Sponsor

Novartis

Generic Drug Name

Sotrastaurin

Trial Indication(s)

CD79-mutant or activated B-cell (ABC) subtype diffuse large B-cell lymphoma (DLBCL)

Protocol Number

COEB071X2103

Protocol Title

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

Clinical Trial Phase

Phase Ib/II

Phase of Drug Development

Phase I

Study Start/End Dates

05-Dec-2013 to 01-Jun-2016

Reason for Termination

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.

Study Design/Methodology

The Phase Ib part was an open-label, dose-escalation study utilizing the Bayesian logistic regression model (BLRM), a well-established method to estimate the maximum tolerated dose/recommended Phase II dose (MTD/RP2D) in cancer patients. The adaptive BLRM was guided by the escalation with overdose criterion (EWOC) principle to control the risk of dose-limiting toxicities (DLT). The adaptive Bayesian methodology provided an estimate of all combination dose levels of sotrastaurin and everolimus that did not exceed the MTD and incorporated all DLT information at all dose levels for this estimation.

Centers

Germany (2), Hong Kong (1), Netherlands (2), South Korea (2), Taiwan (1), United States (2)

Objectives:

Primary Objectives:

- Phase Ib: To estimate the MTD and the RP2D of the sotrastaurin and everolimus combination therapy in patients with DLBCL.
- Phase II: To assess the preliminary evidence for anti-tumor activity at R2PD for sotrastaurin and everolimus in patients with a CD79 mutation and in those wild-type for the mutation but of the ABC subtype.

Secondary objectives:

- Phase Ib: To characterize the pharmacokinetic (PK) profiles of sotrastaurin and everolimus, as well as to evaluate their active metabolites

- Phase Ib/II: To further characterize the safety and tolerability of the combination of sotrastaurin and everolimus, including acute and chronic toxicities
- Phase Ib/II: To evaluate the preliminary anti-tumor activity for sotrastaurin and everolimus
- Phase II: To compare the anti-tumor activity at RP2D between patients with a CD79 mutation and those wild-type for the mutation but of the ABC subtype

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

Sotrastaurin and everolimus were to be taken continuously for 28-day cycles until disease progression or until criteria for premature patient withdrawal were met. Patients were to receive sotrastaurin orally, twice daily (at approximately 12-hour intervals) and everolimus once daily. The starting dose of study treatment was 400 mg sotrastaurin, twice daily, and 2.5 mg everolimus, once daily.

Statistical Methods

Background and demographic characteristics including age, gender, race, ethnicity, height, weight, WHO/ Eastern Cooperative Oncology Group (ECOG) performance status, medical conditions, etc., were listed, and were summarized by treatment group using standard descriptive statistics and/or contingency tables (qualitative data). The following listings were provided: CD79 mutational status and ABC-subtype status; disease history; relevant medical history and current medical conditions; and prior anti-neoplastic therapies.

Estimation of the MTD during the dose escalation phase of the study was based upon the estimation of the posterior distribution of the probability of DLTs in Cycle 1 (28 days) in patients in the dose-determining set (DDS). An adaptive BLRM (with 5 parameters) guided by the EWOC principle was used to make dose recommendations and estimate the MTD during the dose escalation phase of the study.

Efficacy for all patients was evaluated by the Investigator using the Cheson criteria. A waterfall plot for best percentage change from baseline in sum of product diameters based on local radiology review was provided. Overall response per patient and by assessment cycle was listed by treatment group.

With the exception of DLT summaries (for which the DDS was used), all safety analyses were based on the Safety Set. Safety reports included all adverse events (AEs), serious adverse events (SAEs), and the regular monitoring of laboratory evaluations, physical examination, vital signs, weight, performance status evaluation and ECGs. Total dose, dose intensity, and relative dose intensity of sotrastaurin and everolimus were summarized. Dose administration record by treatment group was listed for the Safety Set. Deaths were summarized by treatment group.

PK parameters (including Tmax, Cmax, and AUC0-8hr) were determined for both sotrastaurin and everolimus on PK profiles after the first dose and at steady-state (Cycle 1 Day 15) using non-compartmental method(s).

Study Population: Key Inclusion/Exclusion Criteria

The patient population for the study was comprised of male or female patients ≥ 18 years of age with CD79 mutant or ABC-subtype DLBCL, who experienced relapse following chemotherapy or were refractory to prior therapy.

To ensure that only patients with relevant CD79 mutations in the ITAM region or ABC-subtype DLBCL were included in the study, molecular pre-screening was performed prior to screening the patient for study eligibility. Patients were required to have at least one measurable nodal or extra-nodal lesion greater than 20 mm in the long axis.

Participant Flow Table

Patient disposition by treatment group (FAS)

Disposition Reason	Sotrastaurin 200 mg twice daily + everolimus 2.5 mg once daily N=3 n (%)	Sotrastaurin 250 mg twice daily + everolimus 2.5 mg once daily N=16 n (%)	Sotrastaurin 300 mg twice daily + everolimus 2.5 mg once daily N=6 n (%)	Sotrastaurin 400 mg twice daily + everolimus 2.5 mg once daily N=6 n (%)	All patients N=31 n (%)
Patients treated					
Treatment discontinued	3 (100)	16 (100)	6 (100)	6 (100)	31 (100)
Primary reason for end of treatment					
Adverse Event(s)	0	9 (56.3)	1 (16.7)	0	10 (32.3)
Subject withdrew consent	1 (33.3)	1 (6.3)	2 (33.3)	1 (16.7)	5 (16.1)
Death	0	2 (12.5)	0	0	2 (6.5)
Disease progression	2 (66.7)	4 (25.0)	3 (50.0)	5 (83.3)	14 (45.2)
Primary reason for study evaluation completion					
Adverse Event(s)	0	3 (18.8)	0	0	3 (9.7)

Disposition Reason	Sotrastaurin 200 mg twice daily + everolimus 2.5 mg once daily N=3 n (%)	Sotrastaurin 250 mg twice daily + everolimus 2.5 mg once daily N=16 n (%)	Sotrastaurin 300 mg twice daily + everolimus 2.5 mg once daily N=6 n (%)	Sotrastaurin 400 mg twice daily + everolimus 2.5 mg once daily N=6 n (%)	All patients N=31 n (%)
Subject withdrew consent	1 (33.3)	1 (6.3)	2 (33.3)	2 (33.3)	6 (19.4)
Lost to Follow-up	0	1 (6.3)	0	0	1 (3.2)
Death	0	4 (25.0)	1 (16.7)	2 (33.3)	7 (22.6)
Follow-up phase completed as per protocol	2 (66.7)	7 (43.8)	2 (33.3)	2 (33.3)	13 (41.9)
Physician's decision	0	0	1 (16.7)	0	1 (3.2)

- Study evaluation completion performed 30 days following treatment discontinuation.

Baseline Characteristics

Demographic and baseline characteristics by treatment group (FAS)

	Sotrastaurin 200 mg twice daily + everolimus 2.5 mg once daily N=3	Sotrastaurin 250 mg twice daily + everolimus 2.5 mg once daily N=16	Sotrastaurin 300 mg twice daily + everolimus 2.5 mg once daily N=6	Sotrastaurin 400 mg twice daily + everolimus 2.5 mg once daily N=6	All patients N=31
Age (Years)					
n	3	16	6	6	31
Mean	58.0	64.8	59.2	55.5	61.3
SD	7.00	10.62	14.06	13.52	11.76
Median	58.0	65.5	56.0	60.5	63.0
Minimum	51.0	43.0	47.0	36.0	36.0
Maximum	65.0	80.0	79.0	71.0	80.0
Age category (Years) -n (%)					

	Sotrastaurin 200 mg twice daily + everolimus 2.5 mg once daily	Sotrastaurin 250 mg twice daily + everolimus 2.5 mg once daily	Sotrastaurin 300 mg twice daily + everolimus 2.5 mg once daily	Sotrastaurin 400 mg twice daily + everolimus 2.5 mg once daily	All patients
	N=3	N=16	N=6	N=6	N=31
<65	2 (66.7)	6 (37.5)	3 (50.0)	5 (83.3)	16 (51.6)
65 to <85	1 (33.3)	10 (62.5)	3 (50.0)	1 (16.7)	15 (48.4)
Sex -n (%)					
Male	2 (66.7)	12 (75.0)	6 (100)	3 (50.0)	23 (74.2)
Female	1 (33.3)	4 (25.0)	0	3 (50.0)	8 (25.8)
Race -n (%)					
Caucasian	1 (33.3)	6 (37.5)	1 (16.7)	2 (33.3)	10 (32.3)
Black	1 (33.3)	0	1 (16.7)	1 (16.7)	3 (9.7)
Asian	1 (33.3)	10 (62.5)	4 (66.7)	3 (50.0)	18 (58.1)
Ethnicity -n (%)					
Chinese	0	5 (31.3)	0	1 (16.7)	6 (19.4)
Other	3 (100)	11 (68.8)	6 (100)	5 (83.3)	25 (80.6)
WHO performance status ($) -n (%)					
0	1 (33.3)	4 (25.0)	2 (33.3)	2 (33.3)	9 (29.0)
1	2 (66.7)	10 (62.5)	3 (50.0)	2 (33.3)	17 (54.8)
2	0	2 (12.5)	1 (16.7)	2 (33.3)	5 (16.1)

($) 0 - Fully active, able to carry on all pre-disease performance without restriction.
1-Restricted in physically strenuous activity but ambulatory and able to carry out 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 selfcare, confined to bed or chair more than 50% of waking hours.
4- Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.

Summary of Efficacy

Primary Outcome Result(s)

- **Determination of MTD**

Summary of posterior distribution of DLT rates at time of last dose escalation meeting (Dose Determining Set)

Dose-escalation Teleconference: 4, everolimus = 2.5-mg once daily

	Posterior probabilities (%) that Pr(DLT) is in interval:					Quantiles		
Sotrastaurin dose (mg, twice daily)	0-0.16	0.16-0.35	0.35-1	Mean	SDev	2.5%	50%	97.5%
250	0.370	0.616	0.014	0.187	0.065	0.078	0.181	0.328
300	0.231	0.738	0.031	0.213	0.068	0.099	0.207	0.359
350	0.137	0.783	0.080	0.240	0.074	0.115	0.235	0.402
400	0.086	0.743	0.171	0.270	0.086	0.126	0.263	0.464
450	0.061	0.660	0.279	0.301	0.103	0.135	0.291	0.534

Dose-escalation Teleconference: 4, everolimus = 5-mg once daily

	Posterior probabilities (%) that Pr(DLT) is in interval:					Quantiles		
Sotrastaurin dose (mg, twice daily)	0-0.16	0.16-0.35	0.35-1	Mean	SDev	2.5%	50%	97.5%
250	0.155	0.682	0.162	0.256	0.095	0.097	0.246	0.464
300	0.098	0.602	0.300	0.297	0.111	0.114	0.287	0.539
350	0.069	0.488	0.443	0.341	0.131	0.121	0.33	0.618

Secondary Outcome Result(s)

- **Best overall radiological response**

Evaluation of preliminary anti-tumor activity (best overall radiological response)

	Number of patients				
	Complete response	**Partial response**	**Stable disease**	**Progressive disease**	**Unknown best overall response**
All dose cohorts	1	4	9	6	11

- **Pharmacokinetics results**

Primary PK parameters for whole blood sotrastaurin by treatment group (Pharmacokinetic Analysis Set)

		Cycle 1 Day 1			Cycle 1 Day 15			
Treatment	**Statistics**	**AUC0-8hr (hr*ng/mL)**	**Cmax (ng/ml)**	**Tmax (hr)**	**AUC0-8hr (hr*ng/mL)**	**Cmax (ng/ml)**	**Tmax (hr)**	**Racc**
Sotrastaurin 200 mg twice daily + everolimus 2.5 mg once daily (N=3)	n	1	1	1	3	3	3	1
	Mean (SDev)	7660	3420	-	14000 (2990)	2570 (278)	-	1.51
	CV% mean	-	-	-	21.3	10.8	-	
	Geo-mean	7660	3420	-	13800	2560	-	1.51
	CV% geo-mean	-	-	-	21.0	10.7	-	
	Median	7660	3420	1.00	13200	2530	1.08	1.51
	[Min; Max]	[7660; 7660]	[3420; 3420]	[1.00; 1.00]	[11500; 17400]	[2320; 2870]	[1.00; 1.93]	[1.51; 1.51]

Treatment	Statistics	Cycle 1 Day 1			Cycle 1 Day 15			
		AUC0-8hr (hr*ng/mL)	Cmax (ng/ml)	Tmax (hr)	AUC0-8hr (hr*ng/mL)	Cmax (ng/ml)	Tmax (hr)	Racc
Sotrastaurin 250 mg twice daily + everolimus 2.5 mg once daily (N=16)	n	14	14	14	12	12	12	10
	Mean (SDev)	14700 (8960)	2830 (1570)	-	21300 (11300)	3820 (1700)	-	1.74 (1.11)
	CV% mean	61.1	55.4	-	53.0	44.4	-	63.9
	Geo-mean	12300	2390	-	18400	3450	-	1.54
	CV% geo-mean	69.8	70.6	-	63.3	52.3	-	49.8
	Median	14000	2970	2.00	19100	3840	2.00	1.41
	[Min; Max]	[3960; 35800]	[718; 5780]	[0.500; 5.98]	[8590; 37200]	[1770; 6280]	[0.500; 4.05]	[1.04; 4.70]
Sotrastaurin 300 mg twice daily + everolimus 2.5 mg once daily (N=6)	n	3	3	3	3	3	3	1
	Mean (SDev)	18900 (4920)	3150 (587)	-	45100 (32000)	6990 (5150)	-	1.26
	CV% mean	26.1	18.6	-	71.0	73.6	-	
	Geo-mean	18500	3110	-	38600	5910	-	1.26
	CV% geo-mean	26.9	19.7	-	74.3	78.2	-	
	Median	18600	3310	3.97	30100	4610	4.05	1.26
	[Min; Max]	[14100; 23900]	[2500; 3640]	[0.967; 4.17]	[23400; 81900]	[3470; 12900]	[2.00; 4.25]	[1.26; 1.26]
Sotrastaurin 400 mg twice daily + everolimus 2.5 mg once daily (N=6)	n	2	2	2	3	3	3	2
	Mean (SDev)	29000 (1870)	7690 (445)	-	34200 (18900)	6280 (3210)	-	1.11 (0.846)
	CV% mean	6.44	5.80	-	55.4	51.1	-	76.4
	Geo-mean	29000	7680	-	29900	5770	-	0.933
	CV% geo-mean	6.45	5.80	-	75.8	52.9	-	104
	Median	29000	7690	0.992	36800	5270	1.00	1.11

Treatment	Statistics	Cycle 1 Day 1			Cycle 1 Day 15			
		AUC0-8hr (hr*ng/mL)	Cmax (ng/ml)	Tmax (hr)	AUC0-8hr (hr*ng/mL)	Cmax (ng/ml)	Tmax (hr)	Racc
	[Min; Max]	[27700; 30300]	[7370; 8000]	[0.983; 1.00]	[14100; 51700]	[3700; 9870]	[0.533; 2.05]	[0.510; 1.71]

n: number of patients with non-missing values.
CV% = coefficient of variation (%) = sd/mean*100, CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.
Racc = AUC0-8hr at Cycle 1, Day 15/AUC0-8hr at Cycle 1, Day 1.

Primary PK parameters for whole blood everolimus by treatment group (Pharmacokinetic Analysis Set)

Treatment	Statistics	Cycle 1 Day 1			Cycle 1 Day 15			
		AUC0-8hr (hr*ng/mL)	Cmax (ng/ml)	Tmax (hr)	AUC0-8hr (hr*ng/mL)	Cmax (ng/ml)	Tmax (hr)	Racc
Sotrastaurin 200 mg twice daily + everolimus 2.5 mg once daily (N=3)	n	1	1	1	3	3	3	1
	Mean (SDev)	40.7	7.62	-	105 (31.8)	18.4 (5.41)	-	2.41
	CV% mean	-	-	-	30.2	29.4	-	
	Geo-mean	40.7	7.621.54	-	102	17	-	2.41
	CV% geo-mean	-	-	-	30.3	31.6	-	
	Median	40.7	7.62	4.00	98.0	18.7	1.93	2.41
	[Min; Max]	[40.7; 40.7]	[7.62; 7.62]	[4.00; 4.00]	[78.0; 140]	[12.8; 23.6]	[1.08; 3.98]	[2.41; 2.41]
Sotrastaurin 250 mg twice daily + everolimus 2.5 mg once daily (N=16)	n	12	12	12	11	11	11	9
	Mean (SDev)	76.1 (32.5)	15.7 (7.27)	-	117 (35.6)	21.1 (7.27)	-	1.62 (0.501)
	CV% mean	42.6	46.2	-	30.5	34.5	-	30.9
	Geo-mean	71.3	14.5	-	112	20.1	-	1.56
	CV% geo-mean	36.7	42.9	-	33.8	32.4	-	28.6
	Median	62.6	12.5	1.54	115	17.5	2.00	1.37

Treatment	Statistics	Cycle 1 Day 1			Cycle 1 Day 15			
		AUC0-8hr (hr*ng/mL)	Cmax (ng/ml)	Tmax (hr)	AUC0-8hr (hr*ng/mL)	Cmax (ng/ml)	Tmax (hr)	Racc
Sotrastaurin 300 mg twice daily + everolimus 2.5 mg once daily (N=6)	[Min; Max]	[51.0; 152]	[8.78; 31.9]	[0.500; 6.00]	[56.6; 181]	[13.7; 37.6]	[0; 4.05]	[1.19; 2.62]
	n	4	4	4	3	3	3	1
	Mean (SDev)	75.1 (47.5)	17.7 (15.5)	-	215 (27.2)	34.1 (6.12)	-	1.64
	CV% mean	63.2	87.8	-	12.6	17.9	-	
	Geo-mean	66.3	13.9	-	214	33.8	-	1.64
	CV% geo-mean	59.1	88.3	-	13.0	17.6	-	
	Median	57.1	11.4	2.48	221	32.5	1.03	1.64
Sotrastaurin 400 mg twice daily + everolimus 2.5 mg once daily (N=6)	[Min; Max]	[41.0; 145]	[7.36; 40.6]	[0.967; 4.17]	[185; 238]	[29.0; 40.9]	[1.00; 4.10]	[1.64; 1.64]
	n	5	5	5	3	3	3	3
	Mean (SD)	66.7 (41.4)	15.0 (12.2)	-	157 (7.21)	27.4 (3.72)	-	3.00 (2.38)
	CV% mean	62.1	80.9	-	4.59	13.6	-	79.2
	Geo-mean	57.2	11.6	-	157	27.3	-	2.44
	CV% geo-mean	69.0	95.6	-	4.66	13.9	-	92.0
	Median	58.9	11.0	2.00	161	27.9	1.00	2.08
	[Min; Max]	[26.1; 132]	[4.57; 34.6]	[0.967; 6.00]	[149; 161]	[23.5; 30.9]	[1.00; 2.05]	[1.22; 5.70]

n: number of patients with non-missing values.
CV% = coefficient of variation (%) = sd/mean*100, CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.
Racc = AUC0-8hr at Cycle 1, Day 15/AUC0-8hr at Cycle 1, Day 1.

Summary of Safety

Safety Results

Dose limiting toxicities occurring during the first cycle by primary system organ class, preferred term and treatment group (Dose determining set)

Primary system organ class Preferred term	Sotrastaurin 200 mg twice daily + everolimus 2.5 mg once daily N=3 n (%)	Sotrastaurin 250 mg twice daily + everolimus 2.5 mg once daily N=14 n (%)	Sotrastaurin 300 mg twice daily + everolimus 2.5 mg once daily N=5 n (%)	Sotrastaurin 400 mg twice daily + everolimus 2.5 mg once daily N=6 n (%)	All patients N=28 n (%)
Any primary system organ class	1 (33.3)	3 (21.4)	1 (20.0)	2 (33.3)	7 (25.0)
Blood and lymphatic system disorders	0	1 (7.1)	0	0	1 (3.6)
Thrombocytopenia	0	1 (7.1)	0	0	1 (3.6)
Gastrointestinal disorders	1 (33.3)	0	0	2 (33.3)	3 (10.7)
Nausea	0	0	0	2 (33.3)	2 (7.1)
Vomiting	0	0	0	2 (33.3)	2 (7.1)
Diarrhoea	0	0	0	1 (16.7)	1 (3.6)
Stomatitis	1 (33.3)	0	0	0	1 (3.6)
Infections and infestations	0	1 (7.1)	0	0	1 (3.6)
Pneumocystis jirovecii pneumonia	0	1 (7.1)	0	0	1 (3.6)
Metabolism and nutrition disorders	0	1 (7.1)	1 (20.0)	0	2 (7.1)
Decreased appetite	0	0	1 (20.0)	0	1 (3.6)
Hypertriglyceridaemia	0	1 (7.1)	0	0	1 (3.6)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency, as reported in the All patients column.
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.

Adverse events, regardless of study treatment relationship by primary system organ class, maximum grade and treatment group (Safety set)

Primary system organ class	Sotrastaurin 200 mg twice daily + everolimus 2.5 mg once daily N=3		Sotrastaurin 250 mg twice daily + everolimus 2.5 mg once daily N=16		Sotrastaurin 300 mg twice daily + everolimus 2.5 mg once daily N=6		Sotrastaurin 400 mg twice daily + everolimus 2.5 mg once daily N=6		All patients N=31	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Any primary system organ class	3 (100)	3 (100)	16 (100)	15 (93.8)	6 (100)	4 (66.7)	6 (100)	6 (100)	31 (100)	28 (90.3)
Gastrointestinal disorders	3 (100)	1 (33.3)	13 (81.3)	0	5 (83.3)	1 (16.7)	6 (100)	1 (16.7)	27 (87.1)	3 (9.7)
Metabolism and nutrition disorders	1 (33.3)	0	9 (56.3)	5 (31.3)	5 (83.3)	3 (50.0)	6 (100)	2 (33.3)	21 (67.7)	10 (32.3)
Blood and lymphatic system disorders	2 (66.7)	2 (66.7)	10 (62.5)	7 (43.8)	3 (50.0)	2 (33.3)	3 (50.0)	1 (16.7)	18 (58.1)	12 (38.7)
General disorders and administration site conditions	1 (33.3)	0	7 (43.8)	1 (6.3)	3 (50.0)	0	4 (66.7)	1 (16.7)	15 (48.4)	2 (6.5)
Respiratory, thoracic and mediastinal disorders	2 (66.7)	1 (33.3)	7 (43.8)	4 (25.0)	2 (33.3)	0	4 (66.7)	3 (50.0)	15 (48.4)	8 (25.8)
Infections and infestations	1 (33.3)	1 (33.3)	6 (37.5)	6 (37.5)	2 (33.3)	1 (16.7)	5 (83.3)	1 (16.7)	14 (45.2)	9 (29.0)
Investigations	1 (33.3)	0	3 (18.8)	2 (12.5)	3 (50.0)	1 (16.7)	4 (66.7)	3 (50.0)	11 (35.5)	6 (19.4)
Renal and urinary disorders	0	0	5 (31.3)	0	1 (16.7)	0	3 (50.0)	1 (16.7)	9 (29.0)	1 (3.2)
Skin and subcutaneous tissue disorders	0	0	4 (25.0)	2 (12.5)	2 (33.3)	0	3 (50.0)	0	9 (29.0)	2 (6.5)
Musculoskeletal and connective tissue disorders	0	0	3 (18.8)	0	4 (66.7)	0	1 (16.7)	0	8 (25.8)	0
Nervous system disorders	1 (33.3)	0	1 (6.3)	0	0	0	2 (33.3)	0	4 (12.9)	0

Primary system organ class	Sotrastaurin 200 mg twice daily + everolimus 2.5 mg once daily N=3		Sotrastaurin 250 mg twice daily + everolimus 2.5 mg once daily N=16		Sotrastaurin 300 mg twice daily + everolimus 2.5 mg once daily N=6		Sotrastaurin 400 mg twice daily + everolimus 2.5 mg once daily N=6		All patients N=31	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Cardiac disorders	0	0	2 (12.5)	2 (12.5)	0	0	0	0	2 (6.5)	2 (6.5)
Eye disorders	0	0	0	0	0	0	2 (33.3)	0	2 (6.5)	0
Injury, poisoning and procedural complications	0	0	1 (6.3)	0	0	0	1 (16.7)	0	2 (6.5)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	2 (12.5)	1 (6.3)	0	0	0	0	2 (6.5)	1 (3.2)
Psychiatric disorders	0	0	1 (6.3)	0	1 (16.7)	0	0	0	2 (6.5)	0
Ear and labyrinth disorders	0	0	1 (6.3)	0	0	0	0	0	1 (3.2)	0
Endocrine disorders	0	0	0	0	1 (16.7)	0	0	0	1 (3.2)	0
Hepatobiliary disorders	0	0	1 (6.3)	0	0	0	0	0	1 (3.2)	0
Reproductive system and breast disorders	0	0	0	0	0	0	1 (16.7)	0	1 (3.2)	0
Vascular disorders	0	0	1 (6.3)	1 (6.3)	0	0	0	0	1 (3.2)	1 (3.2)

Primary system organ classes are sorted in descending frequency of 'All grades' column, as reported in the 'All patients' column.
A patient with multiple adverse events within a primary system organ class is counted only once in the total row.
A patient with multiple severity grades for an AE while on a treatment is only counted under the maximum grade.
Only AEs occurring during treatment or within 30 days of the last study medication are reported.

Adverse events, regardless of study treatment relationship by preferred term, maximum grade and treatment group (> 5%) (Safety set)

	Sotrastaurin 200 mg twice daily + everolimus 2.5 mg once daily		Sotrastaurin 250 mg twice daily + everolimus 2.5 mg once daily		Sotrastaurin 300 mg twice daily + everolimus 2.5 mg once daily		Sotrastaurin 400 mg twice daily + everolimus 2.5 mg once daily		All patients	
	N=3		N=16		N=6		N=6		N=31	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
-Total	3 (100)	3 (100)	16 (100)	15 (93.8)	6 (100)	4 (66.7)	6 (100)	6 (100)	31 (100)	28 (90.3)
Nausea	2 (66.7)	0	9 (56.3)	0	4 (66.7)	0	6 (100)	1 (16.7)	21 (67.7)	1 (3.2)
Decreased appetite	1 (33.3)	0	6 (37.5)	1 (6.3)	4 (66.7)	1 (16.7)	4 (66.7)	1 (16.7)	15 (48.4)	3 (9.7)
Vomiting	0	0	6 (37.5)	0	3 (50.0)	0	6 (100)	1 (16.7)	15 (48.4)	1 (3.2)
Diarrhoea	0	0	3 (18.8)	0	3 (50.0)	0	6 (100)	0	12 (38.7)	0
Anaemia	1 (33.3)	1 (33.3)	6 (37.5)	4 (25.0)	2 (33.3)	1 (16.7)	1 (16.7)	0	10 (32.3)	6 (19.4)
Constipation	1 (33.3)	0	5 (31.3)	0	3 (50.0)	0	1 (16.7)	0	10 (32.3)	0
Thrombocytopenia	1 (33.3)	0	7 (43.8)	6 (37.5)	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	10 (32.3)	8 (25.8)
Fatigue	1 (33.3)	0	2 (12.5)	0	3 (50.0)	0	3 (50.0)	1 (16.7)	9 (29.0)	1 (3.2)
Stomatitis	1 (33.3)	1 (33.3)	3 (18.8)	0	1 (16.7)	1 (16.7)	3 (50.0)	0	8 (25.8)	2 (6.5)
Neutropenia	1 (33.3)	1 (33.3)	3 (18.8)	3 (18.8)	1 (16.7)	1 (16.7)	2 (33.3)	1 (16.7)	7 (22.6)	6 (19.4)
Pyrexia	0	0	6 (37.5)	1 (6.3)	1 (16.7)	0	0	0	7 (22.6)	1 (3.2)
Cough	2 (66.7)	0	2 (12.5)	0	0	0	2 (33.3)	0	6 (19.4)	0
Dyspnoea	1 (33.3)	0	3 (18.8)	1 (6.3)	1 (16.7)	0	1 (16.7)	0	6 (19.4)	1 (3.2)
Hypokalaemia	0	0	4 (25.0)	0	1 (16.7)	0	1 (16.7)	0	6 (19.4)	0
Aspartate aminotransferase increased	0	0	1 (6.3)	0	2 (33.3)	0	2 (33.3)	1 (16.7)	5 (16.1)	1 (3.2)
Alanine aminotransferase increased	0	0	0	0	1 (16.7)	0	3 (50.0)	2 (33.3)	4 (12.9)	2 (6.5)
Hyponatraemia	0	0	1 (6.3)	1 (6.3)	2 (33.3)	1 (16.7)	1 (16.7)	1 (16.7)	4 (12.9)	3 (9.7)
Pulmonary embolism	1 (33.3)	1 (33.3)	2 (12.5)	2 (12.5)	0	0	1 (16.7)	1 (16.7)	4 (12.9)	4 (12.9)

	Sotrastaurin 200 mg twice daily + everolimus 2.5 mg once daily		Sotrastaurin 250 mg twice daily + everolimus 2.5 mg once daily		Sotrastaurin 300 mg twice daily + everolimus 2.5 mg once daily		Sotrastaurin 400 mg twice daily + everolimus 2.5 mg once daily		All patients	
	N=3		N=16		N=6		N=6		N=31	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Rash	0	0	3 (18.8)	1 (6.3)	0	0	1 (16.7)	0	4 (12.9)	1 (3.2)
Abdominal pain	0	0	2 (12.5)	0	1 (16.7)	0	0	0	3 (9.7)	0
Dyspepsia	0	0	1 (6.3)	0	2 (33.3)	0	0	0	3 (9.7)	0
Hyperglycaemia	0	0	2 (12.5)	2 (12.5)	1 (16.7)	0	0	0	3 (9.7)	2 (6.5)
Back pain	0	0	1 (6.3)	0	1 (16.7)	0	1 (16.7)	0	3 (9.7)	0
Chromaturia	0	0	2 (12.5)	0	0	0	1 (16.7)	0	3 (9.7)	0
Oropharyngeal pain	0	0	1 (6.3)	0	1 (16.7)	0	1 (16.7)	0	3 (9.7)	0
Pleural effusion	0	0	2 (12.5)	1 (6.3)	1 (16.7)	0	0	0	3 (9.7)	1 (3.2)
Pruritus	0	0	1 (6.3)	0	1 (16.7)	0	1 (16.7)	0	3 (9.7)	0
Neutrophil count decreased	1 (33.3)	0	0	0	0	0	2 (33.3)	1 (16.7)	3 (9.7)	1 (3.2)
Abdominal discomfort	0	0	1 (6.3)	0	0	0	1 (16.7)	0	2 (6.5)	0
Abdominal pain upper	0	0	1 (6.3)	0	1 (16.7)	0	0	0	2 (6.5)	0
Oedema peripheral	0	0	1 (6.3)	0	0	0	1 (16.7)	0	2 (6.5)	0
Pneumocystis jirovecii pneumonia	0	0	1 (6.3)	1 (6.3)	0	0	1 (16.7)	0	2 (6.5)	1 (3.2)
Pneumonia	0	0	2 (12.5)	2 (12.5)	0	0	0	0	2 (6.5)	2 (6.5)
Sepsis	0	0	2 (12.5)	2 (12.5)	0	0	0	0	2 (6.5)	2 (6.5)
Blood alkaline phosphatase increased	0	0	0	0	2 (33.3)	0	0	0	2 (6.5)	0
Lymphocyte count decreased	1 (33.3)	0	0	0	1 (16.7)	1 (16.7)	0	0	2 (6.5)	1 (3.2)
Platelet count decreased	0	0	0	0	2 (33.3)	1 (16.7)	0	0	2 (6.5)	1 (3.2)

	Sotrastaurin 200 mg twice daily + everolimus 2.5 mg once daily		Sotrastaurin 250 mg twice daily + everolimus 2.5 mg once daily		Sotrastaurin 300 mg twice daily + everolimus 2.5 mg once daily		Sotrastaurin 400 mg twice daily + everolimus 2.5 mg once daily		All patients	
	N=3		N=16		N=6		N=6		N=31	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hyperkalaemia	0	0	1 (6.3)	0	1 (16.7)	0	0	0	2 (6.5)	0
Hypocalcaemia	0	0	0	0	0	0	2 (33.3)	0	2 (6.5)	0
Hypophosphataemia	0	0	0	0	2 (33.3)	2 (33.3)	0	0	2 (6.5)	2 (6.5)
Dizziness	0	0	1 (6.3)	0	0	0	1 (16.7)	0	2 (6.5)	0
Dysgeusia	1 (33.3)	0	0	0	0	0	1 (16.7)	0	2 (6.5)	0
Acute kidney injury	0	0	0	0	1 (16.7)	0	1 (16.7)	1 (16.7)	2 (6.5)	1 (3.2)
Haematuria	0	0	2 (12.5)	0	0	0	0	0	2 (6.5)	0
Insomnia	0	0	1 (6.3)	0	1 (16.7)	0	0	0	2 (6.5)	0
Productive cough	1 (33.3)	0	1 (6.3)	0	0	0	0	0	2 (6.5)	0
Respiratory failure	0	0	1 (6.3)	1 (6.3)	0	0	1 (16.7)	1 (16.7)	2 (6.5)	2 (6.5)
Rash maculo-papular	0	0	0	0	1 (16.7)	0	1 (16.7)	0	2 (6.5)	0

Preferred terms are sorted in descending frequency of all grades column, as reported in the all patients column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple AEs is counted only once in the total row.
A patient with multiple severity grades for an AE while on a treatment is only counted under the maximum grade.
Only terms with a frequency greater than 5% in 'All grades' in 'All patients' column are included.
Only AEs occurring during treatment or within 30 days of the last study medication are reported.

On-treatment deaths, serious adverse events and adverse events leading to study treatment discontinuation

	Sotrastaurin 200 mg twice daily + everolimus 2.5 mg once daily N=3 n (%)	Sotrastaurin 250 mg twice daily + everolimus 2.5 mg once daily N=16 n (%)	Sotrastaurin 300 mg twice daily + everolimus 2.5 mg once daily N=6 n (%)	Sotrastaurin 400 mg twice daily + everolimus 2.5 mg once daily N=6 n (%)	All patients N=31 n (%)
-Death	0	4 (25.0)	1 (16.7)	2 (33.3)	7 (22.6)
-SAE	1 (33.3)	11 (68.8)	3 (50.0)	5 (83.3)	20 (64.5)
-Discontinued due to AE(s)	0	9 (56.3%)	1 (16.7%)	2 (33.3%)	12 (38.7)

Other Relevant Findings

None

Conclusion:

Phase I: The primary objective of the Phase Ib part of this study was to determine the MTD/RP2D of sotrastaurin and everolimus combination therapy in CD79 mutant or ABC subtype DLBCL. Based on the adaptive BLRM design with overdose control and available safety and tolerability information, 400 mg sotrastaurin twice daily plus 2.5 mg everolimus once daily was determined to be the MTD.

Six patients were treated with the combination of 400 mg sotrastaurin twice daily plus 2.5 mg everolimus once daily which satisfied the overdose criterion of which the posterior probability of targeted toxicity exceeded 50% and was the highest among potential doses. Based on available safety and PK data for this treatment cohort, lower dose cohorts (200 mg, 250 mg, and 300 mg sotrastaurin plus 2.5 mg everolimus) were also explored.

The combination of sotrastaurin at various doses twice daily with 2.5 mg everolimus once daily was unfortunately, generally not well tolerated. Most patients experienced at least one AE, regardless of causality, with the most common AEs being gastrointestinal-related. The type of AEs observed in this study are consistent with the known safety profiles of sotrastaurin and everolimus when dosed as monotherapies, however the severity of AEs experienced may have been more than expected when dosed in combination. As of the final CSR, there were no serious safety concerns associated with the combination that led to the decision to not continue the study into Phase II expansion, rather the decision was based on a synthesis of available data taking into account the advanced nature of the disease in this patient population, sub-optimal tolerability of the combination and availability of other agents already approved for this indication.

Phase II: The Phase II part (dose expansion) was not initiated and conducted.

Date of Clinical Trial Report

Final report: 09-Dec-2016

Interim report: 17-Mar-2016