CLINICAL PROTOCOL	
Title:	**RAD 1805/UAB 1917: Phase II Clinical Trial of Abemaciclib in Combination with Androgen Deprivation Therapy for Locally Advanced Prostate Cancer**
Protocol Number:	RAD 1805/UAB 1917 (I3Y-US-I001)
Study Sponsor:	UAB Department of Radiation Oncology
Study Support:	Eli Lilly and Company
Principal Investigator:	Eddy S. Yang, MD, PhD
Co-Investigators:	Mollie DeShazo, MD Lakshminarayanan Nandagopal, MD John Fiveash, MD Robert Kim, MD Rojymon Jacob, MD Michael Dobelbower, MD Andrew McDonald, MD Soroush-Rais Bahrami, MD Jeffrey Nix, MD
Biostatistician	Sejong Bae, PhD
Signature & Date:	Signed:  Print: EDDY YANG Dated: 5/21/21

CLINICAL PROTOCOL	
Version Date:	Amendment # 4 13 April 2021 Amendment # 3 12 March 2021 Amendment # 2: 13 February 2020 Amendment # 1: 6 February 2020 Protocol Update: 6 September 2019 Original Protocol: 10 December 2017

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone number
Medical Monitor	Sharon Spencer, MD	University of Alabama at Birmingham (UAB) Department of Radiation Oncology 1700 6th Avenue South, Suite 2232F Birmingham, Alabama 35249 Phone#: (205) 934-2762
Secondary Medical Monitor		

1. SYNOPSIS

Name of Company: Eli Lilly Pharma.	
Name of Investigational Product: Abemaciclib	
Name of Active Ingredient: Abemaciclib	
Title of Study: **Phase II Clinical Trial of Abemaciclib in Combination with Androgen Deprivation Therapy for Locally Advanced Prostate Cancer**	
Study center(s): This study will be performed at University of Alabama at Birmingham (UAB).	
Principal Investigator: Dr. Eddy S. Yang, MD, PhD	
Studied period: Date first patient enrolled: April 2020 Estimated date endpoint obtained: April 2024 Estimated date last patient completed: April 2023 Total number of estimated patients: 30 Estimated duration of treatment per patient: Until toxicity, progression, withdrawal or maximum of 24 months of Androgen Deprivation Therapy (ADT).	**Phase of Development:** 2

Rationale:

Recently, CDK4/6 inhibition in combination with the anti-estrogen fulvestrant was found in a randomized phase III study to prolong the progression free survival of patients with advanced hormone receptor positive, HER2 negative breast cancer refractory to previous endocrine therapy compared to fulvestrant alone, irrespective of the menopausal status of patients enrolled in the study[1]. A prolonged progression free survival was also found in a randomized phase II study in combination with letrozole in the front-line setting compared to letrozole alone[2]. The basis of this synergy involves the dependence of estrogen receptor positive breast cancers to CDK4/6 for growth and proliferation. Additionally, activation of growth factor receptor signaling is a hallmark for endocrine therapy resistance.

A similar hormone-driven cancer akin to breast cancers is prostate cancer. These tumors are driven by androgen receptor signaling, and CDK4/6 has also been found to be a bona fide target preclinically for advanced prostate cancer cell models[3]. Moreover, CDK4/6 inhibition can act as a radiation sensitizer through its effects on the DNA damage response and interactions with cell cycle pathway proteins[4,5]. For example, it has been found that expression of DNA repair proteins can be regulated

by E2F, a transcription factor necessary for the G1 to S phase transition[6]. Also, cyclin D1 has been found to exert a direct role on dna repair[7-9]. Lastly, CDK4/6 inhibition has been found to modulate the DNA damage response[10]. These data support the use of CDK4/6 inhibitors as a modulator of DNA damage to enhance sensitivity to radiation.

Given the role of CDK4/6 in tumor resistance to endocrine therapy, in activation of the DNA damage response, and in promoting radiation resistance, we hypothesize that the targeting of CDK4/6 with abemaciclib will enhance the cytotoxicity in combination with blockade of the androgen receptor pathway.

Objectives:

Primary:

- To assess clinical response rates using
  - Proportion of patients with PSA nadir of ≤ 0.5 ng/ml on treatment

Secondary:

- Proportion of patients with PSA declines prior to radiotherapy
- Time to PSA failure
- To study the tolerability and feasibility of combining abemaciclib with androgen deprivation therapy (ADT) for localized high-risk or locally advanced prostate cancer.

Exploratory:

- MRI-US fusion imaging pre-treatment and at 6 months post RT with comparison with historical controls receiving RT + ADT
- Baseline (mandatory) and 6 months (optional) post RT tumor tissue profiling (MRI-US fusion guided) to identify association of molecular profile with PSA decline at 1 year
- Baseline, pre-radiotherapy, and 6 months post-RT blood collection and profiling for molecular analysis

Methodology:

Abemaciclib at 150 mg PO BID, ADT by administering LHRH analogues (goserelin, leuprolide, etc), and radiation therapy in conjunction with ADT

Overall design:

A single institution (UAB) phase II trial is proposed to evaluate the clinical and radiologic response as well as safety and tolerability of abemaciclib in combination with ADT neoadjuvantly and adjuvantly for patients with high-risk localized or locally advanced prostate cancer who will receive

definitive RT+ADT. Simon's optimal two-stage design (Simon, 1989) will be used for conducting the trial. The null hypothesis is that the proportion of patients with PSA <0.5 without any treatment is 5%, and the alternative hypothesis is that the proportion of patient with PSA <0.5 at 6 weeks into treatment is 30% or higher. The trial is carried out in two stages. In stage I, a total number of 5 patients is accrued. If there are 0 response (PSA< 0.5) among these 5 patients, the study will be early stopped. Otherwise, additional 18 patients will be accrued in stage II, resulting in a total number sample size of 23. If there are 4 or more responses (PSA< 0.5) among these 23 patients, we reject the null hypothesis and claim that the treatment is promising. The design controls the type I error rate at one-sided 0.025 and yields the power of 80%. If we reject the null hypothesis, seven additional patients will be enrolled to explore the association between biomarkers and clinical activities.
Patients receive ADT x 2 years and will start 3 months before RT. Abemaciclib will start with initiation of ADT and pause 2 weeks prior to start of RT. Abemaciclib will resume with the first ADT administration post-radiation, which typically is at 1 month post radiation therapy. Abemaciclib and ADT will continue for a total ADT period of 24 months. Patients will have laboratory evaluation every 2 weeks for the first 2 months and monthly thereafter for the next 2 months. Patients are also seen and evaluated every 4 weeks with laboratory evaluation. Labs may be drawn at outside laboratories at the PI's discretion. For toxicity or adverse event, patients will undergo labs, physical examination and grades of toxicities will be determined using NCI CTCAE version 4.03. Disease response and biochemical failure will be assessed by PSA prior to the start of radiation and every 3 months following the end of radiotherapy and by the investigator (physical exam). The determination of disease progression for the study requires a confirmation of 3 consecutive rises of PSA 3 months apart in the setting of testosterone recovery. Patients will be withdrawn from study for following toxicities,

Toxicity Category	**Drug-Related Toxicity/Grade**
Hematologic	Grade 4 neutropenia for ≥5 days
	Febrile neutropenia: ANC < 1000/mm^3 with a single temperature of >38.3ºC (101 ºF) or a sustained temperature of ≥ 38 ºC (100.4 ºF) for more than one hour.
	Neutropenic infection: Grade ≥3 neutropenia with Grade ≥3 infection
	Grade ≥4 Anemia
	Grade ≥4 thrombocytopenia or Grade ≥3 thrombocytopenia with Grade ≥3 hemorrhage
Non-hematologic	Grade 2 (>3.0 x ULN) ALT/AST with total bilirubin >2 x ULN, in the absence of cholestasis Grade 3 or 4 non-hematologic toxicity with the following exceptions: • Asymptomatic electrolyte abnormality that resolve within 48 hours.

	• Grade 3 headache lasting <48 hours

Number of Patients (planned):

30 patients with localized or locally advanced prostate cancer will be enrolled in the study.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

1. Histologically confirmed (core biopsy proven) adenocarcinoma of prostate, localized high-risk or locally advanced.
2. One of the below:
   • Gleason 7-8, any T-stage, and PSA > 20,
   • Gleason 8, ≥ T2, any PSA,
   • Gleason 9-10, any T-stage, any PSA
   • T3, any Gleason, any PSA
   • Positive pelvic lymph nodes are permitted.
3. Available biopsy of primary tumor or resected tumor specimen with adequate samples.
4. Prior treatment with systemic anti-cancer agents is not allowed.
5. ECOG PS = 0 or 1
6. Must have at least 1 target lesion
7. Life expectancy > 6 months
8. Adequate hematologic and end-organ function
   - ANC ≥ 1500/mm^3
   - Platelet count ≥ 100,000/mm^3
   - Hb ≥ 8g/dl
   - Creatinine ≤ ULN or Creatinine Clearance (CrCl) ≥ 60 ml/min
   - Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert syndrome, who can have total Bilirubin < 2.0 x ULN and direct bilirubin within normal limits are permitted)
   - AST and ALT ≤ 3.0 x ULN
9. Agreement to remain abstinent or use appropriate contraception.
10. Willingness and ability to consent for self to participate in study.
11. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Exclusion Criteria:

1. Prior treatment with CDK 4/6 inhibitor.
2. Prior treatment with systemic agents or radiation treatment for the primary cancer.

3. Major surgical procedure or significant traumatic injury within 4 weeks prior to study treatment, and must have fully recovered from any such procedure.
4. Personal history of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest.
5. Angina, myocardial infarction (MI), symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack TIA), arterial embolism, pulmonary embolism, percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass grafting (CABG) within 6 months prior to study treatment.
6. Known active viral or non-viral hepatitis or cirrhosis.
7. Any active infection requiring systemic treatment, positive tests for Hepatitis B surface antigen or Hepatitis C ribonucleic acid (RNA).
8. Known history of AIDS (acquired immunodeficiency syndrome)-defining illness.
9. Patients must be surgically sterile or must agree to use effective contraception during the study treatment (including temporary breaks from treatment), and for at least 180 days after stopping last dose of Abemaciclib The definition of effective contraception is provided in Section 2.6.1 of this protocol.
10. Other severe and/or uncontrolled acute or chronic medical or psychiatric condition or laboratory abnormality that, in the judgement of the investigator, may increase the risk associated with study participation or may interfere with the interpretation of study results and would make the patient inappropriate for this study (for example, interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, severe renal impairment [e.g. estimated creatinine clearance <30ml/min], history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea).
11. Secondary malignancy requiring active treatment. Past history of malignancy other than prostate cancer treated with curative intent and not requiring additional treatment may be eligible after discussion with PI.
12. Patients with active autoimmune disease and history of inflammatory bowel disease. Brachytherapy boost will not be permitted.

Abemaciclib Investigational Product Dose and Administration:

All patients will receive 150 mg Abemaciclib PO BID for 28 days. Patients will receive treatment with Abemaciclib until there is (are) toxicity(ies) or disease progression on treatment or withdrawal from study for any reason. All patients will receive ADT using LHRH analogues every 3 months along with Abemaciclib. There will be no intra patient dose escalation in dosing of Abemaciclib. Patients will take Abemaciclib in clinic on Day 1 of each cycle. They can take the rest of the pills at home. Radiation Therapy will be scheduled at 3 months after C1D1 (Abemaciclib and ADT). Abemaciclib will be stopped 2 weeks before Radiation Therapy and resumed with first dose of ADT after Radiation therapy is completed (usually 1 month after completion of RT). Abemaciclib will continue along with ADT for 24 months (+/- 3 days).

ADT Dose and Administration:

ADT using LHRH analogues will be administered SC beginning on C1D1 and continue during radiation and after radiation for a total of 24 months (+/-3 days) in the absence of toxicity. Dose modification of the ADT is not allowed.

Duration of Treatment:

Patients are eligible for abemaciclib treatment until unacceptable toxicity, or withdrawal of consent, or progression of disease on treatment or maximum of 24 months of ADT on the study. A patient should be withdrawn from study treatment if, in the opinion of the Investigator, it is medically necessary, or if it is the wish of the patient. In addition, patients will be withdrawn from treatment in the case of:

1. A need for surgery, radiation, or for other anticancer therapy not permitted by this protocol
2. Lost to follow-up or noncompliant with the protocol
3. Any Abemaciclib dose delay > 7 days during the first cycle

Parameters to be Assessed:

Safety:

Safety assessments will include physical examinations, vital signs, ECOG performance status, laboratory tests (complete blood counts [CBC] and serum chemistry), 12-lead electrocardiograms (ECGs), and additional studies as may be clinically indicated.

Exploratory Biomarkers:

Baseline archived tumor samples will be analyzed for mutations via the Strata Oncology platform (Oncomine), which includes analysis of genetic alteration of the CDK4/6 pathway. If sufficient sample is available, Nanostring analysis with the PanCancer pathways panel will be performed on pre-treatment and 6 month post treatment biopsy samples. Additionally, blood will be collected at baseline, 1 month, and q 3 month and analyzed for ctDNA. These will be used to correlate molecular profiling with responses.

Efficacy:

PSA values will be obtained to assess response and progression.

TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADCC	Antibody-dependent T-cell-mediated cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
AFP	Alpha fetoprotein

AIDS	Acquired immune deficiency syndrome
ALK	Activin receptor-like kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APA	Anti-product antibody
AST	Aspartate aminotransferase
BP	Blood pressure
CABG	Coronary Artery Bypass Graft
CBC	Complete blood count
CD	Cluster of differentiation antigen
iCR	Immune Complete response
CRF	Case report form
iCPD	Immune Confirmed progressive disease
CT	Computed tomography
CTA	Clinical Trials Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CxDx	Cycle x Day x
DEHP	Diethylhexyl-phthalate
dL	Deciliter
EBUS	Endoscopic Bronchoscopic Ultrasound
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
EGD	Esophagogastroduodenoscopy
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay

EOS	End of study
EOT	End of treatment
FDA	Food and Drug Administration
Fe	Iron studies
FFPE	Formalin fixed, paraffin-embedded
g	Gram
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRA	Health Regulatory Authority
IB	Investigational Brochure
ICH	International Council on Harmonization
IEC	Independent ethics committee
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IM	Intramuscular
INR	International normalized ratio
IRB	Institutional review board
IUD	Intra-uterine device
IV	Intravenous
kDa	KiloDalton
kg	Kilogram
L	Liter
µL	Microliter
mg	Milligram
mL	Milliliter
MDSC	Myeloid derived suppressor cell

MedDRA	Medical Dictionary for Regulatory Activities
min	Minute
mm	Millimeter
mm Hg	Millimeters of mercury
MRI	Magnetic resonance imaging
ms	Millisecond
MTD	Maximum tolerated dose
NCI	National Cancer Institute
ng	Nanogram
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PET	Positron emission tomography
PFS	Progression-free survival
PlGF	Placental growth factor
PD-1	Programmed death receptor 1
PD-L1,PD-L2	Programmed death receptor ligands
PK	Pharmacokinetic
pM	Picomolar
PR	Partial response
PT	Preferred Term for adverse event in MedDRA
PTCA	Percutaneous transluminal coronary angioplasty
PUD	Peptic ulcer disease
QA	Quality assurance
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
ROS-1	Proto-oncogene tyrosine-protein kinase

RPTD	Recommended Phase 2 dose
SAE	Serious adverse event
sCD105	Soluble CD105/endoglin
SC	subcutaneous
SCID	Severe combined immunodeficient
SCLC	Small cell lung cancer
iSD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	Systemic Organ Class in MedDRA
SOP	Standard operating procedure
TGF	Transforming growth factor
TIA	Transient ischemia attack
TPS	Tumor proportion score
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
UPCR	Urine protein-creatinine ratio
iUPD	Immune Unconfirmed progressive disease
US	United States of America
VEGF	Vascular endothelial growth factor

2. BACKGROUND

2.1. High Risk Localized or Locally Advanced Prostate Cancer

Prostate cancer is the highest cause of incident cancer in men while it is 3rd highest cause of cancer deaths in US. In recent years, prostate cancer is increasingly being diagnosed at younger aged men and early in the disease stage. However, some men with newly diagnosed prostate cancer are detected at later stages with extensive primary tumors (T2b and above), presence of regional lymph node metastasis (N1) or other factors that are considered high risk for recurrence of tumor, such as PSA >= 20 or Gleason score of 8 or above.

For localized disease, multiple options exist – active surveillance (AS), radical prostatectomy and external beam radiotherapy / brachytherapy (NCCN, 2018). Interventional options, however, carry risks. Radical prostatectomy (open or robotic) has long term risks of erectile dysfunction and urinary incontinence. External beam radiation therapy (EBRT) and brachytherapy also carry risks, such as erectile dysfunction, urinary incontinence and bowel complications. While AS has emerged as one of the recommended options for low risk localized prostate cancer, a more aggressive approach is required for high risk disease.

While radical prostatectomy with pelvic lymph node dissection is an option for selected high risk patients without tumor fixation to adjacent structures, adjuvant RT is often required especially for positive margins or lymph node involvement or PSA recurrence. Thus, ADT with definitive RT is often considered a standard approach in high risk disease, with the ability to radiate clinically occult lymph nodes which could harbor micrometastatic disease. ADT alone has proven to be inferior to combination therapy with definitive EBRT [11,12]. ADT combined with definitive EBRT has consistently shown improvements in cancer specific and overall survival in multiple randomized trials [13,14]. However, one in four patients will still have local recurrence and remain at risk of distant metastasis, with approximately 10-20% risk of long term prostate cancer specific mortality[15]. Although ADT is often continued for 2 years post-EBRT, recurrences can occur after completion of ADT, likely due to the presence of microscopic disease in the prostatic bed or in lymph nodes. Thus, we need strategies to improve the efficacy of combination ADT and EBRT.

2.2. ADT and Prostate Cancer

While prostate cancer is heavily androgen dependent, multiple studies have demonstrated that ADT alone is inferior compared to ADT plus RT for localized high risk prostate cancer [11,12,16,17]. However, even with combination ADT + EBRT, high risk patients remain at significant risk of developing distant metastasis, biochemical failure and prostate cancer-specific mortality [13,14,18].

2.3. Abemaciclib Background

2.3.1. Cyclin D Kinase 4/6 inhibition in cancer

During the cell cycle, the G1 restriction point controls entry into S phase and is essential for maintaining control of cell division [19,20]. The cyclin-dependent kinases (CDKs), CDK4 and CDK6, participate in a complex with D-type cyclins to initiate the transition through the G1 restriction point by phosphorylating and inactivating the retinoblastoma (Rb) tumor-suppressor protein. Alterations in this pathway occur frequently in human cancers and involve (1) loss of CDK inhibitors by mutation or epigenetic silencing, (2) mutation/overexpression of either CDK4 and CDK6 or cyclin D, or (3) inactivation of Rb. These alterations render cells less dependent on mitogenic signaling for proliferation. With the possible exception of those tumors with complete inactivation of Rb, which functions downstream of the CDK4 and CDK6–cyclin D complex, all of these cancers are potentially sensitive to pharmacologic inhibition of CDK4 and CDK6. From a therapeutic standpoint, the goal of inhibiting CDK4 and CDK6 with a small-molecule inhibitor is to prevent cell cycle progression through the G1 restriction point, thus arresting tumor growth.

2.3.2. Abemaciclib Background Information

Abemaciclib represents a selective and potent small-molecule CDK4 and CDK6 dual inhibitor with a broad antitumor activity in preclinical pharmacology models, acceptable physical and pharmacokinetic (PK) properties, and an acceptable toxicity profile in nonclinical species. This compound demonstrates significant inhibition of tumor growth as monotherapy in multiple human xenograft models including models for: breast cancer, colorectal cancer, glioblastoma multiforme, acute myeloid leukemia, melanoma, mantle cell lymphoma (MCL), and non–small-cell lung cancer (NSCLC). Although characterized by a different constellation of genomic mutations, each of these human xenografts has an intact, functional Rb protein. Xenograft growth inhibition is generally dose dependent from 25 to 100 mg/kg following daily oral administration for 21 to 28 days. Additional nonclinical studies in xenograft models for human NSCLC and melanoma also show that abemaciclib may be used in combination with standard cytotoxic or targeted therapies to improve efficacy of these agents.

In nonclinical species, abemaciclib distributes efficiently to the brain and potentially provides a unique opportunity to treat primary brain tumors as well as cancers that have metastasized to the brain. As a result of its brain exposure, treatment with abemaciclib in a rat orthotropic brain tumor model produces statistically significant and dose-dependent improvement in survival. Abemaciclib demonstrates moderate-to-high bioavailability in preclinical species. In repeat-dose toxicokinetic studies, abemaciclib showed generally dose-dependent exposure with no gender differences. Abemaciclib is highly metabolized, and hepatic elimination plays a major role in the clearance of abemaciclib and its metabolites in rats, dogs, and humans. In humans, the terminal elimination half-life (t1/2) in plasma ranges from approximately 17 to 38 hours across the doserange tested. At a single dose of 200 mg, the mean apparent oral clearance (CL/F) is 38.3 L/hour with a high interindividual variability (105% coefficient of variation [CV]) and the

apparent volume of distribution is large at 1300 L (96% CV). In the xenograft models and skin biopsies from patients, abemaciclib inhibited phosphorylated Rb (pRb) and topoisomerase II alpha (TopoIIα) at clinically relevant doses and exposures.

In preclinical species, the primary target organs for toxicity (associated with up to 3 months of continuous daily dosing) are bone marrow (resulting in pancytopenia), gastrointestinal tract, lymphoid tissues, and male reproductive tract. All of these changes demonstrated complete or partial reversibility during the recovery period. In humans, the most common (≥10%) treatment-emergent adverse events (TEAEs) possibly related to the study drug for patients who received single-agent abemaciclib include diarrhea, nausea, fatigue, neutropenia, vomiting, decreased appetite, leukopenia, thrombocytopenia, anemia, abdominal pain, and blood creatinine increased. Increased rates of skeletal and cardiac variations and malformations, accompanied by decreased fetal weights, were observed in an embryo–fetal development study of abemaciclib in rats.

After determining a recommended dose of 150 mg bid in a phase 1 study [21], abemaciclib monotherapy showed superior response rates in the MONARCH-1 study in a heavily pre-treated patient population [22]. It has subsequently demonstrated impressive response rates and improvement in PFS in 2 randomized phase 3 studies [23,24]. In the neoadjuvant breast cancer setting, the ongoing neoMONARCH Phase 2 open-label, randomized study (I3Y-MC-JPBY) showed an acceptable safety profile for abemaciclib (150 mg twice daily) as monotherapy and in combination with anastrozole, with reduction of breast cancer tumor cell proliferation marker (Ki67 index) to a significantly greater extent than anastrozole alone [25]. Abemaciclib has been well studied in breast cancer, and common side effects encountered in clinical studies include diarrhea (86%), neutropenia (46%), nausea (45%) and fatigue (40%) [23]. but the major grade 3 or higher side effect remains neutropenia in upto 20% of patients [23,24]. Thus patients on CDK4/6 inhibitors require frequent lab checks to monitor development of neutropenia, though the clinical significance of CKD4/6 inhibition – related neutropenia is debatable as the incidence of febrile neutropenia remains very low [23]. More significantly, compared to the 2 other approved CDK4/6 inhibitors, abemaciclib has a significantly reduced incidence of grade 3 or higher neutropenia [26]. Thus, abemaciclib represents a significant new option for CDK4/6 inhibition with impressive clinical efficacy and decreased incidence of significant neutropenia.

2.4. Study Rationale

Recently, CDK4/6 inhibition in combination with the anti-estrogen fulvestrant was found in a randomized phase III study to prolong the progression free survival of patients with advanced hormone receptor positive, HER2 negative breast cancer refractory to previous endocrine therapy compared to fulvestrant alone, irrespective of the menopausal status of patients enrolled in the study[1]. A prolonged progression free survival was also found in a randomized phase II study in combination with letrozole in the front-line setting compared to letrozole alone[2]. Abemaciclib has demonstrated significant improvement in PFS in combination with fulvestrant and with letrozole in the MONARCH 2 and MONARCH 3 studies leading to its approval in the post endocrine therapy and also, frontline setting for hormone receptor positive, HER2 negative breast cancer [23,24]. The basis of this synergy involves the dependence of estrogen receptor

positive breast cancers to CDK4/6 for growth and proliferation. Additionally, activation of growth factor receptor signaling is a hallmark for endocrine therapy resistance.

A similar hormone-driven cancer akin to breast cancers is prostate cancer. These tumors are driven by androgen receptor signaling, and CDK4/6 has also been found to be a bona fide target preclinically for advanced prostate cancer cell models[3]. Moreover, CDK4/6 inhibition can act as a radiation sensitizer through its effects on the DNA damage response and interactions with cell cycle pathway proteins[4,5]. For example, it has been found that expression of DNA repair proteins can be regulated by E2F, a transcription factor necessary for the G1 to S phase transition[6]. Also, cyclin D1 has been found to exert a direct role on dna repair[7-9]. Lastly, CDK4/6 inhibition has been found to modulate the DNA damage response[10]. These data support the use of CDK4/6 inhibitors as a modulator of DNA damage to enhance sensitivity to radiation.

Given the role of CDK4/6 in tumor resistance to endocrine therapy, in activation of the DNA damage response, and in promoting radiation resistance, we hypothesize that the targeting of CDK4/6 with abemaciclib will enhance the cytotoxicity in combination with blockade of the androgen receptor pathway. Therefore, we propose a pilot phase II investigator initiated trial in patients with high-risk prostate cancer patients testing the tolerability and toxicity of abemaciclib in combination with ADT.

2.5. Population to be Studied

Patients with high risk localized or locally advanced prostate cancer who will be eligible for definitive treatment with Radiation therapy and ADT.

2.6. Potential Risks and Benefits to Human Patients

2.6.1. Potential Risks

Abemaciclib

Based on clinical experience with abemaciclib, the adverse events of special interest (AESIs) are neutropenia, infections, diarrhea, blood creatinine increased, hepatic events (increases in aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), and embolism (mainly pulmonary embolism and deep vein thrombosis)); furthermore, interstitial lung disease/pneumonitis is considered an adverse event (AE) of note.

Computed Tomography (CT) Scans

Patients will be exposed to a relatively small amount of radiation as a result of the CT scans required in this study. This degree of exposure has not been associated with harmful health effects. In addition, the frequency of CT scans performed in this study is similar to the standard of care frequency. Patients with a medical contraindication to CT scans or known iodinated contrast allergies may instead undergo magnetic resonance imaging (MRI). There is minimal risk of MRI imaging in patients able to undergo this type of exam including very rare reports of gadolinium-induce nephrogenic systemic fibrosis in patients with poor renal function.

MRI-US imaging.

Patients will undergo MRI-US fusion imaging pre-treatment and at 6 months post RT with comparison with historical controls receiving RT + ADT. There is minimal risk of MRI imaging in patients able to undergo this type of exam including very rare reports of gadolinium-induce nephrogenic systemic fibrosis in patients with poor renal function.

Prostate biopsy

Patients will have undergone MRI-US guided biopsy of the prostate at the time of diagnosis and archived tumor tissue will be used at screening for baseline analysis. An optional biopsy will be scheduled at 6 months post RT for tumor tissue profiling to identify association of molecular profile with PSA decline at 1 year. Risks include but are not limited to bleeding from biopsy site, increased risk of infection and complications related to anesthesia for the procedure.

Venipuncture

Patients could also experience side effects from venipuncture for tests that will be done as part of this study, including pain, tenderness, and bruising at the site of collection, and rarely infection may occur at the spot where the needle is inserted.

Other Risks

This study treatment may involve risks to unborn children and therefore patients should not father a baby while participating in this study.

Men must agree to use 2 effective and highly reliable methods of contraception at the same time (i.e., vasectomy, male latex condom with or without spermicide, partner's tubal sterilization, partner's use of an IUD, partner's use of diaphragm with spermicide, cervical cap with spermicide, or vaginal sponge that contains spermicide) during study treatment (including temporary breaks from treatment), and for at least 180 days after stopping Abemaciclib. The long-term risk of infertility is unknown.

Potential Benefits

Abemaciclib is an investigational product and its efficacy in combination with ADT has not been established. ADT is approved for treatment of localized or locally advanced prostate cancer. It is expected that the administration of Abemaciclib and ADT may result in clinical benefit (i.e. Tumor response).

2.7. Justification of the Dose, Schedule, and Route of Administration

The dose, schedule, and route of administration of Abemaciclib (150 mg BID) was selected based on safety, pharmacokinetics, and evidence of activity in the Phase 1b study (JBIF). Dose reduction is possible for treatment of adverse events, including anemia. Refer to section 6.3.1, Table 4 and section 6.3.3

ADT with LHRH analogues will be admisitered at Standard of care doses.

2.8. Study Conduct

This clinical trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

3. TRIAL OBJECTIVES AND PURPOSE

The purpose of this study is to evaluate the safety and tolerability of Abemaciclib in combination with ADT.

Primary Objective:

- To assess clinical response rates using
  - Proportion of patients with PSA nadir of ≤ 0.5 ng/ml on treatment

Secondary Objectives:

- Proportion of patients with PSA declines prior to radiotherapy
- Time to PSA failure
- To study the tolerability and feasibility of combining Abemaciclib with ADT for localized high risk or locally advanced prostate cancer.

Exploratory Objective:

1) MRI-US fusion imaging pre-treatment and at 6 months post RT with comparison with historical controls receiving RT + ADT.
2) Baseline (mandatory) and 6 months (optional) post RT tumor tissue profiling (MRI-US fusion guided) to identify association of molecular profile with PSA decline at 1 year.
3) Baseline, pre-radiotherapy and 6 months post-RT blood collection and profiling for molecular analysis.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

4.1.1. Overview

This is a single center, Phase II, single arm, open-label study of Abemaciclib in combination with ADT in patients with localized high-risk or locally advanced prostate cancer who are eligible for definitive RT and ADT.

All patients must sign and date a consent form prior to undertaking any study-related procedures. Prospective patients will be screened to determine if they qualify for the study within 28 days of enrollment. Patients will receive ADT with LHRH analogues every 3 months and will receive Abemaciclib starting on C1D1 at 150 mg PO BID for 28 day cycles Table 3 (see Abemaciclib Administration Section 6.1.4 and ADT Administration). Patients receive ADT x 2 years and will start 3 months before RT. Abemaciclib will start with initiation of ADT and pause 2 weeks prior to start of RT. Abemaciclib will resume with the first ADT administration post-radiation, which typically is at 1 month post radiation therapy. Abemaciclib and ADT will continue for a total ADT period of 24 months (+/- 3 days ~~to allow for holidays and weekends~~). Patients will have laboratory evaluation every 2 weeks for the first 2 months and monthly thereafter for the next 2 months. Patients are also seen and evaluated every 4 weeks with laboratory evaluation. Labs may be drawn at outside laboratories at the PI's discretion.

Patients will receive study treatment until development of toxicity or disease progression on treatment or any reasons of withdrawal or a maximum of 24 months of therapy with ADT. Adverse events will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

All patients will receive Abemaciclib at 150 mg BID PO dose. The trial is carried out in two stages. In stage I, a total number of 5 patients are accrued. If there are 0 response (PSA< 0.5) among these 5 patients, the study will be early stopped. Otherwise, additional 18 patients will be accrued in stage II, resulting in a total number sample size of 23. If there are 4 or more responses (PSA< 0.5) among these 23 patients, we reject the null hypothesis and claim that the treatment is promising. The design controls the type I error rate at one-sided 0.025 and yields the power of 80%. If we reject the null hypothesis, seven additional patients will be enrolled to explore the association between biomarkers and clinical activities. To account for 10% screen failure, total of 33 patients will be recruited to the study.

Table 1: Toxicities leading to withdrawal of subjects

Toxicity Category	Drug-Related Toxicity/Grade
Hematologic	Grade 4 neutropenia for ≥5 days
	Febrile neutropenia: ANC < 1000/mm^3 with a single temperature of >38.3ºC (101 ºF) or a sustained temperature of ≥ 38 ºC (100.4 ºF) for more than one hour.
	Neutropenic infection: Grade ≥3 neutropenia with Grade ≥3 infection
	Grade ≥4 Anemia
	Grade ≥4 thrombocytopenia or Grade ≥3 thrombocytopenia with Grade ≥3 hemorrhage
Non-hematologic	Grade 2 (>3.0 x ULN) ALT/AST with total bilirubin >2 x ULN, in the absence of cholestasis Grade 3 or 4 non-hematologic toxicity with the following exceptions: • Asymptomatic electrolyte abnormality that resolve within 48 hours. • Grade 3 headache lasting <48 hours

4.1.2. Trial Procedures

All on-study procedures are permitted within the time window indicated in the Schedule of Assessments (Table 2).

4.1.2.1. Screening

The following screening procedures must be performed within 28 days prior to the first day of study therapy unless indicated. Qualifying hematology, serum chemistry (including thyroid-stimulating hormone [TSH] testing), coagulation, physical examination, ECG, and urinalysis collected within 7 days of Cycle 1 Day 1 (C1D1) do not need to be repeated. The following will be performed according to the Schedule of Assessments (Table 2).

- Patient signature and date on current Institutional Review Board (IRB)-approved informed consent form - Prior to undergoing any study-specific procedure, patients must read, sign, and date the current IRB)-approved informed consent form. Patients may sign consent prior to the 28-day screening period.
- Medical history, baseline signs and symptoms, drug allergies, primary diagnosis, and demographics
- Physical examination, including examination of all major body systems, ECOG performance status, and vital signs - The patient's height will be obtained only at this Screening visit.

- Hematology, coagulation (prothrombin time and INR), and serum chemistry (including liver function tests and TSH) to be performed locally
- Hepatitis B and C serology will be done for all patients.
- Urinalysis to be performed locally - Microscopic analysis and/or urine protein-creatinine ratio (UPCR) should be performed as clinically indicated.
- CT or MRI scans of abdomen and pelvis to rule out metastatic disease. (within 3 months)
- Bone scans are to be performed if metastases to bone are suspected at screening (within 3 months) and to rule out bone metastases.
- Single tracing 12-Lead ECG (QT, PR, and QRS intervals and heart rate will be captured)
- Assessment of concomitant medications and treatments from 28 days prior to the start of study treatment
- Pre-operative baseline core tumor biopsy - Archival Tumor Tissue Specimens: Archival specimens (formalin-fixed, paraffin-embedded) of the primary cancer specimen for each study participant. It is preferable that the entire paraffin block be submitted, but if this is not feasible, then at least 20 unstained slides are requested for immunohistochemical and molecular analysis (sections of ~ 5 microns are preferred).

4.1.2.2. Study Drug Treatment Period

Qualifying hematology, blood chemistry (including TSH testing), coagulation, urinalysis, physical examination, and ECG test do not need to be repeated on C1D1 if acceptable screening assessments are performed within 7 days prior to the start of study therapy. On days of dosing, all assessments should be performed prior to dosing with Abemaciclib unless otherwise indicated in the Schedule of Assessments (Table 2). Patients will be eligible to receive Abemaciclib until unacceptable toxicity, withdrawal of consent, progression of disease or end of study. Each cycle is 28 days in duration (+/- 3 days). The following will be performed according to the Schedule of Assessments (Table 2).

- Physical examination including examination of all major body systems, ECOG performance status, weight, and vital signs (heart rate, temperature, blood pressure, respiratory rate)
- Hematology, coagulation (prothrombin time and INR) and serum chemistry (including liver function tests and TSH) to be performed locally
- Urinalysis to be performed locally - Microscopic analysis and/or UPCR should be performed as clinically indicated.
- Administration of Abemaciclib: Abemaciclib will be administered at a dose of 150 mg twice daily and it is provided as 50-mg tablets. Abemaciclib should be taken twice daily (with at least 6-hour separating doses) at the same time each day with a glass of water. Patients should be instructed to swallow tablets whole and not open, chew, or crush. Intrasubject dose escalation of Abemaciclib is not permitted. Abemaciclib will be briefly

stopped 2 weeks prior to radiation therapy and will be restarted a month after radiation therapy is completed. Abemaciclib may be given up to a maximum of 24 months.

- Administration of ADT: Administer ADT as given in standard of care dosing on C1D1 along with Abemaciclib. ADT is given every 3 months. The maximum treatment duration with ADT is 24 months
    - Radiation Therapy: This is administered after 2 and half cycles of Abemaciclib and ADT regimen. RT will be given as administered standard of care at the institution – 180 cGy x 28 fractions to the whole pelvis and boost to prostate with 250 cGy x 28 fractions. After RT is completed, both ADT and Abemaciclib are resumed and can be continued up to 24 months. See **Section 6.3** and **Appendix 3: UAB Department of Radiation Oncology Treatment Practice Guidelines** for further details of radiation therapy.
- Assessment of adverse events (AEs)
- Assessment of concomitant medications and concomitant treatments

4.1.3. Follow-up

Safety Follow-up

All subjects will complete a safety follow-up visit approximately 30 (+7) days after the last dose of study treatment. Serious adverse events and any concomitant medications associated with serious adverse events observed by the investigators or reported by the subjects that occur through 90 (+7) days after the cessation of all study treatment or 30 (+7) days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, will be reported to Eli Lilly and recorded in the CRF.

Long-term Follow-up

After the safety follow-up visit, all subjects will enter the long-term follow-up. Subjects will be followed for survival and subsequent anticancer therapies every 12 weeks (± 28 days) **from safety follow-up** for approximately 12 months after the end of treatment. In addition, Abemaciclib related adverse events that occur through the end of the long-term follow-up will be reported.

For subjects who discontinue study treatment without documented PD and have not **initiated a new** anticancer therapy, every effort should be made to continue monitoring tumor response status by clinical and radiographic tumor assessments.

Table 2: Schedule of Assessments

Protocol Activities	Screening	Cycle 1 (28 days)	Cycle 2-3 (+/- 3 days)	Cycle 4 onwards[h] (+/-3days)	EOT/Follow up[a]
	Day -28	Day 1	Day 1	Day 1	
Baseline Documentation					
Informed Consent	X				
Medical/Oncology History	X				X
Baseline Signs and Symptoms	X				
Physical Examination	X	X	X	X	X
Vital Signs	X	X	X	X	X
Laboratory Studies[i]					
PSA (at screening, prior to RT, and q month after RT)[i]	X	X	X	X	X
Hematology[i]	X	X	X	X	X
Coagulation[i]	X	X			
Blood Chemistry including LFTs [i]	X	X	X	X	X
Serology for Hepatitis B and C	X				
Urinalysis	X	X	X	X	
Testosterone level to confirm chemical castration	X		X	X	
Treatment with Study Drug					
Abemaciclib Dosing[b]		X	X[g]	X	

Protocol Activities	Screening	Cycle 1 (28 days)	Cycle 2-3 (+/- 3 days)	Cycle 4 onwards[h] (+/-3days)	EOT/Follow up[a]
	Day -28	Day 1	Day 1	Day 1	
LHRH analogues (SC)[c]		X			
RT			X[e]		
Tumor Assessments					
CT or MRI Scans	X[f]				X[f]
Other Clinical Assessments					
12-Lead ECG	X	X			X
Concomitant Medications/Treatments	X	X	X	X	X
Adverse Events		X	X	X	
Special Laboratory Assessments					
Optional Tumor Biopsy[d]			X[d]		
Archival Tumor Tissue	X				

a. Refer Section 4.1.3 for frequency of follow-up (safety and long-term).

b. BID PO dosing Abemaciclib. Abemaciclib will be stopped 2 weeks before RT and will be resumed 1 month after RT.

c. LHRH analogues will be administered on C1D1 and continued every 3 months for a maximum of 24 months.

d. An optional MRI-TRUS guided biopsy will be performed at 6 months post radiotherapy,

e. Radiotherapy will be started after 3 months of start of abemaciclib and ADT.

f. CT scan or MRI scan will be done to rule out metastatic disease (within 3 months). It will be conducted again at the time of PSA rise (biochemical failure).

g. Abemaciclib will be stopped 2 weeks before scheduled RT. It will be administered for half a cycle in cycle 3.

h. Abemaciclib and ADT will be resumed after 1 month of completing RT. This will be counted as 4th cycle and future cycles will continue monthly for Abemaciclib. ADT will be given quarterly. Study treatment will continue until patient progresses, has toxicities or withdraws from study.

i. Laboratory Studies: The first 2 cycles, labs will be drawn every 2 weeks and may be drawn at outside lab at the PI's discretion.

5. SELECTION AND WITHDRAWAL OF PATIENTS

5.1. Patient Inclusion Criteria

1. Histologically confirmed (core biopsy proven) adenocarcinoma of prostate, localized high-risk or locally advanced
2. One of the below:
   • Gleason 7-8, any T-stage, and PSA > 20,
   • Gleason 8, ≥ T2, any PSA,
   • Gleason 9-10, any T-stage, any PSA.
   • T3, any Gleason, any PSA
   • Subjects with positive pelvic lymph node(s) are eligible
3. Available biopsy of primary tumor or resected tumor specimen with adequate samples.
4. Prior treatment with systemic anti-cancer agents is not allowed.
5. ECOG PS = 0 or 1
6. Must have at least 1 target lesion
7. Life expectancy > 6 months
8. Adequate hematologic and end-organ function
   - ANC ≥ 1500/mm^3
   - Platelet count ≥ 100,000/mm^3
   - Hb ≥ 8g/dl
   - Creatinine ≤ ULN or Creatinine Clearance (CrCl) ≥ 60 ml/min
   - Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert syndrome, who can have total Bilirubin < 2.x ULN and direct bilirubin within normal limits are permitted)
   - AST and ALT ≤ 3.0 x ULN
9. Agreement to remain abstinent or use appropriate contraception.
10. Willingness and ability to consent for self to participate in study.
11. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

5.2. Exclusion Criteria:

1. Prior treatment with CDK 4/6 inhibitor.
2. Prior treatment with systemic or radiation treatment for the primary cancer.
3. Major surgical procedure or significant traumatic injury within 4 weeks prior to study treatment, and must have fully recovered from any such procedure.
4. Personal history of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest.
5. Angina, myocardial infarction (MI), symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack TIA), arterial embolism,

pulmonary embolism, percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass grafting (CABG) within 6 months prior to study treatment.

6. Known active viral or non-viral hepatitis or cirrhosis.
7. Any active infection requiring systemic treatment, positive tests for Hepatitis B surface antigen or Hepatitis C ribonucleic acid (RNA).
8. Known history of AIDS (acquired immunodeficiency syndrome)- defining illness.
9. Patients must be surgically sterile or must agree to use effective contraception during the study treatment (including temporary breaks from treatment), and at least 180 days after stopping last dose of Abemaciclib. The definition of effective contraception is provided in Section 2.6.1 of this protocol.
10. Other severe and/or uncontrolled acute or chronic medical or psychiatric condition or laboratory abnormality that, in the judgement of the investigator, may increase the risk associated with study participation or may interfere with the interpretation of study results and would make the patient inappropriate for this study (for example, interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, severe renal impairment [e.g. estimated creatinine clearance <30ml/min], history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea).
11. Secondary malignancy requiring active treatment. Past history of malignancy other than prostate cancer treated with curative intent and not requiring additional treatment may be eligible after discussion with PI.
12. Patients with active autoimmune disease and history of inflammatory bowel disease will be excluded. Brachytherapy boost will not be permitted.

5.3. Patient Withdrawal Criteria

A patient should be withdrawn from study treatment if, in the opinion of the Investigator, it is medically necessary, or if it is the wish of the patient. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome. Data to be collected at the end of study visit are described in the Schedule of Assessments (Table 2). Patients will be followed for at least 28 days after the last dose of study drug (Abemaciclib or ADT) for AEs. If the patient withdraws consent, no further evaluations should be performed, and no attempts should be made to collect additional data. In addition, patients will be withdrawn from treatment in the case of:

1. Lost to follow-up or noncompliant with the protocol

2. Any Abemaciclib dose delay > 7 days during the first cycle

3. Arterial thrombosis of any grade (including cerebrovascular ischemia, cardiac ischemia/infarction, or peripheral or visceral arterial ischemia) or Grade 3 or 4 venous thrombosis (including pulmonary embolism)

5.4. General Guidelines

Eligible patients will be entered on study at Kirklin clinic, UAB Hospital and Acton Road clinic. Site clinical research coordinator (CRC) will ensure study agent availability before enrolling patients. Following enrollment and registration by site CRC, patients should begin protocol treatment within 28 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be cancelled. The Study Monitor should be notified of cancellations as soon as possible.

5.5. Registration Process

The Clinical Trials Network Monitoring Office (CTNMO) of the UAB Comprehensive Cancer Center (CCC) coordinates investigator-initiated clinical trials under Good Clinical Practice conditions at UAB to achieve timely study subject enrolment. Once a study subject has been screened and deemed eligible for study entry by the site CRC, a study-specific number is assigned to the study subject and a Registration Form is completed. Queries regarding data accuracy are forwarded from the CTNMO to the site CRC for clarification or correction.

6. TREATMENT OF PATIENTS

6.1. Description of Abemaciclib Study Drug

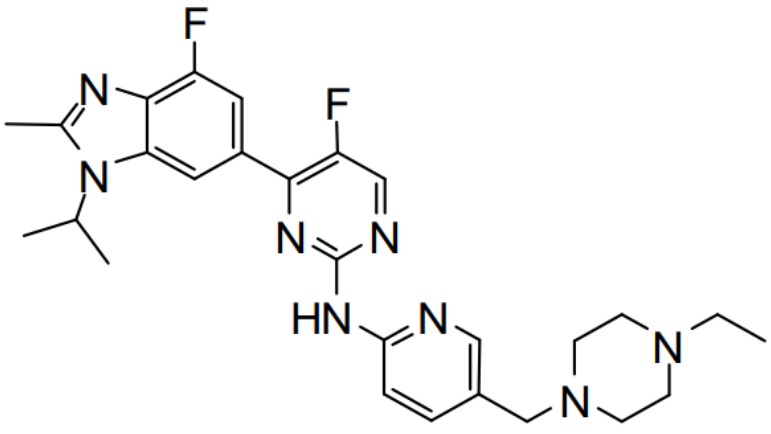
Abemaciclib is an oral, selective, and potent ATP-competitive inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6, respectively). CDK4 and CDK6 promote cell growth by facilitate ing the progression of cells from the G1 to the S-phase of the mammalian cell cycle. This promotion of cell growth occurs primarily by counteracting the effects of a growth suppressor protein known as the retinoblastoma (Rb) protein, whereby the reversal of Rb mediated suppression is achieved by the phosphorylation of this protein by CDK4 and/or CDK6.

The CDK4/CDK6-Rb pathway is commonly altered in cancer cells, whereby the activation of this pathway contributes to enhanced growth. Accordingly in cancer cells, abemaciclib inhibits CDK4/CDK6-dependent phosphorylation of Rb, which subsequently blocks proliferation by inhibiting the progression of these cells from the G1 phase into the S and G2/M phases of the cell cycle.

Abemaciclib showed antitumor activity within multiple preclinical pharmacology models and an acceptable toxicity profile in nonclinical species. Abemaciclib has been shown to significantly inhibit tumor growth in multiple murine xenograft models for human cancer.

6.1.1. Abemaciclib Composition

The chemical name of Abemaciclib is (2-Pyrimidinamine, N-[5-[(4-ethyl-1-piperazinyl)methyl]-2-pyridinyl]-5-fluoro-4-[4-fluoro-2-methyl-1-(1-ethylethyl)-1Hbenzimidazol-6-yl]-N-(5-((4-ethylpiperazin-1-yl)methyl)pyridin-2-yl)-5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-amine and the structural formula is presented in Figure 2. Abemaciclib has a molecular formula of $C_{27}H_{32}F_2N_8$ and a molecular weight of 506.60.



Structure of abemaciclib.

6.1.2. Abemaciclib Dose Levels

Subjects in this phase II study will receive 150 mg BID PO dose of Abemaciclib. There will be no intra-patient dose escalation of Abemaciclib

6.1.3. Abemaciclib Packaging and Labelling

Abemaciclib will be provided by Lilly. Clinical trial materials will be labeled according to the country's regulatory requirements.

6.1.4. Abemaciclib Administration

Abemaciclib will be administered at a dose of 150 mg twice daily and it is provided as 50-mg tablets. Abemaciclib should be taken twice daily (with at least 6-hour separating doses) at the same time each day with a glass of water. Patients should be instructed to swallow tablets whole and not open, chew, or crush.

Doses of Abemaciclib will be self-administered except on the days scheduled to be given at the study clinic. Abemaciclib will be given daily in combination with ADT as long as subjects do not have toxicity, disease progression, have not met any criteria for study withdrawal or up to a maximum of 24 months. Intrasubject dose escalation of Abemaciclib is not permitted.

Table 3: Ideal Dosing Schema for Study Drugs and Abemaciclib Premedications

Sequence	Drugs	C1D1 and onwards
1	Abemaciclib PO (BID)	150 mg

6.1.5. Abemaciclib Dose Modification/Dose Delays

6.1.5.1. Rationale for Dose modifications

Modifications to Abemaciclib dose regimens are planned and independent of the determination of tolerability during the study, subjects may require modification of Abemaciclib if necessitated by drug-related or unrelated AEs.

6.1.6. Abemaciclib Drug Accountability

The Investigator must maintain an accurate accounting of Abemaciclib supplies. During the study, the following information must be recorded:

- Date of receipt, quantity, and lot number of the Abemaciclib study drug received.
- Identification number of the patient to whom the product is dispensed.
- The date(s) and quantity of the product dispensed.
- Dates and quantity of product returned, lost, or accidentally or deliberately destroyed.

Investigational Drug Accountability Logs should be maintained by the site and must be readily available for inspection.

6.1.7. Abemaciclib Study Drug Handling and Disposal

The Investigator must maintain an accurate accounting of the Abemaciclib product that is used. During the study, the following information must be maintained:

- Identification number of the patient to whom the product is dispensed.
- Lot number dispensed.
- The date(s) and quantity of the product dispensed.

6.2. Description of Androgen Deprivation Therapy

The commonly used preparations are listed below. However any of the other preparations with FDA approval, that result in androgen suppression are acceptable.

Goserelin acetate implant (Zoladex®) / Leuprolide (Lupron)

a. PHARMACOLOGY
Mechanism of Action: Following initial administration in males, goserelin causes an initial increase in serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels with subsequent increases in serum levels of testosterone. Chronic administration of goserelin leads to sustained suppression of pituitary gonadotropins, and serum levels of testosterone consequently fall into the range normally seen in surgically castrated men approximately 2-4 weeks after initiation of therapy.
b. PHARMACOKINETICS
1. Absorption: Goserelin 3.6 mg is released slowly in first 8 days, and then rapid and continuous release for the remainder of the 28 day dosing period. Time to peak concentration for goserelin 3.6 mg is 12-15 days in males and 8-22 days in females. Goserelin 10.8 mg exhibits an initial rapid release resulting in a peak concentration at 2 hours after dosing. From Day 4 until the end of the 12-week dosing interval, the sustained release of goserelin produces a reasonably stable systemic exposure.
2. Distribution: Apparent volumes of distribution determined after subcutaneous administration of 250 mcg aqueous solution of goserelin were 44.1 and 20.3 liters for males and females, respectively. Goserelin is approximately 27% protein bound.
3. Metabolism: Metabolism of goserelin by hydrolysis of the C-terminal amino acids is the major clearance mechanism. The half-life elimination (t1/2)) is approximately 4 hours in males and 2 hours in females
4. Elimination: Clearance of goserelin is very rapid and occurs primarily via urinary excretion (>90%; 20% as unchanged drug).
c. ADVERSE EFFECTS
1. Refer to the package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.
Side Effects
Adverse events associated with the use of Leuprolide/Goserelin may include, but are not limited to, the following:
• hot flashes

- injection site reactions
- weight gain
- increase in liver enzymes
- tiredness
- hypertension
- back and joint pain
- chills
- urinary tract infection
- decreased sex drive and trouble with erectile function

Adverse effects occurring in <1%, postmarketing, and/or case reports:
1. ALT increased, anaphylaxis, AST increased, diabetes, glucose tolerance decreased, hypercalcemia, hypercholesterolemia, hyperlipidemia, hypersensitivity reactions, hypotension, ovarian cyst, pituitary apoplexy, psychotic disorders, urticaria.
2. Pregnancy and Lactation: Not applicable as this study only enrolls male patients. Pregnancy category X in patients with endometriosis and endometrial thinning. Pregnancy category D in patients with advanced breast cancer. It is not known if goserelin is excreted in human milk, however goserelin is excreted in the milk of lactating rats.
3. Drug Interactions: Luteinizing hormone-releasing hormone analogs may diminish the therapeutic effect of antidiabetic agents. No formal drug-drug interaction studies have been performed. Please refer to the current FDA-approved package insert for additional information.
4. The FDA issued a safety communication in October 2010 based on their ongoing safety review of LHRH agonists. The safety communication discusses the potential for an increased risk of diabetes and cardiovascular disease (myocardial infarction, sudden cardiac death, stroke) associated with these agents. The risk is thought to be low in men receiving LHRH agonists for prostate cancer. In this trial, LHRH agonists are being administered for a short period of time. FDA recommendations include management of cardiovascular risk factors according to current standards of practice.
d. DOSING & ADMINISTRATION
1. Dosing – See Package Insert of preparation used.
2. Goserelin is administered subcutaneously into the anterior abdominal wall below the navel line using aseptic technique.
e. STORAGE & STABILITY
Refer to the current FDA-approved package insert for storage, stability and special handling information.

f. HOW SUPPLIED
1. Goserelin acetate implant is available in a 10.8 mg disposable syringe device. The unit is sterile and comes in a sealed, light- and moisture-proof, aluminum foil laminate pouch containing a desiccant capsule.
2. Goserelin is commercially available and will not be supplied. Refer to the current FDA-approved package insert for additional information.

Leuprolide (Eligard®, Lupron Depot®) (NSC-377526)
a. PHARMACOLOGY
Mechanism of Action: Leuprolide inhibits gonadotropin secretion by acting as an luteinizing hormone-releasing hormone (LHRH) agonist. Continuous administration results in

suppression of ovarian and testicular steroidogenesis due to decreased levels of LH and FSH with subsequent decrease in testosterone (male) and estrogen (female) levels. In males, testosterone levels are reduced to below castrate levels. Leuprolide may also act directly on the testes as well as act by a different mechanism not directly related to reduction in serum testosterone.
d. DOSING & ADMINISTRATION
1. Dosing – Per package insert. Typically 22.5 mg every 3 months
2. Leuprolide is administered intramuscular (Lupron Depot®) or subcutaneous (Eligard®) injection based on commercial depot formulation. Injection sites should be varied periodically.
e. STORAGE & STABILITY
Refer to the current FDA-approved package insert for storage, stability and special handling information.
f. HOW SUPPLIED
1. Leuprolide acetate is available in 3.75 mg, 7.5 mg, 11.25 mg, 22.5 mg, 30mg, or 45 mg depot formulation kit with accompanying diluent. The prefilled dual chamber syringe contains lyophilized microspheres of leuprolide acetate incorporated in a biodegradable lactic acid polymer.
2. Leuprolide/Goserelin is commercially available and will not be supplied.

Other LHRH agents can be utilized per the FDA approved dose and schedule. GNRH antagonists cannot be used.

6.3. Radiation Therapy

Refer to **Appendix 3 for UAB Department of Radiation Oncology Treatment Practice Guidelines** for further details of radiation therapy.

Brachytherapy boost will not be permitted.

6.3.1 Target Volume

Dose inhomogeneity ranges for PTV coverage will be 95% of PTV volume will receive 100% of prescribed dose; 100% of PTV volume will receive 95% of dose. Global hotspot <107%.

Minor deviation that is acceptable: 90% of PTV receiving 100% of dose; 95% PTV receive 95% of dose; global hotspot 110%.

6.3.2 Compliance

Treatment plans will be peer-reviewed for compliance prior to starting radiation at the weekly treatment planning conference.

6.4. Dose modifications of Study drugs

6.4.1. Planned Dose modifications

Intrasubject dose escalations are not permitted. Table 4 describes Abemaciclib dose reductions that may occur due to any related AEs. There will be no dose reductions of LHRH analogues allowed for the management of toxicities of individual subjects. Doses of ADT may be delayed for toxicity management.

Table 4: Allowable Abemaciclib Dose Modifications for Toxicity Attributed to Abemaciclib

Cohort	Current Dose	Dose Reduction
1	150 mg BID	100 mg BID

6.4.2. Criteria and Procedure for interruption

In some circumstances, it may be necessary to temporarily interrupt study treatments as a result of AEs that may have an unclear relationship to the study drug(s). If an interruption is necessary, both study treatments should be interrupted.

Any dose interruptions of > 2 weeks for LFT abnormalities must be discussed with the medical monitor before resuming treatment. Treatment with both study drugs should be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 (including laboratory abnormalities), and severe or life-threatening AEs.

Except in cases of emergency, it is recommended that the investigator consult with the sponsor's medical monitor (or other representative of the sponsor) before temporarily interrupting therapy for reasons other than Protocol-mandated medication hold. Additionally, the investigator must notify the sponsor's medical monitor and study project manager via email or during safety teleconferences before restarting study drug that was temporarily interrupted because of an AE.

Dose modifications for hematologic and non-hematologic AEs related to chemotherapy may be managed per institutional guidelines.

6.4.3. Procedures for management of Abemaciclib related adverse event(s)

Guidelines for Diarrhea Management

Clinical trial data indicates the majority of patients who receive abemaciclib will develop diarrhea. Our experience indicates early identification and intervention for the management of diarrhea has been helpful to patients.

At enrollment, patients should receive instructions on the prompt management of diarrhea. In the event of diarrhea, supportive care measures should be initiated as early as possible. These include the following:

- At the first sign of loose stools, the patient should initiate antidiarrheal therapy (e.g. loperamide) and notify the investigator for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (e.g., 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- Refer to Table 5 for additional information for diarrhea management and dose modification.

Table 5: Dose Modification and Management- Diarrhea

At the first sign of loose stools, start treatment with antidiarrheal agents, such as loperamide.	
CTCAE Grade	**Abemaciclib Dose Modifications**
Grade 1	No dose modification is required.
Grade 2	If toxicity does not resolve within 24 hours to ⩽Grade 1, suspend dose until resolution. Dose reduction is not required.
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	Suspend dose until toxicity resolves to ⩽Grade 1. Resume at next lower dose.
Grade 3 or 4 or requires hospitalization	

General Guidance for Increases in Serum Creatinine and Assessment of Renal Insufficiency

Elevation of serum creatinine is observed with abemaciclib, and is due to a pharmacological inhibitory effect of abemaciclib on renal tubular transporters without affecting glomerular function. The rise in serum creatinine (mean increase, 0.2 mg/dL) occurs within the first 28-day cycle of abemaciclib, and remains elevated but stable throughout the treatment period, and were reversible upon treatment discontinuation. Alternative markers (such as BUN, cystatin C level, or cystatin C calculated GFR) which are not based on creatinine, may be considered to determine whether renal function is impaired.

General Guidance for Interstitial lung disease (ILD)/Pneumonitis events

Interstitial lung disease (ILD) /pneumonitis has been identified as an adverse drug reaction for abemaciclib. The majority of events observed in clinical trials were Grade 1 or Grade 2 with serious cases and fatal events reported. Additional information is available in the IB.

Monitor for clinical symptoms or radiological changes indicative of ILD/pneumonitis and ask your patients to report any new or worsening pulmonary symptoms such as dyspnea, cough, and fever, and investigate and treat as per your local clinical practice (including corticosteroids as appropriate). If ILD/pneumonitis is suspected, investigations may include imaging, such as high resolution computed tomography, broncheoalveolar lavage, and biopsy as clinically indicated. Discontinue abemaciclib in cases of severe (Grade 3 or 4) ILD/pneumonitis.

Table 6: Dose Modification and Management — Interstitial Lung Disease/Pneumonitis

CTCAE Grade	Abemaciclib Dose Modifications
Grade 1 or 2	No dose modification is required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 3 or 4	Discontinue abemaciclib.

General Guidance for Hepatic Monitoring

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation are considered as ADR with the use of abemaciclib. **The following information in Table 7 on hepatic monitoring:**

Table 7: Dose Modification and Management — Increased ALT/AST

Monitor ALT/AST prior to the start of abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.	
CTCAE Grade	**Abemaciclib Dose Modifications**
Grade 1 (>ULN-3.0 x ULN) Grade 2 (>3.0-5.0 x ULN)	No dose modification is required.
Persistent or Recurrent Grade 2, or Grade 3 (>5.0-20.0 x ULN) that does not resolve with maximal supportivemeasures within 7 days to baseline or Grade 1: suspend dose until toxicity resolves to baseline or Grade 1.	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
≥Grade 2 (>3.0 x ULN) with **total bilirubin >2 x** ULN, in the absence of cholestasis	Discontinue abemaciclib
Grade 4 (>20.0 x ULN)	Discontinue abemaciclib.

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities are shown below in Table 7.

Table 8: Hepatic Monitoring Tests for a Hepatic Treatment Emergent Abnormality.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
HAV total antibody	Immunoglobulin IgM (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) [a]
HBV DNA [c]	Anti-actin antibody [b]
Hepatis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA [c]	EBV DNA [c]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA [c]

HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [c]	HSV (Type 1 and 2) DNA [c]
Microbiology	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

[a] Not required if anti-actin antibody is tested.

[b] Not required if anti-smooth muscle antibody (ASMA) is tested.

[c] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

General Guidance for Hematology Toxicity and Dose Modification

Hematologic toxicities including neutropenia, leukopenia, anemia, and thrombocytopenia have been observed in patients treated with abemaciclib, and causality has been established. Severe (Grade 3 and 4) neutropenia was observed in patients receiving abemaciclib. Patients should be monitored closely for signs of infection, anemia, and bleeding. **Table 9 provides guidance on dose modification and management of hematologic toxicities.**

Table 9: Dose Modification and Management — Hematologic Toxicities

Monitor complete blood counts prior to the start of abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.	
CTCAE Grade	**Abemaciclib Dose Modifications**
Grade 1 or 2	No dose modification is required.
Grade 3	Suspend dose until toxicity resolves to ⩽Grade 2. Dose reduction is not required.
Grade 3, recurrent, or Grade 4	Suspend dose until toxicity resolves to ⩽Grade 2. Resume at next lower dose.
Patient requires administration of a blood cell growth factor	Suspend abemaciclib dose for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ⩽Grade 2. Resume abemaciclib at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor.

General Guidance for Non-hematologic Toxicities (excluding diarrhea, ILD/Pneumonitis and increased ALT/AST) Monitoring

Table 10: Dose Modification and Management — Non-hematologic Toxicities Excluding Diarrhea and ALT Increased

CTCAE Grade	Abemaciclib Dose Modifications
Grade 1 or 2	No dose modification is required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 3 or 4	

6.4.3.1. Therapy for Febrile Neutropenia

Patients experiencing febrile neutropenia, especially with diarrhea or dyspnea, should be managed in a hospital setting according to standard procedures, with the urgent initiation of IV antibiotic therapy. Events that require a patient to be hospitalized are considered SAEs

6.4.3.2. Growth Factor Therapy

Growth factors should not be administered to a patient to satisfy study inclusion criteria. Growth factors may be administered in accordance with ASCO guidelines (Smith et al. 2015). Dosing of abemaciclib must be suspended if the administration of growth factors is required and must not be recommenced within 48 hours of the last dose of growth factors having been administered. Following the administration of growth factors, the dose of abemaciclib must be reduced to the previous dosing level on recommencement, if a dose reduction for the specific event necessitating the use of the growth factors has not already occurred.

6.5. Criteria for permanent discontinuation of study drug(s)

Subjects may withdraw consent at any time for any reason or be withdrawn from the study at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the sponsor if enrollment into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.
Subjects must be withdrawn from the study treatment for the following reasons:

- In the investigator's medical judgment, further participation would be injurious to the subject's health or well-being.

- Consent is withdrawn by the subject or legal representative (such as parent or legal guardian).

・The study is terminated by the sponsor.

・The study is terminated by the local health authority or IRB/IEC.

・The subject has experienced an unacceptable toxicity or a toxicity that does not recover in 2 weeks.
Investigators who wish to continue treatment after a treatment delay of 2 weeks should consult with the sponsor's medical monitor for approval.

・Noncompliance with study treatment or procedure requirements.

・The subject is lost to follow-up.

6.6. Study Completion

6.6.1. Study completion criteria

Subjects will be considered completing the study if they met any of the following criteria:

・Subject dies and a date of death is available.

・Subject is known to have died; however, the date of death cannot be obtained.

(NOTE: every effort must be made to obtain the date of death.)

・Consent is withdrawn for any further contact related to this study.

・Subjects may choose to withdraw from the study at any time without penalty of jeopardizing their health care or loss of benefits to which the subject is otherwise entitled. Every reasonable effort should be made to determine the reason a subject withdraws prematurely, and this information should be recorded in the eCRF.

・The study is terminated by the sponsor.

・The study is terminated by the local health authority or IRB or IEC.

6.6.2. Withdrawal procedures

In the event that any subject discontinues study drug and, subsequently, withdraws from the study before completion, regardless of reason, reasonable efforts should be made to have the subject return for the EOT procedures to be completed. The date the subject was withdrawn from the study and the specific reason for withdrawal will be recorded in the eCRF.

If a subject is withdrawn from the study:

・The study monitor or sponsor must be notified.

・The reason(s) for withdrawal must be documented in the subject's medical record and in the eCRF.

・The EOT or early termination visit should be performed.

・Subjects must be followed for safety until the time of the follow-up visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer.

6.7. Concomitant Medications

No other approved or investigational anticancer treatment will be permitted during the study period. No other investigational drug may be used during treatment on this protocol, and concurrent participation in another clinical trial is not allowed.

Abemaciclib is predominantly cleared by oxidative metabolism via CYP3A4. Clinical drug interaction studies with a CYP3A inhibitor and CYP3A inducer significantly altered the PK of abemaciclib and its circulating major metabolites.

CYP3A inducers

Avoid concomitant use of CYP3A inducers and consider alternative agents.

CYP3A inhibitors

Avoid concomitant use of strong CYP3A inhibitors (for example, voriconazole) and use caution with coadministered moderate (for example, ciprofloxacin) or weak (for example, ranitidine) CYP3A inhibitors. If concomitant use cannot be avoided, abemaciclib dose adjustments may be required:

- Patients who must take CYP3A inhibitors such as clarithromycin, diltiazem, or verapamil should reduce the abemaciclib dose to 100 mg twice daily.
- Patients who must take itraconazole should reduce the abemaciclib dose to 50 mg twice daily.
- Patients who must take ketoconazole should reduce the abemaciclib dose to 50 mg once daily.
- Patients should avoid grapefruit or grapefruit juice.

  Strong CYP3A inhibitors and/or inducers should not be used until the completion of the dose-limiting evaluation period.

Patients who receive nonsteroidal anti-inflammatory drugs (NSAIDs) on study should also receive peptic ulcer disease (PUD) prophylaxis with a histamine-2 (H2) blocker or proton pump inhibitor.

Narcotic analgesics, NSAIDs, ketorolac and triptans (e.g., sumatriptan) may be offered as needed for relief of pain or headaches. Antihistamines and decongestants may be offered for the treatment of sinus congestion.

Antibiotic prophylaxis should be used for invasive dental procedures.

Packed red blood cells, colony stimulating factors, and platelet transfusions should be administered as clinically indicated.

6.8. Treatment Compliance

All infusions (ADT) and oral intake of Abemaciclib will occur at the investigational site under the direct supervision of the Investigator or his or her designee.

6.9. Patient Enrollment

Patients will be manually enrolled by site research coordinator in Oncore database and assigned an 8-digit patient number. This 8-digit number will be used to identify patients throughout their participation in the trial. A regulatory binder will be provided and will include detailed instructions for the manual enrollment process.

6.10. Beginning and End of the Study

The study begins when the first subject signs the informed consent. The end of the study may be designated as the timepoint when all subjects have discontinued the study. At this point a database lock of the study may occur to allow the analysis of the study data.

7. ASSESSMENT OF EFFICACY

7.1. PSA serial measurements

Serum samples for assessment of PSA levels will be collected at all study visits and analyzed by the central laboratory. Additional assessments of PSA levels during the subject's participation in the study, either done for-cause or per standard of care, should be done through the central laboratory as well. Before the start of the study, sampling and storing procedures will be provided in a laboratory manual.

8. ASSESSMENT OF SAFETY

8.1. Safety Parameters

Safety will be characterized in terms of the incidence, timing, severity graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03), seriousness, and drug-relatedness of adverse events (AEs) and laboratory abnormalities. In addition, physical examination, vital signs, and ECOG performance status will be serially monitored. Laboratory safety analyses will be based on the data from which labs are collected, and will include hematology (including iron studies at baseline), serum chemistry (including liver and kidney function, and TSH), urinalysis, and coagulation profile (baseline only). Serum will also be assessed for immunogenicity to Abemaciclib (including anti-product antibody titers). In addition, single tracing 12-lead ECGs will be performed at the time points indicated in the Schedule of Assessments (Table 2). QT, PR and QRS intervals and heart rate will be captured. ECGs will also be collected as clinically indicated throughout the study.

8.1.1. Laboratory Safety Assessments

Abnormal and clinically significant laboratory tests should be recorded as adverse events. To meet the definition of clinically significant, the test result generally requires a change in medical management (e.g., new medication, unplanned treatment, additional tests, etc.).

8.1.1.1. Hematology, Serum Chemistry, and Coagulation Test

Assessments will be performed at the time points indicated in the Schedule of Assessments (Table) and analyzed at laboratories where collected. Investigators may have additional blood tests performed for the purpose of planning treatment administration, or for following AEs, as clinically indicated.

- Hematology: Complete blood count (CBC) with differential and platelet count.
- Coagulation: Prothrombin time and International Normalized Ratio (INR).
- Serum Chemistry: Total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, lipase, amylase, sodium, potassium, bicarbonate, chloride, calcium, phosphorus, blood urea nitrogen, creatinine, magnesium, thyroid stimulating hormone (TSH), and glucose.
- Patients must agree to use effective contraception during the study and for ≥ 180 days following last dose of study drug (Abemaciclib). The definition of effective contraception is provided in Section 2.6.1 of this protocol.

8.1.1.2. Urinalysis

Urinalysis (without microscopic analysis, unless indicated) will be performed at time points indicated in the Schedule of Assessments (Table 2) and analyzed by local laboratories. Microscopic analysis, urine protein-creatinine ratio (UPCR), and 24-hour urine collection for protein should be performed as clinically indicated.

8.1.2. Physical Examination

A physical examination including, but not limited to, general appearance, head, eyes, ears, nose, throat, neck, heart, chest, abdomen, musculoskeletal, extremities, skin, lymph nodes, neurological, genitourinary (as appropriate), and rectal (as appropriate) will be assessed at time points indicated within the Schedule of Assessments (2). The physical examination will include examination of known and suspected sites of disease.

8.1.3. Vital Signs

Heart rate, temperature, blood pressure, respiratory rate, and weight will be assessed at time points indicated within the Schedule of Assessments (Table 2). Height will be assessed only at the Screening visit. Heart rate, temperature, blood pressure, and respiratory rate will also be assessed during Abemaciclib as described in Section 4.1.2.2 and the footnotes of the Schedule of Assessments (Table 2).

8.1.4. Performance Status

The ECOG scale will be used to assess performance status at Screening and at time points indicated within the Schedule of Assessments (Table 2).

8.1.5. Electrocardiogram (ECG)

A single tracing 12-lead tracing will be used for all ECGs. It is preferable that the machine used has a capacity to calculate standard intervals automatically. ECG will be performed at the time points indicated in the Schedule of Assessments (Table 2) and as clinically indicated throughout the study.

8.2. Adverse Events

All observed or volunteered AEs regardless of suspected causal relationship to study drug (Abemaciclib) will be reported as described below.

8.2.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a trial patient who is administered a drug or biologic (medicinal product); the event may or may not have a causal relationship with the medicinal product. Examples of AEs include, but are not limited to the following:

- Clinically significant symptoms and signs including:
  - Worsening of signs and symptoms of the malignancy under study drug treatment (Note: Disease progression with or without worsening of signs and symptoms assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs unless the outcome is fatal during the study or within the safety reporting period for the study.)
  - Signs and symptoms resulting from drug overdose, abuse, misuse, withdrawal, sensitivity, dependency, interaction, or toxicity
  - All treatment-emergent possibly related and unrelated illnesses, including the worsening of a preexisting illness
  - Injury or accidents - Note that if a medical condition is known to have caused the injury or accident (e.g., hip fracture from a fall secondary to dizziness), the

medical condition (dizziness) and the outcome of the accident (hip fracture from a fall) should be reported as 2 separate AEs.

  - Symptoms or signs resulting from exposure *in utero*

- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat confirmatory test)
- Laboratory abnormalities that meet any of the following criteria (Note: Merely repeating an abnormal test, in the absence of any of the below conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.)
  - Test result that is associated with accompanying symptoms
  - Test result that requires additional diagnostic testing or medical/surgical intervention
  - Test result that leads to a change in study drug (Abemaciclib) dosing other than protocol-stipulated dose adjustments or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy
  - Test result that is considered to be an AE by the Investigator or ELI LILLY

8.2.2. Serious Adverse Events

An AE that meets one or more of the following criteria/outcomes is classified as a serious /ae (SAE):

- Results in death
- Is life-threatening (i.e., at immediate risk of death)
- Requires in patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defect
- Other Important Medical Events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependence or drug abuse.

Serious also includes any other AE that the Investigator or sponsor judges to be serious, or which is defined as serious by the Health Regulatory Authority (HRA) in the country in which the event occurred.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal during the study or within the safety reporting period for the study. Hospitalizations due to signs and symptoms of disease progression should not be reported as SAEs. However, if the malignancy has a fatal outcome

during the study or within the safety reporting period for the study, then the AE leading to death must be recorded as an SAE with CTCAE Grade 5.

The onset date of an SAE is defined as the date on which the event initially met serious criteria (e.g., the date of admission to a hospital). The end date is the date on which the event no longer met serious criteria (e.g., the date the patient was discharged from a hospital).

8.2.2.1. Hospitalization

AEs associated with in-patient hospitalization, or prolongation of an existing hospitalization, are considered serious. Any initial admission, even if the duration is less than 24 hours, is considered serious. In addition, any transfer within the hospital to an acute/intensive care unit is considered serious (e.g., transfer from the psychiatric wing to a medical floor or transfer from a medical floor to a coronary care unit). However, the following hospitalizations **should not** per se constitute a serious AE:

- Rehabilitation facility admission
- Hospice facility admission
- Respite care
- Skilled nursing facility admission
- Nursing home admission
- Emergency room visit, including observation unit visit
- Outpatient same day surgery/procedure
- Hospitalization or prolongation of hospitalization in the absence of precipitating clinical adverse events as follows:
  - Admission for treatment of preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition
  - Social admission
  - Administrative admission (e.g., for yearly physical exam)
  - Protocol-specified admission during a clinical trial
  - Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery)
  - Preplanned treatments or surgical procedures that are not related to an SAE
- Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. The medical condition for which the procedure was performed should be reported if it meets the definition of an AE (e.g., acute appendicitis that begins during the AE reporting period should be reported as an AE and the appendectomy should be recorded as a concomitant treatment).

8.3. Reporting Adverse Events

8.3.1. Eliciting Adverse Event Information

The Investigator is to report all directly observed AEs and all AEs reported by the study patient using concise medical terminology. In addition, each study patient will be questioned about AEs at each clinic visit following initiation of treatment. The question asked will be, or words to the effect, "Since your last clinic visit have you had any health problems?"

8.3.2. Adverse Event Reporting Period

Safety information for each patient will be collected from the date of informed consent. AEs occurring prior to the initiation of the study treatment with Abemaciclib study drug will be considered " baseline-emergent adverse events," will be recorded on corresponding CRFS and will not be retained for patients who fail screening. The AE reporting period for this study begins when the patient has received even a portion of the first dose of Abemaciclib study drug and ends 28 days after the last dose of the latest study treatment (i.e., Abemaciclib study drug) is administered.

All AEs that occur in study patients during the AE reporting period specified in the protocol must be reported to ELI LILLY, whether or not the event is considered study treatment-related. In addition, any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as possibly related to either investigational medication/product should also be reported as an AE.

8.3.3. Reporting Requirements

- To comply with applicable laws, regulations and standards regarding Investigator's and Institution's obligations, as the sponsor of the Study, to collect and report adverse events to regulatory authorities, IRBs, Ethics Committees or other third parties. In addition to the obligations set forth below, Investigator and Institution agree to provide Lilly with a copy of all information Investigator and/or Institution submit to regulators related to any adverse events for the Study Drug that occur during the Study that Investigator and/or Institution have not otherwise provided Lilly;

- To notify Lilly, sub-investigators, and the IRB of any problems involving risk to Study patients and report new safety information to IRBs in accordance with applicable requirements;

- to notify Lilly within twenty-four (24) hours of Investigator and/or Institution receiving notification of any "serious" adverse event experienced by a patient participating in the Study and receiving Study Drug. For purposes of this requirement, "serious" means: (1) death; (2) in-patient hospitalization or prolonged hospitalization; (3) life-threatening; (4) persistent or significant disability or incapacity; (5) congenital anomaly or birth defect; or (6) other serious events that may jeopardize the patient and may require medical or surgical intervention to prevent one of the other five listed outcomes. Serious adverse events should be reported to Lilly using a CIOMS Form or other form acceptable to Lilly. Investigator and Institution further agree to make available promptly to Lilly such records as may be necessary and pertinent for Lilly to further investigate an adverse event in the Study that is possibly associated with the Study Drug.

For SAEs which are fatal or life-threatening, unexpected, and associated with use of the study drug (Abemaciclib), a 7-Day Alert Report will be submitted to the FDA within 7 calendar days of receipt of the SAE information. For all other SAES that are unexpected and associated with use of the study drug (Abemaciclib), a written report will be made no more than 15 calendar days from the date Eli Lilly learns of the event. Participating clinical sites will be notified of these events in parallel with FDA notification.

All AEs, including SAEs, are to be reported on the AE CRFs.

8.3.4. Recording Adverse Events in the Case Report Forms

The Investigator is to report all directly observed AES and all AEs reported by the study patient. In addition, each study patient will be questioned about AEs. All AEs that meet the criteria specified in Section 8.2.1 are to be recorded on patient source documents and on the CRFs. AEs should be reported using concise medical terminology on the CRFs.

8.3.5. Grading of Adverse Event Severity

To report AEs on the CRFs, the Investigator will use the severity grading as described in NCI CTCAE (Version 4.03). Every effort should be made by the Investigator to assess the AE according to CTCAE criteria. If the Investigator is unable to assess severity because the term is not described in NCI CTCAE (Version 4.03), then severity of MILD, MODERATE, SEVERE, LIFE-THREATENING, or FATAL may be used to describe the maximum intensity of the AE, as guided by Table 10 Note that the selection of the most appropriate verbatim term for AEs is not restricted to only those toxicities represented in NCI CTCAE. For purposes of consistency, these intensity grades are defined as follows:

Table 10: Adverse Event Grading

Grade	Non-CTCAE Severity	Definition
1	Mild	Does not interfere with patient's usual function
2	Moderate	Interferes to some extent with patient's usual function
3	Severe	Interferes significantly with patient's usual function
4	Life-Threatening	Results in immediate risk of patient's death
5	Fatal	Results in patient's death

Note the distinction between the severity and the seriousness of an AE. A severe AE is not necessarily a serious AE. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for serious events.

8.3.6. Relationship to Treatment Drugs (Abemaciclib)

In this study, there are 2 study drugs; the investigational drug Abemaciclib is given in combination with ADT. The relationship of each AE to each study drug will be made and

should be guided in part by the known safety profile of each drug, including the Abemaciclib IB. The relatedness should be classified by the Investigator using the following guidelines:

- Suspected Adverse Reaction: There is a reasonable possibility that study drug caused the AE (i.e., there is evidence to suggest a causal relationship between study drug and the AE).
- Not Related: There is no reasonable possibility that the AE is associated with study drug.

AEs related to study drug are considered Adverse Drug Reactions (ADR).

8.3.7. Expectedness

All AEs and ADRs are considered "unexpected" if not listed in the Abemaciclib IB. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected ADRs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.3.8. Exposure in Utero

If the partner of a study patient becomes or is found to be pregnant during the study or within 90 days of discontinuing the investigational medication/product, the Investigator must report the information to ELI LILLY, or designee via the Pregnancy Notification Report Form within 24 hours of awareness of the pregnancy. This must be done irrespective of whether an AE has occurred. The information submitted should include the anticipated date of delivery.

The Investigator will follow the pregnant partner of a study patient until completion of the pregnancy or until pregnancy termination (i.e., induced abortion) and then notify ELI LILLY, or its designee, of the outcome within 5 days or as specified below. The Investigator will provide this information as a follow-up to the initial report. The reason(s) for an induced abortion must be specified.

The Investigator should follow procedures for reporting an SAE if pregnancy outcome meets criteria for an SAE (e.g., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]).

In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth and the Pregnancy Outcome Report Form should be completed (i.e., no minimum follow-up period of a presumably normal infant must pass before a Pregnancy Outcome Report Form can be completed). The "normality" of an aborted fetus can be assessed by gross visual inspection unless pre-abortion laboratory findings are suggestive of a congenital anomaly.

Additional information about pregnancy outcomes that are classified as SAEs follows:

- "Spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 1 month that the

Investigator assesses as possibly related to the *in utero* exposure to the study drug should also be reported.

8.3.9. Follow-up of Unresolved Adverse Events

All AEs should be followed until resolved, improved to the patient's pre-treatment baseline severity or better, or the patient's participation in the study is completed, whichever occurs first. All serious adverse events and those non-serious events assessed by the Investigator as suspected reactions (i.e., at least possibly related) to a Abemaciclib must be followed, even after the patient's withdrawal from study, until the event is either resolved, improved to the patient's pre-treatment baseline or better, stable without anticipated future change, or the patient is lost to follow-up, or, in the case of a suspected adverse reaction, later determined to be not related to the ELI LILLY investigational medicinal product. Any increase or decrease in AE grade should be recorded as a new adverse event. All AEs should also be documented on the AE CRF.

8.4. Safety Monitoring

Data and Safety Monitoring Plan

Dr. Eddy Yang will function as the sponsor of the trial at UAB. The UAB Comprehensive Cancer Center Data and Safety Monitoring Plan (DSMP) instituted by the CTNMO will monitor subjects treated at UAB in the trial. The Clinical Trials Monitoring Committee (CTMC) on a weekly basis will closely monitor adverse reactions observed during treatment. The CTMC is responsible for data and safety monitoring of the trial and adherence to the DSMP. The independent Quality Assurance Committee (QAC) is responsible for oversight of the operation of CTMC, including adherence to the DSMP. Reports from the CTMC are reviewed annually by the QAC.

These committees will monitor safety throughout this study and all studies of Abemaciclib via the following activities:

- Surveillance for SAEs according to regulatory guidelines
- Routine monitoring of non-serious AES as they are recorded in the CRFs and the source documents at study sites

Toxicity information that may affect the treatment of patients on this study will be promptly communicated in writing to all participating Abemaciclib clinical sites, as well as institutions participating in this clinical trial.

9. OTHER ASSESSMENTS

9.1. Other Laboratory Assessments

9.1.1. Tumor Biopsies

Tumor biopsies will be fixed in formalin and embedded in paraffin, and immune cell markers will be assessed by immunohistochemistry and immunofluorescence, focusing on CD8+ T-cells, T regulatory cells, and MDSCs.

9.1.2. Biomarker analysis

The current standard extended-sextant 12 core prostate biopsy technique is essentially a random but systematic sampling in various regions of the prostate gland, serving as a surrogate sampling technique. However, the natural course of most clinically-significant prostate cancer appears to be driven by dominant intra-prostatic lesions (IPL). Advances in multi-parametric prostate MRI (mpMRI) have allowed for identification and radiographic risk stratification of these IPLs, and real-time fusion of mpMRI with trans-rectal ultrasound (TRUS) now allows urologists to perform targeted biopsies of IPLs with optimized detection of clinical significant prostate cancer foci. At UAB, we have analyzed specimens obtained from targeted biopsies from high risk (Gleason score 8 and above) and low risk (Gleason score 6). Using the Nanostring nCounter platform, we were able to find deregulation of various cancer driver pathways (DNA repair, Wnt, Notch, cell cycle, PI3K, and ras) in high risk vs. low risk cancers14. Furthermore, imaging metrics such as DCE and PiRADS scores also correlated with pathway deregulation. Given these findings, we also propose to use archived tumor tissue from diagnostic biopsy as well as imaging with MRI-US fusion and conducting an optional biopsy at 6 months post-RT. Tumor samples will be assessed for mutations using the Strata Oncology panel and for gene expression analysis using the Nanostring nCounter platform and the PanCancer Pathways panel. Imaging characteristics, such as DCE and PiRADs scores, will be correlated with PSA response and outcomes. Given the emergence of blood-based analysis of biomarkers, we will also collect blood at baseline, pre-radiotherapy (2-3 months of ADT+abemaciclib), 1 and 6 months post-RT to perform molecular analysis to correlate with PSA responses

10. STATISTICS

10.1. Statistical Design/Sample Size

Simon's optimal two-stage design (Simon, 1989) will be used for conducting the trial. The null hypothesis is that the proportion of patients with PSA <0.5 without treatment is 5%, and the alternative hypothesis is that the proportion of patients with PSA <0.5 at 6 weeks into treatment is 30% or higher. The trial is carried out in two stages. In stage I, a total number of 5 patients is accrued. If there are 0 response (PSA< 0.5) among these 5 patients, the study will be early stopped. Otherwise, additional 18 patients will be accrued in stage II, resulting in a total number sample size of 23. If there are 4 or more responses (PSA< 0.5) among these 23 patients, we reject the null hypothesis and claim that the treatment is promising. The design controls the type I error rate at one-sided 0.025 and yields the power of 80%. If we reject the null hypothesis, seven additional patients will be enrolled to explore the association between biomarkers and clinical activities. To account for 10% screen failure, total 33 patients will be recruited to the study.

10.1.1. Definition of Analyzed Study Populations

The following study populations will be considered when reporting study results:

- The study population for safety includes all patients receiving at least a portion of 1 dose of study drug (Abemaciclib).
- The study population for efficacy will include all safety population patients who have baseline and follow-up tumor measurements as required for assessment by iRECIST.

Only those patients who are deemed ineligible (e.g., do not satisfy eligibility criteria) or who receive no study drug (i.e., no Abemaciclib) will be eliminated from the analysis. Ineligible patients who receive therapy will not be included in the assessment of efficacy endpoints, but their data will be included in the assessment of all AE reporting.

10.2. Data Analysis

Simon's optimal two-stage design (Simon, 1989) will be used for conducting the trial. The null hypothesis is that the proportion of patient with PSA <0.5 without treatment is 5%, and the alternative hypothesis is that the proportion of patient with PSA <0.5 at 6 weeks into treatment is 30% or higher. The trial is carried out in two stages. In stage I, a total number of 5 patients is accrued. If there are 0 response (PSA< 0.5) among these 5 patients, the study will be early stopped. Otherwise, additional 18 patients will be accrued in stage II, resulting in a total number sample size of 23. If there are 4 or more responses (PSA< 0.5) among these 23 patients, we reject the null hypothesis and claim that the treatment is promising. The design controls the type I error rate at one-sided 0.025 and yields the power of 80%. This response rate will be summarized using both a point estimate and its 2-sided 95% confidence limits. If we reject the null hypothesis, seven additional patients will be enrolled to explore the association between biomarkers and clinical activities. Descriptive statistics will be used to summarize patient demographics, baseline characteristics, treatment administration/compliance, efficacy, biomarkers, and archival tumor tissue, safety, and efficacy parameters. Time to PSA failure will be analyzed using the Kaplan-Meier method. The assessment of safety data will be based on the summarization of treatment related AEs, SAEs, AEs leading to discontinuation from study treatment or efficacy follow-up, and clinical laboratory tests. Data will also be displayed graphically, where appropriate.

10.2.1. Analysis of Primary Objective

For each patient, PSA will be measured on systemic treatment with Abemaciclib and ADT after radiotherapy. The primary endpoint is percentage of patients who achieve the PSA nadir levels of ≤ 0.5 ng/ml during their treatment. Simon's optimal two-stage design (Simon, 1989) will be used for conducting the trial. The null hypothesis is that the proportion of patient with PSA <0.5 is 5%, and the alternative hypothesis is that the proportion of patient with PSA <0.5 is 30% or higher. The trial is carried out in two stages. In stage I, a total number of 5 patients is accrued. If there are 0 response (PSA< 0.5) among these 5 patients, the study will be early stopped. Otherwise, additional 18 patients will be accrued in stage II, resulting in a total number sample size of 23. If there are 4 or more responses (PSA< 0.5) among these 23 patients, we reject the null hypothesis and claim that the treatment is promising. The design controls the type I error rate at one-sided 0.025 and yields the power of 80%. This response rate will be summarized using both a point estimate and its 2-sided 95% confidence limits.

10.2.2. Analysis of Secondary Objective

For each patient, PSA declines prior to radiotherapy- calculated from nadir level prior to initiation of radiation therapy compared from pre-treatment baseline - will be listed. The secondary endpoint will be reported as percentage of patients who achieve a PSA decline prior to radiotherapy with combination treatment of ADT and Abemaciclib compared to their baseline PSA levels. This response rate will be summarized using both a point estimate and its 2-sided 95% confidence limits.

Another secondary endpoint will be time to PSA failure. Time to PSA failure will be analyzed using the Kaplan-Meier method. SAEs (including deaths) will be tabulated. Subject listings of all AEs, SAEs (including deaths), and their attribution will be provided.

All AEs with an onset after initiation of treatment will be considered as treatment-emergent AEs. A preexisting condition that worsens after study drug treatment will also be considered as a treatment-emergent AE. All AEs will be coded by MedDRA SOC and PT.

The number and percentage of patients with the following types of treatment-emergent AEs will be summarized: all AEs, all SAEs, AEs related to study drug ((Abemaciclib), AEs resulting in study drug discontinuation, and clinically significant laboratory abnormalities. Non-treatment-emergent serious AEs will be presented separately from treatment-emergent AEs. Deaths will be reported with demographic information. Laboratory results will be summarized descriptively by dose level. Additional exploratory statistical analysis will be performed as it deemed necessary.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

All data entered on CRFs/electronic CRFs (eCRFs) must be verifiable within the patients' source documents (written or electronic record). UAB PI, CTNMO, QAC, and appropriate regulatory authorities direct access to the original source records for the duration of the agreed study record retention period. Printouts of source records that are electronically obtained and stored will not be acceptable for audit/inspection unless provided as certified exact copies and the data remains as meaningful and useful as in its original electronic state.

Legally protected patient identification and other personal health information must be securely stored with limited access by the participating institutions. Unless secure provisions are established by the institution to allow ELI LILLY (or designee) to perform remote monitoring of electronic source records, ELI LILLY (or designee) will review source records/data on site and will not remove any such protected health information.

12. QUALITY CONTROL AND QUALITY ASSURANCE

CTNMO and QAC committee at UAB will conduct monitoring periodically during the trial to ensure that GCPs and all aspects of the protocol are being followed.

The trial site will also be subject to possible inspection by the institutional review board (IRB) or independent ethics committee (IEC) or other appropriate regulatory authority. The trial site is also subject to quality assurance audits performed by UAB CTNMO and QAC.

It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits, audits, and inspections and that sufficient attention, time, and support is devoted to the process.

UAB CTNMO and QAC will be governed by applicable regulations, GCP standards, and internal standard operating procedures (SOPs) for the conduct of monitoring visits and quality assurance (QA) audits.

13. ETHICS

13.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the Investigator to have approval of the study protocol, protocol amendments, informed consent forms, advertisements from the IRB/IEC, and any other patient-distributed materials before potential patients are consented for participation on the trial. All correspondence and other evidence of appropriate and timely communications with the IRB/IEC should be retained in the Investigator/site files. Copies of all IRB/IEC approvals should also be forwarded to ELI LILLY.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the Investigator must notify the IRB/IEC and ELI LILLY in writing within 5 business days after the implementation.

13.2. Ethical Conduct of the Study

The trial will be performed in accordance with the protocol, applicable local regulatory requirements and laws, and the International Council on Harmonization (ICH) Guideline on Good Clinical Practice (GCP), which supports the application of ethical principles that have their origin in the Declaration of Helsinki (see ICH E6, § 2.1).

13.3. Written Informed Consent

The informed consent form language must be agreed upon by UAB PI and the IRB/IEC and must be in compliance with ICH GCP, local regulatory requirements, and legal requirements. The informed consent information must not be changed without prior approval by UAB PI and the IRB/IEC. The informed consent form used in this trial, and any changes made during the course of the study, must be approved by both the IRB/IEC and UAB PI, before use.

It is the responsibility of the Investigator to give each patient full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. This information must be provided to the patient prior to undertaking any protocol-specified procedure. Patients must be informed about their right to withdraw from the trial at any time. Furthermore, it is the responsibility of the Investigator to ensure all patients are appropriately informed before obtaining their signed and dated consent. Signatures from the Investigator conducting the informed consent discussion should also be obtained, prior to undertaking any trial-related procedure. Consent by a legally authorized representative is not permitted. Should an impartial witness be needed, ICH E6 requirements for impartial witnesses will apply.

The Investigator will retain the original of each patient's signed consent form in the Investigator/site files.

13.4. Patient Compensation

Patients will not be compensated for participation in this study; this will be outlined in the patient informed consent form.

14. DATA HANDLING AND RECORDKEEPING

14.1. Inspection of Records

CRFs/eCRFs are required and should be completed for each patient who receives treatment with Abemaciclib. Screen failure CRF's will not be collected. Nevertheless, records of potential patients identified and screened shall be retained on site screening logs. The completed original CRFs/eCRFs are the sole property of UAB Comprehensive Cancer Center and should not be made available in any form to third parties without written permission from UAB PI (except for authorized representatives of the HRA and in accordance with Health Insurance Portability and Accountability Act [HIPAA] regulations).

It is the Investigator's responsibility to ensure completion and to review and approve all CRF data. The investigator will sign off on his/her data per patient. These signatures serve to attest that the Investigator has reviewed and approved the information contained on the CRFs and that the information is complete, accurate, and true. At all times, the Investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs.

The use of electronic CRFs (eCRFs) to capture study data using automated computerized data capture systems does not change the principles and requirements for collecting study data. The Investigator still retains final personal responsibility for eCRF data and any associated data pertaining to it (e.g., metadata including any record of change to the originally recorded data). The Investigator's signed approval of the eCRF data serves to attest that the electronic data and all of its associated metadata (including changes) has been reviewed and accepted as complete, accurate, and true for each patient in the study.

14.2. Retention of Records

To allow for appropriate evaluations and/or audits by regulatory authorities UAB PI agrees to keep records, including the identity of all participating patients (sufficient information to link records, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, source documents, and detailed records of treatment disposition. The Investigator should retain these records according to local regulations or as specified in the Clinical Trial Agreement, whichever is longer.

If the Investigator relocates, retires, or for any reason withdraws from the study, then ELI LILLY should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution. The Investigator must inform ELI LILLY of any such transfer of responsibilities and properly identify the person or institution assuming the responsibility. The responsible institution must obtain UAB PI's written permission before disposing of any records.

15. DEFINITION OF END OF TRIAL

15.1. End of Trial

End of trial is defined as the time at which all patients enrolled in the study have completed the treatment follow-up period.

.

15.2. ELI LILLY Discontinuation Criteria

Premature termination of this trial may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of ELI LILLY. In addition, ELI LILLY retains the right to discontinue development of Abemaciclib at any time.

ELI LILLY reserves the right to discontinue the trial prior to inclusion of the intended number of patients, but intends only to exercise this right for valid scientific or administrative reasons. If a trial is prematurely terminated or discontinued, ELI LILLY will promptly notify the Investigator. After notification, the Investigator must contact all participating patients within a 28-day time period. As directed by UAB PI, all trial materials must be collected and all CRF data must be completed to the greatest extent possible.

16. PUBLICATION OF TRIAL RESULTS

Publication of trial results is discussed in the Clinical Trial Agreement.

17. FINANCING AND INSURANCE

Financing and Insurance are discussed in the Clinical Trial Agreement.

18. REFERENCES

1. Turner NC, Ro J, Andre F, et al. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. The New England journal of medicine 2015.

2. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. The Lancet Oncology 2015;16:25-35.

3. Comstock CE, Augello MA, Goodwin JF, et al. Targeting cell cycle and hormone receptor pathways in cancer. Oncogene 2013;32:5481-91.

4. Whiteway SL, Harris PS, Venkataraman S, et al. Inhibition of cyclin-dependent kinase 6 suppresses cell proliferation and enhances radiation sensitivity in medulloblastoma cells. Journal of neuro-oncology 2013;111:113-21.

5. Hagen KR, Zeng X, Lee MY, et al. Silencing CDK4 radiosensitizes breast cancer cells by promoting apoptosis. Cell division 2013;8:10.

6. Zhussupova A, Hayashida T, Takahashi M, et al. An E2F1-HOXB9 transcriptional circuit is associated with breast cancer progression. PloS one 2014;9:e105285.

7. Jirawatnotai S, Hu Y, Livingston DM, Sicinski P. Proteomic identification of a direct role for cyclin d1 in DNA damage repair. Cancer research 2012;72:4289-93.

8. Shimura T, Kakuda S, Ochiai Y, et al. Acquired radioresistance of human tumor cells by DNA-PK/AKT/GSK3beta-mediated cyclin D1 overexpression. Oncogene 2010;29:4826-37.

9. Dok R, Kalev P, Van Limbergen EJ, et al. p16INK4a impairs homologous recombination-mediated DNA repair in human papillomavirus-positive head and neck tumors. Cancer research 2014;74:1739-51.

10. Dean JL, McClendon AK, Knudsen ES. Modification of the DNA damage response by therapeutic CDK4/6 inhibition. The Journal of biological chemistry 2012;287:29075-87.

11. Warde P, Mason M, Ding K, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. Lancet 2011;378:2104-11.

12. Mason MD, Parulekar WR, Sydes MR, et al. Final Report of the Intergroup Randomized Study of Combined Androgen-Deprivation Therapy Plus Radiotherapy Versus Androgen-Deprivation Therapy Alone in Locally Advanced Prostate Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2015;33:2143-50.

13. Roach M, 3rd, Bae K, Speight J, et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2008;26:585-91.

14. Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. The Lancet Oncology 2010;11:1066-73.

15. Lawton CA, Winter K, Grignon D, Pilepich MV. Androgen suppression plus radiation versus radiation alone for patients with stage D1/pathologic node-positive adenocarcinoma of the prostate: updated results based on national prospective randomized trial Radiation Therapy Oncology Group 85-31. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2005;23:800-7.

16. Fossa SD, Wiklund F, Klepp O, et al. Ten- and 15-yr Prostate Cancer-specific Mortality in Patients with Nonmetastatic Locally Advanced or Aggressive Intermediate Prostate Cancer, Randomized to Lifelong Endocrine Treatment Alone or Combined with Radiotherapy: Final Results of The Scandinavian Prostate Cancer Group-7. European urology 2016;70:684-91.

17. Brundage M, Sydes MR, Parulekar WR, et al. Impact of Radiotherapy When Added to Androgen-Deprivation Therapy for Locally Advanced Prostate Cancer: Long-Term Quality-of-Life Outcomes From the NCIC CTG PR3/MRC PR07 Randomized Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2015;33:2151-7.

18. Pilepich MV, Winter K, Lawton CA, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase III RTOG 85-31. International journal of radiation oncology, biology, physics 2005;61:1285-90.

19. Ortega S, Malumbres M, Barbacid M. Cyclin D-dependent kinases, INK4 inhibitors and cancer. Biochim Biophys Acta 2002;1602:73-87.

20. Sherr CJ. Cancer cell cycles. Science 1996;274:1672-7.

21. Fujiwara Y, Tamura K, Kondo S, et al. Phase 1 study of abemaciclib, an inhibitor of CDK 4 and 6, as a single agent for Japanese patients with advanced cancer. Cancer Chemother Pharmacol 2016;78:281-8.

22. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR(+)/HER2(-) Metastatic Breast Cancer. Clin Cancer Res 2017;23:5218-24.

23. Sledge GW, Jr., Toi M, Neven P, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2017;35:2875-84.

24. Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2017;35:3638-46.

25. Hurvitz S, Abad MF, Rostorfer R, et al. breast cancer, early stageInterim results from neoMONARCH: A neoadjuvant phase II study of abemaciclib in postmenopausal women with HR + /HER2- breast cancer (BC). Annals of Oncology 2016;27:LBA13-LBA.

26. Iwata H. Clinical development of CDK4/6 inhibitor for breast cancer. Breast Cancer 2018.

19. APPENDICES

19.1. Appendix 1: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

The NCI CTCAE (Version 4.03) should be used to assess adverse events and may be reviewed on-line at the following NCI website:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

19.2. Appendix 2: ECOG Performance Status

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

19.3. Appendix 3: UAB Department of Radiation Oncology Treatment Practice Guidelines

Version 11-30-2017
Sunset Date 6-1-2020

University of Alabama at Birmingham Department of Radiation Oncology
Radiation Oncology Practice Guidelines
Prostate Cancer

Table of Contents

These guidelines represent a consensus of appropriate practices for the management of men with clinically localized prostate cancer within the University of Alabama at Birmingham (UAB) Department of Radiation Oncology. These guidelines will cover the treatment of clinically localized prostate only; treatment of lymph node positive prostate cancer and metastatic cancer are not included. The purpose of this document is to serve as a general reference not to dictate treatment as we recognize that every man with prostate cancer is unique and requires individual management. UAB is a National Cancer Institute designated comprehensive cancer center and member of the National Comprehensive Cancer Network (NCCN). We endorse the NCCN Clinical Practice Guidelines for Prostate Cancer[1] as a general resource for general management of men with prostate cancer; these UAB guidelines are meant to supplement the NCCN Guidelines. Though some overlap with the NCCN Guidelines is necessary, this document will focus on the unique aspects of the UAB approach. We will strive to highlight any areas where the UAB approach is unique with respect to other common clinical practices.

1

Indications/Work Up

- The initial diagnosis of localized prostate cancer is generally made by a urologist who has performed a prostate biopsy. The initial risk stratification of men with prostate cancer requires
    - Tissue sampling
        - Specimens obtained at outside institutions should be re-reviewed by the UAB Department of Pathology for consensus as to the grade
    - Prostate specific antigen (PSA) testing
    - Digital rectal examination (DRE)
- The need for further clinical staging is determined by the risk stratification as defined by the NCCN:

Low Risk (all of the following) - T1c or T2a - PSA ≤ 10 ng/mL - Gleason ≤ 6	- No additional imaging needed. - May consider prostate MRI to aid in treatment planning - Pelvic MRI indicated if SBRT is considered -
Intermediate Risk (any of the following) - T2b or T2c - PSA 10-20 ng/mL - Gleason 7	- For patients with nomogram assessed probability of LN involvement exceeding 10% pelvic imaging (CT or MRI [preferred]) is indicated - Pelvic MRI indicated if SBRT is considered - Pelvic MRI may also be indicated if considering omission of seminal vesicles in CTV
High Risk (any of the following) - T3 or T4 - PSA > 20 ng/mL - Gleason ≥ 8	- Pelvic imaging (MRI [preferred] or CT) - Nuclear medicine bone scan or NaF PET/CT - The role of other PET agents such as fluciclovine can be considered in select cases.

Radiotherapy Options for Primary Therapy

- As with global treatment options, appropriate radiotherapy techniques and choice of the use of androgen suppression is also based on disease and patient characteristics. For men who choose to proceed with a definitive radiotherapy modality a table of recommendations is presented below:

Low Risk	**Life expectancy >20 years:** - Fractionated external beam radiotherapy - Stereotactic body radiotherapy (SBRT) **Life expectancy <20 years:** - Active surveillance
Intermediate Risk	**Life expectancy >10 years:** - External beam radiotherapy +/- short term androgen suppression - SBRT +/- short term androgen suppression (see Appendix B) **Life expectancy <10 years:** - Active surveillance
High Risk	**Life expectancy >5 years:** - External beam radiotherapy + long term androgen suppression (preferred) (see Appendix B) **Life expectancy <5 years:** - Consider androgen suppression therapy (See Appendix B) - Observation

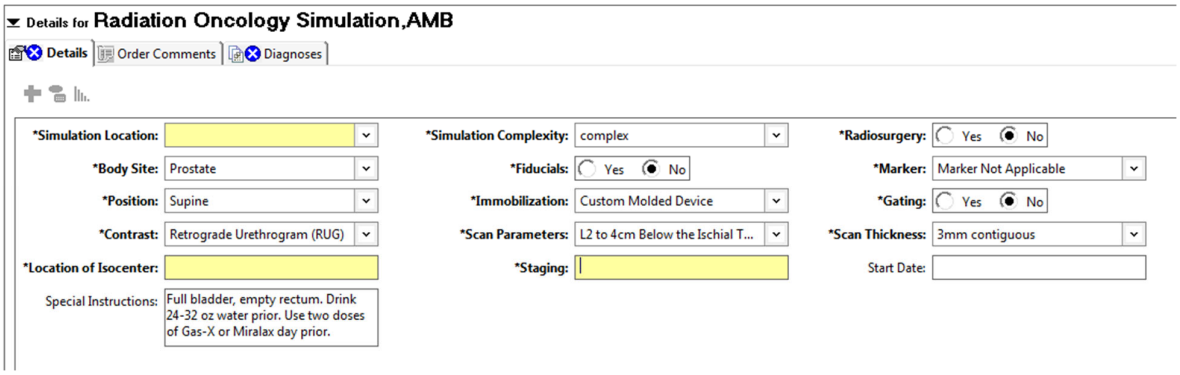
Choice of Fractionation Schedule

- We recommend moderate hypofractionation as the default dosing schedule for men undergoing definitive EBRT
    - See Appendix A for discussion
- Consider protracted fractionation schedule for patients with high IPSS score (>15), inability to meet standard dosimetric constraints, and inflammatory bowel disease

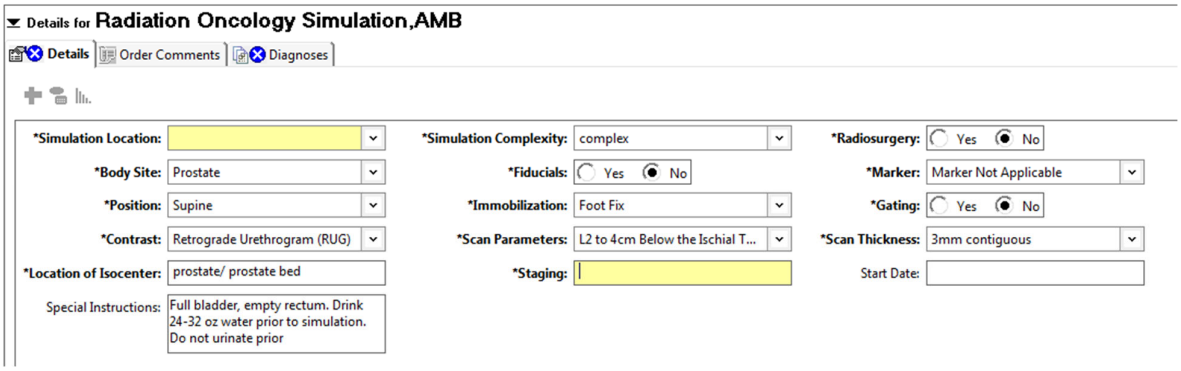
Simulation

- CT simulation is recommended for all men for whom EBRT or SBRT is planned
- Supine position is preferred
    - Foot fix or other immobilization device at the discretion of the treatment team
- Men will be asked to have a full bladder and empty rectum at the time of simulation
    - With respect to bladder fullness, care should be taken that the volume is reproducible.
        - Instruct patients to drink 24-32 oz of fluid 1 hour prior to simulation and treatments
    - A retrograde urethrogram is suggested to aid in the visualization of the apex of the prostate
    - Oral contrast to improve visualization of the small bowel is optional
    - IV contrast is rarely indicated
    - Consider IV contrast in the setting of malignant lymphadenopathy
- The scan should include L2 through the upper femur with 2-2.5mm slices.
- MRI fusion with axial T2 sequence for any patient with an MRI data set

- **Sample Conventionally Fractionated Simulation Order**



- **Sample Prostate (non-SBRT) Simulation Order**



Target Volumes

- **Moderate hypofractionation and conventional fractionation**
    - The Gross Tumor Volume (GTV) within the prostate is not routinely defined
    - The Clinical Target Volume (CTV)
        - CTV1 will always include entire prostate and any gross disease beyond the prostate
            - For men with high risk disease CTV1 should be expanded to include at least the proximal 1-2cm of the seminal vesicles (SV)
                - Inclusion of the entire seminal vesicles should be considered based on clinical judgment
            - For men with intermediate risk disease CTV1 may be expanded beyond the prostate to include the proximal 1-2cm of the SV
                - Alternatively the proximal seminal vesicles may be omitted from CTV1 if an MRI has been obtained and no SV invasion

identified ***or*** the nomogram assessed risk of SV invasion is felt to be very low

- CTV2 is defined for men with high risk prostate cancer
  - CTV2 consists of at-risk lymphatics. Lymph node regions included are:
    - Obturator
    - Internal and external iliac
    - Common iliac
    - Pre-sacral
    - Reference: RTOG Pelvic Node Contouring Atlas (Link)
  - The cranial extent of CTV2 may be variable but should not routinely extend above the superior aspect of the L4 vertebral body

- The Planning Target Volume (PTV)
  - PTV1 will be a geometric expansion around CTV1. Size of the expansion will be 7mm in all directions except posteriorly, where 4mm will be used.
  - PTV2 will be a geometric expansion around CTV2. Size of the expansion will be ***at least*** 8mm in all directions

Dose Prescription

- **Moderate Hypofractionation**
  - PTV1 prescribed 70 Gy in 28 fractions
  - PTV2 prescribed 50.4 Gy in 28 fractions, simultaneously
- **Conventional fractionation**
  - PTV1 prescribed 75-80 Gy in fractions of 1.8-2.0 Gy
  - PTV2 prescribed 45-50.4 Gy in fractions of 1.8 Gy, with sequential cone down to boost PTV1

Dose-Volume Analysis

- Treatment planning goals for moderately hypofractionated and conventionally fractionated regimens are available in the UAB Department of Radiation Oncology Treatment Planning Guide (See Appendix D)

Daily Image Guidance

- The use of daily image guidance (IGRT) is recommended for all men undergoing EBRT
- For fixed field IMRT, images should be triggered by MU, at an interval of approximately 3% of the total MU of the plan. **Fractionated EBRT (conventional or hypofractionated)**
  - Daily CBCT without implanting fiducial markers is felt to be adequate image guidance for men undergoing fractionated EBRT
    - CBCT allows for assessment of bladder, rectal, and prostate anatomy

        - For men with intact prostate cancer the focus of alignment will be at the prostate-rectum interface
            - Where possible, the visible portion of the nodal PTV should also be assessed to ensure that the associated vessels fall within the target volumes. Note that field-of-view limitations may impair ability to visualize upper aspect of the pelvis with CBCT, depending on isocenter placement
        - For men receiving post-prostatectomy RT the focus of alignment will be at the anterior rectal wall at the level of the VUA (vesicoureteral anastomosis)
    - Alignment to implanted fiducial markers may be used instead of daily CBCT
        - Weekly CBCT is strongly recommended to assess soft tissue anatomy and bladder and rectal filling.

Follow up

Disease monitoring	PSA every 3 months for first year and then every 6-12 months thereafter. First follow-up PSA should not be drawn sooner than 3 months post-radiation DRE if PSA is detectable and not actively declining
Androgen suppression monitoring (if applicable)	Bone density monitoring Consider repeating testosterone profile 6-12 months after initiating androgen suppression for men receiving long term therapy
Late toxicity evaluation	IPSS at each visit SHIM at each visit CTCAE assessed lower GI toxicity CTCAE assessed GU toxicity
Imaging	Not routinely indicated

Contributing authors

- Eddy Yang, MD, PhD (Site Leader)
- Andrew McDonald, MD (First Author)
- M. Chris Dobelbower, MD, PhD
- D. Hunter Boggs, MD
- John Fiveash, MD
- Richard Popple, PhD
- Christina Blalock, CMD
- Leesa Cordell, RT(R,T)
- Allen Jamerson, RT(R,T,CT)

References

1. Mohler JL, Armstrong AJ, Bahnson RR, et al. Prostate Cancer, Version 1.2016. Journal of the National Comprehensive Cancer Network : JNCCN 2016;14:19-30.
2. Shipley WU, Seiferheld W, Lukka HR, et al. Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer. The New England journal of medicine 2017;376:417-28.
3. Carrie C, Hasbini A, de Laroche G, et al. Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial. The Lancet Oncology 2016;17:747-56.
4. Dulaney CR, Osula DO, Yang ES, Rais-Bahrami S. Prostate Radiotherapy in the Era of Advanced Imaging and Precision Medicine. Prostate cancer 2016;2016:4897515.
5. Pollack A, Walker G, Horwitz EM, et al. Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2013;31:3860-8.
6. Lee WR, Dignam JJ, Amin MB, et al. Randomized Phase III Noninferiority Study Comparing Two Radiotherapy Fractionation Schedules in Patients With Low-Risk Prostate Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2016;34:2325-32.
7. McDonald AM, Baker CB, Popple RA, Cardan RA, Fiveash JB. Increased radiation dose heterogeneity within the prostate predisposes to urethral strictures in patients receiving moderately hypofractionated prostate radiation therapy. Practical radiation oncology 2015;5:338-42.
8. Pisansky TM, Hunt D, Gomella LG, et al. Duration of androgen suppression before radiotherapy for localized prostate cancer: radiation therapy oncology group randomized clinical trial 9910. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2015;33:332-9.
9. Nabid A, Carrier N, Martin A-G, et al. High-risk prostate cancer treated with pelvic radiotherapy and 36 versus 18 months of androgen blockade: Results of a phase III randomized study. American Society of Clinical Oncology; 2013.
10. Zapatero A, Guerrero A, Maldonado X, et al. High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR): a randomised, controlled, phase 3 trial. The Lancet Oncology 2015;16:320-7.

11. Nguyen PL, Alibhai SM, Basaria S, et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. European urology 2015;67:825-36.

12. Saad F, Adachi JD, Brown JP, et al. Cancer treatment-induced bone loss in breast and prostate cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2008;26:5465-76.

13. Berruti A, Dogliotti L, Terrone C, et al. Changes in bone mineral density, lean body mass and fat content as measured by dual energy x-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. The Journal of urology 2002;167:2361-7; discussion 7.

14. Smith MR, Saad F, Egerdie B, et al. Sarcopenia during androgen-deprivation therapy for prostate cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2012;30:3271-6.

15. Loprinzi CL, Dueck AC, Khoyratty BS, et al. A phase III randomized, double-blind, placebo-controlled trial of gabapentin in the management of hot flashes in men (N00CB). Annals of oncology : official journal of the European Society for Medical Oncology 2009;20:542-9.

16. Irani J, Salomon L, Oba R, Bouchard P, Mottet N. Efficacy of venlafaxine, medroxyprogesterone acetate, and cyproterone acetate for the treatment of vasomotor hot flushes in men taking gonadotropin-releasing hormone analogues for prostate cancer: a double-blind, randomised trial. The Lancet Oncology 2010;11:147-54.

17. Vitolins MZ, Griffin L, Tomlinson WV, et al. Randomized trial to assess the impact of venlafaxine and soy protein on hot flashes and quality of life in men with prostate cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2013;31:4092-8.

Appendix A: Fractionation Schedules

- Moderately hypofractionated dose schedules have been compared to conventionally fractionated dosing schedules in multiple large randomized trials
    - Dulaney *et al.* published a review of the recent literature that readers are referred to for additional reading[4].
- Given this large body of evidence we recommend moderate hypofractionation as the default dosing schedule for men undergoing definitive EBRT
    - Despite this recommendation we recognize that some authors have noted slightly worse late grade 2 GU morbidity with moderate hypofractionation5,6
    - In the Fox Chase randomized trial by Pollack et al. the slightly worse GU morbidity with hypofractionation was limited to those patients with initial IPSS scores of greater than 12, thus for this group of patients conventional fractionation is considered an acceptable alternative5.

- The committee has also expressed concerns about moderate hypofractionation in men who have a history of prior TURP, thus for this group of patients conventional fractionation is also considered an acceptable alternative though we do note that in our institutional series reporting late GU morbidity no patient with prior TURP developed a late urethral stricture7
- Consider protracted fractionation schedule for patients with high IPSS score (>15), inability to meet standard dosimetric constraints, and inflammatory bowel disease

Appendix B: Androgen Deprivation Therapy

- **Patient selection**
  - High risk localized prostate cancer
    - We recommend long-term androgen suppression for all men with high risk prostate cancer in the absence of significant contraindications
      - For men with high risk disease the use of androgen suppression has been associated with an overall survival advantage in multiple randomized trials
  - Intermediate risk localized prostate cancer
    - For men with intermediate risk prostate cancer we recommend *at least* discussing the risks and benefits of androgen suppression
      - For men with intermediate risk disease whether a survival advantage accompanies short term androgen suppression is controversial
      - Trials that have reported improved overall survival with androgen suppression for intermediate risk disease have not utilized the escalated doses of radiation that are now considered standard
    - The decision to proceed with androgen suppression for men with intermediate risk prostate cancer is highly individualized. Some key factors include:
      - Life expectancy
      - Comorbidities
      - Baseline sexual function
      - Goals of care
    - One reasonable strategy is to reserve androgen suppression for men with Gleason 4+3=7 disease or multiple intermediate risk factors (e.g. T2c and PSA > 10ng/mL)
- **Androgen suppression regimens**
  - Androgen deprivation vs. total androgen blockade
    - For men with clinically localized prostate cancer, total androgen blockade for at least 4 months is a historical standard
    - ADT vs. TAB have not been compared head-to-head in localized prostate cancer

        - Among men with metastatic castrate sensitive prostate cancer TAB has not consistently shown an advantage over ADT alone, but one large non-inferiority trial failed to confirm non-inferiority
    - Our recommendation is that an anti-androgen be combined with ADT for at least 2 weeks to prevent testosterone flare associated with GnRH agonists
        - Strong consideration should be given to completing a 4 month course of oral anti-androgen medication for men with high risk disease
    - We endorse the following regimens
        - Leuprolide +/- 2 weeks or 4 months of bicalutmide 50mg
        - Goserelin +/- 2 weeks or 4 months of bicalutamide 50mg
        - Degarelix <u>without</u> bicalutamide
    - The use of second generation anti-androgen medication such as enzalutamide is considered investigational
    - We do not recommend routine use of bicalutamide monotherapy (150mg QD) or orchiectomy

- **Length of androgen suppression**
    - The ideal length of androgen suppression is controversial
    - For intermediate risk prostate cancer 6 months of androgen suppression has been a historical standard
        - A recent clinical trial by the RTOG/NRG found equivalent outcomes among patients who received either 4 or 9 months of androgen suppression[8], thus we also consider 4 months of androgen suppression acceptable
    - For men with high risk prostate cancer the historical standard is 28 (RTOG) or 36 (EORTC) months
        - Recently, a Canadian trial, reported in abstract, found that 18 months of androgen suppression resulted in equivalent outcomes to 36 months[9]. One study has compared short term androgen suppression with long term androgen suppression in the dose-escalated RT era and prostate cancer mortality outcomes were improved with long-term androgen suppression[10].
        - Thus, we recognize an ideal duration of 18-28 months, depending on patient tolerance
- **Monitoring of men during androgen suppression**
    - We strongly recommend assessing testosterone and PSA response at approximately 8 weeks following the initiation of androgen suppression
        - Goal testosterone levels are <50
- **Supportive care of men receiving androgen suppression**

- Androgen suppression therapy has been associated with a variety of adverse effects that can be associated with significant bother and morbidity

- The most common manifestations and supportive strategies are outlined here. For more information please refer to the excellent review article by Nguyen *et al.*[11]
- *Bone effects:* Decreases in bone mineral density (BMD) typically occur within 1 year of beginning androgen suppression therapy[12,13]. This decline in BMD has been associated with an increased risk of hip and vertebral compression fractures. To mitigate these effects we recommend the following:
    - **Fracture risk assessment should be performed for all patients using the FRAX clinical fracture risk estimator**. For these purposes androgen suppression therapy is considered secondary osteoporosis.
    - Men with a 10-year hip fracture risk ≥3% or major osteoporotic fracture risk ≥20% should be referred to an osteoporosis specialist.
    - Dual energy x-ray absorptiometry (DXA) should be considered for men at elevated risk but who do not meet the above threshold.
    - Consider DXA measurement at 1 year following the initiation of androgen suppression.
    - All men who receive androgen suppression should be counseled on calcium and vitamin D supplementation in accordance with the NOF guidelines. A minimum of 1,200 mg/day calcium and 800-1,000 IU vitamin D are recommended.
    - Weight bearing exercise should be encouraged in order to improve bone health.
- *Cardiac effects*: The pathogenesis of cardiac morbidity among men who receive androgen suppression is controversial. Recent reviews and meta-analyses have generally concluded that androgen suppression increases the risks of cardiovascular events but not mortality.
    - In terms of managing cardiovascular risks we recommend close communication with patients' other physicians such as primary care providers and cardiologists.
    - The decision to use androgen suppressing agents in men with pre-existing cardiac morbidity should be undertaken on an individual basis as evidence is conflicting on the risks and benefits.
- *Muscle mass:* Significant changes in body composition can manifest within months of initiation of androgen suppression[14].
    - To combat these changes weight bearing exercise, cardiovascular exercise, and maintenance of a healthy diet should be encouraged.
    - For patients with unfavorable body composition at baseline we recommend consideration of consultation with a registered dietician.
- *Hot flashes:* Hot flashes develop in a majority of men with castrate levels of testosterone.
    - The pathophysiology of hot flashes in men receiving androgen suppression therapy appears to differ somewhat compared to the pathophysiology of hot flashes in menopausal women
        - Thus the agents that have shown efficacy at reducing the severity of hot flashes differ between the populations.

        - Prior to initiating any pharmacologic therapy clinicians and patients should be aware of the natural history of hot flashes following the initiation of androgen suppression
            - Generally the severity of hot flashes will begin to decrease after 1-2 months.
        - A number of small randomized trials have been conducted to assess the efficacy of different agents and, to date, the most effective therapies appear to be gabapentin 300mg TID and medroxyprogesterone 20mg QD[15,16].
            - Venlafaxine and soy products have not been shown in randomized trials to be superior to placebo[17].
            - A few single arm studies have suggested that acupuncture may be effective at reducing the severity of hot flashes for select patients with interest in alternative therapies.
    - *Gynecomastia:* Androgen suppression therapy, particularly when an anti-androgen is used, can lead to gynecomastia.
        - For men who are scheduled to receive long-term anti-androgen therapy prophylactic measures against gynecomastia should be considered.
            - Traditionally external beam RT (1-5 fractions) to the breast have resulted in acceptable prevention of gynecomastia.
            - Tamoxifen at a dose of 10-20mg QD is also an effective prophylactic regimen and was significantly more effective at preventing gynecomastia in one moderately sized randomized trial[18, 19].
    - *Decreased libido*: Decreased libido occurs in the vast majority of men with castrate levels of testosterone.
        - **We emphasize the distinction between decreased libido and mechanical erectile dysfunction**.
        - Androgen suppression does not generally lead to mechanical erectile dysfunction, thus response rates to PDE-5 inhibitors are substantially less than 20%[20].
        - The most effective strategies to preserve sexual activity during androgen suppression are appropriate counseling of the patient/partner and cardiovascular exercise.
    - *Emotional support:* Men with castrate levels of testosterone are at increased risk for depression.
        - Members of the treatment team should screen patients for depression and have a low threshold for referral to a supportive care specialist.

Appendix C: Documentation

- We believe that prostate cancer is conducive to synoptic style documentation
    - Appropriate documentation is considered a quality measure by many accrediting bodies
    - In addition to standard documentation that accompanies any patient encounter, we strongly recommend documentation of all of the following parameters at the time of initial consultation:
        - Disease characteristics

- Intact prostate:
    - T-stage (and modality by which T stage was determined)
    - Biopsy Gleason score
    - Most recent PSA
- Post-prostatectomy:
    - Surgical stage
    - Most recent PSA
    - PSA doubling time

▪ Patient characteristics - Baseline IPSS
- Baseline SHIM
- Life expectancy
- FRAX estimated 10 year fracture risk
- Charlson comorbidity index

▪ Staging studies - Pelvic imaging:
- Results vs. planned vs. not indicated (why?)

▪ Bone scan:
- Results vs. planned vs. not indicated (why?)

o Treatment recommendations - radiotherapy recommendation
▪ Androgen suppression recommendation
- Yes (planned duration) vs. No (why?)

- The committee has created a PowerChart template that is available for all practitioners to guide proper documentation at the time of consultation of men with intact localized prostate cancer.
- We are actively working to create templates for men seen after prior prostatectomy and for follow-up visits.

Appendix D: Dose Volume Analysis

-Dose inhomogeneity ranges and coverage parameters 95% of PTV volume should receive 100% of the prescribed dose.
-Due to potential OARs, it is acceptable to have 90% of PTV receive 100%; 100% of PTV volume should receive 95% of the prescribed dose.
-Due to potential OARs, it is acceptable that 100% of PTV receive 90%.
Global hotspot should be $\leq$107%; it may be acceptable that hotspot could be $\leq$110%

Conventional Fractionation

Organ	Constraint	Priority*
Rectum	V75 Gy < 15%	2
	V70 Gy < 25% or V70 Gy < 20%	2
	V65 Gy < 35%	2

	V60 Gy < 50%	2
	V50 Gy < 50%	2
Bladder	V80 Gy < 15%	2
	V75 Gy <25%	2
	V70 Gy <30%	2
	V65 Gy < 50%	2
	V55 Gy < 50%	2
Small Bowel	Max Dose 52Gy	2
Femoral Heads	V50<10%	2

* 1 = Do not violate. Achieving constraint is more important than target coverage.

2 = Planning goal, but less important than target coverage.

UAB Hypofractionation

Organ	Constraint	Priority*
Rectum	V70 Gy < 3cc	2
	V60 Gy < 10 cc	2
	V50 Gy < 17%	2
	V40 Gy < 35%	2
	V35 Gy < 60% if ENI used	2
Bladder	V60 < 10%	2
	V50 < 25 %	2
	V31< 50%	2
Small Bowel	Max dose 54Gy	2
	V54<20cc	1
Femoral Heads	V50<10%	2

* 1 = Do not violate. Achieving constraint is more important than target coverage.

2 = Planning goal, but less important than target coverage.