**RTOG FOUNDATION**

# RTOG 3506

***(ClinicalTrials.gov NCT #:* 03809000*)***

**STEEL: A Randomized Phase II Trial of Salvage Radiotherapy with Standard vs Enhanced Androgen Deprivation Therapy (with Enzalutamide) in Patients with Post Prostatectomy PSA Recurrences with Aggressive Disease Features**

**Amendment 7: July 12, 2022**

**RTOG Foundation Collaboration with Pfizer/Astellas**

**RTOG Foundation Trial 3506**
***(Hereafter RTOG 3506)***

**A Limited Participation Study**

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Protocol Version Date: July 12, 2022

Sponsor: RTOG Foundation

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Protocol Acceptance
On behalf of the RTOG Foundation, Inc.

Quynh Le, RTOG Foundation Chair — July 12, 2022 Date

**RTOG Foundation Trial 3506**
***(Hereafter RTOG 3506)***
***(ClinicalTrials.gov NCT # 03809000)(22-AUG-2019)***

**A Limited Participation Study**

**STEEL: A Randomized Phase II Trial of Salvage Radiotherapy with Standard vs Enhanced Androgen Deprivation Therapy (with Enzalutamide) in Patients with Post-Prostatectomy PSA Recurrences with Aggressive Disease Features**

**(03-FEB-2022)**


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**Protocol Agent**

| Agent | Supply | IND # | IND Sponsor |
|---|---|---|---|
| Enzalutamide | Pfizer/Astellas | Exempt | N/A |
| Bicalutamide | Commercial | Exempt | N/A |
| GnRH analog | Commercial | Exempt | N/A |

**Document History**

| | Version Date |
|---|---|
| **Amendment 7** | **July 12, 2022** |
| Amendment 6 | February 03, 2022 |
| Amendment 5 | June 17, 2021 |
| Amendment 4 | May 20, 2021 |
| Amendment 3 | March 16, 2021 |
| Amendment 2 | December 02, 2019 |
| Amendment 1 | August 22, 2019 |
| Initial | November 7, 2018 |

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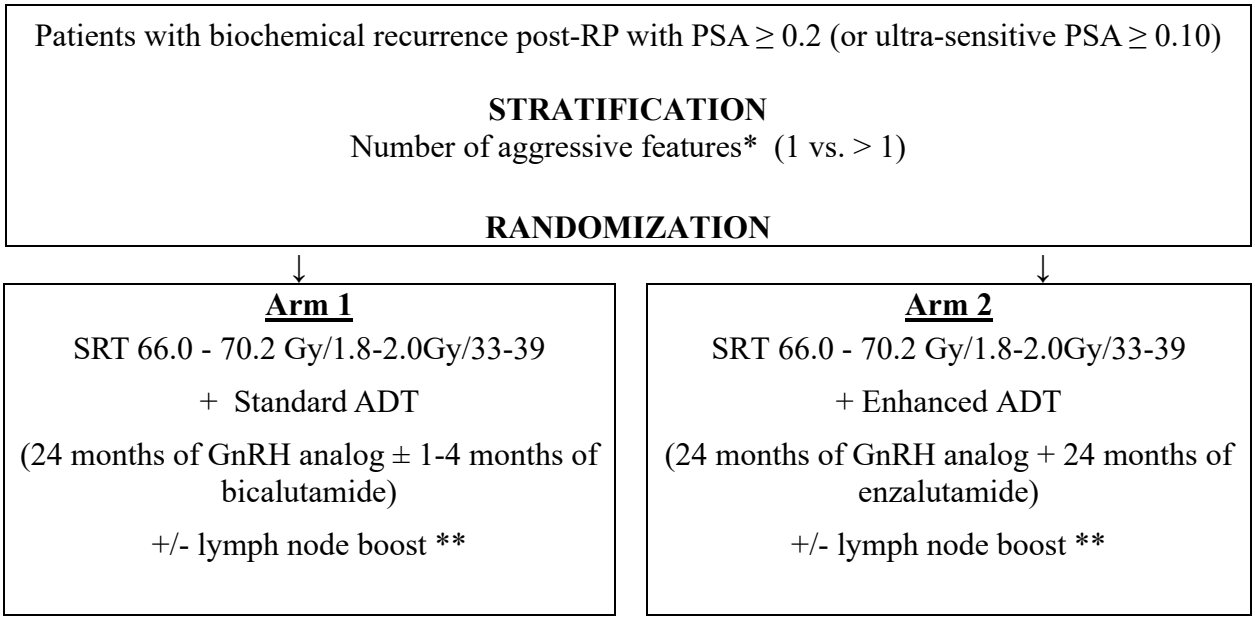
**STEEL: A Randomized Phase II Trial of Salvage Radiotherapy with Standard vs Enhanced Androgen Deprivation Therapy (with Enzalutamide) in Patients with Post-Prostatectomy PSA Recurrences with Aggressive Disease Features**

**SCHEMA (16-MAR-2021)**




Sample size: 242

* In addition to PSA ≥ 0.2 ng/mL (or ultra-sensitive PSA ≥ 0.10), the following aggressive features are included in the stratification (Please see 3.1.5 for details):

- Gleason score of 8-10 (note any Gleason score is eligible)
- Seminal vesicle invasion (SVI) (note any pT stage is eligible [AJCC v8.0] but pT stage ≥ pT3b is considered aggressive)
- Locoregional node involvement at radical prostatectomy (pN1)
- Persistently elevated PSA post-RP (PEPP) defined as PSA ≥ 0.1 ng/mL after radical prostatectomy
- PSA ≥0.7 ng/mL

** At the discretion of the radiation oncologist, suspicious lymph nodes for locoregional (obturator, prescral, perirectal, pelvic,inguinal or low paraaortic lymph nodes below T12/L1) disease in the radiology report (CT, MRI, molecular imaging [i.e. choline PET, FACBC, PSMA]) and/or biopsy proven lymph nodes may be sequentially or concurrently boosted.

# 1. OBJECTIVES

## 1.1 Primary Objective

The primary goal of this study is to determine whether, in men with post-prostatectomy PSA (prostate specific antigen) recurrences with aggressive disease features, salvage radiotherapy (SRT) with enhanced androgen deprivation therapy (ADT), consisting of enzalutamide (MDV3100) and a GnRH analog, will improve progression-free survival compared to SRT with standard GnRH analog -based ADT.

## 1.2 Secondary Objectives

**1.2.1** To compare the rates of biochemical failure, an alternative biochemical failure endpoint, hormone-refractory disease (HRD), distant metastasis, cause-specific mortality, and overall mortality between patients who receive SRT with standard GnRH analog-based ADT and those who receive SRT with enhanced ADT.

**1.2.2** To compare acute and late physician- and patient-reported toxicity between patients who receive SRT with standard GnRH analog-based ADT and those who receive SRT with enhanced ADT.

**1.2.3** To compare fatigue using the PROMIS-F SF 7a between patients who receive SRT with standard GnRH analog-based ADT and those who receive SRT with enhanced ADT.

**1.2.4** To assess global quality of life using the EQ-5D-5L between patients who receive SRT with standard GnRH analog-based ADT and those who receive SRT with enhanced ADT.

## 1.3 Exploratory Objectives (16-MAR-2021)

**1.3.1** To assess the prognostic and predictive value of the genomic classifier Decipher.

**1.3.2** To assess whether molecular classification by the PAM50 gene expression clustering will identify subsets of prostate cancer (Luminal A or Basal, Luminal B) which derive the greatest benefit from enhanced ADT.

# 2. BACKGROUND

## 2.1 The Importance of Salvage Radiation Therapy (SRT) for Post-Prostatectomy PSA Recurrences

Radical prostatectomy (RP) is a standard treatment option for patients with localized prostate cancer. However, greater than 30% of patients treated with RP will experience biochemical recurrence (BR), as represented by a rising prostate specific antigen (PSA) [Han 2001, Roehl 2004]. A common option for initial management of patients with BR post-RP is salvage radiation therapy (SRT). While no randomized data exist comparing SRT to observation alone, many retrospective analyses have shown that SRT can provide long-term durable responses [Goenka 2012, Katz 2003, Stephenson 2007], and two large retrospective studies have suggested an improvement in prostate cancer-specific mortality as compared to observation for

patients treated with SRT following BR [Cotter 2011, Trock 2008]. Trock et al found that SRT was associated with a 3-fold decrease in risk of prostate cancer-specific mortality compared to observation, and that this was primarily true in patients with aggressive disease features [Trock 2008]. Cotter et al similarly found that SRT improved all-cause mortality in both low- and high-risk patients, but that when controlling for patient comorbidities, this improvement was greatest in patients with high-risk features, with a 15% reduction in actuarial all-cause mortality [Cotter 2011]. Thus, SRT is a well-accepted standard practice for patients with post-prostatectomy PSA recurrences, including those with aggressive disease features.

### 2.2 The Need to Improve Outcomes for Patients With PSA Recurrences With Aggressive Features

While SRT has been shown to provide durable responses and a survival benefit for many patients experiencing BR post-RP, up to 50% of patients treated with SRT, on average, will experience disease progression [Goenka 2012, Stephenson 2007]. Previous studies have demonstrated that an even larger proportion of patients with aggressive pathologic and clinical features, such as a persistently elevated PSA post-RP (PEPP), a pre-RT PSA >1 ng/mL, Gleason score 8-10, and seminal vesicle invasion, will have BR following SRT [Katz 2003, Stephenson 2007, Stephenson 2004, Song 2002]. Analysis of a large patient database maintained at the University of Michigan shows that, when defining BR as the post-SRT PSA nadir + 2 ng/mL, the 5-year post-SRT event-free survival is 30% for those with aggressive pathologic and clinical features treated solely with SRT, thus highlighting the critical need for better treatments for these patients.

### 2.3 The Rationale for Adding Androgen Deprivation Therapy (ADT) to SRT

Augmenting SRT with ADT represents one approach to improving long-term outcomes for post-prostatectomy patients treated with SRT for BR with aggressive disease features. The addition of ADT has resulted in significant improvements in rates of BR, metastasis-free survival, and overall survival in the context of definitive radiation therapy for localized prostate cancer [Bolla 2010, Horwitz 2008, Jones 2011, Lawton 2001]. More recently, it was demonstrated that the addition of ADT to SRT also confers a benefit [Shipley 2011]. Initial results from RTOG 9601, which randomized post-RP patients with BR to SRT + bicalutamide x 24 months or SRT alone, have shown that the addition of bicalutamide provided a benefit in reducing PSA progression and decreased the incidence of metastatic disease [Shipley 2011]. Overall, patients treated with SRT + bicalutamide were 17% less likely to experience PSA progression and 6% less likely to develop metastases. The decrease in risk for PSA progression was largest in patients with GS 8-10, who were 30% less likely to have PSA progression if receiving bicalutamide [Shipley 2011]. The final results of RTOG 9601 are notable for significant improvements in all clinical endpoints, including overall survival, distant metastases-free survival, and freedom from biochemical progression with the addition of bicalutamide [Shipley 2017].

RTOG 9601 assessed the addition of high-dose bicalutamide in a relatively unselected patient population with PSA recurrences following prostatectomy; in fact,

the primary selection in RTOG 9601 was to restrict eligibility to patients with a pre-radiation PSA of 0.2 to 4 ng/mL, thus preventing enrollment of patients with higher pre-radiation PSA levels. In contrast, this trial will actively select for patients with aggressive disease features (Gleason 8-10 disease, pre-radiation PSA >1, seminal vesicle invasion, or a persistently elevated PSA following prostatectomy), as these patients have very poor outcomes. Thus, we expect to potentially achieve even greater gains given the selection for these patients with aggressive disease features.

### 2.4 The Rationale for the Design of the Study Control Arm

To enhance the risk/benefit ratio in this trial, we will preselect for patients with the highest risk of disease recurrence following salvage radiation (due to aggressive pathologic or clinical features) based on currently available data and develop treatment strategies aimed at intensifying therapy while preserving the tolerability of therapy. The control arm will receive SRT + 24 months ADT with a GnRH analog. Per physician preference, patients on the control arm will be allowed to receive up to 1-4 months of bicalutamide as lead-in therapy with the GnRH analog, for prevention of a testosterone flare.

The use of GnRH analog therapy was chosen for this study in place of the high-dose bicalutamide regimen (150 mg) utilized in the RTOG 9601 trial for several reasons. Despite the studies conducted with high-dose bicalutamide, this regimen has not been widely adopted as a replacement for GnRH analogs with or without a non-steroidal anti-androgen. In the metastatic population, bicalutamide monotherapy was found to be less effective than castration, with a hazard ratio of 1.30 for time to death from onset of therapy favoring castration [Tyrrell 1998]. The complementary portion of this study that focused on high-risk, non-metastatic patients was not able to complete enrollment due to the demonstration of the inferior outcomes associated with bicalutamide monotherapy [Boccardo 2002]. A recent poll of 40 members of the RTOG GU Steering Committee confirmed that the predominant ADT regimen used, in the context of salvage radiotherapy, by this group was a GnRH analog, either alone or with up to 1 month of lead-in bicalutamide. Even with the RTOG 9601 data, high-dose bicalutamide monotherapy has not been broadly adopted even in this setting. Thus, to maximize the clinical relevance and scientific merit of this study, a control arm of GnRH analog therapy (with up to 1-4 month of bicalutamide) will be used. The duration of 24 months of GnRH analog therapy was selected based on RTOG 9601, as this is the duration of therapy used in this study.

### 2.5 The Rationale for Selecting Enzalutamide-Based Therapy in the Study Experimental Arm (22-AUG-2019)

The use of next-generation anti-androgens provides a promising strategy for further intensifying ADT for SRT patients with aggressive disease characteristics. In particular, enzalutamide (MDV3100) is a next generation anti-androgen that has a 5-fold higher binding affinity for the androgen receptor (AR) compared to the first-generation anti-androgen bicalutamide [Tran 2009]. As opposed to bicalutamide, enzalutamide prevents binding of AR to DNA and to co-activator proteins [Tran 2009]. In addition, while bicalutamide has been shown to have analog activity in the setting of AR overexpression, enzalutamide acts as a pure analog [Tran 2009].

In the AFFIRM study, enzalutamide was shown to improve overall survival for patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel-based chemotherapy [Scher 2012, Howard 2012]. In this setting, PSA declines with enzalutamide have been impressive, with more than half of patients experiencing greater than a 50% reduction in serum PSA level and 25% having a greater than 90% decline from initial PSA [Scher 2012]. The PREVAIL study showed that even prior to docetaxel, enzalutamide was effective in delaying the need for chemotherapy (HR 0.35), preventing skeletal-related events (HR 0.72), and preventing disease progression by PSA (HR 0.17) [Beer 2014]. The final analysis of PREVAIL showed improvement in radiographic progression (HR 0.32) and an improvement in overall survival (HR 0.77) compared to placebo [Beer 2017]. In an earlier population of men with CRPC without metastases, the PROSPER study demonstrated that enzalutamide reduced the risk of metastatic progression (HR 0.29) [Hussain 2018]. When comparing bicalutamide and enzalutamide in CRPC, the randomized, double-blind, phase 2, STRIVE trial, showed an improvement in PFS for enzalutamide over bicalutamide (HR 0.24) [Person 2016].

Most relevant to this study was the activity of enzalutamide demonstrated in the castration sensitive (CSPC) space. The ARCHES study showed a reduction in the rate radiographic progression (HR 0.39) [Armstrong 2019] compared to placebo. ENZAMET showed that in metastatic CSPC, enzalutamide showed superior activity to bicalutamide with a 33% improvement in overall survival as well as improvements in PSA progression free survival (HR 0.39) and clinical progression free survival (HR 0.40). [Davis 2019]

At the time of trial activation, there are two FDA-approved next-generation androgen receptor-targeting therapies: abiraterone and enzalutamide. Abiraterone is a CYP17 inhibitor that inhibits androgen biosynthesis. Like enzalutamide, this agent has shown efficacy in both the pre- and post-chemotherapy populations [Ryan 2013, Fizazi 2012]. However, abiraterone alters steroidogenesis and requires administration with corticosteroids to avoid potential toxicities resulting from this alteration. Enzalutamide was chosen for this study for ease of administration that may impact patient compliance in this setting. Therefore, the goal of this study is to determine if the addition of enzalutamide to standard androgen deprivation therapy can further improve SRT outcomes for patients with aggressive pathologic or clinical features.

**2.6 The Rationale for the Primary Endpoint of This Study (12-JUL-2022)**

The primary endpoint of this study is progression-free survival, defined as a detectable serum PSA concentration or initiation of salvage hormones, absence of (as noted by the initiation of salvage hormone therapy) clinical failure, and absence of death from any cause. It is expected that the vast majority of events contributing to the primary endpoint will result from biochemical recurrence. The definition of a detectable serum PSA will be any concentration greater than 0.05 ng/mL. Given that all patients have undergone radical prostatectomy, it is anticipated that successful salvage therapy will result in an undetectable PSA. Given the range of RTOG

performance sties and changes in PSA detection thresholds since RTOG 9601, a threshold of 0.05 ng/mL was recognized as deployable across participating sites.

### 2.7 The Potential Impact and Significance of This Study

Radical prostatectomy (RP) is the most common treatment for prostate cancer, according to the National Cancer Institute's (NCI) Patterns of Care study from 14 regional cancer registries. Greater than 30% of patients treated with RP will experience BR, as represented by a rising serum PSA concentration [Han 2001, Roehl 2004]. The failure rate is significantly higher for patients with aggressive clinical or pathologic features. Patients with Gleason scores 8-10 or SVI more than 70% will experience BR by 10 years post-RP [Han 2001]. While SRT has been shown to improve prostate cancer-specific mortality, many patients do not experience a long-term durable response to treatment. The addition of ADT to RT has recently been shown to improve patient outcomes, with greater benefit observed in patients with aggressive features. However, the ideal ADT agents in this setting have yet to be established, and improved treatment options are needed.

By investigating the addition of enzalutamide to ADT with SRT, this trial may identify a more effective approach for treating patients with high-risk post-RP BR. Additionally, this study has the potential to provide the foundation for a future paradigm change for how next-generation anti-androgens are currently given, moving them from the context of metastatic disease to earlier in disease progression. This trial also tests the hypothesis that a transcriptomic signature can be used to identify patients who will respond to SRT + standard (or enhanced). The same studies may also identify dominant biological pathways associated with resistance to these AR targeted approaches. Finally, given that patient-reported outcomes (PRO) have not been well studied in the post-prostatectomy setting, this study will provide critical information on PROs in the context of enzalutamide versus control therapy, which may help future patients considering whether to pursue these therapies after prostatectomy.

## 3. PATIENT SELECTION, INCLUSION, AND EXCLUSION CRITERIA

**Note: Exceptions to inclusion and exclusion criteria are not permitted.** For questions concerning eligibility, please contact the Biostatistics/Data Management Center (via the contact list on the protocol cover page). For radiation therapy-related eligibility questions, please contact RTQA (via the contact list on the protocol cover page).

### 3.1 Inclusion Criteria (16-MAR-2021)

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

**3.1.1** Pathologically (histologically) proven adenocarcinoma confirmed by prostatectomy performed within 10 years prior to registration and any type of radical prostatectomy is permitted, including retropubic, perineal, laparoscopic or robotically assisted.

**3.1.2** Serum PSA concentration of ≥0.20 ng/mL within 120 days prior to registration. Patients must have a PSA ≥ 0.2 ng/mL **prior to starting ADT**. For patients being followed by an ultrasensitive PSA assay, a serum PSA concentration of ≥ 0.10 ng/mL will be considered eligible.

**3.1.3** GnRH analog may be started no more than 42 days prior study entry.

**3.1.4** Hemoglobin ≥9.0 g/dL, independent of transfusion and/or growth factors within 90 days prior to registration;

**3.1.5** Platelet count ≥75,000 x $10^9$/μL independent of transfusion and/or growth factors within 90 days prior to registration;

**3.1.6** At least 1 of the following aggressive features:

- Gleason score of 8-10 (note any Gleason score is eligible)
- Seminal vesicle invasion (SVI) (note any pT stage [AJCC v8.0] is eligible but a pT stage ≥ pT3b is considered aggressive)
- Locoregional node involvement at radical prostatectomy (pN1)
- Persistently elevated PSA post-RP nadir (PEPP) defined as PSA > 0.1 ng/mL after radical prostatectomy
- PSA ≥0.7 ng/mL

**3.1.7** Serum albumin ≥3.0 g/dL within 90 days prior to registration

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

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

**3.1.9** Serum total bilirubin ≤1.5 × ULN (Note: In subjects with Gilbert's syndrome, if total bilirubin is >1.5 × ULN, measure direct and indirect bilirubin and if direct bilirubin is ≤1.5 × ULN, subject is eligible) within 90 days prior to registration;

**3.1.10** Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) <2.5 × ULN within 90 days prior to registration;

**3.1.11** Age ≥ 18;

**3.1.12** History and physical with ECOG Performance Status 0-1 or within 90 days prior to registration;

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

**3.2 Exclusion Criteria (02-DEC-2019)**

***Patients with one or more of the following conditions are NOT eligible for this study.***

**3.2.1** Definitive clinical or radiologic evidence of metastatic disease with the exception of locoregional lymph nodes;

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

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

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

**3.2.5** History of any of the following:

- History of documented inflammatory bowel disease
- Transmural myocardial infarction within the last 4 months prior to registration.
- New York Heart Association Functional Classification III/IV within 4 months prior to registration.
- Unstable angina requiring hospitalization within the last 4 months prior to registration
- History of loss of consciousness or transient ischemic attack within 12 months prior to randomization.
- History of seizure disorder or condition that may predispose to seizure (e.g. prior cortical stroke or significant brain trauma)
- History of uncontrolled hypertension defined as a sustained systolic blood pressure in excess of 150 mmHg or a sustained diastolic blood pressure in excess of 90 mmHg despite optimized antihypertensive therapy.
- History of repeated falls and fractures over the past 12 months that in the opinion of the treating investigator would put the patient at risk for poor bone outcomes from androgen receptor targeted therapy.

**3.2.6** Current evidence of any of the following:

- Known gastrointestinal disorder affecting absorption of oral medications
- Active uncontrolled infection defined as an identified infectious condition that requires active therapy that has not yet been completed

**3.2.7** HIV positive patients with CD4 count < 200 cells/microliter within 30 days prior to registration OR HIV patients under treatment with highly active antiretroviral therapy (HAART) within 30 days prior to registration regardless of CD4 count. Note also that HIV testing is not required for eligibility for this protocol as it is self-reported. This exclusion criterion is necessary because the treatments involved in this protocol may be immunosuppressive and/or interact with HAART.

## 4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP (20-MAY-2021)

### ASSESSMENTS: PRE-TREATMENT

| *Timepoint* | *Procedure/test* | *Notes* |
|---|---|---|

| | | |
|---|---|---|
| ≤ 10 years of registration | ☐ Prostatectomy<br>☐ Gleason score<br>☐ Decipher Prostate RP (to be sent directly to Decipher Biosciences) | Gleason score from prostatectomy<br>Decipher Prostate RP will be collected for those who consented to the collection. |
| ≤ 120 days of registration | ☐ PSA | |
| ≤ 90 days of registration | ☐ Medical history<br>☐ Physical Exam incl. height and weight<br>☐ Vital signs<br>☐ Smoking history<br>☐ ECOG Performance Status<br>☐ CBC<br>☐ Albumin<br>☐ AST or ALT<br>☐ Total bilirubin<br>☐ eGFR<br>☐ PROMIS-F SF 7a, EQ-5D-5L, PRO-CTCAE | History and Physical with review of prostate cancer diagnosis<br><br>CBC for hemoglobin and platelets.<br><br>QOL forms can be completed any time after consent is signed and must be completed prior to any treatment start unless hormone therapy started prior to registration and then they must be completed prior to the start of RT |

**ARM 1 and ARM 2 ASSESSMENTS: ON TREATMENT**

- For Arm 1, labs (CBC, albumin, hepatic and renal function) are as clinically indicated and per institutional standard
- For both Arms, ADT must begin no more than 42 days prior to registration and no later than 21 days after registration. ADT GnRh analog will be given for 24 months. For Arm 1, bicalutamide may be given for 1-4 months. For Arm 2, enzalutamide will be given for 24 months.

| ***Timepoint*** | ***Procedure/test/treatment*** | ***Notes*** |
|---|---|---|
| At end of RT | ☐ Medical history<br>☐ Physical Exam incl. weight<br>☐ Vital signs<br>☐ CBC<br>☐ Albumin<br>☐ AST or ALT<br>☐ Serum total bilirubin<br>☐ eGFR<br>☐ PSA<br>☐ Testosterone<br>☐ PRO-CTCAE<br>☐ PROMIS-F SF 7a, EQ-5D-5L | CBC for hemoglobin and platelets; ARM 2 only: CBC, albumin, hepatic and renal function |

| | | |
|---|---|---|
| | ☐ AE Evaluation | |

**ASSESSMENTS: FOLLOW--UP**

**Follow up assessments from end of RT**

- For Arm 1, labs (CBC, albumin, hepatic and renal function) are as clinically indicated and per institutional standard

| ***Timepoint*** | ***Procedure/test/treatment*** | ***Notes*** |
|---|---|---|
| q3 months (+/- 1 month) for 2 years | ☐ Medical history<br>☐ Physical Exam incl. weight<br>☐ Vital signs<br>☐ AE Evaluation<br>☐ CBC<br>☐ Albumin<br>☐ AST or ALT<br>☐ Serum total bilirubin<br>☐ eGFR<br>☐ PSA<br>☐ Testosterone<br>☐ PRO-CTCAE<br>☐ PROMIS-F SF 7a, EQ-5D* | CBC for hemoglobin and platelets; ARM 2 only: CBC, albumin, hepatic and renal function<br><br>*1 and 2 years from end of RT |
| q6 months (+/- 1 month) for years 3-5 | ☐ Medical history<br>☐ Physical Exam incl. weight<br>☐ Vital signs<br>☐ AE Evaluation<br>☐ PSA<br>☐ Testosterone<br>☐ PRO-CTCAE | Testosterone q6mos x 1 yr (only) |

****Participating sites in Canada: please see Appendix A for further monitoring assessments recommended by Health Canada.**

Definition of Disease Assessments

- Biochemical failure: Two definitions of biochemical failure will be assessed:
  - Primary (noted as PBF): PSA ≥ nadir+2 ng/mL, or initiation of salvage hormones in the absence of PBF, after completion of RT and hormone therapy
  - Alternate (noted as ABF): PSA ≥ 0.4 ng/mL and rising at 5 years after randomization (i.e. PSA ≥ 0.4 ng/mL followed by a value higher than the first by any amount), or initiation of salvage hormones
- Local failure: development of a new biopsy-proven mass in the prostate bed, after enrollment in the protocol
- Regional failure: radiographic evidence (CT or MRI) of lymphadenopathy (lymph node size ≥ 1.0 cm in the short axis) in a patient without the diagnosis of a hematologic/lymphomatous disorder associated with adenopathy
- Distant metastases: radiographic evidence of hematogenous spread (e.g., bone scan, CT, MRI)

- Progression: first occurrence of biochemical failure, local failure, regional failure, distant metastasis, initiation of new unplanned anticancer treatment, or death from any cause
- Hormone-refractory disease: 3 rises in PSA during salvage androgen deprivation

## 5. TREATMENT PLAN/REGIMEN DESCRIPTION

### 5.1 Hormonal Therapy/Other Agent-Based Therapy (12-JUL-2022)

**ADT must begin no more than 42 days prior to registration and no later than 21 days after registration.**

**If a patient has been randomized to the enzalutamide arm and was started on bicalutamide prior, the bicalutamide should be stopped prior to starting enzalutamide.**

**If a patient was started on abiraterone prior, abiraterone must be stopped prior to randomization.**

#### 5.1.1 GnRH analog

Administration: GNRH analogs should be administered per the package insert in any formulation, eg, monthly, multi-monthly, yearly, that is available to the site to provide a total of 24 month of therapy.

#### 5.1.2 Bicalutamide

Administration: Patients randomized to the standard ADT arm may receive, at the physician's discretion, bicalutamide 50 mg orally taken at approximately the same time each day (not mandatory).

Duration of Treatment: 1-4 months total

#### 5.1.3 Enzalutamide

Administration: Patients randomized to enzalutamide will receive 160 mg (four 40 mg capsules) orally once daily. Patients should take enzalutamide at approximately the same time each day. Enzalutamide should be started no later than 21 days after registration.

Duration of Treatment: 24 months total (1 cycle = 90 days)

Enzalutamide may be taken with or without food. Each capsule should be swallowed whole. Do not chew, dissolve or open the capsules.

If a dose is missed, administer an additional dose and take the next dose of enzalutamide at the scheduled time.

See Section 6.0 for Enzalutamide dose management.

## 5.2 Radiation Therapy ( 17-JUN-2021)

**Radiation treatment must begin within 0-70 days of initiation of GnRH analog therapy. Radiotherapy should be delivered over approximately 7-8 weeks.**

**Radiation Therapy Schema**
***Prostatic Fossa***
66.6 – 70.2 Gy 1.8 Gy/fraction in 37-39 fractions
66 – 70 Gy 2.0 Gy/fraction in 33-35 fractions

***Required Regional Pelvic Lymph Nodes***
45-50.4 Gy 1.8 Gy/fraction in 25-28 fractions
44-50 Gy 2.0 Gy/fraction in 22-25 fractions

There is great variability among physicians on how suspected or biopsy-proven lymph node(s) and/or prostatic fossa lesion are boosted. The following attempts to radiation oncologists significant flexibility. Consider the bulkiness of the suspected or biopsy proven lymph node and/or prostatic fossa lesion, small bowel, colon, bladder, sigmoid and rectum proximity when choosing the dose. Note that some boost strategies are more biologically aggressive than others. Section **5.2.7** has EQD2 calculations that may be helpful when choosing the dose. **Prioritize normal tissue dose constraints above dose escalation.**

**There are 5 main decisions that the radiation oncologist has to make:**

1. Select 1.8 or 2 Gy fractions and the total dose to the prostatic fossa and dose to the regional pelvic lymph nodes. The next 4 items are at the discretion of the radiation oncologist and not mandatory.
2. Are suspicious on imaging or biopsy proven lymph nodes being boosted?
3. Are para-aortic lymph nodes from L5/S1 up to T12/L1 being treated electively (**only** if there is radiographic suspicion or biopsy proven lymph nodes in this area)?
4. Is a prostatic fossa lesion (suspicious on imaging or biopsy proven) being boosted?
5. If lymph nodes and/or a prostatic fossa lesion being boosted, is the approach concurrent or sequential? Choose ONE dose for all the lymph nodes.

**First choose either 1.8 Gy or 2 Gy fractions for treating the pelvis :**

- ***If 1.8 Gy per fraction,***
  - Prostatic fossa 66.6 - 70.2 Gy in 1.8 Gy fractions
  - Pelvic lymph nodes to L5/S1 45 Gy – 50.4 Gy in 1.8 Gy fractions
  - **Optional:** If lymph node boost **only**. Choose either sequential or

concurrent:
  - If sequential 54 - 73.8 Gy in 1.8 Gy fractions
  - If concurrent with 45 Gy - 50.4 Gy pelvic lymph node radiation: 50 – 61.6 Gy in 2 - 2.2 Gy fractions (25 – 28 fractions), respectively
  - Special case: If concurrent with 66.6 Gy pelvic lymph node **and** prostatic fossa radiation: 74 Gy in 2 Gy per fraction (37 fractions). May be useful if just one very large/bulky lymph node is being boosted.
- **Optional:** Para-aortics from L5/S1 anywhere up to T12/L1 at discretion of radiation oncologist**, only** if there is radiographic suspicion or biopsy proven lymph nodes in this area. Elective dose 45– 50.4 Gy in 1.8 Gy fractions.
- **Optional** Prostate fossa lesion boost with or without lymph node boost(s):
  - Prostatic fossa **lesion**: **sequential** up to 73.8 Gy in 1.8 Gy fractions or the special case of **concurrent** to 74 Gy in 37 fractions of 2 Gy fractions when treating the prostate fossa to 66.6 Gy in 1.8 Gy fractions and NOT treating any lymph nodes in the prostate fossa
  - If lymph node boost. **sequential only** from 54 - 73.8 Gy in 1.8 Gy fractions

- ***If 2 Gy per fraction,***
  - Prostatic fossa 66 - 70 Gy in 2 Gy fractions
  - Pelvic lymph nodes 44 – 50 Gy in 2 Gy fractions
  - **Optional**: Lymph node boost **only** (not boosting prostatic fossa lesion). Choose either sequential or concurrent:
    - If sequential 54 - 70 Gy in 2 Gy fractions
    - If concurrent with 44 – 50 Gy pelvic lymph node radiation: 48.4 – 60 Gy in 2.2 - 2.4 Gy fractions (22-25 fractions), respectively
  - **Optional:** Para-aortics from L5/S1 anywhere up to T12/L1 at discretion of radiation oncologist**, only** if there is radiographic suspicion or biopsy proven lymph nodes in this area. Elective dose 44 – 50 Gy in 2 Gy fractions.
  - **Optional**: Prostate fossa lesion boost with or without lymph node boost(s):
    - Prostatic fossa lesion boost: **sequential only** up to 74 Gy in 2 Gy fractions
    - If lymph node boost: **sequential only** 54 - 70 Gy in 2 Gy fractions

**5.2.1** Radiation Treatment Technology

Photon energies ranging from $^{60}$Co to <18 MV are allowed. Treatment techniques such as 3D-conformal radiation therapy (CRT), intensity modulated radiation therapy (IMRT), volume modulated arc therapy (VMAT), MRLinac, Cyberknife or Tomotherapy are allowed. Use of IMRT is strongly encouraged to limit the radiation dose to bone marrow and normal structures in the pelvis. All patients must undergo daily image guided radiation therapy (IGRT).

**5.2.2** Immobilization

Proper immobilization of patients is critical for this protocol. An effective patient immobilization system reduces the inherent setup variability and minimizes margins. Patient setup reproducibility must be achieved using appropriate immobilization devices.

**5.2.3** Simulation Imaging

A treatment planning CT scan will be required to define the clinical and planning target volumes, and the critical normal structures. This CT will be acquired with the patient set up in the same position as for daily treatments. Each patient will be positioned in the supine position. 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 slice thickness should be ≤ 0.3 cm through the region that contains the target volumes.

Rectal Filling - An overly distended rectum can introduce a systematic positioning error that may increase the probability of missing the clinical target volume (CTV). Patients should be simulated with the rectum as empty as possible and <3 cm in the anterior-posterior dimension is ideal. This can be achieved with an enema 1-2 hours prior to simulation. If the size of the rectum is large due to flatus, a hollow catheter introduced into the rectum may be helpful. Rectal balloons for planning and treatment are not permitted on this protocol.

Bladder Filling - Patients should also have a comfortably full bladder (the patient should not be uncomfortable at simulation because it is likely that he will have more difficulty maintaining a full bladder during treatment).

**5.2.4** Imaging for Structure Definition, Image Registration/Fusion and Follow-up

MRI may be used to assist in volume delineation and precision in all eligible patients. However, care should be taken to ensure that the geometric and special orientation of the structure set are accurate on the treatment planning CT because CT is used for the dose calculation and basis for image guidance.

A urethrogram or MRI may be performed, but is not required, to establish the most inferior portion of the prostate bed. Use of contrast, other than for the urethrogram, is discouraged. 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

**Note:** All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated. Please refer to Section 5.2.6 for a list and description of normal

structures to be contoured.

| Standard Name | Description | Validation |
|---|---|---|
| CTV_N_xxxx<br>*if 1.8 Gy fractions:*<br>*xxxx = 4500- 5040*<br>*if 2.0 Gy fractions:*<br>*xxxx = 4400-5000* | Regional pelvic lymph nodes: presacral nodes, the bilateral distal common iliac, external iliac, obturator nodes, or internal iliac to L5/S1<br><br>**Optional:** Para-aortics from L5/S1 anywhere up to T12/L1 at discretion of radiation oncologist, **only** if there is radiographic suspicion or biopsy proven lymph nodes in this area. | Required |
| PTV_N_xxxx<br>*(xxxx = 4500 - 5040 or 4400- 5000 as above)* | PTV expansion for the CTV_N_xxxx | Required |
| CTV_P_xxxx<br>*if 1.8 Gy fractions:*<br>*xxxx = 6660 - 7020*<br>*if 2.0 Gy fractions:*<br>*xxxx = 6600 - 7000* | CTV including prostatic fossa and seminal vesicle remnants when present | Required |
| PTV_P_xxxx<br>*(xxxx = 6600 - 7020 as above)* | PTV expansion for the CTV_P_xxxx | Required |
| CTV_PELVIC_xxxx<br>*(xxxx = 4500 - 5040 or 4400 - 5000 per the CTV_N_xxxx)* | CTV_P_xxxx (including prostatic fossa, seminal vesicle remnants when present) **and** the CTV_N_xxxx **(**regional lymph nodes: presacral nodes, and the bilateral distal common iliac, external iliac, internal iliac, and obturator nodes)<br><br>**Optional**:Para-aortics from L5/S1 anywhere up to T12/L1 at discretion of radiation oncologist**, only** if there is radiographic suspicion or biopsy proven lymph nodes in this area. | Required |
| PTV_PELVIC_xxxx<br>*(xxxx = 4500- 5040 or 4400 - 5000 as above)* | PTV expansion for the CTV_PELVIC_xxxx | Required |
| **Optional Lymph Node Treatment** | | |
| GTV_LNX_xxxx<br>*(X= 1-10*<br>*xxxx = 4840 – 7400)*<br>Select ONE dose for all lymph nodes. **See section 5.2.7 for dosing details** | At the discretion of the radiation oncologist, suspicious lymph nodes for metastatic disease in the radiology report (CT, MRI, molecular imaging [i.e. choline PET, FACBC, PSMA]) and/or biopsy proven lymph nodes may be boosted no higher than T12/L1. These may be presacral, bilateral distal common iliac, external iliac, obturator, internal iliac, perirectal, inguinal or low paraaortic lymph nodes. | Required when applicable |

| | | |
|---|---|---|
| GTV_LN_xxxx<br>*(xxxx = 4840 – 7400 as above)* | All GTV_LNX_xxxx summed | Required when applicable |
| CTV_LN_xxxx<br>*(xxxx= 4840 – 7400 as above)* | CTV expansion of the GTV_LN_xxxx | Required when applicable |
| PTV_LN_xxxx<br>*(xxxx= 4840 – 7400 as above)* | PTV expansion of the CTV_LN_xxxx | Required when applicable |
| **Optional Prostatic Fossa Lesion Boost**<br>*Please note that these contours **ONLY** apply when boosting a prostate fossa lesion/nodule.* | | |
| GTV_PB_xxxx<br><br>***if 1.8 Gy fractions**,*<br>*xxxx = up to 7380 sequential*<br>*xxxx = 7400 in 37 fractions of 2 Gy concurrent when treating the prostate fossa to 6660 cGy in 1.8 Gy fractions*<br><br>***if 2.0 Gy fractions**:*<br>*xxxx = up to 7400* | **ONLY SEQUENTIAL** if boosting **both** Prostatic Fossa Lesion(s) Lymph Node volume(s).<br><br>**SEQUENTIAL** prostatic fossa lesion boosts are allowed when treating the prostatic fossa at 1.8 Gy or 2 Gy per fraction<br><br>**CONCURRENT prostatic fossa lesion boosts** allowed **ONLY** in the following Special Case:<br>74 Gy in 37 fractions of 2 Gy fractions when treating the prostate fossa to 66.6 Gy in 1.8 Gy fractions.<br>*****No Lymph Node boost(s) treatment allowed with the special case*****<br><br>At the discretion of the radiation oncologist, a suspicious prostatic fossa lesion in the radiology report (CT, MRI, molecular imaging [i.e. choline PET, FACBC, PSMA]) and/or biopsy proven prostatic fossa lesion may be boosted. | Required when applicable |
| CTV_PB_xxxx | CTV expansion of the GTV_PB_xxxx | Required when applicable |
| PTV_PB_xxxx | PTV expansion of the PTV_PB_xxxx | Required when applicable |

*Abbreviations: P = Prostatic fossa; LN = lymph node; N = nodal; PB = Prostatic fossa boost*

**Detailed Specifications**
**CTV_N_xxxx**: Regional pelvic lymph nodes: presacral nodes, the bilateral distal common iliac, external iliac, obturator nodes, or internal iliac to L5/S1

**Pelvic Lymph Node Volumes for Prostate Cancer Atlas**
http://www.rtog.org/CoreLab/ContouringAtlases/ProstatePelvicLymphNodes.aspx

The iliac nodes will be derived by contouring the distal common iliac, and external and internal iliac vessels starting superiorly at L5-S1. First, the external iliac vessels will be contoured inferiorly to the top of the femoral heads and the internal iliac vessels will be contoured inferiorly until they are no longer visible on the CT scan or exit through the true pelvis via the greater sciatic notch.

Second, the iliac vessels are expanded by 7 mm in the anterior, posterior and lateral dimensions, but not the superior and inferior dimensions. Muscles and bone should be excluded from the 7 mm expansion. Bowel and bladder may be excluded after the 7 mm expansion.

Third, with an approximately 1 cm diameter brush (use your clinical judgement) the obturator and presacral nodes are added avoiding bone and muscle. The obturator nodes will encompass tissue medial to the obturator internus muscles extending from the anterior border of the ilium to the posterior border of the ilium. The obturator nodes will be contoured starting superiorly where the internal and external iliac vessel contours stop and extend inferiorly to the top of the symphysis pubis. The presacral nodes will extend from L5-S1 to the top of S3.

**Optional:** Para-aortics from L5/S1 anywhere up to T12/L1 at discretion of radiation oncologist, only if there is radiographic suspicion or biopsy proven lymph nodes in this area.

**PTV_N_xxxx**: The PTV_N_xxxx will be a direct expansion of 0.5-1.0 cm beyond the CTV_N_xxxx.
***More generous PTV expansion of the nodal CTV_N_xxxx within this range as compared to the prostatic fossa CTV_P_xxxx is allowed to account for potentially more set-up variability in the CTV_N_xxxx when daily set-up is defined by prostatic fossa CTV parameters. Additional expansion within this range is required to account for the penumbra when 3D CRT is used.*

**CTV_P_xxxx:** The contouring of the **prostate bed** should be in accordance with the RTOG consensus guidelines (Michalski 2010).
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2847420/

Briefly, the CTV should extend superiorly from the level of the caudal vas deferens remnant to >8-12 mm inferior to vesicourethral anastomosis (VUA). Below the superior border of the pubic symphysis, the anterior border extends to the posterior aspect of the pubis and posteriorly to the rectum, where it may be concave at the level of the VUA. At this level, the lateral border extends to the levator ani. Above the pubic symphysis, the anterior border should encompass the posterior 1-2 cm of the bladder wall; posteriorly, it is bounded by the mesorectal fascia. At this level, the lateral border is the sacrorectogenitopubic fascia. Seminal vesicle remnants, if present, should be included in the CTV if there is pathologic evidence of their involvement.

**Prostate Bed Positive Apex Margins Sample Contour**
https://www.rtog.org/LinkClick.aspx?fileticket=mF9BE8qM8xA%3d&tabid=232

**Prostate Bed Positive Seminal Vesicle Sample Contour**
https://www.rtog.org/LinkClick.aspx?fileticket=_znZLMP1yco%3d&tabid=232

**PTV_P_xxxx:** The PTV_P_xxxx margins should be a minimum of 0.5 cm and a maximum of 1.0 cm in all dimensions beyond the CTV_P_xxxx. 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.

**CTV_PELVIC_xxxx:** The CTV_PELVIC_xxxx will include the CTV_P_xxxx (including prostatic fossa, seminal vesicle remnants when present) **and** the CTV_N_xxxx **(**regional lymph nodes: presacral nodes, and the bilateral distal common iliac, external iliac, internal iliac, and obturator nodes).

**PTV_PELVIC_xxxx**: The PTV_PEVLIC_xxxx will include the PTV_P_xxxx (including prostatic fossa, seminal vesicle remnants when present) **and** the PTV_N_xxxx **(**regional lymph nodes: presacral nodes, and the bilateral distal common iliac, external iliac, internal iliac, and obturator nodes)

**Optional lymph node treatment (imaging suspicious or biopsy proven)**

**GTV_LNX_xxxx:** At the discretion of the radiation oncologist, suspicious lymph nodes for metastatic disease in the radiology report (CT, MRI, molecular imaging [i.e. choline PET, FACBC, PSMA]) and/or biopsy proven lymph nodes may be boosted no higher than T12/L1.

Fusing the simulation CT and the diagnostic imaging showing the suspicious lymph node(s) and discussing the findings with the radiologist is encouraged.

**GTV_LN_xxxx:** A summation of all the GTV_LNX_xxxx.

**CTV_LN_xxxx:** CTV expansion of the GTV_LN_xxxx is at the discretion of the radiation oncologist. Keep in mind the **total expansion** from the GTV_LN_xxxx to the PTV_LN_xxxx should be a minimum of 0.5 cm and a maximum of 1 cm.

**PTV_LN_xxxx:** PTV expansion of the CTV_LN_xxxx. The total expansion from the GTV_LN_xxxx to the PTV_LN_xxxx should be a minimum of 0.5 cm and a maximum of 1 cm. The PTV_LN_xxxx should not overlap more than 0.5 cm with a bowel loop and ideally abut it at the most.

The simplest strategy to meet the lymph node expansion criteria is to expand the GTV_LN_xxxx by 0.5 cm, and then expand the resulting CTV_LN_xxxx between 0 to

0.5 cm to get the PTV_LN_xxxx. You can then erase the PTV_LN_xxxx as far back as the CTV_LN_xxxx where the bowel is close by to any given node (see **Figure 1**).

**Optional prostate fossa boost (imaging suspicious or biopsy proven)**

**GTV_PB_xxxx:** At the discretion of the radiation oncologist, a suspicious prostatic fossa lesion in the radiology report (CT, MRI, molecular imaging [i.e. choline PET, FACBC, PSMA]) and/or biopsy proven prostatic fossa lesion may be boosted.
** *See previous table for further guidance*
**CTV_PB_xxxx**: expand the **GTV_PB_xxxx** by 0.5 cm.

**PTV_PB_xxxx:** expand the **CTV_PB_xxxx** between 0.5 and 1 cm.

### 5.2.6 Definition of Critical Structures and Margins

**Note:** All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Resubmission of data will be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing, and use of underscores must be applied exactly as indicated.

| Standard Name | Description | Validation |
|---|---|---|
| Rectum | Per Male RTOG Normal Pelvis Atlas | Required |
| Bladder | Per Male RTOG Normal Pelvis Atlas | Required |
| Femur_L | Per Male RTOG Normal Pelvis Atlas | Required |
| Femur_R | Per Male RTOG Normal Pelvis Atlas | Required |
| PenileBulb | Per Male RTOG Normal Pelvis Atlas | Required |
| External | External patient contour | Required |
| E-PTV | External minus PTVs | Required |
| Bowel | BowelBag per Male RTOG Normal Pelvis Atlas, but close to the lymph node(s) being treated you may reduce the volume to include just the bowel loops (Colon, Small Bowel, and/or Sigmoid) to help meet dose constraints. | Required |

**Male Pelvic Atlas**
http://www.rtog.org/CoreLab/ContouringAtlases/MaleRTOGNormalPelvisAtlas.aspx

**Rectum:** Inferiorly from the lowest level of the ischial tuberosities (right or left). Contouring ends superiorly before the rectum loses its round shape in the axial plane and connects anteriorly with the sigmoid.

**Bladder:** Inferiorly from its base, and superiorly to the dome

**Femurs:** The proximal femur inferiorly from the lowest level of the ischial tuberosities (right or left) and superiorly to the top of the ball of the femur, including the trochanters. Tips: Auto-contouring threshold parameters with bone can facilitate this process, but requires editing any auto-contouring artifacts.

**PenileBulb:** That portion of the bulbous spongiosum of the penis immediately inferior to the GU diaphragm. Do not extend this structure anteriorly into the shaft or pendulous portion of the penis. Tips: The penile bulb is best identified with MRI (bright on T2) or CT when there is contrast in the urethra. On CT, the penile bulb will be posterior to the urethra and has a round shape. Refer to article by Wallner et al. PubMed ID: 12095559

**External:** The skin encompassing all CT slices from 1.5 cm inferior to superior of the radiation fields.

**E-PTV:** External patient contour minus all PTV volumes.

**Bowel:** BowelBag per Male RTOG Normal Pelvis Atlas, but close to the lymph node(s) being treated you may reduce the volume to include just the bowel loops (colon, small bowel, and/or sigmoid) to meet dose constraints.

Most importantly, carefully delineate the bowel next to the PTV_LN_xxxx **which is what is most relevant.** The PTV_LN_xxxx should not overlap more than 0.5 cm with a bowel loop and ideally abut it at the most.

### 5.2.7 Dose Prescription

**Note:** The information provided in this section can be used for adjusting the dose constraints for treatment planning purposes. This table together with the planning priority table should be used during dose optimization. It is important to remember that ideal plans might not be achievable in all cases. Thus, the Compliance Criteria table could be different than the information given here. Cases will be scored using the Compliance Criteria table.

**Mandatory PTVs**

| Target Standard Name | Dose (Gy) | Fraction Size (Gy) | # of fractions | Dose specification technique |
|---|---|---|---|---|
| **PTV_P_xxxx** | 66.6 - 70.2 | 1.8 | 37 - 39 | Covering ≥ 95% of PTV |
| | 66 - 70 | 2.0 | 33 - 35 | Covering ≥ 95% of PTV |
| **PTV_N_xxxx** | 45 – 50.4 | 1.8 | 25 - 28 | Covering ≥ 95% of PTV |

| | | | | |
|---|---|---|---|---|
| | 44 - 50 | 2.0 | 22 - 25 | Covering ≥ 95% of PTV |
| **PTV_PELVIC_xxxx** | 45 - 50.4 | 1.8 | 25 - 28 | Covering ≥ 95% of PTV |
| | 44 -50 | 2.0 | 22 - 25 | Covering ≥ 95% of PTV |

**Optional lymph node boost**
The optional lymph node(s) boost can be done either sequentially or concurrently as described below. The dose and fractionation is left at the discretion of the radiation oncologist but should be within the concurrent and sequential ranges below. **Prioritize normal tissue dose constraints above dose escalation.**

Select **ONE** dose for all lymph nodes. If also boosting the prostatic fossa (PTV_PB_xxxx), **SEQUENTIAL** prostatic fossa **AND** lymph node boosts are allowed. (**Concurrent boosts to prostatic fossa lesions are only allowed in one special case as described in the section 5.2.5 table).**

***WARNING:*** When boosting lymph nodes using a concurrent approach, if the lymph nodes are inferior enough, clinically significant hot spots may result. This is bound to happen when the concurrent boost delivered to the lymph nodes overlaps with scattered dose from the subsequent prostate bed boost. This could result in hot spots near the rectum, bladder or small bowel. A sequential approach may be best in these situations.

| **Target Standard Name** | **Lymph Node Boost Type (Choose one)** | **Dose (Gy)** | **Fraction Size (Gy)** | **# of fractions** | **Dose specification technique** |
|---|---|---|---|---|---|
| **Using 1.8 Gy fractions:** | | | | | |
| PTV_LN_xxxx | Sequential to PTV_PELVIC_xxxx | 54 - 73.8 | 1.8 | 30 - 41 | Covering ≥ 95% of PTV |
| PTV_LN_xxxx | Concurrent with PTV_PELVIC_xxxx | 50 – 61.6 | 2 – 2.2 | 25 - 28 | Covering ≥ 95% of PTV |
| PTV_LN_xxxx (special case) | Concurrent with PTV_PELVIC_4500 and PTV_P_6660 | 74 | 2 | 37 | Covering ≥ 95% of PTV |
| **Using 2.0 Gy fractions:** | | | | | |
| PTV_LN_xxxx | Sequential to PTV_PELVIC_xxxx | 54 - 70 | 2 | 27 - 35 | Covering ≥ 95% of PTV |
| PTV_LN_xxxx | Concurrent with PTV_PELVIC_xxxx | 48.4 - 60 | 2.2 - 2.4 | 22-25 | Covering ≥ 95% of PTV |

**EQD2 for the Lymph Node Boost Various Fractionation Schemes if choice was 1.8 Gy fractions for pelvis and prostatic fossa:**

| Dose (Gy) | Fraction Size (Gy) | # of fractions | $EQD_2$ (Gy) normal tissues ($\alpha/\beta = 3$) | $EQD_2$ (Gy) prostate cancer ($\alpha/\beta = 1.5$) | Boost technique |
|---|---|---|---|---|---|
| 54 - 73.8 | 1.8 | 30 - 41 | 52 - 71 | 51 - 70 | Sequential to PTV_PELVIC_xxxx |
| 50 – 61.6 | 2 - 2.2 | 25 - 28 | 50 - 64 | 50 - 65 | Concurrent with PTV_PELVIC_xxxx |
| 74 | 2.0 | 37 | 74 | 74 | Special case: concurrent with PTV_PELVIC_4500 and PTV_P_6660 |

**EQD2 for the Lymph Node Boost Various Fractionation Schemes if choice was 2.0 Gy fractions for pelvis and prostatic fossa:**

| Dose (Gy) | Fraction Size (Gy) | # of fractions | $EQD_2$ (Gy) normal tissues ($\alpha/\beta = 3$) | $EQD_2$ (Gy) prostate cancer ($\alpha/\beta = 1.5$) | Boost technique |
|---|---|---|---|---|---|
| 54 - 70 | 2.0 | 27 - 35 | 54 - 70 | 54 - 70 | Sequential to PTV_PELVIC_xxxx |
| 48.4 - 60 | 2.2 - 2.4 | 22 - 25 | 50 - 65 | 51 - 67 | Concurrent with PTV_PELVIC_xxxx |

**Optional prostatic fossa boost**

| Target Standard Name | Dose (Gy) | Fraction Size (Gy) | # of fractions | Dose specification technique |
|---|---|---|---|---|
| **PTV_PB_xxxx** | Sequential up to 73.8 | 1.8 | up to 41 | Covering ≥ 95% of PTV |
| | Sequential up to 74 | 2.0 | up to 37 | Covering ≥ 95% of PTV |
| | ** Concurrent to 74 | 2.0 | Up to 37 | Covering ≥ 95% of PTV |

****Concurrent prostatic fossa lesion boost allowed in Special Case Only (see Section 5.2.5)**

**5.2.8** Compliance Criteria

The compliance criteria listed here will be used to score each case. Given the limitations inherent in the treatment planning process, the numbers given in this section can be different than the prescription table. The Per Protocol and Variation Acceptable categories are both considered to be acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results. A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal and additional treatment planning optimization is recommended.

**Normalization of Dose.** The plan is normalized such that 95% of the PTV_P_xxxx volume receives prescription dose of 66.0-70.2 Gy.

**Note:** Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met

**Target Volume Constraints and Compliance Criteria**

| **Structure** | **Dosimetric Parameter** | **Per Protocol** | **Variation Acceptable** |
|---|---|---|---|
| PTV_P_xxxx | V100%[%] | >= 95 | >=94 |
| | D0.03cc[%] | <= 115 | <= 120 |
| | D99%[%] | >= 95 | >= 93 |
| PTV_PELVIC_4500 (4680, 4860, 5040) **(1.8 Gy/fraction)** | D95%[Gy] | >=45 >= (46.8, 48.6, 50.4) | >=43 >= (44.8, 46.6, 48.4) |
| PTV_PELVIC_4400 (4600, 4800, 5000) **(2.0 Gy/fraction)** | D95%[Gy] | >=44 >= (46, 48, 50) | >=42 >= (44, 46, 48) |
| PTV_LN_xxxx (optional) | D95%[%] | >=95 | >=85 |
| PTV_PB_xxxx (Optional) | D95%[%] | >=95 | >=85 |

Per Protocol, range is excluded from Variation Acceptable range.

**Normal Structure Constraints and Compliance Criteria**

The following normal tissue dose constraints represent the minimum level of acceptability for protocol therapy. Whenever possible, maximal sparing of normal tissues should be achieved to minimize the risk of toxicity.

Normal Tissue Dose Constraints

| **Structure** | **Dosimetric** | **Per Protocol** | **Variation Acceptable** |
|---|---|---|---|

| | Parameter | | |
|---|---|---|---|
| Rectum | V40 Gy[%]<br>V65 Gy[%] | <= 55<br><= 35 | <= 60<br><= 39 |
| Bladder | V40 Gy[%]<br>V65 Gy[%] | <= 70<br><= 50 | <= 77<br><= 55 |
| Femur_L | V50 Gy[%] | < 10 | < 11 |
| Femur_R | V50 Gy[%] | < 10 | < 11 |
| E-PTV | D0.03cc[%]* | <=110 | <=112 |

*If the global maximum exceeds 107% check if a concurrently treated lymph node overlaps with the sequentially treated prostate bed.

Carefully delineate the bowel next to the PTV_LN_xxxx. The PTV_LN_xxxx should not overlap more than 0.5 cm with a bowel loop and ideally abut it at the most.

**Figure 1 A.** PTV_LN_xxxx (pink) ideally abutting small bowel. GTV_LN1_xxxx, red.

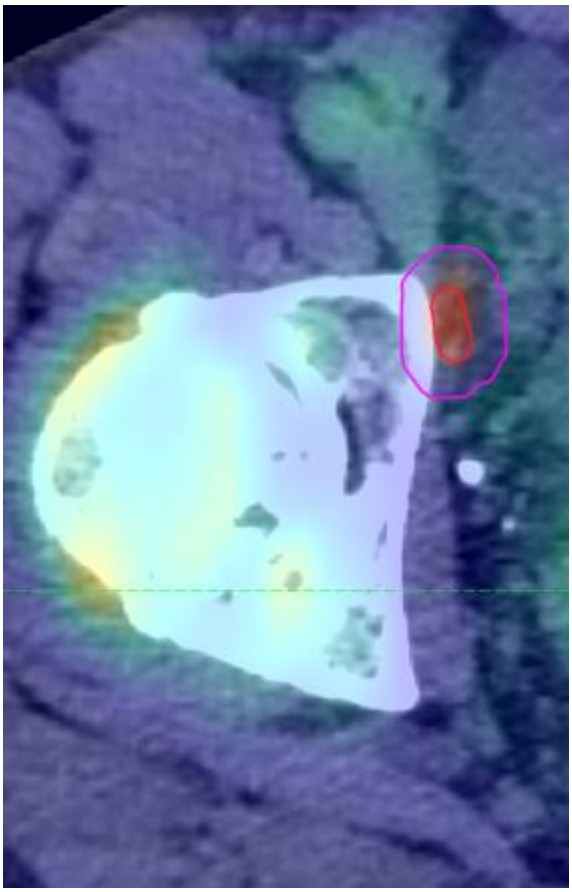
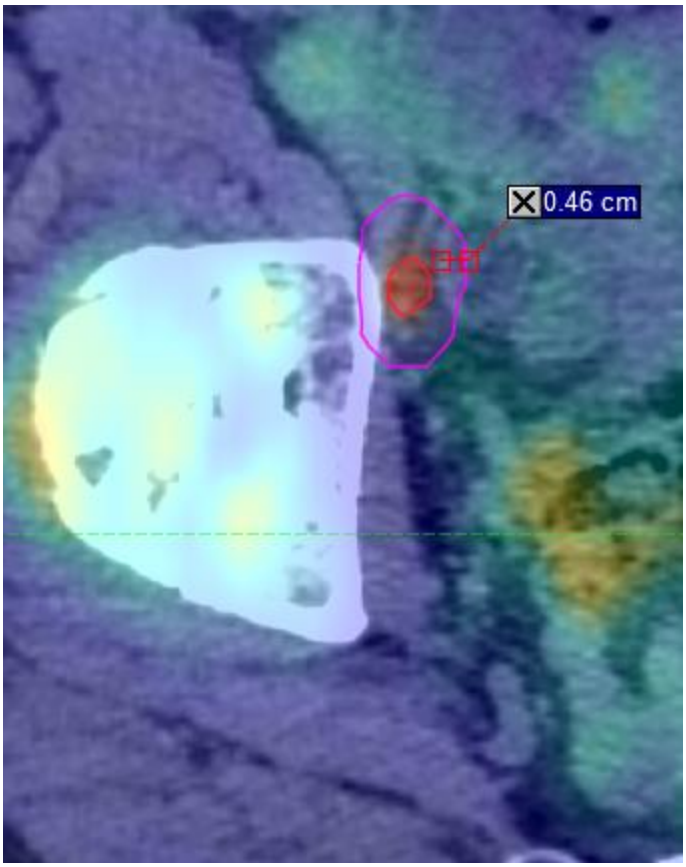


**Figure 1 B.** PTV_LN_xxxx (pink) overlaps less than 0.5 cm of small bowel. GTV_LN1_xxxx, red.




| Structure | Lymph Node Boost Type | Dosimetric Parameter | Per Protocol | Variation Acceptable |
|---|---|---|---|---|
| Bowel (Optional) | Concurrent | V53 Gy[cc]<br>V60 Gy[cc] | <= 3.5 * (# of lymph nodes)<br><= 1 * (# of lymph nodes) | <= 4.5 * (# of lymph nodes)<br><= 2 * (# of lymph nodes) |
| Bowel (Optional) | Sequential 1.8 or 2.0 Gy/fraction | V55 Gy [cc]<br>V65 Gy [cc] | <= 3.5 * (# of lymph nodes)<br><= 1 * (# of lymph nodes) | <= 4.5 * (# of lymph nodes)<br><= 2 * (# of lymph nodes) |

For example, a patient with 3 lymph nodes receives a sequential boost of 64.8 Gy. Meeting the **Bowel** V55 Gy<= (3.5 * 3) = 10.5 cc, and the V65 Gy<= (1 * 3) = 3 cc would be per protocol. A patient with 2 lymph nodes receives a concurrent boost of 55 Gy. Meeting the **Bowel** V53 Gy<= (3.5 * 2) = 7 cc, and the V60 Gy<= (1 * 2) = 2 cc would be per protocol.

**Recommended dose acceptance criteria for other normal tissue, but not to be used for plan score**

| Structure | Recommended dose acceptance criteria |
|---|---|
| PenileBulb | Mean[Gy] <= 52.5 Gy |

**Delivery Compliance criteria**

| | Per Protocol | Variation Acceptable |
|---|---|---|
| RT start date | <= 70 days after start of GnRH therapy | N/A |
| Interruptions | 1-7 days | 8-14 days |

**Note**: A delay in RT start outside the Per Protocol window is considered a Protocol Deviation.

**5.2.9** Treatment Planning Priorities and Instructions

In order of priority, the following critical structures are listed in order of decreasing importance. The following list is given as an example

1. PTV_P_xxxx
2. PTV_PB_xxxx
3. PTV_PELVIC_xxxx
4. Bowel
5. Rectum
6. PTV_LN_xxxx
7. Bladder
8. Femurs_L\R
9. PenileBulb

- 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 is recommended.

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

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

**5.2.10** 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 when excluding points less than 10% of the maximum dose.

**5.2.11** Daily Treatment Localization/IGRT

Image-guided radiation therapy (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.

At the start of each fraction, patients should be initially positioned by laser alignment of skin surface tattoos.

Daily IGRT is required. Fiducial marker placement is preferred but not required. Daily fiducial based volumetric IGRT is ideal because fiducials aid in the interpretation by radiation therapists. If fiducial markers are not present, volumetric IGRT based on soft-tissue alignment needs to be performed. Finally, volumetric 3D IGRT is preferred because bladder and rectal filling can be assessed for patient coaching purposes. Orthogonal 2D kV imaging requires fiducials. Electromagnetic transponders or transabdominal ultrasound to identify the VUA may also be used for daily IGRT.

Three fiducial markers or electromagnetic transponders may be placed in the prostate bed. At least one near the vesicourethral anastomosis (VUA) and two in the retrovesical (RV) space under sterile conditions with antibiotic prophylaxis consistent with local practice standards. The three markers or electromagnetic transponders should be identified and contoured on the simulation CT. The appropriate shifts should be made to ensure daily registration of the markers or transponders with the position defined by the treatment plan.

All image/signal-guidance data should be recorded, archived at the site, and available for review, if requested.

**Management of Radiation Dose to the Patient from IGRT**

RTOG Foundation 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.

## 5.3 General Concomitant Medication and Supportive Care Guidelines

### 5.3.1 Permitted Supportive/Ancillary Care and Concomitant Medications

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

- Anticonvulsants
- Antiemetics
- Anticoagulants
- Antidiarrheals
- Analgesics
- Hematopoietic Growth Factors
- Herbal products
- Nutritional supplementation

### 5.3.2 Drugs That May Affect Exposure to Enzalutamide

**Drugs That Inhibit or Induce CYP2C8**

Coadministration of a strong CYP2C8 inhibitor (eg, gemfibrozil) increased the composite AUC0-∞ of enzalutamide plus its active metabolite in healthy volunteers by 2.2-fold; therefore, coadministration of enzalutamide with strong CYP2C8 inhibitors should be avoided if possible. If coadministration of enzalutamide with strong CYP2C8 inhibitors cannot be avoided, the enzalutamide dose should be reduced to 80 mg once daily. If coadministration of the strong inhibitor is discontinued, the enzalutamide dose should be returned to the dose used before initiation of the strong CYP2C8 inhibitor.

The effects of CYP2C8 inducers on the PK of enzalutamide have not been evaluated in vivo. Coadministration of enzalutamide with strong or moderate CYP2C8 inducers (eg, rifampin) may alter the plasma exposure of enzalutamide and should be avoided if possible. Selection of a concomitant medication with no or minimal CYP2C8 induction potential is recommended.

**Drugs That Induce CYP3A4**

The effects of CYP3A4 inducers on the PK of enzalutamide have not been evaluated *in vivo.* Coadministration of enzalutamide with strong CYP3A4 inducers (eg, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) may decrease the plasma exposure of enzalutamide and should be avoided if possible. Selection of a concomitant medication with no or minimal CYP3A4 induction potential is recommended. Moderate CYP3A4 inducers (eg, bosentan, efavirenz, etravirine, modafinil, nafcillin) and St. John's Wort may also reduce the plasma exposure of enzalutamide and should be avoided if possible.

### 5.3.3 Prohibited Concomitant Medications

Medications that lower seizure threshold and other investigational compounds (non-FDA approved therapies for prostate cancer).

## 5.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable

# 6. TREATMENT MODIFICATIONS/MANAGEMENT

**NOTE:** PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol directed action.

## 6.1 Dose Levels

| | **Enzalutamide** | **# of Capsules** (taken at approximately the same time each day) |
|---|---|---|
| **Original dose** | 160 mg | 4 |
| **Dose level -1** | 120 mg | 3 |
| **Dose level -2** | 80 mg | 2 |

Dose reductions, once initiated, are permanent for all future cycles. Re-escalation may be attempted after discussion with the Principal Investigator, Dr. Edwin Posadas.

If enzalutamide is co-administered with a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg (two 40 mg capsules) once daily. If co-administration of the strong CYP2C8 inhibitor is discontinued, the enzalutamide dose should return to the dose used before initiation of the strong CYP2C8 inhibitor.

## 6.2 Management of Toxicity Related to Enzalutamide (16-MAR-2021)

Patients who experience a grade 3 or higher toxicity that is attributed to enzalutamide and cannot be ameliorated by the use of adequate medical intervention will interrupt treatment with enzalutamide for 1 week or until the toxicity grade improves to grade 2 or lower severity. Similarly, patients with persistent and intolerable grade 2 toxicity that does not improve with adequate medical intervention may also have enzalutamide held for 1 week or until the toxicity improves to grade 1 or better. Subsequently, study drug dosing may be restarted at the original dose or a reduced dose (see table above) in consultation

with the medical oncology co-chair.

For grade ≥ 3 events of ischemic heart disease, treatment with enzalutamide should be stopped.

If enzalutamide must be held for more than 4 weeks, the patient should permanently discontinue therapy.

### 6.3 Overdose Management

The medical oncology chair, Dr. Edwin Posadas must be contacted in the event of an enzalutamide overdose.

An overdose is defined as any dose greater than the protocol-specified dose of enzalutamide 160 mg once daily. In the event of an overdose, treatment with study drug should be stopped and general supportive measures initiated, taking into consideration the half-life is 5.8 days for enzalutamide. Patients may be at increased risk of seizures following an overdose of enzalutamide. There is no known antidote to overdose.

## 7. ADVERSE EVENTS REPORTING REQUIREMENTS

### 7.1 Protocol Agents (22-AUG-2019)

Investigational Agent

The investigational agent, enzalutamide, administered in RTOG 3506 is IND exempt and is distributed by a third party drug distributor.

Commercial Agents

The commercial agents in RTOG 3506 are Bicalutamide and GnRH analog.

To determine whether an adverse event meets expedited reporting criteria see the reporting tables in section 7.4 of the protocol.

#### 7.1.1 Adverse Events for Investigational Study Agents (Enzalutamide)

Investigators must obtain the current version of the enzalutamide Investigator Brochure (IB) for comprehensive pharmacologic and safety information. The IB can be accessed on the RTOG Foundation 3506 protocol page of the RTOG website, www.rtog.org. Sites must use their username and password to access the protocol page and the IB.

#### 7.1.2 Adverse Events for Commercial Study Agents

**Refer to the package insert for detailed pharmacologic and safety information**

### 7.2 Adverse Events (AEs) (02-DEC-2019)

This study will use the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for adverse event reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

### 7.2.1 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug 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 (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1).

Clinician graded CTCAE is the AE safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items but no protocol directed action will be taken. The specific PRO-CTCAE items for this protocol can be found on the forms section of the 3506 protocol webpage on the RTOG Foundation website and is titled "RTOGF 3506 NCI PRO-CTCAE Item Library." PRO-CTCAE is not intended for expedited reporting, real time review or safety reporting. PRO-CTCAE data are not currently intended for use in data safety monitoring or adverse event stopping rules.

**NOTE:** If the event is a Serious Adverse Event (SAE) (see next section), further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.

### 7.2.2 Adverse Event of Special Interest

The following adverse events of special interest must be reported expeditiously via the SAE report form in Rave within 24 hours of awareness regardless of grade:

- Seizure or loss of consciousness
- Posterior reversible encephalopathy syndrome (symptoms include seizure, headache, confusion, reduced eyesight, blurred vision)

### 7.2.3 Overdose

An overdose as defined in Section 6.3 should be reported expeditiously via the SAE report form in Rave within 24 hours of awareness.

### 7.2.4 Adverse Events and PRO-CTCAE

The PRO-CTCAE instrument will be used to assess patient reported toxicity outcomes.

PRO-CTCAE is a validated instrument developed by the National Cancer Institute to assess clinical trial toxicity outcomes by patient report; it complements information collected by physician-reported CTCAE. It characterizes the frequency,

severity and interference of 78 symptomatic treatment toxicities [Basch 2014]. These include symptomatic toxicities such as pain, fatigue, nausea, and cutaneous side effects such as rash and hand-foot syndrome. Items are scored on a Likert scale (e.g., for severity, 0=none, 1=mild, 2=moderate, 3=severe, and 4=very severe). PRO-CTCAE is available in English, Spanish, and French for this study.

PRO-CTCAE assessments will be collected before registration and as specified in the Section 4 assessment tables.

The patient-reported AEs that will be assessed using PRO-CTCAE are listed in the table below. These adverse events are considered expected and, if reported, should also be clinician graded using the CTCAE v.5.

| **CTCAE v.5** | **PRO-CTCAE Items With Attributes** |
|---|---|
| Fatigue | Fatigue (severity, interference) |
| Pain | Pain (frequency, severity, interference) |
| Abdominal Pain | Abdominal Pain (frequency, severity, interference) |
| Breast pain; Gynecomastia | Breast swelling and tenderness (severity) |
| Hot flashes | Hot flashes (frequency, severity) |
| Concentration impairment | Concentration (severity, interference) |
| Memory impairment | Memory (severity, interference) |
| Nausea | Nausea (frequency, severity) |
| Palpitations | Pounding or racing heartbeat (frequency, severity) |
| Diarrhea | Diarrhea (frequency) |
| Fecal incontinence | Fecal incontinence (frequency, interference) |
| Constipation | Constipation (severity) |
| Headache | Headache (frequency, severity, interference) |
| Dysgeusia | Taste changes (severity) |
| Anorexia | Decreased appetite (severity, interference) |
| Rash maculo-papular; Refer to Skin and subcutaneous tissue disorders for clinically accurate CTCAE term | Rash (presence/absence/amount) |
| Pruritus | Itching (severity) |
| Urinary tract pain | Painful urination (severity) |
| Urinary urgency | Urinary urgency (frequency, interference) |
| Urinary frequency | Urinary frequency (presence/absence/amount, interference) |
| Urinary incontinence | Urinary incontinence (frequency, interference) |
| Erectile dysfunction | Achieve and maintain erection (severity) |
| Ejaculation disorder | Ejaculation (frequency) |
| Libido decreased | Decreased libido (severity) |
| Delayed orgasm | Delayed orgasm (presence/absence/amount) |
| Anorgasmia | Unable to have orgasm (presence/absence/amount) |

## 7.3 Serious Adverse Events (SAEs)

Serious Adverse Events as defined below will be reported via the SAE report form.

Definition of an SAE: Any adverse drug event (experience) occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization ≥24 hours;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- Other serious/important medical events;
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

## 7.4 Serious Adverse Event (SAE) Reporting Requirements (22-AUG-2019)

An SAE that occurs during any part of protocol treatment and 30 days after end of treatment, whether or not related to protocol treatment, must be reported by the investigator via the RTOG SAE Report Form in RAVE per the reporting table below. In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions also must be reported.

The SAE report should comprise a full written summary, detailing relevant aspects of the SAE in question. The SAE summary also must include the investigator's assessment of relatedness to specific protocol treatment. Amend the SAE report with follow-up information, when it becomes available. In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to RTOG Operations Office by phone, 215-574-3191. An electronic report must be submitted immediately upon re-establish of the Internet connection.

SAEs that occur during the follow-up period beginning 30 days after end of treatment and are considered by the investigator to be possibly, probably, or definitely related to protocol treatment must be reported expeditiously via the SAE Report Form.

**For Arm 2, all SAEs must be reported in RAVE within 24 hours of awareness. RTOG will complete a preliminary review of the SAE details and will contact the site with queries, as applicable. RTOG will report the SAE to Astellas within 24 hours or 1 business day of notification of the event. RTOG will report to the FDA per 21 CFR 312. Note: The individual completing the SAE**

**Report Form should remain vigilant for RTOG's review and be prepared to respond expeditiously in order to ensure regulatory reporting within FDA-mandated timeframes.**

***For Canadian Sites ONLY:***

During a clinical trial the sponsor is required to inform Health Canada, in an expedited manner, of any serious unexpected adverse drug reaction, in respect of the drug that has occurred inside or outside Canada [C.05.014]:

a) Where it is neither fatal nor life-threatening, within 15 days after becoming aware of the information;

b) Where it is fatal or life-threatening, within 7 days after becoming aware of the information. Within 8 days after having initially informed Health Canada of the fatal or life-threatening ADR, submit as complete a report as possible. Follow-up reports of fatal or life-threatening reactions must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar drugs.

Arm 2 Expedited Reporting Requirements for Serious Adverse Events
Report all adverse events that meet seriousness criteria within 24 hours of awareness.

In addition, the following adverse events should be reported expeditiously within 24 hours regardless of grade or seriousness criteria met: Seizure or loss of consciousness, posterior reversible encephalopathy syndrome (symptoms include seizure, headache, confusion, reduced eyesight, blurred vision), and overdose.

The 24 hour report must include, at a minimum, CTCAE term and grade, reporter information, event description with available information, and attribution to all components of protocol treatment. All other report fields must be completed within 5 days. The report must be amended within 24 hours of receipt of any additional information.

SAEs that occur during the follow-up period beginning 30 days after end of treatment and are considered by the investigator to be possibly, probably, or definitely related to protocol treatment must be reported within 24 hours of awareness.

## ARM 1 Expedited Reporting Requirements: Any Phase Study Utilizing a Commercial Agent[1]

**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 to RTOG via the SAE Report Form within the timeframes detailed in the table below.

| Attribution | Grade 4 | | Grade 5 | |
|---|---|---|---|---|
| | Unexpected | Expected | Unexpected | Expected |
| Unrelated<br>Unlikely | | | 10 day | 10 day |
| Possible<br>Probable<br>Definite | 24-h/5 day | | 24-h/5 day | 24-h/5 day |

**Expedited AE reporting timelines are defined as:**

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via the SAE Report Form 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 protocol treatment and are related to protocol treatment require reporting as follows:

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

- Unexpected Grade 4 and all Grade 5 AEs

## 8. REGISTRATION AND STUDY ENTRY PROCEDURES

Each individual user must have an RTOG user name and password in order to access all protocol-specific documents and to register patients on the RTOG web site. To get a user name and password:

- The investigator and research staff must have completed Human Subjects Training
- The investigator and research staff must complete the Password Authorization Form on the RTOG website. https://www.rtog.org/AboutUs/RTOGPasswordApplication.aspx. RTOG Headquarters requires 3-4 days to process the requests and grant user access.

### 8.1 Regulatory and RT Credentialing Requirements for Patient Enrollment

Please refer to the RTOG Foundation 3506 Study Guide on the RTOG website www.rtog.org for: patient enrollment instructions, regulatory collection requirements, and RT credentialing requirements.

Access requirements for Medidata Rave and TRIAD Installation**:**
Medidata Rave and TRIAD installation is needed prior to patient enrollment. See the Data Management Plan of the Study Guide for installation instructions.

## 9.0 DRUG INFORMATION

### 9.1 Investigational Study Agent: Enzalutamide, IND Exempt **(20-MAY-2021)**

To supplement the toxicity information contained in this document, investigators must obtain the current version of the Enzalutamide (Astellas-MDV3100) Investigator Brochure for comprehensive pharmacologic and safety information. The IB can be found on the RTOG Foundation 3506 protocol page of the RTOG website, www.rtog.org

How supplied: Enzalutamide is provided as 40 mg capsules for oral administration. Enzalutamide will be provided in 30-day supply bottles of 124-capsules.

Appearance: The 40 mg enzalutamide capsules are white to off-white oblong soft gelatin imprinted in black ink with ENZ.

Classification: Androgen receptor inhibitor

Route of Administration: Take by mouth with or without food

Stability: Refer to the package label for expiration.

Storage and Handling: Enzalutamide will be shipped from McKesson at refrigerated temperatures (2 to 8°C). Upon receipt drug must be stored at room temperature 20° to 25°C (68° to 77°F), excursions permitted between 15 to 30°C (59 to 85°F). If a storage temperature excursion is identified, promptly return enzalutamide to controlled room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to

clinicalresearchservices@mckesson.com for determination of suitability. For more information, please follow the storage instructions provided in the package insert.

Enzalutamide should not be handled by persons other than the patient and his caregivers, and especially not by females who are or may become pregnant.

Drug Supply and Accountability: Pfizer will supply enzalutamide free of charge to subjects enrolled on study.

Adverse events
Please refer to the investigator brochure for enzalutamide for toxicity information and Section 7. In addition, the pharmacovigilance section of Health Canada has also noted the following risk information:

- very likely development of shortness of breath (21%) on enzalutamide and is rarely fatal
- risk of hyperglycemia
- rare incidence of severe cutaneous adverse reactions [including Stevens-Johnson syndrome (SJS), erythema multiforme, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP)].

The drug will be packaged and labeled by Pfizer and sent to a third-party vendor, under contract to RTOG Foundation, for distribution. Drug accountability records must be maintained at all sites according to good clinical practices.

**See the study-specific guide on the RTOG Foundation 3506 protocol page of the RTOG website, www.rtog.org , for details of drug shipment and destruction logistics.**

### 9.2 Commercial Agent: Bicalutamide

Please refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage. Please see Section 5 for administration instructions.

### 9.3 Commercial Agent: GnRH analog

Please refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage. Please see Section 5 for administration instructions.

## 10. PATHOLOGY/BIOSPECIMENS (16-MAR-2021)

### 10.1 Biospecimen Submission Tables (17-JUN-2021)

#### 10.1.1 Optional Decipher Prostate RP Testing

Patients must be offered the chance to participate in a data acquisition study from radical prostatectomy (RP) tissue that has been analyzed using the commercially available Prostate RP assay from Decipher Biosciences.

This assay is a standard of care genomic classifier that is indicated for men undergoing salvage radiotherapy following BCR that ensures after RP. This genomic classifier has been shown to be predictive of metastasis and prostate cancer mortality and is endorsed by the National Comprehensive Cancer Network guidelines.

RP tissue must be sent directly to Decipher Biosciences using a study specific requisition. For patients within the United States, the service will be considered standard of care and will be billed by the company through typical channels. For Canadian patients, the cost of the Decipher RP assay will be covered by the RTOG foundation. **Tissue should ONLY be sent to Decipher Biosciences.**

If a patient has already had the RP assay done, it does not need to be repeated, but the requisition form should be completed and noted that the test has already been completed so that the information is tagged for extraction at the conclusion of the study.

Gene expression data from the Decipher RP will be used to look at molecular classifiers including PAM50 to evaluate their utility in distinguishing molecular subtypes of prostate cancer with greater benefit from intensifier AR suppression via enzalutamide at the conclusion of the study.

**Optional Study: Decipher RP Analysis for Subtyping via the PAM50 and other classifiers**

To subtype prostate cancers into luminal versus basal subtypes via the PAM50 classifier, gene expression in prostate cancer specimens (from prostatectomy blocks) will be assessed using high-density oligonucleotide microarrays (Affymetrix Human Exon (HuEx) 1.0 ST GeneChips) in a CLIA-certified laboratory in collaboration with Decipher Biosciences.

Forms to include with tissue submission: 1) RTOG-3506 Study Specific Requisition Form and 2) redacted pathology report.

**Please note: If the patient has already had Decipher analysis of his tumor specimen then a copy of the original Decipher report and the forms listed above must be emailed to Decipher Biosciences** (RUO@decipherbio.com) for validation and for Decipher Biosciences to provide the Decipher score needed for researchers. Please be sure that the original Decipher report is redacted as only the Accession ID # is necessary along with the study/case number as an identifier. If result is validated by Decipher then the patient does not have to submit tissue to Decipher for analysis.

Decipher RUO Biospecimen Collection Kits can be requested from the Decipher Biosciences via an email to RUO@decipherbio.com.

For questions about FFPE specimen submission, contact:
Decipher Biosciences Laboratory
Department of Clinical Development
6925 Lusk Blvd, Suite 200 San Diego, California 92121
Email: RUO@decipherbio.com
Phone: 1-888-520-8718

| Specimen Type | Collection Time Points | Collection Information and Requirements/Instructions for Site | Shipping |
|---|---|---|---|

| | | | |
|---|---|---|---|
| FFPE Block and a representative H&E slide<br>OR<br>Unstained sections from a block. Either:<br>a) 6 unstained sections (five micron thickness) or<br>b) 5 unstained sections (five micron thickness) and 1 H&E slide | Pre-treatment | Using a Decipher Specimen collection Kit provide: H&E and FFPE Block or unstained slides (6 unstained slides or 5 unstained slides and 1 H&E slide) | Ship ambient or with cold pack in a specimen collection kit to Decipher Biosciences at above address. |

## 11. SPECIAL STUDIES (NON-TISSUE) (20-MAY-2021)

The Patient Reported outcomes (PROs) include the PROMIS Fatigue Scale and EQ-5D. The forms are available in English, French, and Spanish. Patients able to read and speak these languages will participate in this component of the study.

### 11.1 The PROMIS Fatigue Scale (7 items)

The PROMIS Fatigue Scale (7 items) was developed by the Patient-Reported Outcome Measurement Information System (PROMIS), part of the NIH Roadmap Initiative, focused on developing a publicly available resource of standardized, accurate, and efficient patient-reported outcome (PRO) measures of symptoms, distress, and functioning. Using item response theory and extensive testing and validation, the PROMIS investigators identified efficient, flexible, and precise measurement of common PRO domains [Cella 2010]. This process identified fatigue (defined as "an overwhelming, debilitating, and sustained sense of exhaustion that decreases one's ability to carry out daily activities") as a core domain of PROMIS.

A 7 item PROMIS-derived fatigue short-form (PROMIS-F SF 7a) survey was created with the purpose of measuring fatigue within cancer populations undergoing clinical trials [Garcia 2007]. First, to generally create a fatigue-related question bank, two content domains of fatigue, experience and impact, were identified by a panel of experts. An item pool of 54 fatigue experience and 58 fatigue impact items were developed. The psychometric properties of these items were evaluated in a sample of 450 individuals from the general US population using classical test theory indices, monotonicity, and scalability. From this item pool, to enhance the cancer relevance of the PROMIS-F SF 7a, domain experts selected the 10 best items in each domain based on statistical and conceptual considerations. These 20 items were presented to a panel of clinical cancer experts. Only one item was dropped because of redundancy. From the remaining 19 items, a preliminary fatigue short-form measure of 7 items was created using items selected for consistency in the response scale, broad coverage across the fatigue continuum (i.e., high to low), and good precision of measurement (discrimination function) [Garcia 2007]. The PROMIS-F SF 7a has been validated for diverse populations [Ameringer 2016].

PROMIS- SF 7a was chosen as the PRO instrument to assess differences in quality of life at 1 and 2 years rather than a prostate cancer-specific instrument such as the Expanded Prostate Index Composite (EPIC) because it is hypothesized that differences in quality of life will be concentrated in domains relevant to differences in

type of enhanced ADT (4 months of bicalutamide vs. 24 months of enzalutamide), since the prostate-directed local therapy is identical in both control and experimental arms of this study. Physician-reported early-onset fatigue occurred slightly more frequently in enzalutamide treated patients in a pooled analysis of four clinical trials [Chowdhury 2016]. Furthermore, dose-dependent fatigue was the most common grade 3 / 4 adverse event in initial trials of enzalutamide [Scher 2010]. Therefore, if there are differences in patient reported outcomes; fatigue is the most likely domain.

## 11.2 EQ-5D-5L

The EQ-5D-5L is a 6-item validated utility assessment instrument that takes less than 5 minutes to complete [Janssen 2013, Herdman 2011]. The first part consists of 5 items covering 5 dimensions including: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is graded on 5 levels: 1-no problems, 2-slight problems, 3-moderate problems, 4-severe problems, and 5-unable to perform/extreme problems. The sixth item is a visual analogue scale for overall health. The 5-item index score is transformed into a utility score between 0, "Worst health state," and 1, "Best health state."

## 11.3 Optional Online Completion of Patient-Reported QOL Assessments (02-DEC-2019)

Typically, QOL forms are filled out in hardcopy (paper). To provide a more convenient method of completing QOL assessments, RTOG Foundation is working with VisionTree Software, Inc., San Diego, CA. VisionTree offers patients on this study the option of completing their QOL forms online from any location that has a computer, mobile device or tablet with Internet access, including the patient's home, and provides reminders to patients to complete the assessments.

VisionTree Optimal Care (VTOC), a HIPAA-secure, user friendly, web-based software system (Gorgulho 2005; Gorgulho 2007; Pedroso 2006). The VTOC tool contains a web-based system for global patient and trial administration access, which allows improved compliance and accuracy of data collection, validation, and reporting. It is compliant with the Title 21, Code of Federal Regulations, Part 11 statistical process control system and provides a mobile solution for clinical trials. QOL data are collected with Microsoft Excel and PDF export of reports. VTOC also has mobile messaging and e-mail reminders. Surveys can be "pushed" to patients for completion at timed intervals (see http://www.visiontree.com for details). This technology allows patients on this study to fill out their QOL forms online from any location and to receive e-mail reminders to complete assessments. E-mail reminders also can be sent to research associates (RAs) at the appropriate institutions to remind them that a QOL time point window is about to close so that a patient can be contacted to fill out QOL information on time, before it becomes "missing data."

RTOG Foundation is offering VisionTree as an option for other studies, including this one. Patients preferring to complete hardcopy QOL assessments can do so. The QOL forms completed via VTOC are identical to the hardcopy forms; this technology does not add to or change the QOL assessments in this study.

For this trial, the baseline QOL forms must be completed in hardcopy (on paper) prior to registration. The PROMIS fatigue short form 7a, and EQ-5D-5L.To complete subsequent QOL forms online, patients will be asked for an e-mail address that they consent to use so that e-mail reminders may be sent to them. The patient's e-mail address also will be used for password-protected access to VTOC. Patients who are interested in participating but do not yet have an e-mail address can obtain one for free from a number of sources (e.g. Yahoo!, Hotmail, or AOL). Note: The site RA is responsible for setting up the patient's account on VTOC. The RA may do so by logging on the VTOC portal at the following link: https://rtog.optimalcare.com - medical team. RA login information will be provided by VTOC after the patient is randomized to the study. The patient's VTOC account must be set up within 14 days after randomization.

Patients will receive a login card (either printed or sent via e-mail) with which to log in using the secure, web-based VTOC portal. VTOC meets all HIPAA guidelines and is encrypted (via 128-bit SSL) for the security, privacy, and confidentiality of QOL information. It is similar to the secure login commonly used when performing online banking. The login card can then be kept and maintained by the patient.

Patients will be sent e-mail reminders to complete QOL forms. The patient's e-mail address only will be used by VisionTree for this purpose. The reminders will be created and placed into a study template that will be sent to patients at customized intervals (at the time points when QOL forms are due). The first reminder will be sent at the beginning of the "window" to complete a QOL form, with a second reminder halfway through the window period if the QOL forms are not yet completed at that time point. A maximum of 3 reminders will be sent for each of the PRO time points following the baseline QOL forms, which are completed in hardcopy.

After a patient has completed all forms in the VTOC portal, a dialogue box will appear that says "Thank you for completing your Quality of Life forms," and the patient will no longer receive any remaining notices for that time point. The site RA or study administrator will be informed through the VTOC "At-A-Glance" form management system when QOL forms have been completed.

## 12. MODALITY REVIEWS

### 12.1 Radiation Therapy Quality Assurance Reviews

The Radiation Oncology co-chair, Dr. Hiram Gay, MD, and his designee(s), will perform the RT Quality Assurance Review for cases enrolled and complete data has been received in TRIAD. The RT reviews will be ongoing and performed remotely. The final cases will be reviewed within 6 months after this study has reached the target accrual or as soon as complete data has been received in TRIAD for all cases enrolled, whichever occurs first. The scoring mechanism is: **Per Protocol, Variation Acceptable, and Unacceptable Deviation**.

### 12.2 Medical Oncology Modality Quality Assurance Reviews

The Medical Oncology Co-Chair, Edwin Posadas, M.D., will perform a Hormonal Therapy Assurance Review of all patients who receive or are to receive hormonal therapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of hormonal therapy treatment data. The scoring mechanism is: **1) Per Protocol, 2) Unacceptable Deviation, and 3) Not Evaluable**.

Dr. Posadas will perform a Quality Assurance Review after RTOG Headquarters has received complete data for the first 20 cases enrolled. Dr. Posadas will perform the next review after Headquarters has received complete data for the next 20 cases enrolled. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as Headquarters has received complete data for all cases enrolled, whichever occurs first.

## 13. DATA AND RECORDS

**This study will utilize Medidata Rave.**

### 13.1 Summary of Data Submission and Dosimetry Digital Data Submission

Please refer to the RTOG Foundation 3506 Study Guide on the RTOG website www.rtog.org.

## 14. STATISTICAL CONSIDERATIONS

### 14.1 Study Design (02-DEC-2019)

This is a randomized phase II trial in which patients will be stratified by number of aggressive features (1 vs. >1) and then randomized 1:1 to receive standard ADT or to enhanced ADT using permuted block randomization [Zelen 1974]. Aggressive features, fully defined in Section 3.1.5, consist of a Gleason score of 8-10, SVI, pN1, PEPP and PSA ≥0.7 ng/mL.

The target accrual is 242 patients. All analyses will be conducted on an intent-to-treat basis of all at-risk patients (regardless of eligibility). The primary endpoint analysis will take place once 99 PFS events have occurred.

## 14.2 Study Endpoints

**14.2.1** Primary endpoint: Progression-free survival

**14.2.2** Secondary endpoints:

- Biochemical failure
- Biochemical failure using an alternative definition
- Development of hormone-refractory disease
- Distant metastasis
- Cause-specific mortality
- Overall survival
- Acute and late toxicity, as measured by CTCAE v5 and PRO-CTCAE
- Quality of life, as measured by EQ-5D-5L
- Fatigue, as measured by PROMIS-F SF 7a

## 14.3 Primary Objectives Study Design (12-JUL-2022)

**14.3.1** Primary Hypothesis and Endpoints

The primary hypothesis is to determine whether, in men with post-prostatectomy PSA recurrences with aggressive disease features, salvage radiotherapy (SRT) with enhanced androgen deprivation therapy (ADT), consisting of enzalutamide (MDV3100) and a GnRH analog, will improve progression-free survival (PFS) compared to SRT with standard GnRH analog-based ADT.

**14.3.2** How Primary Endpoints Will Be Analyzed

Progression is defined as first occurrence of biochemical failure, clinical failure, or initiation of new unplanned anticancer treatment. Biochemical failure is defined as first post-RT detectable PSA (PSA ≥ 0.05). Clinical failure is defined as either a local, regional, or distant failure as defined in Section 4. PFS is defined as the time from randomization to the date of progression, death from any cause, or last known follow-up time. The PFS function will be estimated using the Kaplan-Meier method [Kaplan 1958]. The null and alternative hypotheses are:

$$H_0: HR \geq 1.0 \; vs. \; H_A: HR < 1.00$$

A stratified log rank test with one-sided significance level of 0.1 will be used to test this hypothesis [Mantel 1966]. The Cox proportional hazards regression model will be used to compare treatment differences, computing both unadjusted and covariate-adjusted hazard ratios (HRs) with respective 95% confidence interval [Cox 1972]. Typical covariates, such as treatment arm and stratification variables will be adjusted for in the multiple regression analysis.

**14.3.3** Sample Size and Power Calculations:

The standard ADT arm is expected to have 41.7% of patients progression-free at 5 years which corresponds to a hazard rate of 0.175. It is hypothesized that 56.6% of patients will be progression-free at 5 years on the enhanced ADT arm (hazard rate of 0.114), providing a hazard ratio of 0.65 (treatment/control). Assuming an accrual period of 2 years at a rate of 115 patients per year with 3 years of additional follow-up and one interim analysis, a one-sided log-rank test with alpha=0.10 would require 99 events for

80% statistical power. In order to obtain 99 events, 229 patients would need to be enrolled. Adjusting for 5% lost to follow-up, the target accrual would be 242 patients.

Updated Sample Size Calculation
Due to the change in eligibility of making PSA ≥ 0.7 ng/mL an aggressive feature (as opposed to being required in addition to at least 1 aggressive feature), the 5 year PFS rate on the standard ADT arm is expected to be higher, 48.0% (hazard rate of 0.147). Lowering the hazard ratio to 0.63 (treatment/control) results in a hypothesized 5 year PFS rate of 64.4% on the enhanced ADT arm (hazard rate of 0.092). Assuming an accrual period of 2 years at a rate of 115 patients per year with 3 years of additional follow-up and one interim analysis, a one-sided log-rank test with alpha=0.10 would require 86 events from 230 patients for 80% statistical power. Adjusting for 5% lost to follow-up, the target accrual is 242 patients.

Updated Sample Size Calculation
Due to the change in the PFS definition, the 3-year PFS rate on the standard ADT arm is expected to be 24.0% (hazard rate of 0.476). Assuming a hazard ratio of 0.65 (treatment/control) results in a hypothesized 3-year PFS rate of 39.5% on the enhanced ADT arm (hazard rate of 0.309). Assuming an accrual period of 2 years at a rate of 51.7 patients/year (based on actual accrual) and a second period of 82.6 patients/year, with just over 1 year of additional follow-up, one interim analysis, and 5% drop-out up to 5 years, a one-sided log-rank test with alpha=0.10 would require 101 events from 170 patients for 80% statistical power. Thus the target accrual is 170 patients.

## 14.4 Study Monitoring of Primary Objectives (12-JUL-2022)

(Interim Analysis)
Interim Analysis for the DMC
The RTOG Foundation Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity. The DMC also will review the study on an "as needed" basis.

There is one interim analysis for both efficacy and futility that will occur once 75% of the events (76) have occurred. For the futility analysis, if the observed HR is ≥1.0, the study statistician and DMC will consider early release of these findings, with the conclusion that the experimental arm may not provide acceptable disease control. If the observed hazard ratio is < 1.0, then the statistician will recommend that the trial continue as planned.

The interim efficacy analysis will follow an O'Brien and Fleming boundary as outlined in the table below. If the boundary is crossed, the study statistician and DMC will consider early release of these findings, with the conclusion that the experimental arm provides acceptable disease control. If the boundary is not crossed, then the statistician will recommend that the trial continue as planned.

| Look | Information Fraction | Events | Cumulative α spent | Boundaries (Z-scale) |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 1 | 0.75 | 76 | 0.058 | -1.572 |
| 2 | 1.0 | 101 | 0.100 | -1.38 |

## 14.5 Accrual/Study Duration Considerations (12-JUL-2022)

Based on patient accrual in previous RTOG randomized prostate studies, it is expected that there will be no enrollment during the initial 6 months while institutions are obtaining IRB approval. An average uniform accrual rate of 115 patients per year is projected over 2 years, with an additional 3 years of follow-up required. The total duration of the study is expected to be 5.5 years from the time the study opens to the time of the final analysis. The interim analysis is projected to occur 39 months from activation.

For the first 26 months, the study accrued at a rate of 51.7 patients/year. Assuming a higher accrual of 82.6 patients/year, 170 patients will be met in just under 3 years from study activation. The number of events is projected to be reached just over a year later.

## 14.6 Secondary Endpoints (12-JUL-2022)

### 14.6.1 Secondary Hypotheses and Endpoints:

- Biochemical failure
- Biochemical failure as determined by an alternate definition
- Development of hormone-refractory disease
- Distant metastasis
- Cause-specific mortality
- Overall survival
- Acute and late toxicity, as measured by CTCAE v5 and PRO-CTCAE
- Fatigue, as measured by PROMIS-F SF 7a
- Quality of life as measured by the EQ-5D-5L

### 14.6.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

Efficacy endpoints

Overall survival (OS) is defined as the time from randomization to the date of death or last known follow-up time. OS will be estimated by the Kaplan-Meier method [Kaplan 1958] and compared with the log-rank test [Mantel 1966]. Two definitions of biochemical will be assessed. The definition used in the primary endpoint of PFS (noted as PBF), PSA $\geq$ 0.05 or initiation of salvage hormones, and an alternative definition (ABF), post-RT PSA $\geq$ 0.1 ng/mL or initiation of salvage hormones. Biochemical failure will be measured from the date of randomization to the date of failure or last known PSA assessment. Hormone-refractory disease (HRD) will be measured from the date of randomization to the midway date between the last non-rising PSA and the first-rise PSA out of three consecutive rises in PSA during treatment with salvage androgen deprivation. Cause-specific mortality (CSM) will be measured from the date of randomization to the date of death due to prostate cancer. Distant metastasis (DM) will be measured from the date of randomization to the date of documented distant metastasis/clinical and/or radiographic appearance of disseminated disease. Competing-risk endpoints BF, ABF, HRD, CSM, and DM will be estimated by the cumulative

incidence method [Gray 1988]. Cox regression [Cox 1972] will be used to obtain HRs for OS. Fine and Gray's regression [Fine 1999] also will be used for the endpoints with competing risks. Both unadjusted and adjusted HRs and the respective 95% confidence interval will be computed.

Adverse events

Adverse events (AEs) will be scored according to the CTCAE v5. Counts of all AEs by grade will be provided by treatment arm. Counts and frequencies will be provided for the worst grade AE experienced by the patient by treatment arm and within the subset of AEs related to treatment.

An acute AE will be defined as the first occurrence of worst severity of the AE occurring less than or equal to 30 days after the completion of treatment. Logistic regression [Agresti 1990], both univariate and multivariate, will be used to model the distribution of acute AEs. Both unadjusted and adjusted odds ratios and the respective 95% confidence interval will be computed and tested. Late grade 3+ AEs will be defined as grade 3+ AEs occurring more than 30 days after the completion of RT. The time to late grade 3+ AE will be measured from randomization to the time of the worst late grade 3+ AE. If no such late adverse event is observed at the time of the analysis, the patient will be censored at the time of the analysis. Death without a late AE will be considered as the competing risk and the distribution of time to late grade 3+ AEs will be estimated using the cumulative incidence approach [Gray 1988]. A Fine and Gray's regression model [Fine 1999] will be used to compare the treatment differences of time to late AE with and without adjusting for other covariates. Both unadjusted and adjusted hazard ratios and the respective 95% confidence interval will be computed. At least the treatment arm, the stratification variables, and, as appropriate, age, and race will be adjusted for in the analysis.

Adverse events will also be assessed using PRO-CTCAE items. The specific symptoms to be evaluated for this study are listed in Section 7.2.2. Assessments will be collected before the start of radiotherapy treatment and as specified in the Section 4 assessment tables. For each symptom and each domain (i.e., frequency, severity, and interference), counts and frequencies will be provided for the worst score experienced by the patient by treatment arm. The proportion of patients with scores ≥1 and ≥3 will be compared between groups using a chi-square test, or Fisher's exact test if cell frequencies are < 5. Analysis of changes in patient reported outcomes over time will analyzed by fitting GEE models using a logit link (dichotomizing the symptom scores as 0 vs. ≥1 and 0-2 vs. 3-4) with time of assessment, treatment arm, and treatment-by-time interaction terms in the model.

Fatigue

Fatigue will be measured by the 7-question PROMIS-F SF 7a (Patient-Reported Outcome Measurement Information System fatigue short form) questionnaire. It is collected at baseline and end of RT, and 1 and 2 years post RT. Scores are translated into a T score for each participant, rescaling the raw score into a standardized score with a mean of 50 and standard deviation of 10. A higher T score indicates worse fatigue. Change scores

from baseline to each follow-up time point will be presented by treatment arm and between arm differences compared using a t-test. Whether patients experience moderate fatigue (T score 55-74) or severe fatigue (>=75) [Cella 2014] is also of interest and will be compared between treatment arms using a chi-square test at each follow-up time point.

A generalized linear mixed effects model will be used to assess the dichotomous variable, moderate to severe fatigue, over time, adjusting for baseline fatigue, treatment arm, components of the stratification factor (PSA, Gleason score, SVI, and PEPP), age, race, and other covariates as applicable.

Prior to performing analyses, an evaluation of the amount, reasons and patterns of missing data will be performed, using the well-known categories of missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR) [Fairclough 2010, Verbeke 2000]. If ≥15% of the data is missing at any time point, patient characteristics will be compared between patients with completed assessments and those with missing assessments. If any are found to differ significantly, they will be included in the mixed effects model, which assumes that the data is MAR. If the missingness is determined to be non-ignorable, other methods may be applied. Specifically, a joint model that allows a shared parameter between the repeated measurements and time to death or drop out can be used if considered MNAR due to the high number of patient deaths or dropouts [Rizopoulos 2012]. Other options for MNAR data are pattern mixture and selection models [Fairclough 2010, Little 1995]. Sensitivity analyses will be performed to compare the results of different analytic strategies [Fairclough 1998].

Health-Related Quality of Life

Global HQOL will be measured by EuroQol's EQ-5D-5L. It is collected at baseline and end of RT, and 1 and 2 years post RT. Changes scores from baseline to each follow-up time point will be presented by treatment arm and between arm differences compared using a t-test.

An exploratory longitudinal analysis incorporating all of the follow-up time points will be conducted separately for the index and VAS scores using longitudinal linear modeling methods, adjusting for baseline score, treatment arm, components of the stratification factor (PSA, Gleason score, SVI, and PEPP), age, race, and other covariates as applicable. Missing data will be assessed as described above for fatigue.

## 14.7 EXPLORATORY ENDPOINTS (16-MAR-2021)

Both PAM50 (Luminal A or Basal vs. Luminal B) and the 22-marker genomic classifier (GC) Decipher, a continuous variable ranging in score from 0 to 1, are of interest. The GC score will also be analyzed as a categorical variable (<0.4, 0,4-0.6, >0.6) since both the continuous and categorical variables have been found to be associated with incidence of metastasis in prostate cancer [Karnes 2013]. The Cox proportional hazards regression model will be used to determine associations between these variables and OS and PFS and cause-specific Cox models will be used for BF, ABF, HRD, CSM, and DM [Cox 1972] while adjusting for typical covariates, such as treatment arm and stratification

variables. The interaction of treatment arm with PAM50 and the GC score (both categorical and continuous) will also be considered in the model to assess predictive ability of these markers.

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## APPENDIX A. ADDITIONAL ASSESSMENTS FOR CANADIAN SITES (22-AUG-2019)

The use of potent AR signaling inhibitors such as enzalutamide has been associated with adverse events including cardiac and endocrine events that are important for optimization of care. Use of such agents should be conducted following standards of good medical practice as outlined in the NCCN guidelines (https://www.nccn.org/professionals/physician_gls/pdf/prostate_blocks.pdf). We would recommend consultation and collaboration with a medical oncologist experienced with the administration of enzalutamide to address the known risks to heart and bone health. Given these concerns and by working in concert with Health Canada, we had included additional monitoring guidance that will be required of Canadian sites as listed below.

### I. Additions to Section 4, Assessments: Pre-Treatment

- In order to identify patients at risk for cardiac adverse events including QTc prolongation, assess electrolytes and perform an ECG.
- Screening recommendation for osteoporosis should follow the guidelines established by the National Osteoporosis Foundation (www.nof.org) (see section III below).

### II. Additions to Section 4, Assessments: On Treatment

- In order to identify patients at risk for cardiac adverse events including QTc prolongation, assess electrolytes and an ECG every cycle (1 cycle=90 days) for the first 36 weeks of exposure to drug
- Evaluate for bone health support (see section III below).

### III. MANAGEMENT RECOMMENDATIONS

A. Electrolytes

Electrolyte abnormalities should be corrected and monitored during the course of enzalutamide therapy within limits consistent with good medical practice.

In particular, we recommend maintenance of a K+ and Mg2+ within institutionally established normal ranges for the duration of trial therapy.

B. QT prolongation

Patients on agents associated with a risk of a QT prolongation should be advised of the risk of serious ventricular dysthymia and advised to identify safer agents when available.

Patients with QTc intervals in excess of 440 ms should have regular monitoring by ECG (e.g. every 3 months or more frequently at the discretion of the treatment team) while receiving enzalutamide and should be considered for consultation with a cardiologist.

C. Osteoporosis

Screening recommendation for osteoporosis follow the guidelines established by the National Osteoporosis Foundation (www.nof.org)

The following recommendations are part of a thorough evaluation of bone health; refer to the NOF and the NCCN guidelines (www.nccn.org) for detailed recommendations:

- Bone mineral density should be assessed by dual-energy X-ray absorptiometry (DXA) as clinically indicated.
- Calcium (1000-1200 mg daily from food and supplements) and vitamin D3 (400–1000 IU daily) should be initiated upon start of therapy.
- Additional treatment for men should be started for men with a 10-y probability of hip fracture ≥3% or a 10-y probability of a major osteoporosis-related fracture ≥20%. Fracture risk can be assessed using FRAX®, the algorithm recently released by WHO.
- Treatment options to increase bone density, a surrogate for fracture risk in men without metastases, include denosumab (60 mg SQ every 6 mo), zoledronic acid (5 mg IV annually), and alendronate (70 mg PO weekly). Treatment should be initiated in consultation with an internist or medical oncologist.

**PHARMACOLOGIC AGENTS ASSOCIATED WITH QT PROLONGATION**
PLEASE REFER TO THE FOLLOWING WEBSITE AS A REFERENCE:
HTTPS://WWW.CREDIBLEMEDS.ORG/