Cancer Research Consortium of West Michigan
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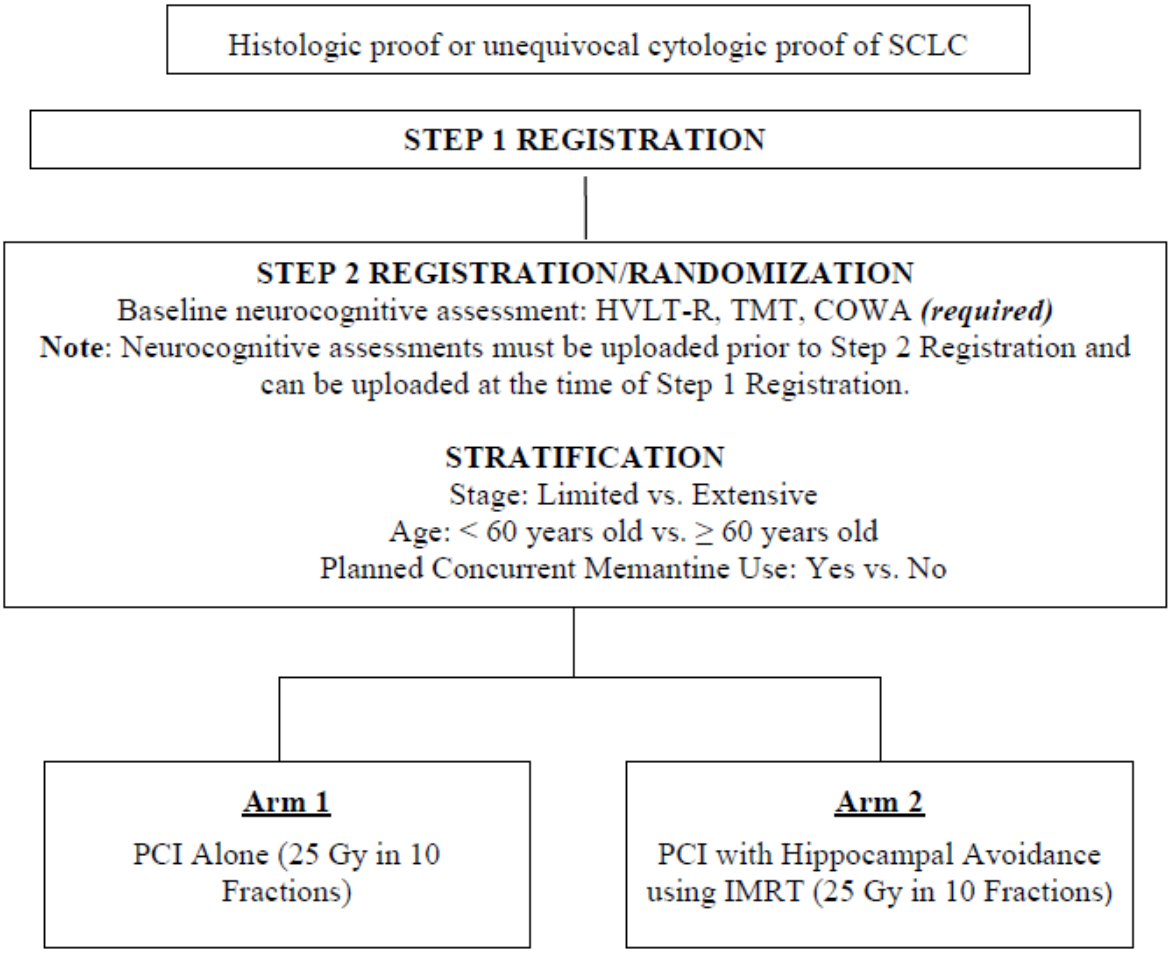
FAST FACTS

NRG CC003: Randomized Phase II/III Trial of Prophylactic Cranial Irradiation With or Without Hippocampal Avoidance for Small Cell Lung Cancer



NOTE: If the trial proceeds to the phase III component, all patients enrolled on the randomized phase II component will be included in the primary and secondary endpoint analysis of the phase III component.

Patient Selection Guidelines

1. Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.
2. Women of childbearing potential and men who are sexually active should be willing and able to use medically acceptable forms of contraception during the therapy (PCI alone or PCI with hippocampal avoidance) part of the trial.

3. Submission of serum and whole blood is strongly encouraged for all patients. Samples will be submitted for banking for the translational research portion of this protocol and for future studies. (See Section 10 for further details).

Eligibility Criteria

Prior to Step 1 Registration

1. Histologic proof or unequivocal cytologic proof (fine needle aspiration, biopsy or two positive sputa) of SCLC within 250 days prior to Step 1 registration;
    a. High-grade neuroendocrine carcinoma or combined SCLC and NSCLC is permitted.
2. Patients must have received chemotherapy and be registered to Step 1 registration no earlier than 7 days and no later than 56 days after completing chemotherapy. Note:
    • Post-chemotherapy restaging imaging must be completed no more than 56 days prior to Step 1 registration.
        • For patients with extensive-stage small cell lung cancer who are being considered for consolidative thoracic radiotherapy after chemotherapy, concomitant administration of consolidative thoracic radiotherapy and protocol-specified prophylactic cranial irradiation with or without hippocampal avoidance is permitted.
3. Patients must have a gadolinium contrast-enhanced three-dimensional (3D), spoiled gradient (SPGR), magnetization-prepared rapid gradient echo (MP-RAGE), or turbo field echo (TFE) MRI scan and an axial T2/FLAIR sequence. To yield acceptable image quality, the gadolinium contrast-enhanced three-dimensional SPGR, MP-RAGE or TFE axial MRI scan must use the smallest possible axial slice thickness not exceeding 1.5 mm. Sites may contact the Imaging Co-Chairs for further information or assistance if needed.
    a. This MRI must be obtained within 56 days of Step 1 registration.

Note: The MRI study is mandatory irrespective of randomization to the experimental or control arm of this study.

4. Prior to chemotherapy +/- thoracic radiotherapy, patients must be defined as limited-stage or extensive-stage SCLC after clinical staging evaluation involving the following:
    a. History/physical examination;
    b. CT of the chest and abdomen with contrast (does not have to be done if the patient has had a PET/CT scan prior to initiating chemotherapy or thoracic radiotherapy);

    c. MRI of the brain with contrast or diagnostic head CT with contrast;
    d.
5. For patients without evidence of extensive-stage SCLC on chest and abdomen CT and brain MRI or head CT, a PET/CT or bone scan is required to confirm limited-stage SCLC. After chemotherapy, patients must be restaged prior to Step 1 registration using the same diagnostic work-up as required pre-chemotherapy (see Section 3.2.4). Repeat PET/CT or bone scan is not required. Patients must have:
    - History/physical examination within 30 days of Step 1 registration;
    - No CNS metastases (Repeat MRI required; see Section 3.2.3 for details) within 56 days prior to Step 1 registration;
    - No progression in any site;

- Radiographic partial or complete response to chemotherapy in at least one disease site within 56 days prior to Step 1 registration.
    - If PET/CT was obtained prior to chemotherapy, either a repeat PET/CT or CT of the chest and abdomen with contrast can be obtained for response assessment.
    - Patients who underwent resection for limited-stage SCLC prior to chemotherapy and have no radiographically evident disease for response assessment remain eligible if post-chemotherapy imaging demonstrates no progression.

6. Zubrod performance status 0-2 within 30 days prior to Step 1 registration;
7. Age ≥18;
8. Women of childbearing potential must have a negative qualitative serum pregnancy test ≤ 14 days prior to Step 1 registration.
9. Patients who are primary English or French speakers are eligible.
10. Patients must sign a study-specific informed consent prior to study entry.

Prior to Step 2 Registration

11. The following baseline neurocognitive assessments must be completed and uploaded within 10 calendar days after or at the time of Step 1 registration: HVLT-R (recall, delayed recall, and recognition), TMT (Parts A and B), and COWA. The neurocognitive assessments will be uploaded into the NRG Oncology RAVE System for evaluation by Dr. Wefel. Once the upload is complete, within 3 business days, a notification email will be sent to the site to proceed to Step 2 registration. At minimum, the HVLT-R delayed recall must be able to be scored (i.e. completed without error) in order to be eligible.
12. Patients must have a baseline raw score greater than 2 on the HVLT-R Delayed Recall, as determined by central assessment by the Neurocognitive Co-Chair, Dr. Wefel.

Ineligibility Criteria

Patients with any of the following conditions are NOT eligible for this study.

1. Prior radiotherapy to the head or neck (except for T1 glottic cancer), resulting in overlap of radiation fields;
2. Radiographic evidence of CNS metastases;
3. Radiographic evidence of hydrocephalus or other architectural distortion of the ventricular system, including placement of external ventricular drain or ventriculoperitoneal shunt;
4. Planned concurrent chemotherapy during PCI;
   • Concurrent atezolizumab permitted
5. Concomitant invasive malignancy or invasive malignancy within the past five years other than non-melanomatous skin cancer; history of in situ carcinoma (e.g. ductal carcinoma in situ of breast, in situ carcinoma of the cervix, vulva or larynx) is permitted.
6. Contraindication to MR imaging, such as implanted metal devices or foreign bodies or severe claustrophobia;
7. Severe, active comorbidity, 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;

- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects;
- Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;
- Uncontrolled, clinically significant cardiac arrhythmias;
- HIV positive with CD4 count < 200 cells/microliter;
- Note: Patients who are HIV positive are eligible, provided they are under treatment with highly active antiretroviral therapy (HAART) and have a CD4 count ≥ 200 cells/microliter within 30 days prior to Step 1 registration.
- Note: HIV testing is not required for eligibility for this protocol.

8. Pregnant or lactating women or women of childbearing potential and male participants who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the radiation treatment involved in this study may be significantly teratogenic.

Pre-study Parameters

Prior to Step 1 Registration	**Prior to Step 2 Registration**
Histo/cyto proof of SCLC	Baseline neurocognitive: HVLT-R, TMT, COWA
History/physical examination	QOL: EORTC QLQ-C30 , BN20, EQ- Pre-treatment
Restaging imaging, per Section 3.2.5	5D, AHS, and PHQ 2
MRI of the brain	Whole blood and serum collection
Zubrod performance status	
Serum pregnancy test	
Thin slice MRI required as outlined in Section 3.2.3	