NRG-LU001: Randomized Phase II Trial of Concurrent Chemoradiotherapy +/- Metformin HCL in Locally Advanced NSCLC

Fast Facts

PATIENT SELECTION

1. ***Conditions for Patient Eligibility***
   a. Pathologically (histologically or cytologically) proven diagnosis of Stage IIIA or IIIB non-small cell lung cancer within 84 days of registration; eligible histologies include adenocarcinoma, adenosquamous, large cell carcinoma, squamous carcinoma, non-lobar and non-diffuse bronchoalveolar cell carcinoma or non-small cell lung cancer NOS).
   b. Patients must have measurable disease;
   c. Patients must have unresectable disease, be medically inoperable, or unwilling to undergo surgical management;
   d. Appropriate stage for protocol entry, including no distant metastases, based upon the following minimum diagnostic workup:
      - History/physical examination, including documentation of height, weight, BSA, and vital signs, within 30 days prior to registration;
      - CT scan with IV contrast or MRI imaging (if CT scan with contrast is medically contraindicated) of the lung and upper abdomen through the adrenal glands, required within 45 days prior to registration (recommended within 30 days).
      - MRI of the brain with contrast (or CT with contrast if MRI is medically contraindicated) within 45 days prior to registration; **note:** The use of intravenous contrast is required for the MRI or CT. An MRI without contrast is only permitted if the patient has a contrast allergy.
      - Whole-body FDG-PET/CT required within 45 days prior to registration (recommended within 30 days prior to registration); **note:** patients do not need to have a separate CT of the chest and upper abdomen with contrast if PET/CT imaging includes a high quality CT with contrast.
   e. Zubrod Performance Status 0-1;
   f. Age ≥ 18;
   g. CBC/differential obtained within 14 days prior to registration on study, with adequate bone marrow function defined as follows:
      - Absolute neutrophil count (ANC) ≥ 1,500 cells/mm3
      - Platelets ≥ 100,000 cells/mm3
      - Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.)
   h. Adequate renal function within 14 days prior to registration, defined as serum creatinine within normal institutional limits or creatinine clearance must be at least 60 ml/min
   i. Adequate hepatic function within 14 days prior to registration, defined as total bilirubin ≤ 1.5 x upper limit of normal (ULN) for the institution and ALT, AST, and alkaline phosphatase ≤ 2.5 x ULN for the institution;
   j. Fasting blood glucose ≤ 125 mg/dL within 14 days prior to registration;

k. Serum albumin > 3.0 g/dl within 14 days prior to registration;
l. For women of childbearing potential, a serum pregnancy test within 72 hours prior to registration;
m. Patients with post-obstructive pneumonia are eligible provided they no longer require intravenous antibiotics at registration;
n. Patients must be at least 3 weeks from prior thoracotomy (if performed);
o. If a pleural effusion is present, the following criteria must be met at registration to exclude malignant involvement (incurable M1a disease):
    - When pleural fluid is visible on both the CT scan and on a chest x-ray, a pleuracentesis is required to confirm that the pleural fluid is cytologically negative;
    - Effusions that are minimal (i.e. not visible under ultrasound guidance) and that are too small to safely tap are eligible.
p. Women of childbearing potential and male participants must practice adequate contraception throughout the study;
q. Patient must provide study specific informed consent prior to study entry.

2. Conditions for Patient Ineligibility

a. Patients with mixed small cell and non-small cell histologies;
b. Patients with distant metastasis;
c. Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years (for example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible)
d. Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable;
e. Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;
f. Patients currently using metformin, other oral hypoglycemic agents or insulin;
g. Patients with any history of allergic reaction to paclitaxel or other taxanes or carboplatin;
h. Patients with a history of chronic kidney disease or lactic acidosis;
i. Patients with ≥ 10% weight loss within the past month;
j. Severe, active co-morbidity, defined as follows:
    - Diagnosis of Type I or Type II Diabetes Mellitus;
    - Uncontrolled neuropathy ≥ grade 2 regardless of cause;
    - Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;
    - Transmural myocardial infarction within the last 6 months;
    - Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
    - Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days of registration;
    - Severe hepatic disease, defined as a diagnosis of Child-Pugh Class B or C hepatic disease.
    - HIV positive with CD4 count < 200 cells/microliter. Note that patients who are HIV positive are eligible, provided they are under treatment with highly active antiretroviral

therapy (HAART) and have a CD4 count ≥ 200 cells/microliter within 30 days prior to registration. Note also that HIV testing is not required for eligibility for this protocol.

- End-stage renal disease (ie, on dialysis or dialysis has been recommended).

k. Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

TREATMENT

Arm 1: Patients randomized to concurrent chemotherapy and radiation therapy must begin treatment within 14 days after randomization.

Arm 2: Patients randomized to metformin must begin metformin within 14 days after randomization and every effort must be made to begin concurrent chemotherapy and radiation therapy 14 days after beginning metformin. Concurrent chemoradiotherapy and metformin ideally should start on a Monday.

PRE-STUDY PARAMETERS

- History/physical exam including height, weight, BSA, performance status, and vitals
- CT with contrast or MRI of lungs and upper ab through adrenals
- MRI or CT of brain
- Whole-body FDG-PET/CT
- CBC/diff, ANC, platelets, hemoglobin
- Serum creatinine or creatinine clearance
- CMP
- Serum Pregnancy
- Examination by Rad Onc or Med Onc
- Nutritional Assessment
- Tissue, serum, and plasma submission