ZIOPHARM Oncology, Inc.

Clinical Study Report:

Study Title:	A Multi-Center, Open-Label, Adaptive, Randomized Study of Palifosfamide-tris, 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. The MATISSE Study
Study Number:	IPM3002 IND # 115,288 EudraCT # 2011-006134-17
Study Phase:	3
Study Design:	Multinational, multi-center, randomized, controlled, open-label, adaptive study
Product Name:	Palifosfamide (Zymafos™, ZIO-201)
Formulation:	Tromethamine (tris) formulation
Indication:	Extensive-Stage Small Cell Lung Cancer
Study Initiated (first subject enrolled):	08 Jun 2012
Study Completed (last subject last follow-up):	02 Dec 2014
Coordinating Investigator:	Lawrence Einhorn, MD Indiana University Melvin and Bren Simon Cancer Center 535 Barnhill Drive, RT 473 Indianapolis, IN 46202
Sponsor:	ZIOPHARM Oncology, Inc. One First Avenue, Parris Building 34 Boston, MA 02129 USA (617) 259-1970
Responsible Medical Officer:	Francois Lebel, MD Executive Vice President & Chief Medical Officer ZIOPHARM Oncology, Inc.
GCP Statement:	This study was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents.
Final Date:	20 April 2015

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2 SYNOPSIS

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Study Title: A Multi-Center, Open-Label, Adaptive, Randomized Study of Palifosfamide-tris, 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. The MATISSE Study

Investigators and Study Centers: 109 centers (70 centers enrolled subjects) located in 13 countries worldwide

Publication (reference): None

Studied Period:

08 Jun 2012 (first subject enrolled) to 02 Dec 2014 (last subject last follow-up)

Study Phase: 3

Objectives:

Primary: 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 extensive-stage small cell lung cancer (SCLC).

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)

Methodology:

This was a multinational, multi-center, randomized, controlled, open-label, adaptive study to evaluate the efficacy of PaCE chemotherapy in chemotherapy-naive subjects with extensive-stage SCLC. Eligible subjects were stratified according to age, gender, and ECOG PS before being randomized in a 1:1 ratio to receive either PaCE or CE chemotherapy. The primary efficacy endpoint was OS. The safety of study treatments was assessed by the frequency and severity of SAEs.

Number of Subjects (Planned and Analyzed):

The original sample size for this study was determined based on 8.4 and 11.2 months median survival for the control (CE) and treatment (PaCE) groups, respectively, and a Weibull survival shape at kappa=1.2, with 0.7 hazard ratio (HR) calculated as $(8.4/11.2)^{1.2}$. Subjects were allocated to treatment and control in a 1:1 ratio. With a 1-sided 2.5% Type I error, an O'Brien-Fleming boundary at 0.5 information rate for early efficacy, and a non-binding futility of alpha=0.5, the power of the study was 87%. Based on the number of events required, the

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expected number of subjects was 464 (not accounting for loss to follow-up). A maximum of 548 subjects (274/group) were to be enrolled in this study.

The study stopped at 188 subjects randomized over an 11-month accrual period (08 Jun 2012 to 22 Apr 2013) with the average subject having 11 months follow up (some subjects had less follow-up while others had more follow-up) resulting in 36% power for a 0.75 HR assuming exponentially distributed survival.

Diagnosis and Main Criteria for Inclusion:
Adults subjects with histological or cytological diagnosis of extensive-stage SCLC defined as disease beyond the ipsilateral hemithorax, mediastinum, and ipsilateral supraclavicular area and including malignant pleural or pericardial effusion or hematogenous metastases

Test Product, Dose, and Mode of Administration, Lot Number:
Palifosfamide-tris was supplied by the Sponsor as a powder in single-use glass vials and stored frozen (-20°C or colder) until dispensation. Dosing was to be completed within 2.5 hours from the time of reconstitution in the vial.
Lot numbers: 1J001A-1

Duration of Treatment:

Subjects were to have a minimum of 4 and a maximum of 6 treatment cycles with 21 days/cycle.

Reference Therapy, Dose and Mode of Administration, Lot Number:
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

Criteria for Evaluation:

Efficacy:
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.

Safety:
An AE was defined as any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug related. Any worsening of a pre-existing condition, which was temporally associated with the use of the study drug, was also an AE.
Treatment-emergent adverse events (TEAEs) were AEs that started on or after the date of the

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first dose of any study drug. The maximum intensity of events was recorded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03. The Investigator determined the potential relationship of events to the study drugs based on his/her clinical judgment.

An AE was considered to be an SAE if it fit 1 or more of the following conditions: resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, was a persistent or significant disability/incapacity, or was a congenital anomaly/birth defect. For the purposes of this protocol, the occurrence or diagnosis of a new cancer during the study was considered an SAE. This did not include metastasis of current disease.

Note: After Amendment 2 (26 Apr 2013), the Sponsor only collected AE data for serious events. As a result, the TEAE database was not completely monitored or queried to resolution (due to the protocol amendment on 26 April 2013) before database lock.

Statistical Methods:

Study Populations:

The 2 treatment groups (PaCE and CE) were assessed for comparability of demographic and baseline characteristics in a descriptive fashion. Demographic categories included age, gender, race, ethnicity, and country/region (US and non-US), BSA, body mass index (BMI), weight loss in the prior 6 months, and smoking status and number of packs per year. Clinical characteristics included disease duration (time since initial diagnosis), histology, method of histological diagnosis, initial ECOG PS (0-1, 2), and metastatic sites (lung, brain, other). Categorical data (e.g., gender) were compared between the 2 treatment groups using a 2-sided Fisher exact test; ordinal data (e.g., ECOG PS) were compared using a singly ordered exact test; and continuous data (e.g., age, body mass index [BMI], and body surface area [BSA]) were compared using an unpaired t-test.

Efficacy:

The OS null (H_0) and alternative hypotheses (H_a) were as follows:

H_0: h PaCE / h CE = 1

vs.

H_a: h PaCE / h CE < 1

In these hypotheses, h PaCE was the test treatment (PaCE) hazard rate and h CE was the control treatment hazard rate. It was assumed that the HR between the treatment and control group would be constant over time.

Efficacy was evaluated in the intent-to-treat population (ITT) consisting of all 188 randomized subjects. The primary analysis of the primary endpoint (OS) was performed using a Cox regression model that included treatment as well as the 3 randomization stratification factors (age, gender, ECOG PS) as well as region (United States [US]/non-US) with the 4 respective treatment interaction terms added to a confirmatory model for OS. Kaplan-Meier lifetables

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comparing treatments were constructed overall and within each stratification variable level. A log rank test was also performed to compare the 2 treatment groups. In addition, a stratified log rank analysis was also performed for each of the following 4 stratification variables: age, gender, ECOG PS, and region (US/non-US); treatment effect was separately assessed according to the 4 individual stratification variables using a stratified log rank test.

Safety:

Safety summaries were presented for TEAEs and SAEs. The Safety population was used for these analyses; this population consisted of 183 subjects who received any study drug. The TEAE and SAE summaries displayed the number (%) of subjects and the corresponding number of events by Medical Dictionary for Regulatory Activities (MedDRA) Version 17.0 System Organ Class (SOC), Preferred Term (PT), and treatment group. The number (%) of subjects with TEAEs and SAEs in the 2 treatment groups were compared using a 2-sided Fisher's exact test.

Summary of Results

Efficacy: 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. The unadjusted HR was 1.30 (95% confidence interval [95% CI]: 0.95, 1.78), and the adjusted hazard ratio was 0.98 (95%CI: 0.44, 2.18). The differences between the 2 treatment groups were not statistically significant.

Kaplan-Meier analyses were also performed by baseline age category (<65 vs ≥65 years), gender, ECOG PS (0-1 vs 2), and region (US vs non-US). Overall survival was similar (p>0.05) except for the age stratified analysis which favored CE chemotherapy (p=0.044).

Safety: Approximately 20% of subjects in both treatment groups experienced at least 1 TEAE. At the system organ class (SOC) level, the differences between the groups in the distribution of TEAEs were not statistically significant except for nervous system disorders (p=0.048) which were reported more frequently in the CE chemotherapy group (11.0% of subjects) than the PaCE chemotherapy group (3.3%). Within nervous system disorders, the most common events were dysgeusia, dizziness, and headache. When only TEAEs considered at least possibly related to study therapy were considered, there was no statistically significant difference between the 2 treatment groups at the SOC level.

Slightly more than 25% of subjects in both treatment groups had at least 1 SAE (regardless of whether treatment-emergent or not). There was no significant difference between the 2 treatment groups in the percentage of subjects with any SAE or any related SAE using a 2-sided Fisher exact test. The overall percentages of subjects with any SAEs were 28.3% for the PaCE

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chemotherapy group (26 subjects had a total of 59 events) versus 27.5% for the CE chemotherapy group (25 subjects had a total of 52 events). For 16 of the 26 subjects taking PaCE chemotherapy and 11 of the 25 subjects taking CE chemotherapy with SAEs, at least 1 SAE was considered at least possibly related to study therapy. At the SOC level, there was no statistically significant difference between the 2 treatment groups for either all SAEs or related SAEs. The most commonly reported SAEs for the PaCE chemotherapy group were in the following SOCs: blood and lymphatic systems disorders; respiratory, thoracic, and mediastinal disorders; and general disorders and administrative site conditions. The most commonly reported SAEs for the CE chemotherapy group were in the following SOCs: infections and infestations; blood and lymphatic systems disorders; and respiratory, thoracic, and mediastinal disorders. The differences in the percentages of subjects with any SAEs were <5% for all SOCs and preferred terms.

When only related SAEs were considered, there were only 2 SOCs with events in more than 2 subjects in either treatment group. All of the serious blood and lymphatic system disorders were considered at least possibly related to study therapy. Six subjects in the PaCE chemotherapy group and 1 subject in the CE chemotherapy group had serious gastrointestinal disorders considered at least possibly related to study therapy.

CONCLUSIONS: The addition of palifosfamide-tris to CE chemotherapy did not negatively affect either efficacy or safety. Median OS was 10.03 months for the PaCE chemotherapy group compared with 10.37 months for the CE chemotherapy group (p=0.096). Overall, there was no statistically significant difference between the 2 treatment groups in terms of percentages of subjects (and number of events) with TEAEs, related TEAEs, SAEs, and related SAEs.

Final Date: 20 April 2015

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