Clinical trial results:
A Phase 1b/2 Double-Blind Randomized Trial of the Hedgehog/SMO Antagonist LY2940680 in Combination with Carboplatin and Etoposide Followed by LY2940680 versus Carboplatin and Etoposide Plus Placebo Followed by Placebo in Patients with Extensive-Stage Small Cell Lung Cancer

Summary

EudraCT number	2012-003174-83
Trial protocol	GB BE
Global end of trial date	19 February 2015

Results information

Result version number	v1 (current)
This version publication date	01 November 2018
First version publication date	01 November 2018

Trial information

Trial identification

Sponsor protocol code	I4J-MC-HHBE

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01722292
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 14631

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly, 1 877CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly, 1 8772854559,
Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 8772854559,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
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	19 February 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 February 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to find a recommended dose of LY2940680 that can be safely given in combination with etoposide and carboplatin followed by LY2940680 alone in participants with extensive-disease small cell lung cancer. The study will also compare progression-free survival in participants who are administered etoposide, carboplatin and LY2940680 followed by LY2940680 alone versus etoposide, carboplatin, and placebo followed by placebo alone.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 January 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 20
Country: Number of subjects enrolled	United Kingdom: 6
Worldwide total number of subjects	26
EEA total number of subjects	6

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
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)	15
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Due to strategic reasons, the Phase 2 portion was not initiated, and further clinical development was stopped. Phase 1b study completer was defined as completion of the dose-limiting toxicity (DLT) period (1 cycle- 21 days cycle for LY2940680 in combination with carboplatin and etoposide.

Pre-assignment

Screening details:

No Text Entered

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1b: 100 mg LY2940680 + C + E

Arm description:

100 milligrams (mg) LY2940680 administered orally once daily (QD) for 6 cycles.
100 mg per square meter (mg/m^2) etoposide (E) administered by intravenous (IV) infusion on days 1, 2, 3 of each cycle.
Area under the Curve (AUC) 5 milligrams*minute*milliliters (mg•min/mL) carboplatin (C) administered by IV infusion on day 1 each cycle.
Maintenance:
Single-agent LY2940680 administered orally QD at the same dose as induction at Cycles 7+ (21 day cycles). Participants receiving benefit may continue until disease progression, unacceptable toxicity, or discontinuation.

Arm type	Experimental
Investigational medicinal product name	LY2940680
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

100 milligrams (mg) LY2940680 administered orally once daily (QD) for 6 cycles.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

100 mg per square meter (mg/m^2) etoposide (E) administered by intravenous (IV) infusion on days 1, 2, 3 of each cycle.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Area under the Curve (AUC) 5 milligrams*minute*milliliters (mg•min/mL) carboplatin (C) administered by IV infusion on day 1 each cycle.

Arm title	Phase 1b: 200 mg LY2940680 + C + E

Arm description:

200 mg LY2940680 administered orally once daily (QD) for 6 cycles.
100 mg per square meter (mg/m^2) etoposide (E) administered by intravenous (IV) infusion on days 1, 2, 3 of each cycle.
Area under the Curve (AUC) 5 milligrams*minute*milliliters (mg•min/mL) carboplatin (C) administered by IV infusion on day 1 each cycle.
Maintenance:
Single-agent LY2940680 administered orally QD at the same dose as induction at Cycles 7+ (21 day cycles). Participants receiving benefit may continue until disease progression, unacceptable toxicity, or discontinuation.

Arm type	Experimental
Investigational medicinal product name	LY2940680
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

200 mg LY2940680 administered orally once daily (QD) for 6 cycles.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

100 mg per square meter (mg/m^2) etoposide (E) administered by intravenous (IV) infusion on days 1, 2, 3 of each cycle.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Area under the Curve (AUC) 5 milligrams*minute*milliliters (mg•min/mL) carboplatin (C) administered by IV infusion on day 1 each cycle.
Maintenance:

Arm title	Phase 1b: 400 mg LY2940680 + C + E

Arm description:

400 mg LY2940680 administered orally once daily (QD) for 6 cycles.
100 mg per square meter (mg/m^2) etoposide (E) administered by intravenous (IV) infusion on days 1, 2, 3 of each cycle.
Area under the Curve (AUC) 5 milligrams*minute*milliliters (mg•min/mL) carboplatin (C) administered by IV infusion on day 1 each cycle.
Maintenance:
Single-agent LY2940680 administered orally QD at the same dose as induction at Cycles 7+ (21 day cycles). Participants receiving benefit may continue until disease progression, unacceptable toxicity, or discontinuation.

Arm type	Experimental
Investigational medicinal product name	LY2940680
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

400 mg LY2940680 administered orally once daily (QD) for 6 cycles.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

100 mg per square meter (mg/m^2) etoposide (E) administered by intravenous (IV) infusion on days 1, 2, 3 of each cycle.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Area under the Curve (AUC) 5 milligrams*minute*milliliters (mg•min/mL) carboplatin (C) administered by IV infusion on day 1 each cycle.

Number of subjects in period 1	Phase 1b: 100 mg LY2940680 + C + E	Phase 1b: 200 mg LY2940680 + C + E	Phase 1b: 400 mg LY2940680 + C + E
Started	6	6	14
Received at Least One Dose of Study	6	6	14
Completed	6	6	14

Baseline characteristics

Reporting groups	
Reporting group title	Phase 1b: 100 mg LY2940680 + C + E
Reporting group description:	
100 milligrams (mg) LY2940680 administered orally once daily (QD) for 6 cycles. 100 mg per square meter (mg/m^2) etoposide (E) administered by intravenous (IV) infusion on days 1, 2, 3 of each cycle. Area under the Curve (AUC) 5 milligrams*minute*milliliters (mg•min/mL) carboplatin (C) administered by IV infusion on day 1 each cycle. Maintenance: Single-agent LY2940680 administered orally QD at the same dose as induction at Cycles 7+ (21 day cycles). Participants receiving benefit may continue until disease progression, unacceptable toxicity, or discontinuation.	
Reporting group title	Phase 1b: 200 mg LY2940680 + C + E
Reporting group description:	
200 mg LY2940680 administered orally once daily (QD) for 6 cycles. 100 mg per square meter (mg/m^2) etoposide (E) administered by intravenous (IV) infusion on days 1, 2, 3 of each cycle. Area under the Curve (AUC) 5 milligrams*minute*milliliters (mg•min/mL) carboplatin (C) administered by IV infusion on day 1 each cycle. Maintenance: Single-agent LY2940680 administered orally QD at the same dose as induction at Cycles 7+ (21 day cycles). Participants receiving benefit may continue until disease progression, unacceptable toxicity, or discontinuation.	
Reporting group title	Phase 1b: 400 mg LY2940680 + C + E
Reporting group description:	
400 mg LY2940680 administered orally once daily (QD) for 6 cycles. 100 mg per square meter (mg/m^2) etoposide (E) administered by intravenous (IV) infusion on days 1, 2, 3 of each cycle. Area under the Curve (AUC) 5 milligrams*minute*milliliters (mg•min/mL) carboplatin (C) administered by IV infusion on day 1 each cycle. Maintenance: Single-agent LY2940680 administered orally QD at the same dose as induction at Cycles 7+ (21 day cycles). Participants receiving benefit may continue until disease progression, unacceptable toxicity, or discontinuation.	

Reporting group values	Phase 1b: 100 mg LY2940680 + C + E	Phase 1b: 200 mg LY2940680 + C + E	Phase 1b: 400 mg LY2940680 + C + E
Number of subjects	6	6	14
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	64.3	64.8	60.2
standard deviation	± 9.35	± 11.96	± 12.19

Gender categorical Units: Subjects			
Female	3	3	7
Male	3	3	7
Race Units: Subjects			
Black or African American	0	2	1
White	6	3	13
Unknown or Not Reported	0	1	0
Ethnicity Units: Subjects			
Hispanic or Latino	0	1	0
Not Hispanic or Latino	6	5	14
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			
United States	5	5	10
United Kingdom	1	1	4

Reporting group values	Total		
Number of subjects	26		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	13		
Male	13		
Race Units: Subjects			
Black or African American	3		
White	22		
Unknown or Not Reported	1		
Ethnicity Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	25		
Unknown or Not Reported	0		

Region of Enrollment Units: Subjects			
United States	20		
United Kingdom	6		

End points

End points reporting groups

Reporting group title	Phase 1b: 100 mg LY2940680 + C + E

Reporting group description:

100 milligrams (mg) LY2940680 administered orally once daily (QD) for 6 cycles.
100 mg per square meter (mg/m^2) etoposide (E) administered by intravenous (IV) infusion on days 1, 2, 3 of each cycle.
Area under the Curve (AUC) 5 milligrams*minute*milliliters (mg•min/mL) carboplatin (C) administered by IV infusion on day 1 each cycle.
Maintenance:
Single-agent LY2940680 administered orally QD at the same dose as induction at Cycles 7+ (21 day cycles). Participants receiving benefit may continue until disease progression, unacceptable toxicity, or discontinuation.

Reporting group title	Phase 1b: 200 mg LY2940680 + C + E

Reporting group description:

200 mg LY2940680 administered orally once daily (QD) for 6 cycles.
100 mg per square meter (mg/m^2) etoposide (E) administered by intravenous (IV) infusion on days 1, 2, 3 of each cycle.
Area under the Curve (AUC) 5 milligrams*minute*milliliters (mg•min/mL) carboplatin (C) administered by IV infusion on day 1 each cycle.
Maintenance:
Single-agent LY2940680 administered orally QD at the same dose as induction at Cycles 7+ (21 day cycles). Participants receiving benefit may continue until disease progression, unacceptable toxicity, or discontinuation.

Reporting group title	Phase 1b: 400 mg LY2940680 + C + E

Reporting group description:

400 mg LY2940680 administered orally once daily (QD) for 6 cycles.
100 mg per square meter (mg/m^2) etoposide (E) administered by intravenous (IV) infusion on days 1, 2, 3 of each cycle.
Area under the Curve (AUC) 5 milligrams*minute*milliliters (mg•min/mL) carboplatin (C) administered by IV infusion on day 1 each cycle.
Maintenance:
Single-agent LY2940680 administered orally QD at the same dose as induction at Cycles 7+ (21 day cycles). Participants receiving benefit may continue until disease progression, unacceptable toxicity, or discontinuation.

Subject analysis set title	Phase 1b
Subject analysis set type	Safety analysis

Subject analysis set description:

Cohort 1:

100 milligrams (mg) LY2940680 administered orally once daily (QD) for 6 cycles. 100 mg per square meter (mg/m^2) etoposide (E) administered by intravenous (IV) infusion on days 1, 2, 3 of each cycle.

Area under the Curve [AUC] 5 (mg•min/mL) carboplatin (C) administered by IV infusion on day 1 each cycle.

Cohort 2:

200 milligrams (mg) LY2940680 administered orally once daily (QD) for 6 cycles. 100 mg per square meter (mg/m^2) etoposide (E) administered by intravenous (IV) infusion on days 1, 2, 3 of each cycle.

Area under the Curve [AUC] 5 (mg•min/mL) carboplatin (C) administered by IV infusion on day 1 each cycle.

Cohort 3:

400 milligrams (mg) LY2940680 administered orally once daily (QD) for 6 cycles. 100 mg per square meter (mg/m^2) etoposide (E) administered by intravenous (IV) infusion on days 1, 2, 3 of each cycle.

Area under the Curve [AUC] 5 (mg•min/mL) carboplatin (C) administered by IV infusion on day 1 each cycle.

Subject analysis set title	Phase 2: 400 mg LY2940680 + C+ E

Subject analysis set type	Intention-to-treat

Subject analysis set description:

400 mg LY2940680 administered orally QD cycles 1-6 (21 day cycle).

(AUC) 5 carboplatin (C) administered by IV infusion on day 1 each cycle.

100 mg/m² etoposide (E) administered by IV infusion on days 1, 2, 3 of each cycle, followed by a single agent of LY2940680.

26 participants completed Phase 1 and zero participants analyzed for phase 2.
Due to strategic reasons, the Phase 2 portion was not initiated, and further clinical development was stopped.

Subject analysis set title	Phase 2: Placebo + C + E
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Placebo administered orally QD for 6 cycles.

(AUC) 5 carboplatin administered by IV infusion on day 1 of each cycle.

100 mg/m² etoposide administered by IV infusion on days 1, 2, 3 of each cycle.

26 participants completed Phase 1 and zero participants analyzed for phase 2.
Due to strategic reasons, the Phase 2 portion was not initiated, and further clinical development was stopped.

Primary: Phase 1b: Recommended Phase 2 Dose of LY2940680: Maximum Tolerated Dose (MTD)

End point title	Phase 1b: Recommended Phase 2 Dose of LY2940680: Maximum Tolerated Dose (MTD)[1]

End point description:

MTD was defined as the highest tested dose that has<33% probability of causing a dose-limiting toxicity(DLT).DLT was defined as an AE during Cycle 1 that is possibly related to the study drug and fulfills any one of the following criterion using the National Cancer Institute(NCI) Common Terminology Criteria for Adverse Events(CTCAE),version 4.0:Grade 3 non-hematological toxicity except nausea, vomiting, constipation, diarrhea, fatigue, or anorexia that is manageable with appropriate care,transient(i.e., ≤5 days) Grade 3 elevations of alanine aminotransferase(ALT) and/or aspartate aminotransferase(AST), without evidence of other hepatic injury, in the setting of preexisting hepatic metastasis,≥Grade 3 thrombocytopenia with bleeding or Grade 4 thrombocytopenia of any duration,CTCAE Grade 4 hematological toxicity of >5 days duration and any febrile neutropenia or any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be

End point type	Primary

End point timeframe:

Timeframe: Baseline to Completion of the Phase 1b (Up To 12 Months)
Analysis Population Description (APD) - All participants who received at least one dose of study drug and were enrolled in Phase1b of the study.

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: No arm comparison analyses were planned or conducted.

End point values	Phase 1b			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: milligrams (mg)				
number (not applicable)	400			

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Progression-Free Survival

End point title	Phase 2: Progression-Free Survival[2]

End point description:

Zero participants analyzed. Due to strategic reasons, the Phase 2 portion was not initiated, and further clinical development was stopped.

End point type	Primary

End point timeframe:

Randomization to Measured Progressive Disease or Death of Any Cause (Estimated as 18 Months)

Notes:

[2] - 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: Zero participants analyzed. Due to strategic reasons, the Phase 2 portion was not initiated, and further clinical development was stopped.

End point values	Phase 2: 400 mg LY2940680 + C+ E	Phase 2: Placebo + C + E		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[3]	0[4]		
Units: months				
number (confidence interval 95%)	(to)	(to)		

Notes:

[3] - 26 participants completed Phase 1b. Phase 2 portion was not initiated.

[4] - 26 participants completed Phase 1b. Phase 2 portion was not initiated.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and 2: Pharmacokinetics (PK): Maximum Concentration (Cmax) of LY2940680, LSN3185556, Carboplatin, and Etoposide at the Recommended Dose

End point title	Phase 1b and 2: Pharmacokinetics (PK): Maximum Concentration (Cmax) of LY2940680, LSN3185556, Carboplatin, and Etoposide at the Recommended Dose

End point description:

APD: All participants who received at least one dose of study drug and were enrolled in Phase 1b study. Due to strategic reasons, the Phase 2 portion was not initiated, and further clinical development was stopped.

9999=Not Applicable (NA). Carboplatin and Etoposide are given as fixed dose whatever cohort the participants are for the LY2940680 dose. PK analysis results were grouped together in the Phase 1b: 200 mg LY2940680 + C + E arm.

End point type	Secondary

End point timeframe:

Cycle(C)1 Day(D)1:Predose(Pr),0.5 hour(h),1h,2h,4h,6h,8h;C1 D2: Pr,0.5h;C1 D3,Pr,0.5h;C2 D1:Pr,0.5h,1h,2h,4h,6h,8h;C2 D2:Pr,0.5h;C2 D3:Pr,0.5h;C6 D1:Pr;C7 D1: Pr,0.5h,1h,2h,4h,6h,8h;C7

End point values	Phase 1b: 100 mg LY2940680 + C + E	Phase 1b: 200 mg LY2940680 + C + E	Phase 1b: 400 mg LY2940680 + C + E	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	14	
Units: microgram per milliliter (µg/mL)				
geometric mean (geometric coefficient of variation)				
LY2940680 Cycle 1, Day 1	0.491 (± 64)	1.01 (± 36)	1.56 (± 35)	
LY2940680 Cycle 2, Day 1	0.578 (± 71)	1.16 (± 66)	3.29 (± 33)	
LSN3185556 Cycle 1, Day 1	0.444 (± 33)	0.737 (± 138)	1.75 (± 47)	
LSN3185556 Cycle 2, Day 1	1.6 (± 35)	2.1 (± 90)	6 (± 59)	
Total Carboplatin Cycle 1, Day 1	9999 (± 9999)	16.7 (± 33)	9999 (± 9999)	
Total Carboplatin Cycle 2, Day 1	9999 (± 9999)	13.1 (± 42)	9999 (± 9999)	
Etoposide Cycle 1, Day 1	9999 (± 9999)	20.9 (± 18)	9999 (± 9999)	
Etoposide Cycle 2, Day 1	9999 (± 9999)	18.4 (± 28)	9999 (± 9999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and 2: Pharmacokinetics: Area Under the Curve (AUC-) for LY2940680, LSN3185556 and Etoposide and as AUC- for Carboplatin at the Recommended Dose

End point title	Phase 1b and 2: Pharmacokinetics: Area Under the Curve (AUC-) for LY2940680, LSN3185556 and Etoposide and as AUC- for Carboplatin at the Recommended Dose

End point description:

APD: Carboplatin and Etoposide are given as fixed dose whatever cohort the participants are for the LY2940680 dose. PK analysis results were grouped together in the Phase 1b: 200 mg LY2940680 + C + E arm.

9999=Not Applicable (NA). Carboplatin and Etoposide are given as fixed dose whatever cohort the participants are for the LY2940680 dose. PK analysis results were grouped together in the Phase 1b: 200 mg LY2940680 + C + E arm.

End point type	Secondary

End point timeframe:

C1 D1:Pr,0.5 h,1h,2h,4h,6h,8h;C1 D2: Pr,0.5h;C1 D3:Pr,0.5h;C2 D1:Pr,0.5h,1h,2h,4h,6h,8h;C2 D2:Pr,0.5h;C2 D3:Pr,0.5h;C6 D1:Pr;C7 D1: Pr,0.5h,1h,2h,4h,6h,8h;C7 D2: Pr

End point values	Phase 1b: 100 mg LY2940680 + C + E	Phase 1b: 200 mg LY2940680 + C + E	Phase 1b: 400 mg LY2940680 + C + E	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	14	
Units: Hour*microgram per milliliter (h.µg/mL)				
geometric mean (geometric coefficient of variation)				
LY2940680 Cycle 1, Day 1	6.34 (± 57)	8.96 (± 39)	15.9 (± 27)	
LY2940680 Cycle 2, Day 1	7.86 (± 67)	15.5 (± 64)	37.6 (± 43)	
LSN3185556 Cycle 1, Day 1	7.23 (± 49)	16.2 (± 67)	26 (± 37)	
LSN3185556 Cycle 2, Day 1	22.7 (± 58)	31.1 (± 111)	92.5 (± 72)	
Total Carboplatin Cycle 1, Day 1	9999 (± 9999)	37.2 (± 23)	9999 (± 9999)	
Total Carboplatin Cycle 2, Day 1	9999 (± 9999)	32.0 (± 25)	9999 (± 9999)	
Etoposide Cycle 1, Day 1	9999 (± 9999)	104 (± 22)	9999 (± 9999)	
Etoposide Cycle 2, Day 1	9999 (± 9999)	96.1 (± 20)	9999 (± 9999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Percentage of Participants With Complete Response (CR) or Partial Response (PR) (Overall Response Rate [ORR])

End point title	Phase 1b: Percentage of Participants With Complete Response (CR) or Partial Response (PR) (Overall Response Rate [ORR])

End point description:

ORR was defined as the percentage of all randomized participants with the best overall response of PR or CR using Response Evaluation Criteria in Solid Tumors (RECIST v1.1). CR is the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Tumor marker results must have normalized. PR is at least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters.

APD: All participants who received at least one dose of drug.

End point type	Secondary

End point timeframe:

Baseline to Study Completion Up to 39 Months

End point values	Phase 1b: 100 mg LY2940680 + C + E	Phase 1b: 200 mg LY2940680 + C + E	Phase 1b: 400 mg LY2940680 + C + E	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	14	
Units: Percentage of participnats				
arithmetic mean (confidence interval	50 (16.4 to	50 (16.4 to	57.1 (35.4 to	

90%)	83.6)	83.6)	78.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Percentage Inhibition of Expression Levels of Gli1 in Skin Cells

End point title	Phase 1b: Percentage Inhibition of Expression Levels of Gli1 in Skin Cells

End point description:

The gene expression data (Gli1) was normalized and the level of percentage of Gli1 inhibition post treatment was calculated.

APD: All participants who received at least one dose of drug and had samples available.

End point type	Secondary

End point timeframe:

Baseline, Cycle 2 Day 1, Cycle 7 Day 1

End point values	Phase 1b: 100 mg LY2940680 + C + E	Phase 1b: 200 mg LY2940680 + C + E	Phase 1b: 400 mg LY2940680 + C + E	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	12	
Units: Percentage of Gli 1 Inhibition				
median (inter-quartile range (Q1-Q3))	94.7 (75.9 to 94.9)	95.1 (94.5 to 97.2)	94.8 (90.7 to 97.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Overall Survival

End point title	Phase 2: Overall Survival

End point description:

APD: Zero participants analyzed. Due to strategic reasons, the Phase 2 portion was not initiated, and further clinical development was stopped.

End point type	Secondary

End point timeframe:

Randomization to Study Completion (Estimated as 38 Months)

End point values	Phase 2: 400 mg LY2940680 + C+ E	Phase 2: Placebo + C + E		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[5]	0[6]		
Units: months				
number (confidence interval 95%)	(to)	(to)		

Notes:

[5] - 26 participants completed Phase 1b. Phase 2 portion was not initiated.

[6] - 26 participants completed Phase 1b. Phase 2 portion was not initiated.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Percent Change in Tumor Size (CTS)

End point title	Phase 2: Percent Change in Tumor Size (CTS)

End point description:

APD: Zero participants analyzed. Due to strategic reasons, the Phase 2 portion was not initiated, and further clinical development was stopped.

End point type	Secondary

End point timeframe:

Randomization to End of Cycle 2 (Estimated as 24 Months)

End point values	Phase 2: 400 mg LY2940680 + C+ E	Phase 2: Placebo + C + E		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[7]	0[8]		
Units: Percent Tumor change				
number (not applicable)				

Notes:

[7] - 26 participants completed Phase 1b. Phase 2 portion was not initiated.

[8] - 26 participants completed Phase 1b. Phase 2 portion was not initiated.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Number of Participants With a Complete or Partial Tumor Response (Overall Response Rate)

End point title	Phase 2: Number of Participants With a Complete or Partial Tumor Response (Overall Response Rate)

End point description:

APD: Zero participants analyzed. Due to strategic reasons, the Phase 2 portion was not initiated, and further clinical development was stopped.

End point type	Secondary

End point timeframe:

Randomization to Study Completion (Estimated as 38 Months)

End point values	Phase 2: 400 mg LY2940680 + C+ E	Phase 2: Placebo + C + E		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[9]	0[10]		
Units: Participants				
number (not applicable)				

Notes:

[9] - 26 participants completed Phase 1b. Phase 2 portion was not initiated.

[10] - 26 participants completed Phase 1b. Phase 2 portion was not initiated.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and 2: Pharmacokinetics: Time to Maximal Concentration (Tmax) of LY2940680, LSN3185556, Carboplatin, and Etoposide at the Recommended Dose

End point title	Phase 1b and 2: Pharmacokinetics: Time to Maximal Concentration (Tmax) of LY2940680, LSN3185556, Carboplatin, and Etoposide at the Recommended Dose

End point description:

APD: All participants who received at least one dose of study drug and were enrolled in phase 1b study. Due to strategic reasons, the Phase 2 portion was not initiated, and further clinical development was stopped.

9999=Not Applicable (NA). Carboplatin and Etoposide are given as fixed dose whatever cohort the participants are for the LY2940680 dose. PK analysis results were grouped together in the Phase 1b: 200 mg LY2940680 + C + E arm.

End point type	Secondary

End point timeframe:

C1 D1: Pr,0.5h,1h,2h,4h,6h,8h;C1 D2: Pr,0.5h;C1 D3:Pr,0.5h;C2 D1:Pr,0.5h,1h,2h,4h,6h,8h;C2 D2:Pr,0.5h;C2 D3:Pr,0.5h;C6 D1:Pr;C7 D1: Pr,0.5h,1h,2h,4h,6h,8h;C7 D2: Pr

End point values	Phase 1b: 100 mg LY2940680 + C + E	Phase 1b: 200 mg LY2940680 + C + E	Phase 1b: 400 mg LY2940680 + C + E	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	14	
Units: Hour (h)				
median (full range (min-max))				
LY2940680 Cycle 1, Day 1	2.05 (1 to 3.98)	2.01 (1.03 to 2.05)	1.51 (0.5 to 6)	
LY2940680 Cycle 2, Day 1	2.96 (0.08 to 5.83)	4 (1.88 to 4.08)	1 (0.5 to 6)	
LSN3185556 Cycle 1, Day 2	6.14 (2 to 24.03)	5.87 (2.07 to 24.97)	6 (2.05 to 24)	

LSN3185556 Cycle 2, Day 2	2.3 (0 to 4)	4.08 (4 to 23.83)	2.21 (0.5 to 6)	
Total Carboplatin Cycle 1, Day 1	9999 (9999 to 9999)	0.5 (0.42 to 1.08)	9999 (9999 to 9999)	
Total Carboplatin Cycle 2, Day 1	9999 (9999 to 9999)	0.5 (0.42 to 1.05)	9999 (9999 to 9999)	
Etoposide Cycle 1, Day 1	9999 (9999 to 9999)	0.96 (0.48 to 1.5)	9999 (9999 to 9999)	
Etoposide Cycle 2 ,Day 1	9999 (9999 to 9999)	0.99 (0.33 to 1.17)	9999 (9999 to 9999)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Phase 1b

Adverse event reporting additional description:

I4J-MC-HHBE

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Phase 1b: 100 mg LY2940680 + C + E

Reporting group description:

100 mg LY2940680 administered orally once daily (QD) for 6 cycles. 100 mg per square meter (mg/m^2) etoposide (E) administered by intravenous (IV) infusion on days 1, 2, 3 of each cycle.

Area under the Curve [AUC] 5 (mg•min/mL) carboplatin (C) administered by IV infusion on day 1 each cycle.

Reporting group title	Phase 1b: 200 mg LY2940680 + C + E

Reporting group description:

200 mg LY2940680 administered orally once daily (QD) for 6 cycles. 100 mg per square meter (mg/m^2) etoposide (E) administered by intravenous (IV) infusion on days 1, 2, 3 of each cycle.

Area under the Curve [AUC] 5 (mg•min/mL) carboplatin (C) administered by IV infusion on day 1 each cycle.

Reporting group title	Phase 1b: 400 mg LY2940680 + C + E

Reporting group description:

400 mg LY2940680 administered orally once daily (QD) for 6 cycles. 100 mg per square meter (mg/m^2) etoposide (E) administered by intravenous (IV) infusion on days 1, 2, 3 of each cycle.

Area under the Curve [AUC] 5 (mg•min/mL) carboplatin (C) administered by IV infusion on day 1 each cycle.

Serious adverse events	Phase 1b: 100 mg LY2940680 + C + E	Phase 1b: 200 mg LY2940680 + C + E	Phase 1b: 400 mg LY2940680 + C + E
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	6 / 6 (100.00%)	8 / 14 (57.14%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
malignant neoplasm progression			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 14 (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

Investigations			
neutrophil count decreased			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
hypovolaemic shock			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
acute myocardial infarction			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ventricular extrasystoles			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (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
Nervous system disorders			
cerebral haemorrhage			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
headache			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

nervous system disorder			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (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			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (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
febrile neutropenia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
neutropenia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
thrombocytopenia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 14 (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
General disorders and administration site conditions			
systemic inflammatory response syndrome			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

diarrhoea			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
enterocolitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
nausea			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (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
pancreatitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (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
vomiting			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
acute respiratory failure			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
acute kidney injury			

alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (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
Infections and infestations			
pneumonia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	3 / 14 (21.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
respiratory tract infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
dehydration			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (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

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

Non-serious adverse events	Phase 1b: 100 mg LY2940680 + C + E	Phase 1b: 200 mg LY2940680 + C + E	Phase 1b: 400 mg LY2940680 + C + E
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	6 / 6 (100.00%)	14 / 14 (100.00%)
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
hypotension			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
orthostatic hypotension			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	1 / 14 (7.14%)
occurrences (all)	1	2	1
catheter site pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
fatigue			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	4 / 6 (66.67%)	3 / 6 (50.00%)	11 / 14 (78.57%)
occurrences (all)	4	3	15
gait disturbance			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
influenza like illness			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
non-cardiac chest pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
oedema peripheral			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	1 / 6 (16.67%)	4 / 6 (66.67%)	2 / 14 (14.29%)
occurrences (all)	1	4	2
pyrexia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Immune system disorders			
seasonal allergy			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Reproductive system and breast disorders			
vaginal haemorrhage			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed[1]	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
dyspnoea			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	3 / 14 (21.43%)
occurrences (all)	2	1	3
haemoptysis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
hiccups			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
pleural effusion			
alternative dictionary used:			

MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
productive cough			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
respiratory failure			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
agitation			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
anxiety			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
depression			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
insomnia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
blood creatinine increased			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 14 (7.14%)
occurrences (all)	0	2	2
blood potassium decreased			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
creatinine renal clearance decreased			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
lipase increased			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
platelet count decreased			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
weight decreased			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	6 / 14 (42.86%)
occurrences (all)	0	2	7
white blood cell count decreased			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
fall			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
post procedural inflammation			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
sunburn			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
tooth fracture			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
wound			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
angina pectoris			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
tachycardia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
aphasia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
cognitive disorder			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
dizziness			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	3 / 14 (21.43%)
occurrences (all)	1	1	4
dizziness postural			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
dysgeusia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	4 / 6 (66.67%)	4 / 6 (66.67%)	8 / 14 (57.14%)
occurrences (all)	4	4	9
dyskinesia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
head discomfort			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
neuropathy peripheral			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
paraesthesia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	2
peripheral sensory neuropathy			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	1	1	0

somnolence			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
syncope			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
transient ischaemic attack			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
tremor			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 6 (33.33%)	3 / 6 (50.00%)	8 / 14 (57.14%)
occurrences (all)	3	5	12
febrile neutropenia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
neutropenia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	5 / 6 (83.33%)	5 / 6 (83.33%)	7 / 14 (50.00%)
occurrences (all)	9	8	13
thrombocytopenia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	3 / 6 (50.00%)	3 / 6 (50.00%)	8 / 14 (57.14%)
occurrences (all)	6	3	14
thrombocytosis			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
ear pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
diplopia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
eyelid ptosis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
visual acuity reduced			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
visual impairment			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
abdominal discomfort			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
abdominal pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	2 / 14 (14.29%)
occurrences (all)	0	2	2
abdominal pain upper			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
constipation			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	4 / 6 (66.67%)	1 / 6 (16.67%)	8 / 14 (57.14%)
occurrences (all)	4	1	10
diarrhoea			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	6 / 14 (42.86%)
occurrences (all)	1	1	11
dyspepsia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	2
haematemesis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
intestinal ischaemia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
mouth ulceration			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
nausea			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 6 (33.33%)	4 / 6 (66.67%)	10 / 14 (71.43%)
occurrences (all)	2	5	13
paraesthesia oral			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0

rectal haemorrhage			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
stomatitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	2 / 14 (14.29%)
occurrences (all)	0	3	2
vomiting			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 6 (33.33%)	4 / 6 (66.67%)	5 / 14 (35.71%)
occurrences (all)	5	6	9
Skin and subcutaneous tissue disorders			
alopecia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	3 / 6 (50.00%)	2 / 6 (33.33%)	7 / 14 (50.00%)
occurrences (all)	3	2	7
cold sweat			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
dry skin			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	3 / 14 (21.43%)
occurrences (all)	0	1	3
ecchymosis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
hyperhidrosis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
night sweats			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
petechiae			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
skin discolouration			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
skin plaque			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
dysuria			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
haematuria			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 14 (7.14%)
occurrences (all)	0	2	1
back pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
bone pain			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
muscle spasms			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	4 / 6 (66.67%)	2 / 6 (33.33%)	6 / 14 (42.86%)
occurrences (all)	5	3	7
muscular weakness			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	2 / 14 (14.29%)
occurrences (all)	1	0	2
musculoskeletal chest pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
musculoskeletal pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
myalgia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
neck pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
pain in extremity			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Infections and infestations			
cellulitis			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
escherichia urinary tract infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
folliculitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
furuncle			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
gastrointestinal viral infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
lower respiratory tract infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
oral candidiasis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
pneumonia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
rash pustular			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0

skin infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
tinea cruris			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
upper respiratory tract infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
urinary tract infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
urinary tract infection bacterial			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
viral infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	3 / 6 (50.00%)	3 / 6 (50.00%)	6 / 14 (42.86%)
occurrences (all)	3	3	7
dehydration			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	2	3	0
failure to thrive			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
hypercalcaemia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
hypokalaemia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	3 / 14 (21.43%)
occurrences (all)	1	1	3
hypomagnesaemia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	2 / 14 (14.29%)
occurrences (all)	3	1	2
hyponatraemia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
hypophagia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
hypophosphataemia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 14 (7.14%)
occurrences (all)	0	1	1

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 May 2013	Amendment b : - The restriction for use of colony-stimulating factors (CSFs) during Cycle 1 was changed to allow use according to ASCO guidelines based on investigator feedback regarding clinical practice for carboplatin and etoposide therapy . - Changes were made to the dose reduction tables based on investigator feedback regarding clinical practice for carboplatin and etoposide therapy. - Wording was added regarding the use of 2 forms of medically approved contraception based on emerging animal toxicity data. - The metabolite identification number was corrected throughout the document. - Wording was added regarding the use of the patient diary.

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.

Due to strategic reasons, the Phase 2 portion was not initiated, and further clinical development was stopped.

Notes: