ECOG-ACRIN cancer research group
Reshaping the future of patient care

EA8183

A Phase III Double Blinded Study of **E**arly Intervention after **RADICA**l Prosta**TE**ctomy with Androgen Deprivation Therapy with Darolutamide vs. Placebo in Men at Highest Risk of Prostate Cancer Metastasis by Genomic Stratification (**ERADICATE**)

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Version Date: September 13, 2021

STUDY PARTICIPANTS

ALLIANCE / Alliance for Clinical Trials in Oncology
NRG / NRG Oncology
SWOG / SWOG

ACTIVATION DATE

December 9, 2020
Addendum #1 – Incorporated Prior to Activation
Addendum #2

NCTN GROUP STUDY CHAMPIONS

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Agents	**IND#**	**NSC#**	**Supply**
Darolutamide and matching placebo	152160	815949	Bayer
Leuprolide Acetate		377526	Commercial
Goserelin Acetate		606864	
Triptorelin Pamoate		724666	
Degarelix		771648	
Relugolix		825960	

IND Sponsor: ECOG-ACRIN

Table of Contents

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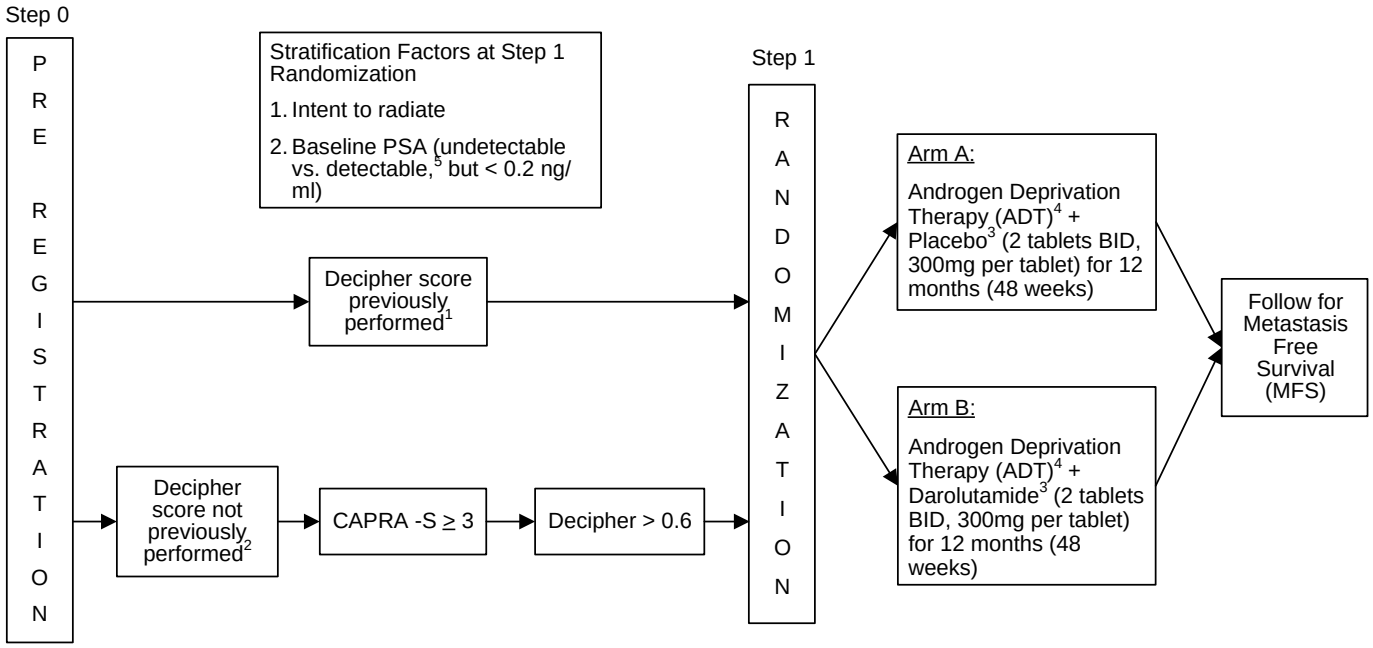
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (i.e., patient eligibility or treatment-related) Contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

Schema



Accrual Goal: 810
Cycle Duration: 28 days

1. Patients with a Decipher score previously performed by through standard of care testing outside the protocol with a score of > 0.6 are eligible and may proceed from pre-registration directly to randomization after uploading Decipher score to Medidata Rave.
2. For patients who do not already have a completed Decipher test, the calculated CAPRA-S score must be ≥ 3 and the post registration Decipher Biosciences assessment must determine Decipher score to be > 0.6.
3. Patients receiving post-operative adjuvant radiation (XRT) can receive it anytime within 52 weeks of prostatectomy.
4. ADT is administered as 1, 3, 4, and 6-month formulations. Some formulations may not be available for specific ADT choices; see section 5.
5. Detectable PSA is defined as 0 > PSA > 0.2.

NOTE: Please note that when a patient has been successfully randomized, the confirmation of randomization will indicate that the patient is on Arm X. The patient will actually be randomized to Arm A or B, but as this is a double-blind trial, that information cannot be displayed.

1. Introduction

1.1 Rationale for selected approach and trial design

Prostate cancer is the most common cancer in men and accounts for approximately 31,000 deaths per year in the United States.[1] More than 90% of patients have clinically localized cancers or loco-regional spread of their disease, with the remainder having distant metastasis at diagnosis.[2] While a significant proportion of patients with clinically localized prostate cancer are cured by definitive local therapy, patients with high-risk features, including Gleason grade 8-10, positive lymph nodes (LN), or positive seminal vesicles, have a 50-75% chance of disease recurrence within 10 years.[3,4] Men with these high risk features have cure rates from prostatectomy of less than 25% after long-term follow-up.[4-7]

Curative treatment for clinically localized, high-risk prostate cancer often includes systemic treatment with androgen deprivation therapy (ADT). Evidence suggests that there is a survival benefit associated with 2-3 years of ADT for men with high-risk disease treated with radiotherapy, and to treatment of men with positive lymph nodes after radical prostatectomy (RP) with indefinite ADT.[8-10] However, despite treatment with ADT, a significant proportion of patients will relapse and ultimately die of metastatic prostate cancer, presumably due to micrometastatic disease that remains.[3,10-12] Thus, although ADT is routinely used in an effort to eradicate remaining disease after local treatment for men with high-risk features, it remains inadequate for men at greatest risk of distant recurrence. A standard systemic therapy that eradicates micrometastatic disease is needed to improve survival among men with high-risk prostate cancer after definitive treatment for localized disease.

1.2 Prior Studies Addressing Adjuvant Radiation therapy

Adjuvant radiation therapy administered to men with certain high-risk features identified by pathology review post-prostatectomy prolongs time to progression and overall survival.[13-16] Based on the evidence in multiple studies the American Urologic Association (AUA) and American Society on Radiation Oncology (ASTRO) established guidelines recommending adjuvant radiation therapy should be offered to men with positive surgical margins, seminal vesicle involvement, or extracapsular extension after prostatectomy.[17] Notably, recently reported data from the RADICALS trial suggests that there may be no difference in biochemical progression-free survival between providing adjuvant radiation to intermediate and high risk patients versus early salvage therapy (HR 1.10 (0.81 – 1.49, p = 0.56).[18] As such, patients will receive guidance regarding adjuvant radiation as an option, but not a requirement for the trial. Recommendations regarding adjuvant or early salvage radiation are incorporated into our patient consent form to ensure that patients are aware of the demonstrated benefits to adjuvant radiation. All men with pT3 disease or positive surgical margins will have the option to be referred to radiation oncology to undergo adjuvant radiation prior to initiating systemic therapy. We do not expect adjuvant radiation therapy to affect overall survival in this population at 5 years.

1.3 Adjuvant Systemic Therapy: Prior Studies and Rationale for Inclusion

In men at high risk for disease recurrence in which radiation alone would not be curative, systemic therapies that target both loco-regional as well as distant micrometastatic disease may further improve survival and cure rates. Chemotherapy has been evaluated in multiple studies[19-22] (Table 1). The use of adjuvant hormonal therapies alone has also been evaluated in several trials[8,10,23,24](Table 2).

Table 1. Adjuvant chemotherapy for high risk localized prostate cancer

Trial/Phase	No. of Pts	Population	Treatment Arms	Primary Analysis	Outcome	Comments
Kibel AS, et al.[19]/Phase II	77	Non-metastatic, high risk of recurrence post-prostatectomy	Docetaxel 35 mg/m2 weekly x 6 cycles (single arm)	Progression free survival (PFS), feasibility	Median PFS = 15.7 mo (95% CI 12.8-25.1 mo)	Demonstrated feasibility of post-prostatectomy chemotherapy, possible improvement in PFS.
TAX-3501[25]/Phase III	228 of planned 1,696	Post-prostatectomy, M0, PSA	Immediate vs delayed (at 1st progression) docetaxel 75 mg/m2 Q3wks x 6 cycles	PFS	Underpowered to assess PFS.	Closed by sponsor due to poor accrual.
SWOG 9921[21]/ Phase III	983 of planned 1,360	High-risk prostate cancer post-prostatectomy	Randomized to ADT plus mitoxantrone 12 mg/m2 Q3 wks x 6 cycles	Overall survival (OS)	Underpowered to assess OS.	Study closed early by DSMB due to 3 cases of leukemia in mitoxantrone arm.
RTOG 0521/ Phase III[22]	563	High risk prostate cancer post-radiation	Randomized to ADT alone vs ADT plus docetaxel 75 mg/m2 Q3 wks x 6 cycles	OS	4% improvement in 4-year OS	One-sided p-value on OS improvement. Chemotherapy may be offered to select high risk men.

Table 2. Adjuvant hormonal therapy for high risk localized prostate cancer.

Messing, et al.[8,10]/Phase III	98 of planned 220	≤pT2, N1, M0 post-prostatectomy	Randomized to immediate vs delayed ADT	OS, PFS	Immediate ADT improves OS, hazard ratio (HR) 1.84 (95% CI 1.01-3.35; p=0.04)	Fewer patients accrued than planned because PSA screening started during the study and fewer men were N1
Wirth, et al.[23]/Phase III	309	Post-prostatectomy, N0	Randomized to flutamide 250 mg TID vs no treatment	Recurrence free survival (RFS), OS	RFS improved with flutamide (P=0.0041), no OS difference (p=0.92)	High toxicity in flutamide group (43% vs 3% in control arm).
RTOG 9601[26]/ Phase III	771	High-risk prostate cancer post-prostatectomy with elevated PSA	Randomized to RT alone vs RT plus 24 mo bicalutamide	OS	OS at 10 years = 82% in RT plus bicalutamide vs 78% with RT alone (p=0.036).	Toxicities similar between arms.

We hypothesize that combined inhibition of androgen receptor signaling will improve metastasis-free survival (MFS) among men with high risk prostate cancer after prostatectomy than ADT alone. Darolutamide, a novel androgen receptor (AR) antagonist, significantly prolongs metastasis-free survival among men with non-metastatic castration-resistant prostate cancer (mCRPC), demonstrating the efficacy of potent androgen receptor antagonist activity in delaying disease progression, even in the setting of low testosterone.[27] We propose employing a similar strategy in the high-risk hormone sensitive non-metastatic setting. Due to differences in its structure from earlier generation androgen receptor inhibitors, darolutamide appears to rarely cross the blood-brain barrier and has minimal toxicity related to the central nervous system (CNS).[27,28] Further, it can be given to patients regardless of a history of seizure disorder or use of medications that lower the seizure threshold, and it appears to have has relatively few drug-drug interactions.[27] These features make it an ideal candidate for combination with Gonadotropin Releasing Hormone (GNRH) agonist in the adjuvant setting.

Duration of Adjuvant therapy

Although multiple adjuvant studies have been performed, the optimal duration of adjuvant systemic therapy remains undefined. As described above, the results of these trials suggest that longer durations of hormonal therapy (18 months to 3 years) may be associated with better prostate-cancer specific outcomes, however are also associated with increase long-term, treatment-related toxicity.[5,7,11,12,29-31] Nabid et al. evaluated 630 patients with high-risk prostate cancer randomized to receive primary radiotherapy with either 18 or 36 months of androgen blockade.[31] No significant differences were reported in overall, disease-specific, or biochemical recurrent-free survival rates between the two arms, suggesting that 18 months of ADT was sufficient when combined with primary radiotherapy. Because the optimal treatment duration for adjuvant hormonal therapy has not been definitively established, we convened a panel of individual experts, including medical oncologists, urologists, and radiation oncologists, to discuss the literature and current opinions. We sought to identify a duration of treatment for use in this study that would be consistent with existing evidence, but limited sufficiently to avoid increasing the risk of long-term therapy-related toxicity. This panel determined that a treatment interval of 12 months would be acceptable, and this was agreed upon by participating medical oncologists, urologists, and radiation oncologists from ECOG-ACRIN, SWOG, and Alliance.

1.4 Quality of Life (QOL) Component

1.4.1 Background and Rationale for QOL Study

Quality of life will be assessed longitudinally by patient reported outcome measures relevant to the population and to the treatments included in the trial. This is a critical aspect of this adjuvant therapy study to provide information for patient and clinician use during treatment decisions and to provide information for clinicians to support patient symptomatology. The QOL analysis has several main objectives. The primary objective is to compare overall quality of life between treatment arms by comparing median FACT-P scores between treatment arms at 12 months (defined in the protocol as 48 weeks). This time point has been chosen because it will be critical to assess QOL after completion of adjuvant therapy. An additional objective is investigating the change in overall QOL by FACT-P total score between baseline and 12 months (48 weeks) within each arm. We will also compare subjective patient reported cognitive function between arms at 12 months (48 weeks) by comparing FACT-Cog scores at that time point when treatment is concluding, and an assessment of the change in patient reported cognitive function from baseline by comparing the change in FACT-Cog from baseline at 12 months (48 weeks) for each arm.[32] A separate secondary objective is to compare patient reported fatigue between treatment arms by comparing responses to the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) instrument at 12 months (48 weeks). The FACIT-Fatigue instrument is a patient-administered validated outcome measure that describes patient reported degree of overall fatigue, fatigue with completing activities, and fatigue as it relates to social behavior.[33]

Rev. Add2

1.4.2 Rationale for Quality-of-Life Measure Selection

1.4.2.1 Quality of Life

As explained above, the primary quality of life analysis has several main objectives, and incorporates multiple patient reported outcome measures (PROMs) to assess the patient experience during and after completion of treatment in this adjuvant trial. The instruments chosen have been used in cancer populations previously, and include the FACT-P, the FACT-Cog, and the FACIT-Fatigue.

Rev. Add2

The quality-of-life analysis has several objectives, including primary, secondary, and exploratory. The primary objective is to compare overall quality of life, measured by FACT-P total score, between the two arms at 12 months (defined as 48 weeks in this protocol). Secondary objectives are to compare the change in overall quality of life from baseline to 12 months (48 weeks) between arms and to compare patient-reported fatigue (FACIT-Fatigue scores) at 12 months (48 weeks) between the two arms. We will use the FACIT-Fatigue subscale (13 questions, range in score from 0 to 52) to evaluate fatigue during the course of this study as a secondary objective. Exploratory objectives will assess cognitive over time within each arm and between treatment arms. We will use the FACT-Cog instrument to assess cognitive function in this trial (37 questions, range in score from 0-148) as an exploratory objective.

The Functional Assessment of Cancer Therapy-Prostate (FACT- P) is a patient-administered validated instrument that assesses both general and disease-specific quality of life.[34] It is comprised of both the FACT-General (FACT-G) and additional prostate specific concerns. The FACT-P (version 4) contains 39 Likert items distributed over 5 subscales: Physical (7 items), Social (7 items), Emotional (6 items), and Functional (7 items) well-being, and the additional concerns related to Prostate Cancer Scale (12 items). The FACT-P total score is calculated by adding the value chosen by the participant for each question, with a range from 0-156. The subscale scores for each domain (physical, social, emotional, functional, and prostate specific concerns) can also be assessed and compared. The FACT-P requires only a sixth-grade reading level and can be completed in its entirety in 8 – 10 minutes, minimizing respondent burden.[34]

The FACT-P instrument has been used in multiple studies to assess the quality of life of men with prostate cancer, and has been identified as a preferred test in systematic reviews of prostate specific QOL instruments.[35] Further, the general quality of life instrument (FACT-G) that is included in the FACT-P has been validated in men with

cancer and is widely used in oncology populations.[36] Internal consistency of the FACT-P (version 4) subscales ranges from .85 to .89, and there is consistent concurrent, construct and discriminant validity.[34] The total score is sensitive to change in performance status and PSA level over two months, as are the Physical Well-being, Functional Well-being, and the Prostate Cancer specific subscale.[34] The clinically meaningful difference for the FACT-P total score is 6-10.[37]

Overall quality of life in men with prostate cancer is affected by symptoms from local therapy, ongoing systemic therapy, and recurrent disease. Because of this, additional instruments are included in an attempt to measure specific treatment effects and complete our understanding of the effects of treatment on QOL in this population.

Treatment-associated and Disease-associated Symptoms

Studies assessing the association between change in cognitive function and treatment of prostate cancer with ADT have reported mixed results.[38-44] A recent prospective, controlled study of the effect of ADT on cognitive function suggests that treatment with ADT is associated with a decline in cognitive function.[41] Separate studies suggest that some treatments for prostate cancer, particularly those that may act as androgen receptor antagonists in the CNS, may be associated with greater cognitive decline.[45,46] This study will assess cognitive function between treatment groups, and over time, in men treated with ADT with or without darolutamide to demonstrate in the largest study to date whether cognitive function changes over time in the setting of ADT alone, and to assess whether a medication that binds to the androgen receptor may be associated with more cognitive change. In preclinical models, darolutamide does not cross the blood brain barrier.[28] As such, it may not be associated with more cognitive change than ADT alone. We will use the FACT-Cog instrument to assess cognitive function in this trial (37 questions, range in score from 0-148) as an exploratory objective. The FACT-Cog includes questions assessing perceived cognitive change and deficits, perceived comments from others, and impact on quality of life. It has been used in studies of patients with cancer, including patients receiving hormonal therapy.[47] The FACT-Cog has strong convergent and discriminant validity, internal consistency, test-retest reliability, and sensitivity to group differences.[48] The minimal clinically important difference (MCID) for the FACT-Cog is considered 6.9-11.3 points, and 4.6 points for the Perceived Cognitive Impairments (PCI) subscale.[49,50]

Fatigue is a complication experienced commonly by men with mCRPC, induced both by disease progression and treatment. It mediates overall QOL, pain, depression, and other complications men experience. We will use the FACIT-Fatigue subscale (13 questions, range in score from 0 to 52) to evaluate fatigue during the course of this study. The minimal clinically important difference (MCID) for the FACT-Cog is considered 6.9-11.3 points, and 4.6 points for the Perceived Cognitive Impairments (PCI) subscale.[33,49,50] The FACIT-Fatigue subscale is a 13-item instrument developed to assess fatigue in the oncology population. The FACIT-Fatigue exhibits strong convergent and discriminant validity, internal consistency, test-retest reliability, and sensitivity to group differences in performance status.[33] The minimal important difference for the FACIT-Fatigue is considered ≥ 3 points.[33]

2. Objectives

2.1 Primary Objectives

Rev. Add2

2.1.1 To determine whether 12 months (48 weeks) of androgen deprivation therapy (ADT) and darolutamide improves metastasis-free survival (MFS) compared to 12 months (48 weeks) of ADT plus placebo in men with high risk prostate cancer (defined by CAPRA-S score ≥3 and a high Decipher score (>0.6) (C3+D+)) that have undergone radical prostatectomy.

2.2 Secondary Objectives

2.2.1 To determine whether 12 months (48 weeks) of ADT and darolutamide improves recurrence-free survival (RFS) compared to 12 months (48 weeks) of ADT plus placebo in men with high-risk prostate cancer that have undergone radical prostatectomy.

2.2.2 To determine whether 12 months (48 weeks) of ADT and darolutamide improves event-free survival (EFS) compared to 12 months (48 weeks) of ADT plus placebo in men with high-risk prostate cancer that have undergone radical prostatectomy.

2.2.3 To determine whether 12 months (48 weeks) of ADT and darolutamide improves overall survival (OS) compared to 12 months (48 weeks) of ADT plus placebo in men with high-risk prostate cancer that have undergone radical prostatectomy.

2.2.4 To determine the rate of testosterone recovery and time to testosterone recovery in each treatment arm.

2.2.5 To evaluate the safety and tolerability of ADT and darolutamide.

2.3 Correlative Objectives for Exploratory Biomarkers:

2.3.1 To discover a novel gene expression signature in the Decipher® transcriptome platforms that is predictive of clinical outcome, as defined by the primary and secondary objectives of this study, in response to ADT by intensification with darolutamide versus ADT alone.

2.3.2 To assess the prevalence of subclasses of established transcriptome expression signatures and prospectively validate their predictive value for ADT response, these include: (i) androgen receptor (AR) activity (ii) Basal-luminal subtyping based on modified PAM50, and (iii) ADT score. We will also explore signatures associated with ethnicity and presence of occult lymph node (LN) metastasis undetected by standard imaging.

2.3.3 To assess whether the spectrum of high Decipher scores (>0.6-1.0), PSA levels at presentation and post-radical prostatectomy and final pathology variables affect the response and outcome to ADT and darolutamide.

2.4 QOL Objectives:

2.4.1 Primary Objective:

Rev. Add2

2.4.1.1 To compare overall quality of life, measured by FACT-P total score, at 12 months (48 weeks) between the two arms.

2.4.2 Secondary Objectives:

2.4.2.1 To compare the change in overall quality of life, measured by FACT-P total score, from baseline to 12 months (48 weeks) between the two arms.

2.4.2.2 To compare patient-reported fatigue (FACIT-Fatigue scores) at 12 months (48 weeks) between the two treatment arms.

2.4.3 Exploratory Objective

2.4.3.1 To compare the change in subjective patient-reported cognitive function (FACT-Cog) from baseline to 12 months (48 weeks) between the treatment arms.

2.4.3.2 To compare subjective patient-reported cognitive function (FACT-Cog scores) at 12 months (48 weeks) between the two treatment arms.

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.

NOTE: This study involves preregistration and randomization (see Section 4).

NOTE: If Decipher score was previously performed through standard of care testing outside of the protocol and the score is > 0.6, eligible patients may proceed after Step 0 Preregistration directly to Step 1 Randomization after entering results and uploading Decipher score report to Medidata Rave. Step 0 Preregistration cannot be bypassed.

If Decipher score was not previously performed through standard of care testing outside of the protocol, tumor tissue must be available for submission for Decipher score assay and results determined prior to proceeding to Step 1 Randomization. See Section 10 for submission of forms and specimens associated with Decipher score status.

3.1 Eligibility Criteria for Preregistration (Step 0)

_____ 3.1.1 Patient must be ≥ 18 years of age.

_____ 3.1.2 Patient must have undergone a radical prostatectomy (RP) completed at least 2 weeks prior to Step 0 pre-registration. Patient must also meet one of the following criteria:

_____ 3.1.2.1 For patients with a Decipher score obtained through standard of care testing outside the protocol prior to registration to Step 0:

- The Decipher score must be > 0.6.
- The patient must be registered to Step 0 no later than 24 weeks (168 days) after surgery.
- The Decipher Score assay results and report must be available for upload to Medidata Rave prior to proceeding to Step 1 Randomization.

_____ 3.1.2.2 For patients without a previous Decipher score performed through standard of care testing outside the protocol prior to registration to Step 0

- The patient must be registered to Step 0 no later than 19 weeks (133 days) after surgery to allow time to have tissue submitted and tested before proceeding to Step 1 randomization.
- The patient must have a CAPRA-S score ≥ 3. The CAPRA-S score is calculated by assigning points for PSA in ng/mL, Gleason score, surgical margin status, seminal vesicle invasion, and extra-capsular extension (See Appendix V). Lymph node involvement will serve as an exclusion criteria and will not count towards CAPRA-S inclusion score.
- Tumor tissue specimen from radical prostatectomy must be available and ready to be shipped within 20 weeks post-surgery as outlined in Section 10.

NOTE: Every effort should be made to submit adequate tumor tissue specimen to Decipher Biosciences for testing immediately. Decipher Biosciences will notify submitting institution of Decipher score results within 21 days of receipt of adequate tumor tissue specimens. Failure to submit adequate tissue will result in request for additional tissue and delays in testing and reporting.

_____ 3.1.3 Patient must not have any previous treatment with androgen deprivation therapy (ADT), chemotherapy, or other physician prescribed systemic therapy for treatment of their prostate cancer.

NOTE: Prior treatment with bicalutamide is permitted.

_____ 3.1.4 Patient must have the ability to understand and the willingness to sign a written informed consent document. Patients with impaired decision-making capacity (IDMC) who have a legally authorized representative (LAR) or caregiver and/or family member available will also be considered eligible.

3.2 Eligibility Criteria for Randomization (Step 1)

_____ 3.2.1 Patient must be randomized to Step 1 a minimum of 6 weeks and a maximum of 24 weeks (168 days) from radical prostatectomy (RP).

_____ 3.2.2 For patients who did not have a Decipher score obtained through standard of care testing outside of the protocol prior to registration to Step 0, the Decipher score is >0.6 assessed from the prostatectomy specimen submitted as per Section 10.

_____ 3.2.3 Patient must not have pathologic evidence of pelvic lymph node involvement.

_____ 3.2.4 Patient must have an ECOG Performance Status (PS) of 0-2.

_____ 3.2.5 Patient must not have an uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure (New York Heart Association Class III and IV heart failure), unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

_____ 3.2.6 Patients with a prior or concurrent malignancy within 5 years of Step 1 randomization, 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.

_____ 3.2.7 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

_____ 3.2.8 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

_____ 3.2.9 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.

_____ 3.2.10 Patient must be able to take oral medications

_____ 3.2.11 Patient must have a PSA < 0.2ng/mL obtained within 2 weeks prior to Step 1 randomization.

_____ 3.2.12 Patient must not have pre or post-operative radiographic evidence of cancer recurrence or metastasis by abdominal and pelvic imaging (CT abdomen/pelvis, whole body MRI, MRI abdomen/pelvis, or equivalent, AND bone scan) within 24 weeks (168 days) prior to Step 1 randomization. If pre-operative risk does not support a need for CT abdomen/pelvis and/or bone scan imaging, the lack of baseline imaging due to low risk disease should be documented.

NOTE: A post-operative Decipher Score of >0.6 indicates an increased risk of metastatic disease and a bone scan or CT scan is required prior to Step 1 randomization.

_____ 3.2.13 Due to the potential harm through seminal transfer to an unborn fetus with the treatment regimens being used, sexually active patients must not expect to father children by using accepted and effective method(s) of contraception or by abstaining from sexual intercourse for the duration of their participation in the study and for 28 days after the last dose of protocol treatment.

_____ 3.2.14 Patient must have adequate organ and marrow function as defined below, obtained within 4 weeks prior to Step 1 randomization.

_____ Leukocytes ≥ 3,000/mcL

Leukocytes:_____ Date of Test:_____

_____ Absolute neutrophil count (ANC) ≥ 1,000/mcL

ANC:_____ Date of Test:_____

_____ Platelets ≥ 75,000/mcL

Platelet:_____ Date of Test:_____

_____ Hgb > 8 g/dL

Hgb:_____Date of Test:_____

_____ Total bilirubin ≤ institutional upper limit of normal (ULN) (or ≤ 3 x ULN for patients with known Gilbert's disease)

Total Bilirubin:_____ Institutional ULN:_____

Gilbert's disease present? _____ (Yes or No)

Date of Test:_____

_____ AST(SGOT)/ALT(SGPT) ≤ 2.5 × institutional ULN

AST:_____ Institutional ULN:_____

Date of Test:_____

ALT:_____Institutional ULN:_____

Date of Test:_____

Rev. Add2

_____ Glomerular Filtration Rate (GFR) >30 mL/min/1.73m2 estimated by MDRD formula:

(GFR (mL/min/1.73 m^2) = 175 × (Scr)-1.154 × (Age)-0.203 × (0.742 if female) × (1.212 if African American) (conventional units), or use calculator at https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease/laboratory-evaluation/glomerular-filtration-rate-calculators/mdrd-adults-conventional-units) or measured directly by 24 hour urine creatinine.

Creatinine:

Date of Test:_____

GFR:_____

Date of Test:_____

_____ _____

Physician Signature Date

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

4. Registration Procedures

Cancer Therapy Evaluation Program Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
HSP/GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a

participating organization (i.e., Alliance). Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>. For questions, please contact the RCR Help Desk by email at <RCRHelpDesk@nih.gov>.

Cancer Trials Support Unit Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval (applies to US and Canadian sites only) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements:

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

Protocol Specific Requirements for EA8183 Site Registration:

This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory

section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. A primary role on any roster is required to update provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, please view the Person Roster Browser under the RUMS link on the CTSU website.

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol.

- Log on to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
  - Enter the protocol # in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand then select ECOG-ACRIN and protocol number EA8183

Click on Documents, select *Site Registration*, and download and complete the forms provided.

NOTE: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log on to the CTSU members' website → Regulatory Tab
→ Regulatory Submission

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

The individual initiating the DTL for the site should upload the above listed training documentation when making the task assignment. The designated reviewer will accept or reject the documentation. A note regarding rejection of any training documents will display on the Site DTL Browser next to the task assignment. The DTL cannot be submitted for CI sign-off until the minimum number of persons are assigned to the task and have met the training requirements.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Log on to the CTSU members'
- Click on Regulatory at the top of your screen;
- Click on Site Registration
- Enter your 5-character CTEP Institution Code and click on Go

NOTE: The status shown only reflects compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Patient Enrollment

Patients must not start protocol treatment prior to Step 0 Preregistration or Step 1 Randomization.

Treatment should start within 14 days after Step 1 randomization

NOTE: When a patient has been successfully randomized, the confirmation of registration will indicate that the patient is on Arm X. The patient will actually be randomized to Arm A or B, but as this is a double blinded trial, that information cannot be displayed.

Rev. Add2 Delayed start of treatment due to toxicity must not exceed the maximum window permitted for dose holds (28 days).

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- The registrars must hold the OPEN Registrar task on the DTL for this site; and
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB

approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.1 Preregistration (Step 0)

The following information is to be provided at the time of Step 0 pre-registration to the trial:

4.1.1 Protocol Number

4.1.2 Site/Investigator Identification

Rev. Add2

- Institution CTEP ID
- Treating Investigator
- Consenting Person
- Site Registrar
- Network Group Credit
- Credit Investigator

4.1.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
- Gender
- Birth date (mm/yyyy)
- Race
- Ethnicity
- Nine-digit ZIP code
- Method of payment
- Country of residence

4.1.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.1.

4.1.5 Additional Requirements

4.1.5.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.1.6 Decipher Score

Prior to Step 1 Randomization the institution must enter the Decipher score results and upload the Decipher score report into Medidata Rave as follows:

- If patient is having Decipher score performed after Step 0 Preregistration, tumor tissue from radical prostatectomy must be submitted within 20 weeks post-surgery as outlined in Section 10. Decipher Biosciences will notify the submitting institution of the results within 21 days of receipt of the tumor tissue specimen.
- If patient had Decipher score obtained through standard of care outside of the protocol prior to Step 0 Preregistration and the score is > 0.6, the institution must enter assay results and upload report to Medidata Rave and then proceed to Step 1 Randomization.

4.2 Randomization (Step 1)

The following information is to be provided at the time of Step 1 Randomization to the trial:

4.2.1 Protocol Number

4.2.2 Site/Investigator Identification

Rev. Add2

- Institution CTEP ID
- Treating Investigator
- Consenting Person
- Site Registrar
- Network Group Credit
- Credit Investigator

4.2.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
- Gender
- Birth date (mm/yyyy)
- Race
- Ethnicity
- Nine-digit ZIP code
- Method of payment
- Country of residence

4.2.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.2.

4.2.5 Stratification Factors

- Intent to radiate
- Baseline PSA (> 0 and < 0.2 ng/mL)

4.2.6 Additional Requirements

4.2.6.1 Tumor tissue is to be submitted per patient consent for future undefined research studies as outlined in Section 10.

4.2.6.2 Peripheral blood is to be submitted per patient consent for future undefined research studies as outlined in Section 10.

4.3 Unblinding Procedures

The information provided below is for the use by a physician, nurse, CRA or pharmacist treating the patient. These contact numbers should not be used by patients. Patients should be instructed to call their doctor's office in the event of an emergency or adverse event that may result in the need to unblind the patient.

In the event of an emergency or severe adverse reaction necessitating identification of the medication for the welfare of the patient, please contact the Study Chair, Dr. Alicia Morgans, at 312-695-2381 or aliciak_morgans@dfci.harvard.edu or through the Study Chair Liaison, Claire Leisner, at 617-582-8373 first to ensure the reason for unblinding is valid. Then call a member of the ECOG-ACRIN Operations Office – Boston Drug Team at (617) 632-3610 Monday through Friday between 9:00 AM and 5:00 PM Eastern Time. For unblinding outside of these hours, contact AnswerConnect at 1-866-296-8940. This service will request the reason for unblinding and then page the on-call ECOG-ACRIN staff who will return your call and provide the unblinded treatment assignment if applicable. Remember, AnswerConnect should only be contacted outside of normal business hours and only in the event of an emergency. The ECOG-ACRIN Operations Office – Boston or AnswerConnect will require the protocol number (i.e., "EA8183"), the patient ID number (e.g., "44444"), and the patient initials (e.g., "FL") to unblind the patient. Note that if a patient is unblinded, they must discontinue protocol treatment.

4.4 Medidata Rave

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account; and
- Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to

https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

- To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type;
- To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR; and
- To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

4.5 Digital Radiation Therapy Data Submission Using Transfer of Images and Data

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images.

TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

Site staff that will be submitting images and RT Data via TRIAD will need to register with CTEP and have a valid and active CTEP-IAM account.

- Must be registered as an Associate, Associate Plus, Non-Physician Investigator, or Investigator registration type. Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in Registration and Credential Repository (RCR).

To submit images, site staff must hold the TRIAD Site User role on an NCTN or ETCTN roster. Individuals requiring a TRIAD Site User role should contact the person holding a primary role at the site for their affiliated NCTN or ETCTN

roster. All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD, and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installation:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account username and password and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

4.6 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

NOTE: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

4.7 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the EA8183 Forms Completion Guidelines.

5. Treatment Plan

5.1 Administration Schedule

We will evaluate post radical prostatectomy high-risk localized prostate cancer patients who are randomized to receive LHRH agonist (goserelin, leuprolide, or triptorelin) or antagonist (degarelix or relugolix) plus placebo vs LHRH agonist (goserelin, leuprolide, or triptorelin) or antagonist (degarelix or relugolix) plus darolutamide for 12 months (48 weeks). Patients must be registered to Step 1 a minimum of 6 weeks and a maximum of 24 weeks after radical prostatectomy. Patients can register to Step 0 as early as 2 weeks after radical prostatectomy. All randomized patients must have a Decipher score > 0.6.

Rev. Add2

5.1.1 Step 0 Preregistration

- Preregistration requires a previously determined Decipher score (from Decipher Biosciences) OR tumor tissue available for submission for Decipher score assay.
- Patients with a Decipher score performed through standard of care outside of the protocol prior to Step 0 Preregistration, with a score > 0.6, may proceed from preregistration directly to Step 1 Randomization after uploading the Decipher score into Medidata Rave.
- Patients without a Decipher score through standard of care outside of the protocol prior to Step 0 Preregistration must have tumor tissue available and submitted for Decipher score assay. See Sections 7.1 and 10 for submission of forms and specimens associated with Decipher score status. The post registration Decipher Biosciences assessment must determine Decipher score to be > 0.6 to be eligible for Step 1 randomization. In addition, the calculated CAPRA-S score must be ≥ 3 (see Appendix V).

5.1.2 Step 1 Randomization Treatment Arms

NOTE: When a patient has been successfully randomized, the confirmation of registration will indicate that the patient is on Arm X. The patient will actually be randomized to Arm A or B, but as this is a double blinded trial, that information cannot be displayed.

1 cycle = 28 days

- Arm A (ADT plus placebo):

  ADT treatment options:

  - Relugolix 120 mg PO once daily. There is a single initial loading dose of 360 mg PO. Relugolix can be taken with or without food and should be taken whole at approximately the same time each day.

    Rev. Add2

    OR

  - Goserelin, leuprolide, triptorelin, or degarelix by injection according to doses in Section 8 and according to one of the following dosing schedules:

    Rev. Add2

	1-month (12 total injections)	3-month (4 total injections)	4-month (3 total injections)	6-month (2 total injections)
Goserelin	X	X		
Leuprolide	X	X	X	X
Triptorelin	X	X		X
Degarelix	X			

PLUS

Placebo administered by mouth daily for 48 weeks. Take 2 tablets of placebo in the morning and 2 tablets in the evening. Each placebo tablet is 300 mg (600 mg per dose, 1200 mg per day). Placebo tablets must be taken with food and swallowed whole.

Please refer to Appendix III for a sample Patient Tablet Calendar.

- Arm B (ADT plus darolutamide):

  ADT treatment options:

  - Relugolix 120 mg PO once daily. There is a single initial loading dose of 360 mg PO. Relugolix can be taken with or without food and should be taken whole at approximately the same time each day.

    OR

  - Goserelin, leuprolide, triptorelin, or degarelix by injection according to doses in Section 8 and according to one of the following dosing schedules:

	1-month (12 total injections)	3-month (4 total injections)	4-month (3 total injections)	6-month (2 total injections)
Goserelin	X	X		
Leuprolide	X	X	X	X
Triptorelin	X	X		X
Degarelix	X			

PLUS

Darolutamide administered by mouth daily for 48 weeks. Take 2 tablets of darolutamide in the morning and 2 pills in the evening. Each darolutamide tablet is 300 mg (600 mg per dose, 1200 mg per day). Darolutamide tablets must be taken with food and swallowed whole.

Please refer to Appendix III for a sample Patient Tablet Calendar.

5.2 Radiation Treatment Plan/Regimen Description

NOTE: Adjuvant Radiotherapy to 64.8-66.6 Gy at 1.8 Gy/36-37 fractions to the prostate bed. Pelvic nodal radiation 45.0-50.4 Gy at 1.8 Gy/25-28 is allowed.

Salvage Radiotherapy to 64.8-70.2 Gy at 1.8 Gy/36-39 fractions to the prostate bed. Pelvic nodal radiation 45.0-50.4 Gy at 1.8 Gy/25-28 is allowed.

5.2.1 Radiation Therapy

Rev. Add2

Adjuvant radiation is defined as intent to deliver radiation in the setting of PSA < 0.2 ng/mL at any time during the 12 months (48 weeks) following prostatectomy.

Intent to deliver adjuvant radiation therapy must be declared prior to randomization, as it is a stratification factor. Radiotherapy should be delivered over approximately 7-8 weeks. Adjuvant radiotherapy will not be considered an event in the EFS endpoint.

Salvage radiation is defined as radiation delivered after randomization that had not been specified prior to randomization. Treatment with salvage radiotherapy will be considered an event in the EFS endpoint (see Section 6.5).

5.2.2 Treatment Technology

Photon treatment. Three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT) techniques, including Tomotherapy and volumetric modulated arc therapy (VMAT). ViewRay, CyberKnife are allowed. Some form of image guidance is required (kilo voltage imaging, cone-beam computed tomography systems [CBCT], electromagnetic transponders, etc.).

5.2.3 Immobilization

Proper immobilization is critical for this protocol. Patient setup reproducibility must be achieved using appropriate clinical devices.

5.2.4 Simulation Imaging

A treatment planning CT scan will be required to define the clinical and planning target volumes, and the critical normal structures. The treatment planning CT will be acquired with the patient set up in the same position as for daily treatments. Each patient will be positioned preferably in the supine position. Prone positioning for treatment is not recommended, but is allowed. The CT scan of the pelvis should start at or above the iliac crest down to below the perineum (below the ischial tuberosities). All tissues to be irradiated must be included in the CT scan. CT scan thickness should be ≤ 0.3 cm through the region that contains the target volumes. The regions above and below the target volume region may be scanned with slice thickness ≤ 1.0 cm.

Use of contrast (IV, PO, or rectal) is up to the treating physician. The placement of contrast in the rectum may cause the rectum to appear more anterior than it will be during treatment.

5.2.5 Definition of Target Volumes and Margins

5.2.5.1 Detailed Specifications:

5.2.5.1.1 Clinical Target Volume (CTV): The CTV will include the prostatic fossa and seminal vesicle remnants when present. Prostatic fossa CTV definition should follow guidelines as provided in the post-prostatectomy contouring atlas at

http://www.rtog.org/CoreLab/ContouringAtlases.aspx. The prostatic fossa CTV will extend inferiorly from the top of the penile bulb (or one CT slice ≤ 0.3 cm above) to just above the pubic symphysis superiorly at a minimum (at least for the anterior-most portion of the bladder). Laterally, the prostatic fossa CTV will extend from the medial edge of one obturator internus muscle to the other. Anteriorly and posteriorly the prostatic fossa CTV will include the entire bladder neck until above the pubic symphysis, where a gradual reduction off the anterior bladder is made. The prostatic fossa CTV may be increased (not decreased) beyond these limits in order to encompass the entirety of the prostate based on pre-prostatectomy imaging information when available. In addition, the superior, lateral, and posterior extent of the prostatic fossa CTV should be increased as needed to cover any defined remnants of the seminal vesicles, which should be included in the prostatic fossa CTV.

5.2.5.1.2 Planning Target Volume (PTV): The PTV will be a direct expansion of 0.5-1.5 cm beyond the CTV. Additional expansion within this range is required to account for penumbra when 3D CRT is used. Reduction in posterior expansion to 0.3-0.5 cm beyond the CTV is considered an acceptable variation when required to meet Rectum constraints or daily CBCT is used.

Use of Cone Beam CT and Plan Adjustment: There may be cases in which the target and surrounding normal tissues are found not to be reproducible relative to the simulation CT and consequent plan. If all attempts to reproduce bladder and rectal filling by coaching the patient do not work and replanning is thought to be necessary, the patient should be replanned in the same supine position with the new contours drawn to reflect any changes in the anatomy.

5.2.6 Prostate Bed Planning for 3DCRT:

The definition of volumes will be in accordance with International Commission on Radiation Units (ICRU) Report #62.

The PTV margins from CTV should be a minimum of 0.5 cm and a maximum of 1.5 cm in all dimensions. A posterior margin of < 0.6 cm

is not recommended. Care should be taken to conform the prescribed dose as closely to the PTV as possible, so as to avoid including the entire width of the rectum in the posterior blocked margin at the bladder neck-rectum interface. The planned dose between 64.8 to 70.2 Gy will be declared after the patient is planned and all dosimetric parameters finalized.

5.2.7 Prostate Bed Planning for IMRT

Target volumes: The definitions of volumes will be in accordance with the 1999 ICRU Report #62.

The CTV and PTV will be the same as for 3D-CRT. There is no need to add margin for penumbra. CTV margin to PTV should be between 0.5-1.5 cm. A posterior margin of 0.3-0.5 cm is acceptable if daily CBCT is being used. < 0.3 cm posterior margin is not recommended.

5.2.7.1 Definition of Critical Structures and Margins

The critical normal structures are the bladder, rectum, and femoral heads. The normal tissues will be contoured and considered as solid organs.

Rectum: The rectum contour will include the rectum and anal canal and will be contoured on every slice from the rectosigmoid junction superiorly to the level of the ischial tuberosities inferiorly.

Bladder: The bladder contour will include the entirely of the bladder as defined on the simulation CT. The bladder should be moderately full so that a portion lies outside the PTV (the patient should not be uncomfortable at simulation and probably will have more difficulty maintaining a full bladder during treatment).

- Bladder-CTV: The bladder volume outside the CTV as defined in Section 5.2.5.
- Femurs: The femoral heads should be contoured down to the region between the greater and lesser trochanters.
- Penile Bulb: The entirety of the penile bulb should be contoured. The penile bulb is the portion of the bulbous spongiosum of the penis immediately inferior to the GU diaphragm.
- External: The skin encompassing all CT slices from 1.5 cm inferior to superior of the radiation fields.

5.2.8 Dose Prescription and Constraints

The information provided in this section can be used for adjusting the dose constraints for treatment planning purposes. It is important to remember that ideal plans might not be achievable in all cases.

- PTV: At least 95% of the PTV should receive the prescribed dose (64.8-70.2 Gy). The maximum dose heterogeneity allowable in the PTV will be 10%. Since the dose is prescribed to the minimum

isodose line of the PTV, the dose variability is seen in portions of the target volume receiving higher than the specified dose.

- Rectum: Less than or equal to 20% and 50% of the rectum should receive ≥ 68.4 Gy and ≥ 50 Gy, respectively.
- Bladder: Less than or equal to 40% and 60% of the bladder (minus prostate bed CTV) should receive ≥ 68.4 Gy and ≥ 50 Gy, respectively.
- Femoral Heads: Less than or equal to 10% of each femoral head should receive ≥ 50 Gy.
- Penile Bulb: The penile bulb should receive a mean dose <52.5 Gy.

5.2.9 Treatment Planning Priorities and Instructions

Critical Structure and Target priorities must be listed in order of decreasing importance

- PTV
- Rectum
- Bladder-CTV
- Femurs
- Penile Bulb

5.2.10 Beam arrangement

Static gantry IMRT beam arrangements must be designed with a minimum of 5 gantry angles. If the beams are intercepted by a non-IGRT couch, the couch should be included in the treatment plan. For VMAT plans ≤2 arcs are recommended.

5.2.11 Acceptable algorithms

The following is a list of acceptable algorithms for dose calculation: Convolution/Superposition, AAA, Monte Carlo, Boltzmann Transport, and Collapsed Cone Convolution. All doses should be reported in terms of dose-to-water and not in terms of dose-to-medium.

5.2.11.1 Dose matrix resolution

Dose grid size should be ≤ 3 mm in all directions.

5.2.12 Patient-Specific QA

Any patient-specific QA that needs to be performed should follow institutional guidelines.

For photon IMRT/VMAT plans, patient specific QA is highly recommended. QA is performed by delivering the plan onto a phantom and measuring the dose using an ion chamber array or other 2D/3D device. Measured dose distribution will be compared to planned dose distribution using a Gamma criterion of 3% dose difference and 3 mm distance to agreement. The pass rate should be ≥ 90% measured for the entire plan.

5.2.13 Daily Treatment Localization/Image-Guided Radiotherapy(IGRT)

IGRT is radiation therapy using imaging to facilitate accuracy and precision throughout its entire process from target and normal tissue delineation, to radiation delivery, to adaptation of therapy to anatomic and biological changes over time in individual patients. In this section we use the terminology IGRT to focus on image-guidance at the time of radiation delivery to ensure its adherence to the planned treatment.

Daily image guidance using either 2D or 3D methods is required. If any deviation is larger than 2 mm, correction should be performed. All image/signal-guidance data should be recorded and archived at the site.

5.2.14 Management of Radiation Dose to the Patient from IGRT

ECOG-ACRIN is concerned about the estimated doses given from IGRT, and is committed to limiting the imaging dose when IGRT is used in any of its protocols. This can be accomplished by avoiding the use of this technology to make small changes in patient positioning that are within the stated PTV margins. The imaging dose to the patient may become significant if repeated studies are done for patients with severe set up problems (e.g., requiring frequent corrections that are larger than the PTV margins). It is recommended that patients demonstrating severe set up problems during the first week of treatment be moved to a treatment with larger margins.

5.2.15 Radiation Therapy Credentialing

- All therapy units used on this protocol must have their calibrations verified by the IROC Houston QA Center.

Radiation Therapy Credentialing is described in the table below.

RT Credentialing Requirements	**Web Link for Credentialing Procedures and Instructions** **http://irochouston.mdanderson.org**		
	Treatment Modality		
	3D	IMRT	Key Information
Facility Questionnaire	X	X	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email irochouston@mdanderson.org to receive your FQ link.
Credentialing Status Inquiry Form	X	X	To determine if your institution has completed the requirements, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org).
Phantom Irradiation		X	The IROC HN phantom treated using IMRT must be successfully completed. Non-standard units such as Tomotherapy or CyberKnife must be credentialed individually. Instructions for requesting and irradiating the phantoms are

RT Credentialing Requirements	Web Link for Credentialing Procedures and Instructions http://irochouston.mdanderson.org		
	Treatment Modality		
	3D	IMRT	Key Information
			found on the IROC Houston web site (http://irochouston.mdanderson.org).
IGRT Verification Study	X	X	Institutions must be credentialed for boney IGRT by IROC Houston. Find details on the IROC Houston QA Center website (http://irochouston.mdanderson.org) Institutions that have previously been approved for IGRT may not need to repeat credentialing.
Credentialing Notification Issued to:			
Institution	X	X	Institution will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center will notify the institution and ECOG-ACRIN that all desired credentialing requirements have been met.

5.2.16 Quality Assurance Documentation

Submission of treatment plans in digital format as DICOM RT is required. Digital data must include CT scans, structures, plan, and dose files. This study uses TRIAD for RT data submission. Use of TRIAD requires several preliminary steps (see Section 4.5). Additional information is available at:

Rev. Add2

https://triadinstall.acr.org/triadclient/

Use of SFTP will also be accepted as an alternate method of data submission on this study. See the instructions for submission of data via SFTP on the IROC Rhode Island website under Digital Data.

Any items on the list below that are not part of the digital submission may be included with the transmission of the digital RT data.

Within one week following the completion of radiotherapy, the following data must be submitted for all patients:

- RT treatment plans including treatment planning CT, structures, dose and plan files. These items are included in the digital plan.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.
- RT-1 Dosimetry Summary Form
- The RT-2 Radiotherapy Total Dose Record Form
- A copy of the patient's radiotherapy record including the prescription, and the daily and cumulative doses to all required areas.

  Supportive data and forms may be included with the transmission of the digital RT data or submitted separately via e-mail to DataSubmission@qarc.org.

Questions regarding the dose calculations or documentation should be directed to:
Protocol Dosimetrist
IROC Rhode Island QA Center
Phone: (401) 753-7600
Email: physics@qarc.org

5.3 Adverse Event Reporting Requirements

All toxicity grades described throughout this protocol and all reportable adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

5.3.1 Purpose

Adverse event (AE) data collection and reporting, which are a required part of every clinical trial, are done so investigators and regulatory agencies can detect and analyze adverse events and risk situations to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

5.3.2 Routine Reporting of Adverse Events (Medidata Rave)

Adverse events are reported in a routine manner at scheduled times during a trial using the Medidata Rave clinical data management system. Please refer to Section 4 of the protocol for more information on how to access the Medidata Rave system and the EA8183 forms packet for instructions on where, when and what adverse events are to be reported routinely on this protocol.

5.3.3 Expedited Reporting of Adverse Events (CTEP-AERS)

In addition to routine reporting, certain adverse events must be also reported in an expedited manner for timelier monitoring of patient safety and care. The remainder of this section provides information and instructions regarding expedited adverse event reporting

5.3.4 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of an agent in humans, whether or not considered agent related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to protocol treatment.
Unlikely	The AE is *doubtfully related* to protocol treatment.
Possible	The AE *may be related* to protocol treatment.
Probable	The AE is *likely related* to protocol treatment.
Definite	The AE is *clearly related* to protocol treatment.

- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
- **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.
- **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:
  - Death
  - A life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours)
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  - A congenital anomaly/birth defect
  - Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

5.3.5 Expedited Adverse Event Reporting Procedure

Adverse events requiring expedited reporting will use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov.

A CTEP-AERS report must be submitted electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov, so that ECOG-ACRIN and all appropriate regulatory agencies will be notified of the event in an expeditious manner.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (857-504-2900)

An electronic report MUST be submitted via CTEP-AERS immediately upon re-establishment of internet connection.

Supporting and follow-up data: Any supporting or follow-up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours.

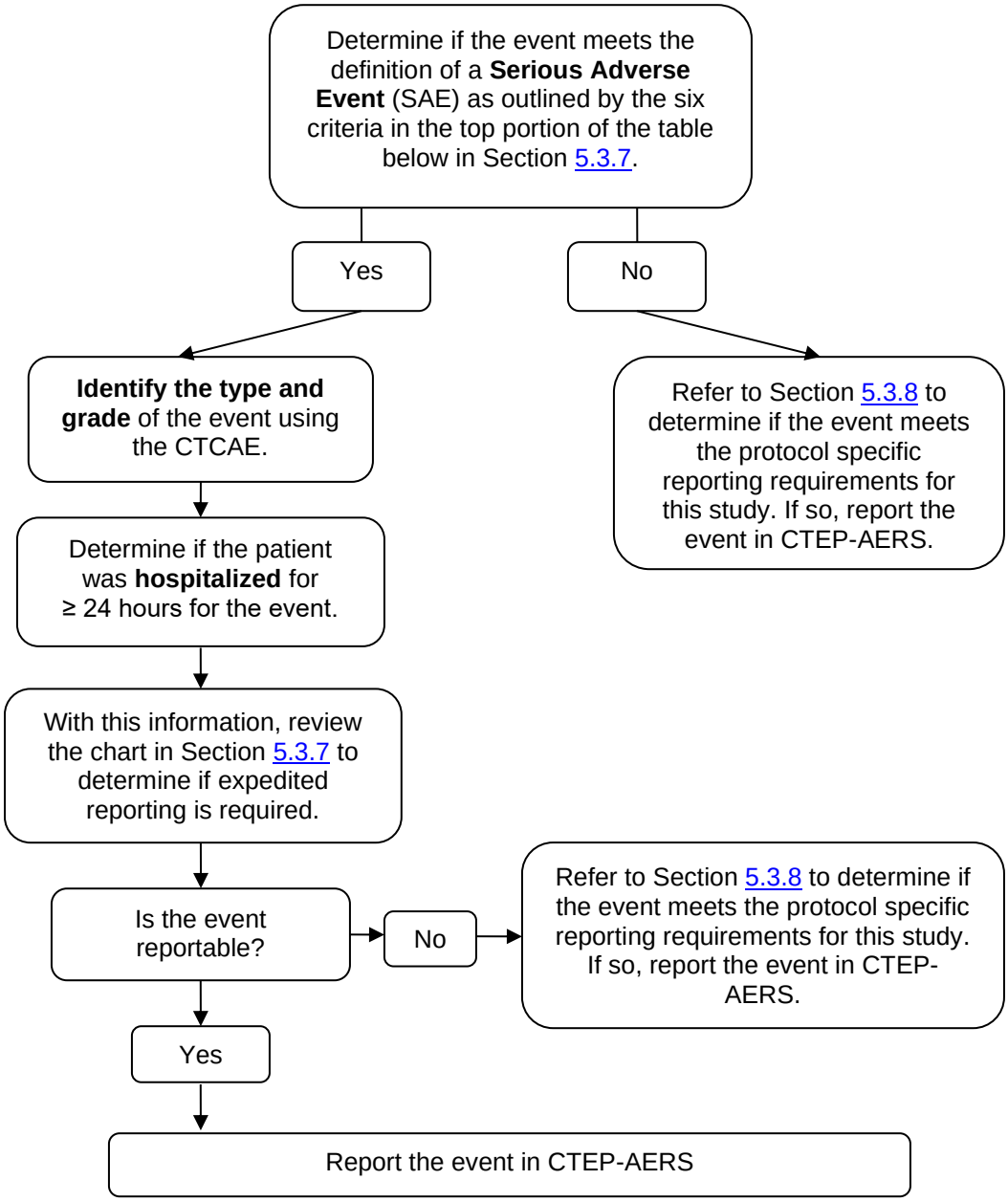
CTEP Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

Many factors determine the requirements for expedited reporting of adverse events on each individual protocol. The instructions and tables in the following sections have been customized for protocol EA8183 and outline the specific expedited adverse event reporting requirements for study EA8183.

5.3.6 Steps to determine if an adverse event is to be reported in an expedited manner – Arm X (Arms A and B)

NOTE: Since this is a double blinded study, the treatment arm code will appear as Arm X within the CTEP-AERS program

5.3.6.1 Guidelines for reporting adverse events **OCCURRING WHILE ON PROTOCOL TREATMENT AND WITHIN 30 DAYS** of the last administration of the investigational agent(s).


Determine if the event meets the definition of a **Serious Adverse Event** (SAE) as outlined by the six criteria in the top portion of the table below in Section 5.3.7.
Yes
No
Identify the type and grade of the event using the CTCAE.
Refer to Section 5.3.8 to determine if the event meets the protocol specific reporting requirements for this study. If so, report the event in CTEP-AERS.
Determine if the patient was **hospitalized** for ≥ 24 hours for the event.
With this information, review the chart in Section 5.3.7 to determine if expedited reporting is required.
Is the event reportable?
No
Refer to Section 5.3.8 to determine if the event meets the protocol specific reporting requirements for this study. If so, report the event in CTEP-AERS.
Yes
Report the event in CTEP-AERS

5.3.6.2 Guidelines for reporting adverse **events OCCURRING GREATER THAN 30 DAYS** after the last administration of the investigational agent(s).

If the adverse event meets the definition of a **Serious Adverse Event (SAE)** as outlined by the six criteria in the top portion of the table below in Section 5.3.7, OR the protocol specific requirements in Section 5.3.8, AND has an attribution of possible, probably or definite, require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4 and Grade 5 AEs

NOTE: Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported expeditiously in CTEP-AERS even if the patient is off study.

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

5.3.7 Expedited Reporting Requirements for Arm on protocol EA8183

Investigational Agents: Darolutamide/Placebo

Rev. Add2

Commercial Agents: Leuprolide, Goserelin, Triptorelin, Relugolix, and Degarelix

Late Phase 2 and Phase 3 Studies

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND *within 30 Days of the Last Administration of the Investigational Agent/Intervention.*[1]

NOTE: Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention.

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization
≥ 24 hrs</td><td colspan="2">10 Calendar Days</td><td rowspan="2">24-Hour; 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization
≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" – The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

5.3.8 Additional instructions, requirements and exceptions for protocol EA8183

Additional Instructions

- For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.
- **Reporting a death on study:** A death occurring while on study treatment or within 30 days of the last dose of study treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

  NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

NOTE: There are no protocol specific requirements or exceptions for expedited adverse event reporting on protocol EA8183.

5.3.9 Other recipients of adverse event reports and supplemental data

ECOG-ACRIN, the IND sponsor, will forward CTEP-AERS reports to all appropriate regulatory agencies and pharmaceutical company.

A drug supporter representative may call a site for additional or supplemental information regarding a serious adverse event. Any additional written AE information requested by the drug supporter MUST be submitted to BOTH ECOG-ACRIN and the drug supporter.

Adverse events determined to require expedited reporting must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.3.10 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported as follows:

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**

1. Complete a Second Primary Form in Medidata Rave within 14 days.
2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.

- **A <u>secondary malignancy</u> is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**

1. Complete a Second Primary Form in Medidata Rave within 14 days.

Rev. Add2

2. Report the diagnosis on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration Folder in Medidata Rave.

   Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy

   NOTE: When reporting attribution on the AE Form, assess the relationship between the secondary malignancy and the current protocol treatment ONLY (and NOT relationship to any anti-cancer treatment received either before or after protocol treatment).

3. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov.
4. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
5. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The ECOG-ACRIN Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the ECOG-ACRIN Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should

be submitted in CTEP-AERS or by the ECOG-ACRIN Second Primary Form.

5.4 Dose Modifications for Darolutamide/ Placebo

Adverse events can be addressed via instructions in Table 3 below. Dosing delays for grade 1 or 2 adverse events for up to 28 days are allowed per the Investigator's discretion.

Table 3. Dose modification and/or delay for toxicities considered related to study treatment (darolutamide/ placebo)

NOTE: This excludes clinically nonsignificant and asymptomatic laboratory abnormalities

Grade of Adverse Event	Dose modifications and treatment interruptions/ delays	Study treatment withdrawal
Grades 0-2	• Recommend maintaining treatment schedule. • However, the decision to delay/ interrupt or reduce study treatment will be left to the investigator's discretion [a, b]	
Grades 3-4	• Treatment with darolutamide/ placebo should be delayed/ interrupted until event resolves to < grade 2[a] • When the severity is grade < 2, restart darolutamide/ placebo at a reduced dose of 300 mg BID [b, c]	If the dosing of the study treatment is temporally or permanently reduced to 300 mg BID and a grade 3 or higher treatment-related AE occurs while the patient is on a dose of 300 mg PO BID, the patient must be permanently discontinued from study treatment.

Rev. Add2

[a] If there is no recovery after 28 consecutive days, study treatment should be permanently discontinued.

[b] If a dose reduction took place, when the AE returns to baseline or is resolved, dose escalation to 600 mg BID may be considered at the discretion of the investigator.

[c] If dose is re- escalated to 600 mg and a second treatment-related AE with a severity of grade 3 or higher occurs, a permanent dose reduction is required. If there is a third occurrence of a grade 3 or higher treatment-related AE, the study treatment must be permanently discontinued.

Rev. Add2

5.5 Supportive Care

5.5.1 All supportive measures consistent with optimal patient care will be given throughout the study.

5.6 Concomitant Medications

5.6.1 Avoid concomitant use of strong or moderate CYP3A inducers.

5.6.1.1 Examples include phenobarbital, phenytoin, rifampicin, St. John's Wort (Hypericum perforatum) and glucocorticoids; this is not an exhaustive list.

5.6.2 If administering darolutamide/placebo concurrently with strong CYP3A inhibitors, monitor patients more frequently for adverse reactions to darolutamide/placebo.

5.6.2.1 Examples of strong CYP3A inhibitors include itraconazole, ketoconazole, clarithromycin, erythromycin and diltiazem; this is not an exhaustive list.

5.6.3 Avoid concomitant use of drugs that are BCRP (Breast Cancer Resistance Protein) substrates where possible. If used concomitantly, monitor patients more frequently for adverse reactions and consider reducing the dose of the BCRP substrate medication.

NOTE: Examples of BCRP substrate medications include rosuvastatin, sulfasalazine, cimetidine and glyburide. This is not an exhaustive list.

5.7 Quality of Life Test Administration

5.7.1 Quality of Life Instruments to be administered

5.7.1.1 FACT-P

5.7.1.2 FACT-Cog

5.7.1.3 FACIT-Fatigue

5.7.2 Quality of Life Assessment Schedule

Patients will be assessed according to the following schedule:

1.) Baseline – FACT-P, FACT-Cog, FACIT-Fatigue

2.) 24 weeks (from Day 1 of treatment) - FACT-P, FACT-Cog, FACIT-Fatigue

3.) 48 weeks (from Day 1 of treatment) - FACT-P, FACT-Cog, FACIT-Fatigue

4.) 72 weeks (from Day 1 of treatment) - FACT-P, FACT-Cog, FACIT-Fatigue

5.7.3 Quality of Life Administration Instructions

Rev. Add2

5.7.3.1 The questionnaires must be administered within two weeks of the time points listed above. The patient should be instructed to respond to the questionnaires in terms of his experience during the timeframe specified on each questionnaire.

5.7.3.2 The patient should be asked to read the instructions at the beginning of each questionnaire and complete all the items. It is permissible to assist the patient with the completion of the questionnaires as long as the staff person does not influence the patient's responses.

5.7.3.3 The questionnaires must be reviewed by the protocol nurse or research coordinator as soon as the patient completes them to ensure all items were marked appropriately. If more than one answer was marked, the patient should be asked to choose the answer which best

reflects how he is feeling. If a question was not answered, the patient should be asked if he would like to answer it. The patient should always have the option to refuse. If the patient refuses, it should be indicated on the questionnaire that he declined to answer the item.

5.7.3.4 If the patient cannot complete a questionnaire, or if the patient refuses to complete the questionnaire, the reason should be noted according to the instructions in the EA8183 Forms Completion Guidelines.

5.8 Duration of Therapy

Patients will receive protocol therapy unless:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the EA8183 Forms Packet.
- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol therapies are administered.
- Patient experiences progression of disease during treatment.

5.9 Duration of Follow-up

Rev. Add2

For this protocol, all patients who completed randomization to Step 1, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 15 years from Step 1 randomization (every 3 months (12 weeks) if patient is < 2 years from Step1 randomization, every 6 months (24 weeks) if patient is 2-5 years from Step 1 randomization, every 12 months (48 weeks) if patient is 5-10 years from Step 1 randomization, once annually (48 weeks) by telephone if patient is > 10 years from Step 1 randomization. There are no specific follow-up requirements if patient is more than 15 years from Step 1 randomization). All patients must also be followed through completion of all protocol therapy.

6. Measurement of Recurrent Disease

6.1 CT Scans

CT scans of the abdomen and pelvis (or equivalent, e.g., whole body MRI, MRI abdomen/pelvis), chest imaging (CT chest or Chest X-Ray) and technetium bone scan should be done as clinically indicated. Subsequent imaging with the same modality will be performed as clinically indicated for new or worsening symptoms as reported by the patient or concerning findings on laboratory assessments or increase in PSA ≥ 0.2 ng/mL with subsequent confirmatory PSA ≥ 0.2 ng/mL checked at least one week later. Treating clinicians can also use an optional PET/CT per standard of care to guide subsequent treatment in the setting of a PSA ≥ 0.2 ng/mL with a second confirmatory PSA ≥ 0.2 ng/mL.

If no evidence of disease is identified on the first CT scans of the abdomen and pelvis (or equivalent, e.g., whole body MRI, MRI abdomen/pelvis) and chest imaging (CT chest or Chest X-Ray) and bone scan in the setting of a PSA ≥ 0.2 ng/mL and subsequent confirmatory PSA ≥ 0.2 ng/mL, PET scans can be used at the discretion of the treating physician after PSA ≥ 0.2 ng/mL. PET scans are a more sensitive method to detect disease recurrence and guide subsequent treatment. Repeat CT scans of the abdomen and pelvis (or equivalent, e.g., whole body MRI, MRI abdomen/pelvis) and chest imaging (CT chest or Chest X-Ray) and bone scans should be repeated at least every 6 months after initial detection of PSA ≥ 0.2 ng/mL (and subsequent confirmatory PSA ≥ 0.2 ng/mL) in the setting of continued rise in PSA or development of clinical symptoms to detect radiographic evidence of disease and to guide subsequent treatment. Repeat PET scans can be performed after PSA ≥ 0.2 ng/mL (and subsequent confirmatory PSA ≥ 0.2 ng/mL) in the setting of continued rise in PSA as clinically indicated to guide subsequent treatment.

6.2 Radiographic Documentation of Disease Recurrence

6.2.1 Metastasis Identification by Conventional Imaging: CT and Bone Scan:

New lesions seen on CT or bone scan will be defined as the appearance of new malignant lesions. The finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). The study defines recurrence of disease by the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) and Prostate Cancer Working Group 3 Guidelines (PCWG3).[51] For this reason, new bone lesions will be determined primarily from the bone scan, and other non-bone lesions from the CT. If a new lesion is equivocal, for example because of its small size, follow-up evaluation will clarify if it represents truly new disease per the PCWG3 criteria. If repeat scans confirm there is a new lesion other than a pelvic nodal recurrence, then a metastatic event should be declared using the date of the initial scan (this can be repeat CT or bone scan showing ongoing progression or use of PET/CT to better characterize the equivocal

lesion). If a pelvic nodal recurrence is identified, this is an event by the event free survival and recurrence-free survival endpoints, but does not meet criteria for an event by the metastasis-free survival endpoint.

6.2.2 Metastasis Identification by PET Imaging (Only perform in setting of PSA ≥ 0.2 ng/ mL with second confirmatory PSA ≥ 0.2 ng/mL)

In the setting of PSA increase (PSA ≥ 0.2 ng/mL with second confirmatory PSA ≥ 0.2 ng/mL), FDA approved diagnostic PET/CT (e.g., Axumin, Choline, PSMA) will be allowed per institutional standard of care to confirm presence of radiographic metastasis. Uptake in prostate bed alone or pelvic nodal recurrence would not be considered a metastatic event, but both would be considered a recurrence event in the RFS endpoint and event for the event free survival (EFS) endpoint. If a new lesion is equivocal, for example because of its small size or low uptake, follow-up evaluation (or biopsy) will clarify if it represents truly new disease. If repeat scans performed in the setting of continued rise in PSA (or additional imaging) confirm there is a new lesion (outside of pelvic nodal recurrence), then this is an event by the metastasis-free survival endpoint and should be declared using the date of the initial scan. If a pelvic nodal recurrence is identified in the setting of a confirmed PSA (PSA ≥ 0.2 ng/mL) using PET imaging, this is an event by the event free survival endpoint, but does not meet criteria for an event by the metastasis-free survival endpoint.

6.2.3 Standard Guidance for Conventional CT and MRI

This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up must be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

6.2.4 Methods for Evaluation of Bone Disease

Bone disease will be evaluated using radionuclide bone scan, which should be performed as clinically indicated during follow-up.

Subsequent imaging with the same modality will be performed as clinically indicated (for new or worsening symptoms as reported by the patient or concerning findings on laboratory assessments, or increase in PSA > 0.2 ng/mL after confirmatory PSA (≥ 0.2 ng/mL) checked at least one week later. Treating clinicians can also use an optional PET/CT per standard of care in the setting of a PSA ≥ 0.2 ng/mL with a second confirmatory PSA ≥ 0.2 ng/mL.

If no evidence of disease is identified on the first CT scans of the abdomen and pelvis (or equivalent, e.g., whole body MRI, MRI abdomen/pelvis) and chest imaging (CT chest or Chest X-Ray) and bone scan in the setting of a PSA ≥ 0.2 ng/mL, PET scans can be used at the discretion of the treating physician after PSA ≥ 0.2 ng/mL. PET scans are a more sensitive method to detect disease recurrence and guide subsequent treatment. Repeat CT scans of the abdomen and pelvis (or equivalent, e.g., whole body MRI, MRI abdomen/pelvis) and chest imaging (CT chest or Chest X-Ray) and bone scans should be repeated at least every 6 months (24 weeks) after initial detection of PSA ≥ 0.2 ng/mL (and subsequent confirmatory PSA ≥ 0.2 ng/mL) in the setting of continued increase in PSA to detect radiographic evidence of disease and to guide subsequent treatment. Repeat PET scans can be performed after PSA ≥ 0.2 ng/mL as clinically indicated to guide subsequent treatment.

6.2.5 Evaluation of Radionuclide Bone Scans

New osseous lesions on bone scintigraphy consistent with bone metastasis will meet criteria for radiographic progression. Equivocal lesions should be either confirmed with additional imaging (e.g., MRI, PET) or repeated after 8 weeks to document resolution or confirm metastasis.

Interpretation of serial changes in a radionuclide bone scan is well recognized to be highly subjective. Thus, the primary outcome will be whether the bone scan is stable, vs. worse or progression.

6.3 Serological Recurrence

Rev. Add2

PSA levels will be assessed at baseline, then every 4 weeks for the first 12 weeks and then every 12 weeks thereafter. Patient's PSA will be assigned a response according to the following criteria:

Stable Serological Control: PSA level < 0.2 ng/mL.

Serological Recurrence: Increase in PSA to ≥ 0.2 ng/mL with confirmatory PSA ≥ 0.2 ng/mL at least one week later. On occasions, there may be an intermediate fluctuant value. This will not restart the evaluation period so long as the intermediate value was not below the previous nadir. The date of the first recorded increase that meets the criteria above (not defeated by a subsequent drop in PSA level to create a new nadir) will be deemed the date of progression by PSA. Any PSA rise without clinical or radiographic progression does not constitute events by the primary endpoint (metastasis free survival) and should be addressed per standard of care management.[52] See Section 6.5.

6.4 Endpoint Definitions

6.4.1 Metastasis-Free Survival (MFS)

MFS is defined as time from randomization to development of metastatic disease or death, whichever occurs first. Metastasis includes development of bone, visceral, or lymph node metastasis outside of the pelvis (not local pelvic nodal recurrence) on conventional imaging (bone scan or CT chest/abdomen/pelvis) or PET imaging (in the setting of a PSA ≥ 0.2 ng/mL with confirmatory second value at least 1 week apart that is ≥ 0.2 ng/mL or higher). A pelvic lymph-node recurrence will not be captured as a metastatic event, but will be captured if treatment ensues in the RFS and EFS endpoints.

6.4.2 Recurrence-Free Survival (RFS)

RFS is defined as the time from randomization to any of the MFS events, a PSA (≥ 0.2 ng/mL) (with confirmatory PSA ≥ 0.2 ng/mL at least one week later), or the appearance of pelvic lymph node recurrence, whichever occurs first.

6.4.3 Event-Free Survival (EFS)

EFS is defined as the time from randomization to any of the RFS events or treatment events defined as delivery of treatment with salvage radiation or initiation of systemic therapy, whichever comes first.

6.4.4 Time to PSA recurrence

Time to PSA recurrence is defined as time from randomization to PSA recurrence.

6.4.5 Overall survival (OS)

OS is defined as time from randomization to death or date last known alive.

6.5 Definitions and Management after Recurrence

6.5.1 Definitions

6.5.1.1 Salvage Radiation

Salvage radiation is defined as radiation delivered at any point during the study that was not planned prior to randomization. Study teams must record the reason for salvage radiation, including rising PSA, local recurrence, distant recurrence, patient or physician preference, or other. This would be considered an event in the EFS endpoint.

6.5.1.2 PSA Recurrence

Management of PSA recurrence in patients with local therapy only (prostatectomy alone) who have not received adjuvant radiation therapy should proceed per standard of care with consideration of appropriate imaging studies (bone scan and CT abdomen/pelvis and/or PET imaging (e.g., PSMA, fluciclovine, choline).[52] Pelvic radiation with or

without systemic hormonal therapy in the setting of biochemical recurrence is recommended for appropriate patients per guidelines.[52] Per protocol, documentation of recurrence type (PSA only, radiographic evidence disease on standard imaging, or radiographic evidence of disease on PET imaging with detectable PSA) should be documented thoroughly. This would be considered an event in the RFS and EFS endpoints.

7. Study Parameters

7.1 Therapeutic Parameters

1. Prestudy scans used to assess all sites of disease must be done within 24 weeks prior to Step 1 Randomization.
2. Prestudy CBC (with differential and platelet count) must be done ≤ 4 weeks before Step 1 Randomization.
3. All required prestudy chemistries, as outlined in Section 3, must be done ≤ 4 weeks before Step 1 Randomization.

	Prior to Step 0 Pre-registration	**Prior to Step 1 Randomization**	**Baseline Day 1 of Study Treatment)**	**At 4 and 8 weeks from Baseline.**	**Every 12 weeks (+/- 2 weeks) from weeks 9 to 48 weeks**	**Every 12 weeks (+/- 2 weeks) from weeks 49-96**	**At progression**	**Post96 weeks to 15 years from Step 1 randomization [5]**
Informed Consent	X							
Physical Exam[1] and		X	X	X	X			
ECOG performance status		X		X	X			
Concomitant medications			X	X	X			
PSA and Testosterone[2]		X		X	X	X	X	X
CBC with differential, CMP[3]		X	X	X	X			
Tablet Count/Diary				X	X			
Patient Reported Quality of Life Assessment[4]			X		See QOL timepoints outlined below			
Toxicity assessment			X	X	X			
Decipher Score Assay[6]	X							
Biological Specimen Submissions[7]	See Section 10							
CT/ MRI Scans of the Pelvis and bone scan[9]		X[9]			X[10]			X[10]
Tumor Tissue	X[8]		X[7]					
Peripheral Blood (one 10mL EDTA purple top tube)[11]			X		X[12]		X	

Peripheral Blood (one 10mL SST red top tube)[11]			X		X[12]		X	

1. History & Physical (H&P) consists of height, weight, blood pressure, vitals, respiratory rate and temperature. Cycle 1 Day 1 Physical Exam (PE) does not need to be done if the PE completed for Step 1 randomization was done within 14 days of Cycle 1 Day 1.
2. Baseline PSA assessment must be done within 2 weeks prior to Step 1 Randomization. PSA is done every 4 weeks from start of treatment (Cycle 1 Day 1) for first 12 weeks, then every 12 weeks until confirmed seriological recurrence. (See Section 6). Testosterone is also checked when PSA is assessed.
3. CBCs (with differential and platelet count) includes WBC, ANC, Platelets, Hgb, and Hct. CMPs includes sodium, potassium, chloride, CO2, BUN, creatinine, creatinine clearance, alkaline phosphatase, ALT, AST, total bilirubin, albumin, and calcium. Cycle 1 Day 1 labs do not need to be done if labs completed for Step 1 randomization were done within 14 days of Cycle 1 Day 1.
4. Patient reported quality of life assessment includes FACT-P, FACT-Cog, and FACIT-Fatigue patient reported outcome measures. QOL assessments are done at baseline and weeks 24, 48 and 72 (+/- 2 weeks). (See Section 5.7)
5. Survival status should be assessed every 12 weeks if patient is < 2 years from Step 1 randomization, every 24 weeks if patient is 2-5 years from Step 1 randomization, every 48 weeks if patient is 5-10 years from Step 1 randomization. Once annually (48 weeks) by telephone if patient is > 10 years from Step 1 randomization. No specific requirements if patient is more than 15 years from Step 1 randomization.
6. Decipher score assay performed by through standard of care outside of the protocol prior to Step 0 Preregistration (see Sections 4 and 10). Enter assay results and upload report to Medidata Rave and proceed to Step 1 Randomization.
7. All specimens submitted must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS).
8. MANDATORY from patients with no Decipher score determined prior to Step 0 Preregistration. Tumor tissue specimen from radical prostatectomy must be submitted to Decipher Biosciences for testing within 20 weeks post-surgery. Kits will be provided for collection and shipment of tumor tissue specimens. See Section 10 for instructions.
9. Imaging can be pre- or post-operative but within 24 weeks prior to randomization and should confirm absence of radiographic evidence of cancer recurrence or metastasis by abdominal and pelvic imaging (CT abdomen/pelvis, whole body MRI, MRI abdomen/pelvis, or equivalent, AND bone scan). A post-operative Decipher score of > 0.6 indicates an increased risk of metastatic disease and obtaining a CT abdomen/pelvis and bone scan prior to randomization will be required. If pre-operative risk does not support a need for CT abdomen/pelvis and/or bone scan imaging, the lack of baseline imaging due to low risk disease should be documented. Imaging should then be performed when triggered by an abnormal PSA (≥ 0.2 ng/mL, confirmed by a subsequent PSA ≥ 0.2 ng/mL) as described in Footnote #10 below
10. Follow-up imaging should occur as clinically indicated when triggered by an abnormal PSA (≥ 0.2 ng/mL, confirmed by a subsequent PSA ≥ 0.2 ng/mL 1 week later). If no evidence of disease is identified on CT scans of the abdomen and pelvis (or equivalent, e.g., whole body MRI, MRI abdomen/pelvis) and chest imaging (CT chest or Chest X-Ray) and bone scan in the setting of a PSA ≥ 0.2 ng/mL, the patient can continue to be followed with plans to repeat PSA assessments every 12 weeks and repeat imaging within 24 weeks in the setting of a continuously rising PSA. PET scans can also be used as a more sensitive method to detect disease recurrence when PSA is ≥ 0.2 ng/mL. Repeat CT scans of the abdomen and pelvis (or equivalent, e.g., whole body MRI, MRI abdomen/pelvis) and chest imaging (CT chest or Chest X-Ray) and bone scans should be repeated at least every 24 weeks after initial detection of PSA ≥ 0.2 ng/mL (confirmed by a subsequent PSA ≥ 0.2 ng/mL) in patients in whom the PSA continues to rise to detect radiographic evidence of disease and guide further treatment. Repeat PET scans can be performed as clinically indicated to guide further treatment
11. Submit from patients who consent to future undefined research studies to the ECOG-ACRIN Central Biorepository and Pathology Facility.

12. At time of best PSA response or 12 weeks from initiation of therapy.

8. Drug Formulation and Procurement

This information has been prepared by the ECOG-ACRIN Pharmacy and Nursing Committees.

8.1 Darolutamide and Matching Placebo (NSC #815949)

8.1.1 Other Names

BAY 1841788, ODM-201

8.1.2 Classification

Androgen receptor inhibitor

8.1.3 Mode of Action

Darolutamide is an androgen receptor (AR) inhibitor. Darolutamide competitively inhibits androgen binding, AR nuclear translocation, and AR-mediated transcription. A major metabolite, keto-darolutamide, exhibited similar in vitro activity to darolutamide. In addition, darolutamide functioned as a progesterone receptor (PR) antagonist in vitro (approximately 1% activity compared to AR). Darolutamide decreased prostate cancer cell proliferation in vitro and tumor volume in mouse xenograft models of prostate cancer.

8.1.4 Storage and Stability

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). Do not store above 30 °C.

8.1.5 Dose Specifics

Rev. Add2

600 mg taken by mouth twice daily. See Appendix III for a sample Patient Tablet Calendar.

NOTE: If the patient vomits immediately or shortly after taking their dose of darolutamide/placebo, the new dose should be taken as soon as possible if their vomiting is under control. Patients should not take two doses together to make up for a missed/vomited dose. The patient should discuss with their treating physician if they are unsure of whether to take another dose or wait until their next dose due to timing or being unable to keep solids.

8.1.6 Preparation

The study drugs darolutamide or matching placebo will be provided in a bottle. Each bottle will contain 140 tablets. Each tablet is 300 mg.

Same bottle for placebo.

8.1.7 Route of Administration

Oral

Darolutamide and/or matching placebo will be taken twice a day (BID) with 2 tablets in the morning and 2 tablets in the evening. Darolutamide and/or matching placebo is to be taken with food and should be swallowed whole.

8.1.8 Incompatibilities

None

8.1.9 Availability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of darolutamide/placebo received using the appropriate NCI Oral Investigational Agent (Drug) Accountability Record (Oral DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each participant and ordering investigator on this protocol.

The EA8183 Investigational Product Destruction Record must be submitted to document any unused darolutamide and matching placebo at the completion of the study.

Drug Orders:

Each bottle will contain 140 tablets of darolutamide and/ or matching placebo with a tablet dosage of 300 mg. There will be 3 cycles dispensed at a time per drug request form. Please follow the EA8183 Drug Request Form for ordering.

Initial Orders:

Following submission of the required regulatory documents and patient Step 1 Randomization, a supply of darolutamide and/or matching placebo may be ordered from the ECOG-ACRIN Drug Team. Institutions must email the completed EA8183 Drug Request Form to the ECOG-ACRIN Drug Team at DrugOrder@ecog-acrin.org. A copy of the EA8183 Drug Request Form is available for download from the CTSU site under the Pharmacy tab of the EA8183 study page. No blinded starter supplies are available for this protocol.

Rev. Add2

Important Information for Drug Orders:

At the time of Step 1 Randomization each patient will be assigned a patient specific Blinded Drug ID number, for example DR1117. The Blinded Drug ID number will appear on the patient's Confirmation of Registration Form.

The EA8183 Drug Request Form must include the patient specific Blinded Drug ID number with each drug request in order for the drug order to be processed. Failure to provide this information on the drug order form will result in a delay of the drug order being processed and shipped.

This study is a double-blinded treatment protocol. Bottles of darolutamide and matching placebo MAY NOT be transferred from one patient to another patient.

Reorders:

Reorders using the EA8183 Drug Request Form should be emailed to the ECOG-ACRIN Drug Team at DrugOrder@ecog-acrin.org. Once the reorder is approved, the drug will be received on site within 4 business days. Shipments will be made from Patwell Pharmaceutical

Solutions on Monday through Thursday for delivery onsite Tuesday through Friday. There will be no weekend or holiday delivery of drugs. Institutions should keep in mind that shipments take up to 4 business days from the date the drug request is received by Patwell Pharmaceutical Solutions.

Drug Inventory Records:

Investigational Product Records at Investigational Site(s): It is the responsibility of the Investigator to ensure that a current record of investigational production disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines. The EA8183 Investigational Product Destruction Record must be submitted to document any unused darolutamide and matching placebo at the completion of the study.

Drug Destruction and Return:

At the completion of each patient's treatment at your institution, all unused drugs, partially used, or empty containers must be destroyed at the site according to the institution's policy for drug destruction. Please maintain appropriate records of the disposal, including dates and quantities.

8.1.10 Side Effects

For treatment of patients with prostate cancer, darolutamide is given in addition to the ADT. While ADT reduces testosterone levels in blood, darolutamide blocks the action of the androgens (e.g., testosterone) in the tumor cells and in the body. Thus the effects of darolutamide and ADT enhance each other because they both block the androgen hormone that helps tumors grow. However the blocking of androgen hormones in other body systems may lead to side effects, which are well-known consequences of ADT such as:

- Softening of your bones leading to osteoporosis (fragile and brittle bones), osteopenia (bone loss) and increased risk for bone fractures
- Change in the body make up with a tendency to lose muscle tissue and gain fat tissue. This change may be associated with reduced physical fitness and increased risk for falls
- Changes in how your body processes sugar and fats.
- Increased risk of heart – and blood vessel problems, including the brain, e.g., heart attack, high blood pressure, stroke.

8.2 Androgen Deprivation Therapy (ADT)

Please refer to the individual package inserts for more information

8.2.1 Goserelin Acetate (NSC #606864)

8.2.1.1 Other names

ZOLADEX® (goserelin acetate implant)

8.2.1.2 Classification

Gonadotropin Releasing Hormone (GnRH) agonist

8.2.1.3 Mode of Action

Rev. Add2

Goserelin acetate implant is a Gonadotropin Releasing Hormone (GnRH) agonist. Stimulation of goserelin results in suppression of serum levels of luteinizing hormone (LH) and follicular stimulating hormone (FSH).

8.2.1.4 Storage and Stability

Goserelin acetate implant is supplied as a sterile and totally biodegradable D,L-lactic and glycolic acids copolymer (13.3-14.3 mg/dose) impregnated with goserelin acetate equivalent to 3.6 mg of goserelin in a disposable syringe device fitted with a 16-gauge x 36 +/- 0.5 mm siliconized hypodermic needle with protective needle sleeve [SafeSystem™ Syringe] (NDC 0310-0950¬ 36). The unit is sterile and comes in a sealed, light- and moisture-proof, aluminum foil laminate pouch containing a desiccant capsule. Store at room temperature (do not exceed 25°C [77°F]).

8.2.1.5 Dose Specifics

Goserelin acetate implant must be administered into the anterior abdominal wall below the navel line using an aseptic technique under the supervision of a physician at one of the following desired dosing schedules:

- Goserelin acetate 3.6 mg for 1-month administration, given as an injection once every 4 weeks.
- Goserelin acetate 10.8 mg for 3-month administration, given as an injection once every 12 weeks.

8.2.1.6 Solution preparation

Goserelin acetate implant is supplied as a sterile and totally biodegradable D,L-lactic and glycolic acids copolymer (13.3-14.3 mg/dose) impregnated with goserelin acetate equivalent to 1 or 3 month dose of goserelin in a disposable syringe device fitted with a 16-gauge x 36 +/- 0.5 mm siliconized hypodermic needle with protective needle sleeve [SafeSystem™ Syringe] (NDC 0310-0950¬ 36).

8.2.1.7 Route of Administration

Subcutaneous injection

8.2.1.8 Availability

Commercial

8.2.1.9 Side Effects

See package insert

8.2.2 Leuprolide acetate (NSC #377526)

8.2.2.1 Other names

LUPRON® INJECTION, ELIGARD

8.2.2.2 Classification

Gonadotropin releasing hormone (GnRH) agonist

8.2.2.3 Mode of Action

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH). The analog possesses greater potency than the natural hormone. The chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-Lprolinamide acetate (salt).

8.2.2.4 Storage and Stability

Store at 25°C (77°F); excursions permitted to 15ºC–30°C (59ºF–86°F)

8.2.2.5 Dose Specifics

Leuprolide acetate must be administered under the supervision of a physician. Due to different release characteristics, the dosage strengths are not additive and must be selected based upon the desired dosing schedule.

- Leuprolide acetate 7.5 mg for 1-month administration, given as an injection once every 4 weeks.
- Leuprolide acetate 22.5 mg for 3-month administration, given as an injection once every 12 weeks.
- Leuprolide acetate 30 mg for 4-month administration, given as an injection once every 16 weeks.

Rev. Add2

- Leuprolide acetate 45 mg for 6-month administration, given as an injection once every 24 weeks.

8.2.2.6 Solution preparation

Leuprolide acetate is a sterile, aqueous solution intended for subcutaneous or intramuscular injection. It is available in a 2.8 mL multiple-dose vial containing leuprolide acetate (5 mg/mL), sodium chloride, USP (6.3 mg/mL) for tonicity adjustment, benzyl alcohol, NF as a preservative (9 mg/mL), and water for injection, USP. The pH may have been adjusted with sodium hydroxide, NF and/or acetic acid, NF.

8.2.2.7 Route of Administration

Leuprolide acetate's route of administration depends on the brand selected. Either is acceptable for this trial.

Intramuscular injection for LUPRON.

Subcutaneous injection for ELIGARD.

8.2.2.8 Availability

Commercial

8.2.2.9 Side effects

See Package Insert

8.2.3 Triptorelin (NSC #724666)

8.2.3.1 Other names

TRIPTODUR, TRELSTAR, Decapeptyl, Gonapeptyl

8.2.3.2 Classification

Gonadotropin releasing hormone (GnRH) agonist

8.2.3.3 Mode of Action

Rev. Add2

Triptorelin is a GnRH analog; it decreases levels of luteinizing hormone (LH) and follicular stimulating hormone (FSH) resulting in suppression of steroidogenesis with subsequent decrease in testosterone (male) and estrogen (female) levels; a sustained decrease in LH and FSH secretion occurs after chronic and continuous administration.

8.2.3.4 Storage and Stability

Store at 20-25°C (68-77°F)

8.2.3.5 Dose Specifics

Triptorelin must be administered under the supervision of a physician at one of the following desired dosing schedules:

- Triptorelin 3.75 mg for 1-month administration, given as an injection once every 4 weeks.
- Triptorelin 11.25 mg for 3-month administration, given as an injection once every 12 weeks.
- Triptorelin 22.5 mg for 6-month administration, given as an injection once every 24 weeks.

8.2.3.6 Solution preparation

Triptorelin is reconstituted with accompanying diluent (Sterile Water) 2 mL, and administered as a single intramuscular injection once every 4 weeks, 12 weeks, or 24 weeks.

8.2.3.7 Route of Administration

Intramuscular injection

8.2.3.8 Availability

Commercial

8.2.3.9 Side Effects

See package insert.

8.2.4 Degarelix (NSC #7711648)

8.2.4.1 Other names

FIRMAGON

8.2.4.2 Classification

Gonadotropin releasing hormone (GnRH) antagonist

8.2.4.3 Mode of Action

Degarelix targets and blocks GnRH receptors located on the surface of gonadotroph cells in the anterior pituitary, thus reducing secretion of luteinizing hormone by those cells, which decreases testosterone production in the testes.

8.2.4.4 Storage and Stability

Store at 20-25°C (68-77°F)

8.2.4.5 Dose Specifics

Degarelix is given in one month dose formulations only. Dosing schedules of 3, 4, or 6 months are not available. The initial dose is 240 mg given as two subcutaneous injections of 120 mg each. The starting dose is followed by maintenance doses every 28 days afterwards of a single 80 mg subcutaneous injection each.

8.2.4.6 Solution Preparation

Degarelix is provided as a powder to be reconstituted with sterile water for injection. The reconstituted drug must be administered within one hour of addition of water. Do not shake the vials.

Starting dose: FIRMAGON (degarelix for injection) two single-dose vials; 120 mg per vial with 3 ml of sterile water to be injected at a concentration of 40 mg/ml.

Maintenance dose: FIRMAGON (degarelix for injection) one single dose vial; 80 mg per vial with 4 ml of sterile water to be injected at a concentration of 20 mg/ml.

8.2.4.7 Route of Administration

Subcutaneous injection

8.2.4.8 Availability

Commercial

8.2.4.9 Side Effects

See package insert.

Rev. Add2

8.2.5 Relugolix (NSC #825960)

8.2.5.1 Other names

Relumina, ORGOVYX

8.2.5.2 Classification

Gonadotropin releasing hormone (GnRH) receptor antagonist

8.2.5.3 Mode of Action

Relugolix is a nonpeptide GnRH receptor antagonist that competitively binds to pituitary GnRH receptors, thereby reducing the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and consequently testosterone.

8.2.5.4 Storage and Stability

Store at room temperature. Do not store above 30°C (86°F).

8.2.5.5 Dose Specifics

Relugolix is given PO at a dosage of 120 mg once daily after a single initial loading dose of 360 mg PO. Relugolix can be taken with or without food and should be taken whole at approximately the same time each day.

8.2.5.6 Route of Administration

Oral tablet

8.2.5.7 Availability

Commercial

8.2.5.8 Side Effects

See package insert.

9. Statistical Considerations

9.1 Primary Endpoint

This is a randomized phase III trial in prostate cancer patients who have undergone radical prostatectomy. These patients have undetectable PSA and are considered disease-free at study entry but also have high risk of recurrence characterized by a CAPRA-S score (cancer of the prostate risk assessment score; new postsurgical score) ≥ 3. A Decipher score (tissue-based genomic classifier) will also be assessed for each patient at registration and a score of > 0.6 indicates high risk of recurrence. Eligible patients with CAPRA-S score ≥ 3 and Decipher score > 0.6 will be randomized to either androgen deprivation therapy (ADT) plus placebo or ADT in combination with darolutamide. Patients will be stratified based on intention to administer adjuvant radiation therapy and baseline PSA (undetectable vs detectable by any assay but < 0.2 ng/mL) at randomization.

The primary endpoint is metastasis-free survival (MFS), defined as the time from randomization to development of metastatic disease or death, whichever occurs first. Metastatic disease includes bone, visceral, or lymph node metastasis outside of the pelvis (not local pelvic nodal recurrence in the true pelvis). A pelvic lymph-node recurrence will not be captured as a MFS event, but will be considered as an event if treatment ensues for the event-free survival endpoint (see below). Metastatic disease could be identified by conventional imaging (any PSA) or novel PET/CT imaging only if PSA becomes detectable (PSA ≥ 0.2 ng/mL, confirmed by a subsequent PSA of the same level or higher at least one week later). Patients who are alive without documented metastasis will be censored at the date of last disease assessment. The primary objective is to evaluate whether ADT plus darolutamide improves MFS when compared to ADT plus placebo. The primary comparison will be an intention-to-treat analysis of all randomized patients.

9.2 Sample size with power justification

The AUA/ASTRO guidelines for treatment with adjuvant radiation are incorporated into the patient consent form to ensure that patients are aware of the benefits to adjuvant radiation. In addition, patients with pT3 disease or positive surgical margins will be referred to radiation oncology to evaluate whether adjuvant radiation is needed or not. It is expected that about 25% of patients will receive adjuvant radiation therapy.

Based on a prior study (Ross et al, 2016), the 5-year metastasis rate for patients with Decipher score of 0.6-0.7 who received no additional treatment after radical prostatectomy is 28%. With administration of ADT to all patients and receipt of adjuvant radiation therapy in 25% of patients, the 5-year metastasis rate (by conventional imaging) is expected to be 15% in the ADT plus placebo arm. As novel PET/CT imaging is allowed when detectable PSA is observed, we expect the metastasis rate to increase by about 30%, so the 5-year MFS rate is expected to be 80% in the placebo arm. Assuming the addition of darolutamide will improve MFS rate at 5 years by 7.5%, the 5-year MFS rate is expected to be 87.5% in the darolutamide arm (HR=0.60). As patients with Decipher score > 0.7 who have even higher risk of developing metastasis will also be enrolled on this study, the accumulation of events will be slightly faster than the assumed rate.

Accrual is anticipated to be 15 patients with Decipher score > 0.6 per month. In order to randomize 15 patients a month, we plan to screen 34 eligible patients (Step 0) with CAPRA-S score ≥ 3 each month as it is expected that 44.2% of patients with CAPRA-S score ≥ 3 will have a Decipher score > 0.6. The entire accrual will be completed in 4.5 years for a total of 810 patients (Step 1 randomization).

The study has 80% power using one-sided 0.025 level stratified logrank test and the overall type I error will be controlled using an O'Brien-Fleming boundary function. Full information will be achieved when 131 patients have developed metastasis or died and the final analysis is scheduled for this time point, about 7.3 years from activation.

9.3 Analysis plan including plans for formal interim analysis

Interim analyses for the MFS endpoint will be performed beginning when approximately 50% of the planned full information has occurred, about 4.7 years from activation, continuing annually until either criteria for early stopping are met or full information is reached. Full information will be achieved when 131 patients have developed metastasis or died and the final analysis is scheduled for this time point, about 7.3 years from activation. The study has 80% power using one-sided 0.025 level stratified logrank test and the overall type I error will be controlled using an O'Brien-Fleming boundary function. The table below summarizes operating characteristics of the proposed monitoring plan.

Repeated analysis	Total number of cases	Total number of events	Information time	Upper boundary	Nominal Significance
1	810	66	0.50	2.9502	0.00159
2	810	92	0.70	2.4611	0.00693
3	810	117	0.89	2.1656	0.01517
4	810	131	1.00	2.0680	0.01932

The study will also be monitored for early stopping for inefficacy based on the Linear 20% Inefficacy method proposed by Freidlin et al.[48] Inefficacy monitoring will be performed at the same information time as the efficacy monitoring and the cut-off values for HRs are shown in the table below. If at any time point, the observed hazard ratio (experimental arm over control arm) is greater than the cut-off values, the trial will be stopped for lack of efficacy.

Repeated interim futility analysis	Information time	Calendar time (years after activation)	Hazard ratio (stopping boundaries)
1	0.50	4.7	0.998
2	0.70	5.7	0.959
3	0.89	6.7	0.923

9.4 Secondary Endpoints

Recurrence-free survival (RFS) is the main secondary endpoint of this study and is defined as the time from randomization to any of the MFS events, pelvic lymph node recurrence or detectable PSA (PSA ≥0.2 ng/mL, confirmed by a second PSA of the same level or higher at least one week later), whichever occurs first. Based on the Ross study, the RFS rate at 5 years is expected to be 47% in a

natural history cohort. After incorporating ADT, adjuvant RT and novel PET/CT imaging, the 5-year RFS rate in the ADT plus placebo arm is expected to be 55%. Assuming the addition of darolutamide will improve 5-year RFS rate to 65% (HR=0.72), the current design will have 80% power for the RFS comparison using a one-sided stratified logrank test with type I error of 0.025. Full information will be achieved when 312 patients have experienced an RFS event (about 7.1 years from activation). With the rapidly changing landscape of prostate cancer management, an amendment to change the primary endpoint from MFS to RFS might be considered if RFS becomes an accepted endpoint for approval.

Another important secondary endpoint is event-free survival (EFS), defined as the time from randomization to any of the RFS events, treatment with salvage radiation therapy with or without systemic therapy, or initiation of systemic therapy for presumed recurrence, whichever occurs first. Additional secondary endpoints include overall survival, testosterone recovery rate, time to testosterone recovery, safety and tolerability, quality of life and change in neurocognitive function. Overall survival is defined as the time from randomization to death by any cause or date last known alive. Time to testosterone recovery is defined as the time from randomization to a return of serum testosterone level to greater than or equal to lower limit of normal for the testosterone assay. The method of Kaplan and Meier will be used to characterize the time-to-event endpoints, and a logrank test will be used to compare these endpoints across treatments. Exact binomial confidence intervals will be used to describe the proportions of patients with testosterone recovery in each arm.

Evaluation of the safety and tolerability of the protocol therapies is also important. Toxicity will be defined using the CTCAE. All patients who receive treatment, regardless of eligibility, will be evaluated for toxicity. The 90% confidence interval for the true probability of observing a toxicity of Grade 4 or higher on a given arm will be no wider than 9% if the study proceeds to complete the accrual of 810 patients. The probability of observing one or more toxicities on a given arm with a true rate of 1% is 98.3%.

Patients are required to have a CAPRA-S score ≥ 3 if they did not have a Decipher score previously performed through standard of care outside of the protocol, and a CAPRA-S score is not required for patients with a Decipher score obtained through standard of care outside of the protocol. Although we do not anticipate any difference in clinical outcomes between patients with and without a CAPRA-S score at baseline, a sensitivity analysis evaluating clinical outcomes among patients with and without a CAPRA-S score will be performed. The distribution and availability of CAPRA-S score in each arm will also be assessed to see if there is an imbalance between arms.

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9.5 Quality-of-Life Assessments

Quality of life (QOL) will be evaluated using FACT-P, FACT-Cog and FACIT-Fatigue instruments at baseline, 24 weeks,48 weeks, and 72 weeks, and descriptive statistics will be used to characterize QOL over time in each arm. Subgroup analysis will be performed among patients who receive adjuvant RT and patients who do not receive adjuvant RT in each arm. As patients can receive adjuvant RT at any time within 48 weeks of surgery, this subgroup analysis applies to QOL assessments at 48 weeks and is descriptive in nature.

The primary objective of the QOL study is to compare overall QOL, measured by FACT-P total score, between two arms at 48 weeks (completion of adjuvant therapy). We hypothesize that the patients in the ADT alone arm will have better QOL (higher FACT-P total scores) than those in the ADT + darolutamide arm. Assuming an attrition rate of 20% for QOL assessment by 48 weeks in both arms, about 648 patients will be included in the primary analysis of the QOL study. A difference of 6-10 points in the FACT-P total score is considered clinically meaningful and the standard deviation is expected to be 21 points based on E3805, a previous prostate cancer study.[37] The standard deviation of the FACT-P total score was about 21 points in both arms of E3805 at each time point (baseline and 3, 6, 9, 12 months). With 324 analyzable patients in each arm, the study will have about 95% power to detect a 6-point difference between the two arms using a two-sample t test with two-sided type I error of 0.05. The power will be greater than 99% if the difference between the two arms is 10 points. The change in FACT-P score from baseline to 48 weeks is also of interest. We hypothesize that there will be a smaller decline in quality of life from baseline to 12 months in the ADT alone arm than in the ADT + darolutamide arm. A paired t test will be used to compare FACT-P scores at these two time points in each arm. A two-sample t test will be performed to compare the changes in FACT-P scores from baseline to 48 weeks between the two arms. As most of the patients are expected to have testosterone recovery by 72 weeks after completion of adjuvant therapy, it's also important to assess QOL at this time point (72 weeks).

A recent study suggests that treatment with ADT is associated with a decline in cognitive function, therefore, cognitive function, measured by FACT-Cog, will be compared between the two arms at 48 weeks (completion of treatment). We hypothesize that there will be a smaller decline in subjective patient-reported cognitive function from baseline to 48 weeks in the ADT alone arm than in the ADT + darolutamide arm. We also hypothesize that subjective patient-reported cognitive function (FACT-Cog score) will be higher (higher) at 48 weeks in the ADT alone arm than in the ADT + darolutamide arm. The FACT-Cog has four subscales: perceived cognitive impairments (PCI), perceived cognitive abilities, impact of perceived cognitive impairment on QOL, and comments from others on cognitive function. Summary statistics will be used to describe each subscale at each time point and the PCI subscale score at 48 weeks will be the primary measurement of this analysis. Although this is an exploratory objective, Bonferroni correction will be employed for the 3 follow-up time points of interest to make the analysis conservative. The PCI subscale consists of 18 questions (subscale score including 2 newly added questions will be presented as well). According to Bell et al, the average standard deviation is about 15.4 and the clinically important differences (CID) for the PCI subscale are 7.4 points and 4.6 points at treatment completion and 26 weeks post treatment completion, respectively.[50] Assuming 80% of patients (324 patients per arm) will complete the FACT-Cog assessment at 48 weeks, the study will have about 92% power to detect a 4.6-point mean difference (0.3 standard deviation) using a two-sample t test with two-sided type I error of 0.0167 (0.05/3; Bonferroni correction). The power will be greater than 99% if the mean difference between the two arms is 7.4 points. A similar analysis will be done to compare the change in FACT-Cog score from baseline to 48 weeks between the two arms.

As fatigue is a commonly reported symptom among patients with cancer treatment, FACIT-Fatigue will be used to evaluate fatigue during the course of

the treatment. We hypothesize that patients in the ADT alone arm will have higher FACIT-Fatigue scores (less fatigue) than patients in the ADT + darolutamide arm. The FACIT-Fatigue scores at 48 weeks will be compared between the two arms using a two-sample t test.

Mixed effect models will be constructed as an exploratory analysis to estimate the time profile of QOL assessments in the two arms and to evaluate treatment-by-time interactions. Assessment time will be considered as a continuous variable if there is a linear trend in QOL assessments over time or a set of dummy variables if non-linear trend exists. Patient demographics and disease characteristics will be adjusted in the mixed effect models.

9.6 Correlative studies for integrated biomarkers

In cases in which funding is not already secured, the analytic plans for all correlative studies will be performed after submission of a protocol amendment defining funding sources and a statistical analysis plan as an amendment. Unfunded correlatives that require an amendment will be noted as such.

9.6.1 Identification of novel gene expression signatures

The availability of Decipher transcriptome expression platform enables the study to identify novel gene expression signatures that are predictive of clinical outcomes. Detailed information on identification of the RNA expression signatures is included in Section 11. The associations between the gene expression signatures and clinical outcomes will be assessed by Cox proportional hazards models and logrank test.

9.6.2 Evaluation of prognostic value of established signatures

The study will also evaluate the prognostic value of molecular subtypes identified by established signatures, including AR activity, basal-luminal subtyping by modified PAM50 and ADT score using Cox proportional hazards models. We estimate that about 20% of patients on this study will harbor low AR-activity tumors and these patients are expected to have poorer outcome (shorter MFS) than those with high AR-activity (see Section 11 for calculation of AR activity score). As the prognostic role of AR activity is not affected by darolutamide, both arms will be pooled together for this analysis. Assuming 80% of patients have AR activity score and 5-year MFS rates are 86% and 75% for patients with high and low AR activity, respectively, the study will have about 87.7% power to detect such difference (HR=0.52) with 2-sided type I error of 0.05. Similar analysis will be performed to evaluate the prognostic value of luminal-basal subtype. Patients with luminal B tumors are expected to have better outcomes than patients with luminal A or basal subtypes when being treated with ADT. The treatment-by-subtype interaction will also be assessed.

As for ADT score, patients will be categorized into either low or high ADT score using a cutoff of 0.36 (the median score derived from validation cohort of a previous study; see Section 11 for more information). Based on prior studies, about 32% of patients with Decipher score > 0.6 will have high ADT score. Patients with high ADT score are expected to have longer MFS than those with low ADT

score. Assuming 80% of patients have ADT score available and 32% of the patients are categorized as having high ADT score with 5 year MFS rate of 89%, the study will have 78% power to detect a hazard ratio of 0.52 with two-sided type I error of 0.05.

9.6.3 Associations between MFS and Decipher scores as well as disease characteristics

Decipher score is a continuous variable ranging from 0 to 1 with higher score representing higher risk of metastasis in this patient population. In order to evaluate the associations between MFS and Decipher score (ranging from > 0.6 to 1 in this study), Cox proportional hazards models will be performed with adjustment for important disease characteristics, including PSA, Gleason score, disease stage, pathology of the radical prostatectomy specimen, etc. Decipher score could be categorized into a few risk groups and the Akaike information criterion (AIC) method will be used to determine the optimal number of cutoff points. To assess whether treatment effect is affected by Decipher score levels, the treatment-by-Decipher interactions will be included in the model as well.

9.6.4 Genome-wide alterations – Analysis will occur after funding has been secured.

Prostate cancer specimens will be banked for future studies to perform genome-wide alterations in coding and non-coding DNA sequences. To identify the genetic alterations that are associated with development of metastasis, Cox proportional hazards models and logrank test will be used. The analysis will focus on actionable alterations first. The treatment-by-alteration interactions will also be assessed to determine whether response to darolutamide is affected by distinct genomic subgroups.

Ultimately, the findings on gene expression signatures and DNA alterations will be assessed in the models simultaneously to identify subsets of patients who might benefit most from the treatment of ADT with or without darolutamide.

NOTE: The proposed study of genome-wide alterations using banked specimens will not occur until an amendment to this treatment protocol (or a separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

9.7 Gender and Ethnicity

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.

Based on previous data from E3886, E9887 and S9921, the anticipated accrual in subgroups defined by gender and race is:

DOMESTIC PLANNED ENROLLMENT REPORT (TREATMENT)					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	75	0	0	75
White	0	727	0	8	735
More Than One Race	0	0	0	0	0
Total	0	802	0	8	810

The accrual targets in individual cells are not large enough for definitive treatment comparisons to be made within these subgroups. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC). The DSMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DSMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DSMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DSMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DSMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DSMC Policy can be obtained from the ECOG-ACRIN Operations Office – Boston.

10. Specimen Submissions

All specimens must be clearly labeled with the ECOG-ACRIN protocol number EA8183, the patient's initials and ECOG-ACRIN patient sequence number, the collection date, and specimen type. For pathology materials, it is strongly recommended that full patient names be provided.

It is required that all specimens submitted on this trial be entered and tracked via the ECOG-ACRIN Sample Tracking System (STS) Section 10.5. An STS shipping manifest form is to be included with every submission. The CBPF will log receipt of tumor tissue residuals from Decipher Biosciences into STS.

Additional guidelines for pathology submissions is outlined in Appendix I.

10.1 Step 0 (Preregistration) Tumor Tissue Submissions to Decipher Biosciences

This section outlines the submission of tumor tissue to determine the Decipher score. This is **mandatory** for patients who have not had the Decipher score previously determined. Every effort should be made to submit tumor tissue specimen from radical prostatectomy to Decipher Biosciences immediately, as patients need to be randomized to Step 1 within 24 weeks from surgery.

For specimen submissions post Step 1 Randomization see Section 10.2.

All residual tumor tissue submitted to Decipher Biosciences during Step 0 Preregistration will be forwarded to the ECOG-ACRIN Central Biorepository and Pathology Facility. Requests for return of blocks for purposes of patient management must be directed to the CBPF.

10.1.1 Ordering the Decipher Prostate Specimen Collection Kit

Following Step 0 Preregistration contact Decipher Biosciences Customer Support and request the Decipher Specimen Collection Prostate Kit from RUO@decipherbio.com. Include Decipher study number (P9010) and ECOG-ACRIN (EA8183) study number in email as well as shipping address.

Kits should be ordered prior to Step 0 Preregistration. Kits will ship FedEx ground and arrive within three to four (3-4) days, please note if an expedited shipment is needed.

Test Requisition Forms are to be completed by ordering physician and pathology laboratory and original included in specimen collection kit. Test requisition forms can be requested from RUO@decipherbio.com. Please indicate Decipher study number P9010 and ECOG-ACRIN study number EA8183.

Before shipping, email copy of completed requisition form and redacted pathology report (report must have specimen ID and Decipher study number P9010, ECOG-ACRIN study number EA8183 and ECOG-ACRIN case ID number) to RUO@decipherbio.com to order Decipher test.

10.1.2 Specimen Requirements for Radical Prostatectomy Tissue

Follow specimen checklist provided in collection kit.

If you have any questions about specimen submission, please contact Decipher Biosciences at 888.520.8718 or email RUO@decipherbio.com.

Block Submission

Select one (1) formalin fixed paraffin embedded (FFPE) tissue block with the highest Grade Group (Gleason score) and at least 0.5 cm^2 of tumor tissue by area. Please ensure block ID # is clearly referenced in the block label.

Slide Submission

Submit one (1) H&E slide and five (5) 5 µm thick serially sectioned unstained slides or six (6) 5 µm thick serially sectioned unstained slides. Label the serial sectioned slides (1-6) in the order in which they were cut for scraping. Store unstained slides at 4 degrees C until shipping.

10.1.3 Shipping Requirements

Tumor tissue specimens must be shipped within 20 weeks post-surgery.

Ship using the FedEx shipping label provided in collection kit. Email RUO@decipherbio.com with shipment tracking number.

Block

1. Place the selected FFPE block into the small zip-lock bag.
2. Place the small zip-lock bag containing the block into the foam insert. Follow instructions below starting at #2.

Slides

1. Place slides into the two (2) slides holders (up to 5 slides each)
2. Fold (a) Test Requisition and (b) Pathology Report and place all paperwork into the specimen kit, between the dividing flap and the foam insert.
3. Fold down the dividing flap, place the provided cold pack on top of the flap and close the specimen kit.
4. Place the closed specimen kit into the FedEx Clinical Lab Pak and apply the shipping label provided.
5. Ship via your regular scheduled FedEx pickup.

10.1.4 Patients Who Had Decipher Score Performed through standard of care outside of the protocol Prior to Step 0

For patients that already had Decipher score assay through standard of care outside of the protocol prior to Step 0 preregistration following must be emailed to RUO@decipherbio.com:

- Redacted copy of Decipher Prostate RP Report with Decipher study number P9010, ECOG-ACRIN study number EA8183, and ECOG-ACRIN case ID number
- Copy of Test Requisition Form

NOTE: Email RUO@decipherbio.com for test requisition, include Decipher (P9010) and ECOG-ACRIN (EA8183) study numbers in email.

10.1.5 Notification of Results

Decipher Biosciences will notify the submitting institution of the Decipher score within 21 days of receipt of the tumor tissue specimen. Submission of inadequate tumor tissue specimen will result in request for additional material and will delay turnaround time for reporting results.

10.2 Submission of Decipher Score Results Prior to Step 1 Randomization

Prior to Step 1 Randomization institution must enter assay results and upload Decipher report via Medidata Rave. If assay results are from prior to Step 0 Preregistration please redact Decipher report and ensure protocol number (EA8183) and ECOG-ACRIN five-digit patient sequence number are on the Decipher report.

10.3 Step 1 (Randomization) Tumor Tissue and Peripheral Blood Submissions to ECOG-ACRIN Central Biorepository and Pathology Facility (EACBPF)

Submit from patients who answer 'Yes' to 'I agree to provide additional samples for research.'

If you have any questions concerning tumor tissue and peripheral blood submissions please contact the ECOG-ACRIN CBPF at (844) 744-2420 or eacbpf@mdanderson.org

10.3.1 Pathology Material Submissions

Guidelines for pathologists are provided in Appendix I.

Submitting pathologist and clinical research associate may refer to Appendix I which outlines the Pathology Submission Guidelines.

The tumor tissue specimens are to be labeled with the institution's assigned pathology ID# as well as the information above.

10.3.1.1 Required Material

Forms: Must be submitted with all pathology submissions.

- STS generated Shipping Manifest Form
- Copy of the institutional diagnostic and surgical pathology report
- Immunological study reports, if available

Tumor Tissue Submissions:

- Representative formalin-fixed paraffin-embedded (FFPE) tumor tissue blocks from surgical biopsy

NOTE: If blocks are unavailable for submission, cores and slides are to be submitted. All cores and slides must be adequately labeled, with slides numbered sequentially in the order cut. Alternative submission requirements:

- One (1) H&E slide
- Twenty (20) 5 µm unstained, positively charged, air-dried plus slides from the thickest part of the tumor
- One (1) or more core punches (minimum of 4mm diameter). If core punch tool is unavailable, request core punch kit from the ECOG-ACRIN CBPF (844) 744-2420. Adequately label every slide and core submitted.

If these criteria cannot be met, please contact the ECOG-ACRIN CBPF (eacbpf@mdanderson.org) to obtain alternative submission requirements.

10.3.2 Peripheral Blood Submissions

Kits for the collection and shipment of the peripheral blood specimens are ordered on-line from Cenetron Central Laboratories. Instructions are provided in Appendix VI. Questions regarding kits can be directed to projectmanagement@cenetron.com or call the Cenetron Clinical Trials Group at (512) 439-2000. Kits must be ordered after the patient has been randomized to the trial and will generally arrive within three (3) business days from when the order was placed.

Peripheral blood specimens are to be collected at the following time points:

- Prior to Start of Treatment (Step 1)
- At time of best PSA Response or 12 weeks from Initiation of Therapy
- Progression

10.3.2.1 Specimen Preparation Guidelines

EDTA Purple Top Tube

- Draw one (1) 10mL EDTA Purple Top tube of whole blood at each time point
- Invert tube gently 8-10 times to ensure proper mixing
- Package and ship the day of collection at ambient temperature

SST Red Top Tube

- Draw one (1) 10mL SST Red Top tube of whole blood at each time point
- Invert tube gently 8-10 times to ensure proper mixing
- Package and ship the day of collection at ambient temperature

10.3.3 Shipping Procedures

Tumor tissue specimens are to be shipped overnight at ambient temperature (cool pack in warm weather) within one (1) month of randomization.

Peripheral blood specimens are to be shipped at ambient temperature the day of collection Monday through Thursday via overnight courier.

The laboratory is open Monday through Friday to receive specimens. Do not ship on Fridays or Saturdays, or the day before holidays. **Friday shipments are ill advised, similarly shipping before holidays is often problematic. The laboratory is closed Saturday, Sunday, and holidays.**

Ship using the CBPF's FedEx account using the FedEx on-line Ship Manager.

Ship to:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3598
1515 Holcombe Boulevard
Houston, TX 77030
Toll Free Phone: (844) 744-2420 (713-745-4440 Local or International Sites)
Fax: (713) 563-6506
Email: eacbpf@mdanderson.org

Access to the shipping account for shipments to the CBPF can only be obtained by logging into fedex.com with an account issued by the CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your institution needs to have an account created, please contact the CBPF by email at eacbpf@mdanderson.org.

An STS Shipping Manifest Form must be generated and shipped with all specimen submissions.

10.4 Use of Specimens in Research

Specimens submitted will be processed to maximize their utility for current and future research projects and may include, but not limited to, extraction of plasma, serum, DNA and RNA.

Specimens from patients who consented to allow their specimens to be used for future approved research studies, including residuals from the currently defined research studies, will be retained in an ECOG-ACRIN-designated central repository. For this trial, specimens will be retained at the ECOG-ACRIN Central Biorepository and Pathology Facility. Specimens will be de – identified prior to distribution for any approved research projects.

If future use is denied or withdrawn by the patient, the specimens will be removed from consideration for use in any future study. Pathology materials may be retained for documentation purposes or returned to the institution. All other specimens will be destroyed per guidelines of the respective repository.

10.5 ECOG-ACRIN Sample Tracking System

It is **required** (barring special circumstances) that all specimens submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). As of June 2007, the software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the specimens required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst.

Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html. Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest must be generated and shipped with all sample submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu.

Study Specific Notes

Generic Specimen Submission Form (#2981v3) will be required only if STS is unavailable at time of specimen submission. Notify the laboratory of the shipment by faxing a copy of the completed form to the laboratory.

Retroactively enter all specimen collection and shipping information when STS is available.

10.6 Sample Inventory Submission Guidelines

Inventories of all specimens submitted will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of specimens forwarded and utilized will be submitted by the investigating laboratories to the ECOG-ACRIN Operations Office - Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office - Boston.

11. Laboratory Research Studies

11.1 Correlative Studies: Critical Need for Integral Biomarkers that Identify the Population at Risk

Clinical and pathologic features of radical prostatectomy (RP) specimens, such as CAPRA-S score, are valuable tools to assess the risk of PC recurrence.[13-16] However, they have been inadequate prognosticators to identify which patients are at highest risk of recurrence, and which may benefit from additional local and/or systemic therapies in order to decrease the risk of metastasis and death from PC, particularly given the adverse impact of these therapies on health and QOL. In high-risk PC, the limitations of clinical and pathologic risk factors stem from frequent and extensive heterogeneity involving multiple distinct subclones that gain significant molecular alterations facilitating early occult dissemination and clinical relapse after definitive local therapies. Therefore, to increase the accuracy of risk stratification for metastasis based on molecular alterations, patients will be selected for high-risk by a Decipher genomic classifier test (score $>$ 0.6), which has been shown to be the best prognostic biomarker for metastasis.[13-16] This enhanced assessment of risk justifies evaluating the efficacy of systemic adjuvant therapy with ADT + darolutamide vs ADT alone.

Decipher testing provides an improved method of risk categorization. It is a tissue-based genomic classifier (GC) obtained from the more representative areas of the primary PC specimen. It is based on a 22-biomarker panel of coding[13-16] and noncoding RNA's that provides an independent, individualized continuous estimate of the risk of metastasis for patients treated with RP or local RT. In studies in which comparisons have been made, it has been shown to have higher sensitivity and specificity as a prognostic marker than the average population-based PC risk factors currently used, and to be an independent prognostic variable for the development of metastasis at 5 and 10 years.

The developer and provider of the Decipher score index is GenomeDx in Vancouver, BC. It has a Clinical Laboratory Improvement Act (CLIA) certified laboratory where, following pathologist review, the most representative tumor area is macro-dissected and processed for RNA extraction, purification, amplification and hybridization to a high-density array expression platform. The Affymetrix Human Exon (HuEx) 1.0 ST GeneChips profiles approximately 1.4 million exons including 22,000 coding genes and hundreds of thousands of non-coding regions of the transcriptome. The GC-risk score (a more precise term for Decipher score) is a continuous variable between 0 (minimum genomic risk for metastases) and 1 (maximum genomic risk for metastases). Cutpoints of the continuous variable identify three distinct risk categories for the development of metastases: low < 0.4, intermediate 0.4-0.6 and high >0.6.[54,55]

The discovery, initial validation and independent validation of Decipher score was performed on 765 unique specimens collected from the Mayo Clinic tumor registry between 1987-2006 (median follow-up,18.2 years) of which 545 passed quality control. The endpoint was clinical metastasis defined as local or distant metastases confirmed by bone or CT scan. The discovery cohort was split by random draw into training (n=359) and test (n=186) sets, balancing for the distribution of CP prognostic variables. Selection of features that prognosticated clinical metastasis was achieved by univariate and relevancy testing followed by regularized logistic regression in a bootstrapping routine. The final feature set of

22 was assembled in a random forest classifier and 'locked'; this is referred to as the genomic classifier (GC). The GC-risk score is a continuous variable between 0 (minimum genomic risk for metastases) and 1 (maximum genomic risk for metastases). Cutpoints of the continuous variable representing distinct risk categories were identified. This GC/Decipher score outperformed CP variables and previously reported gene signatures with an AUC of 0.75 (95% CI 0.67-0.83) and was the predominant predictor of metastasis by multivariable analysis ($p< 0.001$).[56]

Multivariable analysis found the Decipher score to be the sole significant predictor of metastasis.[54] Decipher has been validated as a prognostic biomarker of metastasis for localized PC treated with radical prostatectomy alone or with adjuvant radiation therapy.[5,57] Signatures of response to therapy have also been defined utilizing data collected on the Decipher platform, including the PAM50 signature describing luminal and basal subtypes with differential responses to treatment with hormonal therapy.[58]

11.2 Rationale for Integral Molecular Biomarkers Analysis **Decipher®** Transcriptome Platform and Future DNA Analysis Banked PC Cores for Future Analyses

The availability of a prospectively embedded and comprehensive RNA expression platform required for each patient with a Decipher score > 0.6 accrued to this study offers a unique setting for discovery and validation of signatures predictive of response to hormonal agents and outcome. The aims are: 1. to discover an expression signature predictive of response to ADT with darolutamide versus ADT alone; 2. to search for new biomarker signatures for therapeutic interventions to avoid progression of a population that is at highest risk of recurrent disease; 3. to prospectively assess/validate the predictive role for response to ADT of molecular subtypes identified by established signatures (AR, luminal and basal subtypes, and others). We plan to correlate each signature with the primary and secondary clinical endpoints of this study among others. The expression signatures and clinical correlates analysis will be a collaborative effort between the EA8183 Correlative Sciences Chair, Bioinformatics/Statistician team, Urology Co-chair and the Decipher Biosciences/Chief Scientific Officer. We anticipate these studies will lead to identify new signatures predictive of treatment response and help design more personalized and effective treatments options to eradicate disease progression of high-risk patients in future studies.

Decipher score is a continuous molecular variable representing distinct risk categories in the context of clinical variables. The risk of metastasis increases as the Decipher score rises especially beyond 0.6. The risk of metastasis is also affected by clinical variables at presentation (PSA, Gleason, T stage), the final pathology of the radical prostatectomy specimen (components of the CAPRA score) and the spectrum of PSA levels below < 0.2 post radical prostatectomy. Consequently, we propose to assess whether the response to ADT and darolutamide is affected by the different Decipher score levels (>0.6-1.0) and the clinical and pathology variables reported for each patient.

We plan to collect and store paired PC specimens from patients with Decipher score > 0.6 and in the future, to perform genome wide coding and non-coding DNA sequencing analysis. These studies are aimed identify the prevalence of genetic alterations that drive metastatic progression and whether response to ADT +/- darolutamide is affected by distinct genomic subgroups. In addition we

expect to identify specific gene/pathways alterations that can be blocked with more specifically targeted agents. We anticipate this genomic analysis will provide unprecedented information to maximize the potential to identify treatments that will achieve cure of different subgroups of high risk PC.

11.3 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research studies will be submitted electronically using a secured data transfer to the ECOG-ACRIN Operations Office - Boston by the investigating laboratory on a quarterly basis or per joint agreement between ECOG-ACRIN and the Investigator.

12. Electronic Data Capture

Please refer to the ***EA8183*** Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave

Required submission of patient demographic data for this study will be submitted automatically via OPEN.

NOTE: Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

13. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

14. References

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A Phase III Double Blinded Study of Early Intervention after RADICAl ProstaTEctomy with Androgen Deprivation Therapy with Darolutamide vs. Placebo in Men at Highest Risk of Prostate Cancer Metastasis by Genomic Stratification (ERADICATE)

Appendix I

Pathology Submission Guidelines

The following items are included in Appendix I:

1. Guidelines for Submission of Pathology Materials (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. ECOG-ACRIN Generic Specimen Submission Form (#2981v3)

Guidelines for Submission of Pathology Materials

A. Preregistration (Step 0): Mandatory if Decipher Score not previously performed

Contact Decipher Biosciences (RUO@decipherbio.com) and request Decipher Prostate Specimen Collection Kit.

One Decipher Prostate Specimen Collection Kit and Test Requisition Form should be completed per patient. Kits should be ordered prior to preregistration. Kits will be shipped FedEx ground and arrive within three to four (3-4) days, please note if an expedited shipment is needed.

1. Submit to Decipher Biosciences:

   NOTE: Tumor tissue from radical prostatectomy should be submitted after preregistration.

   - Block Submission

     Select one (1) formalin fixed paraffin embedded (FFPE) tissue block with the highest Grade Group (Gleason score) and at least 0.5 cm^2 of tumor tissue by area. Please ensure block ID # is clearly referenced in the block label.

   - Slide Submission

     Submit one (1) H&E slide and five (5) 5 µm thick serially sectioned unstained slides or six (6) 5 µm thick serially sectioned unstained slides. Label the serial sectioned slides (1-6) in the order in which they were cut for scraping. Store unstained slides at 4 degrees C until shipping.

     - Sample Tracking System (STS) Shipping Manifest Form
     - Completed Original Test Requisition Form
     - Institutional Pathology Report (redacted with Specimen ID, Decipher Study Number P9010, ECOG-ACRIN Study Number EA8183, and ECOG-ACRIN Case ID Number)

     NOTE: After testing all tissue residuals will be forwarded by Decipher Biosciences to the ECOG-ACRIN Tissue Repository.

     If you have any questions concerning the above instructions or if you anticipate any problems in submitting the required pathology materials, contact Decipher Biosciences at: (888) 520-8718 or RUO@decipherbio.com.

2. Decipher Score determined prior to or after preregistration:

   Prior to randomization institution must enter assay results and upload Decipher report via Medidata Rave. If assay results are from prior to registration please redact Decipher report and ensure ECOG-ACRIN protocol number (EA8183) and ECOG-ACRIN five-digit patient sequence number are on the report.

B. Randomization (Step 2)

Pathology materials are to be submitted to the ECOG-ACRIN Central Biorepository and Pathology Facility after randomization from patients consenting to future undefined research.

1. The following materials are to be submitted following randomization:

   Formalin-fixed paraffin-embedded (FFPE) tumor tissue blocks from surgical biopsy

   NOTE: If blocks are unavailable for submission, cores and slides are to be submitted. All cores and slides must be adequately labeled, with slides numbered sequentially in the order cut. Alternative submission requirements:

   - One (1) H&E slide

- Twenty (20) 5 µm unstained, uncharged air-dried plus slides from the thickest part of the tumor
- One (1) or more core punches (minimum of 4mm diameter). If core punch tool is unavailable, request core punch kit from the ECOG-ACRIN CBPF (844) 744-2420

If these criteria cannot be met, please contact the ECOG-ACRIN CBPF (eacbpf@mdanderson.org) to obtain alternative submission requirements.

2. Forms and Reports:

NOTE: Adequate patient identifying information must be included with every submission. It is strongly recommended that full patient names be provided. The information will be used only to identify patient materials, and will help to expedite any required communications with the institution (including pathologists).

The following items are to be included with the pathology materials:

- Institutional Pathology Report
- ECOG-ACRIN Generic Specimen Submission Form (#2981v3) [if STS is unavailable]
- Sample Tracking System (STS) Shipping Manifest Form
- Immunological Study Reports, if available

3. Mail Pathology Materials to:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3598
1515 Holcombe Boulevard
Houston, TX 77030
Phone: Toll Free (844) 744-2420 (713-745-4440 Local or International Sites)
Fax: (713) 563-6506
Email: eacbpf@mdanderson.org

If you have any questions concerning the above instructions or if you anticipate any problems in submitting the required pathology materials contact the ECOG-ACRIN Central Biorepository and Pathology Facility by telephone: (844) 744-2420 or email: eacbpf@mdanderson.org

ECOG-ACRIN
cancer research group
Reshaping the future of patient care

MEMORANDUM

TO: _____
(Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
ECOG-ACRIN Laboratory Science and Pathology Committee

DATE: _____

SUBJECT: Submission of Pathology Materials for EA8183: *A Phase III Double Blinded Study of Early Intervention after RADICAl Prostatectomy with Androgen Deprivation Therapy with Darolutamide vs. Placebo in Men at Highest Risk of Metastasis by Genomic Stratification (ERADICATE)*

The patient named on the attached request has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for determination of Decipher Score and/or banking.

For submission of tumor tissue to Decipher Biosciences for Decipher Score assessment, complete the Test Requisition Form provided in the Decipher Prostate Specimen Collection Kit. All tissue residuals will be forwarded to the ECOG-ACRIN Tissue Repository after testing.

Keep a copy of the submission for your records and return any relevant completed forms, the surgical pathology report(s), the slides and/or blocks and any other required material to the Clinical Research Associate (CRA). The CRA will forward all required pathology material to the appropriate laboratory.

Pathology materials submitted for this study will be retained at the ECOG-ACRIN Tissue Repository for future undefined research studies per patient consent. Paraffin blocks will be returned upon request for purposes of patient management.

If you have any questions regarding this request, please contact the Decipher Biosciences Customer Support (888-792-1601 or cs@decipherbio.com) or the ECOG-ACRIN Central Biorepository and Pathology Facility at (844)-744-2420 (713-745-4440 Local or International Sites) or email: eacbpf@mdanderson.org

The ECOG-ACRIN CRA at your institution is:

Name:_____

Address: _____

Phone: _____

Thank you.

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time- point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.					
Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**	**Peripheral Blasts %**	**Lymphocytes %**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**	**Stop Time 24HR**	
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**		

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments

9/12/14

A Phase III Double Blinded Study of Early Intervention after RADICAl ProstaTEctomy with Androgen Deprivation Therapy with Darolutamide vs. Placebo in Men at Highest Risk of Prostate Cancer Metastasis by Genomic Stratification (ERADICATE)

Appendix II

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we hope to improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and ECOG-ACRIN, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

A Phase III Double Blinded Study of Early Intervention after RADICAl ProstaTEctomy with Androgen Deprivation Therapy with Darolutamide vs. Placebo in Men at Highest Risk of Prostate Cancer Metastasis by Genomic Stratification (ERADICATE)

Appendix III

Patient Medication Calendar

Tablet Calendar Directions

1. Take your scheduled dose of each tablet:

   Take your medication with food. Tablets should be swallowed whole. If you vomit shortly after taking your medication, please contact your study doctor via the staff contact at the number below.

Rev. Add2

2. If you forget, the missed tablets will not be taken later.
3. Please bring the empty bottle or any leftover tablets and your pill calendar to your next clinic visit.

Staff Contact Name and Phone Number: _____

Patient Medication Calendar

This is a calendar on which you are to record the time and number of tablets you take each day. You should take your scheduled dose of each tablet. **Note the times and the number of** tablets **that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused tablets and your completed medication calendar to your doctor's visits.

You should take ____ tablets each day in the AM, and ____ tablets each day in the PM.

Patient ID#:				**Patient Initials:**				
DAY	**Date** **Month**	**Day**	**Year**	**Time tablets taken** **AM**	**PM**	**Number of tablets taken** **AM**	**PM**	**Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)**
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15								
16								
17								
18								
19								
20								
21								
22								
23								
24								

Patient ID#:				**Patient Initials:**				
DAY	**Date Month Day Year**			**Time tablets taken AM**	**PM**	**Number of tablets taken AM**	**PM**	**Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)**
25								
26								
27								
28								

Number of Tablets Provided to Patient: _____

Date Medication and Calendar Provided to Patient:_____

Site Coordinator Signature:_____

Date Medication and Calendar Received by Patient_____

Patient Signature:_____

Date Calendar Returned by Patient:_____

Number of tablets returned:_____

Site Coordinator Signature:_____

A Phase III Double Blinded Study of Early Intervention after RADICAl ProstaTEctomy with Androgen Deprivation Therapy with Darolutamide vs. Placebo in Men at Highest Risk of Prostate Cancer Metastasis by Genomic Stratification (ERADICATE)

Appendix IV

ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

A Phase III Double Blinded Study of Early Intervention after RADICAl ProstaTEctomy with Androgen Deprivation Therapy with Darolutamide vs. Placebo in Men at Highest Risk of Prostate Cancer Metastasis by Genomic Stratification (ERADICATE)

Appendix V

CAPRA-S Scoring

Variable	Level	Points	Variable	Level	Points
PSA (pre-operative prostate-specific antigen)	0-6	0	**Gleason**	2-6	0
	6.01-10	1		3+4	1
	10.1-20	2		4+3	2
	> 20	3		8-10	3
SM (surgical margins)	Negative	0	**ECE (extracapsular extension)**	No	0
	Positive	2		Yes	1
SVI (seminal vesicle invasion)	No	0			
	Yes	2			

Rev. Add2

The CAPRA-S score is calculated by adding a point for each of the criteria listed in the table above. Components include the pre-prostatectomy PSA, surgical margin status (on pathology report), seminal vesicle invasion status (on pathology report), Gleason score (on pathology report), and extracapsular extension status (on pathology report). Patients who have not had Decipher testing and are getting testing through the protocol must have a CAPRA-S score > 3 to undergo testing. Patients who have had Decipher testing prior to screening and enrollment do not need CAPRA-S scores for eligibility.

A Phase III Double Blinded Study of Early Intervention after RADICAl ProstaTEctomy with Androgen Deprivation Therapy with Darolutamide vs. Placebo in Men at Highest Risk of Prostate Cancer Metastasis by Genomic Stratification (ERADICATE)

Appendix VI

EA8183 Collection and Shipping Kit Order Instructions

Specimen Collection/Shipping Kits are being provided by CENETRON CENTRAL LABORATORIES and are to be ordered ONLINE.

Starter kits are not available. Kit requests are to be made AFTER patient randomization.

Questions regarding kits can be directed to projectmanagement@cenetron.com or call the Cenetron Clinical Trials Group at (512) 439-2000.

Ordering Process:

- Following randomization of the patient to the trial, go to the website www.cenetron.com and click on the 'Order Kits' button at the top right. It is recommended that kits be ordered same day as patient randomization.
- The order form is not study specific and can be used for any study. Complete the online form as follows:
  - Sponsor (REQUIRED): ECOG-ACRIN
  - Contact Name (REQUIRED): Name of the institution kit contact.
  - Protocol Number (REQUIRED): EA8183
  - Phone Number (REQUIRED): Phone number of the kit contact. Please ensure that this is a number that can be reached from an external caller
  - Site Number (REQUIRED): Institution NCI Site ID
  - FAX Number: Fax number of the kit contact
  - Investigator: Last name of the kit contact is adequate
  - Email (REQUIRED): Email of the institution kit contact. Must be entered twice to confirm
  - Date Supplies Needed (REQUIRED): Add three (3) business days or more to order date. (Reminder that weekends and holidays must also be considered in this timeline)
  - KIT NAME (REQUIRED): EA8183 Collection Kit
  - Quantity: 1
  - Comments: Provide EA8183 Patient Case ID# and full shipping address
- 'Patient Case ID =' #####
- *'Ship Kit to'* name of the individual to whom the kit is being shipped. (May be different than the kit contact provided above)
- Full street address, town, state and zip code
  - Answer the security question

Please complete this form correctly, including the valid ECOG-ACRIN patient sequence number and complete shipping address. If information is missing the kit processing will be delayed.

A Phase III Double Blinded Study of Early Intervention after RADICAl ProstaTEctomy with Androgen Deprivation Therapy with Darolutamide vs. Placebo in Men at Highest Risk of Prostate Cancer Metastasis by Genomic Stratification (ERADICATE)

Appendix VII

Patient Clinical Trial Wallet Card

NIH NATIONAL CANCER INSTITUTE

CLINCIAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: EA8183

Study Drug(s): Darolutamide or matching placebo

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov