Clinical trial results:
A Multi-center, Open-Label, Adaptive, Randomized Study of Palifosfamidetris, a Novel DNA Crosslinker, in Combination with Carboplatin and Etoposide (PaCE) Chemotherapy versus Carboplatin and Etoposide (CE) Alone in Chemotherapy Naïve Patients with Extensive-Stage Small Cell Lung Cancer

Summary

EudraCT number	2011-006134-17
Trial protocol	GB HU PL IT DE FR
Global end of trial date	02 December 2014

Results information

Result version number	v1 (current)
This version publication date	17 April 2016
First version publication date	17 April 2016
Summary attachment (see zip file)	IPM3002 CSR Summary (IPM3002 CSR-Summary.pdf)

Trial information

Trial identification

Sponsor protocol code	IPM3002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01555710
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ZIOPHARM Oncology Inc.
Sponsor organisation address	One First Avenue, Parris Building 34, Navy Yard Plaza, Boston MA, United States, 02129
Public contact	Caesar Belbel, ZIOPHARM Oncology Inc., +1 617 259-1641, cbelbel@ziopharm.com
Scientific contact	Francois Lebel, ZIOPHARM Oncology Inc., +1 617 778-1756, flebel@ziopharm.com

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	20 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 December 2014
Global end of trial reached?	Yes
Global end of trial date	02 December 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to compare the efficacy of palifosfamide-tris in combination with carboplatin and etoposide (PaCE) chemotherapy to carboplatin and etoposide (CE) alone, as measured by overall survival (OS), in chemotherapy naïve subjects with extensivestage SCLC

Protection of trial subjects:

This study was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents.

Background therapy:

Carboplatin and etoposide were obtained by each study center as commercially available drug products and stored/used per label instructions. For those sites in the European Union that were not able to obtain the comparators commercially, the Sponsor provided the comparator products. Lot numbers N09770 Carboplatin 450 mg/45 mL, N10216 Carboplatin 50 mg/5 mL, 12G02LC Etoposide-Teva active 200 mg/10 mL

Evidence for comparator:

Carboplatin and etoposide were obtained by each study center as commercially available drug products and stored/used per label instructions. For those sites in the European Union that were not able to obtain the comparators commercially, the Sponsor provided the comparator products. Lot numbers N09770 Carboplatin 450 mg/45 mL, N10216 Carboplatin 50 mg/5 mL, 12G02LC Etoposide-Teva active 200 mg/10 mL

Actual start date of recruitment	08 June 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Russian Federation: 45
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	Ukraine: 17
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	United States: 60
Country: Number of subjects enrolled	Canada: 14

Country: Number of subjects enrolled	Israel: 4
Worldwide total number of subjects	188
EEA total number of subjects	41

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)	118
From 65 to 84 years	70
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was initiated on 08 Jun 2012 (first subject enrolled) to 02 Dec 2014 (last subject last follow-up) in a total of 12 countries globally.

Pre-assignment

Screening details:

Screening tests are specified in the Protocol Section 5, Schedule of Study Procedures and Assessments. Principal Investigators (PIs) at each site are responsible for maintaining a record of all subjects screened, including both those who enter the study and those who are excluded.

Period 1

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

Blinding implementation details:

Open-label trial design

Arms

Are arms mutually exclusive?	Yes
Arm title	Palifosfamide-tris with Carboplatin and Etoposide

Arm description:

Palifosfamide-tris, a Novel DNA Crosslinker, in Combination with Carboplatin and Etoposide (PaCE) Chemotherapy: PaCE chemotherapy consisting of palifosfamide-tris (130 mg/m2/day) and etoposide (100 mg/m2/day) on Days 1, 2, and 3, and carboplatin (target AUC of 4 mg/mL/min [maximum of 600 mg]) on Day 1 of a 21-day treatment cycle.

Arm type	Experimental
Investigational medicinal product name	Palifosfamide-tris
Investigational medicinal product code	Palifosfamide
Other name	Zymafos, ZIO-201
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

130 mg/m2 milligram(s)/square meter per day. Intravenous use.

Arm title	Carboplatin and Etoposide (CE) Chemotherapy

Arm description:

Carboplatin and Etoposide (CE) Alone in Chemotherapy Naïve Patients with Extensive-Stage Small Cell Lung Cancer: control group received CE chemotherapy consisting of etoposide (100 mg/m2/day) on Days 1, 2, and 3, and carboplatin (target AUC of 5 mg/mL/min [maximum of 750 mg]) on Day 1 of a 21-day treatment cycle.

Arm type	Background therapy
Investigational medicinal product name	Carboplatin and Etoposide
Investigational medicinal product code	CE
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The control group received CE chemotherapy consisting of etoposide (100 mg/m2/day) on Days 1, 2, and 3, and carboplatin (target AUC of 5 mg/mL/min [maximum of 750 mg]) on Day 1 of a 21-day treatment cycle.

Number of subjects in period 1	Palifosfamide-tris with Carboplatin and Etoposide	Carboplatin and Etoposide (CE) Chemotherapy
Started	94	94
Completed	94	94

Baseline characteristics

Reporting groups	
Reporting group title	Palifosfamide-tris with Carboplatin and Etoposide
Reporting group description:	
Palifosfamide-tris, a Novel DNA Crosslinker, in Combination with Carboplatin and Etoposide (PaCE) Chemotherapy: PaCE chemotherapy consisting of palifosfamide-tris (130 mg/m2/day) and etoposide (100 mg/m2/day) on Days 1, 2, and 3, and carboplatin (target AUC of 4 mg/mL/min [maximum of 600 mg]) on Day 1 of a 21-day treatment cycle.	
Reporting group title	Carboplatin and Etoposide (CE) Chemotherapy
Reporting group description:	
Carboplatin and Etoposide (CE) Alone in Chemotherapy Naïve Patients with Extensive-Stage Small Cell Lung Cancer: control group received CE chemotherapy consisting of etoposide (100 mg/m2/day) on Days 1, 2, and 3, and carboplatin (target AUC of 5 mg/mL/min [maximum of 750 mg]) on Day 1 of a 21-day treatment cycle.	

Reporting group values	Palifosfamide-tris with Carboplatin and Etoposide	Carboplatin and Etoposide (CE) Chemotherapy	Total
Number of subjects	94	94	188
Age categorical Units: Subjects			
Adults (18-64 years)	59	59	118
From 65-84 years	35	35	70
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	28	28	56
Male	66	66	132

End points

End points reporting groups

Reporting group title	Palifosfamide-tris with Carboplatin and Etoposide

Reporting group description:

Palifosfamide-tris, a Novel DNA Crosslinker, in Combination with Carboplatin and Etoposide (PaCE) Chemotherapy: PaCE chemotherapy consisting of palifosfamide-tris (130 mg/m2/day) and etoposide (100 mg/m2/day) on Days 1, 2, and 3, and carboplatin (target AUC of 4 mg/mL/min [maximum of 600 mg]) on Day 1 of a 21-day treatment cycle.

Reporting group title	Carboplatin and Etoposide (CE) Chemotherapy

Reporting group description:

Carboplatin and Etoposide (CE) Alone in Chemotherapy Naïve Patients with Extensive-Stage Small Cell Lung Cancer: control group received CE chemotherapy consisting of etoposide (100 mg/m2/day) on Days 1, 2, and 3, and carboplatin (target AUC of 5 mg/mL/min [maximum of 750 mg]) on Day 1 of a 21-day treatment cycle.

Primary: Efficacy end point

End point title	Efficacy end point

End point description:

Survival was measured from the date of randomization. Follow-up information included vital status and interim cancer history (e.g., anticancer treatments received). This information was recorded at least every 12 ± 2 weeks following the post-treatment safety assessment visit until the targeted number of deaths was observed or until 1 year following the completion of enrollment, whichever was later.

End point type	Primary

End point timeframe:

Overall survival - Time (months)

End point values	Palifosfamide-tris with Carboplatin and Etoposide	Carboplatin and Etoposide (CE) Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	91		
Units: Time (months)				
number (not applicable)	10.03	10.37		

Statistical analyses

Statistical analysis title	Efficacy analysis:

Statistical analysis description:

Median OS times for the PaCE (10.03 months) and CE (10.37 months) chemotherapy groups were not significantly different (p=0.096). Overall, median OS was consistent with study assumptions. The Cox proportional HR without interactions favored CE chemotherapy and the difference was statistically significant (p=0.031) after adjustment for baseline age category, gender, ECOG PS, and region. A Cox proportional hazards regression with interactions was also performed.

Comparison groups	Palifosfamide-tris with Carboplatin and Etoposide v Carboplatin

	and Etoposide (CE) Chemotherapy
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.096
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Confidence interval	
level	95 %
sides	1-sided
lower limit	0.95
upper limit	1.78
Variability estimate	Standard deviation

Notes:

[1] - Median OS times for the PaCE (10.03 months) and CE (10.37 months) chemotherapy groups were not significantly different (p=0.096).

Secondary: Safety: assess progression free survival

End point title	Safety: assess progression free survival

End point description:

Secondary:
-Assess potential prognostic factors for OS (i.e., Eastern Cooperative Oncology Group performance status [ECOG PS], age, gender, and region)
-Assess the safety as characterized by serious adverse events (SAEs)

End point type	Secondary

End point timeframe:

Overall survival:

End point values	Palifosfamide-tris with Carboplatin and Etoposide	Carboplatin and Etoposide (CE) Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	91		
Units: Percentage SAE events per arm	20	20		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The safety of study treatments was assessed by the frequency and severity of SAEs within the overall survival timeframe defined by the protocol, including follow-up after treatment.

Adverse event reporting additional description:

An AE was defined as any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug related. Treatment-emergent AEs defined if started on or after the date of treatment with study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13

Reporting groups

Reporting group title	Palifosfamide-tris with Carboplatin and Etoposide

Reporting group description:

Palifosfamide-tris, a Novel DNA Crosslinker, in Combination with Carboplatin and Etoposide (PaCE) Chemotherapy: PaCE chemotherapy consisting of palifosfamide-tris (130 mg/m2/day) and etoposide (100 mg/m2/day) on Days 1, 2, and 3, and carboplatin (target AUC of 4 mg/mL/min [maximum of 600 mg]) on Day 1 of a 21-day treatment cycle.

Reporting group title	Carboplatin and Etoposide (CE) Chemotherapy

Reporting group description:

Carboplatin and Etoposide (CE) Alone in Chemotherapy Naïve Patients with Extensive-Stage Small Cell Lung Cancer: control group received CE chemotherapy consisting of etoposide (100 mg/m2/day) on Days 1, 2, and 3, and carboplatin (target AUC of 5 mg/mL/min [maximum of 750 mg]) on Day 1 of a 21-day treatment cycle.

Serious adverse events	Palifosfamide-tris with Carboplatin and Etoposide	Carboplatin and Etoposide (CE) Chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 92 (17.39%)	16 / 91 (17.58%)	
number of deaths (all causes)	83	76	
number of deaths resulting from adverse events	1	1	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Congenital, familial and genetic disorders			

subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	1 / 92 (1.09%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	1 / 92 (1.09%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood disorder			
subjects affected / exposed	8 / 92 (8.70%)	8 / 91 (8.79%)	
occurrences causally related to treatment / all	11 / 11	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General disorder	Additional description: disease progression		
subjects affected / exposed	2 / 92 (2.17%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	6 / 92 (6.52%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	6 / 7	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychiatric disorders			

subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Infections and infestations			
Infections and infestations			
subjects affected / exposed	2 / 92 (2.17%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	2 / 92 (2.17%)	2 / 91 (2.20%)	
occurrences causally related to treatment / all	2 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Palifosfamide-tris with Carboplatin and Etoposide	Carboplatin and Etoposide (CE) Chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 92 (2.17%)	4 / 91 (4.40%)	
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	2 / 92 (2.17%)	4 / 91 (4.40%)	
occurrences (all)	4	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 April 2013	Amendment to protocol to enable a temporary halt to recruitment

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 April 2013	Recruitment to this study was halted by the sponsor due to a strategic re-direction of the program and to allow an interim analysis of data.	-

Notes:

Limitations and caveats

None reported