

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

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Primary Objective:

- To compare the overall survival of patients treated with high-dose versus standard-dose conformal radiation therapy in the setting of concurrent chemotherapy
- To compare the overall survival of patients treated with cetuximab versus without cetuximab in the setting of concurrent chemotherapy

Secondary Objective:

- To compare progression-free survival (PFS) and local-regional tumor control between highdose versus standard-dose radiation therapy and between concurrent cetuximab versus no cetuximab
- To compare the toxicity of high-dose versus standard-dose conformal radiation therapy in the setting of concurrent chemotherapy with or without cetuximab
- To investigate the prognostic and predictive effects of gross tumor volume on overall survival
- To assess quality of life (QOL) between high-dose versus standard dose conformal radiation therapy
- To correlate outcomes (survival, toxicity, QOL) with biological parameters
- To analyze the predictive value of pre-treatment SUV of PET scan in predicting survival, distant metastasis, and local-regional control in patients with stage III NSCLC treated with concurrent chemoradiotherapy with conventional radiation dose of 60 Gy and escalated dose of 74 Gy
- To explore biological markers to predict clinical outcome including survival, distant metastasis,

- local-regional control, quality of life including toxicity in patients with stage III NSCLC treated with conventional dose (60 Gy) and high dose (74 Gy) radiation therapy in the setting of concurrent chemotherapy with or without cetuximab
- To prospectively collect and bank tissue specimen, blood and urine samples for future biomarker analyses in predicting clinical outcome including survival, distant metastasis, local regional control, and quality of life in patients with stage III NSCLC treated with conventional dose (60) Gy and high dose (74 Gy) radiation therapy in the setting of concurrent chemotherapy with or without cetuximab
 - To investigate associations between EGFR expression and toxicity, response, overall survival, and progression-free survival.

Study Population: Total: 512 -- Local: 10

Schema: You will be "randomized" into one of the study groups described below.

If you are in group 1 (called "Arm A") ...

You will receive the standard or usual dose of radiation therapy (60 Gray given in 30 treatments). You will receive treatment radiation therapy 5 days per week for about 6 weeks. Chemotherapy consisting of paclitaxel and carboplatin will be given on days 1, 8, 15, 22, 29, 36 during radiation therapy. You will receive two additional cycles of chemotherapy on days 64 and 85 after completion of the combined chemotherapy and radiation.

If you are in group 2 (called "Arm B")...

You will receive a higher than standard dose of radiation therapy (74 Gray given in 37 treatments). You will receive treatment radiation therapy 5 days per week for 7½ weeks. Chemotherapy consisting of paclitaxel and carboplatin will be given weekly on days 1, 8, 15, 22, 29, 36 and 43 during radiation therapy. You will receive two additional cycles of chemotherapy on days 71 and 92 after completion of the combined chemotherapy and radiation.

Both groups 1 and 2 (Arm A and B) will receive chemotherapy with the same drug combination, dose, and schedule. Paclitaxel and carboplatin are given by vein before radiation therapy. The paclitaxel takes one hour to be given after you have been pre-medicated with medicines to ease possible side effects. After the paclitaxel, the carboplatin is given over 30 minutes along with drugs used to prevent or reduce upset stomach and vomiting.

If you are in group 3 (called "Arm C"):

You will receive the standard or usual dose of radiation therapy. You will receive treatment radiation therapy 5 days per week for about 6 weeks. Chemotherapy consisting of paclitaxel and carboplatin will be given on days 8, 15, 22, 29, 36, and 43 during radiation therapy. You also will receive cetuximab on these days. After completion of the radiation, chemotherapy, and cetuximab, you will receive two additional cycles of chemotherapy on days 71 and 92, and you will receive cetuximab on days 50, 57, 64, 71, 78, 85, 92, 99, and 106.

If you are in group 4 (called "Arm D"):

You will receive a higher than standard dose of radiation therapy. You will receive treatment radiation therapy 5 days per week for 7½ weeks. Chemotherapy consisting of paclitaxel and carboplatin will be given on days 1, 8, 15, 22, 29, 36, 43, and 50 during radiation therapy. You also will receive cetuximab on these days. After completion of the radiation, chemotherapy, and cetuximab, you will receive two additional cycles of chemotherapy on days 78 and 99, and you will receive cetuximab on days 57, 64, 71, 78, 85, 92, 99, and 106.

Groups 3 and 4 (Arms C and D): Before the first dose of cetuximab, you will be given some medicine through your vein to prevent an allergic reaction to cetuximab. Then you will proceed to receive the first cetuximab dose. No chemotherapy or radiation will be given on the day of the first dose of cetuximab.

Assessments:

- History and physical examination
- A biopsy of your tumor proving that you have cancer

- CT scan of the chest and upper abdomen (to visualize the structure and function of your chest and upper abdomen)
- MRI scan of the brain (or CT if the MRI cannot be performed for medical reasons)
- Body FDG-PET or PET-CT scan or bone scan (to identify new areas of bone growth or breakdown)
- Routine blood tests
- Pregnancy test (for women)
- Pulmonary function studies (to test your lung function)

Inclusion Criteria:

- 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, 6th edition; see appendix III] within 12 weeks of registration
- Patients must be considered unresectable or inoperable
- Stage III A or B disease, including no distant metastases, based upon the following minimum diagnostic workup are acceptable:
 - History/physical examination, including documentation of height, weight, BSA, and vital signs within 8 weeks prior to registration
 - Computed tomographic (CT)/MRI imaging of the lung and upper abdomen through the adrenal glands within 6 weeks prior to registration
 - An MRI of the brain with contrast (or CT with contrast if MRI is medically contraindicated) within 6 weeks prior to registration; Note: The use of intravenous contrast is required for the MRI or CT, unless the patient has a contrast allergy
 - Whole-body FDG-PET or PET/CT or if no PET is available, a bone scan is required within 6 weeks prior to registration
- If a pleural effusion is present, the following criteria must be met to exclude malignant involvement (incurable T4 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

- Exudative pleural effusions are excluded, regardless of cytology
- Effusions that are minimal (i.e. not visible on chest x-ray) that are too small to safely tap are eligible.
- Patients must have measurable or evaluable disease
- Patients with post-obstructive pneumonia are eligible
- Patients must be at least 3 weeks from prior thoracotomy (if performed)
- Zubrod Performance Status 0-1
- Age ≥ 18
- PFTs including FEV1 within 12 weeks prior to registration; for FEV1, the best value obtained pre- or post bronchodilator must be ≥ 1.45 liters/second
- CBC/differential obtained within 2 weeks prior to registration on study, with adequate bone marrow function defined as follows
 - Absolute neutrophil count (ANC) $\geq 1,800$ cells/mm³
 - Platelets $\geq 100,000$ cells/mm³
 - Hemoglobin ≥ 10.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 10.0 g/dl is acceptable.)
- Serum creatinine within normal institutional limits or creatinine clearance ≥ 60 ml/min
- Bilirubin within normal institutional limits;
- 3.1.14 AST and ALT < 2.5 x the IULN;
- 3.1.15 Patient must sign study specific informed consent prior to study entry.

Exclusion Criteria:

- N3 supraclavicular disease
- Patients for whom treatment is planned with a maximum dose of ≥ 66 Gy to the ipsilateral brachial plexus
- Greater than minimal, exudative, or cytologically positive pleural effusions
- Pancoast tumors
- Involved contralateral hilar nodes (i.e. greater than 1.5 cm on short axis or positive on PET scan)
- $\geq 10\%$ weight loss within the past month
- Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a

- minimum of 3 years; non-invasive conditions such as carcinoma in situ of the breast, oral cavity, or cervix are all permissible
- Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable
 - Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields
 - Prior therapy that specifically and directly targets the EGFR pathway
 - Prior severe infusion reaction to a monoclonal antibody
 - Severe, active co-morbidity, defined as follows:
 - Significant history of uncontrolled cardiac disease; i.e., uncontrolled hypertension, unstable angina, myocardial infarction within the last 6 months, uncontrolled congestive heart failure, and cardiomyopathy with decreased ejection fraction
 - 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 before 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
 - 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
 - Any history of allergic reaction to paclitaxel or other taxanes, or to carboplatin

- Uncontrolled neuropathy grade 2 or greater regardless of cause