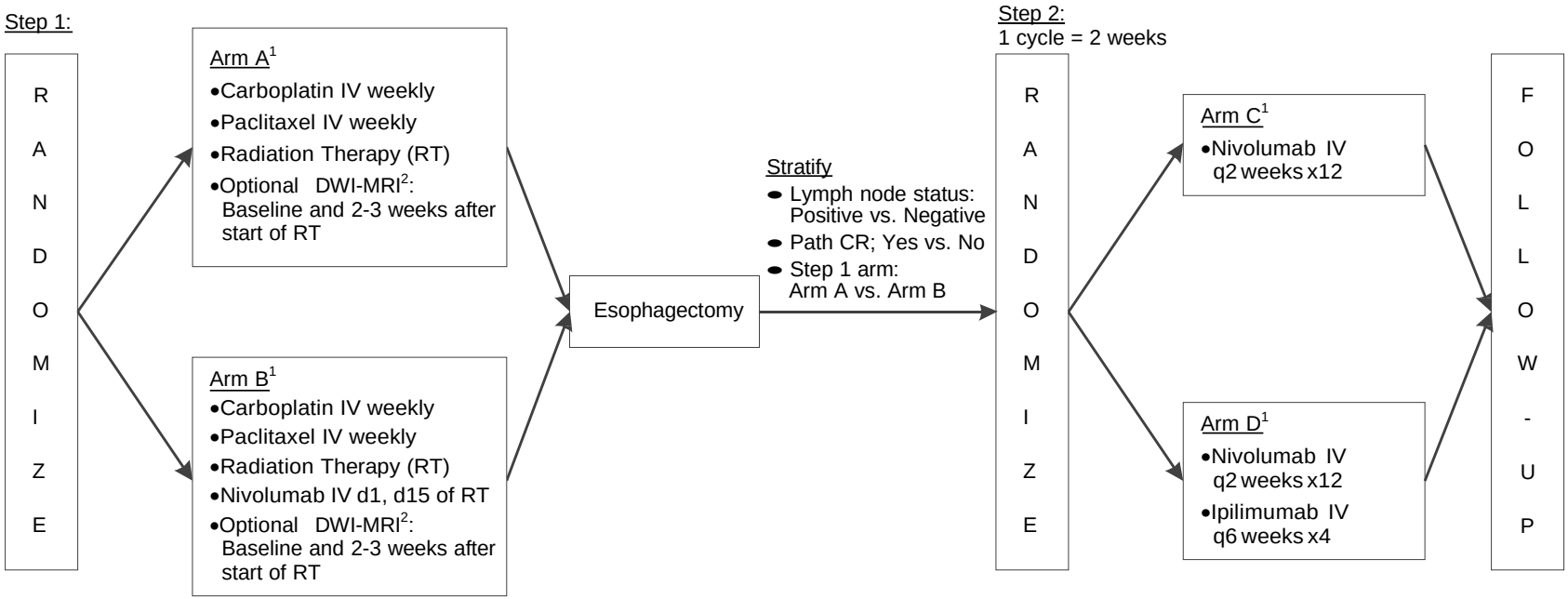
Schema



N=278

1. Please reference Section 5.1 for treatment dosing specifics.
2. Optional Diffusion weighted imaging-MRI (DWI-MRI) should be obtained at step 1 baseline and 2-3 weeks after initiation of protocol treatment.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

3.1 Eligibility Criteria

_____3.1.1 Patients must be age ≥ 18 years.

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_____ 3.1.2 Patients must have histologically confirmed T1N1-3M0 or T2-3N0-2M0 esophageal or gastroesophageal junctional adenocarcinoma (Siewert I and II).

_____3.1.3 Patients must have an ECOG Performance Status 0-1.

_____3.1.4 Patents must be deemed a surgical candidate by a thoracic surgeon, surgical oncologist, or surgeon who is qualified to perform an esophagectomy.

_____3.1.5 Patients must have normal organ and marrow function as defined below within less than or equal to 14 days prior to randomization:

_____ 3.1.5.1 Absolute neutrophil count ≥ 1,500/mcL

Neutrophil count:_____Date: _____

_____ 3.1.5.2 Platelets ≥ 100,000/mcL

Platelets:_____Date: _____

_____ 3.1.5.3 Total bilirubin ≤ institutional upper limit of normal (ULN).

ULN:_____Bilirubin:_____Date: _____

_____3.1.5.4 AST (SGOT)/ALT (SGPT) ≤ 2.5 X institutional ULN

ULN:_____AST_____Date: _____

ULN:_____AST_____Date: _____

_____3.1.5.5 Serum creatinine ≤ 1.5 X institutional ULN

ULN:_____Creatinine:_____Date: _____

_____3.1.5.6 Hgb ≥ 9 g/dL

Hgb:_____Date: _____

_____3.1.5.7 Leukocytes ≥ 3,000/mm^3

Hgb:_____Date: _____

_____3.1.6 Patients may not have received prior chemotherapy or radiation therapy for management for this malignancy.

_____ 3.1.7 Patients may not have received prior immunotherapy for management of this malignancy or for any other past malignancy.

_____3.1.8 Patients must have no contraindication to receiving either carboplatin or paclitaxel chemotherapy.

_____3.1.9 Patients must have no contraindication to receiving radiation therapy

_____3.1.10 Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids, should be excluded. These include but are not limited to patients with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, connective tissue disease, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome should be excluded because of the risk of recurrence or exacerbation of disease. Patients with vitiligo, endocrine deficiencies including thyroiditis managed with replacement hormones including physiologic corticosteroids are eligible. Patients with rheumatoid arthritis and other arthropathies, Sjogren's syndrome and psoriasis controlled with topical medication and patients with positive serology, such as antinuclear antibodies (ANA), anti-thyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible.

_____3.1.11 Patients are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger (precipitating event).

_____ 3.1.12 Patient must NOT have previous or concurrent malignancy. Exceptions are made for patients who meet any of the following conditions:

- Non-melanoma skin cancer, in situ cervical cancer, superficial bladder cancer, or breast cancer in situ

OR

- Prior malignancy completely excised or removed and patient has been continuously disease free for > 5 years.

OR

- Prior malignancy completely excised or removed and patient has been continuously disease free for > 5 years.
- Date of last evidence of disease:

_____3.1.13 Patients must not have a condition requiring systemic treatment with either corticosteroids (>10 mg/day prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses ≤ 10 mg/day prednisone equivalents are permitted in the absence of active autoimmune disease.

_____3.1.14 Adequate cardiac function including EKG and echocardiogram for any patient with a history of CHF or at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs.

_____3.1.15 For patients with evidence of CHF, MI, cardiomyopathy, or myositis, cardiac evaluation including lab tests and cardiology consultations including EKG, CPK, troponin, and echocardiogram.

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_____3.1.16 Patients must not have a positive test result for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV RNA) indicating acute or chronic infection. Testing should be conducted to determine eligibility.

_____3.1.17 Patients with a known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) must have no detectable viral load on a stable anti-viral regimen.

_____3.1.18 Patients must not be receiving any other investigational agents.

_____3.1.19 Patients with an uncontrolled intercurrent illness such as ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia or psychiatric illness/social situations that would limit compliance with study requirements will be excluded.

_____3.1.20 Women must not be pregnant or breast-feeding due to potential harm to the fetus from carboplatin, paclitaxel, or nivolumab.

All females of childbearing potential must have a blood test or urine study done within 2 weeks prior to registration to rule out pregnancy. Those enrolled on Arm B with nivolumab must agree to have a pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours of starting nivolumab to rule out pregnancy.

A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at

least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female?_____(Yes or No)

Date of blood test or urine study: _____

_____ 3.1.21 Women of childbearing potential (WOCBP) and sexually active males must either abstain from sexual intercourse for the duration of their participation in the study or agree to use both double barrier contraception and birth control pills or implants for at least one month (female patients) or one week (male patients) prior to the start of the study drug and continuing for 5 months after the last dose of study drug (for female patients) and for 7 months after the last dose of study drug (for male patients who are sexually active with WOCBP). Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy.

_____ 3.1.22 If patient says 'Yes' to "*I choose to take part in the imaging study and will have the diffusion weighted MRI scans*": patients must be able to tolerate MRI scans:

_____ 3.1.22.1 No history of untreatable claustrophobia.

_____ 3.1.22.2 No MR incompatible implants/devices or metallic foreign bodies.

_____ 3.1.22.3 Weight compatible with limits imposed by the MRI scanner table.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

3.2 Eligibility Criteria: Step 2

_____3.2.1 Patient registration must not exceed 12 weeks from time of esophagectomy.

_____3.2.2 Patients must have a post-operative ECOG performance status of 0-2.

_____3.2.3 Patients must have normal organ and marrow function as definded below within less than or equal to 14 days prior to randomization:

_____3.2.3.1 Absolute neutrophil count ≥ 1,500/mcL

Neutrophil count:_____Date: _____

_____3.2.3.2 Platelets ≥ 100,000/mcL

Platelets:_____Date: _____

_____ 3.2.3.3 Total bilirubin ≤ institutional upper limit of normal (ULN).

ULN:_____Bilirubin:_____Date: _____

_____3.2.3.4 AST (SGOT)/ALT (SGPT) ≤ 2.5 X institutional ULN

ULN:_____AST_____Date: _____

ULN:_____ALT_____Date: _____

_____3.2.3.5 Serum creatinine ≤ 1.5 X institutional ULN

ULN:_____Creatinine:_____Date: _____

_____ 3.2.4 Patients must be disease free following esophagectomy as is demonstrated by having no evidence of disease on a post-surgical CT scan. Patients must also have a negative surgical margin (R0 resection).

_____3.2.5 Patients must not have an active, known or suspected autoimmune disease or a condition requiring treatment with steroids or immunosuppressive agents. Patients are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.

_____3.2.6 Patients must not have a condition requiring systemic treatment with either corticosteroids (> 10 mg/day prednisone equivalents) or other immunosuppressive medications with 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg/day prednisone equivalents are permitted in the absence of active autoimmune disease.

_____ 3.2.7 Patients must not be receiving any other investigational agents.

_____3.2.8 Patients with an uncontrolled intercurrent illness such as ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia or psychiatric illness/social situations that would limit compliance with study requirements will be excluded.

_____ 3.2.9 Women must not be pregnant or breast-feeding due to potential harm to the fetus from nivolumab or ipilimumab.

All females of childbearing potential must have a blood test or urine study done (minimum sensitivity 25 IU/L or equivalent units of HCG) within 2 weeks prior to registration to rule out pregnancy. All patients must also agree to have a pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours of starting nivolumab to rule out pregnancy. Those enrolled on Arm D with ipilimumab must agree to have pregnancy tests within 72 hours of each ipilimumab administration to rule out pregnancy.

Female?_____(Yes or No)

Date of blood test or urine study: _____

_____3.2.10 Women of childbearing potential (WOCBP) and sexually active males must either abstain from sexual intercourse for the duration of their participation in the study or agree to use both double barrier contraception and birth control pills or implants for at least one month (female patients) or one week (male patients) prior to the start of the study drug and continuing for 5 months after the last dose of study drug (for female patients) and for 7 months after the last dose of study drug (for male patients who are sexually active with WOCBP). Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.