Study of TH-302 or Placebo in Combination With Pemetrexed in Patients With Non-squamous Non-small Cell Lung Cancer

The purpose of this study is to determine whether TH-302 in combination with pemetrexed is safe and effective in the treatment of non-squamous non-small cell lung cancer.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
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</thead>
<tbody>
<tr>
<td>Non-small Cell Lung Cancer</td>
<td>Drug: TH-302 combination with pemetrexed &lt;br&gt;Drug: Matched placebo in combination with pemetrexed</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Caregiver, Investigator)
Primary Purpose: Treatment

Official Title: A Randomized Phase 2, Double-blind, Placebo-controlled, Multi-center Study Comparing Pemetrexed in Combination With TH-302 vs. Pemetrexed in Combination With Placebo as Second-line Chemotherapy for Advanced Non-Squamous, Non-Small Cell Lung Cancer

Resource links provided by NLM:

- MedlinePlus related topics: Cancer Lung Cancer
- Drug Information available for: Pemetrexed Pemetrexed disodium
- U.S. FDA Resources

Further study details as provided by Threshold Pharmaceuticals:
Primary Outcome Measures:
- Overall survival [ Time Frame: 2 years ] [ Designated as safety issue: No ]
  To assess the efficacy of pemetrexed in combination with TH-302 as determined by overall survival in patients with advanced non-squamous NSCLC in the second-line chemotherapy setting compared with pemetrexed in combination with placebo.

Secondary Outcome Measures:
- Incidence and severity of adverse events in patients treated with TH-302 in combination with pemetrexed vs pemetrexed alone [ Time Frame: 2 years ] [ Designated as safety issue: Yes ]
  To assess the safety of TH-302 in combination with pemetrexed compared with placebo and pemetrexed in this setting.
- Population PK of TH-302 in patients treated with TH-302 for measures including clearance and volume of distribution [ Time Frame: 2 years ] [ Designated as safety issue: Yes ]
  To investigate the pharmacokinetics of TH-302 in this patient population.
- Evaluate anti-tumor activity as measured by progression-free survival and response rate in patients treated with TH-302 in combination with pemetrexed vs pemetrexed alone [ Time Frame: 2 years ] [ Designated as safety issue: No ]
  To evaluate the anti-tumor activity of pemetrexed in combination with TH-302 compared with pemetrexed in combination with placebo.

Estimated Enrollment: 440
Study Start Date: March 2014
Estimated Study Completion Date: October 2016
Estimated Primary Completion Date: July 2016 (Final data collection date for primary outcome measure)

<table>
<thead>
<tr>
<th>Arms</th>
<th>Assigned Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental: TH-302 and pemetrexed TH-302 in combination with pemetrexed</td>
<td>Drug: TH-302 combination with pemetrexed 400 mg/m2 of TH-302 will be administered by IV infusion over 30 - 60 minutes on Day 1 and Day 8 of a 21-day cycle. Pemetrexed (500 mg/m2) will be administered as an IV infusion on Day 1 two - four hours after TH-302 administration.</td>
</tr>
<tr>
<td>Active Comparator: Placebo and pemetrexed Matching placebo in combination with pemetrexed</td>
<td>Drug: Matched placebo in combination with pemetrexed Matched placebo will be administered by IV infusion over 30 - 60 minutes on Day 1 and Day 8 of a 21-day cycle. Pemetrexed (500 mg/m2) will be administered as an IV infusion on Day 1 two - four hours after placebo administration.</td>
</tr>
</tbody>
</table>

Detailed Description:
TH-302 is designed to target the hypoxic regions of tumors which are generally located distant from tumor vessels. Pemetrexed has poor tissue penetration and targets the regions of tumors that are located in proximity to the tumor vessels. The presence of hypoxia in solid tumors is associated with a more malignant phenotype and resistance to chemotherapy. The hypoxia-activated prodrug, TH-302, is designed to selectively target the hypoxic microenvironment. There is evidence supporting the presence of hypoxia in NSCLC lesions based on a hypoxia PET study. Combining pemetrexed with TH-302 may enable the targeting of both the normoxic and hypoxic regions of NSCLC lesions.

Eligibility
Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria
Inclusion Criteria:
- Men and women ≥ 18 years of age.
- Histologically or cytologically confirmed stage IIIb or IV NSCLC with non-squamous histology
- Recurrent or progressive disease after one prior platinum-based non-pemetrexed chemotherapy treatment for advanced disease with or without maintenance
Neoadjuvant/adjuvant cytotoxic chemotherapy initiated < 12 months prior to study randomization will be counted as one prior treatment

Neoadjuvant/adjuvant cytotoxic chemotherapy initiated ≥ 12 months prior to study randomization will not be counted as one prior chemotherapy treatment

Use of targeted agents (e.g., monoclonal antibodies or kinase inhibitors) will not be counted as a prior chemotherapy treatment

Patients with known EGFR-activating mutations or ALK rearrangements should have received treatment with a targeted kinase inhibitor (e.g., erlotinib, crizotinib) and no longer be considered as a candidate for such treatment

Measurable disease according to RECIST 1.1

ECOG performance status 0-1

Resolution to Grade ≤ 1 Adverse Events, of all clinically significant toxic effects of prior therapy

Adequate hematologic, hepatic, cardiac, and renal function

Female patients of childbearing potential must have a negative serum or urine pregnancy test, whichever is considered standard by the institution

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 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
- Concurrent active malignancy other than adequately treated basal cell or squamous cell carcinoma of the skin or pre-invasive carcinoma of the cervix.
- Pregnant or breast feeding
- Patients who are taking medications that prolong QT interval and have a risk of Torsades de Pointes (Appendix F) or who have a history of long QT syndrome
- Patients who are taking medications that are strong inducers or inhibitors of CYP3A4

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT02093962

Contacts
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Sponsors and Collaborators
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EMD Serono
Investigators
Study Chair: Tillman Pearce, MD Threshold Pharmaceuticals
Principal Investigator: Jonathan Goldman, MD UCLA-Dept of Medicine a Div of Hem/Onc

More Information
No publications provided

Responsible Party: Threshold Pharmaceuticals
ClinicalTrials.gov Identifier: NCT02093962
Other Study ID Numbers: TH-CR-415
Study First Received: March 18, 2014
Last Updated: August 21, 2014
Health Authority: United States: Food and Drug Administration
United States: Institutional Review Board

Keywords provided by Threshold Pharmaceuticals:
TH-302
TH-CR-415
Pemetrexed
Non-small cell lung cancer
Lung cancer

Additional relevant MeSH terms:
Carcinoma, Non-Small-Cell Lung
Lung Neoplasms
Carcinoma, Bronchogenic
Bronchial Neoplasms
Respiratory Tract Neoplasms
Thoracic Neoplasms
Neoplasms by Site
Neoplasms
Lung Diseases
Respiratory Tract Diseases
Pemetrexed
Antimetabolites, Antineoplastic
Antimetabolites
Molecular Mechanisms of Pharmacological Action
Pharmacologic Actions
Antineoplastic Agents
Therapeutic Uses
Enzyme Inhibitors
Folic Acid Antagonists

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