Randomized, Double-Blind, Placebo-Controlled Trial of Evofosfamide (TH-302) in Combination with Pemetrexed in Advanced n-s NSCLC

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Introduction

- Solid tumors often have significant areas of hypoxia, harboring slowly replicating cells that contribute to chemo- and radioresistance.[1-4]
- Hypoxia is a prevalent characteristic found in tumors of patients with non-small cell lung cancer (NSCLC) as detected by PET imaging using the [18-F]-HX4, a hypoxia tracer (Figure 1).[5]
- Evofosfamide (Evo, previously known as TH-302) is a hypoxia-activated prodrug that is reduced at its nitroimidazole group. Under hypoxic conditions, evofosfamide releases the DNA alkylator molecule bromo-isophosphoramide mustard (Br-IPM)[6-8] (Figure 2).
- Evofosfamide is currently under evaluation in two Phase 3 trials: one in combination with doxorubicin versus doxorubicin alone in patients with locally advanced unresectable or metastatic STS (ClinicalTrials.gov Identifier: NCT01440088), and the other in combination with gemcitabine versus gemcitabine and placebo in patients with advanced pancreatic cancer (the MAESTRO trial) (ClinicalTrials.gov Identifier: NCT01746979). Evofosfamide is also being investigated in earlier-stage clinical trials of other solid tumors and hematological malignancies.
- In a Phase 1/2 study (ClinicalTrials.gov Identifier: NCT00743379) that evaluated evofosfamide in combination with full-dose pemetrexed in 18 patients with relapsed/refractory non-squamous NSCLC, median progression-free survival was 7.0 months and median overall survival was 14.9 months. Of 15 patients evaluable for response, 6 (40%) achieved a partial response including 4 confirmed responses, 6 (40%) achieved stable disease, and 3 (20%) had progressive disease. The most common adverse events following combination therapy of evofosfamide and pemetrexed were fatigue, anemia, stomatitis and nausea.[9]
- An international, multicenter, randomized, double-blind, placebo-controlled trial has been initiated to evaluate evofosfamide in combination with pemetrexed as a potential second-line treatment for patients with non-squamous NSCLC (ClinicalTrials.gov Identifier: NCT02093962).

Figure 1: [18F]-HX4 Hypoxia PET/CT Image in left lung mass with mediastinal adenopathy (CT image top right, PET image bottom right, superimposed image on the left)

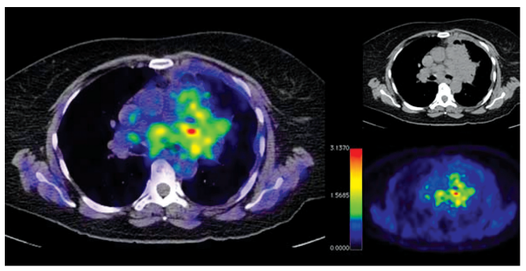
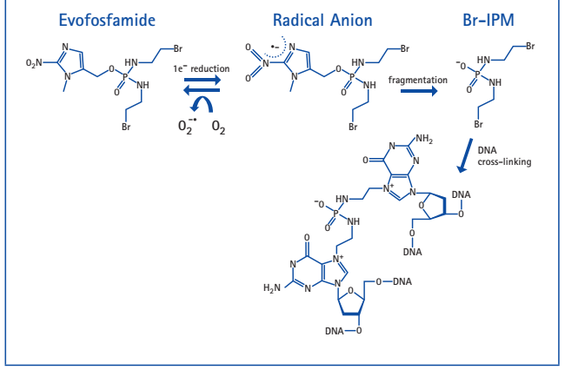


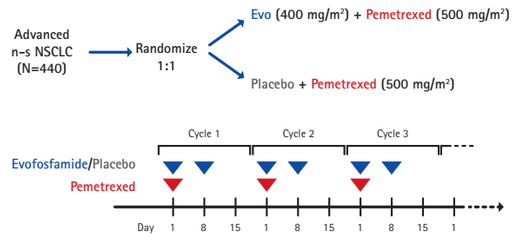
Figure 2. Mechanism of Hypoxia-Selective Prodrug Activation and DNA Cross-Linking Activity of Released Effector Bromo-Isophosphoramide Mustard (Br-IPM)



Study Design

- Randomized, double-blind, placebo-controlled Phase 2 registration trial of evofosfamide in combination with pemetrexed in patients with relapsed/refractory non-squamous NSCLC (Figure 3).
- A total of 440 patients will be randomized 1:1 to receive evofosfamide + pemetrexed or placebo + pemetrexed until 321 deaths are recorded. This yields a 85% power to detect a hazard ratio of 0.71 in overall survival with a one-sided α of 0.025. An Independent Data Safety Monitoring Board will monitor safety. No interim analysis is planned and no cross-over is permitted.
- Evofosfamide will be administered at a dose of 400 mg/m^2 via intravenous (IV) infusion over 30-60 minutes on Days 1 and 8 of every 21-day cycle until progressive disease, intolerable toxicity, or withdrawal of consent.
- Pemetrexed (500 mg/m^2) will be administered on Day 1 of every 21-day cycle as an IV infusion 2-4 hours after evofosfamide administration until progressive disease, intolerable toxicity, or withdrawal of consent.
- After the treatment phase is completed, patients are followed for survival, quality of life, pain, and subsequent cancer treatments.
- Study locations span approximately 10 countries and will encompass approximately 90 sites.
- Regions include North America and Europe.

Figure 3. Study Schema and Dose Schedule



Trial Endpoints

- The primary endpoint is overall survival.
- Secondary/exploratory endpoints include overall response rate, progression-free survival, quality of life, pharmacokinetics, and biomarkers.

Study Timeline

- The first patient was dosed in June 2014. Enrollment is ongoing.
- Continue on target to complete enrollment in 2016.

Inclusion Criteria

- Age greater than or equal to 18.
- Histologically confirmed stage IIIB or IV non-squamous NSCLC.
- Recurrent or progressive disease after one prior platinum-based non-pemetrexed chemotherapy treatment with or without maintenance; Use of targeted agents (e.g., monoclonal antibodies or kinase inhibitors) does not count as a prior chemotherapy treatment (including immune checkpoint inhibitors).
- Patients must undergo testing for EGFR-activating rearrangements and, if negative, ALK rearrangements, and if identified on either, must receive a targeted kinase inhibitor prior to enrollment on this study.
- Measurable disease according to RECIST 1.1.
- ECOG performance status 0-1.
- Adequate hematologic, hepatic, cardiac, and renal function.

Exclusion Criteria

- Diagnosis of small cell carcinoma of the lung, squamous cell carcinoma of the lung or NSCLC NOS.
- Prior therapy with pemetrexed.
- Inability or unwillingness to take folic acid, vitamin B12 supplementation or corticosteroids.
- Inability for patients with mild to moderate renal insufficiency (creatinine clearance of 45 to 79 mL/min) to discontinue non-steroidal anti-inflammatory drugs for 5 days (long half-life) or for 2 days (short half-life, if CrCL <80 mL/min) before pemetrexed dosing and until 2 days after pemetrexed dosing.
- Leptomeningeal disease or any untreated or symptomatic brain metastases, unless the following criteria are met:
  - Brain metastases are stable and have been previously treated with either whole-brain radiotherapy or gamma-knife surgery.
  - Steroids are currently not required and more than 14 days since last steroid treatment.
- Symptomatic pleural effusion (> CTCAE Grade 1 dyspnea) that is not amenable to drainage.
- Treatment with other systemic anticancer therapy within 4 weeks prior to the first dose of study medication.
- Treatment with full field radiation therapy within 4 weeks or limited field radiation therapy within 2 weeks prior to the first dose of study medication.
- Major surgery within 4 weeks or minor surgery within 2 weeks prior the first dose of study medication.
- Elective or a planned major surgery while on study treatment.
- Radiation therapy to greater than 25% of the bone marrow.
- Clinically significant active infection (e.g. tuberculosis, viral hepatitis, HIV).
- Any other serious uncontrolled medical disorders or psychological conditions that may interfere with study conduct.
- Previous malignancy within the past 3 years are excluded other than curatively treated basal cell or squamous cell carcinoma of the skin, early GI or bladder cancer by endoscopic resection, in situ carcinoma of the cervix or any cured cancer that is considered to have no impact on PFS or OS for the current NSCLC.

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