Abstract
Palifosfamide (Pa) is a novel DNA cross linker molecule that consists of the active anti-tumor metabolite of ifosfamide (IF). Potential advantages over IF include the abolition of in vivo metabolized toxicities, increased activity by virtue of increased dose delivery over time, and overcoming resistance mediated by sulfate dehydrogenase (ALDH2) overexpression. ALDH2 overexpression is associated with cancer cell line-like potential in several tumor types. Pa has broad activity in vitro and in preclinical models and has shown early activity in humans. A previous randomized study evaluating the addition of Pa to etoposide and carboplatin in small cell lung cancer (SCLC) demonstrated improved survival, but with disabling toxicity is toxicity with the three-drug combination. We hypothesized that the substitution of Pa for IF could increase the therapeutic advantage of a similar three-drug regimen. We initiated a multicenter phase I/II, open-label, dose-escalation study assessing the safety and efficacy of Pa in combination with etoposide and carboplatin in subjects with malignancies for which Pa has shown activity and an acceptable toxicity profile.

Study Objective
To assess the safety profile of Pa in patients treated in combination with E 90 mg/m² 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, and one radiological partial response in a patient 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 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.

Rationale
Palifosfamide (Pa) is a novel DNA cross linker molecule that consists of the active anti-tumor metabolite of ifosfamide. Potential advantages over IF include the abolition of in vivo metabolized toxicities, increased activity by virtue of increased dose delivery over time, and overcoming resistance mediated by metabolic dehydrogenase (ALDH2) overexpression. ALDH2 overexpression is associated with cancer cell line-like potential in several tumor types. Pa has broad activity in vitro and in preclinical models and has shown early activity in humans. A previous randomized study evaluating the addition of Pa to etoposide and carboplatin in small cell lung cancer (SCLC) demonstrated improved survival, but with disabling toxicity is toxicity with the three-drug combination. We hypothesized that the substitution of Pa for IF 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 in combination with etoposide and carboplatin in subjects with malignancies for which etoposide and carboplatin are appropriate therapeutic choices, including, but not limited to, testicular cancer; thymoma; ovarian cancer; pancreatic adenocarcinoma, non-small cell lung cancer, and small cell lung cancer. Both reductive and treatment-naive patients may be treated as part of this protocol.

Cycles 1-4
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Stable Disease
Radiographic response seen in multiple patients with extensive disease. Median PFS in patients with extensive disease was 3.6 months, including a 43% decrease in tumor burden at end of Cycle 2 and 41% decrease in tumor burden at end of Cycle 4.

Partial Response
Partial response (PR) reported.

Other
Patient is currently on study in Cycle 4

Cohort Palifosfamide-tris Etoposide Carboplatin

Safety

Tumor Assessments

Cancer Types

Other

Germ Cell Tumor

Lung Cancer

Non-Small Cell

Ovarian Cancer

SCLC

Serious Adverse Events Related or Possibly Related to Study Drug

Primary Medialul Nonseminomatous Germ Cell Tumor

• Normalization of tumor markers reported

• Partially treated with surgical wedge resection and chemotherapy (including an ifosfamide containing regimen - developed nephrotoxicity)

• Beta HCG reduction from 3339 to 12 mIU/mL

• Patient completed 4 cycles of therapy

Ovarian Cancer

• Partial response (PR) reported

• Partially treated with chemotherapy, parameter and radionotherapy

• Metastasis to the lymph nodes at baseline

• 43% decrease in tumor burden at end of Cycle 2

• Patient is currently in study in Cycle 4

Grade 3+ Adverse Events Related or Possibly Related to Study Drug

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.