Multicenter Phase Ib Study of the Safety and Efficacy of Palifosfamide Plus Carboplatin/ Etoposide (PaCE) in Patients with Small Cell Lung Cancer or Other Selected Cancers

ZIOPHARM Oncology

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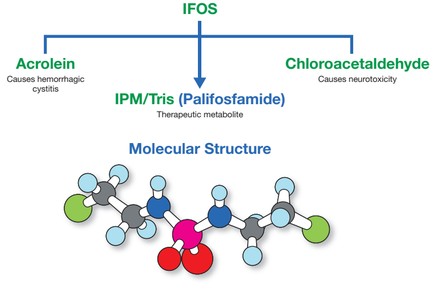
Abstract

Palifosfamide (Pa) is a novel DNA cross linker molecule that consists of the active anti-tumor metabolite of ifosfamide (I). Potential advantages over I include the abrogation of I-metabolite related toxicities, increased activity by virtue of increased dose delivery over time, and overcoming resistance mediated by aldehyde dehydrogenase (ALDH) overexpression. ALDH overexpression is associated with cancer cell stem-like potential in several tumor types. Pa has broad activity *in vitro* and *in vivo* preclinical models and has shown early activity in humans. A previous randomized study evaluating the addition of I to cisplatin and etoposide (E) in small cell lung cancer (SCLC) demonstrated improved survival, but with disabling increase in toxicity with the three-drug combination. We hypothesized that the substitution of Pa for I could increase the therapeutic advantage of a similar three-drug regimen. We initiated a multicenter phase I, open-label, dose-escalation study assessing the safety and efficacy of Pa in combination with carboplatin and E (PaCE regimen) in SCLC and in other cancers in which C+E is considered an appropriate therapeutic option. Tumor responses were assessed by RECIST 1.1 and relevant tumor markers. A total of 22 patients (11 females and 11 males) have been treated to date: 7 with SCLC, 3 with NSCLC, 3 with ovarian, 1 with germ cell and 8 with other cancers. Serious adverse events have been reported in six patients, including, thrombocytopenia (4), leukopenia (2), and neutropenia (2). The maximum tolerated dose of Pa was determined to be 130 mg/m^2 when administered in combination with E 90 mg/m^2 and C AUC4. The dose limiting toxicity was neutropenic fever. To date, two radiological partial responses in patients with SCLC, one radiological partial response in a patient with NSCLC, one radiological partial response in a patient with ovarian cancer, and one partial response assessed by tumor markers in a patient with germ cell tumor have been noted. (Updated abstract)

Conclusion: This study is ongoing, and an additional cohort evaluating Pa 130 mg/m^2 in combination with E 100 mg/m^2 and C AUC 4 is being evaluated. Further clinical data will be presented. The PaCE combination appears to be tolerable and has demonstrated clinical activity. Based on these data, a confirmatory study in SCLC is planned.



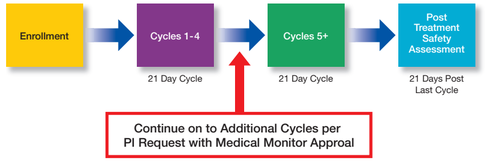
Molecular Structure

Rationale

Palifosfamide (Pa) is a novel DNA cross linker molecule that consists of the active antitumor metabolite of ifosfamide (I). Potential advantages over I include the abrogation of I-metabolite related toxicities, increased activity by virtue of increased dose delivery over time, and overcoming resistance mediated by aldehyde dehydrogenase (ALDH) overexpression. ALDH overexpression is associated with cancer cell stem-like potential in several tumor types. Pa has broad activity *in vitro* and *in vivo* preclinical models and has shown early activity in humans. A previous randomized study evaluating the addition of I to cisplatin and etoposide (E) in small cell lung cancer (SCLC) demonstrated improved survival, but with disabling increase in toxicity with the three-drug combination. We hypothesized that the substitution of Pa for I could increase the therapeutic advantage of a similar three-drug regimen.

Study Design

An open-label, dose-escalation Phase I study to define the safety profile and the maximum tolerated dose (MTD) of intravenously administered palifosfamide-tris in combination with etoposide and carboplatin in subjects with malignancies for which etoposide and carboplatin are an appropriate therapeutic choice, including, but not limited to testicular cancer; thymoma; ovarian cancer; osteosarcoma; non-small cell lung cancer, and small cell lung cancer. Both refractory and treatment naïve patients may be treated as part of this protocol.



Dose Escalation Schedule

Cohort	Palifosfamide-tris	Etoposide	Carboplatin
-1	80 mg/m^2	90 mg/m^2	AUC 4
1	100 mg/m^2	90 mg/m^2	AUC 4
2	130 mg/m^2	90 mg/m^2	AUC 4
3*	150 mg/m^2	90 mg/m^2	AUC 4
2A	130 mg/m^2	100 mg/m^2	AUC 4

* DLT was neutropenic fever in 1 patient in cohort 3. The decision to continue with 300 mg/m2 was made based on the totality of the data available.

Study Objective

Primary: To assess the safety profile of palifosfamide-tris administered in combination with IV etoposide and IV carboplatin in this patient population.

Secondary: To assess early signs of efficacy using this investigational combination in this patient population.

Major Inclusion Criteria

- Age ≥18 years
- Subject with documentation of a malignancy scheduled to receive etoposide and carboplatin therapy (including, but not limited to testicular cancer; thymoma; ovarian cancer; osteosarcoma; non-small cell lung cancer, and small cell lung cancer)
- ECOG Performance Status of 0 or 1
- Adequate bone marrow, liver, and renal function
- Subjects for whom there is no curative standard therapy

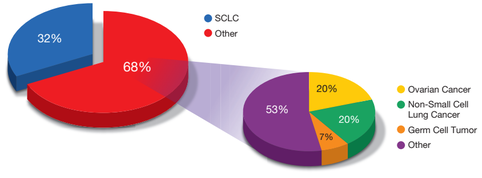
Major Exclusion Criteria

- Unstable or clinically significant concurrent medical condition that would, in the opinion of the investigator, jeopardize the safety of a subject and/or their compliance with the protocol
- Presence or history of any illness or injury to the urinary tract (renal or post-renal) which may make the subject more susceptible to acute renal insufficiency in the case of potential renal adverse events
- Active infection requiring systemic antibacterial/antibiotic, antifungal, or antiviral therapy
- Currently pregnant or nursing
- Subjects who have received other investigational drugs within 30 days of enrolment in this study
- Subjects who are within 4 weeks of their last chemotherapy treatment

Baseline Characteristics

	Number (%)
Gender	
Female	11 (50%)
Male	11 (50%)
Age	
< 65 Years Old	14 (64%)
≥ 65 Years Old	8 (36%)
Prior Therapy	
Chemotherapy	18 (82%)
Radiotherapy	12 (55%)
Surgery	6 (27%)
Immunotherapy	1 (5%)
Other	2 (9%)

Cancer Subtypes



Tumor Assessments

Response Assessment[1]	Number of Patients[2] (22 Enrolled as of 10/26/11)	Cancer Types
PR	5	Germ Cell Tumor (Cohort 1: 1), NSCLC (Cohort 2: 1) Ovarian (Cohort 2: 1), SCLC (Cohort 2: 1, Cohort 3: 1)
SD	4	Ovarian (Cohort 2: 1), NSCLC (Cohort 3: 1), SCLC (Cohort 2: 1), Uterine Leiomyosarcoma (Cohort 2: 1)
PD	4	Adenocarcinoma (Cohort 2: 1), Mediastinal Carcinoid (Cohort 1: 1), Pancreatic (Cohort 3: 1), SCLC (Cohort 1: 1)

1 Response Assessment per RECIST 1.1 definitions; and/or assessed per biomarkers.
2 7 Active patients not yet evaluated for response as their follow-up scans are still pending. 2 Patients did not continue past cycle 1 due to adverse events.

SCLC

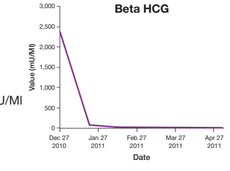
- Partial response (PR) reported
  - Extensive disease
  - Previously treated with chemotherapy and whole brain radiotherapy
  - Metastatic to the liver, lungs and lymph nodes at baseline
  - 34% decrease in tumor burden at end of Cycle 2 and 41% at end of Cycle 4
  - Patient completed 8 cycles of therapy
- Partial response (PR) reported
  - Extensive disease
  - Previously treated with chemotherapy and radiotherapy to the chest and brain
  - Metastatic to the lymph nodes at baseline
  - 43% decrease in tumor burden at end of Cycle 2
  - Patient completed 4 cycles of therapy

NSCLC

- Partial response (PR) reported
  - Previously treated with chemotherapy
  - Metastatic to the liver and lungs at baseline
  - 44% decrease in tumor burden at end of Cycle 2
  - Patient completed 4 cycles of therapy

Primary Mediastinal Nonseminomatous Germ Cell Tumor

- Normalization of tumor markers reported
  - Previously treated with pulmonary wedge resection and chemotherapy (including an ifosfamide containing regimen – developed encephalopathy)
  - Beta HCG reduction from 2358 to 12 mU/Ml
  - Patient completed 4 cycles of therapy



Ovarian Cancer

- Partial response (PR) reported
  - Previously treated with chemotherapy, paracentesis and radiotherapy
  - Metastatic to the lymph nodes at baseline
  - 52% decrease in tumor burden at end of Cycle 2
  - Patient is currently on study in Cycle 4

Serious Adverse Events Related or Possibly Related to Study Drug[1]

Event Term	Frequency N (%)	Patient Cohort #: N
Thrombocytopenia	4 (18%)	Cohort 2: 3; Cohort 3: 1
Neutropenia	2 (9%)	Cohort 1: 1; Cohort 3: 1
Leukopenia	2 (9%)	Cohort 3: 1; Cohort 2: 1
Anemia	1 (5%)	Cohort 1: 1
Ileus	1 (5%)	Cohort 2: 1
Nausea	1 (5%)	Cohort 2: 1
Vomiting	1 (5%)	Cohort 2: 1

1 Adverse event relationship to study drug is determined by the Principal Investigator.

Grade 3+ Adverse Events Related or Possibly Related to Study Drug[1]

Event Term	Frequency N (%)	Patient Cohort #: N
Anemia	3 (14%)	Cohort 2: 2; Cohort 3: 1
Dyspnea	2 (9%)	Cohort 2: 2
Fatigue	4 (18%)	Cohort 2: 2; Cohort 3: 1; Cohort 2A: 1
Hypophosphatemia	2 (9%)	Cohort 2: 1; Cohort 2A: 1
Leukopenia	2 (9%)	Cohort 2: 1; Cohort 3: 1
Lymphocyte Count Decreased	2 (9%)	Cohort 2: 1; Cohort 3: 1
Neutrophil Count Decreased	5 (23%)	Cohort 1: 1; Cohort 2: 1; Cohort 3: 2
Platelet Count Decreased	7 (32%)	Cohort 2: 3; Cohort 3: 3; Cohort 2A: 1

1 Adverse event relationship to study drug is determined by the Principal Investigator.

Conclusion

The PaCE combination appears to be tolerable and has demonstrated clinical activity in SCLC, NSCLC, germ cell tumor, and ovarian cancer. Based on these data, a confirmatory study in SCLC is planned.