Phase IB/II study of enzalutamide with ribociclib in patients with metastatic castrate resistant, chemotherapy naïve prostate cancer that retains RB expression

Prostate Cancer Clinical Trials Consortium, LLC (PCCTC)
Novartis # : CLEE011XUS12T
PCCTC LOI #: c15-153
IND #: 127,016

Thomas Jefferson University

Sponsor Investigator/Principal Investigator
William Kevin Kelly, DO
Thomas Jefferson University
Department of Medical Oncology
1025 Walnut Street
College Bldg., Suite 700
Philadelphia, PA 19107
email: William.kelly@jefferson.edu

Statistician
Benjamin Leiby, PhD
Thomas Jefferson University
Division of Biostatistics
1015 Chestnut St., Suite M100
Philadelphia, PA 19107
email: benjamin.leiby@jefferson.edu

Co-Investigator
Robert Den, MD
Thomas Jefferson University
Department of Radiation Oncology
111 South 11th Street
Philadelphia, PA 19107
email: Robert.den@jefferson.edu

Protocol Manager
Prostate Cancer Clinical Trials Consortium
55 Fifth Avenue, 13th Floor
New York, NY 10003
email: pcctc@mskcc.org

Correlative Science Chair
Karen Knudsen, PhD
Thomas Jefferson University
233 10th Street, BLSB 1008
Philadelphia, PA 19107
email: Karen.knudsen@jefferson.edu

Protocol Date: June 11, 2015

Amended Version Date: January 17, 2020

SPONSOR INVESTIGATOR'S APPROVAL OF PROTOCOL

Title: Phase IB/II study of enzalutamide with ribociclib in patients with metastatic castrate resistant, chemotherapy naïve prostate cancer that retains RB expression

Sponsor Investigator Signature: _____

Sponsor Investigator Print: _____

Date: _____

PCCTC, LLC CEO Signature: _____

PCCTC, LLC CEO Print: _____

Date: _____

PROTOCOL AGREEMENT

INVESTIGATOR'S APPROVAL OF PROTOCOL

Title: **Phase IB/II study of enzalutamide with ribociclib in patients with metastatic castrate resistant, chemotherapy naïve prostate cancer that retains RB expression**

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Thomas Jefferson University with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted Good Clinical Practice (GCP) principles and to abide by the terms of this protocol

Investigator Signature: _____

Investigator Print: _____

Date: _____

TABLE OF CONTENTS

1. INTRODUCTION 6
1.1 Disease Background 6
1.2 Treatment Background 6
1.3 Rationale 15
2. OBJECTIVES 16
2.1 Primary Objective 16
2.2 Secondary Objectives 16
2.3 Correlative/Exploratory/Tertiary Objectives 16
3. PATIENT SELECTION 17
3.1 Inclusion Criteria 17
3.2 Exclusion Criteria 18
4. ENROLLMENT PLAN AND SUBJECT REGISTRATION 21
4.1 Enrollment Plan 21
4.2 Registration Procedure 21
5. TREATMENT PLAN 22
5.1 Screening/Pretreatment Assessment (Day -28 to Day 0) 27
5.2 Treatment Period (Day 1 to POD/EOT ± 2 days) 28
5.3 End of Treatment/Treatment Discontinuation Visit (28 days from last dose ± 7 days) 28
5.4 Post Treatment Follow-up (EOT – 24 months from last dose ± 7 days) 28
5.5 Safety Assessments 28
5.6 Correlative/Special Studies 29
5.7 Dose Modifications 31
5.8 Removing Subjects from the Protocol 38
6. THERAPEUTIC/DIAGNOSTIC AGENT(S) 38
6.1 Ribociclib 38
6.2 Enzalutamide 40
6.3 Concomitant Medications 41
7.0 ADVERSE EVENTS 42
7.1 Definitions 42
7.2 Recording and Grading of Adverse Events 44
7.3 Reporting Adverse Events 45
7.4 Safety Reports 47
8. CRITERIA FOR OUTCOME ASSESSMENT/THERAPEUTIC RESPONSE 47
8.1 Outcome Assessment 47
8.2 Therapeutic Response 48
8.3 Response Criteria for Control/Relieve/Eliminate Endpoints 50
8.4 Confirmatory Measures/Duration of Response 52
8.5 Progressive Disease (PD) 54
9. DATA REPORTING AND REGULATORY REQUIREMENTS 54
9.1 Data Collection and Management 54
9.2 Data and Safety Monitoring 55
10. STATISTICAL CONSIDERATIONS 56
10.1 Study Endpoints 56
10.2 Analysis Populations 57
10.3 Safety Analysis 57
10.4 Statistical Procedures 58
11. REGULATORY AND PROTECTION OF HUMAN SUBJECTS 58
11.1 Role and Responsibilities 58
11.2 Ethical Considerations 59

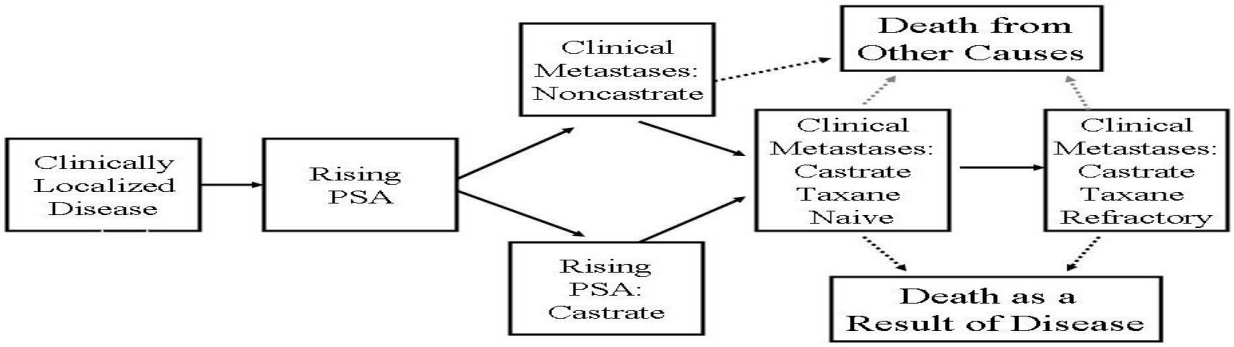
11.3 Protocol Amendments 59
11.4 Written Informed Consent 60
11.5 Protection of Privacy 60
11.6 Terminating or Modifying the Study 60
12. REFERENCES 62
Appendix A: Performance Status Criteria 65
Appendix B: Medications with the Potential for Drug-Drug Interactions 66
Appendix C: Laboratory Manual 71
Appendix D: Glossary of Abbreviations and Acronyms 72
Appendix E. Pill Diary (PHASE I) 75
Appendix F. Pill Diary (PHASE II) 77
Appendix G. Novartis SAE Coversheet 80
Appendix H. PCCTC SAE Report Form 83

1. INTRODUCTION

1.1 Disease Background

Prostate cancer is the second leading cause of cancer deaths in men. According to American Cancer Society estimates in 2014, as many as 233,000 American men will be diagnosed with prostate cancer, and nearly 29,480 will die of the disease.[1] The course of prostate cancer from diagnosis to death is best categorized as a series of clinical states (Figure 1). These clinical states involve the complex interplay of a network of signaling molecules that collectively promote net cell proliferation relative to cell death.

Figure 1. Clinical states of prostate cancer



Treatment options for patients with castrate resistant prostate cancer (CRPC) are limited and until recently only docetaxel was shown to improve survival. In the last several years we had five new agents; abiraterone acetate, cabazitaxel, enzalutamide, radium-223 and sipuleucel-T approved for use in this clinical state.[2-6] However the optimal sequencing of these agents is unknown. Moreover, all patients with CRPC are treated identically and there is no means of identifying which patient population would benefit from a particular agent.

1.2 Treatment Background

Standard treatment approach for patients with progression after primary androgen ablation therapy

Enzalutamide inhibits androgen receptor (AR) signaling in three distinct ways: it inhibits 1) testosterone binding to ARs; 2) nuclear translocation of ARs; and 3) DNA binding and activation by ARs. Based on the AFFIRM trial, enzalutamide was approved by the FDA in 2012, and by the EMA in 2013, for the treatment of men with mCRPC who have progressed on or after first-line docetaxel chemotherapy.[7] Currently the NCCN guidelines recommend enzalutamide in this setting as well as for men with mCRPC who are not candidates for docetaxel. Recently, Beer and colleagues (PREVAIL phase III trial) have shown that enzalutamide significantly reduced the risk for radiographic progression, delayed initiation of chemotherapy and improved overall survival (OS) in men with CRPC that have not received prior chemotherapy.[8] In September 2014, the U.S. Food and Drug Administration (FDA) expanded the use of enzalutamide to include men with CRPC that have not received prior chemotherapy. Thus, enzalutamide has become a standard of care as systemic therapy for men with mCRPC and since there is no need for systemic steroids, it is expected to be the predominant agent to be used in this pre-chemotherapy setting.

Development of CRPC

Extensive work has been performed to increase the understanding of the major mechanism driving resistance to castration (including after treatment with abiraterone acetate). Preclinical and clinical studies have demonstrated that alterations, specifically, up-regulation of the AR is central to the progression to CRPC.[9] Preclinical modeling of AR up-regulation showed that this event alone is sufficient to drive progression to CRPC. Recently reported findings identified perturbations of the RB tumor suppressor as a major mechanism by which AR deregulation occurs and induction of CRPC formation. Principle findings were: a) RB loss is infrequently observed in primary disease, but is predominantly associated with the mCRPC; b) loss of RB function is associated with poor outcome; c) modeling of RB dysfunction *in vitro* and *in vivo* revealed that RB controls AR expression and output via transcriptional regulation of the *AR* locus; d) disruption of the newly identified RB-E2F/AR axis was frequently observed in the transition to castrate resistance in human disease.[10-16] These data suggest that a new paradigm for RB function in controlling prostate tumor progression and lethal tumor phenotypes.

Accessing RB Status in Tumors

Using multiple methods to assess RB expression and activity, it was noted that RB loss of function is highly overrepresented in CRPC. A representative example of the data are shown in Figure 2 and in the study by Sharma et al.[17] Using the combined analyses of RB expression and the RB signature, up to 60% of CRPCs show loss of RB activity. While the initial study examined over 150 CRPC specimens, enrichment of RB loss in the CRPC setting has been further confirmed by the work of Gerald and Sawyers, and in subsequent analyses of cohorts from Dr. Tapio Visakorpi (data not shown). Moreover, recent mouse models confirm the importance of RB function in prostate cancer.[15]

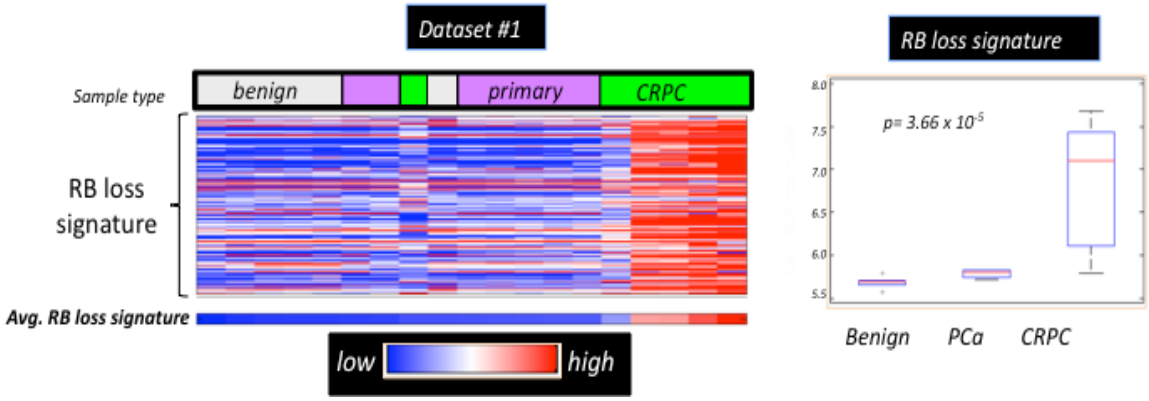


Figure 2. RB function is perturbed in the transition to CRPC. These data are taken from a recent comprehensive study (Sharma et al., J Clin Invest 2010) which assesses RB functional status in multiple tumor sets. As shown, the RB loss signature is highly overrepresented in CRPC (left). Quantification and statistical analyses (right) demonstrate that there is little evidence for loss of RB function in primary disease, whereas this event is frequent in CRPC. Based on this published (Sharma et al., 2010) and new preliminary data, analyses of over 150 CRPCs demonstrate that RB loss of function occurs in up to 60% of CRPCs.

We estimate in the current proposed study populations approximately 50% of the patients will have intact RB function (RB+).

Contemporary means to activate RB function in the clinical setting:

Our new data identify pharmacological means to hyperactivate RB function in tumors that retain the RB protein (RB+). RB function is often downregulated in tumors through hyperphosphorylation of the protein – thus, agents that target the kinases that phosphorylate RB (e.g., Cyclin dependent kinase 4, CDK4) are attractive therapeutic agents.[11] CDK4 initiates RB phosphorylation, thus 'priming' RB for further phosphorylation and resultant diminution of tumor suppressor activity.[18] While first generation CDK inhibitors were both non-specific and toxic, second generation inhibitors are specific, effective, and well tolerated (patients treated for >1 year showed minimal toxicity and stabilization of therapy-refractory disease).[19-21] We utilized cell culture, xenograft, and primary tumor explant strategies to assess the impact of a second generation CDK4 inhibitor on prostate cancer (*Figure 3* and data not shown). The explant studies utilize cutting-edge technology wherein tissue obtained from radical prostatectomy are sampled and therapeutically interrogated in a novel explant assay. In this assay, primary tumor tissue can be cultured for up to 7 days; importantly, the sections retain histology and tumor phenotypes identical to that of the specimen at resection. Moreover, these studies allow for examination of drug effects on the surrounding stroma and normal tissue. As would be expected, the tumors obtained to date from radical prostatectomy retain RB (not shown), and are exquisitely responsive to the CDK4 inhibitor. Investigation to date reveals both cytostatic and cytotoxic effects of the drug that are specific to tumor cells. Moreover, RB was hyperactivated in cells treated with the CDK4 inhibitor. These data strongly support the contention that CDK4 inhibitors can be used to activate RB, and therein suppress tumor growth, survival, and progression.

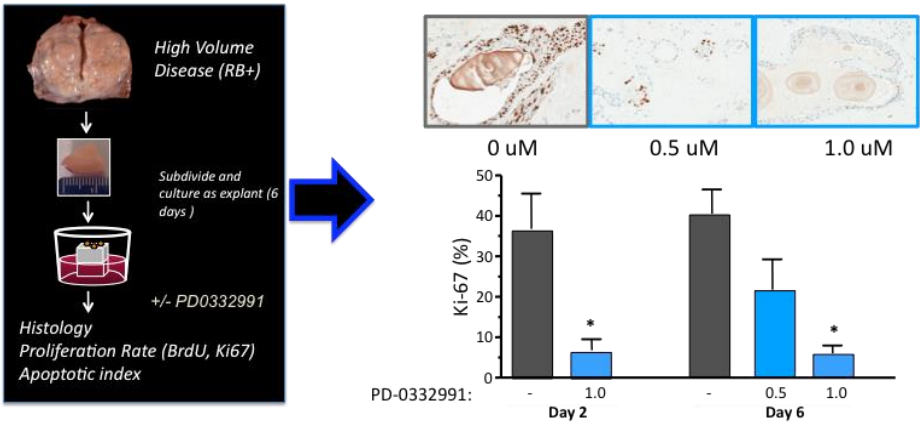


Figure 3. Novel human explant protocol allows for rapid validation of drug efficacy; clinically attainable doses of PD-0332991 effectively suppress tumor growth and survival in RB+ tumors. A brief schematic of the explant protocol is shown on the left. To the right of the arrow, examples of Ki67 staining in the portion of tumor treated without PD-0332991 (0μM) or treated with doses known to be clinically achievable (0.5-1.0 μM) are shown. Data quantification from multiple explant studies is also shown.

Summary

The current data suggests RB function is often attenuated in tumors through hyperphosphorylation-- thus, RB activity can be "re-awakened" in RB+ tumors by suppressing the key kinases that phosphorylate RB (CDK4/6). Indeed, promising clinical data

using next-generation CDK4/6 inhibitors in multiple cancers have shown significant anti-tumor effects, giving further encouragement for this new line of therapeutic intervention.

Hypothesis

Therefore, we hypothesize that the addition of* ribociclib *in combination with enzalutamide in patients with progressive metastatic prostate cancer despite castrate levels of testosterone that retains RB expression will significantly increase the efficacy of enzalutamide.

1.2.1 Description and mechanism of action

1.2.1.1 Nonclinical activity

Overview of the G1 to S phase transition in mammalian cells

Normal mammalian cells proliferate in response to extracellular signals by transitioning through a series of tightly controlled phases that culminate in cell division. The commitment to transition from G1 to S phase and the initiation of cell cycle progression is regulated by the retinoblastoma protein (pRb). In the absence of appropriate growth stimuli, pRb, in its unphosphorylated state, binds and inhibits the activity of the E2F family of transcription factors, preventing these proteins from activating the genes required for S phase transition.[22,23] Upon mitogen stimulation, signaling through pathways such as the MAPK and PI3K pathways increases the abundance of D-cyclins, which bind and activate CDK4/6. Cyclin D-bound CDK4/6 then phosphorylates the pRb protein to deactivate it and release bound E2F. Once freed, E2F activates S phase-specific genes in order to start cell cycle progression. Full deactivation of pRb requires its sequential phosphorylation at different sites by both cyclin D-CDK4/6 and cyclin E-CDK2. The phosphorylation events mediated by CDK4/6 are prerequisites for those catalyzed by CDK2.[24] The kinase activity of CDK4/6 is in turn inhibited by p16, encoded by the INK4a gene.[25,22] The CIP/KIP proteins, inhibitors of cyclin E-CDK2, also bind to the cyclin D-CDK4/6 complex, and this results in further activation of CDK2 by sequestering CIP/KIP proteins from their target.[26] Cyclin D-CDK4/6 is therefore a key enzyme complex that regulates the G1 to S phase transition**.**

Alterations in the D-cyclin-CDK4/6-INK4a-pRb pathway in human malignancies

The D-cyclin-CDK4/6-INK4a-pRb pathway is universally disrupted in cancer to favor cell proliferation. Eighty percent of human neoplasms maintain functional pRb but harbor aberrations that increase the activity of CDK4/6 to effectively inactivate pRb function. These aberrations include genetic or epigenetic changes that directly increase the kinase activity of CDK4/6 or defects that activate the upstream.[22,23] One of the most common events is the inactivation of p16 via mutations, deletion and epigenetic silencing. p16 inactivation is frequently observed in a significant portion of non-small cell lung cancer (NSCLC), melanoma, pancreatic cancer and mesothelioma.[27-30] Moreover, a specific mutation of the CDK4 gene (CDKR24C), that confers resistance to p16 binding, has been shown to play a causal role in rare cases of familial melanoma, suggesting that unchecked CDK4 activity is a key event in these cancers.[31]

Translocations of the genes encoding D-cyclins to the immunoglobulin heavy chain locus are found in a majority of mantle cell lymphomas (MCLs) and in many cases of multiple myeloma.[32] These translocations lead to constitutive expression of D-cyclins, which result in enhanced CDK4/6 kinase activity and unchecked cell proliferation.[33] Amplification of cyclin D1 and overexpression of the protein have also been reported in approximately 50% of

squamous cell esophageal cancers and in 20-30% of breast cancers, suggesting that activation of this pathway may play a role in the growth of these tumors.[34-36] Furthermore, many of the receptor-mediated growth pathways that are activated in human cancers increase D-cyclin transcription and expression to drive cell proliferation. In mouse breast cancers driven by activated Ras or Her2/Neu oncogenes, cyclin D1 and CDK4 have been shown to be necessary for the tumorigenic phenotype in both initiation and maintenance phases, demonstrating that Cyclin-D1/CDK4 is the key effector enzyme complex for Ras- or Her2/Neu-driven cancers.[37,38] Other activating aberrations of mitogen pathways such as V600E B-Raf in the MAPK pathway and PTEN deletions in the PI3K pathway also increase D-cyclins to achieve unchecked proliferation, suggesting that CDK4/6 may also be crucial for the cancers bearing these alterations.[39,40] Finally, the genes encoding CDK4 and CDK6 are amplified in a subset of human neoplasms. The CDK4 gene is amplified in 100% of liposarcomas along with the MDM2 gene, while CDK6 is frequently amplified in T-lymphoblastic lymphoma and/or acute lymphoblastic leukemia.[41,42]

1.2.1.2 Preclinical studies

Nonclinical pharmacokinetics and metabolism of ribociclib

Ribociclib showed high clearance (CL) in the mouse, rat, dog and monkey. The volume of distribution was large across species and the terminal elimination half-life ($T_{1/2}$) was moderate in rodents and monkey (~2 to 5 h) and longer in dog (18 h).

Bioavailability was low to moderate in rat (37%) and cynomolgus monkey (17%), and moderate in mouse (65%) and dog (64%). Following oral administration, time to reach maximal plasma concentrations (T_{max}) occurred between 2 to 4 h across species. Gender-dependent toxicokinetics were observed in rats with higher exposure to ribociclib in males as compared to females and with higher exposure to the metabolite, LEQ803.

Plasma protein binding was moderate in all species (unbound fraction (fu) in human: 30%).

In a rat ADME (absorption, distribution, metabolism and excretion) study, extensive distribution of [3H] ribociclib and its metabolites was seen. In pigmented rats, radioactivity was specifically found in melanin-containing structures, and the highest exposure to total radiolabeled components was observed in eye ciliary body, eye choroid, meninges, tactile hair and hair follicles. Radioactivity was not detected in the brain. T_{last} (last observation timepoint) was ≤ 48h for most tissues, but long (168 to 840h) for lymph nodes, preputial gland, testis, eye and meninges. At one week ≤ 0.04% of the dose was retained in the carcass.

LEQ803 (N-demethylation) was a prominent metabolite found in mouse, rat, dog, monkey and human hepatocytes. This metabolite retains some pharmacologic activity and interacts with human Ether-a-go-go Related Gene (hERG) channels in vitro. In male rats, unchanged ribociclib (24.7% of [3H]AUC0-24h) and its metabolite M11 (26.3% of [3H]AUC0-24h) were the major components in plasma. In rats, ribociclib was eliminated mainly by metabolism. The major metabolism pathway was direct sulfation of ribociclib to M8 and its excretion into the bile. Direct ribociclib secretion accounted for 18.2% of the total plasma clearance.

Results from the ADME (male rats) study showed that 3H-components were predominantly excreted with bile (61.4% of dose). Minor urinary excretion was observed (5.9% of dose after p.o.). The majority of the administered dose (87.3%) was excreted within 24 h via urine, feces (enteric secretion) and bile.

In vitro, ribociclib was a reversible inhibitor of cytochrome P450 (CYP) enzymes CYP1A2, CYP2E1 and CYP3A4 and a time-dependent inhibitor of CYP3A4. ribociclib may inhibit these enzymes under therapeutic conditions. No pregnane X-receptor (PXR)-mediated CYP3A4 induction was observed. The in vitro inhibitory potency of ribociclib observed for the transporters OATP1B1 (organic anion transporting polypeptide 1B1), BCRP (breast cancer resistance protein), OCT1 (organic cation transporter 1), OCT2, MATE1 (multidrug and toxin extrusion protein 1), MATE2K and BSEP (bile salt export pump) may translate into clinically relevant inhibition at therapeutic doses.

Elimination of ribociclib is dominated by oxidative metabolism mainly via CYP3A4 with a minor contribution by flavin-containing monooxygenase 3 (FMO3). The elimination of ribociclib may be affected by co-administered drugs that inhibit or induce CYP3A4. Although ribociclib is a substrate of the P-glycoprotein (P-gp) efflux transporter and subject to active uptake into hepatocytes, these processes are likely not clinically relevant due to the high passive permeability of ribociclib.

Safety pharmacology and toxicology of ribociclib

In vivo cardiac safety studies demonstrated a signal for QT prolongation with the potential to induce incidences of premature ventricular contractions (PVCs) at higher exposure levels.

The effects of ribociclib on the bone marrow (hypocellularity), lymphoid system (lymphoid depletion), intestinal mucosa (atrophy), skin (atrophy), bone (decreased bone formation) and testes (atrophy) are considered to be related to the pharmacological inhibition of cell replication in these tissues due to CDK4/6 inhibition. An increased number of ovarian corpora lutea was observed in a single female dog in the 4-week toxicity study at the highest dose tested (20 mg/kg/day) and this effect could also be related to the pharmacology of ribociclib (arrest of estrous cycle). The liver, bile system and gall bladder (proliferative changes, cholestasis, sand-like gallbladder calculi and inspissated bile) and the kidney (concurrent degeneration and regeneration of tubular epithelial cells) were identified as additional target organs of toxicity which are not likely related to the primary pharmacology of ribociclib. Inflammatory changes in the lungs of dogs were considered secondary to aspiration of test-article and are indicative of the irritant potential of the formulated test-article in the respiratory tract. Correlating hematological and/or biochemistry changes were seen for the effects described in the bone marrow, lymphoid system and liver. Generally all changes demonstrated either reversibility or a clear tendency towards reversibility.

Reproductive studies have demonstrated ribociclib induced embryotoxicity and fetotoxicity in rats and rabbits and teratogenicity in rabbits.

1.2.1.3 Clinical studies

Clinical Study with ribociclib

As of 24 April 2014, 132 patients have been treated with single agent ribociclib in the FIH phase I study; 85 patients have been treated in the dose escalation part and 47 patients in the dose expansion part of the study.

Patients with advanced solid tumors or lymphomas were treated with increasing doses of ribociclib orally, once daily (qd) for 21 days followed by a 1-week rest (28-day cycle). Doses ranging from 50 mg to 1200 mg were evaluated on this schedule. In addition, continuous

dosing of ribociclib at 600 mg was evaluated (qd for 28 days of a 28-day cycle). Doses tested include, 50 mg (n=4), 70 mg (n=2), 140 mg (n=4), 260 mg (n=4), 280 mg (n=4), 350 mg (n=5), 400 mg (n=5), 600 mg (n=67), 600 mg continuous (n=7), 750 mg (n=14), 900 mg (n=13), and 1200 mg (n=3). The median age of patients was 60 years (22 to 84), the male/female ratio was 1, and the distribution of Eastern Cooperative Oncology Group (ECOG) performance status of 0/1 at baseline was 47/84 patients, respectively. The most common cancer types were liposarcoma (33), ER+ breast cancer (20), head and neck (including salivary gland) cancer (16), colon cancer (14), lung cancer (8), and lymphoma (8). Treatment has been discontinued in 111 (84%) patients; the primary reasons for treatment discontinuation were: disease progression (96 [72%] patients); adverse events (AEs) (8 [6%] patients); withdrawal of consent (3 [2%] patient); and loss to follow up (1 [1%] patient).

A total of 10 events meeting dose limited toxicity (DLT) criteria were observed at the indicated doses in the 70 patients evaluable for dose determination and include Grade 3 mucositis/stomatitis (later determined to be due to herpes simplex virus infection) (n=1) at 50 mg, Grade 3 pulmonary embolism (n=1) at 280 mg, Grade 3 hyponatremia (asymptomatic and corrected with saline infusion) (n=1) and prolonged Grade 3/4 neutropenia (n=1) at 400 mg, prolonged Grade 2 elevated creatinine (n=1) at 600 mg, Grade 4 thrombocytopenia (n=1) at 750 mg, Grade 3 asymptomatic QTcF prolongation with Grade 3 neutropenia (n=1) at 900 mg and Grade 4 febrile neutropenia (n=1) and Grade 4 thrombocytopenia (n=1) at 1200 mg. There was also one DLT, prolonged Grade 3 neutropenia (n=1) at 600 mg on the continuous dosing schedule.

The most frequently reported AEs (≥10%), regardless of grade, causality and ribociclib dose were: fatigue (53.8%); nausea (50.8%); neutropenia (47.7%); leukopenia (46.2%); anemia (37.1%); vomiting (34.8%); thrombocytopenia (34.1%); diarrhea (32.6%); lymphopenia (30.3%); decreased appetite, hyperglycemia (21.2% each); constipation (19.7%); hypoalbuminemia (18.9%); dyspnea (18.2%); cough (16.7%); fever, increased creatinine(15.9% each); abdominal pain, AST increase, edema, headache (15.2% each); back pain (14.4%); dizziness (13.6%); ECG QT prolonged (11.4%); blood alkaline phosphatase increased and hypocalcemia (10.6% each).

For either continuous or intermittent dosing, the onset of neutropenia (most frequently Grade 2) occurs by Day 15, reaching a nadir in the third or fourth week with recovery during the week of drug holiday. Some patients require additional time for recovery (7 to 14 days). QT changes become evident in the first cycle by Day 8 and later (once steady state is reached), are associated with the maximum drug levels between 1 to 8 h post-dose, and remain stable or improve in subsequent cycles.

As of 24 April 2014, asymptomatic Grade 2 QTcF prolongation was observed with increasing frequency when increasing the dose starting at 600 mg: twelve patients (18%) in the 600 mg cohort, three patients (21%) in the 750 mg cohort, four patients (31%) in the 900 mg cohort, and two patients (67%) in the 1200 mg cohort. Two patients (3%) at 600 mg and two patients (15%) at 900 mg had asymptomatic QTcF prolongation that resulted in a QTcF interval of 500 ms or more. As compared to baseline value, QTcF prolongation was at least 30 msec in 2 patients (50%) at 250mg, 2 (40%) at 350 mg and 400 mg, 46 (73%) at 600 mg, 10 (71%) at 750 mg, 11 (85%) at 900 mg and 2 (67%) at 1200 mg; and at least 60 msec as compared to baseline in respectively 16%, 0%, 39% and 67% of patients at 600 mg, 750 mg, 900 mg and 1200 mg. One grade 1 atrioventricular block of first degree was reported as related to

ribociclib given at the dose of 140 mg. No other cardiac abnormalities were observed as related adverse events in any patient.

Paired skin biopsies from 55 patients treated with ribociclib at doses ranging from 50 to 900 mg and paired tumor biopsies from 20 patients (16 patients at 600 mg, 2 patients at 900 mg, and 1 patient each at 70 and 750 mg) were assessed for changes in Ki67 and pRb levels. Preliminary results indicate the following: in skin biopsies, reductions in Ki67 from baseline were observed across all dose levels with a more consistent trend from 400 mg onwards; in tumor biopsies, reductions in Ki67 from baseline were observed in 18/20 patients; however, limited samples and varied tumor types prevent conclusions about any dose-response relationship from being drawn. Changes in pRb were not significant or consistent in either skin or tumor samples, possibly due to varied tumor types.

Out of the 114 evaluable patients, 3 partial responses were observed at the 600 mg dose level; one each in BRAF/NRAS wild type with CCND1 amplified melanoma, and head and neck acinar carcinoma with CDKN2A loss (both on the 3 weeks on/1 week off regimen), and ER+/HER2-, PIK3CA mutant, CCND1 amplified b reast cancer (on the continuous daily dosing regimen).

This study is currently evaluating a dosing schedule with ribociclib 400 mg continuous dosing, as well as the safety and PK of the oral solution formulation.

The maximum tolerated dose (MTD) of ribociclib is 900 mg qd with a 3 weeks on/1 week off schedule. The RP2D for future development is 600 mg qd with a 3 weeks on/1 week off schedule which has an acceptable safety profile, lower risk for QT prolongation, adequate exposures, and preliminary evidence of clinical activity.

For additional information, please refer to the [ribociclib Investigator's Brochure].

Clinical pharmacokinetics of ribociclib

The pharmacokinetics (PK) of ribociclib have been evaluated following single and repeat daily doses in the ongoing single agent, phase I study in patients with advanced solid tumors or lymphomas CLEE011X2101. Patients in all but one cohort received escalating doses of ribociclib once daily for 3 weeks followed by 1 week off schedule. In one cohort, patients received once daily continuous dosing of 600 mg ribociclib. PK sampling (pre-dose and 0.5, 1, 2, 4, 6, 8, and 24 h post-dose) was conducted on Days 1 and 18 or 21 of Cycle 1. Additional PK sampling (predose and 1, 2, and 4 h post-dose) was conducted on Days 8 and 15 of Cycle 1. Sparse samples were collected in Cycle 2 and subsequent cycles. The PK parameters from noncompartmental analysis of plasma concentration-time profiles on Day 1 and Day 18 or 21 of Cycle 1 are summarized in the Investigator's Brochure. Following oral dosing, ribociclib was rapidly absorbed with median T_{max} ranging from 1 to 4 h. ribociclib exhibited slightly over-proportional increases in exposure (C_{max} and AUC) across the dose range tested (50 to 1200 mg), with no clear evidence of time-dependent auto-inhibition of its clearance mediated by CYP3A4. Steadystate was generally reached by Day 8 and mean $T_{1/2,acc}$ ranged from 15.9 to 32.6 h across the dose range (50 to 1200 mg). Mean Racc across the studied doses ranged from 1.55 to 2.52. At the 600 mg dose level, LEQ803, an active metabolite of ribociclib, accounted for approximately 8% (geometric mean) of the ribociclib AUC0-24h after a single dose and after multiple doses.

1.2.2 Other agents or interventions

Enzalutamide

Enzalutamide (MDV3100) is an AR signaling inhibitor that targets several steps in the AR signaling pathway. Enzalutamide competitively inhibits binding of androgens to ARs, inhibits nuclear translocation of receptors and inhibits the association of the AR with DNA, even in the setting of AR overexpression and in prostate cancer cells resistant to anti-androgens.

The efficacy of enzalutamide in patients with metastatic prostate cancer who progressed on androgen deprivation therapy has been demonstrated in two randomized controlled phase III studies including MDV3100-03 in asymptomatic or mildly symptomatic patients and CRPC[8] in patients with more advanced disease who previously received docetaxel. Both studies showed a statistically significant advantage of enzalutamide treatment over placebo across multiple clinically relevant endpoints such as OS, rPFS, time to first skeletal-related event, time to PSA progression, PSA response rate, best overall soft tissue response, and quality of life as measured by the FACT-P. Notably, Study MDV3100-03 showed a significant benefit of enzalutamide in time to initiation of cytotoxic chemotherapy. Additional efficacy data from open-label Studies S-3100-1-01, CRPC-MDA-1, and 9785-CL-0111 in patients with mCRPC provided supportive data on PSA response rate, time to PSA progression, and/or best overall soft tissue response, although the magnitude of these treatment effects varied based on the characteristics of the enrolled populations. In general, the treatment effect across these endpoints was larger in patients with mCRPC who had not yet received chemotherapy compared with patients who previously received docetaxel, but the benefit was consistently demonstrated across endpoints within a patient population.

In both phase III studies of patients with mCRPC, the benefit of enzalutamide treatment on OS as measured by the estimated hazard ratio was observed across all prespecified subgroups. The statistically significant benefit on OS was also observed despite substantially higher and earlier use in the placebo groups compared with the enzalutamide groups of subsequent therapies that have demonstrated a survival benefit in patients with prostate cancer. These findings limit the ability to observe the isolated treatment effect of enzalutamide on this endpoint. This is especially true for MDV3100-03, based on the wider availability during this study of subsequent therapies demonstrated to prolong survival in patients with mCRPC.

In Study MDV3100-03, rPFS was a coprimary endpoint and was rigorously evaluated through use of blinded central reviewers as well as through a variety of sensitivity analyses of this endpoint. The magnitude of the relative treatment benefit (unstratified hazard ratio 0.186 [95% CI: 0.149, 0.231]) was coupled with a statistically greater best overall radiographic soft tissue response of 58.8% in the enzalutamide group versus 5.0% in the placebo group (difference of 53.9% [95% CI: 48.53, 59.17%]). Another clinically important finding in this patient population with earlier-stage disease included a 17.2 month delay in the median time to initiation of cytotoxic chemotherapy, which also delays treatment-associated morbidities. The decrease in risk of a skeletal-related event and PSA progression, and improvement in radiographic response in enzalutamide-treated patients provide additional evidence of clinical benefit. Furthermore, the benefit on time to degradation of FACT-P scores suggests that treatment with enzalutamide may prolong quality of life.

The FDA approved dose of enzalutamide, 160 mg daily, will be used in the study.

The benefit of enzalutamide for men with prostate cancer is consistently observed across studies of differing patient populations and across the majority of efficacy endpoints assessed.

1.3 Rationale

Metastatic prostate cancer growth, survival, and progression are intrinsically linked to the activity of the AR. Thus, first line therapies target AR either through suppression of androgen production or direct inhibition of the AR, resulting in the inability of the receptor to bind to chromatin and initiate AR-directed gene expression. Recurrent AR activity is the critical driver of CRPC; therefore, novel AR-targeted therapeutics were developed and show transient clinical benefit. Despite these advances, the vast majority of patients with CRPC succumb to disease within 2-3 years, indicating the need for metrics of precision medicine, and development of additional therapeutics.

Our preclinical studies indicate, tumors that retain RB proved to be exquisitely responsive to CDK4/6 inhibitors, revealing cytostatic and cytotoxic effects specific to the tumor. These analyses strongly support the contention that CDK4/6 inhibitors can be used to activate the RB pathway, and impede the transition to CRPC. Our study showed that: i) CDK4 inhibitors can be used to engage RB activity; ii) CDK4 inhibitors can be used in concert with AR-directed therapeutics; iii) RB activation can selectively enhance the effects of castration + Casodex therapy by further reducing AR signaling (e.g., as observed by further suppressing PSA expression in LAPC4 cells); and iv) Most importantly, CDK4 inhibitors strongly suppressed prostate cancer cell growth in an RB-dependent manner.

These preclinical findings suggest that selective CDK4/6 inhibition is a potential mode of intervention in prostate cancer and warrant future studies to evaluate its clinical efficacy [Comstock et al., 2013]. These findings together with the evidence from the scientific literature, demonstrating the important role of CDK4/6 in CRPC, provide the rationale for combination of ribociclib and enzalutamide in patients with mCRPC.

Since the ribociclib and enzalutamide have not been combined together in patients, the first phase will be a dose escalating study to find a safe dose of the combination. The standard doses of enzalutamide will be used and there will be three dose levels of ribociclib. A traditional 3x3 dose escalation schema will be used to establish the safe dose of ribociclib to combine with enzalutamide. The safe dose of the combination will be used in the phase II portion of the study. This study will evaluate an early readout of the clinical activity, thus the primary endpoint of the phase II portion of the study will be a proportion of patients with ≥ 50% PSA decline at 12 weeks. Secondary endpoints will be rPFS, PSA PFS, OS and safety. If there is clinical activity noted with the combination further testing will be required to establish ribociclib clinical benefit of the combination.

At the time of protocol amendment version 5, the phase I portion of the study determined the RP2D of 600mg ribociclib with 160mg enzalutamide after enrollment of 12 subjects. The randomized phase II portion of the study commenced in November 2017. We have shown that the combination of enzalutamide and ribociclib can be administered safely but also found that the over 90% of all patients enrolled into this study had had expression of RB by IHC, thus the study can be simplified and eliminate the need for re-biopsy and test for RB expression. In addition, due to a change in treatment landscape, recruiting subjects to the initial randomized study design proved to be challenging. Subsequently, the study Sponsor

modified the protocol to a single arm Simon two-stage design using the RP2D of 600mg ribociclib with 160mg enzalutamide. There is now ample long-term historical data on single agent enzalutamide that we can use to gauge the overall efficacy of this combination to decide if further testing in men with mCRPC is warranted.

Correlative Studies

This trial offers an extraordinary opportunity to better understand the mechanisms of AR activity and identify subgroups of patients that would benefit further for AR directed therapy. The overarching supposition of the correlative endpoints is that ribociclib will hyperactivate RB and improve therapeutic response. Patients enrolled in the study will receive optional tumor biopsies at screening (or archival tissue sample within 6 months of enrollment) and at progression along with circulating tumor cells (CTCs) and plasma obtained for circulating DNA/exosome studies.

The tissue obtained will allow researchers to assess the impact of RB- cyclin D1/CDK4/6 alterations on therapeutic response and determine associated clinicopathological features associated with these alterations.

CTCs will be analyzed using the Epic Sciences platform, with which we will be able to assess the correlation of RB expression in the CTC and tumor tissue. More recently, Antonarakis and colleagues detected androgen receptor splice variant 7 (AR-V7) in CTCs from patients with CRPC that showed a correlation of resistance to enzalutamide.[43] These and other possible mechanisms of resistance will be further explored in CTCs and tissue.

The correlative studies will investigate novel methods to determine RB functional status using CTCs and circulating DNA/exosomes but also correlate to more standard tests such as androgen levels. Combined clinical and correlative studies may help us develop and define the first biomarker for stratification of treatment for metastatic prostate cancer.

2. OBJECTIVES

2.1 Primary Objective

The primary objective of the phase IB component of this study is to determine the maximum tolerated dose of ribociclib in combination with 160 mg of enzalutamide.

The primary objective for the phase II component of this study is to determine efficacy with respect to the proportion of subjects that achieve a ≥ 50% reduction in PSA at 12 weeks.

2.2 Secondary Objectives

- PSA progression-free survival
- Radiographic progression-free survival (rPFS)
- Safety
- Pharmacokinetics

2.3 Correlative/Exploratory/Tertiary Objectives

- To evaluate the expression of RB in CTCs and tumor tissue.
- To evaluate other mechanisms of castrate resistance (such as AR-V7) in tumor tissue and CTCs.
- To explore resistance mechanisms of CDK4/6 inhibitors in tumor samples in patients that progress on enzalutamide and ribociclib.

- Explore the use/correlation of circulating DNA/exosomes in CRPC patients treated with enzalutamide with and without ribociclib.
- Androgen profiles and correlation to clinical outcomes
- Development of model explant systems to correlate with the clinical outcome.

3. PATIENT SELECTION

3.1 Inclusion Criteria

- Willing and able to provide written informed consent and HIPAA authorization for the release of personal health information.

  NOTE: HIPAA authorization may be either included in the informed consent or obtained separately. Consent and HIPPA authorization must be obtained prior to any screening procedures.

- Males 18 years of age and above
- Histological or cytological proof of prostate cancer
- Documented progressive mCRPC based on <u>at least one</u> of the following criteria:
  - PSA progression defined as 25% increase over baseline value with an increase in the absolute value of at least 2 ng/mL that is confirmed by another PSA level with a minimum of a 1 week interval and a minimum PSA of 2 ng/mL.
  - Soft-tissue progression defined as an increase ≥ 20% in the sum of the LD of all target lesions based on the smallest sum LD since treatment started or the appearance of one or more new lesions.
  - Progression of bone disease (evaluable disease) or (new bone lesion(s)) by bone scan.
- Have testosterone < 50 ng/dL. Patients must continue primary androgen deprivation with an LHRH analogue (agonist or antagonist) if they have not undergone orchiectomy
- ECOG performance status of 0-1
- Patients on long term (>6 months) anti-androgen therapy (e.g., flutamide, bicalutamide, nilutamide) will need to be off anti-androgen for 4 weeks (wash out period) and show evidence of disease progression off the anti-androgen. Patients that have been on an anti-androgen 6 months or less will need to discontinue anti-androgen therapy prior to *treatment start* (no wash out period required).
- Patient has adequate bone marrow and organ function as defined by the following laboratory values, obtained within 14 days prior to treatment start:
  - Absolute neutrophil count ≥ 1.5×10^9/L.
  - Platelets (UNVPLT) ≥ 100×10^9/L.
  - Hemoglobin (HGB) ≥ 9 g/dl.
  - Potassium (K), total calcium (CA)(corrected for serum albumin), magnesium, and phosphorus within normal limits for the institution or corrected to within normal limits with supplements before first dose of study medication.

- INR ≤ 1.5.
- Serum creatinine (CREAT) ≤ 1.5 mg/dL or creatine clearance ≥ 50 mL/min.
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN. If the patient has liver metastases, ALT and AST must still be ≤ 2.5 x ULN. Patients with liver metastases and AST/ALT above this limit will not be enrolled.
- Total serum bilirubin ≤ 1.5 x ULN; or total bilirubin (TBILI) ≤ 3.0 x ULN with direct bilirubin within normal range in patients with well documented Gilbert's Syndrome.

- The effects of ribociclib on the developing human fetus at the recommended therapeutic dose are unknown. Men must agree to use adequate contraception prior to treatment start, for the duration of study participation and for at least 3 months thereafter.
- Must be able to take oral medication without crushing, dissolving or chewing tablets.

3.2 Exclusion Criteria

- Prior exposure to abiraterone acetate or other specific CYP-17 inhibitors. Abiraterone acetate given in the castration-sensitive setting is permissible if stopped at least 6 months prior to initial protocol treatment.
- Prior exposure to enzalutamide, apalutamide, or other investigational AR directed therapy
- Prior chemotherapy for castration resistant disease. Chemotherapy given in the castration-sensitive setting is permissible if stopped at least 4 weeks prior to *treatment start*.
- Prior isotope therapy with strontium-89, samarium or radium-223 within 12 weeks of *treatment start*.
- Administration of antifungal agents (itraconazole, fluconazole, etc) within 4 weeks of *treatment start* or unrecovered AEs due to agents administered more than 4 weeks of *treatment start*.
- History of pituitary or adrenal dysfunction, active or symptomatic viral hepatitis or chronic liver disease.
- Known symptomatic brain metastases.
- Use of any prohibited concomitant medications: immunotherapy, 5 alpha reductase inhibitors, spironolactone, diethystilbestrol (DES), ketoconazole, newer medications targeting ARs.

  NOTE: Because of the potential for drug-drug interaction, the concurrent use of all other drugs, over-the-counter medications, or alternative therapies must be documented. The principal investigator should be alerted if the patient is taking any agent that interacts with CYP450 system.

- Treatment-related toxicity from prior therapy > Grade 2.
- Peripheral neuropathy ≥ 2

- History of hypersensitivity to ribociclib or compounds of similar chemical or biologic composition to ribociclib including to peanut and soy or other drugs formulated with polysorbate 80; or enzalutamide.
- Currently taking any herbal, alternative or food supplements (i.e., PC-Spes, Saw Palmetto, St John Wort, etc.). All herbal, alternative and food supplements must be discontinued prior to *treatment start*. Patients may continue on a daily Multi-Vitamin, calcium and Vitamin D.
- Planned surgery or radiation therapy during protocol treatment,
- Hormonal-acting agents (including DES, aldosterone, and spironolactone but not including GnRH agonists or antagonists) are forbidden during the trial and must be stopped prior to *treatment start*. No washout period will be required for any of these agents.
- Initiation of bisphosphonate/denosumab therapy during protocol treatment. Patients on stable doses of bisphosphonates or denosumab which have been started no less than 4 weeks prior to *treatment start* may continue on this medication.

  NOTE: Initiation of bisphosphonate/denosumab therapy will be allowed for the treatment of osteoporosis or prevention of skeletal-related events (SRE) during protocol treatment.
- Patient has a concurrent malignancy or malignancy within 3 years of *treatment start*, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer.
- Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
- Patient has a known history of HIV infection (testing not mandatory).
- Patient has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, cause unacceptable safety risks, contraindicate patient participation in the clinical study or compromise compliance with the protocol (e.g., chronic pancreatitis, chronic active hepatitis, active untreated or uncontrolled fungal, bacterial or viral infections, etc.).
- Patient has clinically significant, uncontrolled heart disease and/or recent events including any of the following:
    - History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) or symptomatic pericarditis within 12 months prior to *treatment start*
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    - Documented cardiomyopathy
    - Patient has a Left Ventricular Ejection Fraction (LVEF) < 50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO) at screening
    - History of any cardiac arrhythmias, eg., ventricular, supraventricular, nodal arrhythmias, or conduction abnormality within 12 months prior to *treatment start*.

  - Family history of QTc prolongation or of unexplainable sudden death at <50 years of age.
  - On screening 12 lead ECG, any of the following cardiac parameters: bradycardia (heart rate < 50 at rest), tachycardia (heart rate > 90 at rest), PR interval > 220 msec, QRS interval >109 msec, or QTcF >450 msec. Congenital long QT syndrome or family history of long QT syndrome.
  - Systolic blood pressure (SBP) >160 mmHg or <90 mmHg.
  - Bradycardia (heart rate < 50 at rest), by ECG or pulse, at screening
- On screening, inability to determine the QTcF interval on the ECG (i.e.: unreadable or not interpretable) or QTcF >450 msec (using Fridericia's correction). All as determined by screening ECG (mean of triplicate ECGs)
- Patient is currently receiving any of the following medications and cannot be discontinued 7 days prior to *treatment start*:
  - Known strong inducers or inhibitors of CYP3A4/5, including grapefruit, grapefruit hybrids, pummelos, star-fruit, and Seville oranges.
  - That have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5.
  - That have a known risk to prolong the QT interval or induce Torsades de Pointes.
  - Herbal preparations/medications, dietary supplements
- Patient is currently receiving or has received systemic corticosteroids within <2 weeks prior to *treatment start*, or who have not fully recovered from side effects of such treatment.
  - The following uses of corticosteroids are permitted: a short duration (<5 days) of systemic corticosteroids; any duration of topical applications (e.g. for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular)
- Patient is currently receiving warfarin or other coumarin-derived anticoagulant for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH) or fondaparinux is allowed.
- Participation in other studies involving investigational drug(s) within 30 days prior to randomization or within 5 half-lives of the investigational product (whichever is longer) or participation in any other type of medical research judged not to be scientifically or medically compatible with this study. If the patient is enrolled or planned to be enrolled in another study that does not involve an investigational drug, the agreement of the Novartis study medical lead is required to establish eligibility..
- Patient who has received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to *treatment start*, and who has not recovered to Grade 1 or better from related side effects of such therapy (exceptions include alopecia) and/or in whom ≥ 30% of the bone marrow was irradiated.
- Patients with central nervous system (CNS) involvement unless they meet ALL of the following criteria:
  - At least 4 weeks from prior therapy completion (including radiation and/or surgery) to *treatment start*
  - Clinically stable CNS tumor at the time of screening and not receiving steroids and/or enzyme-inducing anti-epileptic medications for brain metastases

- Patient has had major surgery within 14 days prior to *treatment start* or has not recovered from major side effects (tumor biopsy is not considered as major surgery).
- Patient has not recovered from all toxicities related to prior anticancer therapies to NCI-CTCAE version 4.03 Grade <1 (Exception to this criterion: patients with grade 1 taxane-induced neuropathy, any grade of alopecia, amenorrhea or other toxicities not considered a safety risk for the patient as per investigator's discretion, are allowed to enter the study).
- Patient with a Child-Pugh score B or C.
- Patient has a history of non-compliance to medical regimen or inability to grant consent
- Sexually active males, unless they use a condom during intercourse while taking the study drug and for at least 3 months after stopping study treatment. Sexually active males should not father a child during this period. A condom is required to be used by vasectomized men in order to prevent delivery of the drug via seminal fluid.

4. ENROLLMENT PLAN AND SUBJECT REGISTRATION

4.1 Enrollment Plan

4.1.1 Participating Study Centers

This study is anticipated to be conducted in 4-6 site(s).

4.1.2 Recruitment

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at participating centers from Medical Oncology, Radiation Oncology and Urology offices. Investigators will screen the patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study.

4.1.3 Expected Enrollment

This is a phase IB/II trial in which 9-18 patients will be enrolled onto the phase I portion and 35 patients will be enrolled on the phase II portion receiving enzalutamide and ribociclib.

Accrual is expected to be completed within 4 years after trial activation at participating sites. All patients will be followed for 24 months post-accrual or to death.

4.2 Registration Procedure

After eligibility screening and confirmation that a subject is eligible, subjects who are selected to participate will be registered through Medidata Rave. A record of subjects who fail to meet eligibility criteria (i.e., screen failures) will be maintained. Patient registration must be complete before beginning any treatment or study activities.

4.2.1 PCCTC Registration

Confirm eligibility as defined in Section 3 Patient Selection.

Obtain informed consent, by following procedures in Section 11.3 Written Informed Consent.

Obtain completed or partially completed protocol specific Eligibility Checklist.

All participants will be registered through Medidata Rave.

To complete registration and enroll a participant, the study staff at that site must contact the designated research staff at PCCTC to notify him/her of the participant registration. **The site staff then needs to email registration/eligibility checklist and source documents to the PCCTC at PCCTC@mskcc.org.**

These documents must be sent for each enrollment within 48 hours of the informed consent form being signed.

Upon receipt, the research staff at PCCTC will conduct an interim review of all documents. If the eligibility checklist is not complete, the patient will be registered pending enrollment and the site is responsible for sending a completed form and additional source documents if applicable within 30 days of the consent.

Once eligibility has been established and the participant is registered and assigned to treatment, the participant will be allotted a PCCTC Subject ID. This number is unique to the participant and must be written on all data and correspondence for the participant. This Subject ID will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation.

Participating sites will register subjects locally per their Institutional guidelines.

5. TREATMENT PLAN

This is a phase IB/II study of subjects with mCRPC with RB positive tumors who have not received chemotherapy.

The phase IB portion is a '3+3' study. Enzalutamide will be administered at a dose of 160 mg (40 mg X 4 pills) once daily. Ribociclib will be given daily for 21 out of 28 days and the dose will be escalated from 200, 400 to 600 mg as shown in below in Table 1.

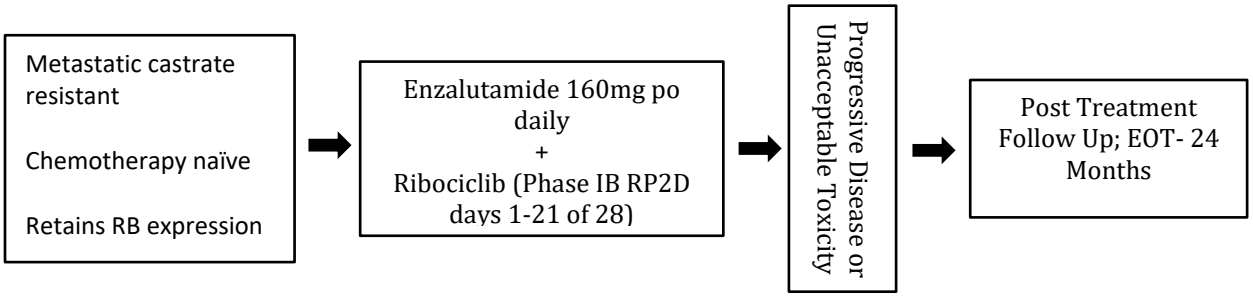
Table 1. Phase IB dose escalation schema

Dose Level	**Dose of ribociclib (days 1-21 of 28 day cycle)**	**Dose of Enzalutamide**
Level 1	200 mg daily	160mg po daily
Level 2	400 mg daily	160mg po daily
Level 3	600 mg daily	160mg po daily

The phase I portion of this study will follow a traditional 3+3 design, escalating to the next higher dose cohort if 3 patients are treated and no DLTs are observed in the first cycle of therapy. A DLT is defined in section ***5.7.1.1 dose limiting toxicity***. If one DLT is recorded then three additional patients will be enrolled into the present cohort. If no further DLTs occur (1 out of 6 DLTs) then the next patient will be enrolled in the next higher cohort. If 2 out 6 patients have an observed DLT in any given cohort, 3 additional patients will be treated at one dose level lower, and if no additional DLTs are observed, this will be the maximum tolerated dose. If no DLTs are observed in all three cohorts then phase II dose will be cohort 3 for the phase II study. The maximum possible sample size will be 18, corresponding to six at each cohort level. Toxicities will be graded according to the National Cancer Institute, Common Toxicity Criteria for Adverse Events version 4.03 (NCI CTCAE v 4.03). If multiple toxicities are seen, the presence of DLT will be based on the most severe toxicity experienced. At the completion of the phase I portion of the study, the investigators will review the toxicity profile and determine the RP2D.

Since protocol amendment version 5, the phase II portion of this study will be a single arm trial utilizing the recommended phase II dose from the phase IB component. Subjects will receive enzalutamide in combination with ribociclib.

Figure 4. Phase II Schema (1 cycle = 28 days)



Subjects will continue treatment until disease progression, unacceptable toxicity, or any criteria in *Section 5.8 Removing Subjects from the Protocol.*

Table 2. Schedule of Study Procedures and Assessments – Phase I

Please note: All visits have a window of ± 2 days													
	Screening		**Cycle 1**				**Cycle 2**		**Cycle 3**		**Cycle 4+**	**EOT**	**Post Treatment Follow up[1]**
Study Day / Visit Day	**-28 to 0**	**-14 to 0**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**15**	**1**	**1**	
Informed consent	X												
Inclusion/ exclusion criteria	X												
Medical history & demographics	X												
Physical exam/Vital Signs/ECOG PS	X		X	X	X	X	X	X	X	X	X	X	
Concomitant Meds	X		X	X	X	X	X	X	X	X	X	X	
AE assessment			X	X	X	X	X	X	X	X	X	X	
Survival Status													X
Laboratory Procedures													
CBC w/ differential		X	X	X	X	X	X	X	X	X	X	X	
Blood chemistries		X	X	X	X	X	X	X	X	X	X	X	
Magnesium, Phosphorus		X											
Coagulation[2]		X					X		X		X	X	
Urinalysis/BUN		X					X		X		X	X	
PSA		X	X	X	X	X	X	X	X	X	X	X	
Lipid Panel		X									X[3]		
Pharmacokinetics [4]			X				X						
ECG[5]		X[5]			X[5]		X[5]	X[5]	X[5]		X[6]	X	
ECHO/MUGA	X		As clinically indicated										
Imaging Procedures													
CT/MRI or CXR (abd/pelvis)	X[7]										X	X	
Bone scan	X[7]										X	X	
Tumor measurement	X[7]										X	X	
Treatment													
Ribociclib[8]			X										
Enzalutamide[9]			X										
Correlative Procedures													
Tumor biopsy	X[10]											X[11]	
CTCs	X										X[13]	X	
Androgen Panel[12]	X											X	

Please note: All visits have a window of ± 2 days													
	Screening		**Cycle 1**				**Cycle 2**		**Cycle 3**		**Cycle 4+**	**EOT**	**Post Treatment Follow up[1]**
Study Day / Visit Day	**-28 to 0**	**-14 to 0**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**15**	**1**	**1**	
Circulating DNA/ Exosomes	X										X[13]	X	

1. After treatment discontinuation, subjects will be followed for 24 months. During this time, survival status will be confirmed every 12 weeks.
2. Coagulation profile includes a prothrombin time (PT) or International normalized ratio (INR)
3. Every 4th cycle.
4. PK assessment schedule: C1D1: Pre-dose, t + 1 hour, t + 2 hours, t + 4 hours; C2D1: Pre-dose
5. Screening ECG will be performed in triplicate approximately 2 minutes apart. ECG will be performed at pre-dose and 2 to 4 hours post dose at Cycles 1 – 3.

   Note: For patients with QTcF ≥481 ms at any time, interrupt study treatment and follow the procedures described in Section 5.7.1. If treatment is resumed, repeat ECGs 7 days and 14 days after dose resumption (and then as clinically indicated). During subsequent cycles, perform pre-dose ECG for every cycle starting at cycle 6, and pre-dose and 2-4 post-dose starting at cycle 9 and every 3rd cycle thereafter.

6. ECG will be performed pre-dose only at cycles 4-6 for all patients.
7. Baseline imaging assessments can be done within 6 weeks of treatment start.
8. Subjects will take ribociclib daily for the first 21 days of each cycle followed by 7 days of rest.
9. Subjects will take Enzalutamide daily throughout each cycle.
10. In the absence of archival metastatic tissue, an optional tumor biopsy should be performed to determine RB status retrospectively. Fresh or archival tissue should be obtained if feasible.
11. A second optional tumor biopsy will be requested for subjects at progression of disease.
12. Serum will be collected for analysis of an Androgen Panel (testosterone, androstenedione, DHEAS).
13. CTCs and Circulating DNA will be collected at 12 weeks post treatment start.

Table 3. Schedule of Study Procedures and Assessments – Phase II

Please note: All visits have a window of ± 2 days											
	Screening		**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4+**	**EOT**	**Post Treatment Follow up[1]**
Study Day/ Visit Day	**-28 to 0**	**-14 to 0**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**1**	
Informed consent	X										
Inclusion/ exclusion criteria	X										
Medical history & demographics	X										
Physical exam/Vital Signs/ECOG PS	X		X	X	X	X	X	X	X	X	
Concomitant Meds	X		X	X	X	X	X	X	X	X	
AE assessment			X	X	X	X	X	X	X	X	
Survival Status											X
Laboratory Procedures											
CBC w/ differential		X	X	X	X	X	X	X	X	X	
Blood chemistries		X	X	X	X	X	X	X	X	X	
Magnesium, Phosphorus		X									
Coagulation[2]		X			X		X		X	X	
Urinalysis/BUN		X			X		X		X	X	
PSA		X	X	X	X	X	X	X	X	X	
Lipid Panel		X							X[3]		
ECG[4]		X[4]		X[4]	X[4]						
ECHO/MUGA	X		As clinically indicated								
Imaging Procedures											
CT/MRI or CXR (abd/pelvis)	X[5]								X	X	
Bone scan	X[5]								X	X	
Tumor measurement	X[5]								X	X	
Treatment											
Ribociclib			X								
Enzalutamide			X								
Correlative Procedures											
Tumor biopsy	X[6]									X[7]	
CTCs	X								X[9]	X	
Androgen Panel[8]	X									X	
Circulating DNA/ Exosomes	X								X[9]	X	

1. After treatment discontinuation, subjects will be followed for 24 months. During this time, survival status will be confirmed every 12 weeks.
2. Coagulation profile includes a prothrombin time (PT) or International normalized ratio (INR)
3. Every 4th cycle.
4. ECG will be performed in triplicate approximately 2 minutes apart. Subsequent ECGs should be performed only if clinically indicated. **Note:** For patients with QTcF ≥481 ms at any time, interrupt study treatment and follow the procedures described in Section 5.7.1. If treatment is resumed, repeat ECGs 7 days and 14 days after dose resumption (and then as clinically indicated).
5. Baseline imaging assessments can be done within 6 weeks of treatment start.
6. In the absence of archival metastatic tissue, an optional tumor biopsy should be performed to determine RB status retrospectively. Fresh or archival tissue should be obtained, if feasible.
7. A second optional tumor biopsy will be requested for subjects at progression of disease.
8. Serum will be collected for analysis of an Androgen Panel (testosterone, androstenedione, DHEAS)
9. CTCs and Circulating DNA/exosomes will be collected at 12 weeks post treatment start.

5.1 Screening/Pretreatment Assessment (Day -28 to Day 0)

Before initiating any screening activities, the scope of the study should be explained to each subject. Subjects should be advised of any known risks inherent in the planned procedures, any alternative treatment options, their right to withdraw from the study at any time for any reason, and their right to privacy. After this explanation, subjects should be asked to sign and date a Notice of Privacy Practice research authorization/HIPAA form and an IRB-approved statement of informed consent that meets the requirements of the Code of Federal Regulations (Federal Register Vol. 46, No. 17, January 27, 1981, part 50).

The screening visit will determine subject eligibility according to the inclusion and exclusions criteria (**Sections 3.1 Inclusion Criteria and 3.2 Exclusion Criteria**). The following assessments will be performed at this visit:

- Obtain informed consent and research authorization
- Record demographics (including age) and medical history (including prior treatment for prostate carcinoma)
- Physical exam
- ECOG performance status
- Vital signs [body temperature, blood pressure, pulse, respiratory rate, weight, height]
- Obtain histologic and radiologic confirmation of disease
- Confirm eligibility according to the inclusion/exclusion criteria
- ECG
- ECHO/MUGA
- Baseline imaging assessments within 6 weeks of treatment start: Bone scan, CT scan or MRI of the abdomen and pelvis and CT scan of the chest or Chest X-ray
- Laboratory tests within 14 days of treatment start: hematology, chemistry, magnesium, phosphorus, PSA, coagulation, lipid panel
- Urinalysis/BUN within 14 days of treatment start
- PSA and Gleason score at the time of diagnosis
- Correlative studies: androgen panel, CTCs by Epic Sciences, circulating DNA, and AR-V7 and other mechanisms of resistance
- Concomitant medications (see Appendix B for a listing of medications with the potential for drug interactions)

- Optional RB status determined by tumor biopsy or archival tissue sample. Fresh or archival tissue should be obtained if feasible (see section 5.6.1 for details regarding RB positivity)

5.2 Treatment Period (Day 1 to POD/EOT ± 2 days)

Subjects in the phase I portion of this study will return to the clinic Day 1, 8, 15 and 22 for cycle 1, then Day 1 and 15 for cycles 2 and 3, and then Day 1 of each cycle starting with cycle 4 until POD.

Subjects in the phase II portion of this study will return to the clinic Day 1 and 15 for cycles 1, 2, and 3 and then Day 1 of each cycle starting with cycle 4 until POD. The following assessments will be performed at these visits:

- Physical exam/Vital Signs/ECOG Performance Status
- Laboratory tests: hematology, chemistry, PSA, coagulation, lipid panel
- Urinalysis/BUN
- Pharmacokinetics (Phase 1 portion only)ECG (C1D15, C2D1) Subsequent ECGs should be performed if only clinically indicated
- Adverse events
- Concomitant medications
- Imaging assessments will be performed every 12 weeks ± 1 week during treatment period
- Correlative studies: CTCs and circulating DNA will be collected at 12 weeks post treatment start

5.3 End of Treatment/Treatment Discontinuation Visit (28 days from last dose ± 7 days)

Subjects that have discontinued the medication for toxicity or POD will return for an End of Treatment visit within 28 days of last treatment dose. The following assessments will be performed:

- Physical exam/Vital Signs/ECOG Performance Status
- Laboratory tests: hematology, chemistry, PSA, coagulationECG (only if clinically indicated)
- AEs
- Concomitant medications
- Imaging assessments
- Correlative studies: CTCs, androgen panel, circulating DNA, and AR-V7 and other mechanisms of resistance
- Optional tumor biopsy

5.4 Post Treatment Follow-up (EOT – 24 months from last dose ± 7 days)

Subjects will be followed every 3 months for 24 months after removal from treatment or until death. During this time, survival status will be confirmed every 3 months.

5.5 Safety assessments

Medical History
Medical history findings (i.e., previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected:

- Pertaining to the study indication
- Start before signing of the informed consent
- Considered relevant to the study

ECOG Performance Status
Performance status will be assessed using ECOG performance status criteria. See Appendix A: Performance Status Criteria for a KPS-ECOG conversion chart.

Vital Signs
Vital signs include body temperature, blood pressure, respiratory rate, pulse, weight and height. Height will be performed at screening only.

Physical Exam
The physical exam will include a full review of the body systems.

Electrocardiogram (ECG)
Twelve-lead ECGs should be obtained after the patient has been resting for 5-10 minutes prior to each time point indicated. All ECGs should be recorded with the patient in the same physical position.

Adverse Event Monitoring
Subjects will be closely monitored throughout the study for AEs. AEs and other symptoms will be graded according to NCI CTCAE v4.03.

Laboratory Test Assessments
- *CBC with differential*: white blood cells count (WBC), red blood cell count (RBC), HGB, hematocrit (HCT), UNVPLT, neutrophils (NEUTP), lymphocytes (LYMP).
- *Chemistry*: CA, ALB, total protein (TP), NA, K, chloride (CL), blood urea nitrogen (BUN), CREAT, alkaline phosphatase (ALK), ALT, AST, TBILI, LDH, Serum PSA (PSA).
- *Coagulation*: prothrombin time (PT) or International normalized ratio (INR)
- *Lipid panel*: cholesterol (CHOL), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides (TRIG)
- Urinalysis/BUN

Tumor Assessment and Bone Scan
Radiographic disease assessment will be obtained every 12 weeks during active treatment.

5.6 Correlative/Special Studies
Each subject will have the following specimens obtained at the study site as described below:

a) A paraffin embedded tumor sample from a metastatic site of disease (via biopsy) within 6 months prior to treatment start, if feasible.

b) In a subject undergoing a soft tissue biopsy or bone biopsy to determine RB status, an additional tumor sample will be collected to be placed in media/serum for explant culture in sites participating in the explant protocol. This will apply to Thomas Jefferson University subjects only.
c) Blood for CTC analysis using the Epic Sciences platform (Screening, Week 12, and upon progression/end of treatment; 1 Streck tube)
d) Blood for androgen panel by HPLC (Screening and upon progression/end of treatment; 1 red top tube).
e) Plasma collected for circulating DNA/exosomes (Screening, Week 12, and upon progression/end of treatment; 1 Streck tube)

The collection and handling procedures for the correlative studies can be found in the Laboratory & Correlative Studies Manual.

5.6.1 RB IHC from Paraffin Blocks

If tissue is available, and a biopsy is determined safe and feasible by the treating investigator, RB status will be determined. Tissue will undergo immunohistochemistry (IHC) staining with the RB monoclonal antibody from Cell Signaling Technology® [Rb (4H1) Mouse mAb #9309L] and will be analyzed for total and phosphorylated RB in a CLIA certified laboratory. An automated IHC staining protocol (ultra View DAB v1.02.0018) will be used on the Ventana automated stainer (Benchmark XT, Ventana Medical Systems, Inc., Tucson, AZ).

The stained slides will be evaluated by two pathologists without access to the clinical data to obtain an unbiased consensus result. The IHC stained TMA slides will then be scanned and analyzed digitally using the Aperio® computer-assisted image analysis system. A standardized nuclear analysis protocol will be used for scoring a minimum of 1,000 cells. The digital scoring will be reported as a percentage and absolute number of nuclear staining with nuclear scores from 0 to 3+ intensity. Endothelial nuclear staining will be used as an internal control. The Aperio® results will be compared to the pathologists' consensus results and the discrepant cases will be excluded. RB will be considered positive when 25% or more of the nuclei have a combination of 2+ and 3+ scores. Samples will be considered weak positives when 10% to 24% of the cells have a combination of 2+ and 3+ scores; and samples will be considered negative when less than 10% of the cells have a combination of 2+ and 3+ scores. This analysis was done prospectively for 25 subjects enrolled onto this study, but upon review of the requirement, the Sponsor Principal Investigator and study team determined that analysis will be done retrospectively for all subjects moving forward.

Depending on tissue availability, other key biomarkers of the RB pathway will be assessed via multiplexed IHC, including cyclin D1, cyclin D1b, p16 (a CDK4/6 inhibitor which is frequently elevated in RB-deficient tumors), key RB target genes (Cyclin A, E2F1, and MCM7), CDK4, CDK6, and the RB family members p107 and p130. Association of each parameter with the proliferative index (as determined by Ki67) and apoptotic indices (as determined by IHC to detect cleaved Caspase 3) will be determined.

RNA-Seq will be performed if there is available tissue to quantify gene expression and correlated with IHC. For biopsy specimens with sufficient tumor tissue, whole exome sequencing will be performed with Sanger sequencing used to identify potential AR variants.

5.7 Dose Modifications

5.7.1 Dose Modifications for ribociclib

Investigators should follow the guidelines described below for the modification of ribociclib treatment. Any plan to deviate from these guidelines in view of the patient safety must be previously discussed with Novartis unless there is an urgent need for action.

All dose modifications should be based on the worst preceding toxicity. If study treatment is being held due to toxicity, scheduled visits and all assessments should continue to occur except the dosing of the study drug. If the patient requires a dose interruption of > 21 days from the previous dose, then the patient must be discontinued from study treatment. Patients who discontinue the treatment due to an AE or an abnormal laboratory value must be followed until resolution or stabilization of the event. All dose changes or interruptions must be recorded appropriately. Provisional dose levels can be found in the table below.

Table 4. Provisional dose levels

Dose level	Proposed dose (mg)	Frequency
1 (starting dose)	600 mg	Daily (21 days followed by 7 days of rest)
2 (First dose reduction)	400 mg	Daily (21 days followed by 7 days of rest)
3 (Second dose reduction)	200 mg	Daily (21 days followed by 7 days of rest)

5.7.1.1 Dose-limiting toxicity

DLT will be defined as an AE or clinically significant abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first 28 days of treatment with ribociclib in cycle 1 and meets any of the criteria included in the

Table 5 below. NCI CTCAE version 4.03 should be used for all grading.

Patients who experience a DLT will have their therapy with ribociclib interrupted and will be followed until the toxicity has resolved to CTCAE grade ≤ 1 or to the patient's baseline value. After recovery from the toxicity in question, if the investigator believes that it is in the patient's best interest to resume therapy with ribociclib, the patient may resume therapy with a new cycle of treatment at a lower dose level.

The investigator must notify Novartis immediately of any unexpected Grade ≥ 3 AEs or laboratory abnormalities. Prior to enrolling patients into a higher dose level, Grade ≥ 2 AEs should be reviewed for all patients at the current dose level. Management of severe or intolerable adverse reactions requires temporary dose reduction and/or interruption of ribociclib therapy.

Table 5. Criteria for defining DLTs

Toxicity	DLT Criteria

General Laboratory Abnormalities	**CTCAE grade 3-4 laboratory abnormalities that result in hospitalization**
Hematology	**CTCAE grade 4 neutropenia lasting more than 7 consecutive days**
	CTCAE grade 4 thrombocytopenia
	CTCAE grade 3 thrombocytopenia with bleeding
	Febrile neutropenia (Grade ≥3 decrease in neutrophils associated a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than 1 hour)
ECG QT interval	**QTc interval ≥501 ms on at least 2 separate ECGs**
Cardiac	**Cardiac toxicity ≥ CTCAE grade 3** **Clinical signs of cardiac disease, such as unstable angina or myocardial infarction, or** **Troponin ≥ CTCAE grade 3**
Gastro-intestinal	**≥ CTCAE grade 3 vomiting ≥48 hours despite optimal anti-emetic therapy** **≥ CTCAE grade 3 diarrhea ≥48 hours despite optimal anti-diarrhea treatment**
Hepato-biliary	**≥ CTCAE grade 2 total bilirubin for more than 7 consecutive days (those patients who recover in less than a week won't be considered as DLT , and those patients who need more than 7 days to recover will be considered as DLT)** **≥ CTCAE grade 3 total bilirubin** **≥ CTCAE grade 2 ALT with a ≥grade 2 bilirubin elevation of any duration in the absence of liver metastases** **≥ CTCAE grade 3 ALT for >4 consecutive days** **CTCAE grade 4 ALT or AST** **Grade 4 serum alkaline phosphatase >7 consecutive days**
Renal	**≥ CTCAE grade ≥3 serum creatinine**
ILD/pneumonitis	**≥ CTCAE grade 3**
Non-hematologic events	**≥ CTCAE grade 3, except for the exclusions noted below:**
Exceptions to DLT criteria	**Grade 3 alopecia**
	<5 days of CTCAE grade 3 fatigue
	Grade 3 fever or infection without neutropenia <5 days duration
	Grade 3 laboratory abnormalities that are responsive to oral supplementation or deemed by the investigator to be clinically insignificant
CTCAE version 4.03 should be used for grading. Optimal therapy for vomiting and diarrhea should be based on institutional guidelines with consideration of the prohibited medications listed in these protocol guidelines.	

Table 6. Ribociclib dose adjustment and management recommendation for hematological adverse reactions

Toxicity/Grade	Dose Adjustment and Management Recommendations
Thrombocytopenia	
Grade 1(≥75 x 10^9/L)	No dose adjustment required.
Grade 2 (≥50 x 10^9/L – <75 x 10^9/L)	Dose interruption until recovery to grade ≤1. Re-initiate ribociclib at the same dose.
Grade 3 (≥25 x 10^9/L - <50 x 10^9/L)	Dose interruption until recovery to grade ≤1. Re-initiate ribociclib at the same dose level. If toxicity recurs at grade 3: temporary dose interruption until recovery to grade ≤1 and reduce ribociclib to the next lower dose level.
Grade 4(<25 x 10^9/L)	Dose interruption until recovery to grade ≤1. Re-initiate ribociclib at the next lower dose level. If toxicity recurs at grade 4: discontinue ribociclib
Absolute neutrophil count (ANC)	

Toxicity/Grade	Dose Adjustment and Management Recommendations
Grade 1 (≥1.5 x 10^9/L)	No dose adjustment required.
Grade 2 (≥1.0 - <1.5 x 10^9/L)	No dose adjustment required.
Grade 3 (≥0.5 - <1.0 x 10^9/L)	Dose interruption until recovery to ≥1.0 x 10^9/L. Re-initiate ribociclib at the same dose level. If toxicity recurs at grade 3: temporary dose interruption until recovery to ≥1.0 x 10^9/L. If resolved in ≤7 days, then maintain dose level. If resolved in >7 days, then reduce ribociclib dose to the next lower dose level.
Grade 4 (<0.5 x 10^9/L)	Dose interruption until recovery to ≥1.0 x 10^9/L. Re-initiate ribociclib at the next lower dose level. If toxicity recurs at grade 4: temporary dose interruption until recovery to ≥1.0 x 10^9/L and reduce ribociclib at the next lower dose level.
Febrile neutropenia	
Grade 3 ANC <1.0 x 10^9/L with a single temperature of >38.3 ºC (101 ºF) or a sustained temperature of ≥38 ºC (100.4 ºF) for more than one hour	Dose interruption until improvement of ANC ≥1.0 x 10^9/L and no fever. Restart at the next lower dose level. If febrile neutropenia recurs, discontinue ribociclib.
Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue ribociclib.
Anemia (Hemoglobin)	
Grade 1 (≥10.0 – LLN g/dL)	No dose adjustment required.
Grade 2 (≥8.0 – <10.0 g/dL)	No dose adjustment required.
Grade 3 (<8.0 g/dL)	Dose interruption until recovery to grade ≤2. Re-initiate ribociclib at the same dose.
Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue ribociclib.

Table 8: Recommendations for ribociclib dose modification in case of hepatic toxicities

HEPATOTOXICITY (BILIRUBIN, SGPT/ALT, SGOT/AST)	
TOTAL BILIRUBIN without ALT/AST increase above baseline value	
Grade 1 (> ULN – 1.5 x ULN) (confirmed 48 to 72hrs later)	Maintain dose level with LFTs monitored every two weeks
Grade 2 (>1.5 – 3.0 x ULN)	Dose interruption of ribociclib If resolved to ≤ grade 1 in ≤21 days, then maintain dose level If resolved to ≤ grade 1 in >21 days or toxicity recurs, then reduce 1 dose level If toxicity recurs after two dose reductions, discontinue ribociclib
Grade 3 (>3.0 – 10.0 x ULN)	Dose interruption of ribociclib If resolved to ≤ grade 1 in ≤21 days, lower 1 dose level of ribociclib If resolved to ≤ grade 1 in >21 days or toxicity recurs, discontinue ribociclib
Grade 4 (>10.0 x ULN)	Discontinue ribociclib

Confounding factors and/or alternative causes for increase of total bilirubin should be excluded before dose interruption/reduction. They include but are not limited to: evidence of obstruction, such as elevated ALP and GGT typical of gall bladder or bile duct disease, hyperbilirubinemia due to the indirect component only (i.e. direct bilirubin component ≤1 x ULN) due to hemolysis or Gilbert Syndrome, pharmacologic treatment, viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs. For patients with Gilbert Syndrome, these dose modifications apply to changes in direct bilirubin only. Bilirubin will be fractionated if elevated.	
HEPATOTOXICITY (BILIRUBIN, SGPT/ALT, SGOT/AST)	
AST or ALT	
AST or ALT without bilirubin elevation >2 x ULN	
Same grade as baseline or increase from baseline grade 0 to grade 1 (confirmed 48 to 72 hrs later)	No dose adjustment required with LFTs monitored per protocol if same grade as baseline or every two weeks in case of increase from baseline grade 0 to 1
Increase from baseline grade 0 or 1 to grade 2 (>3.0 – 5.0 x ULN) **or** from baseline grade 2 to grade 3 (>5.0 – 20.0 x ULN)	Hold ribociclib until resolved to ≤ baseline grade, then lower 1 dose level of ribociclib If recovery to ≤ baseline grade is > 28 days, discontinue ribociclib If toxicity recurs, discontinue ribociclib treatment.
Increase from baseline grade 0 or 1 to grade 3 (>5.0 – 20.0 x ULN)	Hold ribociclib until resolved to ≤ baseline grade, then lower 1 dose level of ribociclib If recovery to ≤ baseline grade is > 28 days, discontinue ribociclib If toxicity recurs, discontinue ribociclib treatment.
Grade 4 (>20.0 x ULN)	Discontinue ribociclib
AST or ALT and concurrent Bilirubin	
AST or ALT ≥ grade 2 (>3 x ULN) in patients with normal values at baseline and total bilirubin >2 x ULN **or** AST or ALT ≥ grade 3 (>5 x ULN) in patients with grade 1 or 2 at baseline, and total bilirubin >2 x ULN	Discontinue ribociclib
Confounding factors and/or alternative causes for increased transaminases should be excluded before dose interruption/reduction. They include but are not limited to: concomitant medications, herbal preparations or dietary supplements, infection, hepato-biliary disorder or obstruction, new or progressive liver metastasis, and alcohol intake.	

Hepatic toxicity monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT. For patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only.

Close observation is recommended in case of AST, ALT, and/or bilirubin increase requiring dose interruption, which involves:

- Repeating liver enzyme and serum bilirubin tests **two or three times weekly**. Frequency of re-testing can decrease to once a week or less if abnormalities stabilize or return to normal values.
- Obtaining a more detailed history of current symptoms.
- Obtaining a more detailed history of prior and/or concurrent diseases.

- Obtaining a history of concomitant drug use (including non-prescription medications, herbal and dietary supplements), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; hepatotropic virus infections (CMV, EBV or HSV); autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.
- Assessing cardiovascular dysfunction or impaired liver oxygenation, including hypotension or right heart failure as possible etiologies for liver dysfunction.

Table 9. Dose modification guidance in case of QT prolongation

Grade	Dose Modification
For all grades	• Check the quality of the ECG and repeat if needed. • Perform analysis of serum electrolytes (K+, Ca++, Phos, Mg++). If below the lower limit of normal, interrupt ribociclib administration, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal. • Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT interval. • Check compliance with correct dose and administration of ribociclib.
1 QTc 450-480 ms	Perform above steps as directed in "For All Grades". No dose adjustment required.
2 QTc 481-500 ms	Interrupt ribociclib. Perform above steps as directed in "For All Grades". • Perform a repeat ECG one hour after the first QTcF of ≥481ms • Repeat ECG as clinically indicated until theIf QTcF returns to < 481 ms, restart ribociclib at the same dose reduced by 1 dose level. Refer to Section 5.7.1 for dosing schedule. No dose adjustment required for first occurrence. • If QTcF remains ≥ 481 ms recurs, ribociclib should be reduced again by 1 dose level. Repeat ECG as clinically indicated until the QTcF returns to < 481 ms and restart ribociclib at the same dose. No dose adjustment required for first occurrence. • If QTcF ≥ 481 ms recurs, ribociclib should be reduced by 1 dose level. Refer to Section 5.7.1 for dosing schedule. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patient who has therapy interrupted due to QTcF ≥481 ms
3 QTc ≥501 ms on at least two separate ECGs	Interrupt ribociclib. Perform above steps as directed in "For All Grades". • Perform a repeat ECG within one hour of the first QTcF of ≥ 501 ms. • If QTcF remains ≥ 501 ms, consult with a cardiologist (or qualified specialist) and repeat cardiac monitoring as indicated until the QTcF returns to < 481 ms.

	• If QTcF returns to < 481 ms, ribociclib will be reduced by 1 dose level. Refer to Section 5.7.1 for dosing schedule. • If QTcF remains ≥ 481 ms after performing steps 1-4 as directed in "For All Grades," discontinue ribociclib. • Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 501 ms • If QTcF of ≥ 501 ms recurs, discontinue ribociclib.
4 QT/QTc ≥501 or >60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia	Discontinue ribociclib. Perform above steps as directed in "For All Grades". • Obtain local cardiologist (or qualified specialist) consultation and repeat cardiac monitoring as indicated until the QTcF returns to <481 ms. •

Guidance for Management of All Other Adverse Reactions

- Consider performing an analysis of serum potassium, calcium, phosphorus, and magnesium for all adverse reactions that are potentially associated with electrolyte imbalance (e.g. diarrhea, nausea/vomiting). If electrolyte values are below the lower limit of normal, interrupt ribociclib administration, correct electrolytes with supplements as soon as possible, and repeat electrolyte testing until documented normalization of the electrolytes.
- For all other adverse events, including Toxic Epidermal Necrolysis (TEN), which is a grade 4 event by CTCAE, ribociclib should be discontinued, and TEN should be treated with appropriate medical therapy.

Table 10. Ribociclib dose adjustment and management recommendation for ILD/pneumonitis (CTCAE v4.03)

Grade	Dose Adjustment and Management Recommendations
1 (asymptomatic)	No dose adjustment required..Initiate appropriate medical therapy and monitor as clinically indicated.
2 (symptomatic)	Interrupt ribociclib dose until recovery to Grade ≤1, then resume ribociclib at the next lower dose level*.
3 and 4 (severe)	Discontinue ribociclib

* An individualized benefit-risk assessment should be performed before resuming ribociclib

Table 11. Ribociclib dose adjustment and management recommendation for all other adverse reactions

Grade	Dose Adjustment and Management Recommendations
1	No dose adjustment recommended. Initiate appropriate medical therapy and monitor.
2	Dose interruption until recovery to grade ≤1. Initiate appropriate medical therapy and monitor. Re-initiate ribociclib at the same dose. If the same toxicity recurs at grade 2, interrupt ribociclib until recovery to grade ≤1. Re-initiate ribociclib at the next lower dose level.
3	Dose interruption until recovery to grade ≤1. Initiate appropriate medical therapy and monitor. Re-initiate ribociclib at the next lower dose level. If toxicity recurs at grade 2: temporary dose interruption until recovery to grade ≤1 and reduce ribociclib dose the next lower dose level. If toxicity recurs at grade 3, discontinue ribociclib.
4	Discontinue ribociclib and treat with appropriate medical therapy.

Adjustment of Starting Dose in Special Populations

Renal impairment
Insufficient data are available to provide a dosage recommendation for ribociclib in patients with renal impairment.

Subjects with baseline renal impairment are excluded from the study (serum creatinine > 1.5 mg/dL or creatinine clearance < 50 mL/min). Subjects who experience renal impairment of grade 2 or higher during the treatment period should discontinue treatment and should be followed for safety assessments.

Elderly
Physicians should exercise caution in monitoring the effects of ribociclib in the elderly. Insufficient data are available to provide a dosage recommendation.

Follow-up for toxicities
Subjects who complete treatment or whose treatment is interrupted or permanently discontinued due to an AE or abnormal laboratory value must be followed at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event. All subjects will be followed up for safety up to 30 days following the last dose of study treatment.

5.7.2 Dose Modifications for Enzalutamide

Table 12. Dose modification for enzalutamide

Dose Level	Enzalutamide
0	160 mg daily
-1	120 mg daily
-2	80 mg daily

All dose adjustments should be made as per the local approved prescribing information and investigator's best judgment. An example from the prescribing information is provided below:

If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld for one week or until symptoms improve to ≤ Grade 2, then resumed at the same or a reduced dose (120 mg or 80 mg) if warranted.

5.8 Removing Subjects from the Protocol

In the absence of treatment delays because of AEs, treatment will continue until one of the following criteria applies:

- subject decides to withdraw from the study
- disease progression
- symptomatic disease progression at any time
- objective clinical disease progression
- intercurrent illness that prevents further administration of treatment
- unacceptable AE(s) that may or may not be directly related to treatment but that, in the judgment of the treating physician, makes it dangerous for the subject to be retreated
- general or specific changes in the patient's condition that render the patient unacceptable for further treatment, in the judgment of the investigator

Because an excessive rate of withdrawals can render the study uninterruptable, unnecessary withdrawal of subjects should be avoided. When a subject discontinues treatment early, the investigator should make every effort to contact the subject and to perform a final evaluation. The reason(s) for withdrawal should be recorded.

6. THERAPEUTIC/DIAGNOSTIC AGENT(S)

6.1 Ribociclib

Ribociclib is an orally bioavailable, small molecule inhibitor of CDK4/6. Ribociclib exhibits highly specific inhibitory activity against CDK4/cyclinD1 and CDK6/cylinD3 complexes, with concentration resulting in 50% inhibition (IC50) values of 10 nM and 39 nM, respectively, in isolated enzyme assays.

6.1.1 Packaging and labeling

The ribociclib drug product is available in the following clinical forms: hard gelatin capsules (10 mg, 50 mg and 200 mg), film-coated tablets (50 mg and 200 mg) and an oral solution (30 mg/mL).

Medication will be labeled for Clinical Trial use and will include storage conditions for the drug and the medication number but no information about the patient.

Packaging and labeling
Study drug: Ribociclib Packaging: Hard gelatin capsules in bottles (50 and 200 mg) **OR** Film-coated tablets in bottles (200 mg) Labeling: Labeled as 'Ribociclib' or 'LEE011'

6.1.2 Supply, receipt and storage

Ribociclib will be supplied by Novartis or its designee. Study drug must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, ribociclib should be stored according to the instructions specified on the medication label. Medication labels will comply with the legal requirements of each country and be printed in the local language.

Patients will be provided with adequate supply of ribociclib for self-administration at home until at least their next scheduled study visit.

6.1.3 Drug Accountability

Clinical drug supply must be accounted for and patients will be asked to return all unused study drug and packaging on a regular basis, at the end of the study or at the time of study drug discontinuation.

Compliance should be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver. Records of study medication used, dosages administered, and intervals between visits and the completion of the study should be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

At the conclusion of the study, and, as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to Novartis.

6.1.4 Drug product administration

Ribociclib will be taken orally, once a day for 21 consecutive days followed by a 7 day planned break.

Patients will be provided with a diary in which to record their intake of study drug (Phase I Diary – Appendix E OR Phase II Diary – Appendix F). However, the actual number of tablets taken by the patient must be calculated from the number of tablets dispensed and returned.

Ribociclib will be administered as a flat-fixed dose (200 mg, 400 mg or 600 mg daily), and not by body weight or body surface area.

Patients must be instructed to return unused study drugs to the site at discontinuation or completion of treatment. The site personnel must ensure that the appropriate dose of each study drug is administered and that the drug accountability is performed.

Ribociclib must be taken as follows:

- Patients should be instructed to take the ribociclib capsules with a large glass of water (~250 ml) at the same time each day.
- Ribociclib can be taken without regard to meals; however dietary habits around the time of dosing should be as consistent as possible throughout the study, and in particular during those periods when samples are being taken for PK analysis.

- Patients should be instructed to swallow the ribociclib capsules whole and not to chew, crush or open them.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose
- Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day.
- Patients must avoid consumption of grapefruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.

On days with PK, ECG sampling, chemistry panel and/or lipid panel sampling, the following additional guidelines should be followed:

- On a day when PK blood collection is scheduled at the clinic, patients must take study treatment in the clinic under the supervision of the Investigator or designee. On all other days, patients may take the study treatment at home.
- On a day of chemistry panel and/or lipid panel sampling, patients must be fasting from all food and drink for at least 8 hours overnight. Water is allowed during all fasting periods; however, coffee, tea and juice are not permitted during the fasting period. Patients must also take study treatment in the clinic under the supervision of the Investigator or designee. On all other days, patients may take the study treatment at home.
- Pre-dose samples should be drawn prior to dosing. The sampling time of the PK samples and the dosing time must be precisely recorded in the CRF. Furthermore, the dosing date and time the study medication was taken on the day before the PK assessment must be precisely recorded in the CRF.
- Post-dose PK samples should be collected after dosing of the study treatment

6.1.5 Disposal and Destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. Study drug destruction at the investigational site will only be permitted if authorized by Novartis in a prior agreement and if permitted by local regulations.

6.2 Enzalutamide

Enzalutamide (MDV3100) is an AR signaling inhibitor that targets several steps in the AR signaling pathway. Enzalutamide competitively inhibits binding of androgens to ARs, inhibits nuclear translocation of receptors and inhibits the association of the AR with DNA, even in the setting of AR overexpression and in prostate cancer cells resistant to antiandrogens.

6.2.1 Description of treatment

Enzalutamide 40-mg capsules are oval, white to off-white and contain enzalutamide, caprylocaproyl macrogolglycerides, butylhydroxyanisole and butylhydroxytoluene.

6.2.2 Handling and dispensing

Enzalutamide will be prescribed by the treating physician and dispensed by a local pharmacy.

6.2.3 Drug product administration

Patients will be instructed to take 4 tablets (160 mg total) of enzalutamide orally (PO) once daily. Enzalutamide can be taken with or without food. Capsules must be swallowed whole, and should not be chewed, dissolved, or opened.

6.3 Concomitant Medications

Because of the potential for drug-drug interaction, the concurrent use of all other drugs, over-the-counter medications, and alternative therapies must be documented. The principal investigator should be alerted if the patient is taking any prohibited agents.

Concurrent enrollment in another therapeutic clinical investigation is prohibited.

Permitted concomitant therapy

Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheals are allowed. Please consult the list of prohibited medications and the list of use with caution medications for further guidance.

The patient must be told to notify the investigational site about any new medications he takes after the start of the study treatment. All medications (other than study drugs) and significant non-drug therapies (including vitamins, herbal medications, physical therapy and blood transfusions) administered within 30 days of study entry and during the study must be listed on the Concomitant medications/Significant non-drug therapies eCRF.

Bisphosphonates and denosumab

Bisphosphonates and denosumab are permitted for the treatment of osteoporosis and prevention of skeletal related events for patients with bone metastases. Chronic concomitant bisphosphonate/denosumab therapy for the prevention of bone metastasis is not permitted.

Hematopoietic growth factors

Hematopoietic growth factors may be used according to ASCO guidelines.

Palliative radiotherapy

Palliative radiation is permitted if done solely for bone pain relief. It should not be delivered to a target lesion and it should not encompass more than 25% of irradiated bone marrow.

If palliative radiotherapy is initiated after the start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be ruled out.

No dose modification of study treatment is needed during palliative radiotherapy.

Permitted concomitant therapy requiring caution

Medications to be used with caution during ribociclib and in this study are listed below. This list is not comprehensive and is only meant to be used as a guide. These medications should be excluded from patient use if possible. If they must be given, then use with caution and consider a ribociclib interruption if the concomitant medication is only needed for a short time.

- Moderate inhibitors or inducers of CYP3A4/5
- Sensitive substrates of CYP3A4/5 that do not have narrow therapeutic index
- Strong inhibitors of BSEP

- Sensitive substrates of the renal transporters, MATE1 and OCT2
- Sensitive substrates of BCRP
- Medications that carry a possible risk for QT prolongation

Prohibited concomitant therapy

The following medications are prohibited during study treatment in the study. This list is not comprehensive and is only meant to be used as a guide (Please see Appendix B):

- Strong inhibitors or inducers of CYP3A4/5
- Substrates of CYP3A4/5 with a narrow therapeutic index
- Medications that carry a known risk for QT prolongation
- Herbal medications/preparations, dietary supplements
- Other investigational and antineoplastic therapies not part of this study

Herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh and ginseng. Patients should stop using all herbal medications and dietary supplements at least 7 days prior to enrollment.

Refer to the ribociclib Investigators Brochure and other drug package insert and Appendix X for information on possible interactions with other drugs.

7.0 ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

An AE will be recorded and followed from treatment administration to 30 days post treatment or resolution.

7.1.2 Expected Adverse Events

Expected AEs are those that have been previously identified as resulting from administration of the agent. An AE can be considered expected when it appears in the current AE list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

7.1.3 Unexpected Adverse Events

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).

Contact the Principal Investigator or sponsor to confirm unexpected AEs when necessary.

7.1.4 Adverse Drug Reaction (ADR)

A noxious and unintended response to a medicinal product related to any dose should be considered ADRs. The phrase "response to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. ''Reasonable possibility'' means there is evidence to suggest a causal relationship between the drug and the AE.

7.1.5 Serious Adverse Event (SAE)

An SAE/ADR as defined in the Code of Federal Regulations (21CFR312.32) is any event that:

- results in death
- is life-threatening
- results in inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- results in congenital anomaly or birth defect
- is medically significant in the opinion of the investigator

Events that are **not** considered SAEs include:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

7.1.6 Progression of malignancy

Progression of a patient's malignancy should not be considered an AE, unless in the investigator's opinion, study treatment resulted in an exacerbation of the patient's condition. If disease progression results in death or hospitalization while on study or within 30 days of the last dose progressive disease will be considered an SAE.

7.1.7 Life-threatening events

A life-threatening event is any AE that places the patient at immediate risk of death from the reaction as it occurs. It is not a reaction that, had it occurred in a more severe form, might have caused death.

7.1.8 Hospitalization or prolongation of hospitalization

Hospitalization encompasses any inpatient admission (even for less than 24 hours) resulting from a precipitating, treatment-emergent AE. For chronic or long-term patients, inpatient admission also includes transfer within the hospital to an acute or intensive care inpatient unit. Hospitalizations for administrative reasons or a non-worsening preexisting condition should not be considered AEs (e.g., admission for workup of a persistent pretreatment laboratory abnormality, yearly physical exam, protocol-specified admission, elective surgery). Preplanned treatments or surgical procedures should be noted in the baseline documentation. Hospitalization because of an unplanned event will be deemed an SAE.

Prolongation of hospitalization is any extension of an inpatient hospitalization beyond the stay anticipated or required for the original reason for admission.

7.1.9 Significant disability

Disability is a substantial disruption of the patient's ability to conduct normal life functions.

7.1.10 Congenital anomaly

If the female partner of a male patient becomes pregnant during the course of the study, the treating physician must be notified immediately. All confirmed pregnancies must be immediately reported to the medical monitor. All pregnancies will be followed until resolution (i.e., voluntary or spontaneous termination or birth) and assessed for congenital anomalies and birth defects.

7.2 Recording and Grading of Adverse Events

7.2.1 Recording

All observed or volunteered AEs, regardless of treatment group, severity, suspected causal relationship, expectedness, or seriousness will be recorded.

A clinically significant change in a physical examination finding or an abnormal test result should be recorded as an AE, if it:

- is associated with accompanying symptoms
- requires additional diagnostic testing or medical or surgical intervention
- leads to a change in study dosing or discontinuation from the study
- requires additional concomitant drug treatment or other therapy, or
- is considered clinically significant by the investigator

An abnormal test result that is subsequently determined to be in error does not require recording as an AE, even if it originally met one or more of the above criteria.

7.2.2 Grading severity

All AEs will be graded based on the NCI CTCAE version 4.03.

7.2.3 Attributing causality

After assigning a grade to an AE, the investigator must evaluate all clinical AEs and abnormal laboratory values for possible causal relationship to enzalutamide or ribociclib. Causality attribution will be decided using the criteria outlined in Table 12.

Table13. Relationship of AE to Study Drug

Relationship	Description
Unrelated	AE is clearly not related
Unlikely	AE is doubtfully related
Possible	AE may be related
Probable	AE is likely related
Definite	AE is clearly related

Abnormal laboratory values of clinical significance that were present at baseline and did not change in grade or frequency during experimental therapy or intervention and those that can obviously be attributed to underlying disease will be recorded as unrelated.

7.3 Reporting Adverse Events

7.3.1 Reporting serious adverse events

All SAEs, events determined to be medically significant by the treating Investigator, and unknown reactions or unexpected events should be reported to PCCTC, within 24 hours of knowledge of the event using the contact information below. The initial report should include the following information at a minimum:

- protocol # and title
- study identification number, sex, age at event
- date the event occurred
- description of the SAE

The PCCTC SAE Report Form (Appendix H) will be used for reporting each SAE and should be submitted to PCCTC within 5 business days.

Severity, causality, action taken, concomitant medications, outcome, etc should be reported to the PCCTC and the lead site as soon as possible.

Follow-up of AEs should continue until the event and any sequela resolve or stabilize at a level acceptable to the investigator and the study site/sponsor or medical monitor.

SAE Contact Information for PCCTC:

Prostate Cancer Clinical Trials Consortium
646-888-0434/646-422-4383
Email: pcctc@mskcc.org

SAE Contact Information for Sponsor Investigator:

Wm. Kevin Kelly, DO
1025 Walnut Street
Thomas Jefferson University
College Building, Suite 700
Philadelphia, PA 19107
Phone: 215-503-5455
e-mail: William.Kelly@jefferson.edu

SAE Contact Information for Novartis:

Drug Safety & Epidemiology (DS&E) Department
fax 1.888.299.4565

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval and otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

The PCCTC will fax the PCCTC SAE Form (Appendix H) and the Novartis SAE Coversheet (Appendix G) to Novartis DS&E Department within 24 hours for deaths or life-threatening events and for all other SAEs. The original PCCTC SAE form, Novartis SAE coversheet, and the fax confirmation sheet must be kept with the case report forms at the study site.

Safety Reporting Requirements for IND Holders

In accordance with Code of Federal Regulations Title 21, Part 312 (21 CFR § 312.32), sponsor-investigators of studies conducted under an IND must comply with following safety reporting requirements:

Expedited IND Safety Reports:

7 Calendar-Day Telephone or Fax Report
The Sponsor-Investigator is required to notify the FDA of any fatal or life-threatening AE that is unexpected and assessed by the investigator to be possibly related to the use of ribociclib with enzalutamide. An unexpected AE is one that is not already described in the Investigator Brochure.

Such reports are to be telephoned or faxed to the FDA within 7 calendar days and PCCTC and Novartis within 24 hours of first learning of the event. Each telephone call or fax transmission (see fax number below) should be directed to the FDA new drug review division in the Center for Drug Evaluation and Research or in the product review division for the Center for Biologics Evaluation and Research, whichever is responsible for the review of the IND.

15 Calendar-Day Written Report
The Sponsor-Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered possibly related to the use of ribociclib with enzalutamide. The PCCTC will facilitate this notification to the FDA and all participating investigators. An unexpected AE is one that is not already described in the Investigator Brochure.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with

the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, PCCTC, Novartis, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500A Form but alternative formats are acceptable (e.g., summary letter).

FDA fax number for IND Safety Reports:

1 (800) FDA – 0178

All written IND Safety Reports submitted to the FDA by the Sponsor-Investigator must also be submitted to:

Prostate Cancer Clinical Trials Consortium
Phone: 646-888-0434/646-422-4383
Email: pcctc@mskcc.org

AND

Thomas Jefferson University IRB

IND Annual Reports
In accordance with the regulation 21 CFR § 312.32, the Sponsor-Investigator shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the progress of the investigation. Please refer to 21 CFR § 312.32 for a list of the elements required for the annual report. All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to PCCTC.

7.4 Safety Reports

- PCCTC will distribute outside safety reports to the participating sites immediately upon receipt.
- Participating sites must submit safety reports to their institution's IRB/PBs within 30 days of receipt from PCCTC or per participating site guidelines.

8. CRITERIA FOR OUTCOME ASSESSMENT/THERAPEUTIC RESPONSE

8.1 Outcome Assessment

All baseline evaluations will be performed as closely as possible to the beginning of treatment. For subsequent evaluations, the method of assessment and techniques will be the same as those used at baseline.

8.1.1 Primary endpoint

The primary endpoint for the phase IB component of this study is dose limiting toxicity (DLT) of ribociclib that can be combined with enzalutamide in patients with mCRPC

The primary endpoint for the phase II component of this study is the proportion of patients with a ≥ 50% reduction in PSA at 12 weeks in patients treated with enzalutamide with and without ribociclib with chemotherapy naïve mCRPC.

8.1.2 Secondary endpoints

To determine PSA PFS in patients treated with enzalutamide with and without ribociclib in patients with chemotherapy naïve mCRPC.

To determine the rPFS in patients treated with enzalutamide with and without ribociclib in patients with chemotherapy naïve mCRPC.

To determine the overall safety and survival for patients treated with enzalutamide with and without ribociclib in patients with chemotherapy naïve mCRPC.

To determine the pharmacokinetics in patients treated with enzalutamide with and without ribociclib in patients with chemotherapy naïve mCRPC.

8.2 Therapeutic Response

Response and progression will be evaluated in this study using a combination of the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee[4] and the guidelines for prostate cancer endpoints developed by the Prostate Cancer Clinical Trials Working Group (PCWG2).[5]

Patients will need to be reevaluated for response every cycle (or more frequently if indicated), according to the guidelines below.

8.2.1 PSA

Perform PSA testing at a minimum of 1-week intervals with the threshold PSA level at 2.0 ng/mL. To report PSA-based outcomes, PCWG2 recommends that the percent of change in PSA from baseline to 12 weeks (or earlier for those who discontinue therapy) and the maximum decline in PSA that occurs at any point after treatment be reported for each patient using a waterfall plot. Because the rate of rise has shown prognostic significance, estimate a pretreatment PSA doubling time (PSA-DT) if at least 3 values are available, but do not delay either treatment or enrollment onto a trial simply to estimate PSA-DT. Because declines in serum PSA, if they occur, may not do so for several weeks, PSA measurements obtained during the first 12 weeks should not be used as the sole criterion for clinical decision making.[5]

8.2.2 Measurable disease

According to RECIST, measurable disease is defined as at least 1 lesion > 20 mm in its longest diameter as measured with conventional techniques (i.e., CT [nonspiral or nonhelical], MRI, physical exam) or > 10 mm as measured with spiral CT scan. All tumor measurements will be taken using a ruler or calipers and recorded in millimeters (or decimal fractions of centimeters).

8.2.3 Nonmeasurable disease

Following RECIST, all other lesions (or sites of disease) will be considered nonmeasurable disease. This includes small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan) and any of the following:

- bone lesions
- ascites
- pleural or pericardial effusion
- lymphangitis cutis or pulmonis

- abdominal masses that are not confirmed and followed by imaging techniques
- cystic lesions
- lesions occurring within a previously irradiated area unless they are documented as new lesions since the completion of radiation therapy

Note: If only a single, asymptomatic bone lesion is present at baseline, and will be irradiated, the metastatic nature of this lesion must be confirmed by x-ray, CT, or MRI.

8.2.4 Target (nodal and visceral) lesions

Following RECIST, progression in a nodal or visceral site (i.e., liver and lung) is sufficient to document disease progression. The presence or absence of nodal and visceral disease before and after treatment should be recorded separately.

All measurable lesions (up to a maximum of 5 lesions per organ and 10 lesions in total) will be identified as target lesions to be measured and recorded at baseline. The target lesions should be representative of all involved organs. Target lesions will be selected on the basis of size (i.e., the largest area) and suitability for accurate, repeated measurements (either by imaging techniques or clinically). The sum of the LD of all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as a reference by which to characterize the objective tumor response.

Because small lymph nodes are difficult to measure accurately and may not be malignant, the greatest diameter of a lymph node must measure at least 2 cm by spiral CT to be considered a target lesion.[5]

8.2.5 Bone lesions

When the bone scan is the sole indicator of progression, disease progression in bone is defined as 2 or more new lesions seen on bone scan compared with a prior scan used for trial entry.[5] In situations where scan findings suggest a flare reaction or where new lesion(s) may represent trauma, confirm these results with other imaging modalities (e.g., MRI or fine-cut CT). If many new areas of uptake are observed, confirmation is generally not necessary.

8.2.6 Nontarget lesions

All other lesions (or sites of disease) will be identified as nontarget lesions and recorded at baseline. Nontarget lesions will include measurable lesions that exceed the maximum number per organ (5) or total of all involved organs (10), as well as nonmeasurable lesions. The presence or absence of these lesions will be recorded on the CRF and should be evaluated at the same assessment time points as all target lesions.

8.2.7 New lesions

The appearance of up to 10 new measurable lesions should be recorded. Each new lesion should be reassessed using the same imaging modality at each time point. If measurable, the LD of each new lesion should be recorded in the CRF and the sum LD of new and old lesions should be calculated. See Table 16for a description of the determination of progression based on the presence of new lesions.

Note: The appearance of a new lesion does not by itself satisfy the criteria for confirmed progressive disease. Rather, the tumor burden imposed by the new lesions must be evaluated within the context of the total tumor burden (i.e., preexisting plus new lesions). Confirming

progression in target lesions, nontarget (i.e., other than bone) lesions, and bone lesions requires two assessment time points. The first must occur at Week 12 (or later) and the second occurring at least 6 weeks after the first. Progression declared at the first time point remains unconfirmed unless assessments at the second time point demonstrate continuing or worsening progression, as described in Section 8.4.

8.3 Response Criteria for Control/Relieve/Eliminate Endpoints

8.3.1 Measurable soft-tissue lesions

When evaluating soft-tissue lesions, the definitions in Table 13 apply.

Table 14. RECIST response criteria for target (soft-tissue) lesions

Response	Evaluation of Soft-Tissue Lesions
Complete response (CR)	the disappearance of clinical and radiological evidence of all target lesions and normalization of tumor marker levels
Partial response (PR)	a decrease from baseline ≥ 30% in the sum of the LD of all target lesions
Progressive disease (PD)	an increase ≥ 20% in the sum of the LD of all target lesions based on the smallest sum LD since treatment started or the appearance of one or more new lesions or the appearance of new lesions
Stable disease (SD)	neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD based on the smallest sum LD recorded since treatment started

Abbreviations: LD, longest diameter.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (e.g., fine needle aspirate or biopsy) before confirming the complete response status.

Changes in nodal and visceral sites should be recorded and reported separately, and lymph nodes in the pelvis must measure at least 2 cm in greatest diameter to be considered target lesions. Complete elimination of disease at a particular site should be recorded separately. Any favorable change should be confirmed using a second follow-up scan.

8.3.2 PSA

As long as patient safety is the primary concern, in the absence of other indicators of disease progression, therapy should not be discontinued solely on the basis of a rise in PSA.

8.3.3 Bone

Record post-treatment changes as either “no new lesions” or “new lesions.”

In the absence of clearly worsening soft-tissue (nodal and visceral) disease or disease-related symptoms, progression at the first scheduled assessment should be confirmed on a second scan performed 6 or more weeks later. In the rare case where visible lesions disappear, this too should be confirmed.

8.3.4 Nontarget lesions

When assessing nontarget lesions, the definitions in Table will apply.

Table 15. RECIST response criteria for nontarget lesions

Response	Evaluation of Nontarget Lesions
Complete response (CR)	the disappearance of all nontarget lesions and normalization of tumor marker levels
Incomplete response/ stable disease (SD)	the persistence of one or more nontarget lesions and/or maintenance of tumor marker levels above the normal limits
Progressive disease (PD)	the appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions

A clear progression of nontarget lesions only is exceptional. In such circumstances, the progression status, as assigned by the investigator, may be reviewed by the Sponsor Investigator.

8.3.6 Evaluating best overall response

The best overall response is the best response recorded from the start of treatment until either disease progression or recurrence. The investigator's determination of best overall response will be based both on response criteria and on confirmation criteria. To be assigned a status of partial response or complete response, changes in tumor measurements must be confirmed by repeat assessment performed 4-6 weeks after the criteria for response are first met. To confirm stable disease, follow-up measurements must meet stable disease (SD) criteria at a minimum interval of 4 weeks after SD was first documented. Table can be used as an assessment tool.

Table 16. Assessing Overall Response

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Patients with global deterioration of health status who require treatment to be discontinued without objective evidence of disease progression should be classified as having symptomatic deterioration. Every effort should be made to document their objective progression, even after discontinuing treatment.

Patients who do not have tumor response assessment due to rapid progression or toxicity will be considered nonresponders, will be included in the denominator for the response rate, and will be classified into one of the categories listed below:

- death attributed to disease progression
- early discontinuation attributed to disease progression

- death attributed to drug toxicity
- early discontinuation attributed to drug toxicity

Note: If a patient receives subsequent therapy before tumor progression is documented, the reason for changing therapy must be reported. Reasons include clinical progression, drug toxicity, or secondary therapy for maintaining tumor response.

8.4 Confirmatory Measures/Duration of Response

8.4.1 Confirming time-to-event outcomes

Any post treatment change in disease status, be it favorable or unfavorable, should be confirmed using a second assessment at 4 weeks later.

8.4.2 Duration of overall response

Duration of overall response is measured from the time when partial response or complete response is first noted until the date when recurrent or progressive disease is objectively documented. Duration of overall complete response is measured from the time the criteria for complete response are first met until the first date that recurrent disease is objectively documented. Duration of stable disease is measured from the start of treatment until the criteria for progression are met.

8.4.3 Radiographic Progression-free survival

Radiographic progression-free survival is a composite endpoint defined as the time from treatment start to disease progression in bone or soft-tissue, or death, whichever occurs first. All assessments of disease should be collected at the same time interval (e.g., bone scan, CT scan, and PSA at 12-week intervals). In addition to PSA, confirm posttreatment changes in measurable target lesions, radionuclide bone scans, and symptoms.

Table 17 Prostate Cancer Clinical Trials Working Group (PCWG2) Outcome Measures[5]

Variable	Control/Relieve/Eliminate Endpoints	Prevent/Delay Endpoints
PSA	Record the percent change from baseline (rise or fall) at 12 weeks and, separately, the maximal change (rise or fall) at any time using a waterfall plot	**Decline from baseline:** record time from start of therapy to first PSA increase that is ~25% and ~2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (i.e., a confirmed rising trend)† Recording the duration of PSA decline of little value **No decline from baseline:** PSA progression ~25% and ~2 ng/mL after 12 weeks
Soft-tissue lesions	Use RECIST with caveats: Only report changes in lymph nodes that were ~2 cm in diameter at baseline Record changes in nodal and visceral soft tissue sites separately Record complete elimination of disease at any site separately Confirm favorable change with second scan Record changes using waterfall plot	Use RECIST criteria for progression, with additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later Note that for some treatments, a lesion may increase in size before it decreases
Bone	Record outcome as either *new lesions* or *no new lesions* First scheduled reassessment: No new lesions: continue therapy New lesions: perform a confirmatory scan 6 or more weeks later Confirmatory scan: No new lesions: continue therapy Additional new lesions: progression Subsequent scheduled reassessments: No new lesions: continue New lesions: progression	The appearance of ~2 new lesions, and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows at least 2 or more additional new lesions The date of progression is the date of the first scan that shows the change
Symptoms	Consider independently of other outcome measures Document pain and analgesia at entry with a lead-in period and measure repeatedly at 3- to 4-week intervals Perform serial assessments of global changes in HRQOL, urinary or bowel compromise, pain management, additional anticancer therapy Ignore early changes (~12 weeks) in pain or HRQOL in absence of compelling evidence of disease progression Confirm response or progression of pain or HRQOL endpoints ~3 weeks later	

Abbreviations: PSA, prostate-specific antigen; HRQOL, health-related quality of life. †Particularly important when anticipated effect on PSA is delayed or for biologic therapies.

8.5 Progressive Disease (PD)

Progressive disease will be defined by any one of the following:

1. Appearance of new metastatic lesions outside the bone
2. New metastatic lesions on bone scan confirmed as described above
3. Unequivocal progression of non-target lesions
4. Global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression as described above

9. DATA REPORTING AND REGULATORY REQUIREMENTS

9.1 Data Collection and Management

Data collected during this study will be entered into a secure database.

9.1.1 Electronic case report forms (eCRFs)

Standardized eCRFs and completion guidelines will be created by the PCCTC for the collection of all study data. Access and training for Medidata Rave will be made available to participating sites upon local regulatory approval. The participating site PI is responsible for ensuring eCRFs are completed accurately and in a timely manner.

9.1.2 Source documents

Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation will be made available to support the subject's research record.

9.1.3 Record retention

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure, the investigator will maintain all source documents and study-related documents. Records are to be retained and securely stored until the later of: (a) two (2) years following the date a New Drug Application (NDA) is approved for the Study Drug that is the subject of the Clinical Trial; or (b) two (2) years after the Investigational NDA for such Study Drug is terminated or withdrawn, or such longer period of time as may be required by Participant policies, applicable laws, rules or regulations.

9.1.4 Source Documentation Submission for Registration at Participating Sites

Participating sites should *email* any source documentation that corresponds to data entered at registration into the eCRFs to PCCTC at PCCTC@mskcc.org.

9.1.5 Data Submission Timelines

All data should be transmitted to PCCTC within 14 days of visit except for SAE submission (see section 7.3.1).

9.1.6 Data Review and Queries

PCCTC will review data and source documentation as it is submitted. Data will be monitored against source documentation as necessary and discrepancies will be sent as queries to the participating sites. In addition, PCCTC will review data for logic, consistency, and obvious anomalies. Queries will be sent by PCCTC to participating sites as needed.

Participating sites should respond to data queries within 14 days of receipt.

9.2 Data and Safety Monitoring

Data and Safety Monitoring Committee (DSMC) is the Data and Safety Monitoring Board (DSMB) for the Thomas Jefferson University Sidney Kimmel Cancer Center (SKCC). The DSMC is a multidisciplinary committee charged with overseeing the monitoring of safety of participants in clinical trials, and the conduct, progress, validity, and integrity of the data for all clinical trials at the Thomas Jefferson University SKCC.

- The DSMC meets quarterly. Additional DSMC meetings are scheduled based on the nature and number of trials being monitored over a specified time period. The DSMC meets (by conference call) within 24 hours following the notification of an unexpected AE felt to be related to the study drug.
- Prior to each DSMC meeting Principal Investigator is provided a printout by PCCTC of all reported AEs and SAEs occurring during the reporting period for this clinical trial for submission to the DSMC. The Principal Investigator provides a detailed and comprehensive narrative assessment of current AEs to date, indicating their possible significance and whether these toxicities have affected the conduct of the trial. A review of outcome results (response, toxicity and AEs) and factors external to the study (such as scientific or therapeutic developments) is discussed, and the Committee votes on the status of the study.
- A summary of the committee's action is sent to each investigator, the Thomas Jefferson University Protocol Review Committee (PRC) and Thomas Jefferson University IRB. The DSMC actions may include recommendations/requirements that will lead to improved patient safety and/or efficacy, significant benefits or risks that have developed, or other changes determined to be necessary. The DSMC may also take note of slow accrual or lack of scientific progress, and refer such issues to the PRC. The DSMC provides the Principal Investigator with the rationale for any decision made, who in turn will submit it to the PCCTC.

The Thomas Jefferson University Data and Safety Monitoring Committee reviews all AE/SAEs on open protocols. Therefore, once AE/SAE reports from participating site are received by the Principle Investigator, a copy will be submitted to the Thomas Jefferson University IRB/Medical Monitor/DSMB. Medical Monitor and DSMB review and monitoring of participating site AEs/SAEs will follow the Thomas Jefferson University DSMP.

9.2.1 Study Monitoring and Quality Assurance

In addition to review by the DSMC, PCCTC will conduct regularly scheduled monitoring visits. Registration reports will be generated by the PCCTC to monitor subject accruals and the completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and the extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period, and potential problems will be brought to the attention of the Principal Investigator for discussion and action.

Each site participating in the accrual of participants to this protocol will be monitored by the PCCTC once shortly after initiation of subject recruitment at a site, annually during the study (or more frequently if indicated), and at the end or closeout of the trial, for protocol and regulatory compliance, data verification and source documentation. At initial visits, the first two subjects will be 100% source data verified (or one subject if site does not accrue 2 in a

year). At a minimum of 10% of all subjects, but at least 2 from each site, will be 100% source data verified by the PCCTC during interim visits (selected subjects). Monitoring visits may be accomplished in one of two ways: (1) sending source documents and research records for selected patients from participating sites to the PCCTC for audit, or (2) on-site auditing of selected patient records at participating sites.

The monitoring visit will include a review of source documentation to evaluate compliance for:

- Regulatory/IRB compliance (review of current protocol and amendments, Informed consent documents and procedures, annual continuing review reports, AEs/SAEs)
- Protocol defined treatment compliance
- Subject records
    - Informed consent for each subject
    - Adherence to eligibility criteria for each subject
    - Medical history/baseline for selected subjects
    - On study and follow-up protocol tests for selected subjects
    - eCRF completion for each subject

Monitoring findings will be review and disseminated to the site PIs and staff. Following monitoring visits, data quality reports will be generated to asses error rate.

All clinical work conducted under this protocol is subject to Good Clinical Practice (GCP) guidelines. This includes inspection of study-related records by the lead site, sponsor, its designee, or health authority representatives at any time.

In addition, lead site/sponsor may conduct audits.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

10.1.1 Analysis of the primary endpoint

The primary endpoint for the phase IB component is identification of a safe dose of the combination of ribociclib and enzalutamide. This phase follows a '3+3' design and all analysis will be descriptive.

The primary endpoint of the phase II component is the proportion of subjects with a ≥ 50% reduction in PSA at 12 weeks. A Simon two-stage design for a 12 week PSA50 endpoint with a null hypothesis of 78%, an alternative hypothesis of 93%, alpha of 0.10, power of 90%, and 11 subjects treated at the first stage will be used. If at least 8 out of the first 11 subjects have a response (PSA50), the study will continue to enroll a total of 35 subjects. If at least 31 subjects respond, the null hypothesis will be rejected. Subjects who were enrolled to the combination arm during the original randomized design will be incorporated into the analysis in the Simon two-stage design.

10.1.2 Analysis of secondary endpoints

PSA progression-free survival will be measured from the time of first dose until progression (25% increase in PSA from nadir) or death and summarized by treatment arm using Kaplan-Meier plots. Median PFS will be estimated from the Kaplan-Meier analysis.

Radiographic progression-free survival will be measured from the time of first dose until progression and summarized using Kaplan-Meier plots. Median rPFS will be estimated from the Kaplan-Meier analysis.

10.1.3 Analysis of exploratory endpoints and correlative studies

The proportion of patients with RB positive tumors among the screened patients by IHC and gene signature will be estimated along with appropriate 95% confidence intervals. Similarly, the proportion of samples where RB status can successfully be obtained will be estimated as a measure of feasibility.

Correlation of IHC and gene expression levels will be measured using Pearson or Spearman correlation coefficients. Analysis of tumor explant data will use linear or generalized linear mixed effects models for repeated measurements depending on the outcome of interest.

Association of androgen profiles with clinical outcomes will use logistic regression or Cox proportional hazards regression, as appropriate.

10.2 Analysis Populations

10.2.1 Efficacy Analysis Set

All subjects who meet eligibility criteria, and receive at least one dose of study medication, and have PSA data at baseline and 12 weeks will be included in the main analysis of the PSA response rate.

Conclusions are to be based on the population of all eligible patients. Subanalyses will be performed on various subsets of subjects, such as those with no major deviations to treatment or those who continued in the study for the entire treatment period (i.e., did not withdraw prematurely). Subanalyses will not serve as the basis for drawing conclusions concerning treatment efficacy.

10.2.2 Safety population

All subjects enrolled and treated with ribociclib plus enzalutamide in the study will be included in the safety analysis population and considered evaluable for toxicity and safety from the time of their first dose.

10.3 Safety Analysis

10.3.1 Evaluation of AEs

Treatment-emergent AEs will be translated from investigator terms to MedDRA v6.0 terminology and summarized (number and percentage of patients) by treatment arm for all subjects who receive at least one dose. AE summaries will be organized by body system, frequency of occurrence, intensity (i.e., severity grade), and causality or attribution. Subjects who experience an AE more than once will be counted only once. The occurrence with the maximum severity will be used to calculate intensity.

10.3.2 Evaluation of SAEs and premature withdrawals

AEs deemed serious and those resulting in treatment withdrawal or death will be summarized separately. Please see section 7.3 for details on reporting SAEs.

10.3.3 Evaluation of laboratory parameters and assays

Selected clinical laboratory parameters will be summarized by treatment arm and clinically significant changes from baseline will be discussed.

10.3.4 Extent of exposure

Treatment exposure will be summarized for all subjects.

10.4 Statistical Procedures

Summary statistics include the number of observations, mean, standard deviation, median, minimum, and maximum values. The PSA50 response rate will be estimated along with an exact 95% confidence interval.

10.4.1 Sample size calculation

The null hypothesis is that the PSA50 response rate is less than or equal to 78% and the alternative is that it is greater than or equal to 93%. The study was designed with a target Type I error rate of 10% and power of 90%. A Simon two-stage design with 11 patients at the first stage (requiring 8 or more responses to continue) and a total sample size of 35 (requiring 31 or more for rejecting the null hypothesis) has an 8.9% probability of concluding the drug is effective, even if it is actually not effective (Type I error), and a 9.6% probability of concluding that it is not effective if it actually is effective (Type II error).

10.4.2 Derived variables

- Change from baseline will be calculated as the rating after baseline minus the rating at baseline
- Time windows will be calculated as the visit day minus the first day of study treatment
- Duration of treatment will be defined as the number of days from the first day of study treatment to the last day of study treatment. If the last day of study treatment is missing, the date of the last visit will be substituted for the missing value (i.e., LOCF).

11. REGULATORY AND PROTECTION OF HUMAN SUBJECTS

11.1 Role and Responsibilities

11.1.1 Sponsor Investigator

The Sponsor Investigator is responsible for performing the following tasks:

- Responsibility for the overall conduct of the study at all participating sites and for monitoring the progress of the study
- Reviewing and ensuring reporting of SAEs
- Reviewing data from all participating sites

11.1.2 PCCTC

The PCCTC is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals and required regulatory documents from each site.
- Managing subject registration
- Developing and maintaining Clinical Data Management documents and procedures
- CRF development, setup of study database, and subsequent design changes
- Participating in review of content of the CRF against the protocol requirements
- EDC system administration (user/site accounts setup, maintenance and revocation)
- Data review, cleaning, query management and resolution
- Establishing procedures for documentation, reporting and submitting of AEs and SAEs to the PCCTC
- Reviewing SAEs
- Training participating sites on EDC
- Collecting and compiling data from each participating site
- Data reviewing from all participating sites
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

11.1.3 Participating Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, the guidelines of GCP, and applicable Standard Operating Procedures (SOPs). Registering all patients with the PCCTC by submitting the eligibility checklist, supporting source documentation, and signed informed consent promptly
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol
- Maintaining regulatory binders on site and providing copies of all required documents to the PCCTC
- Collecting and submitting data according to the schedule specified by the protocol
- Responding to queries in a timely manner

11.2 Ethical Considerations

This study will be conducted in compliance with the protocol, GCP guidelines established by the International Conference on Harmonisation, and the ethical standards set forth in the Declaration of Helsinki 2004 (available at: www.laakariliitto.fi/e/ethics/helsinki.html).

11.3 Protocol Amendments

Before starting the study, the protocol must be approved by each institution's IRB or Independent Ethics Committee (IEC). Amendments to the protocol may be made only with consent of the sponsor investigator and Novartis and are subject to IRB approval before instituting.

11.4 Written Informed Consent

Before obtaining consent, members of the study team will review the rationale for the treatment program with the patient. The discussion will review the alternatives available (including hormonal therapy, chemotherapy, or supportive care as appropriate), the potential benefits of this program, the risks and the probability of their occurrence, and the procedures to minimize these risks. Should an AE occur, the provisions available to ensure medical intervention will also be reviewed. Why the risks are reasonable in relation to the anticipated benefits, incentives, or costs that will or may be incurred as a result of participating in the study, as well as the efforts to maintain confidentiality, will also be discussed with the patient.

Patients will be required to sign and date a statement of informed consent that meets the requirements of the Code of Federal Regulations (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the IRB. The medical record will include a statement that written informed consent was obtained (and document the date that it was obtained) before the patient is enrolled in the study. The original signed document will become part of the patient's medical record and a copy will be forwarded to PCCTC for subject registration.

The consent form will include the following:

- the nature and objectives, potential toxicities, and benefits of the intended study
- the length of therapy and likely follow-up required
- alternatives to the proposed therapy (including available standard and investigational therapies)
- the name of the investigator(s) responsible for the protocol
- the right of the patient to accept or refuse treatment and to withdraw from participation in this study
- informed consent documents and sections in the research authorization/HIPAA forms should include who will have access to the subjects data and medical records including PCCTC

11.5 Protection of Privacy

Subjects will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. After this discussion, they will be asked to sign a Notice of Privacy Practice research authorization/HIPAA form. The original signed documents will become part of the patient's medical records, and each patient will receive a copy of the signed documents. The use and disclosure of protected health information will be limited to the individuals described in the research authorization form. The research authorization form must be completed by the principal investigator and approved by the IRB.

11.6 Terminating or Modifying the Study

AE and laboratory data from this trial will be assessed by the lead site on an ongoing basis. At least quarterly, data from the clinical database will be reviewed. The results of this review will be shared with all investigators either in writing or as part of a teleconference. SAEs will be reviewed as they are reported to the lead site/sponsor, and the medical monitor will make an assessment regarding the safety of continuing or modifying the study. This assessment

will be shared with the investigators either in writing or as part of a teleconference. Should the assessment of either the lead site/sponsor or the principal investigator be that the study should be terminated, the study will be closed to further accrual. Patients who are receiving ribociclib with enzalutamide will be assessed individually by the investigator to see if it is in the patients' best interest to continue, which might be the case for a patient that is responding to the intervention. Follow-up safety assessments will be performed for all patients who are terminated from the study prematurely.

12. REFERENCES

1. The American Cancer Society. Prostate Cancer Statistics 2014. Available at: http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics. Accessed March 2014.
2. U.S. Food and Drug Administration. FDA expands Zytiga's use for late-stage prostate cancer – 2012. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm331492.htm
3. U.S. Food and Drug Administration. FDA approves new treatment for advanced prostate cancer – 2010. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm216143.htm
4. U.S. Food and Drug Administration. FDA approves new treatment for a type of late stage prostate cancer – 2012. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm317838.htm
5. U.S. Food and Drug Administration. FDA approves new drug for advanced prostate cancer – 2013. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm352363.htm
6. U.S. Food and Drug Administration. FDA approves a cellular immunotherapy for men with advanced prostate cancer – 2010. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm210174.htm
7. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, et al. Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy. N Engl J Med 2012; 367: 1187-1197
8. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN. Enzalutamide in Metastatic Prostate Cancer before Chemotherapy. N Engl J Med 2014; 371: 424-433
9. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst. 2000;92:205–216.
10. Scher HI, Halabi S, Tannock I, Morris M, Sternberg C, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testoterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol. 2008;29:1148–1159.
11. Macleod KF. The RB tumor suppressor: a gatekeeper to hormone independence in prostate cancer? J Clin Invest. 2010;120: 4179-4182.
12. Schiewer MJ, Augello MA, Knudsen KE. The AR dependent cell cycle: mechanisms and cancer relevance. Mol Cell Endocrinol. 2012;352: 34-45.
13. Taylor BS, Schultz N, Hieronymus H, et al. Integrative genomic profiling of human prostate cancer. Cancer Cell. 2010;18: 11-22.
14. Knudsen KE, Kelly WK. Outsmarting androgen receptor: creative approaches for targeting aberrant androgen signaling in advanced prostate cancer. Expert Rev Endocrinol Metab. 2011;6: 483-493.
15. Aparicio A, Den RB, Knudsen KE. Time to stratify? The retinoblastoma protein in castrate-resistant prostate cancer. Nat Rev Urol. 2011;8: 562-568.
16. Bosco EE, Wang Y, Xu H, et al. The retinoblastoma tumor suppressor modifies the therapeutic response of breast cancer. J Clin Invest. 2007;117: 218-228
17. Sharma A, Yeow WS, Ertel A, et al. The retinoblastoma tumor suppressor controls androgen ignaling and human prostate cancer progression. J Clin Invest. 2010;120: 4478-4492.
18. Burkhart DL, Sage J. Cellular mechanisms of tumour suppression by the retinoblastoma gene. Nat Rev Cancer. 2008;8: 671-682

19. Flaherty KT, Lorusso PM, Demichele A, et al. Phase I, dose-escalation trial of the oral cyclin-dependent kinase 4/6 inhibitor PD 0332991, administered using a 21-day schedule in patients with advanced cancer. Clin Cancer Res. 2012;18: 568-576.
20. Johnson SM, Torrice CD, Bell JF, et al. Mitigation of hematologic radiation toxicity in mice through pharmacological quiescence induced by CDK4/6 inhibition. J Clin Invest. 2010;120: 2528-2536
21. Schwartz GK, LoRusso PM, Dickson MA, et al. Phase I study of PD 0332991, a cyclin-dependent kinase inhibitor, administered in 3-week cycles (Schedule 2/1). Br J Cancer. 2011;104: 1862-1868.
22. Ortega S, Malumbres M, Barbacid M (2002) Cyclin D-dependent kinases, INK4 inhibitors and cancer. Biochimica et Biophysica Acta-Reviews on Cancer; 1602 (1):73-87.
23. Shapiro GI (2006) Cyclin-dependent kinase pathways as targets for cancer treatment. Journal of Clinical Oncology; 24 (11):1770-1783.
24. Lundberg AS, Weinberg RA (1998) Functional inactivation of the retinoblastoma protein requires sequential modification by at least two distinct cyclin-cdk complexes. Molecular and Cellular Biology; 18 (2):753-761.
25. Kamb A, Gruis NA, Weaverfeldhaus J, et al (1994) A Cell-Cycle Regulator Potentially Involved in Genesis of Many Tumor Types. Science; 264 (5157):436-440.
26. Sherr CJ, Roberts JM (1999) CDK inhibitors: positive and negative regulators of G(1)-phase progression. Genes & Development; 13 (12):1501-1512.
27. Cheng JQ, Jhanwar SC, Klein WM, et al (1994) P16 Alterations and Deletion Mapping of 9P21-P22 in Malignant Mesothelioma. Cancer Research; 54 (21):5547-5551.
28. Cowgill SM, Muscarella P (2003) The genetics of pancreatic cancer. American Journal of Surgery; 186 (3):279-286.
29. Fountain JW, Glendening JM, Flores JF, et al (1995) Is P16 the Gatekeeper in Sporadic Melanoma. American Journal of Human Genetics; 57 (4):226.
30. Gazzeri S, Gouyer V, Vourc'h C, et al (1998) Mechanisms of p16(INK4A) inactivation in non small-cell lung cancers. Oncogene; 16 (4):497-504.
31. Molven A, Grimstvedt MB, Steine SJ, et al (2005) A large Norwegian family with inherited malignant melanoma, multiple atypical nevi, and CDK4 mutation. Genes Chromosomes & Cancer; 44 (1):10-18.
32. Bergsagel PL, Kuehl WM (2003) Critical roles for immunoglobulin translocations and cyclin D dysregulation in multiple myeloma. Immunological Reviews; 194 (1):96-104.
33. Amin HM, McDonnell TJ, Medeiros LJ, et al (2003) Characterization of 4 mantle cell lymphoma cell lines - Establishment of an in vitro study model. Archives of Pathology & Laboratory Medicine; 127 (4):424-431.
34. Huang C, Yang L, Li ZF, et al (2007) Detection of CCND1 amplification using laser capture microdissection coupled with real-time polymerase chain reaction in human esophageal squamous cell carcinoma. Cancer Genetics and Cytogenetics; 175 (1):19-25.
35. Arnold A, Papanikolaou A (2005) Cyclin D1 in breast cancer pathogenesis. Journal of Clinical Oncology; 23 (18):4215-4224.
36. Sutherland RL, Musgrove EA (2004) Cyclins and breast cancer. Journal of Mammary Gland Biology and Neoplasia; 9 (1):95-104.
37. Landis MW, Pawlyk BS, Li T, et al (2006) Cyclin D1-dependent kinase activity in murine development and mammary tumorigenesis. Cancer Cell; 9 (1):13-22.
38. Yu QY, Geng Y, Sicinski P (2001) Specific protection against breast cancers by cyclin D1 ablation. Nature; 411 (6841):1017-1021.

39. Garcia-Echeverria C (2009) Protein and lipid kinase inhibitors as targeted anticancer agents of the Ras/Raf/MEK and PI3K/PKB pathways. Purinergic Signalling; 5 (1):117-125.
40. Gray-Schopfer VC, Dias SD, Marais R (2005) The role of B-RAF in melanoma. Cancer and Metastasis Reviews; 24 (1):165-183.Hafkamp HC, Mooren JJ, Claessen SMH (2009) P21Cip1/WAF1 expression is strongly associated with HPV-positive tonsillar carcinoma and a favorable prognosis. Modern Pathology; 22, 686–698
41. Nagel S, Leich E, Quentmeier H, et al (2008) Amplification at 7q22 targets cyclin-dependent kinase 6 in T-cell lymphoma. Leukemia; 22 (2):387-392.
42. Sirvent N, Coindre JM, Maire G, et al. Detection of MDM2-CDK4 amplification by fluorescence in situ hybridization in 200 paraffin-embedded tumor samples: Utility in diagnosing adipocytic lesions and comparison with immunohistochemistry and real-time PCR. Am J Surg Pathol 31: 1476-1489
43. Antonarakis ES, Lu C, Wang H, Luber B, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med. 2014 Sep 11; 371 (11): 1028-38.

Appendix A: Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Description	%	Description
0	Normal activity. Fully active, able to continue all predisease performance without restriction.	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity, minor signs or symptoms of disease
1	Symptoms, but ambulatory. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).	80	Normal activity with effort, some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance but is able to care for most needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair > 50% of waking hours.	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled, cannot carry on any self-care, totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

Appendix B: Medications with the Potential for Drug-Drug Interactions

Enzalutamide

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans [Xtandi® Prescribing Information] and may decrease the exposure of comedications that are substrates for these metabolizing enzymes.

Ribociclib

Based on in vitro data, ribociclib is primarily metabolized by CYP3A4. Based on clinical data, ritonavir (a strong CYP3A4 inhibitor) and rifampicin (a strong CYP3A4 inducer) markedly increased and decreased ribociclib exposure, respectively. Therefore, drugs that are strong inhibitors or inducers of CYP3A4 should not be co-administered with ribociclib. Patients who receive medications that are moderate inhibitors or inducers of CYP3A4/5 should be observed for signs of overexposure or potential reduced efficacy of ribociclib, respectively.

Ribociclib inhibits transporter proteins in vitro, including human BSEP, MATE1, OCT2, and BCRP. The clinical relevance of these in vitro findings is not known. Co-administration of ribociclib with other drugs that inhibit BSEP may result in intrahepatic cholestasis and hepatic toxicity. Therefore known BSEP inhibitors should be used with caution during treatment with ribociclib. Additionally, caution is recommended with co-administration of sensitive substrates of the renal transporters, MATE1 and OCT2, and with sensitive substrates of BCRP.

Prolongation of the QT interval has been observed with ribociclib. Caution should be exercised with all medications that are known to produce this effect. Those known to have a strong signal will be prohibited and others are to be used with caution.

Concomitant Medications

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, except as specifically prohibited below. Combination administration of study drugs could result in drug-drug interactions (DDI) that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or ribociclib.

The following lists are not comprehensive and are only meant to be used as a guide. The lists are based on the Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: 29 Oct 2012), which was compiled from the Indiana University School of Medicine's P450 Drug Interaction Table (http://medicine.iupui.edu/clinpharm/ddis/main-table/) and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012) (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf), and the University of Washington's Drug Interaction Database (http://www.druginteractioninfo.org/). For current lists of medications that may cause QT prolongation and/or torsades de pointes (TdP), refer to the CredibleMeds® website (https://crediblemeds.org/). Please contact the medical monitor with any questions

Table 18. List of prohibited medications during study treatment

Category	Drug Name

Strong CYP3A4/5 inhibitors	**Atazanavir/ritonavir, boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, darunavir/ritonavir, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, ombitasvir/paritaprevir/dasabuvir/ritonavir (VIEKIRA PAK), posaconazole, ritonavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole**
Strong CYP3A4/5 inducers	**Apalutamide, carbamazepine[3], enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin[3], rifabutin, rifampin (rifampicin)[3], St. John's wort (hypericum perforatum)[2,3]**
CYP3A4/5 substrates with NTI[1]	**Alfentanil, astemizole, cisapride, cyclosporine, diergotamine (dihydroergotamine), ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus**
Medications with a known risk for QT prolongation[4]	**Amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, chloroquine, chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacine, grepafloxacin, halofantrine, haloperidol, ibutilide, levofloxacin, levomepromazine, levosulpiride, methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl (intra-coronary), pentamidine, pimozide, procainamide, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sulpiride, sultopride, terlipressin, terodiline, thioridazine, vandetanib**
Herbal preparations/ medications or dietary supplements	**Herbal preparations/medications or dietary supplements are prohibited throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications or dietary supplements 7 days prior to first dose of study drug.**
Other investigational and antineoplastic therapies	**Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, all SERMS (including raloxifene) biologic or radiation therapy, and surgery) other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must be discontinued study drug.**

[1] NTI = narrow therapeutic index drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes) or drugs which have <2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood.

[2] Herbal product

[3] P-gp inducer

[4] The list provided is as of December 2019.SoCheck https www crediblemeds.org/healthcare-providers/drug-list for the most updated list.www.crediblemeds.org

Drug has warning for risk of hepatotoxicity.As far as possible, avoid co-administration of QT prolonging drugs or any other drugs with the potential to increase the risk of drug-related QT prolongation (e.g., via a potential DDI that increases the exposure of ribociclib or the exposure of the QT prolonging drug). A definitive list of drugs with a known risk, possible risk, or conditional risk of QT prolongation and/or Torsades de Pointes (TdP) is available online at qtdrugs.org.

Source: Novartis PK Sciences Memorandum: Drug-Drug Interactions (DDI) and Co-medication Considerations for Novartis Clinical Trials (January 2018), which is compiled from Indiana University "Clinically Relevant" Flockhart Table™, University of Washington Drug Interaction Database, and FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.

Table 19. List of medications to be used with caution during study treatment

Category	Drug Name
Moderate CYP3A4/5 inhibitors	**Aprepitant, amprenavir, asafoetida resin (Ferula asafoetida) cimetidine, crizotinib, diltiazem, faldaprevir, imatinib, isavuconazole, netupitant, nilotinib, tofisopam, Schisandra sphenanthera (nan wu wei zi), verapamil**
Moderate CYP3A4/5 inducers	**Bosentan, dabrafenib, efavirenz, etravirine, genistein,lopinavir5, modafinil, nafcillin,telotristat**
Sensitive CYP3A4/5 substrates[1]	**Alpha-dihydroergocryptine, aprepitant, atorvastatin, avanafil, bosutinib,brotizolam, budesonide, buspirone, cannabinoids[6], cannabidiol[6] cobimetinib, darifenacin, dasatininb, ebastine, eletriptan, eplerenone, everolimus, felodipine, fluticasone, grazoprevir, ibrutnib, isavuconazole, ivabradine, ivacaftor, , levomethadyl (LAAM), lomitapide, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, naloxegol, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, sildenafil, simeprevir, simvastatin, ticagrelor, tilidine, tolvaptan, triazolam, ulipristal, vardenafil, venetoclax, vicriviroc, voclosporin**
BSEP inhibitors	**Alectinib, atorvastatin, bromocriptine, candesartan, clobetasol, clofaziminie, dabigatran, dipyridamole, glyburide, grazoprevir, ledipasvir, mifepristone,pioglitazone, reserpine,rifamycin, simeprevir, telmisartan,timcodar, troglitazone, valinomycin, velpatasvir**

Medications that carry a possible risk for QT prolongation[2]	**Alfuzosin, apomorphine, aripiprazole, artenimol+piperaquine , asenapine, atomoxetine, bedaquiline, bendamustine, bortezomib, bosutinib, buprenorphine, cabozantinib, capecitabine, ceritinib, clomipramine, crizotinib,clozapine, cyamemazine (cyamepromazine), dabrafenib, dasatinib, degarilix, delamanid, desipramine, dexmedetomidine, dolasetron, efavirenz, eliglustat, epirubicin, eribulin mesylate, ezogabine(retigabine), famotidine, felbamate, fingolimod, flupentixol, gemifloxacin, granisetron, hydrocodone-ER, iloperidone, imipramine (melipramine), isradipine, ketanserin, lapatinib, lenvatinib, leuprolide, lithium, melperone, midostaurin, mifepristone, mirabegron, mirtazapine, moexipril/HCTZ, necitumumab, nicardipine, nilotinib, norfloxacin, nortriptyline, nusinersen, ofloxacin, osimertinib, oxytocin, paliperidone, palonosetron, panabinostat, pasireotide, pazopanib, perflutren lipid microspheres, perphenazine, pilsicainide, pimavanserin, pipamperone, promethazine, prothipendyl, rilpivirine, risperidone, romidepsin, sertindole, sorafenib, sunitinib, tamoxifen, tipiracil/trifluridine, tizanidine, tolterodine, toremifene,trimipramine, tropisetron, vardenafil, vemurafenib, venlafaxine, vorinostat, ziprasidone**
MATE1/2 substrates[3]	**Acyclovir, cephalexin, cimetidine, fexofenadine, ganciclovir, glycopyrronium, metformin, pindolol, plisicainide, ranitidine, topotecan, varenicline**
OCT1/2 substrates[4]	**Amantadine, 6-beta-hydroxycortisol, carboplatin, cisplatin, cephalexin, cephradine, ipratropium, lamivudine, linagliptin, metformin, , oxaliplatin, oxybutynin, phenformin, picoplatin, pilsicainide, pindolol, , ranitidine, sorafenib, tropisetron, trospium, umeclidinium, and zidovudine**
BCRP substrates	**Daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, pitavastatin, rosuvastatin, irinotecan, ethinyl estradiol, simvastatin, sulfasalazine, sofosbuvir, tenofovir, topotecan, venetoclax**

[1] Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor.

[2] The list provided is as of January 2018. Check https www crediblemeds.org/healthcare-providers/drug-list for the most updated list.

[3] MATE1 and MATE2 share considerable substrate specificity.

[4] OCT1 and OCT2 share considerable substrate specificity.

[5] Lopinavir and atazanavir is prohibited when combined with ritonavir (see Table 14-1)

[6] Based data that, exposure of cannabidiol (CBD), tetrahydrocannabinol (THC), 11-hydroxy THC, increased by ~2-3 folds when co-administered with ketoconazole (CYP3A4 inhibitor); Stott et al, Springerplus. 2013; 2: 236

Source: Novartis PK Sciences Memorandum: Drug-Drug Interactions (DDI) and Co-medication Considerations for Novartis Clinical Trials (January 2018), which is compiled from Indiana University “Clinically Relevant” Flockhart Table™, University of Washington Drug Interaction Database, and FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.

Appendix C: Laboratory Manual

Please see the Laboratory & Correlatives Manual.

Appendix D: Glossary of Abbreviations and Acronyms

ADME	absorption, distribution, metabolism and exretion
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AR	androgen receptor
AR-V7	androgen receptor, splice variant 7
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{tau}	area under the concentration-time curve in one dosing interval
BUN	blood urea nitrogen
CBC	complete blood count
CDK	cyclin-dependent kinase
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CNS	central nervous system
CR	complete response
CRF	case report form
CRPC	castration resistant prostate cancer
CS&E	Novartis Clinical Safety & Epidemiology
CT	computerized tomography
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
DES	Diethylstilbestrol
dL	Deciliter
DLT	dose-limiting toxicity
DS&E	Novartis Drug Safety and Epidemiology
DSMC	Data and Safety Monitoring Committee
DSMB	Data and Safety Monitoring Board
ECHO	Echocardiogram
ECG	Electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
FIH	first in human
FM03	flavin-containing monooxygenase 3
GCP	good clinical practice

GnRH	gonadotropin-releasing hormone
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
HSV	herpes simplex virus
IC50	50% inhibition
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IN	Novartis Investigator Notification
IND	investigational new drug
IRB	Institutional Review Board
IV	Intravenous
KPS	Karnofsky Performance Scale
LD	longest diameter
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
MCL	mantle cell lymphoma
mCRPC	metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple gated acquisition
NCI	National Cancer Institute
NDA	New Drug Application
NIH	National Institutes of Health
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
OS	overall survival
PCCTC	Prostate Cancer Clinical Trials Consortium
PCWG2	Prostate Cancer Working Group 2
PD	progressive disease
PFS	progression-free survival
P-gp	P-glycoprotein
PI	principal investigator
PK	Pharmacokinetics
PO	per os (by mouth)

PR	partial response
pRb	retinoblastoma protein
PSA	prostate-specific antigen
PSA PFS	PSA progression-free survival
PT	prothrombin time
QTc	corrected QT interval
Racc	arithmetic mean of accumulation ratio
RB	Retinoblastoma
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	radiographic progression-free survival
SAE	serious adverse event
SD	stable disease
SKCC	Thomas Jefferson University Sidney Kimmel Cancer Center
SOP	Standard Operating Procedures
SUSAR	suspected unexpected serious adverse reaction
SUV	standardized uptake value
$T_{1/2}$	terminal half-life
TJU	Thomas Jefferson University
ULN	upper limit of normal
WBC	white blood cell

Appendix E. Pill Diary (PHASE I)

Phase IB/II study of enzalutamide with and without ribociclib in patients with metastatic castrate resistant, chemotherapy naïve prostate cancer that retains RB expression

PCCTC LOI# c15-153

Study ID #: _____

Cycle #: _____

Patient Name: _____ **Dates**: ___/___/_____ to ____/____/_____

To be completed by MD/RN:	
Total Daily Dose of Enzalutamide: **160** mg	**Take:** **4** 40 mg capsule(s) once daily
Total Daily Dose of Ribociclib: _____ mg	**Take:** _____ 200 mg tablet(s) once daily

INSTRUCTIONS TO THE PATIENT:

1. Please complete one form for each cycle (=28 days) while you are taking the study medication.
2. Please record the date, the number of capsules/tablets you took, and what time you took them. If you did not take your medication, or if you only took part of the required dose, please provide a reason.
3. **Enzalutamide** should be taken orally once daily. Enzalutamide can be taken with or without food.
4. **Ribociclib** should be taken orally once daily for 21 consecutive days, followed by a 7-day break.
5. All medications must be swallowed whole and should not be crushed, chewed, dissolved, or opened.
6. If you forget to take your medication, do not "double-up" on the next dose to make-up for the skipped dose. If you vomit after you take your medication, do not take another dose until the next scheduled dosing.
7. **Please return this diary and all unused study medication to your research nurse.**

All herbal, alternative and food supplements should be avoided while taking study medication.

Day	Date	Indicate number of capsules/tablets taken and time taken		If dose not taken or if full dose not taken, please provide reason.
		Enzalutamide (40 mg capsules)	Ribociclib (200 mg tablets)	
Example	**1/1/2016**	**4 capsules – 8:00 AM**	**1 tablet – 8:00 AM**	**N/A**

Day	Date	Indicate number of capsules/tablets taken and time taken		If dose not taken or if full dose not taken, please provide reason.
		Enzalutamide (40 mg capsules)	Ribociclib (200 mg tablets)	
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22			[redacted]	
23			[redacted]	
24			[redacted]	
25			[redacted]	
26			[redacted]	
27			[redacted]	
28			[redacted]	

Patient's Signature: _____
Date of Signature: _____/_____/_____

Physician's/Research Nurse's Signature: _____ ____
Date of Signature: _____/_____/_____

Appendix F. Pill Diary (PHASE II)

Phase IB/II study of enzalutamide with ribociclib in patients with metastatic castrate resistant, chemotherapy naïve prostate cancer that retains RB expression

PCCTC LOI# c15-153

Study ID #: _____

Cycle #: _____ **Assigned Treatment Arm:** _____

Patient Name: _____ **Dates**: ___/___/_____ to ____/____/_____

To be completed by MD/RN:	
Total Daily Dose of Enzalutamide: 160 mg	**Take: 4** 40 mg capsule(s) once daily
Total Daily Dose of Ribociclib: _____ mg	**Take:** _____ 200 mg tablet(s) once daily

INSTRUCTIONS TO THE PATIENT:

1. Please complete one form for each cycle (=28 days) while you are taking the study medication.
2. Please record the date, the number of capsules/tablets you took, and what time you took them. If you did not take your medication, or if you only took part of the required dose, please provide a reason.
3. **Enzalutamide** should be taken orally once daily. Enzalutamide can be taken with or without food.
4. **Ribociclib** should be taken orally once daily for 21 consecutive days, followed by a 7-day break.
5. All medications must be swallowed whole and should not be crushed, chewed, dissolved, or opened.
6. If you forget to take your medication, do not "double-up" on the next dose to make-up for the skipped dose. If you vomit after you take your medication, do not take another dose until the next scheduled dosing.
7. **Please return this diary and all unused study medication to your research nurse.**

   All herbal, alternative and food supplements should be avoided while taking study medication.

Day	Date	Indicate number of capsules/tablets taken and time taken		If dose not taken or if full dose not taken, please provide reason.
		Enzalutamide (40 mg capsules)	Ribociclib (200 mg tablets)	
Example	**1/1/2016**	**4 capsules – 8:00 AM**	**1 tablet – 8:00 AM**	**N/A**
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

Patient's Signature: _____
Date of Signature: ____/____/_____

Physician's/Research Nurse's Signature: _____ ____
Date of Signature: _____/_____/_____

Appendix G. Novartis SAE Coversheet

NOVARTIS

Interventional Clinical Trial SAE Fax Cover Sheet

To: Local Novartis Drug Safety and Epidemiology Safety Desk **1-877-778-9739**

Investigator contact details:

Fax number : _____

Phone number : _____

Study Name	
Centre Number	
Patient Number	

Relationship between study treatment and event(s) is:

Suspected/Unknown

Investigator Signature	

This document contains important safety information.
If fax is received in error, please forward to 1-877-778-9739

NOVARTIS

Interventional Clinical Trial SAE Fax Cover Sheet

To: Local Novartis Drug Safety and Epidemiology Safety Desk **1-877-778-9739**

Investigator contact details:

Fax number : _____

Phone number : _____

Study Name	
Centre Number	
Patient Number	

Relationship between study treatment and event(s) is:

Not Suspected

Investigator Signature	

This document contains important safety information.
If fax is received in error, please forward to 1-877-778-9739

Appendix H. PCCTC SAE Report Form

Please see the PCCTC SAE Report form.