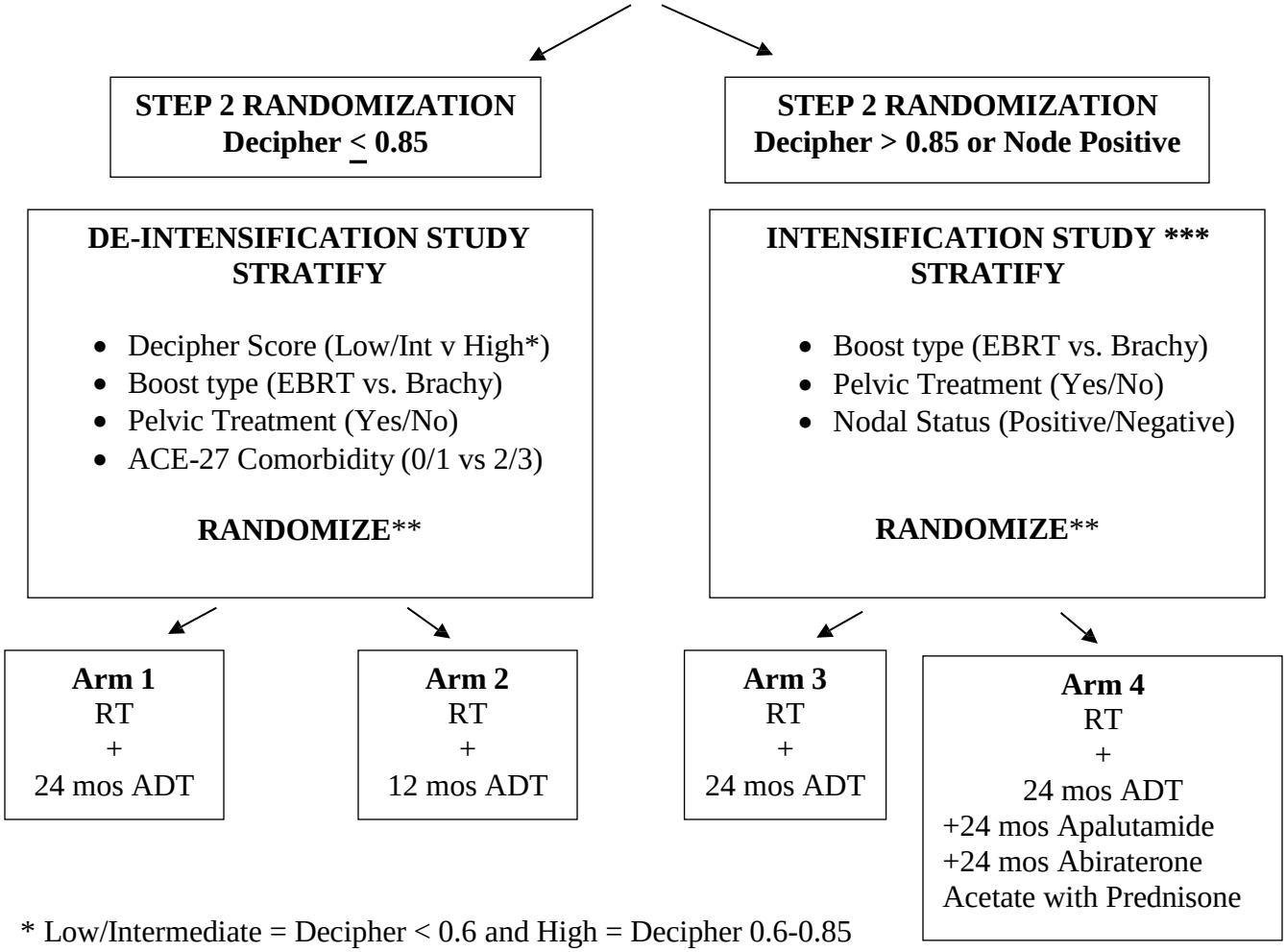
NRG-GU009
SCHEMA

STEP 1 REGISTRATION

Completion of Step 1 eligibility checklist in OPEN and then submission of tissue for Decipher analysis

Note: Decipher analysis results must be completed before **Step 2 randomization** can occur. If Decipher results have already been obtained, in lieu of tissue, after completion of Step 1 eligibility checklist in OPEN, the original Decipher report must be submitted to Decipher Biosciences for validation (see Decipher Analysis information at the end of section 3.0).



* Low/Intermediate = Decipher < 0.6 and High = Decipher 0.6-0.85
**Randomization is 1:1
*** Up to 200 patients who consent to imaging sub study will receive F-18 PET. See Section 4.0 and 11.3 for more details and time points.

Note:
A radiation treatment approach change post registration involving the pelvic lymph node treatment or prostate boost type stratification factors will result in a protocol deviation.
RT = radiation therapy; ADT = androgen deprivation therapy

3 ELIGIBILITY AND INELIGIBILITY CRITERIA

Notes: 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).

Inclusion of Minorities

NIH policy requires that members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf

3.1 Eligibility Criteria

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

Prior to Step 1 Registration

3.1.1 Pathologically proven diagnosis of adenocarcinoma of prostate cancer within 180 days prior to registration;

3.1.2 High-risk disease defined as having at least one or more of the following:

- PSA>20 ng/mL prior to starting ADT
- cT3a-T4 by digital exam or imaging (AJCC 8th Ed.)
- Gleason Score of 8-10
- Node positive by conventional imaging with a short axis of at least 1.0 cm

3.1.3 Appropriate stage for study entry based on the following diagnostic workup:

- History/physical examination within 120 days prior to registration;
- Bone imaging within 120 days prior to registration;
  Note: To be eligible, patient must have no definitive evidence of bone metastases (M0) on bone scan or NaF PET within 120 days prior to registration (Negative Na F PET/CT or Negative Axumin or Choline PET or Negative fluciclovine, choline or PSMA PET within 120 days prior to registration is an acceptable substitute if they have been performed). Patients who have bone metastases established only fluciclovine, choline, or PSMA PET but not definitive on bone scan or NaF PET will still be eligible.
- CT or MRI of the pelvis within 120 days prior to registration (Negative fluciclovine, choline, or PSMA PET within 120 days prior to registration is an acceptable substitute). As with bone staging, nodal staging for trial purposes will be based off of conventional imaging findings only.
- Patients with confirmed N1 metastases on conventional imaging (CT/MRI) as defined by $\geq$10mm on short axis are eligible but will be automatically assigned to the intensification study. Patients who are positive by fluciclovine, choline, or PSMA PET (i.e. N1),but whose nodes do not meet traditional size criteria for positivity(i.e. they measure $\leq$10mm on either the CT or MRI portion of the PET or on a dedicated CT or MRI)will not be considered N1 for the trial and will not automatically be assigned to the intensification study.

3.1.4 Age $\geq$ 18;

3.1.5 ECOG Performance Status of 0-2 within 120 days prior to registration;

3.1.6 Adequate hematologic function within 120 days prior to registration defined as follows:

- Hemoglobin $\geq$ 9.0 g/dL, independent of transfusion and/or growth factors
- Platelet count $\geq$ 100,000 x 10^9/µL independent of transfusion and/or growth factors

3.1.7 Adequate renal function within 120 days prior to registration defined as follows:
Creatinine Clearance (CrCl) $\geq$30 mL/min estimated by Cockcroft-Gault Equation:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg / dL)}}$$

For Black patients whose renal function is not considered adequate by the formula above, an alternative formula that takes race into account (Chronic Kidney Disease Epidemiology Collaboration CKD-EPI formula) may be used for calculating creatinine clearance for trial eligibility:

$$\text{CrCl} = 141 \times \min(S_{cr}/\kappa, 1)^{-0.411} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.159 \text{ [if black]}$$

where:
S_{cr} is serum creatinine in mg/dL,

κ is 0.9 for males,
min indicates the minimum of S_{cr}/κ or 1, and
max indicates the maximum of S_{cr}/κ or 1

A calculator for this formula is available at: https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease/laboratory-evaluation/glomerular-filtration-rate-calculators/ckd-epi-adults-conventional-units

3.1.8 Adequate hepatic function within 120 days prior to registration defined as follows:

- Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN) *(Note: In subjects with Gilbert's syndrome, if total bilirubin is >1.5 × ULN, measure direct and indirect bilirubin and if direct bilirubin is ≤1.5 × ULN, subject is eligible)*
- AST(SGOT) or ALT(SGPT) ≤ 2.5 × institutional ULN
- Serum albumin ≥ 3.0 g/dL

3.1.9 The patient must agree to use a condom (even men with vasectomies) and another effective method of birth control if he is having sex with a woman of childbearing potential or agree to use a condom if he is having sex with a woman who is pregnant while on study drug and for 3 months following the last dose of study drug.

3.1.10 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy (didanosine (DDI) is not permitted see section 3.2.6) with undetectable viral load within 6 months are eligible for this trial and have a CD4 count ≥ 200 cells/microliter within 60 days prior to registration. *Note: HIV testing is not required for eligibility for this protocol.* Of note, for patients with HIV in the intensification trial randomized to abiraterone acetate and apalutamide, HAART may need to be adjusted to medications that do not interact with abiraterone acetate and apalutamide.

3.1.11 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable after or on suppressive therapy within 60 days prior to registration, if indicated. *Note: HBV viral testing is not required for eligibility for this protocol.*

3.1.12 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial. *Note: Any patient with a cancer (other than keratinocyte carcinoma or carcinoma in situ or low-grade non-muscle invasive bladder cancer) who has been disease-free for less than 3 years must contact the Principal Investigator.*

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

3.2 Ineligibility Criteria

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

Prior to Step 1 Registration

3.2.1 Definitive radiologic evidence of metastatic disease outside of the pelvic nodes (M1a, M1b or M1c) on conventional imaging (i.e. bone scan, CT scan, MRI);

3.2.2 Prior systemic chemotherapy within ≤3 years prior to registration; note that prior chemotherapy for a different cancer is allowed (completed > 3 years prior to registration);

3.2.3 Prior radical prostatectomy;

3.2.4 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;

3.2.5 Current use of 5-alpha reductase inhibitor. NOTE: If the alpha reductase inhibitor is stopped prior to randomization the patient is eligible.

3.2.6 Didanosine (DDI) antiretroviral therapy is not permitted;

3.2.7 History of any of the following:

- Seizure disorder;
- Current severe or unstable angina;
- New York Heart Association Functional Classification III/IV (Note: Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification.)
- History of any condition that in the opinion of the investigator, would preclude participation in this study

3.2.8 Evidence of any of the following at registration:

- Active uncontrolled infection requiring IV antibiotics
- Baseline moderate and severe hepatic impairment (ChildPugh Class B & C)
- Inability to swallow oral pills
- Any current condition that in the opinion of the investigator, would preclude participation in this study

3.2.9 Prior pharmacologic androgen ablation for prostate cancer is allowed only if the onset of androgen ablation (both LHRH agonist and oral anti-androgen) is ≤ 60 days prior to registration; ***Please note: baseline PSA and testosterone must be obtained prior to the start of any ADT.***

3.3 Eligibility Criteria

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

Prior to Step 2 Randomization

3.3.1 Confirmation of Decipher score.

3.3.2 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load within 60 days prior *Note: Apalutamide may interfere with HCV drugs. Patients on HCV medications should alert their infectious diseases physician if they get randomized to apalutamide due to the possibility that apalutamide can affect the bioavailability of some HCV medications. HCV viral testing is not required for eligibility for this protocol*

For patients entering the Intensification Cohort ONLY:

3.3.3 Patients must discontinue or substitute concomitant medications known to lower the seizure threshold at least 30 days prior to Step 2 randomization (see list under prohibited medications in Section 5.3.2).

3.3.4 Serum Potassium ≥ 3.5 mmol/L prior to Step 2 randomization.

3.4 Ineligibility Criteria

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

Prior to Step 2 Randomization:

3.4.1 Evidence of known gastrointestinal disorder affecting absorption of oral medications at registration.

For patients entering the Intensification Cohort ONLY:

3.4.2 Any chronic medical condition requiring a higher dose of corticosteroid than 10 mg prednisone/prednisolone once daily

3.4.3 Presence of uncontrolled hypertension (persistent systolic blood pressure [BP] ≥160 mmHg or diastolic BP ≥100 mmHg). Subjects with a history of hypertension are allowed, provided that BP is controlled to within these limits by anti-hypertensive treatment.

Decipher Analysis

Submission of tumor tissue sample from the prostate biopsy is required for all patients without a prior Decipher score. For patients who have not undergone prior Decipher analysis, submission of the specimen to Decipher Biosciences should be done as soon as possible after **Step 1 registration** as these results can take up to 21 days after the specimen is received at Decipher Biosciences.

Tissue submission should occur as soon as possible after **Step 1 Registration** and then **Step 2 Randomization** must occur within 90 days of Step 1. If Decipher results have already been obtained, in lieu of tissue, results (redacted original report) must be submitted to Decipher Biosciences for validation (see section 10.1.1 for specific instructions). The Decipher results must be obtained prior to proceeding to complete Step 2 randomization as these results are used to stratify the patient. If a Decipher result cannot be obtained then the patient will be ineligible.

NOTES: Results will be conveyed to NRG headquarters for patient stratification and randomization within 21 business days after Decipher Biosciences receives sufficient material

for analysis. Once results of the Decipher analysis are made known to NRG headquarters, the registering site will be contacted by NRG HQ with an email to proceed to Step 2 randomization. **Do not proceed to Step 2 without this notification.** If the specimen was inadequate for analysis Decipher Biosciences will contact the site directly for more material and if none can be provided then the patient will be deemed ineligible to proceed to protocol therapy. The site will need to complete Step 2 to enter the reason why the patient cannot be randomized.