Cancer Research Consortium of West Michigan
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FAST FACTS

EA2182 - A Randomized Phase II Study of De-Intensified ChemoRadiation for Early- Stage Anal Squamous Cell Carcinoma (DECREASE)

Eligibility Criteria for Step 0 (Pre-Registration)

Patients who are HIV-negative and meet the below criteria may proceed directly to Step 1 Randomization.

1. Patient must be ≥ 18 years of age.
2. Patients must be English speaking to participate in the trial. (Please note that this requirement is due to the fact that the quality-of-life studies are mandatory and we currently do not have full translated versions of the questionnaires into other languages).
3. Patient must have histologically proven T1-2N0M0 invasive anal canal or anal margin squamous cell carcinoma measuring ≤4 cm. This may include tumors of non-keratinizing histology such as basaloid, transitional cell or cloacogenic histology.
   Measurable disease is not required.
4. Patients who are status/post local excision or excisional biopsy procedure are eligible provided there was tumor involvement of the anal canal and/or anal verge prior to the reaction, if the margins were positive, and/or if the stage is T2N0 based on tumor size before the procedure. This means that patients with T1N0M0 anal margin squamous cell carcinoma who underwent surgical excision with negative margins and no involvement of the anal verge and/or anal canal are not eligible (please see exclusion criteria 3.2.6 for further explanation).
5. Tumor size must be documented based on physical examination including digital rectal exam and/or anoscopy/proctoscopy within 4 weeks prior to Step 0 pre-registration.
6. Patient's HIV status must be known and documented at baseline.
   NOTE: For patients without a history of HIV infection, it is recommended (but not required) that updated HIV testing be performed within one year of study enrollment.
7. Patients who are HIV-negative will be registered to Arm R. They must not have lymph nodes that are radiographically-concerning for cancer involvement using CT and FDG-PET/CT-based criteria (see table and bullet list below).
   NOTE: Patients who are HIV-negative and meet the below criteria may proceed directly to Step 1 Randomization (Section 3.2).

Anatomic Location	CT/MRI-based Size **OR**	CT/MRI-based Morphology **OR**	PET-based FDG uptake
Mesorectal, Presacral	Short axis > 5mm	Irregular Border **OR** Central necrosis (only for LN > 3mm on MRI)	> Blood pool (Deauville 3-5)
Internal Iliac, Obturator	Short axis > 7mm	Irregular Border **OR** Central necrosis	> Blood pool (Deauville 3-5)
Common Iliac and External Iliac	Short axis > 10mm	Irregular Border **OR** Central necrosis	> Blood pool (Deauville 3-5)
Inguinal	No size criteria	Irregular Border **OR** Central necrosis	> Liver (Deauville 4-5)

a. 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:

i. Mesorectal, Presacral, LN with:

1. Short axis measuring > 5mm based on CT / MRI

OR

2. Morphologic features of irregular border or central necrosis if assessed on MRI and LN measures > 3 mm

OR

3. FDG uptake > blood pool (Deauville 3-5) based on FDG-PET/CT or PET/MRI.

ii. Internal Iliac or Obturator LN with:

1. Short-axis measuring > 7mm based on CT / MRI

OR

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

OR

3. FDG uptake > blood pool (Deauville 3-5) based on FDG-PET/CT or PET/MRI

iii. Common Illiac andExternal Iliac:

1. Short-axis measuring > 10mm based on CT / MRI

OR

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

OR

3. FDG uptake > blood pool (Deauville 3-5) based on FDG-PET/CT or PET/MRI.

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

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

ii. FDG uptake > liver (Deauville 4) based on FDG-PET/CT.

iii. 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.

8. Patients who are HIV-positive will be registered to Arm S. They must meet the eligibility criteria below:
   a. A CD4 count ≥ 200.
   b. Imaging submitted to ECOG-ACRIN for central review for confirmation of no lymph node involvement per Section 10.

c. No history of AIDS-related complications within past year other than a history of low CD4+ T-cell count (>200/mm3) prior to initiation of combination antiretroviral therapy
d. Patient must be healthy on the basis of HIV disease with high likelihood of near normal life span were it not for the anal cancer
e. Patient MUST receive appropriate care and treatment for HIV infection, including antiretroviral medications when clinically indicated, and should be under the care of a physician experienced in HIV management. Participants will be eligible regardless of antiretroviral medication provided the regimen has been stable for at least 4 weeks.

Eligibility Criteria for Step 1 (Randomization)

1. Patient must have met the eligibility criteria as outlined in Section 3.1.
2. Patient must have ECOG-ACRIN performance status of 0-2.
3. Patient must have no history of prior chemotherapy for this malignancy.
4. Patients must not have undergone previous radiation to the pelvis such that overlapping radiation fields would be expected.
5. Patient must not have had prior potentially curative surgery (i.e. abdominal-perineal resection) for carcinoma of the anus. However, patients who undergo local excision or excisional biopsy are eligible provided they meet inclusion criteria described in 3.1.4.
6. Patients with T1N0M0 anal margin squamous cell carcinoma must not have undergone surgical excision with negative margins and no involvement of the anal verge and/or anal canal (please see inclusion criteria 3.1.4).
7. Patient must not be receiving any other standard anti-cancer therapy or experimental agent concurrently with the study drugs.
8. 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.
9. 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 prior to Step 1 Randomization.
10. 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.
    Exceptions to this rule are individuals with cervical cancer in situ, non-melanoma skin cancers, and colon polyps.
11. Patient must not have active inflammatory bowel disease (patients requiring current medical interventions or who are symptomatic).
12. Patients must not have an active autoimmune or connective tissue disease that has required systemic treatment in the past two years (i.e., with the use of modifying agents, corticosteroids, or immunosuppressive drugs) Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
13. Patients who are on anti-coagulation with warfarin within 2 weeks prior to Step 1 Randomization 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.
14. Patients who will receive capecitabine and are on Dilantin for a seizure disorder must have Dilantin levels checked weekly.
15. Within 2 weeks prior to Step 1 Randomization, patient must ha
    a. Hemoglobin > 10g/dL

Hgb:_____ Date of Test:_____

i. Platelets ≥ 100,000/mm3
Plt:_____ Date of Test:_____

ii. Absolute Neutrophil Count ≥ 1500/mm3
ANC:_____ Date of Test:_____

b. Serum creatinine must be <1.5 X ULN, or calculated creatinine clearance must be > 50 ml/min.
Serum creatinine _____ ULN:_____
Date of Test:_____
or
Creatinine clearance:_____ Date of Test:_____

c. Evidence of adequate hepatic function by:

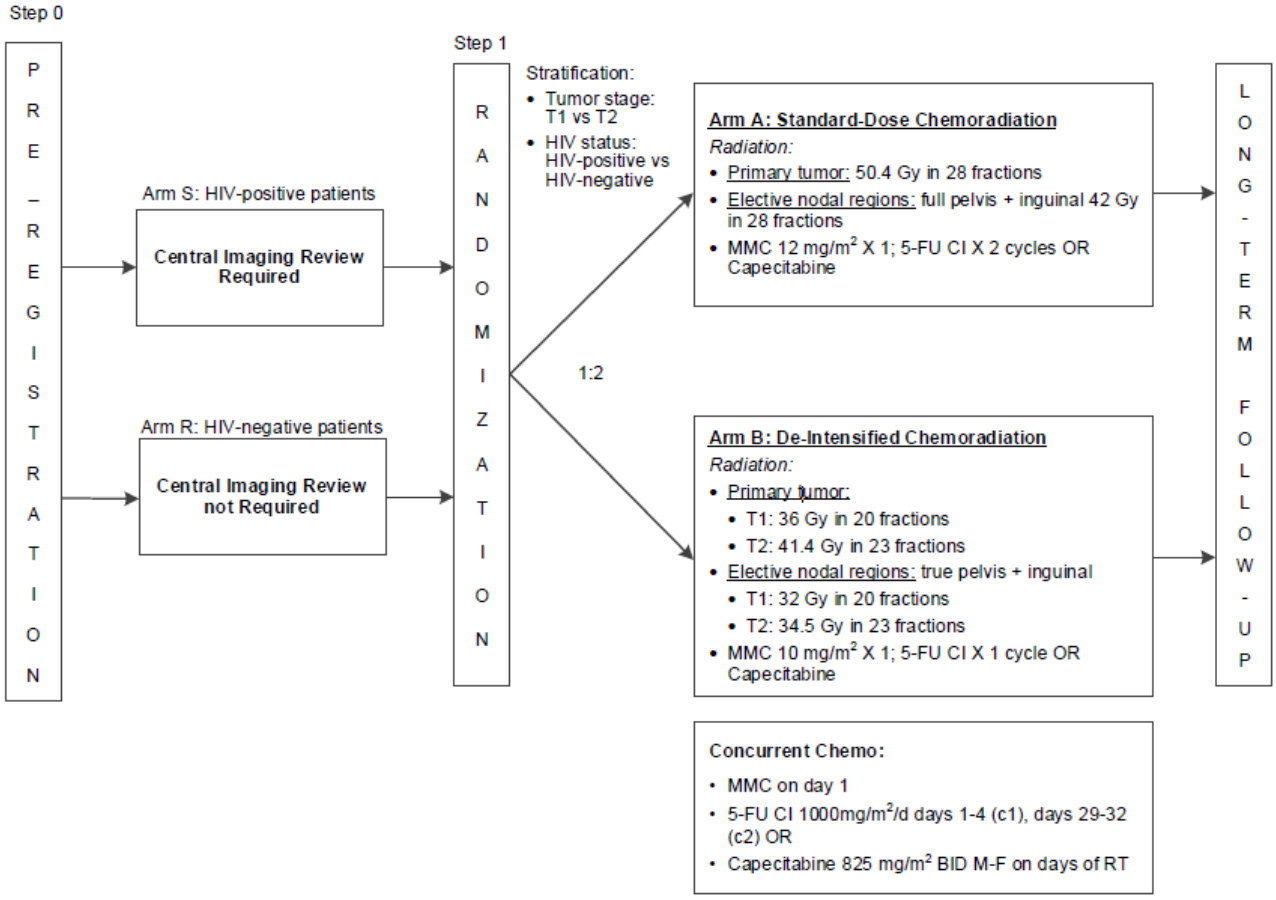
i. Total bilirubin must be < 2X Institutional ULN.
Bilirubin:_____
Institutional ULN:_____
Date of Test:_____

ii. AST/ALT ≤ 2.5 X institutional ULN.
ALT:_____ Institutional ULN:_____
Date of Test:_____
AST:_____Institutional ULN:_____
Date of Test:_____

d. Albumin ≥ 3.0 g/dL.
Albumin:_____ Date of Test:_____

16. 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 Step 1 Randomization to rule out pregnancy.
A female of childbearing potential is defined as 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 3) 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: _____
17. 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.

Schema


Step 0
PRE-REGISTRATION
Arm S: HIV-positive patients
Central Imaging Review Required
Arm R: HIV-negative patients
Central Imaging Review not Required
Step 1
RANDOMIZATION
Stratification:
• Tumor stage: T1 vs T2
• HIV status: HIV-positive vs HIV-negative
1:2
Arm A: Standard-Dose Chemoradiation
Radiation:
• Primary tumor: 50.4 Gy in 28 fractions
• Elective nodal regions: full pelvis + inguinal 42 Gy in 28 fractions
• MMC 12 mg/m² X 1; 5-FU CI X 2 cycles OR Capecitabine
Arm B: De-Intensified Chemoradiation
Radiation:
• Primary tumor:
• T1: 36 Gy in 20 fractions
• T2: 41.4 Gy in 23 fractions
• Elective nodal regions: true pelvis + inguinal
• T1: 32 Gy in 20 fractions
• T2: 34.5 Gy in 23 fractions
• MMC 10 mg/m² X 1; 5-FU CI X 1 cycle OR Capecitabine
Concurrent Chemo:
• MMC on day 1
• 5-FU CI 1000mg/m²/d days 1-4 (c1), days 29-32 (c2) OR
• Capecitabine 825 mg/m² BID M-F on days of RT
LONG-TERM FOLLOW-UP