2.0 OBJECTIVES

2.1 Primary Objective

2.1.1 To assess whether patients with unresectable local-regionally advanced NSCLC treated with targeted agents based on molecular characteristics have a longer progression-free survival than those treated with standard care therapy alone

2.2 Secondary Objectives

2.2.1 To evaluate response rate;
2.2.2 To assess toxicity;
2.2.3 To assess overall survival;
2.2.4 To correlate clinical outcomes with tumor molecular aberrations identified from deep sequencing of selected kinomes in patients from whom adequate baseline tissue is available.

3.0 PATIENT SELECTION (7/29/13)

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED. For questions concerning eligibility, please contact RTOG Data Management (via the RTOG contact list on the RTOG web site) or the Principal Investigator, Dr. Govindan, (see the title page of the protocol for contact information).

3.1 Conditions for Patient Eligibility

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 within 30 days prior to registration.
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). Tumor measurements must be taken within 42 days prior to registration.
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 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 of the chest with contrast (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) ≥ 1,500 cells/mm^3;
- Platelets ≥ 100,000 cells/mm^3;
- 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:
- Calculated Creatinine Clearance ≥ 50 ml/min (by Cockroft-Gault formula) within 14 days prior to registration;
- AST/ALT < 3 X ULN within 14 days prior to registration;
- Bilirubin < 3 X ULN 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

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; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol.
- 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.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Highly Recommended Evaluations/Management

Note that these evaluations/interventions are highly recommended as part of good clinical care of patients on this trial but are not required.

4.1.1 Comprehensive pulmonary consultation and pulmonary function testing, including spirometry and diffusing capacity of carbon monoxide within 56 days prior to start of treatment;

4.1.2 EKG and/or echocardiogram within 56 days prior to start of treatment;