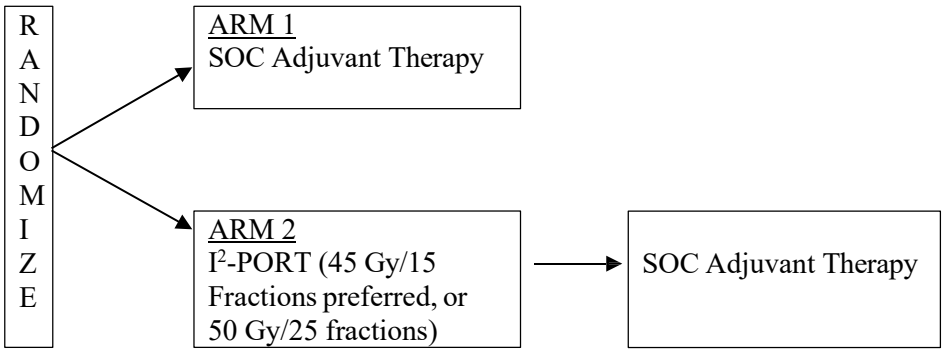
INVOLVED-STATION, INTENSITY-MODULATED POST-OPERATIVE RADIATION THERAPY (I²-PORT) FOR RESECTED NON-SMALL CELL LUNG CANCER WITH RESIDUAL MEDIASTINAL ADENOPATHY AFTER NEOADJUVANT THERAPY (YPN2)

Eligibility Criteria (see Section 3.0)	**Required Initial Laboratory Values**
Histologic diagnosis of NSCLC No metastatic disease No known EGFR mutation or ALK rearrangement Neoadjuvant systemic therapy and complete surgical resection (R0) with ypN2 disease per Section 3.2.2 Age ≥ 18 years ECOG Performance Status ≤ 2 Non-pregnant Comorbid conditions per Section 3.2.7	ANC ≥ 1000/mm^3 Platelet count: ≥ 50,000/mm^3 Calc. creatinine clearance: ≥ 30 mL/min Total bilirubin: ≤ 3 x ULN AST/ALT: ≤ 5 x ULN

Schema



Stratification Factors

Patients will be stratified according to the following factors prior to randomization:

1. Single-station (N2a) vs. multi-station (N2b) nodal disease per AJCC 9th edition
2. Adequate vs. inadequate regional nodal sampling
   Adequate sampling is defined as surgical assessment of at least one hilar (N1) and at least three mediastinal (N2) nodal stations

Treatment is to continue until completion of Standard of Care (SOC) Adjuvant Therapy, disease recurrence/progression or unacceptable adverse event. Patients will be followed for 5 years from registration or until death, whichever comes first.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

Post-Operative Radiation Therapy (PORT) will be conducted at the registering institution. SOC Adjuvant Therapy may be conducted at a non-registering institution.

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient: for example, medical conditions such as cardiac or inflammatory lung disease, which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient. Clinicians should use their clinical judgement and have discussions with potential trial participants to assess their ability to follow protocol requirements safely.

Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Reproductive status and discussions about birth control measures should be documented in the patient's record. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

3.2 Registration Eligibility Criteria (Step 1)

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s). Please note that an optional signature line has been provided for use by institutions wishing to use the eligibility checklist as source documentation.

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

_____ 3.2.1 Documentation of Disease:

- — Histopathologic diagnosis of NSCLC, may have mixed or multiple histologies but no small cell component.
- — No known EGFR mutation or ALK rearrangement.
- — No metastatic disease (M0) per most recent PET/CT and head CT/MRI imaging.
- — No disease progression per CT chest (including upper abdomen as per standard practice) with IV contrast (unless IV contrast is contraindicated) or FDG-PET performed post-neoadjuvant therapy ≤ 90 days prior to registration, either before or after surgery.
- — No metastatic disease (M0) per head CT/MRI imaging.

___ **3.2.2 Prior Treatment/Surgery:**

___ Prior treatment with 2–4 cycles of neoadjuvant systemic therapy with any guideline (NCCN) concordant regimen.

___ Lobectomy or greater oncologic surgical resection within 8 weeks prior to registration.

___ Complete (R0) resection showing ypN2 disease**.**

___ No prior radiotherapy to the lungs or mediastinum.

___ **No treatment with a VEGF inhibitor ≤ 90 days prior to registration or plan to treat with adjuvant systemic therapy including a VEGF inhibitor.**

___ **3.2.3 Age ≥ 18 years**

___ **3.2.4 ECOG Performance Status ≤ 2**

___ **3.2.5 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC)	≥ 1,000/mm^3
Platelet Count	≥ 50,000/mm^3
Calc. Creatinine Clearance	≥ 30 mL/min
Total Bilirubin	≤ 3 x upper limit of normal (ULN)
AST (SGOT)/ALT (SGPT)	≤ 5 x upper limit of normal (ULN)

___ **3.2.6 Not pregnant,** because this study involves radiation therapy, which has known genotoxic, mutagenic and teratogenic effects. Therefore, for women of childbearing potential only, a negative urine or serum pregnancy test done ≤ 7 days prior to registration is required.

___ **3.2.7 Comorbid Conditions**

___ **Patients with a prior or concurrent malignancy** whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

___ **Cardiac function:** Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

___ **No idiopathic pulmonary fibrosis requiring anti-fibrotic medication:** Patients with idiopathic pulmonary fibrosis or inflammatory/interstitial lung disease compromising pulmonary function or requiring ongoing treatment with nintedanib, pirfenidone, or other anti-fibrotic drug are excluded.

___ **3.2.8 HIV-infected patients on effective anti-retroviral therapy with an undetectable viral load within 6 months are eligible for this trial.**