NRG-GU006
SCHEMA

STEP 1 REGISTRATION
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, results must be submitted to GenomeDx for validation.

↓

STEP 2 REGISTRATION

STRATIFY
Surgical Margins: Positive vs. Negative
Pre-SRT PSA: <0.5 ng/mL vs ≥0.5-1.0 ng/mL
PAM50 Molecular Subtype (per Decipher analysis): Luminal B vs (Luminal A/Basal/Unknown)

Randomize 1:1

↓ ↓

Arm 1 (Blinded)*
External Beam Radiation:
64.8 to 70.2, 1.8 Gy/36-39 fractions
Plus

Blinded placebo daily for 6 months (~180 days) to start on Day 1 of radiation therapy (+/- 2 weeks)

vs.

Arm 2 (Blinded)*
External Beam Radiation:
64.8 to 70.2, 1.8 Gy/36-39 fractions
Plus

Blinded apalutamide daily for 6 months (~180 days) to start on Day 1 of radiation therapy (+/- 2 weeks)

*See Section 5.1 for apalutamide/placebo treatment details and Section 5.2 for radiation therapy details.
Abbreviations: PSA, prostate specific antigen; SRT, salvage radiation therapy

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 Submission of tumor tissue sample from prostatectomy is required for all patients. **Investigators should check with their Pathology department (or site where surgery was done) regarding release of biospecimens before approaching patients about participation in the trial. If the pathology specimen cannot be obtained, the patient will be ineligible. If Decipher results have already been obtained, in lieu of tissue, results must be submitted to GenomeDx for validation.**

3.2 Eligibility Criteria (14Jun2018)

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 Pathologically (histologically) proven diagnosis of prostate adenocarcinoma. Prostatectomy must have been performed within 10 years prior to Step 1 registration and any type of radical prostatectomy is permitted, including retropubic, perineal, laparoscopic or robotically assisted.

3.2.2 Post-prostatectomy patients with a detectable serum PSA (≥0.1, but ≤1.0 ng/mL) at study entry (within 90 days of Step 1 registration) and at least one of the following:

- Gleason score 7-10 (ISUP grade group 2 to 5)*

  * ISUP grade group:
  a. Grade Group 1 = Gleason score ≤ 6,
  b. Grade Group 2 = Gleason score 3 + 4 = 7,
  c. Grade Group 3 = Gleason score 4 + 3 = 7,
  d. Grade Group 4 = Gleason score 8,
  e. Grade Group 5 = Gleason scores 9 and 10.
- ≥T3a disease
- Persistent elevation of PSA after prostatectomy measured within 90 days after surgery (PSA never became undetectable) of >0.04 but <0.2 ng/mL (PSA nadir)

3.2.3 pN0 or pNx

3.2.4 History/physical examination within 90 days prior to Step 1 registration;

3.2.5 Karnofsky performance status of 70-100 within 90 days prior to Step 1 registration;

3.2.6 Age ≥ 18;

3.2.7 Surgical FFPE specimen must be available for submission to GenomeDx for genomic analysis on Decipher GRID platform. Note: If Decipher results have already been obtained, in lieu of tissue, results must be submitted to GenomeDx for validation and for GenomeDx to provide the subtyping needed for stratification.

3.2.8 Prior androgen deprivation therapy (LHRH agonist and/or non-steroidal anti-androgen) is allowed if discontinued at least 90 days prior to Step 1 registration and given for ≤ 90 days duration.

- For example: Patients on prior LHRH analogs (post-prostatectomy), the discontinuation date should be calculated based on the expected duration of the sustained release injection, not simply the injection date of the drug. For instance, if a 22.5 mg sustained release dose of leuprolide acetate is given (3 month duration), then the expected duration of such a dose would be 90 days after the injection date. For a 7.5 mg leuprolide (1 month duration), the discontinuation date would be 30 days after the injection date.
- Please note: Finasteride or dutasteride must be stopped before treatment starts but prior usage will not affect eligibility.

3.2.9 Hemoglobin ≥9.0 g/dL, independent of transfusion and/or growth factors within 90 days prior to Step 1 registration

3.2.10 Platelet count ≥100,000 x 10^9/μL independent of transfusion and/or growth factors within 90 days prior to step 1 registration

3.2.11 Serum albumin ≥3.0 g/dL within 90 days prior to Step 1 registration

3.2.12 GFR ≥35 mL/min estimated by Cockcroft-Gault or measured directly by 24 hour urine creatinine within 90 days prior to Step 1 registration

- Cockcroft-Gault formula is as follows:
  https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation
  CrCl (eGFR) = Sex * ((140 - Age) / (SerumCreat)) * (Weight / 72)

3.2.13 Serum total bilirubin ≤1.5 × 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) within 90 days prior to Step 1 registration

3.2.14 Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) <2.5 × ULN within 90 days prior to Step 1 registration

3.2.15 Testosterone >50 ng/dL within 90 days prior to Step 1 registration

3.2.16 Concomitant medications known to lower the seizure threshold (see list under prohibited medications in section 5.3.2) discontinued or substituted at least 4 weeks (30 days) prior to Step 1 registration.

3.2.17 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.

3.2.18 The patient must agree not to donate sperm during the study treatment and for 3 months after receiving the last dose of study drug.

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

3.3 Ineligibility Criteria

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

Prior to Step 1 Registration

3.3.1 Definitive clinical, radiologic, or pathologic evidence of metastatic disease (M1) or lymph node involvement (N1).

3.3.2 Prior invasive malignancy (except non-melanomatous skin cancer, carcinoma in situ of the male breast, penis, oral cavity, or stage Ta of the bladder, or stage I completely resected melanoma) unless disease free for a minimum of 2 years;

3.3.3 Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable;

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

3.3.5 History of any of the following:

- Seizure or known condition that may pre-dispose to seizure (e.g. prior stroke within 1 year prior to Step 1 registration).
- History of documented inflammatory bowel disease
- Transmural myocardial infarction within the last 4 months prior to Step 1 registration.
- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months prior to Step 1 registration
- History of any condition that in the opinion of the investigator, would preclude participation in this study

3.3.6 Current evidence of any of the following:

- Known gastrointestinal disorder affecting absorption of oral medications
- Active uncontrolled infection (eg, human immunodeficiency virus [HIV] or viral hepatitis)
- Uncontrolled hypertension
- Any current condition that in the opinion of the investigator, would preclude participation in this study

3.3.7 Prior whole gland ablative therapy [i.e. cryoablation or high intensity focused ultrasound (HIFU)] for prostate cancer is not allowed

3.3.8 HIV positive patients with CD4 count < 200 cells/microliter within 30 days prior to registration .

3.3.9 HIV patients under treatment with highly active antiretroviral therapy (HAART) within 30 days prior to registration regardless of CD4 count. (Note: HIV testing is not required for eligibility for this protocol as it is self-reported. This exclusion criterion is necessary because the treatments involved in this protocol may be immunosuppressive and/or interact with HAART.)

3.3.10 Patients must not plan to participate in any other clinical trials while receiving treatment on this study or being followed post-protocol therapy.

Prior to Step 2 Randomization (14Jun2018)

For patients who have not undergone prior Decipher analysis, submission of the specimen to GenomeDx should be as soon as possible after study registration (Step 1) as these results can take up 21 days after the specimen is received at GenomeDx. Step 2 registration must occur within 6 weeks (42 days) of Step 1 registration. If Decipher results have already been obtained, in lieu of tissue, results must be submitted to GenomeDx for validation.

GenomeDx will run the sample for the commercial test "Decipher" and simultaneously run the PAM50 test that will be used for biomarker stratification. For patients who have already previously undergone Decipher testing, a new sample is not needed and the prior sample can be used to run the PAM50 test. The PAM50 test will subtype patients into one of four subtypes, Luminal A, Luminal B, Basal, or Unknown. These results must be obtained prior to proceeding and completing Step 2 randomization.