44-67	47-76	44-76
WHO PS- n (%) [1]			
0	3 (42.9)	0	3 (25.0)
1	4 (57.1)	5 (100.0)	9 (75.0)

[1] Key: 0=Fully active, able to carry out normal activity without restriction, 1=Restricted in physical strenuous activity but ambulatory and able to carry work of a light or sedentary nature e.g. light house work, office work, 2=Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours, 3=Capable of only limited self-care, confined to bed or chair more than 50% of waking hours, 4=Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.

Primary Objective Result(s)

Posterior end-of-Cycle 1 DLT rate based on the Bayesian model (Dose-determining Population)

Non- G-CSF patients:

	Daily		Weekly	
	Everolimus 2.5mg + EP N=4	**Everolimus 5mg + EP N=6**	**Everolimus 20mg + EP N=5**	**Everolimus 30mg + EP N=13**
Mean SD	0.173	0.261	0.073	0.119
SD	0.072	0.092	0.035	0.047
Median	0.164	0.253	0.067	0.112
Probability of under dosing [0%, 20%)	0.685	0.273	0.996	0.942
Probability of targeted toxicity [20%, 35%)	0.298	0.558	0.004	0.057
Probability of excessive toxicity [35%, 60%)	0.017	0.168	0.000	0.001

Probability of unacceptable toxicity [60%,100%]	0.000	0.001	0.000	0.000

G-CSF patients:

	Everolimus 2.5mg + EP N=4	**Everolimus 5mg + EP N=6**
Mean	0.064	0.106
SD	0.036	0.055
Median	0.057	0.095
Probability of under dosing [0%, 20%)	0.995	0.939
Probability of targeted toxicity [20%, 35%)	0.005	0.060
Probability of excessive toxicity [35%, 60%)	0.000	0.001
Probability of unacceptable toxicity [60%,100%]	0.000	0.000

Secondary Objective Result(s)

Relative dose intensity (Full Analysis Set)

Non-G-CSF patients:

	Daily					
	Everolimus 2.5mg + EP			Everolimus 5mg + EP		
	Everolimus N=4 (mg)	Etoposide N=4 (mg/m^2)	Cisplatin N=4 (mg/m^2)	Everolimus N=6 (mg)	Etoposide N=6 (mg/m^2)	Cisplatin N=6 (mg/m^2)
Relative dose intensity						
n	4	4	4	6	6	6
Mean	0.822	0.977	0.977	0.651	0.889	0.888
SD	0.1462	0.0278	0.0265	0.2511	0.1106	0.1101
Median	0.819	0.980	0.980	0.682	0.902	0.896
Range	0.65 - 1.00	0.95 - 1.00	0.95 - 1.00	0.30 - 0.99	0.75 - 1.00	0.75 - 1.00
Relative dose intensity cut-off 80%-n(%)						
0.00 - < 0.80	2 (50.0)	0	0	4 (66.7)	2 (33.3)	2 (33.3)
>=0.80	2 (50.0)	4 (100.0)	4 (100.0)	2 (33.3)	4 (66.7)	4 (66.7)

Relative dose intensity = dose intensity / planned dose intensity.

Cumulative dose = total dose received.

Dose intensity = cumulative dose / duration of exposure

	Weekly					
	Everolimus 20mg + EP			Everolimus 30mg + EP		
	Everolimus N=5 (mg)	Etoposide N=5 (mg/m^2)	Cisplatin N=5 (mg/m^2)	Everolimus N=13 (mg)	Etoposide N=13 (mg/m^2)	Cisplatin N=13 (mg/m^2)
Relative dose intensity						
n	5	5	5	13	13	13
Mean	0.824	0.900	0.903	0.799	0.927	0.927
SD	0.1677	0.0704	0.0651	0.1255	0.0529	0.0519
Median	0.895	0.926	0.926	0.833	0.927	0.927
Range	0.54 - 0.95	0.78 - 0.95	0.80 - 0.95	0.63 - 1.00	0.84 - 1.00	0.84 - 1.00
Relative dose intensity cut-off 80%-n(%)						
0.00 - < 0.80	2 (40.0)	1 (20.0)	1 (20.0)0	6 (46.2)	0	0
>=0.80	3 (60.0)	4 (80.0)	4 (80.0)	7 (53.8)	13 (100.0)	13 (100.0)

Relative dose intensity = dose intensity / planned dose intensity.
Cumulative dose = total dose received.
Dose intensity = cumulative dose / duration of exposure

G-CSF patients:

	Daily					
	Everolimus 2.5mg + EP			Everolimus 5mg + EP		
	Everolimus N=7 (mg)	Etoposide N=7 (mg/m^2)	Cisplatin N=7 (mg/m^2)	Everolimus N=5 (mg)	Etoposide N=5 (mg/m^2)	Cisplatin N=5 (mg/m^2)
Relative dose intensity						
n	7	7	7	5	5	5
Mean	0.779	0.978	0.935	0.763	0.878	0.894
SD	0.3017	0.0546	0.1256	0.3458	0.0771	0.0702
Median	0.904	1.000	1.001	0.845	0.888	0.890
Range	0.25 - 1.00	0.87 - 1.02	0.72 - 1.03	0.16 - 1.00	0.75 - 0.94	0.79 - 0.97
Relative dose intensity cut-off 80%-n(%)						
0.00 - < 0.80	2 (28.6)	0	2 (28.6)	1 (20.0)	1 (20.0)	1 (20.0)
>=0.80	5 (71.4)	7 (100.0)	5 (71.4)	4 (80.0)	4 (80.0)	4 (80.0)

Relative dose intensity = dose intensity / planned dose intensity.
Cumulative dose = total dose received.
Dose intensity = cumulative dose / duration of exposure.

Best overall response (Full Analysis Set)

Non-G-CSF patients:

	Daily		
	Everolimus 2.5mg + EP N=4 n (%)	Everolimus 5mg + EP N=6 n (%)	All QD patients N=10 n (%)
Complete response (CR)	0	0	0
Partial response (PR)	2 (50.0)	2 (33.3)	4 (40.0)
Stable disease (SD)	1 (25.0)	1 (16.7)	2 (20.0)
Progressive disease (PD)	0	0	0
Unknown (UNK)	1 (25.0)	3 (50.0)	4 (40.0)
Objective response rate (CR or PR)	2 (50.0)	2 (33.3)	4 (40.0)
95% CI of response rate	[6.8, 93.2]	[4.3, 77.7]	[12.2, 73.8]
Disease control rate DCR (CR or PR or SD)	3 (75.0)	3 (50.0)	6 (60.0)
95% CI of disease control rate	[19.4, 99.4]	[11.8, 88.2]	[26.2, 87.8]

The best overall response is determined based on investigator assessments of overall lesion response as recorded in the eCRF.
The Clopper-Pearson method is used to determine the confidence intervals.

	Weekly		
	Everolimus 20mg + EP N=5 n (%)	**Everolimus 30mg + EP N=13 n (%)**	**All QW patients N=18 n (%)**
Complete response (CR)	0	0	0
Partial response (PR)	3 (60.0)	8 (61.5)	11 (61.1)
Stable disease (SD)	1 (20.0)	2 (15.4)	3 (16.7)
Progressive disease (PD)	0	2 (15.4)	2 (11.1)
Unknown (UNK)	1 (20.0)	1 (7.7)	2 (11.1)
Objective response rate (CR or PR)	3 (60.0)	8 (61.5)	11(61.1)
95% CI of response rate	[14.7, 94.7]	[31.6, 86.1]	[35.7, 82.7]
Disease control rate DCR (CR or PR or SD)	4 (80.0)	10 (76.9)	14 (77.8)
95% CI of disease control rate	[28.4, 99.5]	[46.2, 95.0]	[52.4, 93.6]

The best overall response is determined based on investigator assessments of overall lesion response as recorded in the eCRF.
The Clopper-Pearson method is used to determine the confidence intervals.

G-CSF patients:

	Daily		
	Everolimus 2.5mg + EP N=7 n (%)	**Everolimus 5mg + EP N=5 n (%)**	**All QD patients N=12 n (%)**
Complete response (CR)	0	0	0
Partial response (PR)	4 (57.1)	3 (60.0)	7 (58.3)
Stable disease (SD)	0	0	0
Progressive disease (PD)	0	2 (40.0)	2 (16.7)
Unknown (UNK)	3 (42.9)	0	3 (25.0)
Objective response rate (CR or PR)	4 (57.1)	3 (60.0)	7 (58.3)
95% CI of response rate	[18.4, 90.1]	[14.7, 94.7]	[27.7, 84.8]
Disease control rate DCR (CR or PR or SD)	4 (57.1)	3 (60.0)	7 (58.3)
95% CI of disease control rate	[18.4, 90.1]	[14.7, 94.7]	[27.7, 84.8]

The best overall response is determined based on investigator assessments of overall lesion response as recorded in the eCRF.
The Clopper-Pearson method is used to determine the confidence intervals.

Everolimus PK profile parameters (Safety Population).

Non-G-CSF Patients:

Daily					
PK parameter (units)	**Profile day/ cycle***	**Summary stats**	**Everolimus 2.5mg + EP**	**Everolimus 5mg + EP**	**Everolimus 10mg + EP**
$AUC_{0\text{-}tlast}$ (ng.h/mL)	D8 C1	N	3	2	0
		Mean ± SD	325.99 ± 156.985	432.73 ± 88.668	
		CV%	48.2	20.5	
	D1 C2	N	4	2	1
		Mean ± SD	267.44 ± 146.984	755.9 ± 141.761	1748.74
		CV%	55.0	18.8	
$AUC_{0\text{-}tau}$ (ng.h/mL)	D8 C1	N	3	2	0
		Mean ± SD	387.00 ± 139.101	438.03 ± 97.153	
		CV%	35.9	22.2	
	D1 C2	N	4	3	1
		Mean ± SD	272.49 ± 144.379	657.17 ± 188.042	1740.73
		CV%	53.0	28.6	
C_{max} (ng/mL)	D8 C1	N	4	2	0
		Mean ± SD	30.85 ± 23.351	74.90 ± 11.455	
		CV%	75.7	15.3	
	D1 C2	N	4	3	1
		Mean ± SD	31.18 ± 20.486	57.10± 23.786	188
		CV%	65.7	41.7	
C_{min} (ng/mL)	D8 C1	N	4	4	0
		Mean ± SD	6.58 ± 3.959	11.82 ± 5.482	
		CV%	60.2	46.4	
	D1 C2	N	1	2	0
		Mean ± SD	4.36	15.39 ± 4.126	
		CV%		26.8	
C_{avg} (ng/mL)	D8 C1	N	3	2	0
		Mean ± SD	11.48 ± 9.817	18.25 ± 4.048	
		CV%	85.5	22.2	
	D1 C2	N	4	3	1
		Mean ± SD	9.90 ± 7.896	27.38 ± 7.835	72.53

		CV%	79.8	28.6	
CL/F (L/h)	D8 C1	N	3	2	0
		Mean ± SD	7.108 ± 2.7625	11.703 ± 2.5956	
		CV%	38.86	22.18	
	D1 C2	N	4	3	1
		Mean ± SD	11.568 ± 6.1104	8.059 ± 2.3947	5.745
		CV%	52.82	29.71	
CL/Fbsa (L/h/m2)	D8C1	N	3	2	0
		Mean ± SD	3.541 ± 1.2738	6.189 ± 1.4852	
		CV%	35.97	24.00	
	D1 C2	N	4	3	1
		Mean ± SD	5.931 ± 3.0499	4.528 ± 1.5746	3.072
		CV%	51.42	34.78	
T_{max} (h)	D8 C1	N	4	2	0
		Median	0.75	0.75	
		Range	0.5 - 2.0	0.5 - 1.0	
	D1C2	N	4	3	1
		Median	1.5	2.0	0.52
		Range	0.5 – 2.0	1.1 – 2.1	0.5 – 0.5

* - D1 C1 Cisplatin + Etoposide; D8 C1 Everolimus alone; D1 C2 Everolimus + Cisplatin + Etoposide in combination.

C_{min} values are only reported when a full profile was planned and presented under the leading dose.

Weekly				
PK parameter (units)	**Profile day/cycle***	**Summary stats**	**Everolimus 20mg + EP**	**Everolimus 30mg + EP**
$AUC_{0\text{-tlast}}$ (ng.h/mL)	D8 C1	n	3	6
		Mean ± SD	3045.46 ± 827.463	3348.38 ± 1649.839
		CV%	27.2	49.3
	D1 C2	n	5	7
		Mean ± SD	4719.53 ± 3754.407	3692.67 ± 1414.329
		CV%	76.6	38.3

$AUC_{0\text{-}tau}$ (ng.h/mL)	D8 C1	n	3	6	
		Mean ± SD	3043.99 ± 827.785	3337.74 ± 1645.092	
		CV%	27.2	49.3	
	D1 C2	n	5	7	
		Mean ± SD	4723.61 ± 3760.953	3687.9 ± 1409.383	
		CV%	79.6	38.2	
C_{max} (ng/mL)	D8 C1	n	3	13	
		Mean ± SD	177.67 ± 23.965	143.08 ± 47.134	
		CV%	13.5	32.9	
	D1 C2	n	7	10	
		Mean ± SD	153.36 ± 63.768	141.38 ± 58.109	
		CV%	41.6	41.1	
C_{min} (ng/mL)	D8 C1	n	3	11	
		Mean ± SD	1.00 ± 0.152	10.42 ± 29.055	
		CV%	15.2	278.9	
	D1 C2	n	5	7	
		Mean ± SD	1.39 ± 1.179	1.42 ± 1.775	
		CV%	84.7	125.0	
C_{avg} (ng/mL)	D8 C1	n	3	6	
		Mean ± SD	18.12 ± 4.927	19.87 ± 9.792	
		CV%	27.2	49.3	
	D1 C2	n	5	7	
		Mean ± SD	28.12 ± 22.387	21.95 ± 8.389	
		CV%	79.6	38.2	
CL/F (L/h)	D8 C1	n	3	6	
		Mean ± SD	6.883 ± 1.7375	11.276 ± 5.9945	
		CV%	25.25	53.16	
	D1 C2	n	5	7	
		Mean ± SD	7.367 ± 5.5951	9.524 ± 4.4196	
		CV%	75.95	46.40	
CL/Fbsa (L/h/m2)	D8 C1	n	3	6	
		Mean ± SD	3.494 ± 0.8166	6.473 ± 3.9963	
		CV%	23.37	61.74	
	D1 C2	n	5	7	
		Mean ± SD	3.788 ± 2.8977	5.163 ± 2.3556	
		CV%	76.51	45.62	
T_{max} (h)	D8 C1	n	3	13	
		Median	1.00	1.00	
		Range	0.8 - 1.1	0.5 - 4.0	
	D1 C2	n	7	10	
		Median	1.00	1.53	

		Range	0.5 – 2.0	0.5 – 4.0

* - D1 C1 Cisplatin + Etoposide; D8 C1 Everolimus alone; D1 C2 Everolimus + Cisplatin + Etoposide in combination.

C_{min} values are only reported when a full profile was planned and presented under the leading dose.

Drug Interaction for Everolimus by PK parameter (Safety Population)

Non-G-CSF-Patients-Daily Schedule:

					Ratio of geometric means [3]		Intra-patient
PK parameter (units) [1]	**Actual Everolimus Dose (mg)**	**Profile Day/Cycle***	**n**	**Geometric Mean [2]**	**Ratio**	**90% CI**	**CV% [4]**
$AUC_{0\text{-}tlast}$ (ng.h/mL)	2.5	A: D8 C1 (ref)	3	303.91			
		B: D1 C2 (test)	4	236.09	0.78	(0.40, 1.52)	
	5	A: D8 C1 (ref)	2	428.16			
		B: D1 C2 (test)	2	749.22	1.75	(0.73, 4.21)	
	10	B: D1 C2 (test)	1	1748.73			49.0
$AUC_{0\text{-}tau}$ (ng.h/mL)	2.5	A: D8 C1 (ref)	3	369.40			
		B: D1 C2 (test)	4	242.64	0.66	(0.36, 1.21)	
	5	A: D8 C1 (ref)	2	432.61			
		B: D1 C2 (test)	3	638.77	1.48	(0.71, 3.06)	
	10	B: D1 C2 (test)	1	1740.73			45.0
C_{max} (ng/mL)	2.5	A: D8 C1 (ref)	4	24.44			
		B: D1 C2 (test)	4	25.78	1.05	(0.45, 2.48)	
	5	A: D8 C1 (ref)	2	74.46			
		B: D1 C2 (test)	3	54.13	0.73	(0.24, 2.19)	
	10	B: D1 C2 (test)	1	188.00			73.7

* - D1 C1 Cisplatin + Etoposide; D8 C1 Everolimus alone; D1 C2 Everolimus + Cisplatin + Etoposide in combination.

[1] The log-transformed PK parameter is modeled by means of a linear model including terms for treatment (i.e. combination or alone), actual dose at sample time and treatment*actual dose at sample time interaction, and patient as a random effect.

[2] The geometric mean is obtained by back-transforming on the original scale the mean of the log-transformed PK parameters.

[3] Comparison of interest: B/A (test/ref).

[4] Intra-patient CV: calculated from the variance of the residual error of the model, by means of the formula: CV = SQRT(EXP(variance)-1)*100.

Non-G-CSF-Patients-Weekly Schedule:

					Ratio of geometric means [3]		Intra-patient
PK parameter (units) [1]	**Actual Everolimus Dose (mg)**	**Profile Day/Cycle***	**n**	**Geometric Mean [2]**	**Ratio**	**90% CI**	**CV% [4]**
$AUC_{0\text{-}tlast}$ (ng.h/mL)	20	A: D8 C1 (ref)	3	3396.76			
		B: D1 C2 (test)	5	3463.51	1.02	(0.45, 2.33)	
	30	A: D8 C1 (ref)	6	2919.80			
		B: D1 C2 (test)	7	3496.41	1.20	(0.64, 2.24)	53.9
$AUC_{0\text{-}tau}$ (ng.h/mL)	20	A: D8 C1 (ref)	3	3433.71			
		B: D1 C2 (test)	5	3458.07	1.01	(0.45, 2.27)	
	30	A: D8 C1 (ref)	6	2904.68			
		B: D1 C2 (test)	7	3498.23	1.20	(0.65, 2.23)	53.2
C_{max} (ng/mL)	20	A: D8 C1 (ref)	3	182.37			
		B: D1 C2 (test)	7	145.02	0.80	(0.46, 1.37)	
	30	A: D8 C1 (ref)	13	130.44			
		B: D1 C2 (test)	10	128.45	0.98	(0.71, 1.36)	45.2

* - D1 C1 Cisplatin + Etoposide; D8 C1 Everolimus alone; D1 C2 Everolimus + Cisplatin + Etoposide in combination.

[1] The log-transformed PK parameter is modeled by means of a linear model including terms for treatment (i.e. combination or alone), actual dose at sample time and treatment*actual dose at sample time interaction, and patient as a random effect.

[2] The geometric mean is obtained by back-transforming on the original scale the mean of the log-transformed PK parameters.

[3] Comparison of interest: B/A (test/ref).

[4] Intra-patient CV: calculated from the variance of the residual error of the model, by means of the formula: CV = SQRT(EXP(variance)-1)*100.

Safety Results

Adverse Events by System Organ Class (Safety Population)

Non-G-CSF Patients:

	Daily			Weekly		
Primary system organ class **Preferred term**	**Everolimus 2.5mg + EP N=4 n (%)**	**Everolimus 5mg + EP N=6 n (%)**	**All QD patients N=10 n (%)**	**Everolimus 20mg + EP N=5 n (%)**	**Everolimus 30mg + EP N=13 n (%)**	**All QW patients N=18 n (%)**
Any primary system organ class	4 (100.0)	6 (100.0)	10 (100.0)	5 (100.0)	13 (100.0)	18 (100.0)
Blood and lymphatic system disorders	3 (75.0)	5 (83.3)	8 (80.0)	5 (100.0)	12 (92.3)	17 (94.4)
Gastrointestinal disorders	4 (100.0)	6 (100.0)	10 (100.0)	3 (60.0)	11 (84.6)	14 (77.8)
General disorders and administration site conditions	3 (75.0)	3 (50.0)	6 (60.0)	3 (60.0)	11 (84.6)	14 (77.8)
Metabolism and nutrition disorders	2 (50.0)	6 (100.0)	8 (80.0)	4 (80.0)	8 (61.5)	12 (66.7)
Infections and infestations	3 (75.0)	5 (83.3)	8 (80.0)	3 (60.0)	8 (61.5)	11 (61.1)
Nervous system disorders	3 (75.0)	4 (66.7)	7 (70.0)	3 (60.0)	7 (53.8)	10 (55.6)
Skin and subcutaneous tissue disorders	3 (75.0)	5 (83.3)	8 (80.0)	2 (40.0)	7 (53.8)	9 (50.0)
Respiratory, thoracic and mediastinal disorders	2 (50.0)	5 (83.3)	7 (70.0)	1 (20.0)	8 (61.5)	9 (50.0)
Musculoskeletal and connective tissue disorders	1 (25.0)	3 (50.0)	4 (40.0)	1 (20.0)	5 (38.5)	6 (33.3)
Investigations	0	2 (33.3)	2 (20.0)	1 (20.0)	6 (46.2)	7 (38.9)
Psychiatric disorders	1 (25.0)	5 (83.3)	6 (60.0)	1 (20.0)	2 (15.4)	3 (16.7)
Vascular disorders	1 (25.0)	3 (50.0)	4 (40.0)	2 (40.0)	3 (23.1)	5 (27.8)
Ear and labyrinth disorders	0	1 (16.7)	1 (10.0)	1 (20.0)	3 (23.1)	4 (22.2)
Renal and urinary disorders	1 (25.0)	1 (16.7)	2 (20.0)	2 (40.0)	0	2 (11.1)
Cardiac disorders	0	2 (33.3)	2 (20.0)	0	1 (7.7)	1 (5.6)
Eye disorders	0	0	0	1 (20.0)	1 (7.7)	2 (11.1)
Endocrine disorders	0	0	0	0	1 (7.7)	1 (5.6)
Injury, poisoning and procedural complications	0	0	0	0	1 (7.7)	1 (5.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	1 (7.7)	1 (5.6)

- Primary system organ classes are sorted in descending frequency, over all treatment regimens.
- A patient with multiple occurrences of an AE is counted only once in the AE category.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

G-CSF Patients:

	Daily

Primary system organ class Preferred term	Everolimus 2.5mg + EP N=7 n (%)	Everolimus 5mg + EP N=5 n (%)	All QD patients N=12 n (%)
Any primary system organ class	7 (100.0)	5 (100.0)	12 (100.0)
Gastrointestinal disorders	6 (85.7)	5 (100.0)	11 (91.7)
General disorders and administration site conditions	4 (57.1)	5 (100.0)	9 (75.0)
Metabolism and nutrition disorders	5 (71.4)	4 (80.0)	9 (75.0)
Nervous system disorders	5 (71.4)	2 (40.0)	7 (58.3)
Respiratory, thoracic and mediastinal disorders	3 (42.9)	4 (80.0)	7 (58.3)
Blood and lymphatic system disorders	2 (28.6)	4 (80.0)	6 (50.0)
Infections and infestations	2 (28.6)	3 (60.0)	5 (41.7)
Investigations	2 (28.6)	2 (40.0)	4 (33.3)
Renal and urinary disorders	2 (28.6)	2 (40.0)	4 (33.3)
Skin and subcutaneous tissue disorders	3 (42.9)	1 (20.0)	4 (33.3)
Vascular disorders	3 (42.9)	1 (20.0)	4 (33.3)
Ear and labyrinth disorders	2 (28.6)	0	2 (16.7)
Cardiac disorders	0	1 (20.0)	1 (8.3)
Eye disorders	1 (14.3)	0	1 (8.3)
Injury, poisoning and procedural complications	0	1 (20.0)	1 (8.3)
Musculoskeletal and connective tissue disorders	1 (14.3)	0	1 (8.3)
Reproductive system and breast disorders	1 (14.3)	0	1 (8.3)

- Primary system organ classes are sorted in descending frequency, over all treatment regimens.
- A patient with multiple occurrences of an AE is counted only once in the AE category.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

10 Most Frequently Reported AEs Overall by Preferred Term

(Safety Population)

Non-G-CSF Patients:

	Daily			Weekly		
Preferred term	**Everolimus 2.5mg + EP N=4 n (%)**	**Everolimus 5mg + EP N=6 n (%)**	**All QD patients N=10 n (%)**	**Everolimus 20mg + EP N=5 n (%)**	**Everolimus 30mg + EP N=13 n (%)**	**All QW patients N=18 n (%)**
Neutropenia	3 (75.0)	4 (66.7)	7 (70.0)	5 (100.0)	9 (69.2)	14 (77.8)
Nausea	4 (100.0)	5 (83.3)	9 (90.0)	3 (60.0)	9 (69.2)	12 (66.7)
Anaemia	1 (25.0)	1 (16.7)	2 (20.0)	3 (60.0)	5 (38.5)	8 (44.4)
Stomatitis	3 (75.0)	3 (50.0)	6 (60.0)	3 (60.0)	5 (38.5)	8 (44.4)
Vomiting	2 (50.0)	3 (50.0)	5 (50.0)	2 (40.0)	6 (46.2)	8 (44.4)
Fatigue	2 (50.0)	1 (16.7)	3 (30.0)	1 (20.0)	7 (53.8)	8 (44.4)
Asthenia	1 (25.0)	2 (33.3)	3 (30.0)	2 (40.0)	5 (38.5)	7 (38.9)
Headache	3 (75.0)	1 (16.7)	4 (40.0)	3 (60.0)	4 (30.8)	7 (38.9)
Constipation	2 (50.0)	3 (50.0)	5 (50.0)	3 (60.0)	3 (23.1)	6 (33.3)
Alopecia	2 (50.0)	3 (50.0)	5 (50.0)	1 (20.0)	5 (38.5)	6 (33.3)

The most frequently occurring AEs have been compiled (from all AE tables) for the entire study irrespective of schedule and dose levels

G-CSF Patients:

	Daily		
Preferred term	**Everolimus 2.5mg + EP N=7 n (%)**	**Everolimus 5mg + EP N=5 n (%)**	**All QD patients N=12 n (%)**
Nausea	3 (42.9)	4 (80.0)	7 (58.3)
Constipation	3 (42.9)	2 (40.0)	5 (41.7)
Stomatitis	3 (42.9)	2 (40.0)	5 (41.7)
Alopecia	3 (42.9)	1 (20.0)	4 (33.3)
Diarrhoea	2 (28.6)	2 (40.0)	4 (33.3)
Thrombocytopenia	1 (14.3)	3 (60.0)	4 (33.3)
Anaemia	2 (28.6)	1 (20.0)	3 (25.0)
Asthenia	1 (14.3)	2 (40.0)	3 (25.0)
Decreased appetite	1 (14.3)	2 (40.0)	3 (25.0)
Dehydration	2 (28.6)	1 (20.0)	3 (25.0)
Dizziness	2 (28.6)	1 (20.0)	3 (25.0)

The most frequently occurring AEs have been compiled (from all AE tables) for the entire study irrespective of schedule and dose levels

Serious Adverse Events and Deaths

Summary of Deaths and SAEs

Non -G-CSF patients:

	Daily			Weekly		
	Everolimus 2.5mg+EP N=4 n (%)	**Everolimus 5mg + EP N=6 n (%)**	**All QD patients N=10 n (%)**	**Everolimus 30mg +EP N=5 n (%)**	**Everolimus 30mg+EP N=13 n (%)**	**All QW patients N=18 n (%)**
All deaths [1]	0	0	0	0	3 (23.1)	3 (16.7)
On treatment deaths [2]	0	0	0	0	0	0
Serious adverse events	0	4 (66.7)	4 (40.0)	3 (60.0)	4 (30.8)	7 (38.9)
Discontinued due to SAE(s)	0	1 (16.7)	1 (10.0)	0	0	0

[1] Include all deaths regardless of whether they are within 28 days of last treatment.

[2] Death occurring not more than 28 days after the end-of-study treatment.

- Categories are not mutually exclusive.

G-CSF patients:

	Daily		
	Everolimus 2.5mg + EP N=4 n (%)	**Everolimus 5mg + EP N=6 n (%)**	**All QD patients N=10 n (%)**
All deaths [1]	1 (14.3)	0	1 (8.3)
On treatment deaths [2]	1 (14.3)	0	1 (8.3)
Serious adverse events	2 (28.6)	4 (80.0)	6 (50.0)
Discontinued due to SAE(s)	0	0	0

[1] Include all deaths regardless of whether they are within 28 days of last treatment.

[2] Death occurring not more than 28 days after the end-of-study treatment.

- Categories are not mutually exclusive.

Serious adverse events regardless of study treatment relationship by preferred term (Safety Population)

Non -G-CSF patients:

	Daily			Weekly		
	Everolimus	**Everolimus**	**All QD**	**Everolimus**	**Everolimus**	**All QW**
SAE Preferred term	**2.5mg + EP N=4 n (%)**	**5mg + EP N=6 n (%)**	**patients N=10 n (%)**	**20mg + EP N=5 n (%)**	**30mg + EP N=13 n (%)**	**patients N=18 n (%)**
Febrile neutropenia	0	3 (50.0)	3 (30.0)	0	1 (7.7)	1 (5.6)
Anaemia	0	0	0	0	1 (7.7)	1 (5.6)
Neutropenia	0	0	0	1 (20.0)	0	1 (5.6)
Thrombocytopenia	0	0	0	0	1 (7.7)	1 (5.6)
Dehydration	0	1 (16.7)	1 (10.0)	1 (20.0)	0	1 (5.6)

Hypokalaemia	0	0	0	0	1 (7.7)	1 (5.6)
Hypomagnesaemia	0	1 (16.7)	1 (10.0)	0	0	0
Nausea	0	0	0	1 (20.0)	1 (7.7)	2 (11.1)
Oesophagitis ulcerative	0	0	0	0	1 (7.7)	1 (5.6)
Stomatitis	0	1 (16.7)	1 (10.0)	0	0	0
Bronchitis	0	0	0	0	1 (7.7)	1 (5.6)
Localised infection	0	0	0	1 (20.0)	0	1 (5.6)
Pneumonia	0	1 (16.7)	1 (10.0)	0	0	0
Dyspnoea	0	0	0	0	1 (7.7)	1 (5.6)
Oropharyngeal pain	0	1 (16.7)	1 (10.0)	0	0	0
Pulmonary embolism	0	0	0	0	1 (7.7)	1 (5.6)
Respiratory failure	0	0	0	0	1 (7.7)	1 (5.6)
Asthenia	0	1 (16.7)	1 (10.0)	0	0	0
Fatigue	0	0	0	1 (20.0)	0	1 (5.6)
Pyrexia	0	1 (16.7)	1 (10.0)	0	0	0
Tachycardia	0	1 (16.7)	1 (10.0)	0	0	0
Cushing's syndrome	0	0	0	0	1 (7.7)	1 (5.6)
Blood creatinine increased	0	0	0	0	1 (7.7)	1 (5.6)
Depressed level of consciousness	0	0	0	0	1 (7.7)	1 (5.6)
Deep vein thrombosis	0	0	0	1 (20.0)	0	1 (5.6)

- Preferred terms are sorted in descending frequency, over all treatment regimens.
- A patient with multiple occurrences of an AE is counted only once in the AE category.

G-CSF patients:

	Daily		
SAE Preferred term	**Everolimus 2.5mg + EP N=7 n (%)**	**Everolimus 5mg + EP N=5 n (%)**	**All QD patients N=12 n (%)**
Febrile neutropenia	1 (14.3)	0	1 (8.3)
Thrombocytopenia	0	1 (20.0)	1 (8.3)
Epistaxis	0	1 (20.0)	1 (8.3)
Haemoptysis	0	1 (20.0)	1 (8.3)
Fall	0	1 (20.0)	1 (8.3)
Dizziness	0	1 (20.0)	1 (8.3)
Headache	0	1 (20.0)	1 (8.3)
Renal failure	1 (14.3)	0	1 (8.3)

- Preferred terms are sorted in descending frequency, over all treatment regimens.
- A patient with multiple occurrences of an AE is counted only once in the AE category.

Other Relevant Findings

Summary of DLTs by cycle, schedule and dose level (Dose-determining Population)

Non-G-CSF Patients:

		Daily			Weekly		
		Everolimus 2.5mg + EP	Everolimus 5mg + EP	All QD patients	Everolimus 20mg + E P	Everolimus 30mg + EP	All QW patients
		N=4	N=6	N=10	N=5	N=13	N=18
Cycle		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Total no. of patients with DLT	2 (50.0)	5 (83.3)	7 (70.0)	1 (20.0)	6 (46.2)	7 (38.9)
	Total number of DLTs	2	11	13	1	8	9
1	No. patients exposed	4	6	10	5	13	18
	No. of patients with DLT	2 (50.0)	3 (50.0)	5 (50.0)	0	4 (30.8)	4 (22.2)
	No. of DLTs	2	3	5	0	4	4
2	No. patients exposed	3	5	8	5	13	18
	No. of patients with DLT	0	2 (40.0)	2 (25.0)	0	0	0
	No. of DLTs	0	2	2	0	0	0
3	No. patients exposed	3	3	6	5	10	15
	No. of patients with DLT	0	1 (33.3)	1 (16.7)	1 (20.0)	0	1 (6.7)
	No. of DLTs	0	1	1	1	0	1
4	No. patients exposed	3	3	6	4	10	14
	No. of patients with DLT	0	2 (66.7)	2 (33.3)	0	2 (20.0)	2 (14.3)
	No. of DLTs	0	2	2	0	2	2
5	No. patients exposed	2	2	4	3	9	12
	No. of patients with DLT	0	0	0	0	1 (11.1)	1 (8.3)
	No. of DLTs	0	0	0	0	1	1
6	No. patients exposed	2	2	4	3	9	12
	No. of patients with DLT	0	2 (100.0)	2 (50.0)	0	1 (11.1)	1 (8.3)
	No. of DLTs	0	3	3	0	1	1

- The denominator for cycle rate is the number of patients who reached that cycle (i.e. had at least one administration of any study treatment during that cycle).
- Total includes all DLTs over all cycles.

G-CSF patients:

	Daily

Cycle		Everolimus 2.5mg + EP N=7 n (%)	Everolimus 5mg + EP N=5 n (%)	All QD patients N=12 n (%)
	Total no. of patients with DLT	1	2	3
		(14.3)	(40.0)	(25.0)
	Total number of DLTs	1	3	4
1	No. patients exposed	7	5	12
	No. of patients with DLT	1	1	2
		(14.3)	(20.0)	(16.7)
	No. of DLTs	1	1	2
2	No. patients exposed	5	4	9
	No. of patients with DLT	0	0	0
	No. of DLTs	0	0	0
3	No. patients exposed	4	4	8
	No. of patients with DLT	0	1	1
			(25.0)	(12.5)
	No. of DLTs	0	1	1
4	No. patients exposed	4	4	8
	No. of patients with DLT	0	0	0
	No. of DLTs	0	0	0
5	No. patients exposed	4	3	7
	No. of patients with DLT	0	1	1
			(33.3)	(14.3)
	No. of DLTs	0	1	1
6	No. patients exposed	3	3	6
	No. of patients with DLT	0	0	0
	No. of DLTs	0	0	0

Date of Clinical Trial Report

31 Oct 2011

Date Inclusion on Novartis Clinical Trial Results Database

21 Nov 2011

Date of Latest Update