NRG ONCOLOGY

RTOG 1306

A Randomized Phase II Study of Individualized Combined Modality Therapy for Stage III Non-small Cell Lung Cancer (NSCLC)

SCHEMA (5/29/14)

Institution’s Screening for Biomarkers Prior to Randomization: Mandatory
The enrolling institution is responsible for screening (must be done at CLIA certified lab) for documentation of EGFR TK mutation and EML4-ALK fusion arrangement.

For EGFR mutation testing, any genotyping method to detect exon 19 deletion, L858, and T790M mutation may be used as long as it is performed in a CLIA certified laboratory. Note: The enrolling institution must provide the method of testing and the specific result (i.e. specific mutation).

For ALK testing, the FDA approved Vysis dual color FISH assay must be used for the detection of an ALK rearrangement. Note: The enrolling institution must provide the testing laboratory and the specific result (% of positive cells).

Patients with both the EGFR mutation and ALK arrangement will be placed in the ALK Cohort. See Section 10.0 for details of retrospective central review and biomarker analyses.

<table>
<thead>
<tr>
<th>Weight Loss (in prior 6 mos.)</th>
<th>Stratification</th>
<th>Chemothrapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ≤ 5%</td>
<td>1. IIIA</td>
<td>1. cisplatin &amp; etoposide</td>
</tr>
<tr>
<td>2. &gt; 5%</td>
<td>2. IIIB</td>
<td>2. paclitaxel &amp; carboplatin</td>
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**EGFR TK Mutation Cohort**

**Arm 1:** Induction Therapy:
Erlotinib, 150 mg/day for 12 weeks*

**Arm 2:** Concurrent †chemotherapy and radiation, 60 Gy

**ALK Tran L Cohort**

**Arm 3:** Induction Therapy:
Crizotinib, 250 mg/bid for 12 weeks*

**Arm 4:** Concurrent †chemotherapy and radiation, 60 Gy

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Concurrent †chemotherapy and IMRT or 3D-CRT
60 Gy in 30 fx

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†Per treating physician’s discretion, a choice of 2 chemotherapy regimens:
- Cisplatin and etoposide, every 4 weeks, for 2 cycles;
- Paclitaxel and carboplatin weekly for 6 weeks followed by 2 cycles of consolidation.
  Consolidation chemotherapy will begin 4-6 weeks after completion of chemoradiation.
- CT scans will be obtained 4-6 weeks after chemoradiation is completed and prior to consolidation chemotherapy administration. See Section 11.2.3 for additional monitoring.

*If CT at 6 weeks into induction therapy does not show at least PR, the patient will proceed directly to concurrent chemotherapy and IMRT or 3D-CRT, provided there is no progression that would preclude definitive chemoradiotherapy, in which case the patient will go off protocol treatment and be treated as appropriate for systemic disease. See Section 11.3 for definitions of responses.

**Patient Population:** (See Section 3.0 for Eligibility)
Histologically or cytologically confirmed non-squamous NSCLC; unresectable stage IIIA or IIIB disease; patients must be surgically staged to confirm N2 or N3 disease.

**Required Sample Size:** 156 for the EGFR mutation cohort and 78 for the ALK translocation cohort
3.0 PATIENT SELECTION (5/29/14)
NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED. For questions concerning eligibility, please contact the study data manager.

3.1 Conditions for Patient Eligibility (6/26/15)
3.1.1 Histologically or cytologically confirmed, newly diagnosed non-squamous NSCLC;
3.1.2 Unresectable stage IIIA or IIIB disease; patients must be surgically staged to confirm N2 or N3 disease. Patients may have invasive mediastinal staging by mediastinoscopy, mediastinotomy, EBUS-TBNA, EUS, or VATS.
3.1.3 Patients with any T with N2 or N3 are eligible. Patients with T3, N1-N3 disease are eligible if deemed unresectable. Patients with T4, any N are eligible.
3.1.4 Patients must have measurable disease, i.e., lesions that can be accurately measured in at least 1 dimension (longest dimension in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
3.1.5 Patients with a pleural effusion, which is a transudate, cytologically negative and non-bloody, are eligible if the radiation oncologist feels the tumor can be encompassed within a reasonable field of radiotherapy.
3.1.6 If a pleural effusion can be seen on the chest CT but not on chest x-ray and is too small to tap, the patient will be eligible. Patients who develop a new pleural effusion after thoracotomy or other invasive thoracic procedure will be eligible.
3.1.7 The institution’s pre-enrollment biomarker screening at a CLIA certified lab documents presence of known “sensitive” mutations in EGFR TK domain (exon 19 deletion, L858) and/or EML4-ALK fusion arrangement. Either the primary tumor or the metastatic lymph node tissue may be used for testing of mutations.
3.1.8 The institution’s pre-enrollment biomarker screening at a CLIA certified lab documents absence of T790M mutation in the EGFR TK domain;
3.1.9 Appropriate stage for protocol entry, including no distant metastases, based upon the following minimum diagnostic workup:
- History/physical examination, including recording of pulse, BP, weight, and body surface area, within 45 days prior to registration;
- Whole body FDG-PET/CT (orbits to mid-thighs) within 30 days prior to registration; PET/CT must be negative for distant metastasis.
- CT scan with contrast of the chest and upper abdomen to include liver and adrenals (unless medically contraindicated) within 30 days prior to registration;
- MRI of the brain with contrast (or CT scan with contrast, if MRI medically contraindicated) within 30 days prior to registration.
3.1.10 Zubrod Performance Status 0-1 within 14 days prior to registration;
3.1.11 Age ≥ 18;
3.1.12 CBC/differential obtained within 14 days prior to registration, with adequate bone marrow function defined as follows:
- Absolute neutrophil count (ANC) ≥ 1,000 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.);
3.1.13 Adequate renal and hepatic function, defined as follows:
- Serum creatinine < 1.5 mg/dL or Calculated Creatinine Clearance ≥ 50 ml/min (by Cockcroft-Gault formula) within 14 days prior to registration;
- AST/ALT ≤ 2.5 X ULN within 14 days prior to registration;
- Bilirubin within normal institutional limits within 14 days prior to registration
3.1.14 Negative serum pregnancy test within 14 days prior to registration for women of childbearing potential;
3.1.15 Patient must provide study specific informed consent prior to study entry, including consent for mandatory screening of tissue.

3.2 Conditions for Patient Ineligibility (5/29/14)
3.2.1 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 730 days [2 years] (For example, carcinoma in situ of the breast, oral cavity, or cervix
are all permissible);
3.2.2 Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable;
3.2.3 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;
3.2.4 Atelectasis of the entire lung;
3.2.5 Contralateral hilar node involvement;
3.2.6 Exudative, bloody, or cytologically malignant effusions;
3.2.7 Severe, active co-morbidity, defined as follows:
   - 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 at the time of registration;
   - Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects;
   - Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.
3.2.8 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.
3.2.9 Prior allergic reaction to the study drug(s) involved in this protocol.