

**RTOG (0617): A Randomized Phase III Comparison Of Standard- Dose (60 Gy) Versus High-Dose (74 Gy) Conformal Radiotherapy With Concurrent And Consolidation Carboplatin/Paclitaxel +/- Cetuximab (IND #103444) In Patients With Stage IIIA/IIIB Non-Small Cell Lung Cancer**

*Fast Facts*

**Eligibly Criteria**

1. Pathologically proven (either histologic or cytologic) diagnosis of Stage IIIA or IIIB non-small cell lung cancer; excluding patients with N3 disease based on supraclavicular or contralateral hilar adenopathy, [according to AJCC Staging, 6<sup>th</sup> edition; see appendix III] within 12 weeks of registration.
2. Patients must be considered unresectable or inoperable; **Note:** Patients who have had a nodal recurrence after surgery for an early-stage NSCLC are eligible if the following criteria are met:
  - Nodal recurrence must be N1 or N2; N3 is not eligible.
  - The initial primary must have been staged as T1-2, N0, M0.
  - The node must be biopsied within 12 weeks of registration.
  - The node must be measurable.
  - The patient must not have received prior chemotherapy or radiation for this lung cancer.
  - Prior curative surgery must have been at least 6 months prior to the nodal recurrence.
  - The exception to a prior invasive malignancy (Section 3.2.7) does not apply to the initial lung primary.
3. Stage IIIA or IIIB disease, including no distant metastases, based upon the following minimum diagnostic workup are exceptable:
  - a. History/physical examination including height, weight, BSA, and vital signs within 8 weeks prior to registration.
  - b. Computed tomographic (CT)/MRI imaging of the lung and upper abdomen through the adrenal glands within 6 weeks prior to registration.
  - c. An MRI without contrast is only permitted if the patient has a contrast allergy. Note: the use of contrast is required for the MRI or CT unless patient has an allergy.
  - d. Whole body FDG-PET or PET/CT of if no PET is available, a bone scan is required within 6 weeks of registration. Note: If a PET is done that shows clear adrenals and lungs, then a CT scan of chest only is permitted.
4. If a pleural effusion is present, the following criteria must be met to exclude malignant involvement (incurable T4 disease):
  - a. When plural 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.
  - b. Exudative pleural effusions are excluded, regardless of cytology.
  - c. Effusion that are minimal (ie not visible on chest x-ray) that are too small to safely tap are eligible.
5. Patients must have measurable or evaluable disease.
6. Patients with post-obstructive pneumonia are eligible.
7. Patients must be at least 3 weeks from prior thoracotomy (if performed).
8. Zubrod performance status 0-1.
9. Age  $\geq$  18.
10. PFT's including FEV1 within 12 weeks prior to registration; for FEV1, the best value obtained pre- or post-bronchodilator must be  $\geq$  1.2 liters/second or 50% predicted.
11. CBC/differential obtained within 2 weeks prior to registration on study, with adequate bone marrow function defined as follows:
  - a. ANC  $\geq$  1,800 cells/mm<sup>3</sup>
  - b. Platelets  $\geq$  100,000 cells/mm<sup>3</sup>
  - c. Hemoglobin  $\geq$  10.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb  $\geq$  10.0 g/dl is acceptable.)
  - d. Serum creatinine within normal institutional limits or creatinine clearance  $\geq$  60 ml/min
  - e. Bilirubin within normal institutional limits
  - f. AST and ALT  $<$  the IULN
12. Patients must be informed of the investigational nature of this study and give written informed consent according to institutional and federal guidelines

**Ineligibility Criteria**

1. N3 supraclavicular disease
2. Patients for whom treatment is planned with a maximum dose of  $\geq 66$  Gy to the ipsilateral brachial plexus
3. Greater than minimal, exudative, or cytologically positive pleural effusions.
4. Pancoast tumor
5. Involved contralateral hilar nodes (ie greater than 1.5 cm on short axis or positive PET scan)
6.  $\geq 10\%$  weight loss within the past month.
7. Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of three years. Non-invasive conditions such as carcinoma in situ of the breast, oral cavity or cervix are all permissible.
8. Prior systemic chemotherapy for the study cancer; Note that prior chemotherapy for a different cancer is allowable.
9. Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields.
10. Prior therapy that specifically targets the EGFR pathway.
11. Prior severe infusion reaction to a monoclonal antibody.
12. Severe, active co-morbidity, defined as follows:
  - a. Significant history of uncontrollable cardiac disease; i.e. uncontrollable hypertension, unstable angina, myocardial infarction within the last 6 months uncontrolled congestive heart failure, and cardiomyopathy with decreased ejection fraction.
  - b. Transmural myocardial infarction within the last 6 months.
  - c. Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration.
  - d. Chronic Obstructive Pulmonary Disease exacerbated or other respiratory illness requiring hospitalization or precluding study therapy within 30 days before registration
  - e. Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; Note: however, that laboratory test for liver function and coagulation parameters are not required for entry into this protocol.
  - f. 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.
13. 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.
14. Any history of allergic reaction to paclitaxel or other taxans, or to carboplatin.
15. Uncontrolled neuropathy grade 2 or greater regardless of cause.

**Pre-treatment Parameters**

1. History and physical including weight, performance status
2. CBC with differential, CMP
3. CT/MRI chest and upper abdomen
4. FDG-PET, PET/CT or bone scan
5. PFT's (including DLCO and FEV1)
6. MRI of the brain with contrast

**Schema**

		Concurrent Treatment	Consolidation Treatment
S T R A T I F Y	<b>RT Technique</b> 1. 3D-CRT 2. IMRT  <b>Zubrod</b> 1. 0 2. 1  <b>PET Staging</b> 1. No 2. Yes  <b>Histology</b> 1. Squamous 2. Non-Squamous	<b>Arm A</b>  <u>Concurrent chemotherapy:</u> Carboplatin & Paclitaxel  RT to 60 Gy, 5 x per week for 6 weeks	<b>Arm A</b>  <u>Consolidation chemotherapy:</u> Carboplatin & Paclitaxel
		<b>Arm B</b>  <u>Concurrent chemotherapy:</u> Carboplatin & Paclitaxel,  RT to 74 Gy, 5 x per week for 7.5 weeks	<b>Arm B</b>  <u>Consolidation chemotherapy:</u> Carboplatin & Paclitaxel
		<b>Arm C</b>  <u>Cetuximab Loading Dose:</u> Week 1, Day 1 then <u>Concurrent chemotherapy, Carboplatin &amp; Paclitaxel, and Cetuximab:</u>  RT to 60 Gy, 5 x per week for 6 weeks	<b>Arm C</b>  <u>Consolidation therapy:</u>  Cetuximab and Carboplatin & Paclitaxel
		<b>Arm D</b>  <u>Cetuximab Loading Dose:</u> Week 1, Day 1 then <u>Concurrent chemotherapy, Carboplatin &amp; Paclitaxel, and Cetuximab:</u>  RT to 74 Gy, 5 x per week for 7.5 weeks	<b>Arm D</b>  <u>Consolidation therapy:</u>  Cetuximab and Carboplatin & Paclitaxel

See Section 5.0 for credentialing requirements for radiation therapy