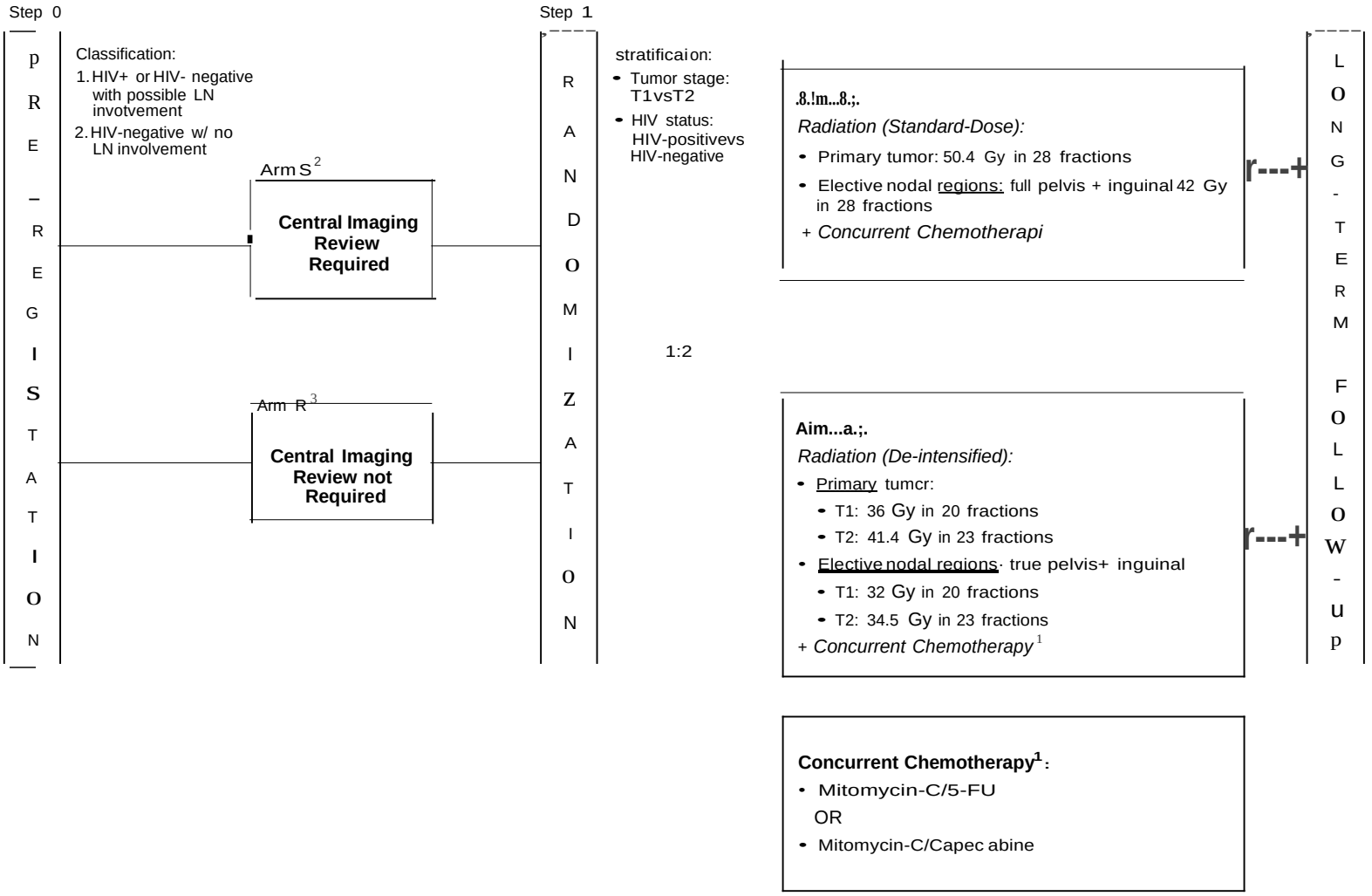
Schema



Accrual Goal= 252

1. See section 5.3 for detailed chemotherapy regimens and dosings.
2. Patients who are HIV+ or HIV-negative with possible LN invdvement must submit imaging per Section 10 for central imaging review to determine patient eligibility.
3. HIV-negative patients v.ith no LN disease involvement.

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 Patient must be ≥ 18 years of age.

_____ 3.1.2 Patient must have histologically proven T1-2N0M0 invasive anal canal or anal margin squamous cell carcinoma with tumors measuring ≤ 4cm within 4 weeks prior to randomization. This may include tumors of non-keratinizing histology such as basaloid, transitional cell or cloacogenic histology. Measurable disease is as defined in Section 6.1.2.

Patients with T1N0M0 anal margin squamous cell carcinoma who underwent surgical excision with negative margins are not eligible.

_____ 3.1.3 Patients who are HIV-negative must not have lymph nodes that are radiographically-concerning for cancer involvement using CT and PET/CT-based criteria.

Measurable disease is not required.

_____3.1.3.1 Patients who are HIV-negative and do not have lymph nodes classified as lymph node positive as defined in Section 3.1.3.2 or 3.1.3.3, but are felt to be borderline for cancer involvement must undergo central imaging review per Section 10.

NOTE: Patients requiring central imaging review will be pre-registered to Arm S. Upon central confirmation of no lymph node involvement, eligible patients may proceed to randomization on Step 1.

_____3.1.3.2 Patients will be considered to be lymph node (LN) positive and thereby not eligible in this study if the lymph nodes meet any of the following criteria:

- Mesorectal, presacral, internal iliac or obturator LN with:
  - Short axis measuring > 5mm based on CT / MRI
    OR
  - Morphologic features of irregular border or central necrosis if assessed on MRI and LN measures > 3 mm
    OR
  - FDG uptake > blood pool (Deauville 3-5) based on PET/CT.
- External Iliac and Common Iliac:
  - Short-axis measuring > 1cm based on CT / MRI
    OR
  - Morphologic features of irregular border or central necrosis based on CT / MRI
    OR
  - FDG uptake > blood pool (Deauville 3-5) based on PET/CT.

_____3.1.3.3 Inguinal LN (superficial and deep) meeting any of the following criteria will be ineligible unless an FNA is performed and resulting cytology is negative.

_____3.1.3.3.1 Morphologic features of irregular border or central necrosis based on CT / MRI

_____ 3.1.3.3.2 FDG uptake > liver (Deauville 4) based on PET/CT.

Anatomic Location	CT/MRI-based Size **OR**	CT/MRI-based Morphology **OR**	PET/CT-based FDG uptake
Mesorectal, Presacral, Internal Iliac, Obturator	Short axis > 5mm	Irregular Border **OR** Central necrosis (only for LN > 3mm on MRI)	> Blood pool (Deauville 3-5)
Common Iliac and External Iliac	Short axis > 1cm	Irregular Border **OR** Central necrosis	> Blood pool (Deauville 3-5)
Inguinal	No size criteria	Irregular Border **OR** Central necrosis	> Liver (Deauville 3-5)

_____3.1.3.3.3 Patients who are HIV-negative and have inguinal lymph nodes that do not meet the above criteria must undergo fine needle aspiration and have negative histology to be eligible.

_____3.1.4 Patients who are HIV-positive must have

_____3.1.4.1 A CD4 count ≥ 300.

_____3.1.4.2 Confirmation of no lymph node involvement by central real-time review of imaging per Section 10.

NOTE: Patients will be pre-registered to Arm S. Upon central confirmation of no lymph node involvement, eligible patients may proceed to randomization on Step 1.

_____3.1.5 Patient must have ECOG-ACRIN performance status of 0-2.

_____3.1.6 Patient must have no history of prior radiation or chemotherapy for this malignancy.

_____ 3.1.7 Patient must not have had prior potentially curative surgery (i.e. abdominal-perineal resection) for carcinoma of the anus.

_____ 3.1.8 Patients with excisional biopsy procedure are eligible provided there was tumor involvement of the anal canal and/or anal verge prior to resection.

_____3.1.9 Patient must not be receiving any other standard anti-cancer therapy or experimental agent concurrently with the study drugs.

_____3.1.10 Patient must not have intercurrent illness including, but not limited to, ongoing or active infection or psychiatric/social situations that, in the judgement of the investigator, would limit compliance with study requirements.

_____3.1.11 Patient must not have had significant cardiovascular disease including myocardial infarction, unstable angina, stroke, transient ischemic attack, symptomatic coronary artery disease, symptomatic congestive heart failure, or uncontrolled cardiac arrhythmia within 6 months of randomization.

_____3.1.12 Patient must not have a history of a different malignancy unless they have been disease-free for at least 2 years and are deemed by the investigator to be at low risk of recurrence.

Individuals with the following cancers are eligible if diagnosed and treated within the past 5 years: cervical cancer in situ and basal cell or squamous cell carcinoma of the skin.

_____3.1.13 Patient must not have active autoimmune or connective disease.

_____ 3.1.14 Patients who are on anti-coagulation with warfarin within 2 weeks prior to registration and are considering the use of capecitabine, must use an alternative anti-coagulant.

NOTE: Low molecular weight heparin is permitted provided the patient's PT/INR is < 1.5.

_____ 3.1.15 Patients who will receive capecitabine and are on Dilantin for a seizure disorder must have Dilantin levels checked weekly.

_____3.1.16 Within 2 weeks prior to registration, patient must have

_____3.1.16.1 Evidence of adequate hematologic function by:

_____3.1.16.1.1 Hemoglobin > 10g/dL

_____3.1.16.1.2 Platelets ≥ 100,000/mm^3

_____3.1.16.1.3 Absolute Neutrophil Count ≥ 1500/mm^3

_____3.1.16.2 Serum creatinine must be <1.5 X ULN, or calculated creatinine clearance must be > 60 ml/min.

_____ 3.1.16.3 Evidence of adequate hepatic function by:

_____3.1.16.3.1 Total bilirubin must be < 2X ULN.

_____ 3.1.16.3.2 AST/ALT ≤ 2.5 X institutional ULN.

_____3.1.16.4 Albumin ≥ 3.0 g/dL.

_____ 3.1.17 Women must not be pregnant or breast-feeding because the study treatment administered may cause harm to an unborn fetus or breastfeeding child.

All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration 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 achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female of child bearing potential? _____(Yes or No)

Date of blood test or urine study: _____

_____ 3.1.18 Women of childbearing potential and sexually active males must be strongly advised to use accepted and effective method(s) of contraception or to abstain from sexual intercourse for the duration of their participation in the study and for at least 6 months after the completion of treatment.