



Clinical trial results:

An Open-Label, Single-arm, Phase Ib/II study of AEB071 (a Protein Kinase C Inhibitor) and Everolimus (mTOR inhibitor) in Patients with CD79-mutant or ABC subtype Diffuse Large B-Cell Lymphoma

Summary

EudraCT number	2013-001265-16
Trial protocol	IT DE NL FR
Global end of trial date	01 June 2016

Results information

Result version number	v1 (current)
This version publication date	08 June 2017
First version publication date	08 June 2017

Trial information

Trial identification

Sponsor protocol code	COEB071X2103
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01854606
WHO universal trial number (UTN)	-
Other trial identifiers	ND: ND

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceuticals AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Novartis Pharmaceuticals AG, Novartis Pharmaceuticals AG, 41 613241111,
Scientific contact	Novartis Pharmaceuticals AG, Novartis Pharmaceuticals AG, 41 613241111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 June 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 June 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The Phase Ib part of the study was to estimate the maximum tolerated dose/recommended Phase II dose (MTD/RP2D) of the combination of sotrastaurin and everolimus in patients with CD79 mutant and/or activated B-cell (ABC) subtype diffuse large B-cell lymphoma (DLBCL). The Phase II part was to assess the preliminary evidence of anti-tumor activity at the RP2D for the combination of sotrastaurin and everolimus in the same patient population (i.e. patients with a CD79 mutation and in those wild-type for the mutation but of the ABC subtype). However, due to suboptimal tolerability of the combination treatment of sotrastaurin and everolimus in the Phase Ib part of the study, the Phase II part was not initiated nor conducted.

Protection of trial subjects:

This study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hong Kong: 5
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	United States: 6
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Germany: 3
Worldwide total number of subjects	31
EEA total number of subjects	7

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	16
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

At the study termination date (01-Jun-2016), all 31 patients had discontinued study.

Pre-assignment

Screening details:

A minimum of 70 patients (at least 15 for Phase Ib and approximately 55 for Phase II) were to be enrolled. At the time of enrollment halt, a total of 31 patients were enrolled into the Phase Ib part of the study. Treatment arms were described by sotrastaurin dose and regimen only since the dose and regimen of everolimus remained constant.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	200mg Sotrastaurin + 2.5 mg everolimus

Arm description:

Sotrastaurin 200 mg twice daily + everolimus 2.5 mg once daily

Arm type	Experimental
Investigational medicinal product name	AEB071
Investigational medicinal product code	
Other name	Sotrastaurin
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to receive sotrastaurin orally, twice a day (at approximately 12-hour intervals). The patient's dose of each study drug depended upon which dose level the patient was assigned to. Patients were dosed on a flat, fixed dose and not by body weight or body surface area.

Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	RAD001
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to receive 2.5mg everolimus once daily. The patient's dose of each study drug depended upon which dose level the patient was assigned to. Patients were dosed on a flat, fixed dose and not by body weight or body surface area.

Arm title	250mg Sotrastaurin + 2.5 mg everolimus
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Arm description:

Sotrastaurin 250 mg twice daily + everolimus 2.5 mg once daily

Arm type	Experimental
Investigational medicinal product name	AEB071
Investigational medicinal product code	
Other name	Sotrastaurin
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to receive sotrastaurin orally, twice a day (at approximately 12-hour intervals). The

patient's dose of each study drug depended upon which dose level the patient was assigned to. Patients were dosed on a flat, fixed dose and not by body weight or body surface area.

Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	RAD001
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to receive everolimus once daily. The patient's dose of each study drug depended upon which dose level the patient was assigned to. Patients were dosed on a flat, fixed dose and not by body weight or body surface area.

Arm title	300mg Sotrastaurin + 2.5 mg everolimus
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Arm description:

Sotrastaurin 300 mg twice daily + everolimus 2.5 mg once daily

Arm type	Experimental
Investigational medicinal product name	AEB071
Investigational medicinal product code	
Other name	Sotrastaurin
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to receive sotrastaurin orally, twice a day (at approximately 12-hour intervals). The patient's dose of each study drug depended upon which dose level the patient was assigned to. Patients were dosed on a flat, fixed dose and not by body weight or body surface area.

Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	RAD001
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to receive everolimus once daily. The patient's dose of each study drug depended upon which dose level the patient was assigned to. Patients were dosed on a flat, fixed dose and not by body weight or body surface area.

Arm title	400mg Sotrastaurin + 2.5 mg everolimus
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Arm description:

Sotrastaurin 400 mg twice daily + everolimus 2.5 mg once daily

Arm type	Experimental
Investigational medicinal product name	AEB071
Investigational medicinal product code	
Other name	Sotrastaurin
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to receive sotrastaurin orally, twice a day (at approximately 12-hour intervals). The patient's dose of each study drug depended upon which dose level the patient was assigned to. Patients were dosed on a flat, fixed dose and not by body weight or body surface area.

Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	RAD001
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to receive everolimus once daily. The patient's dose of each study drug depended upon which dose level the patient was assigned to. Patients were dosed on a flat, fixed dose and not by body weight or body surface area.

weight or body surface area.

Number of subjects in period 1	200mg Sotrastaurin + 2.5 mg everolimus	250mg Sotrastaurin + 2.5 mg everolimus	300mg Sotrastaurin + 2.5 mg everolimus
Started	3	16	6
Completed	0	0	0
Not completed	3	16	6
Adverse event, serious fatal	-	4	1
Consent withdrawn by subject	1	1	2
Physician decision	-	-	1
Adverse event, non-fatal	-	3	-
Follow-up phase completed as per protocol	2	7	2
Lost to follow-up	-	1	-

Number of subjects in period 1	400mg Sotrastaurin + 2.5 mg everolimus
Started	6
Completed	0
Not completed	6
Adverse event, serious fatal	2
Consent withdrawn by subject	2
Physician decision	-
Adverse event, non-fatal	-
Follow-up phase completed as per protocol	2
Lost to follow-up	-

Baseline characteristics

Reporting groups

Reporting group title	200mg Sotrastaurin + 2.5 mg everolimus
Reporting group description:	
Sotrastaurin 200 mg twice daily + everolimus 2.5 mg once daily	
Reporting group title	250mg Sotrastaurin + 2.5 mg everolimus
Reporting group description:	
Sotrastaurin 250 mg twice daily + everolimus 2.5 mg once daily	
Reporting group title	300mg Sotrastaurin + 2.5 mg everolimus
Reporting group description:	
Sotrastaurin 300 mg twice daily + everolimus 2.5 mg once daily	
Reporting group title	400mg Sotrastaurin + 2.5 mg everolimus
Reporting group description:	
Sotrastaurin 400 mg twice daily + everolimus 2.5 mg once daily	

Reporting group values	200mg Sotrastaurin + 2.5 mg everolimus	250mg Sotrastaurin + 2.5 mg everolimus	300mg Sotrastaurin + 2.5 mg everolimus
Number of subjects	3	16	6
Age categorical			
Units: Subjects			
< 65 Years	2	6	3
65 to < 85 Years	1	10	3
Age continuous			
Full Analysis Set (FAS): Consisted of all patients who received at least one full or partial dose of sotrastaurin or everolimus. Patient data were analyzed according to the planned treatment combination. Unless otherwise specified, FAS is the default set for Phase Ib data analysis.			
Units: years			
arithmetic mean	58	64.8	59.2
standard deviation	± 7	± 10.62	± 14.06
Gender categorical			
Units: Subjects			
Female	1	4	0
Male	2	12	6

Reporting group values	400mg Sotrastaurin + 2.5 mg everolimus	Total	
Number of subjects	6	31	
Age categorical			
Units: Subjects			
< 65 Years	5	16	
65 to < 85 Years	1	15	
Age continuous			
Full Analysis Set (FAS): Consisted of all patients who received at least one full or partial dose of sotrastaurin or everolimus. Patient data were analyzed according to the planned treatment combination. Unless otherwise specified, FAS is the default set for Phase Ib data analysis.			
Units: years			
arithmetic mean	55.5		
standard deviation	± 13.52	-	

Gender categorical			
Units: Subjects			
Female	3	8	
Male	3	23	

End points

End points reporting groups

Reporting group title	200mg Sotrastaurin + 2.5 mg everolimus
Reporting group description: Sotrastaurin 200 mg twice daily + everolimus 2.5 mg once daily	
Reporting group title	250mg Sotrastaurin + 2.5 mg everolimus
Reporting group description: Sotrastaurin 250 mg twice daily + everolimus 2.5 mg once daily	
Reporting group title	300mg Sotrastaurin + 2.5 mg everolimus
Reporting group description: Sotrastaurin 300 mg twice daily + everolimus 2.5 mg once daily	
Reporting group title	400mg Sotrastaurin + 2.5 mg everolimus
Reporting group description: Sotrastaurin 400 mg twice daily + everolimus 2.5 mg once daily	
Subject analysis set title	0-0.16
Subject analysis set type	Sub-group analysis
Subject analysis set description: Dose determining set (DDS): The DDS consisted of all patients from the Safety Set who either met the minimum exposure criterion and had sufficient safety evaluations during Cycle 1, or experienced a DLT during Cycle 1. A patient was considered to have met the minimum exposure criterion if they received at least 21 out of the 28 planned daily combination doses of sotrastaurin (bid) and everolimus (qd) in the first 28 days of dosing. Patients who did not experience a DLT during the first cycle were considered to have sufficient safety evaluations if they were observed for at least 28 days following the first dose and were considered by both Novartis and Investigators to have had enough safety data to conclude that a DLT did not occur.	
Subject analysis set title	0.16-0.35
Subject analysis set type	Sub-group analysis
Subject analysis set description: Dose determining set (DDS).	
Subject analysis set title	0.35-1
Subject analysis set type	Sub-group analysis
Subject analysis set description: Dose determining set (DDS).	
Subject analysis set title	All Dose Cohorts
Subject analysis set type	Full analysis
Subject analysis set description: Full Analysis Set (FAS): Consisted of all patients who received at least one full or partial dose of sotrastaurin or everolimus. Patient data were analyzed according to the planned treatment combination. Unless otherwise specified, FAS is the default set for Phase Ib data analysis.	

Primary: Posterior Distribution of Dose Limiting Toxicities (DLTs) rates at time of last dose escalation meeting, 2.5 mg Everolimus

End point title	Posterior Distribution of Dose Limiting Toxicities (DLTs) rates at time of last dose escalation meeting, 2.5 mg Everolimus ^[1]
End point description: Dose determining set (DDS): The DDS consisted of all patients from the Safety Set who either met the minimum exposure criterion and had sufficient safety evaluations during Cycle 1, or experienced a DLT during Cycle 1. A patient was considered to have met the minimum exposure criterion if they received at least 21 out of the 28 planned daily combination doses of sotrastaurin (bid) and everolimus (qd) in the first 28 days of dosing. Patients who did not experience a DLT during the first cycle were considered to have sufficient safety evaluations if they were observed for at least 28 days following the first dose and were considered by both Novartis and Investigators to have had enough safety data to conclude that a DLT did not occur.	
End point type	Primary

End point timeframe:

Approximately 12 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive analyses.

End point values	0-0.16	0.16-0.35	0.35-1	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	28 ^[2]	28 ^[3]	28 ^[4]	
Units: probability				
number (not applicable)				
250mg sotrastaurin	0.37	0.616	0.014	
300mg sotrastaurin	0.231	0.738	0.031	
350mg sotrastaurin	0.137	0.783	0.08	
400mg sotrastaurin	0.086	0.743	0.171	
450mg sotrastaurin	0.061	0.66	0.279	

Notes:

[2] - all patients in DDS

[3] - all patients in DDS

[4] - all patients in DDS

Statistical analyses

No statistical analyses for this end point

Primary: Posterior Distribution of Dose Limiting Toxicities (DLTs) Rates at time of last dose escalation meeting, 5.0 mg Everilimus

End point title	Posterior Distribution of Dose Limiting Toxicities (DLTs) Rates at time of last dose escalation meeting, 5.0 mg Everilimus ^[5]
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End point description:

Analysis done in the Dose determining set (DDS).

End point type	Primary
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End point timeframe:

Approximately 12 months

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive analyses.

End point values	0-0.16	0.16-0.35	0.35-1	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	28 ^[6]	28 ^[7]	28 ^[8]	
Units: Probability				
number (not applicable)				
250mg sotrastaurin	0.155	0.682	0.162	
300mg sotrastaurin	0.098	0.602	0.3	
350mg sotrastaurin	0.069	0.488	0.443	

Notes:

[6] - All patients in the DDS

[7] - All patients in the DDS

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of Dose Limiting Toxicities (DLTs) in Cycle 1

End point title	Incidence of Dose Limiting Toxicities (DLTs) in Cycle 1 ^[9]
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End point description:

Estimate the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D) of the AEB071and EVEROLIMUS combination therapy in patients with DLBCL in the Dose determining set (DDS).

A patient with multiple occurrences of DLTs under one treatment is counted only once in the AE category for that treatment.

A patient with multiple DLTs within a primary system organ class is counted only once in the total row.

End point type	Primary
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End point timeframe:

Approximately 12 months

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive analyses.

End point values	200mg Sotrastaurin + 2.5 mg everolimus	250mg Sotrastaurin + 2.5 mg everolimus	300mg Sotrastaurin + 2.5 mg everolimus	400mg Sotrastaurin + 2.5 mg everolimus
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	14	5	6
Units: Participants				
Blood and lymphatic system disorders	0	1	0	0
-Thrombocytopenia	0	1	0	0
Gastrointestinal disorders	1	0	0	2
-Nausea	0	0	0	2
-Vomiting	0	0	0	2
-Diarrhoea	0	0	0	1
-Stomatitis	1	0	0	0
Infections and infestations	0	1	0	0
-Pneumocystis jirovecii pneumonia	0	1	0	0
Metabolism and nutrition disorders	0	1	1	0
-Decreased appetite	0	0	1	0
-Hypertriglyceridaemia	0	1	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Radiological Response

End point title	Best Overall Radiological Response
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End point description:

Evaluate preliminary anti-tumor activity for AE071 and EVEROLIMUS in the Dose determining set (DDS).

End point type	Secondary
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End point timeframe:

approximately 24 months

End point values	All Dose Cohorts			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: Patients				
Complete response	1			
Partial response	4			
Stable disease	9			
Progressive disease	6			
Unknown best overall response	11			

Statistical analyses

No statistical analyses for this end point

Secondary: Primary PK Parameters for Whole Blood Sotrastaurin by Treatment Group - Area Under Curve

End point title	Primary PK Parameters for Whole Blood Sotrastaurin by Treatment Group - Area Under Curve
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End point description:

Pharmacokinetic Analysis Set: Consisted of all patients who had evaluable PK data. The Pharmacokinetic Analysis Set was used for summaries (tables and figures) and listings of derived PK data. Patients could be removed from the estimation of certain PK parameters on an individual basis depending on the number of available blood samples. These patients were identified at the time of the analyses.

Area Under Curve (AUC_{0-8h}) = Area under the concentration-time curve from time 0 to 8 hours post-dose [mass x time x volume⁻¹]

End point type	Secondary
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End point timeframe:

Approximately 24 months (Day 1 and Day 15 of Cycle 1)

End point values	200mg Sotrastaurin + 2.5 mg everolimus	250mg Sotrastaurin + 2.5 mg everolimus	300mg Sotrastaurin + 2.5 mg everolimus	400mg Sotrastaurin + 2.5 mg everolimus
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	16	6	6
Units: hr*ng/mL				

median (full range (min-max))				
Day 1	7660 (7660 to 7660)	14000 (3960 to 35800)	18600 (14100 to 23900)	29000 (27700 to 30300)
Day 15	13200 (11500 to 17400)	19100 (8590 to 37200)	30100 (23400 to 81900)	36800 (14100 to 51700)

Statistical analyses

No statistical analyses for this end point

Secondary: Primary PK Parameters for Whole Blood Sotrastaurin by Treatment Group - Cmax

End point title	Primary PK Parameters for Whole Blood Sotrastaurin by Treatment Group - Cmax
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End point description:

Analysis done in the Pharmacokinetic Analysis Set.

Cmax=Maximum observed concentration after drug administration [mass x volume-1].

End point type	Secondary
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End point timeframe:

Approximately 24 months (Day 1 and Day 15 of Cycle 1)

End point values	200mg Sotrastaurin + 2.5 mg everolimus	250mg Sotrastaurin + 2.5 mg everolimus	300mg Sotrastaurin + 2.5 mg everolimus	400mg Sotrastaurin + 2.5 mg everolimus
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	16	6	6
Units: ng/ml				
median (full range (min-max))				
Day 1	3420 (3420 to 3420)	2970 (718 to 5780)	3310 (2500 to 3640)	7690 (7370 to 8000)
Day 15	2530 (2320 to 2870)	3840 (1770 to 6280)	4610 (3470 to 12900)	5270 (3700 to 9870)

Statistical analyses

No statistical analyses for this end point

Secondary: Primary PK Parameters for Whole Blood Sotrastaurin by Treatment Group - Tmax

End point title	Primary PK Parameters for Whole Blood Sotrastaurin by Treatment Group - Tmax
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End point description:

Analysis done in the Pharmacokinetic Analysis Set.

Tmax=Time to reach Cmax [time]

End point type	Secondary
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End point timeframe:

Approximately 24 months (Day 1 and Day 15 of Cycle 1)

End point values	200mg Sotrastaurin + 2.5 mg everolimus	250mg Sotrastaurin + 2.5 mg everolimus	300mg Sotrastaurin + 2.5 mg everolimus	400mg Sotrastaurin + 2.5 mg everolimus
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	16	6	6
Units: hr				
median (full range (min-max))				
Day 1	1 (1 to 1)	2 (0.5 to 5.98)	3.97 (0.967 to 4.17)	0.992 (0.983 to 1)
Day 15	1.08 (1 to 1.93)	2 (0.5 to 4.05)	4.05 (2 to 4.25)	1 (0.533 to 2.05)

Statistical analyses

No statistical analyses for this end point

Secondary: Primary PK Parameters for Whole Blood Sotrastaurin by Treatment Group - Racc

End point title	Primary PK Parameters for Whole Blood Sotrastaurin by Treatment Group - Racc
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End point description:

Analysis done in the Pharmacokinetic Analysis Set.

Racc = Accumulation ratio calculated as AUC0-8h or AUCtau at Day 15/AUC0-8h or AUCtau at Day 1

End point type	Secondary
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End point timeframe:

Approximately 24 months (Day 1 and Day 15 of Cycle 1)

End point values	200mg Sotrastaurin + 2.5 mg everolimus	250mg Sotrastaurin + 2.5 mg everolimus	300mg Sotrastaurin + 2.5 mg everolimus	400mg Sotrastaurin + 2.5 mg everolimus
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	16	6	6
Units: Ratio				
median (full range (min-max))				
Day 15	1.51 (1.51 to 1.51)	1.41 (1.04 to 4.7)	1.26 (1.26 to 1.26)	1.11 (0.51 to 1.71)

Statistical analyses

No statistical analyses for this end point

Secondary: Primary PK Parameters for Whole Blood Everolimus by Treatment Group - Area Under Curve

End point title	Primary PK Parameters for Whole Blood Everolimus by Treatment Group - Area Under Curve
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End point description:

Analysis done in the Pharmacokinetic Analysis Set.

Area Under Curve (AUC_{0-8h}) = Area under the concentration-time curve from time 0 to 8 hours post-dose [mass x time x volume⁻¹]

End point type	Secondary
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End point timeframe:

Approximately 24 months (Day 1 and Day 15 of Cycle 1)

End point values	200mg Sotrastaurin + 2.5 mg everolimus	250mg Sotrastaurin + 2.5 mg everolimus	300mg Sotrastaurin + 2.5 mg everolimus	400mg Sotrastaurin + 2.5 mg everolimus
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	16	6	6
Units: hr*ng/mL				
median (full range (min-max))				
Day 1	40.7 (40.7 to 40.7)	62.6 (51 to 152)	57.1 (41 to 145)	58.9 (26.1 to 132)
Day 15	98 (78 to 140)	115 (56.6 to 181)	221 (185 to 238)	161 (149 to 161)

Statistical analyses

No statistical analyses for this end point

Secondary: Primary PK Parameters for Whole Blood Everolimus by Treatment Group - C_{max}

End point title	Primary PK Parameters for Whole Blood Everolimus by Treatment Group - C _{max}
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End point description:

Analysis done in the Pharmacokinetic Analysis Set.

C_{max}=Maximum observed concentration after drug administration [mass x volume⁻¹].

End point type	Secondary
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End point timeframe:

Approximately 24 months (Day 1 and Day 15 of Cycle 1)

End point values	200mg Sotrastaurin + 2.5 mg everolimus	250mg Sotrastaurin + 2.5 mg everolimus	300mg Sotrastaurin + 2.5 mg everolimus	400mg Sotrastaurin + 2.5 mg everolimus
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	16	6	6
Units: ng/ml				
median (full range (min-max))				
Day 1	7.62 (7.62 to 7.62)	12.5 (7.78 to 31.9)	11.4 (7.36 to 40.6)	11 (4.57 to 34.6)
Day 15	18.7 (12.8 to 23.6)	17.5 (13.7 to 37.6)	32.5 (29 to 40.9)	27.9 (23.5 to 30.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Primary PK Parameters for Whole Blood Everolimus by Treatment Group – Tmax

End point title	Primary PK Parameters for Whole Blood Everolimus by Treatment Group – Tmax
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End point description:

Analysis done in the Pharmacokinetic Analysis Set.

Tmax = Time to reach Cmax [time]

End point type	Secondary
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End point timeframe:

Approximately 24 months (Day 1 and Day 15 of Cycle 1)

End point values	200mg Sotrastaurin + 2.5 mg everolimus	250mg Sotrastaurin + 2.5 mg everolimus	300mg Sotrastaurin + 2.5 mg everolimus	400mg Sotrastaurin + 2.5 mg everolimus
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	16	6	6
Units: hr				
median (full range (min-max))				
Day 1	4 (4 to 4)	1.54 (0.5 to 6)	2.48 (0.967 to 4.17)	2 (0.967 to 6)
Day 15	1.93 (1.08 to 3.98)	2 (0 to 4.05)	1.64 (1.64 to 1.64)	2.08 (1.22 to 5.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Primary PK Parameters for Whole Blood Everolimus by Treatment Group

- Racc

End point title	Primary PK Parameters for Whole Blood Everolimus by Treatment Group – Racc
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End point description:

Analysis done in the Pharmacokinetic Analysis Set.

Racc = Accumulation ratio calculated as AUC0-8h or AUCtau at Day 15/AUC0-8h or AUCtau at Day 1

End point type	Secondary
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End point timeframe:

Approximately 24 months (Day 1 and Day 15 of Cycle 1)

End point values	200mg Sotrastaurin + 2.5 mg everolimus	250mg Sotrastaurin + 2.5 mg everolimus	300mg Sotrastaurin + 2.5 mg everolimus	400mg Sotrastaurin + 2.5 mg everolimus
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	16	6	6
Units: Ratio				
median (full range (min-max))				
Day 15	2.41 (2.41 to 2.41)	1.37 (1.19 to 2.62)	1.64 (1.64 to 1.64)	2.08 (1.22 to 5.07)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	AEB 200 mg bid +@ RAD 2.5 mg qd
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Reporting group description:

AEB 200 mg bid +@ RAD 2.5 mg qd

Reporting group title	AEB 250 mg bid +@ RAD 2.5 mg qd
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Reporting group description:

AEB 250 mg bid +@ RAD 2.5 mg qd

Reporting group title	AEB 300 mg bid +@ RAD 2.5 mg qd
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Reporting group description:

AEB 300 mg bid +@ RAD 2.5 mg qd

Reporting group title	AEB 400 mg bid +@ RAD 2.5 mg qd
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Reporting group description:

AEB 400 mg bid +@ RAD 2.5 mg qd

Reporting group title	All@patients
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Reporting group description:

All@patients

Serious adverse events	AEB 200 mg bid +@ RAD 2.5 mg qd	AEB 250 mg bid +@ RAD 2.5 mg qd	AEB 300 mg bid +@ RAD 2.5 mg qd
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	11 / 16 (68.75%)	3 / 6 (50.00%)
number of deaths (all causes)	0	4	1
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			

subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Intracardiac mass			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	4 / 16 (25.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intestinal perforation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			

subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)	2 / 16 (12.50%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 3 (33.33%)	2 / 16 (12.50%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			

subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Catheter site infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Citrobacter infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 16 (12.50%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 16 (12.50%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Septic shock			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	AEB 400 mg bid +@ RAD 2.5 mg qd	All@patients	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 6 (83.33%)	20 / 31 (64.52%)	
number of deaths (all causes)	2	7	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Intracardiac mass			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	4 / 31 (12.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal perforation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 6 (16.67%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	2 / 31 (6.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 6 (16.67%)	4 / 31 (12.90%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 6 (16.67%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	1 / 6 (16.67%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Catheter site infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Citrobacter infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 31 (6.45%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 31 (6.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 31 (6.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 6 (16.67%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	1 / 6 (16.67%)	3 / 31 (9.68%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	AEB 200 mg bid +@ RAD 2.5 mg qd	AEB 250 mg bid +@ RAD 2.5 mg qd	AEB 300 mg bid +@ RAD 2.5 mg qd
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	15 / 16 (93.75%)	6 / 6 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Superior vena cava occlusion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Catheter site swelling			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Face oedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	2 / 16 (12.50%)	3 / 6 (50.00%)
occurrences (all)	1	2	3
Mucosal inflammation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			

subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 16 (12.50%)	1 / 6 (16.67%)
occurrences (all)	0	3	2
Reproductive system and breast disorders			
Vaginal discharge			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 3 (66.67%)	2 / 16 (12.50%)	0 / 6 (0.00%)
occurrences (all)	2	2	0
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	3 / 16 (18.75%)	1 / 6 (16.67%)
occurrences (all)	0	3	1
Epistaxis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Lung infiltration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Oropharyngeal plaque			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pleural effusion			

subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	1 / 3 (33.33%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Rhinitis allergic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
Biopsy skin			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Blood cholesterol abnormal			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Blood potassium decreased			

subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
International normalised ratio increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Lymphocyte count decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Neutrophil count decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Platelet count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Urine output decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Procedural pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			

Pericardial effusion subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 16 (6.25%) 1	0 / 6 (0.00%) 0
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 16 (6.25%) 1	0 / 6 (0.00%) 0
Dysgeusia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 16 (0.00%) 0	0 / 6 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 16 (0.00%) 0	0 / 6 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	6 / 16 (37.50%) 8	2 / 6 (33.33%) 3
Leukopenia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 16 (6.25%) 3	0 / 6 (0.00%) 0
Lymph node pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 16 (0.00%) 0	0 / 6 (0.00%) 0
Neutropenia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	3 / 16 (18.75%) 3	1 / 6 (16.67%) 7
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	7 / 16 (43.75%) 15	1 / 6 (16.67%) 7
Ear and labyrinth disorders			
Vertigo subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 16 (6.25%) 1	0 / 6 (0.00%) 0
Eye disorders			
Eyelids pruritus subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 16 (0.00%) 0	0 / 6 (0.00%) 0

Periorbital oedema subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 16 (0.00%) 0	0 / 6 (0.00%) 0
Visual acuity reduced subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 16 (0.00%) 0	0 / 6 (0.00%) 0
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 16 (6.25%) 1	0 / 6 (0.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 16 (12.50%) 2	1 / 6 (16.67%) 1
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 16 (6.25%) 1	1 / 6 (16.67%) 1
Constipation subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	5 / 16 (31.25%) 6	3 / 6 (50.00%) 5
Diarrhoea subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	3 / 16 (18.75%) 3	3 / 6 (50.00%) 9
Dry mouth subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 16 (6.25%) 1	0 / 6 (0.00%) 0
Duodenal obstruction subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 16 (0.00%) 0	1 / 6 (16.67%) 1
Dyspepsia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 16 (6.25%) 1	2 / 6 (33.33%) 3
Epigastric discomfort subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 16 (0.00%) 0	0 / 6 (0.00%) 0
Impaired gastric emptying			

subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Melaena			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	2 / 3 (66.67%)	9 / 16 (56.25%)	4 / 6 (66.67%)
occurrences (all)	2	9	7
Stomatitis			
subjects affected / exposed	1 / 3 (33.33%)	3 / 16 (18.75%)	1 / 6 (16.67%)
occurrences (all)	1	3	1
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	6 / 16 (37.50%)	3 / 6 (50.00%)
occurrences (all)	0	8	6
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Rash			
subjects affected / exposed	0 / 3 (0.00%)	3 / 16 (18.75%)	0 / 6 (0.00%)
occurrences (all)	0	5	0
Rash maculo-papular			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Rash papular			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin discolouration			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 16 (0.00%) 0	0 / 6 (0.00%) 0
Skin hyperpigmentation subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 16 (0.00%) 0	0 / 6 (0.00%) 0
Skin texture abnormal subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 16 (6.25%) 1	0 / 6 (0.00%) 0
Renal and urinary disorders			
Acute kidney injury subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 16 (0.00%) 0	1 / 6 (16.67%) 1
Chromaturia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 16 (12.50%) 2	0 / 6 (0.00%) 0
Dysuria subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 16 (0.00%) 0	0 / 6 (0.00%) 0
Enuresis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 16 (6.25%) 1	0 / 6 (0.00%) 0
Haematuria subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 16 (12.50%) 2	0 / 6 (0.00%) 0
Oliguria subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 16 (0.00%) 0	0 / 6 (0.00%) 0
Ureteric obstruction subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 16 (0.00%) 0	0 / 6 (0.00%) 0
Endocrine disorders			
Adrenal insufficiency subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 16 (0.00%) 0	1 / 6 (16.67%) 1
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Flank pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Musculoskeletal discomfort			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Pain in jaw			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bacterial infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Candida infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Herpes simplex			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			

subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pneumonia bacterial			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pneumonia cytomegaloviral			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Rash pustular			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 3 (33.33%)	6 / 16 (37.50%)	4 / 6 (66.67%)
occurrences (all)	1	7	4
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fluid imbalance			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Fluid retention			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypercholesterolaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

Hyperglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 16 (12.50%)	1 / 6 (16.67%)
occurrences (all)	0	4	1
Hyperkalaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Hypertriglyceridaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hypocalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	4 / 16 (25.00%)	1 / 6 (16.67%)
occurrences (all)	0	5	1
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 16 (6.25%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
Hypophosphataemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Tumour lysis syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	AEB 400 mg bid +@ RAD 2.5 mg qd	All@patients	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	30 / 31 (96.77%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	

Superior vena cava occlusion subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 31 (3.23%) 1	
General disorders and administration site conditions			
Catheter site swelling subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 31 (3.23%) 1	
Face oedema subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 31 (3.23%) 1	
Fatigue subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 4	9 / 31 (29.03%) 10	
Mucosal inflammation subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 31 (3.23%) 1	
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	2 / 31 (6.45%) 2	
Pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 31 (3.23%) 1	
Pyrexia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	3 / 31 (9.68%) 5	
Reproductive system and breast disorders			
Vaginal discharge subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 31 (3.23%) 1	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	6 / 31 (19.35%) 6	
Dyspnoea			

subjects affected / exposed	1 / 6 (16.67%)	5 / 31 (16.13%)	
occurrences (all)	1	5	
Epistaxis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	2	
Lung infiltration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	1 / 6 (16.67%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Oropharyngeal pain			
subjects affected / exposed	1 / 6 (16.67%)	3 / 31 (9.68%)	
occurrences (all)	1	3	
Oropharyngeal plaque			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Productive cough			
subjects affected / exposed	0 / 6 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Respiratory failure			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Rhinitis allergic			
subjects affected / exposed	1 / 6 (16.67%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Rhinorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 6 (50.00%)	4 / 31 (12.90%)	
occurrences (all)	4	5	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 6 (33.33%)	5 / 31 (16.13%)	
occurrences (all)	2	5	
Biopsy skin			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Blood cholesterol abnormal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Blood potassium decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	2	
International normalised ratio increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Lymphocyte count decreased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Neutrophil count decreased			
subjects affected / exposed	2 / 6 (33.33%)	3 / 31 (9.68%)	
occurrences (all)	5	6	
Platelet count decreased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Urine output decreased			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 31 (3.23%) 1	
Weight decreased subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 31 (3.23%) 1	
White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 31 (3.23%) 1	
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 31 (3.23%) 1	
Procedural pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 31 (3.23%) 1	
Cardiac disorders			
Pericardial effusion subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 31 (3.23%) 1	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2	2 / 31 (6.45%) 3	
Dysgeusia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	2 / 31 (6.45%) 2	
Headache subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 31 (3.23%) 1	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	10 / 31 (32.26%) 13	
Leukopenia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 31 (3.23%) 3	

Lymph node pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 31 (3.23%) 1	
Neutropenia subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 3	7 / 31 (22.58%) 14	
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 4	10 / 31 (32.26%) 27	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 31 (3.23%) 1	
Eye disorders Eyelids pruritus subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 31 (3.23%) 1	
Periorbital oedema subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 31 (3.23%) 1	
Visual acuity reduced subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 31 (3.23%) 1	
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	2 / 31 (6.45%) 2	
Abdominal pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	3 / 31 (9.68%) 3	
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	2 / 31 (6.45%) 2	
Constipation subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2	10 / 31 (32.26%) 14	
Diarrhoea			

subjects affected / exposed	6 / 6 (100.00%)	12 / 31 (38.71%)	
occurrences (all)	10	22	
Dry mouth			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Duodenal obstruction			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	3 / 31 (9.68%)	
occurrences (all)	0	4	
Epigastric discomfort			
subjects affected / exposed	1 / 6 (16.67%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Impaired gastric emptying			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Melaena			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	6 / 6 (100.00%)	21 / 31 (67.74%)	
occurrences (all)	11	29	
Stomatitis			
subjects affected / exposed	3 / 6 (50.00%)	8 / 31 (25.81%)	
occurrences (all)	4	9	
Vomiting			
subjects affected / exposed	6 / 6 (100.00%)	15 / 31 (48.39%)	
occurrences (all)	9	23	
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			

subjects affected / exposed	1 / 6 (16.67%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Pruritus			
subjects affected / exposed	1 / 6 (16.67%)	3 / 31 (9.68%)	
occurrences (all)	1	3	
Rash			
subjects affected / exposed	1 / 6 (16.67%)	4 / 31 (12.90%)	
occurrences (all)	1	6	
Rash maculo-papular			
subjects affected / exposed	1 / 6 (16.67%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
Rash papular			
subjects affected / exposed	1 / 6 (16.67%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Skin discolouration			
subjects affected / exposed	1 / 6 (16.67%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Skin hyperpigmentation			
subjects affected / exposed	1 / 6 (16.67%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Skin texture abnormal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Chromaturia			
subjects affected / exposed	1 / 6 (16.67%)	3 / 31 (9.68%)	
occurrences (all)	1	3	
Dysuria			
subjects affected / exposed	1 / 6 (16.67%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Enuresis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	

Haematuria subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	2 / 31 (6.45%) 2	
Oliguria subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 31 (3.23%) 1	
Ureteric obstruction subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 31 (3.23%) 1	
Endocrine disorders Adrenal insufficiency subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 31 (3.23%) 1	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	3 / 31 (9.68%) 3	
Flank pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 31 (3.23%) 1	
Muscle spasms subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 31 (3.23%) 1	
Muscular weakness subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 31 (3.23%) 1	
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 31 (3.23%) 1	
Musculoskeletal discomfort subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 31 (3.23%) 1	
Pain in extremity subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 31 (3.23%) 2	
Pain in jaw			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 31 (3.23%) 1	
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Candida infection			
subjects affected / exposed	1 / 6 (16.67%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Herpes simplex			
subjects affected / exposed	1 / 6 (16.67%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Herpes zoster			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Pneumonia bacterial			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Pneumonia cytomegaloviral			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Rash pustular			
subjects affected / exposed	1 / 6 (16.67%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Skin infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Urinary tract infection			
subjects affected / exposed	1 / 6 (16.67%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	4 / 6 (66.67%)	15 / 31 (48.39%)
occurrences (all)	6	18
Dehydration		
subjects affected / exposed	1 / 6 (16.67%)	1 / 31 (3.23%)
occurrences (all)	2	2
Fluid imbalance		
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	1
Fluid retention		
subjects affected / exposed	1 / 6 (16.67%)	1 / 31 (3.23%)
occurrences (all)	1	1
Hypercholesterolaemia		
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	1
Hyperglycaemia		
subjects affected / exposed	0 / 6 (0.00%)	3 / 31 (9.68%)
occurrences (all)	0	5
Hyperkalaemia		
subjects affected / exposed	0 / 6 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	2
Hypertriglyceridaemia		
subjects affected / exposed	0 / 6 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	1
Hypocalcaemia		
subjects affected / exposed	2 / 6 (33.33%)	2 / 31 (6.45%)
occurrences (all)	2	2
Hypokalaemia		
subjects affected / exposed	1 / 6 (16.67%)	6 / 31 (19.35%)
occurrences (all)	2	8
Hyponatraemia		
subjects affected / exposed	1 / 6 (16.67%)	4 / 31 (12.90%)
occurrences (all)	1	4
Hypophosphataemia		
subjects affected / exposed	0 / 6 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	2
Tumour lysis syndrome		

subjects affected / exposed	1 / 6 (16.67%)	1 / 31 (3.23%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 August 2013	<ul style="list-style-type: none">•Removal of the prior anthracycline treatment criterion for inclusion of patients into the study due to differences in global standard of care in elderly DLBCL patient populations.•Correction of typographical error of exclusion criterion for abnormal laboratory values (absolute neutrophil and platelet counts).•Removal of exclusion criterion of patients with significant coagulopathy or requiring long-term systemic anticoagulation since newly obtained tumor samples was not required per protocol.
24 September 2014	<ul style="list-style-type: none">•As requested by Health Authorities and to align with the everolimus IB, amend protocol exclusion criterion #12 to exclude sexually active male patients unless a condom was used during intercourse while taking study treatment and for 8 weeks after discontinuation of study treatment.•As requested by Health Authorities, include a statement that caution is necessary when administering medications which are substrates of transportation MDR1 (P-gp) and OATP1B1 because sotrastaurin may act as an inhibitor of these transporters.•Modify exclusion criterion #15 to exclude patients who received ibritumomab tiuxetan (Zevalin®) and/or tositumomab (Bexxar®) treatment less than 3 months prior to starting study drug. After 3 months of discontinuing ibritumomab or tositumomab it was expected that any bone marrow suppressive effects would have resolved. This wash-out period allowed for additional patients to be considered for the study.•Clarification of the molecular pre-screening analysis to be performed at a central Novartis-designated laboratory during the Phase Ib escalation phase and the Phase II parts of this study have been included, so it is clear to Investigators.•Allow for a CT/MRI scan that was performed prior to obtaining study informed consent, but performed per standard of care within 28 days of Cycle 1 Day 1 to be used for Screening to avoid an unnecessary repeat of this procedure. In addition, to include an EOT CT/MRI if a CT/MRI was not acquired within 6 weeks prior to the EOT visit date. This was to ensure final radiological response assessment of disease prior to patients coming off study.•Specify the required inclusion criterion for definition of measurable disease to ensure the correct radiological assessment as per non-Hodgkin's Lymphoma International Working Group criteria.•This study only required radiological response assessment, references to additional response criteria that are not applicable for this study were removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The trial did not progress into Phase II due to the suboptimal tolerability of the combination treatment of sotrastaurin and everolimus in the Phase Ib part of the study. There were no serious safety concerns associated with this combination.

Notes: