NRG-GI006

SCHEMA (05-NOV-2020)

STEP 1 REGISTRATION
Register and work on confirmation of payment coverage for treatment (insurance or other)

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STEP 2 RANDOMIZATION*

STRATIFY

- Histology (adenocarcinoma vs. squamous cell carcinoma)
- Stage (I-II vs. III-IVA) per AJCC 8th Edition
- Patient Candidate for Post Chemoradiation Resection (Yes vs. No)
- Type of concurrent chemotherapy (taxane containing vs. oxaliplatin based)

Arm 1	**Arm 2**
PBT + Chemotherapy** Followed by surgery*** 4-8 weeks after completion of chemoradiation	IMRT + Chemotherapy** Followed by surgery*** 4-8 weeks after completion of chemoradiation

*Randomization is 1:1.
**Chemotherapy regimen will be determined by the individual treating physician per institutional standards at the time of study enrollment, chosen from the following 3 chemotherapy regimens: 1) Carboplatin/Paclitaxel, 2) FOLFOX/CAPOX, 3) Docetaxel/5-FU (with capecitabine an acceptable substitute for 5-FU).
***For patients who are candidates for post chemoradiation resection per Section 5.3.

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Biostatistical/Data Management Center (see protocol cover page). For radiation therapy-related eligibility questions, please contact RTQA (see protocol cover page).

3.1 Patient Selection Guidelines

Although the guidelines provided below are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.

3.1.2 Women of childbearing potential and men who are sexually active should be willing and able to use medically acceptable forms of non-hormonal contraception during treatment and for 3 months after end of treatment.

3.2 Eligibility Criteria (05-NOV-2020)

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

Prior to STEP 1 REGISTRATION

3.2.1 Histologically proven diagnosis of adenocarcinoma or squamous cell carcinoma of the thoracic esophagus or gastroesophageal junction (Siewert I-II);

3.2.2 Stage I-IVA, excluding T4b, according to the American Joint Committee on Cancer (AJCC) 8th edition based on the following diagnostic workup:

- History/physical examination;
- Whole-body FDG-PET/CT with or without contrast (preferred) or chest/abdominal (include pelvic if clinically indicated) CT with contrast
    - For patients who DID NOT receive induction chemotherapy, scan must occur within 30 days prior to Step 1 registration;
    - For patients who DID receive induction chemotherapy, scan must occur:
        - Within 30 days after final induction chemotherapy dose; OR
        - Within 30 days prior to Step 1 registration.
    - Note: Patients who had prior endoscopic mucosal resection (EMR) with a diagnosis of AJCC stage I-IVA, excluding T4b, esophageal cancer are eligible;

3.2.3 Surgical consultation to determine whether or not the patient is a candidate for resection after completion of chemoradiation;

3.2.4 Induction chemotherapy for the current malignancy prior to concurrent chemoradiation allowed if last dose is no more than 90 days and no less than 10 days prior to Step 1 registration; Only FOLFOX will be allowed as the induction chemotherapy regimen.

3.2.5 Age ≥ 18;

3.2.6 Zubrod performance status 0, 1, or 2;

3.2.7 Adequate hematologic, renal, and hepatic function within 30 days prior to Step 1 registration defined as follows:

- Absolute neutrophil count (ANC)
  - For patients who DID NOT receive induction chemotherapy: ANC ≥ 1,500 cells/mm^3
  - For patients who DID receive induction chemotherapy: ANC ≥ 1,000 cells/mm^3
- Platelets
  - For patients who DID NOT receive induction chemotherapy: Platelets ≥ 100,000/uL
  - For patients who DID receive induction chemotherapy: Platelets ≥ 75,000/uL
- Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable)
- Serum creatinine ≤ 1.5 X upper limit of normal (ULN) or Creatinine clearance > 40 mL/min estimated by Cockcroft-Gault formula
- Total Bilirubin ≤ 1.5 X ULN
- AST and ALT ≤ 3 X ULN

3.2.8 Negative pregnancy test (serum or urine) within 14 days prior to Step 1 registration for women of child bearing potential.

3.2.9 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry.

3.3 Ineligibility Criteria (05-NOV-2020)

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

3.3.1 Cervical esophageal cancers arisen from 15-18 cm from the incisors;

3.3.2 Patients with T4b disease according to the AJCC 8th Edition;

3.3.3 Definitive clinical or radiologic evidence of metastatic disease;

3.3.4 Any active malignancy within 2 years of study registration that may alter the course of esophageal cancer treatment;

3.3.5 Prior thoracic radiotherapy that would result in overlap of radiation therapy fields;

3.3.6 Severe, active co-morbidity defined as follows:

- Active uncontrolled infection requiring IV antibiotics at the time of Step 1 registration;
- Uncontrolled symptomatic congestive heart failure, unstable angina, or cardiac arrhythmia not controlled by any device or medication at the time of Step 1 registration;
- Myocardial infarction within 3 months prior to Step 1 registration;

3.3.7 Pregnant and/or nursing females;

3.3.8 HIV positive with CD4 count < 200 cells/microliter. Note that 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 registration. Note also that HIV testing is not required for eligibility for this protocol. This exclusion criterion is necessary because the treatments involved in this protocol may be significantly immunosuppressive.

<u>Prior to STEP 2 RANDOMIZATION</u>

3.3.9 Unable to obtain confirmation of payment coverage (insurance or other) for either possible radiation treatment