A Phase II Study of the Addition of Opaganib to Androgen Antagonists in Patients with Prostate Cancer Progression on Enzalutamide or Abiraterone

Study Drug:	**Opaganib** **Enzalutamide** **Abiraterone**
Coordinating Center:	**Medical University of South Carolina-** **Hollings Cancer Center**
Participating Sites:	Medical University of South Carolina, Hollings Cancer Center Emory University Ralph H. Johnson VA Medical Center
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I have read the Protocol entitled
"A Phase II Study of the Addition of Opaganib to Androgen Antagonists in Patients with Prostate Cancer Progression on Enzalutamide or Abiraterone"

I agree to conduct the study as detailed herein and in compliance with ICH Guidelines for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____
Principal investigator printed name

_____ _____
Principal investigator signature Date

_____
Participating Center Name

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PROTOCOL SYNOPSIS

TITLE	**A Phase II Study of the Addition of Opaganib to Androgen Antagonists in Patients with Prostate Cancer Progression on Enzalutamide or Abiraterone**
PHASE	II
STUDY RATIONALE	Opaganib [3-(4-chlorophenyl)-adamantane-1-carboxylic acid (pyridin-4-ylmethyl)amide, hydrochloride salt] is an orally available inhibitor of the enzyme sphingosine kinase-2 (SK2). SK2 is an innovative molecular target for anti-cancer therapy because of its critical role in sphingolipid metabolism, which is known to regulate tumor cell death and proliferation. Preclinical studies demonstrate that opaganib inhibits signaling through the RAS/RAF/MEK/ERK and RAS/PI3K/AKT pathways, promotes tumor cell killing, and inhibits host inflammation in several tumor models. Dysregulation of androgen receptor- (*AR)*- and *MYC*-dependent signaling is characteristic of castration-resistant prostate cancer (CRPC), and confers resistance to many forms of therapy. Opaganib decreases *MYC* and *AR* protein and mRNA expression in prostate cancer cell lines, and inhibits the growth of prostate cancer cells with amplified or splice variant *AR* genes as a single agent, or synergistically with docetaxel. We hypothesize that opaganib will have therapeutic activity in patients with metastatic CRPC (mCRPC) .

STUDY DESIGN	This is a Phase II efficacy study of opaganib in patients with metastatic castration-resistant prostate cancer that is progressing during treatment with androgen signaling blockers abiraterone or enzalutamide. An initial "run in" cohort (cohort 1) of 6 patients with mCRPC will be enrolled, 3 failing treatment with abiraterone (cohort 1a) and 3 failing treatment with enzalutamide (cohort 1b). These subjects will receive opaganib 250 mg po BID, along with continuation of prior abiraterone or enzalutamide, to document tolerability in this new patient population, and to document the effects of opaganib on blood PSA levels. Provided that there is no untoward toxicity in these patients, 2 additional cohorts of patients with worsening disease during abiraterone (cohort 2) or enzalutamide (cohort 3) treatment will be enrolled. They will receive opaganib 500 mg po bid continuously. In addition they will continue previous androgen blocking agents (abiraterone or enzalutamide, and gonadotropin releasing hormone GnRH receptor agonist/antagonist). Treatment will continue until there is 1) unacceptable toxicity (gr 3 or 4 toxicity that does not resolve to grade 1 or less by 28 days), 2) institution of new additional prostate cancer therapy, 3) withdrawal of consent, 4) any condition that, in the opinion of the treating physician, renders continued opaganib treatment to be not in the patient's best interest, 5) lack of compliance with study procedures by the patient, or 6) lack of disease control by study-specified parameters.

OBJECTIVES –	**Primary Objectives** • To measure the proportion of patients with *disease control* during opaganib (plus abiraterone or enzalutamide) therapy, using a composite metric based on PSA, bone scan, and RECIST measurements per Prostate Cancer Working Group 3 (PCWG3) criteria. For purposes of this study, disease control is defined as stable disease or better after four cycles (16 weeks) of treatment. **Secondary Objectives** • To estimate the radiographic progression-free survival (rPFS), PSA progression-free survival (PSA-PFS) times in patients treated with opaganib (plus abiraterone or enzalutamide). • To document the PSA response rate, RECIST response rate, and change in QOL (FACT-P) in mCRPC patients treated with opaganib (plus abiraterone or enzalutamide) after four cycles of treatment • To determine the effects opaganib on regression or progression of mCRPC clones with amplified *AR* or *MYC,* identified by serial ctDNA-based genomic profiling. • To assess safety of opaganib in mCRPC patients, in combination with abiraterone or enzalutamide, GnRHR agonist/antagonist • To monitor changes in numbers or activity of immune cells and myeloid-derived suppressor cells during opaganib therapy (with continued ADT).
NUMBER OF PATIENTS	Up to 60 patients

PATIENT ELIGIBILITY CRITERIA	**Inclusion criteria** 1. Patient must have mCRPC. Each patient must have: a. Tissue diagnosis documented by pathology report, or clinic note attesting to same. b. Radiographically-demonstrated metastases c. Patients may have adenocarcinoma, or ductal carcinoma, or combinations of these entities 2. Voluntary, signed and dated, institutional review board (IRB)-approved informed consent form in accordance with regulatory and institutional guidelines. 3. Documented progression during treatment with enzalutamide or abiraterone, as determined by the enrolling investigator 4. Testosterone level documented to be less than 50ng/dL 5. 18 years of age or older. 6. ECOG performance status of 0-2. 7. Acceptable liver function: a. Bilirubin ≤ 1.5 times upper limit of normal (CTCAE Grade 1 baseline) b. AST (SGOT) & ALT (SGPT) ≤ 3 x ULN (CTCAE Grade 1 baseline) c. Subjects with Gilbert's syndrome may be included if the total bilirubin is < 3x ULN and the direct bilirubin is within normal limits 8. Acceptable kidney function: a. Serum creatinine ≤ 1.5 X ULN (CTCAE Grade 1 baseline) 9. Acceptable hematologic status: a. Absolute neutrophil count ≥ 1000 cells/mm^3, b. Platelet count ≥ 75,000 (plt/mm^3) (CTCAE Grade 1 baseline) c. Hemoglobin ≥ 9.0 g/dL. 10. Acceptable blood sugar control: a. Fasting blood glucose of <165mg/dL or random blood glucose of < 200mg/dL 11. Urinalysis: No clinically significant abnormalities. 12. International normalized ratio (INR) ≤ 1.7 for patients not on anti-coagulation meds 13. Well-controlled blood pressure as determined by the treating investigator. 14. Patients requiring narcotic analgesics must be on stable doses for at least 2 weeks prior to study entry. **Exclusion criteria** 1. New York Heart Association Class III or IV, cardiac disease,

	myocardial infarction within the past 6 months, unstable arrhythmia, or evidence of ischemia on ECG. 2. Underlying psychiatric disorder requiring hospitalization within the last two years. 3. Clinically significant neurological disorder (Parkinson's disease, dementia, multiple sclerosis), as determined by the enrolling investigator 4. Active, uncontrolled bacterial, viral or fungal infection, requiring systemic therapy. 5. Treatment with local or systemic radiation therapy, surgery, or investigational therapy within 28 days prior to registration 6. Unwillingness or inability to comply with procedures required in this protocol. 7. Serious nonmalignant disease that could compromise protocol objectives in the opinion of the Investigator. 8. Patients who are receiving coumadin, apixaban or rivaroxaban Patients who are receiving other drugs that are sensitive substrates of CYP450 1A2, 3A4, 2B6, 2C8, 2C9, 2C19 or 2D6, P-gP, BCRP, and OATP1B1, or strong inhibitors or inducers of all major CYP450 isozymes that cannot be stopped at least 7 days or 5 half-lives (whichever is longer) before starting treatment with opaganib may be treated on this study with careful monitoring for toxic effects or loss of efficacy of the relevant drug. A list of commonly used drugs that are sensitive substrates of CYP450 1A2, 3A4, 2B6, 2C8, 2C9, 2C19 or 2D6, P-gP, BCRP, and OATP1B1, or strong inhibitors or inducers of all major CYP450 isozymes with the half-life of each drug identified, is included as an Appendix C. 9. Patients who are currently participating in any other clinical trial of an investigational product. 10. Other primary malignancy requiring systemic treatment within past 5 years except carcinoma in situ of the cervix or urinary bladder or non-melanoma skin cancer. 11. Any other mental incapacitation or psychiatric illness that would preclude study participation, as determined by the enrolling investigator. 12. Prisoners or patients who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious disease) illness must not be enrolled into this study.

	13. Patients that have had chemotherapy for castration resistant prostate cancer (patients can have had chemotherapy for castration sensitive PC) • Exception: Patients who had prior chemo for CRPC are eligible if they have a PS=0-1 and life expectancy of more than 6 months.

TEST ARTICLE ADMINISTRATION	Opaganib will be administered at the dose of 250 mg (cohorts 1a and 1b) or 500 mg (cohorts 2 and 3) orally twice a day (approximately 12 hours apart) continuously. Opaganib will be dosed after a light to moderate meal. A cycle will be defined as 28 days.
PRESTUDY ASSESSMENTS	**Screening Period** • Informed consent • Eligibility determination **Baseline Period** Within 14 days prior to Cycle 1 Day 1 • Complete medical history • Concomitant medication assessment • Baseline Review of Systems and adverse event (AE) documentation • Physical examination, to include neurologic exam and mini-mental state examination • Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) and weight • ECOG Performance Status • FACT-P Quality of Life questionnaire • 12-lead electrocardiogram • Serum chemistry • Coagulation parameters • CBC with differential • Urinalysis • Urine protein + urine creatinine • PSA, CEA, LDH level Within 28 days prior to Cycle 1 Day 1 • Radiographic tumor measurements. Investigator's choice of CT scans of chest/abdomen/pelvis with contrast or MRI scan of abdomen/pelvis with or without contrast; technetium bone scan for all patients. Optional: fluciclovine PET scan Within 56 days of Cycle 1 Day 1 (with no interval new therapy) • Guardant 360 genomic profile

TREATMENT ASSESSMENTS	Patients will be monitored every 28 days. The patient assessments include: • Review of concomitant medications, including narcotic usage. • Adverse Event monitoring (patient diary, review of systems). • ECOG Performance Status. • Physical exam to include neurologic exam • Weight. • Vital signs (temperature, blood pressure, pulse rate, and respiratory rate). • Serum chemistry. • Coagulation parameters • CBC with differential. • Urinalysis • Urine protein + urine creatinine Period assessments (see schedule of interventions, Appendix A) will also include the following: • Coagulation parameters • Mini-mental Status Exam • PSA • LDH • CEA (if initially elevated) • Radiological assessment will be performed after completion of 4 cycles (112 days) of drug treatment, and then every 2 cycles (56 days) until criteria for study withdrawal are met. If a response is noted, a follow-up radiographic assessment may be performed at 4 weeks to confirm response. Choice of radiologic studies will be at the discretion of the treating physician, but should include studies similar to those baseline studies that showed metastases. • Guardant 360 genomic profile will be repeated after 112 days of treatment, and at the off-study visit (if more than 56 days later).

INVESTIGATIVE SITES	This study will be conducted at the Medical University of South Carolina, Hollings Cancer Center, Charleston, SC 29425; Ralph H. Johnson VA Medical Center, Charleston, SC 29401; Emory University, Atlanta, GA.

STATISTICAL ANALYSIS	Primary endpoint analysis: We will estimate the proportion of patients with disease control during opaganib (plus abiraterone or enzalutamide) therapy, using a composite metric based on PSA, bone scan, and RECIST measurements per PCWG3 criteria (see the definitions in Appendix B). The primary measurement will be determined after four cycles (day 113) of treatment, or at withdrawal from the study. The 95% confidence interval for the proportion of disease control will be presented. A one-sided exact binomial test will be performed based on a null hypothesized proportion of 0.1 with a significance level of 0.05. Secondary endpoint analysis: • Kaplan-Meier estimates of the time-to-event (i.e., rPFS or PSA-PFS) will be constructed using a competing-risks approach which treats death due to cause unrelated to prostate cancer as a competing event. Median time to progression will be estimated and the corresponding 95% confidence intervals constructed using Greenwood's variance estimate (Collett, 1994). • Both PSA response rate and overall response rate will be estimated with the 95% confidence interval. The change in QOL will be summarized graphically and numerically, and tested based on two-sided paired t-test. • The relationship between changes in marker levels (copy number for *AR, MYC* amplified clones based on Guardant 360 genomic profile) and patient response for regression or progression of mCRPC clones will be assessed graphically. Scatterplots of percent change in target lesions versus change in marker levels will be constructed. Variable transformations will be considered as needed, and Pearson or Spearman correlation coefficients will be constructed as appropriate. Based on two-sided Pearson or Spearman correlation coefficients test with alpha = 0.05, the sample size of 27 provides a 77% power to detect a correlation of 0.5 versus a null correlation of 0.

	• The safety analysis will be conducted using descriptive statistics of the incidence of adverse events (AEs) and serious adverse events (SAEs), all events of death, and any study specific issue of concern. Adverse events will be coded by body system, and summary tables with incidence rates of AEs will be generated. Descriptive statistics of AEs will be reported for all patients, patients who discontinue due to AEs, and patients with related AEs. Severity, duration, investigator attributed relationship to treatment, and outcomes of AEs will be reported. AE and SAE reporting criteria are outlined in section 10. • The numbers or activity of immune cells and myeloid-derived suppressor cells (measured at baseline and certain time points) will be summarized graphically. The mean of the difference of cell counts between time points will be described with the 95% confidence interval. The changes in cell counts will be analyzed using a paired t-test to see if the change is significant. Equivalent non-parametric tests (e.g., Wilcoxon rank-sum test) will be used as appropriate.

DURATION OF STUDY	Approximately 30 months, assuming 4 months for study activation, and an enrollment rate of 4 subjects per month, among all sites.

DEFINITIONS OF TERMS USED

OPAGANIB	3-(4-chlorophenyl)-adamantane-1-carboxylic acid (pyridin-4-ylmethyl)amide, hydrochloride salt
ADT	androgen depleting therapy
AE	adverse event
AKT	protein kinase B
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AR	androgen receptor
AST	aspartate aminotransferase
AUC	area under the drug concentration over time curve
BID	twice per day
BUN	blood urea nitrogen
CBC	complete blood count, a blood test consisting of hemoglobin, hematocrit, white blood count, platelet count, mean corpuscular volume, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin
CEA	carcinoembryonic antigen
CI	combination index
CMP	complete metabolic panel, a blood test that includes plasma concentrations of sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, aspartate aminotransferase, alkaline phosphatase, calcium, albumin, total bilirubin, alanine aminotransferase, glucose
c-Myc	myelocytomatosis oncogene
CR	complete response
CRF	Case Report Form
CT	computer-assisted tomography
CTCAE	Common Toxicity Criteria adverse event
CTRC	Clinical and Translation Research Center
CV	cardiovascular
CYP	cytochrome P450
DLT	dose limiting toxicity
DMS	N,N-dimethylsphingosine
DSMC	Data Safety Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture system
EGF	epidermal growth factor
ERK	extracellular signal-related kinase
FDA	Food and Drug Administration
GI	gastrointestinal

GLP	Good Laboratory Practice
GnRH	gonadotropin releasing hormone
HADS	Hospital Anxiety and Depression Scale
HCC	Hollings Cancer Center, MUSC
HED	human equivalent dose
hERG	human ether-a-go-go related gene
HIV	human immunodeficiency virus
HNSTD	highest nonseverely toxic dose
ICH	International Conference on Harmonization
IC50	concentration that inhibits by 50%
IL-1β	interleukin 1-beta
IL-6	interleukin 6
iNOS	inducible nitric oxide synthase
IRB	Institutional Review Board
LC/MS	liquid chromatography with mass-spectrometry detection
LDH	lactate dehydrogenase
mCRPC	metastatic castration-resistant prostate cancer
MDSC	myeloid-derived suppressor cells
MEK	mitogen-activated protein kinase/ERK kinase
MTD	maximum tolerated dose
MMSE	Mini-Mental State Exam
MTOR	mammalian target of rapamycin
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NFκB	nuclear factor kappa-B
NOAEL	no adverse effect level
p	probability factor
PBMC	Peripheral Blood Mononuclear Cells
PCWG3	Prostate Cancer Working Group 3
PD	pharmacodynamics(s)
PDGF	platelet-derived growth factor
PI	Principal Investigator
PI3K	phophatidylinositide 3-kinase
PK	pharmacokinetic(s)
PR	partial response
PSA	prostate-specific antigen
PT	prothrombin
PTT	prothrombin time
Raf	rapidly accelerated fibrosarcoma oncogene
Ras	rat sarcoma oncogene
RECIST	Response Evaluation Criteria in Solid Tumors
S1P	sphingosine 1-phosphate
SAE	serious adverse event
s.c.	subcutaneous
SD	stable disease
SEM	standard error of the mean

SIS Unit	Sponsor-Investigator Support Unit
SK	sphingosine kinase
SK1	sphingosine kinase-1
SK2	sphingosine kinase-2
TNFα	tumor necrosis factor-alpha
TUNEL	terminal deoxynucleotidyl transferase dUTP nick end labeling
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
W	week
WBC	white blood cells

1 BACKGROUND

1.1 PROSTATE CANCER

Localized prostate cancer is usually treated with radiation or surgery, though in many cases watchful waiting is considered appropriate. Patients with high grade tumors and extraprostatic extension have poorer prognoses and may receive additional treatment as part of initial therapy. Some patients have metastatic disease at diagnosis, and others, despite adequate initial treatment, develop metastatic disease over a period of time which may be greater than a decade.

The first, and most classic, therapy for advanced prostate cancer is androgen-depleting treatment (ADT) to reduce signaling through the androgen receptor (*AR*). Such interventions include treatments to deplete *AR* ligands such as testosterone, e.g., orchiectomy, GnRHR agonists/antagonists, 17-lyase inhibitors, estrogen agonists, and treatments that prevent the association of *AR* and its androgen ligands, i.e., anti-androgens (Antonarakis et al 2015). However, resistance usually develops to these therapies, accompanied by continued signaling through the androgen receptor (*AR*). Resistance to antiandrogen therapy is often associated with presence of AR-V7 splice variant (Antonarakis et al, 2014; Antonarakis et al, 2017), mutations in the AR ligand-binding domain, or amplification of *AR, MYC*, and other genes. Androgen blockade has been associated multiple toxicities, including loss of muscle mass (Pezaro et al, 2013), increased body fat, insulin resistance, cognitive decline, and loss of sexual function. In patients with preexisting cardiac disease, androgen blockade has been associated with increased all-cause mortality (Ziehr et al, 2015).

Classic cytotoxic agents such as docetaxel, cabazitaxel, platinum analogs, and mitoxantrone have been shown to have reproducible anti-tumor effects in prostate cancer patients, with improvement in overall survival in some cases. However, as prostate cancer is usually a disease of older men, coexistence of major comorbidities is common and often precludes use of cytotoxic agents in patients who have failed initial, less toxic therapy.

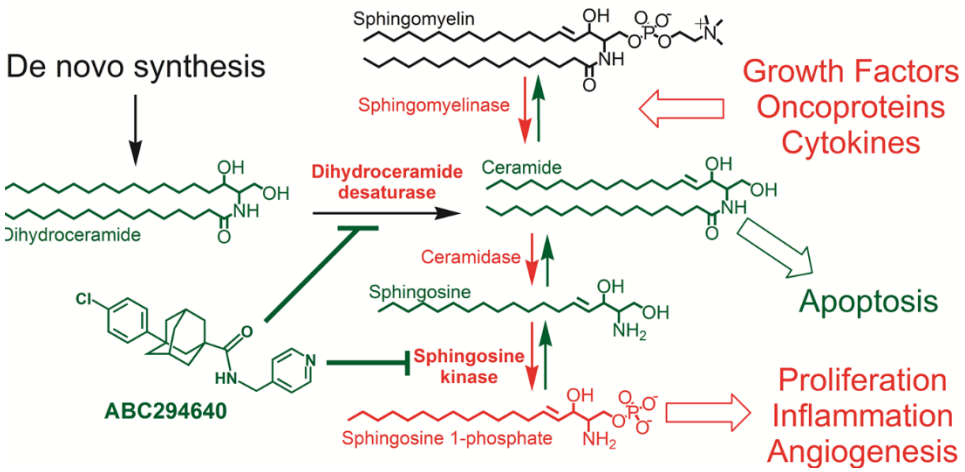
Few effective prostate cancer treatments that are not androgen axis antagonists or cytotoxic agents are available. Sipuleucel-T autologous cellular immunotherapy produces as modest improvement in overall survival, as does radium-223 treatment. However neither agent reliably produces shrinkage of soft tissue masses, or reductions in PSA level, suggesting that there is little direct anti-cancer effect. Rare patients with increased antigenic load (high microsatellite instability, high tumor mutational burden, biallelic silencing of *CDK12* [each <5% of metastatic prostate cancer]) may respond to checkpoint antibodies.

Many kinase inhibitors have been evaluated for use in prostate cancer management, but none are FDA-approved. Several problems have been identified. ***First*,** prostate cancer patients often tolerate multi-targeted kinase inhibitors poorly, with severe fatigue and non-hematologic grade 3 and 4 toxicities. This results in many patients tolerating only half or less of a “typical” full dose of inhibitor. Possibly this results from years of lack of testosterone, and general ill health.

Second, assessment of response to kinase inhibitors is often difficult. The lack of RECIST-evaluable lesions (present only in about 20% of subjects with metastatic prostate cancer) makes evaluation of any therapy difficult. However some kinase inhibitors have been shown to artifactually elevate PSA levels, obscuring potential anti-tumor effects. The hyperacute increase in PSA usually happens within a few days of the start of treatment, resulting in an apparent increase in the PSA velocity. When the kinase inhibitor is stopped the PSA level may drop abruptly as well. This phenomenon has been described for patients treated with CEP-701, imatinib, and sorafenib (Collins, et al., 2007; Dahut, et al., 2008). We have also observed this in prostate cancer patients treated with trametinib (M. Lilly, unpublished 2018). ***Third*,** there are few examples of prostate cancer patients where a mutant kinase plays a dominant, driver role in prostate carcinogenesis. While lung cancer, melanoma, and many hematologic malignancies have activated kinases as drivers, prostate cancer usually results from deficiencies of tumor suppressors or DNA repair mechanisms. Constitutively-active *BRAF* and *PIK3CA* mutants occur in 3% and 8% of PCa subjects respectively, but other active kinase mutants are rare. While kinase inhibitors targeting non-mutant kinases (eg, CDK4/6 inhibitors) have been clinically useful, it is difficult to predict *a priori* whether a patient will benefit from this kind of treatment. Empiric clinical trials are usually required.

1.2 OPAGANIB

Opaganib (formerly ABC294640) is a selective inhibitor of sphingosine kinase 2 (SK2), which converts sphingosine to sphingosine-1-phosphate (S1P) (Figure 1).



Sphingomyelin, an essential component of cellular membranes and which serves as a precursor for important cellular lipid messengers, is converted by sphingomyelinase to ceramide. Ceramidase catalyzes the conversion of ceramide to sphingosine, which is subsequently converted to S1P by sphingosine kinases. Ceramide and sphingosine are pro-apoptotic in tumor cells but do not perturb quiescent normal cells, but S1P is associated with tumor cell proliferation, angiogenesis and inflammation as well as anti-apoptotic activity. The balance between sphingosine and S1P, therefore, appears to play an important role in the survival and

progression of tumor cells. This balance has been referred to as the "rheostat" by several authors (Cuvillier et al, 1996; Pyne and Pyne, 2010).

SK2 is distinguished from sphingosine kinase 1 (SK1) by its primarily nuclear rather than cytosolic location (Neubauer et al, 2016; Ogretmen 2018). Despite catalyzing the same reaction, SK2 inhibition has different effects than SK1 inhibition (ibid). In several models, inhibition of SK2 has a greater anticancer effect than inhibition of SK1 (Gao et al, 2012). In addition to SK2 inhibition, opaganib also inhibits dihydroceramide desaturase, which may be an additional mechanism for its anticancer activity (Venant et al, 2015).

Opaganib is an orally-available selective SK2 inhibitor with several mechanisms of action of relevance to prostate cancer. ***First,*** it attenuates signaling through the Ras/Raf/MEK/ERK and Ras/PI3K/AKT pathways (Gao, et al., 2012) ***Second*****,** it suppresses the activation of NFκB by TNFα, inhibiting TNFα-driven inflammation.(Maines, et al., 2008) ***Third*****,** opaganib appears to target MYC protein for proteasomal degradation [Voelkel-Johnson, et al; unpublished data 2018] through its direct effects on SK2. ***Fourth*****,** through its effects on diydroceramide desaturase opaganib reduces AR protein and mRNA. ***Fifth*****,** opaganib decreased the immunosuppressive potential of MDSCs [unpublished data].

Opaganib has demonstrated anticancer activity in multiple preclinical models of common tumors, including activity in ER positive (Antoon et al, 2010) and triple negative breast (Antoon et al, 2012), non-small cell lung (Dai et al, 2018), ovarian (White et al, 2013), pancreatic (Beljanski et al, 2011; Lewis et al, 2016) and prostate (Gestaut et al, 2014; Schrecengost et al, 2015; Venant et al, 2016) cancer. In addition, opaganib has been shown *in vitro* to potentiate the activity of several common chemotherapeutic agents including doxorubicin (Leili et al, 2018) and 5-fluorouracil and cisplatin (Xun et al, 2015). Based on preclinical data, overexpression of SK2 has been suggested as a marker for opaganib sensitivity (Guan et al, 2016), but to date no clinical correlative markers of opaganib activity have been studied.

1.3 SUMMARY OF OPAGANIB PHASE I DATA.

To the best of our knowledge, opaganib is the only SK2 inhibitor in clinical trials, and thus is a unique, first-in-class compound testing the impact of a novel mechanism on cancer treatment. A first-in-human phase 1 study in advanced solid tumor patients (Britten et al, 2017; NCT01488513), a food effect study in healthy volunteers, and a phase 1 study in advanced myeloma patients (data on file, RedHill Biopharma) have been completed. A phase 2 study in advanced cholangiocarcinoma is under way (NCT03377179). The recommended phase 2 dose has been defined and clinical activity has been seen in both patient studies.

Phase I Study Design

The first-in-human phase I trial employed a 3+3 design. Opaganib was administered orally as 250 mg gelatin capsules on a continuous schedule, with 28 days constituting a Cycle. Tumors were re-imaged every two cycles (8 weeks), and patients were allowed to continue

receiving the drug if there is no disease progression (by RECIST criteria). Primary endpoints were: identification of the Maximum Tolerated Dose (MTD); determination of the Dose Limiting Toxicities (DLT); and evaluation of safety. Secondary endpoints were: determination of pharmacokinetics; evaluation of pharmacodynamics effects; and assessment of antitumor activity.

Phase I Safety Data

Twenty-one patients were treated in the trial, as outlined in Table 1. Three patients (one at 250 mg bid, and two at 500 mg bid) were unable to complete Cycle 1 due to complications from their disease, and were replaced.

The first patient on study at 250 mg qd developed dose-limiting grade 4 hyperglycemia in the setting of rapidly progressing pancreas cancer; no additional patients experienced drug-related hyperglycemia. Among the four patients enrolled at 750 mg bid, one ovarian cancer patient had dose-limiting grade 3 nausea and vomiting, and two patients were unable to complete cycle 1 due to drug-related toxicities (one with grade 2 dysarthria which recurred with grade 2 non-cardiac chest discomfort and grade 2 choking sensation when drug was restarted at 500 mg bid; the other with grade 2 acute kidney injury, grade 3 nausea, and grade 2 agitation). The 750 mg bid dose level was declared not tolerable, and the 500 mg dose level was expanded.

One patient at the expanded 500 mg dose level was dose reduced at Cycle 3 due to grade 3 hallucinations, muscle spasms, and paresthesias: this patient discontinued when spasticity recurred at 250 mg bid. The other five patients at 500 mg bid tolerated the drug well, and the 500 mg bid dose level was established as the recommended phase II dose.

Table 1. Dose Escalation Summary

Cohort	Dose Level	Number of Patients (Evaluable for DLT[a])	DLT
1	250 mg po qd	6 (6)	Grade 4 hyperglycemia (1 patient)
2	250 mg po bid	4 (3[b])	None
3	500 mg po bid	4 (3[c])	None
4	750 mg po bid	4 (2[d])	Grade 3 nausea/vomiting (1 patient)
5	500 mg po bid	3 (3)	None

Treatment has generally been well tolerated. The main adverse reactions noted have been psychiatric: mood changes, hallucinations, anxiety. These reactions have generally occurred at either 500 mg bid or 750 mg bid and resolved either with dose reduction or discontinuation of

treatment. After the food effect study demonstrated that bioavailability was similar with or without food and that absorption was more gradual after food, patients were instructed to take medication after eating; prior to that, dosing was while fasting. Virtually all patients who had psychiatric reactions were also on narcotic analgesics, often given irregularly on an as-needed basis. With the change to dosing after eating and better regulation of analgesic dosing, psychiatric reactions have become much less common and milder. Patients who are not on narcotic analgesics have generally tolerated 750 mg bid.

Phase I Efficacy Data

Among the 15 patients evaluable for anti-tumor activity across all dose levels, one (7%) heavily pretreated cholangiocarcinoma patient developed a partial response after 8 cycles at 250 mg qd, and continued on study for a total of 18 cycles before developing progressive disease. Six patients (40%) had a best response of stable disease: one metastatic urothelial carcinoma patient (at 250 mg qd) ultimately developed progressive disease after 12 courses; one cholangio-carcinoma patient (at 500 mg bid) came off study in course 3 for toxicity; and four patients (1 at 250 mg qd, 2 at 250 mg bid, and 1 at 500 mg bid) came off study for progressive disease at the second disease evaluation (prior to cycle 4). The remaining eight (53%) patients had progressive disease as their best response. No patients with prostate cancer were entered into the phase 1 study.

Phase I Pharmacokinetic Data

Pharmacokinetic profiling was conducted on Days 1 and 28 of Cycle 1; pharmacokinetic data for opaganib is shown in Figure 2. Following oral administration of the drug, plasma concentrations of opaganib typically peak at 1-2 hours, and then declined with a half-time of clearance of approximately 5-15 hours. The C_{max} levels of opaganib were comparable at Day 1 and Day 28 at all dose levels; however, the AUC_{0-T} values at Day 28 were greater than those at Day 1 for the 500 mg bid and 750 mg bid cohorts, suggesting a possibility of accumulation at higher doses. As shown in **Figure 2**, the C_{max} (combining data for Day 1 with Day 28, as well as 250 mg qd with 250 mg bid) was approximately linear with dose between 250 and 500 mg (2.7 ± 0.3 and 5.2 ± 1.1 µg/mL, respectively); however, there was no statistical

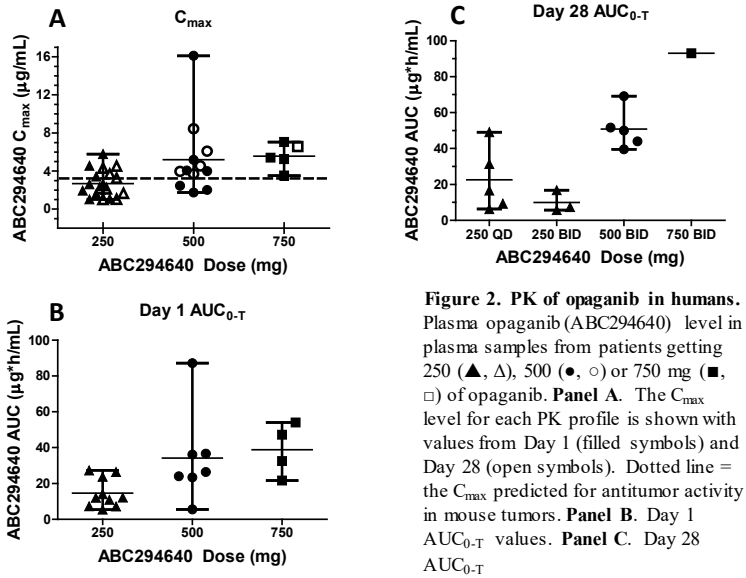


Figure 2. PK of opaganib in humans. Plasma opaganib (ABC294640) level in plasma samples from patients getting 250 (▲, Δ), 500 (●, ○) or 750 mg (■, □) of opaganib. **Panel A**. The C_{max} level for each PK profile is shown with values from Day 1 (filled symbols) and Day 28 (open symbols). Dotted line = the C_{max} predicted for antitumor activity in mouse tumors. **Panel B**. Day 1 AUC_{0-T} values. **Panel C**. Day 28 AUC_{0-T}

further increase at 750 mg (5.6 ± 0.6 µg/mL). Doses of opaganib that provide therapeutic efficacy in mouse xenograft models provide a C_{max} of approximately 3.5 µg/mL (French, et al., 2010), a drug level that was achieved by 33%, 75% and 100% of patients treated with 250, 500 and 750 mg of opaganib, respectively. C_{max} and AUC_{0-T} values at Day 1 suggest an approximately linear increase between the 250 and 500 mg doses; however, further increases in drug exposure were not obtained at the 750 mg dose level. AUC_{0-T} data for Day 28 show a similar linear increase between doses of 250 and 500 mg, with the possibility of further increase suggested by the single data point obtained for the 750 mg dose.

Phase I Pharmacodynamic Data

The target of opaganib, SK2, catalyzes phosphorylation of sphingosine to S1P. In cancer patients, plasma S1P was employed as a biomarker for inhibition of SK2. Plasma samples were assessed for sphingolipid profiles by LC-MS/MS in the Lipidomics Core at MUSC. Opaganib treatment of human patients resulted in rapid decreases in plasma S1P levels very similar to changes observed in mice. In general, plasma S1P levels reached a minimum at approximately 12 hours after opaganib treatment and typically recovered to baseline by 24 hours (Figure 3). Combining data from Days 1 and 28, as well as combining 250 mg qd with 250 mg bid, the maximum S1P decreases for patients receiving 250, 500 and 750 mg of opaganib were 51±6% (n=10), 46±9% (n=5) and 54±14% (n=2), respectively. The kinetics and magnitude of reduction of dihydro-S1P in the plasma virtually paralleled the data for S1P, consistent with the known ability of SK2 to phosphorylate either sphingosine or dihydrosphingosine (sphinganine). In contrast, plasma samples from the 250 and 500 mg treatment groups contained elevated levels of dihydroC16-ceramide, which reached a maximum at 8-12 hr and then returned to baseline at 24 hr. It is noteworthy that the changes in S1P and dihydroS1P were not dose-related in these patients, suggesting that the pharmacodynamic maximal effect is achieved by the 250 mg dose of opaganib. Our findings demonstrated safety and an initial assessment of pharmacokinetic and pharmacodynamic profiles in treated patients.

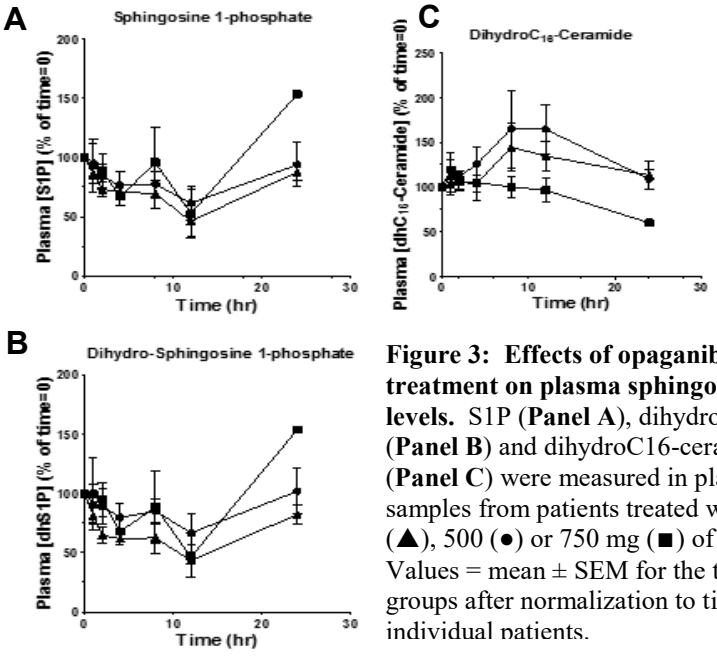


Figure 3: Effects of opaganib treatment on plasma sphingolipid levels. S1P (**Panel A**), dihydroS1P (**Panel B**) and dihydroC16-ceramide (**Panel C**) were measured in plasma samples from patients treated with 250 (▲), 500 (●) or 750 mg (■) of opaganib. Values = mean ± SEM for the treatment groups after normalization to time=0 for individual patients.

1.4 RATIONALE FOR USE OF OPAGANIB FOR TREATMENT OF PROSTATE CANCER

Preclinical data support the utility of opaganib in prostate cancer (Schrecengost et al, 2015):

- Downregulation of *MYC* and *AR* expression and activity; *MYC, AR* are overexpressed in many prostate cancers;
- *In vitro* activity against CRPC cell lines;
- *In vitro* activity against *AR* splice variant cell lines;
- *In vivo* activity in a mouse xenograft prostate cancer model, LNCaP, at a dose well below the equivalent dose tolerated by patients (Schrecengost, et al., 2015). There is also antitumor activity in MycCAP tumors in syngeneic FVB mice, both as a single agent and in combination with enzalutamide (unpublished data, M. Lilly, 2019).

Two additional studies have demonstrated the effects of opaganib on prostate cancer (Gestaut, et al., 2014; Venant, et al, 2015). Data demonstrating key activities of opaganib in prostate cancer are shown in Fig. 4.

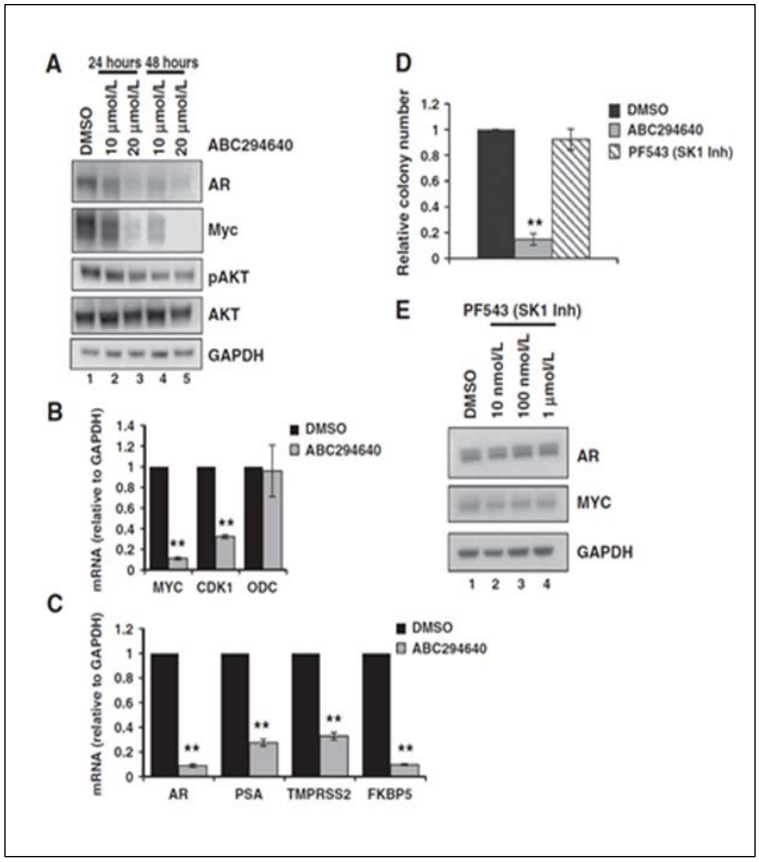


Figure 4. Opaganib (ABC) abrogates multiple proliferative pathways in LNCaP PCa cells. A: Cells were treated with 10 µM, 20 µM ABC or vehicle for 24 or 48 hr, and cell lysates were immunoblotted as indicated. B: Cells were cultured in androgen-depleted media ± ABC, and mRNA for *MYC, CDK1*, and *ODC* were analyzed by qRT-PCR. C: Cells were treated as in B and mRNA for *AR, PSA, TMPRSS2*, and *FKBP5* were analyzed by qRT-PCR. D: Cells were plated at low density and treated with 10 µM ABC, 100 nM PF543 or vehicle for 2 weeks. Cell colonies with fixed, stained with crystal violet and colonies with 50 or greater cells were counted. **$p < 0.01$ compared to DMSO. E: Cells were treated with 10 nM PF543, 100 nM PF543, 1 µM PF543 or vehicle for 72 hr, and lysates were immunoblotted as indicated. From

Myeloid derived suppressor cells (MDSC) have been linked to prostate cancer progression (Lopez-Bujanda et al, 2017; Santegoets et al, 2014). In a myeloma model, SK2 knockout inhibited production of MDSC and growth of myeloma (Kang et al, 2018). In a murine model, opaganib inhibits the function of MDSC, enhancing activity of T cells (Mehrotra, preliminary

unpublished data, 2019). Thus, opaganib may inhibit growth of prostate cancer through multiple mechanisms and act at least additively with hormone blocking therapy.

2 STUDY DESIGN

2.1 STUDY DESIGN

This is a Phase II efficacy study of opaganib in patients with metastatic castration-resistant prostate cancer who have experienced disease progression while receiving abiraterone or enzalutamide. Patients will receive opaganib continuously while continuing abiraterone or enzalutamide, and will continue on therapy until the development of progressive disease, intolerable toxicity, withdrawal of patient consent or other event as outlined in patient discontinuation Section 8.

2.2 OBJECTIVES

Primary Objectives

- To measure the proportion of patients with *disease control* during opaganib (plus abiraterone or enzalutamide) therapy, using a composite metric based on PSA, bone scan, and RECIST measurements per PCWG3 criteria (Appendix B; Scher, et al., 2016). For purposes of this study, disease control is defined as stable disease or better after four cycles (16 weeks) of treatment. A cycle will be 28 days of therapy.

Secondary Objectives

- To estimate the overall survival (OS), radiographic progression-free survival (rPFS), and PSA progression-free survival (PSA-PFS) times in patients treated with opaganib (plus abiraterone or enzalutamide).
- To document the PSA response rate, RECIST response rate, and change in QOL (FACT-P) and pain score (Likert Pain Score) in mCRPC patients treated with opaganib (plus abiraterone or enzalutamide) after four cycles of treatment
- To determine the effects opaganib on regression or progression of mCRPC clones with amplified *AR* or *MYC,* identified by serial ctDNA-based genomic profiling.
- To assess safety of opaganib in mCRPC patients, in combination with abiraterone or enzalutamide, GnRHR agonist/antagonist (this is the primary objective for the run-in cohort)
- To monitor changes in numbers or activity of immune cells and myeloid-derived suppressor cells during opaganib therapy (with continued ADT).

3 STUDY PATIENTS

Patients with metastatic castration-resistant prostate cancer (mCRPC) who have shown disease progression while being treated with abiraterone (cohort 1a or 2) or enzalutamide (cohort 1b or 3) are eligible for this trial. Potential study patients will be screened according to the Inclusion, Exclusion Criteria. Each of the following criteria must be met

in order for a patient to be considered eligible for enrollment. Study-specific evaluations may be performed only after written informed consent has been obtained.

3.1 INCLUSION CRITERIA

1. Patient must have mCRPC. Each patient must have:
    - Tissue diagnosis documented by pathology report, or clinic note attesting to same.
    - Radiographically-demonstrated metastases
    - Patients must have adenocarcinoma, or ductal carcinoma, or combinations of these two entities

2. Voluntary, signed and dated, institutional review board (IRB)-approved informed consent form in accordance with regulatory and institutional guidelines.

3. Documented progression during treatment with enzalutamide or abiraterone, as determined by the enrolling investigator.

4. Testosterone level documented to be less than 50ng/dL

5. 18 years of age or older.

6. ECOG performance status of 0-2.

7. Acceptable liver function:
    - Bilirubin $\leq$ 1.5 times upper limit of normal (CTCAE Grade 1 baseline)
    - AST (SGOT) & ALT (SGPT) $\leq$ 3 x ULN (CTCAE Grade 1 baseline)
    - Subjects with Gilbert's syndrome may be included if the total bilirubin is < 3x ULN and the direct bilirubin is within normal limits

8. Acceptable kidney function indicated by serum creatinine $\leq$ 1.5 X ULN (CTCAE Grade 1 baseline)

9. Acceptable hematologic status:
    - Absolute neutrophil count $\geq$ 1000 cells/mm^3,
    - Platelet count $\geq$ 75,000 (plt/mm^3) (CTCAE Grade 1 baseline)
    - Hemoglobin $\geq$ 9.0 g/dL.

10. Fasting blood glucose of <165mg/dL or random blood glucose of < 200mg/dL

11. Urinalysis: no clinically significant abnormalities

12. International normalized ratio (INR) ≤1.7 for patients not on anti-coagulation meds

13. Well-controlled blood pressure as determined by the treating investigator

14. Patients requiring narcotic analgesics must be on stable doses for at least 2 weeks prior to study entry.

3.2 EXCLUSION CRITERIA

1. New York Heart Association Class III or IV, cardiac disease, myocardial infarction within the past 6 months, unstable arrhythmia, or evidence of ischemia on ECG.

2. Underlying psychiatric disorder requiring hospitalization within the last two years.

3. Clinically significant neurological disorder (Parkinson's disease, dementia, multiple sclerosis), as determined by the enrolling investigator.

4. Active, uncontrolled bacterial, viral or fungal infection, requiring systemic therapy.

5. Treatment with radiation therapy, surgery, or investigational therapy within 28 days prior to registration.

6. Unwillingness or inability to comply with procedures required in this protocol.

7. Serious nonmalignant disease that could compromise protocol objectives in the opinion of the Investigator.

8. Patients who are receiving coumadin, apixaban or rivaroxaban. Patients who are receiving other drugs that are sensitive substrates of CYP450 1A2, 3A4, 2B6, 2C8, 2C9, 2C19 or 2D6, P-gP, BCRP, and OATP1B1,or strong inhibitors or inducers of all major CYP450 isozymes that cannot be stopped at least 7 days or 5 half-lives (whichever is longer) before starting treatment with opaganib may be treated on this study with careful monitoring for toxic effects or loss of efficacy of the relevant drug. A list of commonly used drugs that are sensitive substrates of CYP450 1A2, 3A4, 2B6, 2C8, 2C9, 2C19 or 2D6, P-gP, BCRP, and OATP1B1, or strong inhibitors or inducers of all major CYP450 isozymes with the half-life of each drug identified, is included as an Appendix C.

9. Patients who are currently participating in any other clinical trial of an investigational product.

10. Other primary malignancy requiring systemic treatment within past 5 years except carcinoma in situ of the cervix or urinary bladder or non-melanoma skin cancer.

11. Any other mental incapacitation or psychiatric illness that would preclude study participation, as determined by the enrolling investigator.

12. Prisoners or patients who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious disease) illness must not be enrolled into this study.

13. Patients that have had chemotherapy for castration resistant prostate cancer (patients can have had chemotherapy for castration sensitive PC)

- Exception: Patients who had prior chemo for CRPC are eligible if they have a PS=0-1 and life expectancy of more than 6 months.

3.3 SUBJECT RECRUITMENT

This study will take place at the MUSC and up to two other cancer centers (to be determined).

- Subjects will be identified by the designated IRB-approved study team or will be referred by colleagues who care for the patient populations under study.
- Designated IRB-approved study research team personnel may screen records to identify potential subjects. Records and/or areas that may be reviewed include pathology/surgical reports, and pharmacy records.
- Potential subjects will only be approached for the study after they have been informed of the study by someone involved with their clinical care.
- Potential subjects who have previously agreed to be contacted for research may be approached by the study team.

3.4 INFORMED CONSENT PROCESS

- Subjects who are interested in participating will be interviewed in clinic. They will be given time to read the consent in private setting and ask questions. A designated IRB approved member of the study will explain the nature of the study, the benefits and risks. Informed consent will be obtained by designated IRB approved research members in clinic. Consent will be documented by obtaining the subject's signature on the approved consent form, and documenting the consent process through a progress note in the participant's clinical or research record.
- Consent may be obtained the same day the patient is presented with the trial.

3.5 PATIENT REGISTRATION

The Hollings Cancer Center's Sponsor-Investigator Support Unit (SIS Unit) will provide patient registration services for the study. The SIS Unit will conduct a patient eligibility audit review of all eligibility source documents prior to patient registration. These procedures are outlined in the MUSC 103193 Operations Manual. After obtaining signed informed consent and completion of required baseline assessments, eligible subjects will be registered. A unique subject number will be assigned to each patient. The SIS Unit will issue a patient registration confirmation email to the enrolling study team at the time of registration which will include the patient's study ID number.

4 TREATMENT PLAN

4.1 STUDY CALENDAR

Patients will be evaluated according to the Study Calendar (Appendix A). The CTCAE 5.0 manual will be used to assess adverse events. All study dates will be +/- 5 days.

The visit at which a response assessment shows disease progression, or shows lack of disease control, or a decision is made to discontinue treatment for other reasons, such as toxicity, will be considered the End of Treatment visit.

Patients completing their treatment should return for Post-30 day visit per Study Calendar (Appendix A). Patients who have an ongoing Grade ≥ 3 or serious adverse event that is at least possibly related to treatment will be contacted by the investigator or designee approximately every week until the event is resolved to baseline or determined to be irreversible.

Patients will be followed for survival by clinic visit, review of medical record, and/or telephone call every 3 months from treatment discontinuation date for a maximum of 30 months after the last patient has been registered to the trial or until at least 80% of patients treated on study in both arms have died, whichever comes first.

4.2 STUDY TREATMENT

Opaganib will be given at 250 mg (cohorts 1a, 1b) or 500 mg (cohorts 2, 3) orally twice a day (approximately 12 hours apart) continuously. A cycle will be defined as 28 days. The dose will be given after a light to moderate meal.

It will be important to assess patient compliance for the administration of opaganib. Patients will be provided a drug diary at the beginning of each cycle, i.e. when additional drug is dispensed to the patient. Patients will be instructed to complete the drug diary and record their daily administration of drug during the morning and afternoon/evening timeframes. Any missed or modified doses should be documented along with the reason for the modification. Patients will be instructed to return their container(s) of opaganib at each clinic visit so that the delegated

research team can conduct a pill count to assess patient compliance. The research team has the ability to withdraw a patient from the study if that patient demonstrates repeated protocol noncompliance.

4.3 DOSE MODIFICATIONS

Individual patients may continue to receive therapy at the same dose provided they do not experience unacceptable toxicity or disease progression. All grade 1 toxicities and adverse events, and tolerable unrelated grade 2 adverse events, can be treated according to standard clinical practice guidelines. Toxicity is an adverse event judged by the investigator to be possibly, probably or definitely related to study medication.

- See Table 2 for the Dose Modification Plan for patients experiencing opaganib-related toxicities
- See Table 3 for the Dose Modification Plan for patients experiencing Grade 3 or 4 adverse events **not** related to opaganib
- Patients who experience opaganib related neurologic and/or psychiatric toxicities will be managed according to Table 2 (grade 2) or Table 3 (grade ≥ 3).

For cohorts 1a and 1b, if one of the first three patients in either cohort develops a dose-limiting toxicity (DLT, as described in Section 4.4, below), the cohort is to be expanded to six patients. If no patient among the first three in cohort 1a or 1b develops a DLT, proceed to cohort 2 or 3, respectively. Similarly, if one patient among the first 3 of cohort 1a or 1b has developed a DLT but no additional patient among the second three develops a DLT, proceed to cohort 2 or 3, respectively.

If a second patient in either cohort 1a or 1b develops a DLT, accrual to that cohort will be discontinued and no patients will be accrued in cohort 2 or 3, respectively.

Stopping rules for cohorts 2 and 3 are shown in Table 5, below.

Patients who develop intolerable grade 2 or ≥ grade 3 OPAGANIB-related toxicity at 250 mg bid will not be permitted further dose reduction, and may be withdrawn from study for toxicity.

Patients who develop grade 4 toxicity which does not resolve to ≤ grade 2 within 48 hours by standard measures, such as antiemetics for vomiting, or electrolyte replacement/modification therapy for electrolyte imbalances, are to permanently discontinue study medication.

If the treating investigator determines that the patient needs to discontinue Abiraterone or Enzalutamide due to toxicity, the patient may continue on Opaganib alone.

Table 2. Dose Modification Plan for Opaganib Related Toxicities

NCI CTC 5.0 Criteria	**Opaganib Dose Modification Instructions**
Any *intolerable* grade 2 toxicity (includes neurologic/psychiatric toxicity)	The investigator should consult the study sponsor regarding opaganib-related grade 2 toxicities that are considered intolerable by the patient or physician. A dose reduction may occur with prior consultation with and approval by the study sponsor.
Grade 3 hematologic, renal or hepatic toxicity	1. Hold study drug. 2. Assess patient weekly. 3. If the toxicity improves to ≤ baseline within 28 days, restart study drug and reduce dose to 250mg BID. 4. If the toxicity recurs at the same grade discontinue study drug. If the dose is held longer than 3 weeks discontinue from study. 5. Omitted doses are not made up
Grade 3 other non-hematologic, toxicity (includes neurologic/psychiatric toxicity)	1. Hold study drug. 2. Assess patient weekly. 3. If the toxicity improves to ≤ baseline within 28 days, restart study drug and reduce dose to 250mg BID 4. If the toxicity recurs at the same grade discontinue study drug. If the dose is held longer than 4 weeks, discontinue from study. 5. Omitted doses are not made up.
Any grade 4 toxicity (includes neurologic/psychiatric toxicity)	For most related grade 4 adverse events of any duration, permanent discontinuation of study drug is required. Exceptions to this criteria include: • clinically insignificant laboratory abnormalities that resolve within two days on optimum treatment • emesis

Table 3. Dose Modification Plan for Adverse Events NOT related to Opaganib

NCI CTC 5.0 Criteria	Opaganib Dose Modification Instructions
≥Grade 3	1. Hold study drug until resolution or improvement to not more than one grade above baseline. 2. If AE improves to within one grade of baseline level within 4 weeks, restart study drug at the same dose. A dose reduction may occur with prior consultation with and approval by the study sponsor. 3. If the AE does not resolve to within one grade of baseline level within 4 weeks, consult the study sponsor. Omitted doses are not made up.

4.4 DEFINITION OF DOSE-LIMITING TOXICITY

The DLT period for this study is 28 days. Safety will be reviewed and confirmed centrally by the safety review committee before the next dose assignment. A DLT is defined as an event considered at least possibly related to opaganib or its combination with abiraterone or enzalutamide and meeting one of the following criteria:

a) Grade 4 thrombocytopenia of any duration

b) Grade 3 thrombocytopenia with significant hemorrhage of any duration

c) Grade 4 neutropenia greater than 5 days

d) Febrile neutropenia

e) Grade ≥3 non-hematologic toxicity of any duration, except:

- Grade 3 nausea, vomiting, or diarrhea and grade 4 vomiting or diarrhea in the absence of maximal medical therapy that resolves in 72 hrs
- Grade 3 fatigue lasting <5 d
- Grade 3 HTN that can be controlled with medical therapy
- An increase of indirect (unconjugated) bilirubin indicative of Gilbert's syndrome
- Serum lipase and/or serum amylase CTCAE Grade 3 ≤ 7 consecutive days without clinical signs or symptoms of pancreatitis
- Neuropsychiatric events (e.g., depression, anxiety) which resolve to ≤grade 1 by modification of concomitant medications, e.g., narcotic pain medication regimen
- Electrolyte imbalances which resolve within 3 days with routine therapy, e.g., modification of electrolyte and/or fluid administration

f) Grade 3 non-hematological toxicity that delays administration of either study drug for more than 2 weeks

g) ALT/AST >3xULN with bilirubin >2xULN without another explanation (e.g., cholestasis)

h) Patients who are not able to tolerate at least 80% of the planned dose over the first 28 days due to toxicity, i.e., adverse events possibly, probably or definitely related to treatment, even if these toxicities are not otherwise listed as DLTs.

4.5 ADDITIONAL MEDICATIONS

Patients should continue ongoing gonadotropin releasing hormone receptor agonists or antagonists for the duration of the study to maintain the testosterone level at <50ng/dL.

Men with the potential to father children must use effective contraceptive methods during the study. The female partner of male subject must be either not of childbearing potential (defined as postmenopausal for ≥ 1 year or surgically sterile) or practicing two forms of contraception. A sexually active male participants must agree to use a physical barrier method (male latex rubber condom with or without spermicide).

4.6 CORRELATIVE STUDIES

Samples will be processed and stored locally in Dr. Mehrotra's lab in HO503. The trial will be carried out at MUSC and one other cancer center (to be determined). Correlative studies will be done and will be exchanged between participating institutions. Samples may be stored for future use.

4.7 PHARMACOKINETICS

PKs for this study are optional. Pharmacokinetics will be collected for 12 patients (6 from cohort 2 and 6 from cohort 3).

Table 4: PK collection

Day[a]	Time (relative to dosing), h[d]	Abiraterone PK Assay	Enzalutamide PK Assay[c]	Opaganib PK Assay
Screening (Day -7 thru 0)	0[b]	X	X	
	1	X	X	
	2	X	X	
	4	X	X	
Day 29 (Day 25 - Day 33)	0	X	X	X
	1	X	X	X
	2	X	X	X
	4	X	X	X

a. Relative to start of opaganib. To be drawn on one day of the range shown; day 0 = day before start of opaganib.
b. Within the hour before dosing
c. At times of enzalutamide sampling, also get blood for N-desmethyl enzalutamide
d. One and two hours post dose: +/- 20 minutes. Four hours post dose: +/- 30 minutes

Following are the volumes of blood (and tubes) required for each of the PK assays:

- Abiraterone – **3mL of blood in EDTA K2** tube

- Enzalutamide – **2mL of blood in EDTA K2** tube
- Opaganib – **3 mL of blood in K3 EDTA** tube

See study lab manual for specimen storage and shipping information.

5 STUDY DRUGS

5.1 OPAGANIB

Opaganib is an orally available inhibitor of the enzyme sphingosine kinase 2. Opaganib will be provided by RedHill Biopharma. The current FDA status of opaganib is "under review".

Formulation

Opaganib is available in 250 mg and 375 mg capsules. Capsules contain the milled active pharmaceutical ingredient (API) opaganib along with the excipients microcrystalline cellulose, USP/NF (Avicel® PH102, FMC) (FMC biopolymer) and colloidal silicon dioxide, NF (Cab-O-Sil® M5P). Opaganib is a white to off-white powder and for clinical use it is encapsulated in white opaque hard gelatin capsules.

Dosage and Administration.

The study drug will be administered orally at 250mg or 500mg every 12 hours (+/- 2 hours), after a light to moderate meal. A dose modification plan is also provided in Section 4.3.

Storage.

Storage conditions: Store at room temperature, 15-30°C (59-86°F) in a secure, locked area, properly labeled and segregated from other materials. This storage area should only be accessible to authorized individuals.

Labeling.

The test article will be labeled with the sponsor name and address, description of contents and storage conditions, and will contain the statement "Investigational Product: To be used in a clinical investigation only."

Test Article Accountability.

The Investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of the test article including the date, quantity, batch or code number and identification of subjects (patient number and initials) who receive the test article. The Investigator will not supply the test article to any person except those named as subinvestigators and submitted to the local regulatory authority, designated staff and patients in this study. The Investigator will not dispense the test article from any sites other

than those submitted to the local regulatory authority. The test article will not be relabeled or reassigned for use by other patients.

Upon completion of the study, unused supplies of the opaganib test article will be returned to RedHill Biopharma or destroyed as directed.

5.2 ABIRATERONE

Abiraterone will be provided by the patient or third party from clinical grade material marketed as Zytiga® or Yonsa®, or from the marketed generic material. The patient will continue to take the dose used before study enrollment, for the duration of the study. Abiraterone will be taken alone, without other drugs or food, at least 1hr prior to, or 2hr after a meal. The patient will also take prednisone 5mg (or methylprednisolone 4mg, if using Yonsa) PO Q AM with breakfast.

5.3 ENZALUTAMIDE

Enzalutamide will be provided by the patient or third party from clinical grade material marketed as Xtandi®. The patient will continue to take the dose used before study enrollment, for the duration of the study. Enzalutamide capsules will be taken all together, or singly in rapid succession, within one hour

6 SAFETY PLAN

6.1 GENERAL PLAN TO MANAGE SAFETY

A number of measures will be taken to ensure the safety of patients participating in this trial. These measures will be addressed through exclusion criteria and routine monitoring as outlined below. In addition, an early stopping monitoring plan is outlined in Section 9.

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations (including neurologic examination, as well as mini-mental state exam), blood pressure, and laboratory measurements (performed by local laboratories). Patients will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study. Patients discontinued from the treatment phase of the study for any reason will be evaluated within 30–42 days after last dose of study drug. Patients who have an ongoing treatment-related Grade $\geq$ 3 or serious adverse event at the time of discontinuation from study treatment will continue to be followed as per Section 4.

If the female partner of a male subject becomes pregnant despite precautions, she should be apprised of the potential risk of fetal morbidity or loss.

Serious adverse events will be reported as outlined in section 10.12.

6.2 SAFETY PLAN FOR PSYCHIATRIC SYMPTOMS FROM STUDY DRUG

Patients will be evaluated at each study clinic visit by a medical oncologist for psychiatric or neurological symptoms potentially related to opaganib. In addition, mini-mental status examination (MMSE) will be conducted at various time points within the study. Patients exhibiting symptoms of psychiatric or neurological impairment on physical exam or a clinically significant decrease in MMSE score in the opinion of the investigator that does not resolve with interruption or discontinuation of opaganib will be referred to specialty psychiatric or neurological care as deemed appropriate.

7 CONCOMITANT AND EXCLUDED THERAPIES

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

7.1 ANTINEOPLASTIC DRUGS

Use of anti-neoplastic or anti-tumor agents not part of the study therapy, including chemotherapy, radiation therapy, immunotherapy, and hormonal anticancer therapy, is not permitted while participating in this study. Use of concurrent investigational agents is not permitted.

7.2 CYP SUBSTRATE DRUGS, INHIBITORS, AND ACTIVATORS

Patients may not receive coumadin, apixaban or rivaroxaban while on the study. Patients requiring anticoagulation may receive anticoagulants which will not be affected by CYP inhibition, i.e., standard or low molecular weight heparin or dabigatran.

When possible, avoid drugs with narrow therapeutic indices and that are CYP isoenzyme substrates. Patients who are receiving drugs that are CYP substrates or must start receiving such drugs while on study should be monitored for toxicities associated with these concomitant medication(s), as exposure to these medications could be increased by opaganib. A list of commonly used drugs that are sensitive substrates of CYP450 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, P-gP, BCRP, and OATP1B1 (with the half-life of each drug identified) is included as Appendix C. It is also shown is shown in a table from Indiana University Department of Medicine Clinical Pharmacology Division, at:
http://www.medicine.iupui.edu/clinpharm/ddis/clinical-table/

7.3 MINIMIZING NEUROPSYCHIATRIC ADVERSE EVENTS

Neuropsychiatric adverse events, including anxiety and hallucinations, were noted in initial clinical studies of opaganib. Administering opaganib after eating results in more gradual absorption with minimal change in bioavailability. This appeared to decrease the incidence and severity of neuropsychiatric adverse events.

In addition, there appears to be an interaction between narcotic analgesics and opaganib with respect to neuropsychiatric adverse events. Many patients entered into this study are likely to require narcotic analgesics for treatment of pain from bone metastases. The adverse events may be avoided or minimized if patients are on nonnarcotic analgesics in addition to stable doses of narcotic analgesic rather than PRN doses. Keeping patients on relatively stable doses of narcotics may minimize the fluctuation of narcotic blood levels. In a previous study, switching patients from PRN to standing doses of analgesics appeared to ameliorate neuropsychiatric adverse events.

8 PATIENT DISCONTINUATION

Patients may discontinue study treatment at any time. Any patient who discontinues treatment will be asked to return to the study center to undergo end of treatment assessments as outlined within Study Calendar (Appendix A). The primary reason for discontinuation should be recorded. Reasons for discontinuation of a patient by the investigator include, but are not limited to, the following:

Subjects who meet the following criteria should be discontinued from study treatment:

- Documented disease progression (loss of disease control) per Appendix B
- Clinically significant deterioration of the patient's condition
- Patient noncompliance
- Adverse events requiring treatment discontinuation, regardless of relationship to study medication
- Investigator determination that it is not in the patient's best interest to continue participation
- Withdrawal of consent by patient

8.1 PATIENTS RESUMING STUDY TREATMENT

Patients that have had a delay in their study treatment of no more than 8 weeks for any reason can re-initiate treatment provided that:

- The patient has not experienced radiographic or clinical progression
- PSA has not increased more than 25% from the PSA level at the time of treatment interruption
- The patient has not received any new anticancer treatment in the interim.

Patients that discontinue study treatment due to PSA progression can resume study treatment if the following conditions are met:

- The patient's PSA has dropped back down below what would have been considered disease progression
- No more than 8 weeks have passed since the patient discontinued study treatment
- The patient did not / does not show any other signs of disease progression (clinical or radiographic)
- No other therapies were initiated since the patient discontinued study treatment

If a patient meets all the above criteria and is resuming study treatment, they will continue as if there has been a treatment delay and will re-initiate therapy at the next corresponding visit on the study calendar (see appendix A).

9 STATISTICAL CONSIDERATIONS

Proportion of patients achieving various efficacy endpoints and times to efficacy events will be calculated from the patients in cohorts 2 and 3. Safety endpoints will be calculated based on all patients, with subgroup analysis for cohorts 2 and 3.

9.1 STATISTICAL ANALYSIS FOR PRIMARY OBJECTIVE

We will estimate the proportion of patients with disease control during opaganib (plus abiraterone or enzalutamide) therapy, using a composite metric based on PSA, bone scan, and RECIST measurements per PCWG3 criteria (see the definitions in Appendix B). The primary measurement will be determined after four cycles (day 113) of treatment. The 95% confidence interval for the proportion of disease control will be presented. A one-sided exact binomial test will be performed based on a null hypothesized proportion of 0.1 with a significance level of 0.05.

9.2 STATSTICAL ANALYSIS FOR SECONDARY OBJECTIVES

Estimate the radiographic progression-free survival (rPFS), PSA progression-free survival (PFS) times in patients treated with opaganib (plus abiraterone or enzalutamide).

rPFS is defined as the length of time from initiation of study treatment until documented disease progression per mRECIST or per PCWG3 criteria for disease progression on bone scans (see Appendix B). Patients who have not radiographic progression by the end of the follow-up will have their rPFS values censored. PSA-PFS is defined as the length of time from initiation of study treatment until documented PSA progression per PCWG3 criteria. These criteria specify an increase in PSA of >25% above the baseline (if no PSA response) or nadir (if PSA response) value, as an indicator of PSA progression. A PSA value felt to indicate progressive disease must be confirmed with a repeated elevated value at least 1 month later. Patients who have not PSA progression by the end of the follow-up will have their PSA-PFS values censored. Kaplan-Meier estimates of the time-to-event (i.e., rPFS or PSA-PFS) will be constructed using a competing-risks approach which treats death due to causes unrelated to prostate cancer as a competing event. Median time to progression will be estimated and the corresponding 95% confidence intervals constructed using Greenwood's variance estimate (Collett, 1994).

Document the PSA response rate, overall response rate, and change in QOL (FACT-P) in mCRPC patients treated with opaganib (plus abiraterone or enzalutamide) 16 weeks after the start of treatment

PSA response rate is the proportion of patients demonstrating a 25% or greater reduction in PSA level compared with the baseline value, at any point during therapy with opaganib (with abiraterone or enzalutamide). This response definition is consistent with the recommendations of the PCWG3 (Scher, et al., 2016). Overall response rate is the proportion of patients

demonstrating a complete or partial response of RECIST-evaluable lesions at any point during therapy with opaganib (with abiraterone or enzalutamide). The definitions of response are well-standardized (Eisenhauer et al, 2009). Both PSA response rate and overall response rate will be estimated with the 95% confidence interval. The change in QOL will be summarized graphically and numerically, and tested based on two-sided paired t-test.

Determine the effects opaganib on regression or progression of mCRPC clones with amplified AR or MYC, identified by serial ctDNA-based genomic profiling.
The relationship between changes in marker levels (copy number for AR, MYC amplified clones based on Guardant 360 genomic profile) and patient response for regression or progression of mCRPC clones will be assessed graphically. Scatterplots of percent change in target lesions versus change in marker levels will be constructed. Variable transformations will be considered as needed, and Pearson or Spearman correlation coefficients will be constructed as appropriate. Based on two-sided Pearson or Spearman correlation coefficients test with alpha = 0.05, the sample size of 27 provides a 77% power to detect a correlation of 0.5 versus a null correlation of 0.

Assess safety of opaganib in mCRPC patients, in combination with abiraterone or enzalutamide, GnRHR agonist/antagonist
The safety analysis will be conducted using descriptive statistics of the incidence of adverse events (AEs) and serious adverse events (SAEs), all events of death, and any study specific issue of concern. Adverse events will be coded by body system, and summary tables with incidence rates of AEs will be generated. Descriptive statistics of AEs will be reported for all patients, patients who discontinue due to AEs, and patients with related AEs. Severity, duration, investigator attributed relationship to treatment, and outcomes of AEs will be reported. AE and SAE reporting criteria are outlined in section 10.

Monitor changes in numbers or activity of immune cells and myeloid-derived suppressor cells during opaganib therapy (with continued ADT). The numbers or activity of immune cells and myeloid-derived suppressor cells (measured at baseline and certain time points) will be summarized graphically. The mean of the difference of cell counts between time points will be described with the 95% confidence interval. The changes in cell counts will be analyzed using a paired t-test to see if the change is significant. Equivalent non-parametric tests (e.g., Wilcoxon rank-sum test) will be used as appropriate.

9.3. ANALYSIS POPULATIONS

Patients with disease progression while receiving abiraterone will constitute cohort 1a and 2 (maximum of 6 and 27 patients, respectively) while those worsening during enzalutamide treatment will be enrolled into cohort 1b and 3 (maximum of 6 and 46 patients, respectively).

Intent to treat population set

Patients who drop out prior to receiving their first dose of opaganib will be replaced. Those who have received at least one dose of opaganib will contribute to the intent-to-treat (ITT) analysis. Patients in the ITT population who withdraw prior to response evaluation at 16 weeks will be treated as non-responders in the ITT analysis.

Analyses for the efficacy endpoints will be performed on patients who are assigned to receive opaganib 500 mg bid along with their antiandrogen. Efficacy results from the patients in cohorts 1a and 1b will be described but will not be included in the calculations for either the primary or secondary efficacy endpoints.

Safety population set
The safety population is defined as all patients who receive at least one dose of study drug. Safety analyses will be performed for the entire safety population (i.e., patients in all cohorts), and subgroup analyses will be performed for cohort 2 and 3.

9.4 SAMPLE SIZE DETERMINATION

The primary endpoint is a binary indicator of disease control for patients in cohort 2 and 3. Each cohort will be analyzed independently. A maximum of 27 subjects will be enrolled in cohorts 2 and 46 subjects in cohort 3. With a null hypothesized disease control of 0.1 and sample size of 27 evaluable patients, the power to detect the difference of 0.2 (i.e., alternative proportion of 0.3) is 86.4% based on one-sided exact binomial test with alpha = 0.05 (type I error rate).

9.5 INTERIM ANALYSES

Futility monitoring
This trial employs a Simon minimax two-stage design (Simon, 1989) for each cohort. The null hypothesis is that the true response rate is 0.1, and the alternative hypothesis is that the true response rate is 0.3. An interim analysis for futility will be performed when a total number of 20 patients is evaluable for disease control according to a multiparameter index (See Appendix B). If there are one or fewer responses for disease control in the first 20 patients, then accrual to that cohort will be halted for futility. At the end of trial, we reject the null hypothesis if there are 6 or more responses for disease control among 27 evaluable patients. When the true response rate is 0.1, the expected sample size for this trial is 24.3 and the probability of early stopping is 39.2%

Safety monitoring
We have incorporated safety stopping rules into our design to ensure patient safety (Table 5). We will stop the trial early if there is significant toxicity, defined as an unacceptable adverse event rate of grade 3 or 4 adverse events, or serious adverse events deemed probably, or definitely related to study drug. We consider an acceptable level to be 15% (null hypothesis H0) and an unacceptable rate to be 30% (alternative hypothesis H1). We will use a likelihood ratio test that allows stopping for strong evidence that the grade 3-4 toxicity/related SAE rate is 30% vs. 15%. Specifically, the stopping threshold is determined by a likelihood ratio value of 10 or greater favoring the alternative adverse event rate of 30%. Given our sample size of 27 and based

on 10,000 simulations, this likelihood-based stopping rule yields a 53.04% chance of early termination if the true grade 3-4 adverse event/SAE rate is 30% and only a 4.14% chance of early stopping if the true rate is 15%.

Table 5: Safety stopping rules for each cohort 2 and 3.

Total number of patients treated	Number of patients with grade 3 or 4 AE, or SAE possibly, probably, or definitely related to study medication, or who discontinued study drug due to toxicity[a]	Observed toxicity rate	Likelihood ratio favoring H_1 versus H_0
<= 6	4	≥0.67	≥10.9
7-10	5	≥0.50	≥12.1
11-15	6	≥0.40	≥11.2
16-20	7	≥0.35	≥10.3
21-24	8	≥0.33	≥11.5
25-27	9	≥0.33	≥15.5

a. Any adverse event considered possibly, probably or definitely related to study drug, regardless of grade.

10 ADVERSE EVENT REPORTING REQUIREMENTS

The local investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the EDC and to the IRB as appropriate.

The study period during which all AEs and SAEs must be reported begins after initiation of study treatment and ends 30 days following the last administration of study treatment. After this period, investigators should only report SAEs that are attributed to prior study treatment.

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study, and actions taken.

10.1 PURPOSE

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in

future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for monitoring of patient safety and care. The following guidelines prescribe routine and expedited adverse event reporting for this protocol.

Throughout the study, the Investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safety of the drug under investigation.

Note: All deaths on study require expedited reporting if they occur during opaganib treatment or within 30 days of the final dose. Deaths will be reported to the IRB and DSMC of record. Attribution to treatment or other cause must be provided.

10.2 DEFINITION OF ADVERSE EVENT

An adverse event (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease temporally associated with the subject's receipt of study medication, whether or not considered related to the subject's participation in the research. All adverse events should be recorded and described in the EDC. Adverse events also include Grade 3 or 4 abnormal laboratory test results that are clinically significant.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency, duration or severity, or a change in the quality, of the disease or condition. Only grade 3 or 4 abnormal lab values that were not noted during the Screening Phase should be recorded; however, any clinical consequences of the abnormality, regardless of grade, should be reported as AEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Progression of cancer also will not be considered an AE.

10.3 DEFINITION OF SERIOUS ADVERSE EVENT

An SAE is defined by regulatory agencies as one that suggests a significant hazard or side effect, regardless of the investigator or sponsor's opinion on the relationship to investigational product. This includes, but may not be limited to, any event that (at any dose):

- Is fatal
- Is life threatening (places the subject at immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Is a persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- A hospitalization meeting the regulatory requirement for the "serious" criteria is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility.

Any event that does not exactly meet this definition yet, in the investigator's opinion represents a significant hazard can be assigned the "other significant hazard" regulatory reporting serious criteria.

Additionally, important medical events that may not be immediately life threatening or result in death or hospitalization but that may jeopardize the subject or require intervention to prevent one of the outcomes listed above, or result in urgent investigation, may be considered serious. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

10.4 DEFINITION OF SEVERITY

Adverse events will be graded according to the revised NCI Common Toxicity Criteria. If toxicities are not defined by the NCI Common Toxicity Criteria v. 5.0, the intensity of each adverse event should be graded as either Mild (grade 1), Moderate (grade 2), Severe (grade 3), or life-threatening (grade 4) by the Investigator.

GRADE 1	MILD: Sign or symptom noticeable, but does not interfere with normal daily activities.
GRADE 2	MODERATE: Sign or symptom sufficient to interfere with normal daily activities.
GRADE 3	SEVERE: Sign or symptom is incapacitating, with inability to perform daily activities.
GRADE 4	LIFE-THREATENING: sign or symptom poses immediate risk of death to this patient.

10.5 DEFINITION OF START DATE, STOP DATE, DURATION

The definitions of AE start/stop dates and duration will be as follows:

Start Date	The date at which the AE is first noted
Stop Date	The date at which the AE is known to be resolved. If it is not known to have stopped, then indicate "ongoing."

10.6 ACTIONS TAKEN

Action(s) taken may consist of the following:

None:	No actions taken

Dose permanently stopped:	Test article was permanently discontinued because of the AE
Dose modified:	Test article was given at a lower dose, at a longer interval between doses, or was temporarily withheld because of the AE
Corrective treatment:	Specified medication (to be listed on the concomitant medication chart) has been used as a countermeasure
Others:	Other actions, such as an operative procedure were required because of the AE

10.7 DEFINITION OF RELATIONSHIP TO STUDY DRUG

The categories for classifying the Investigator's opinion regarding the relationship of an AE to the study drug are listed below.

Definitely related:	An adverse event occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug should be clinically plausible. The event must be definite pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary and feasible.
Probably related:	An adverse event with a reasonable time sequence to administration, and which cannot be explained by concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal. Re-challenge information is not required to fulfill this definition. (Note: there are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists, (e.g. bone marrow suppression, fixed-drug eruptions, and tardive dyskinesias)
Possibly related:	An adverse event with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Not related:	An adverse event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying diseases provide plausible explanations.

10.8 DEFINITION OF OUTCOME AT TIME OF LAST OBSERVATION

The outcome at the time of last observation will be classified as:

- Resolved
- Resolved with Sequelae
- Ongoing
- Death

Death should only be entered as the outcome for an AE when the patient's death is probably or definitely related to the AE (Note: the causal relationship of the AE to the test article is not to be considered in making this decision). If more than one AE is possibly related to the patient's death, the outcome of death should be indicated for each such AE.

10.9 DOCUMENTATION AND ASSESSMENT OF ADVERSE EVENTS

The Investigator will monitor and/or ask about or evaluate AEs using non leading questions at each visit or evaluation. The occurrence of all AEs will be documented in the eCRF with the following information, where appropriate:

- AE name or term
- When the AE first occurred (start date)
- When the AE stopped (stop date), (or an indication of "ongoing")
- Severity of the AE
- Seriousness
- Actions taken
- Outcome
- Investigator opinion regarding the relationship of AE to the study drug(s)

Adverse events should be documented from the day 1 of study treatment until 30 days after the discontinuation of study treatment. After this period, investigators should only report SAEs that are attributed to prior study treatment. The AEs must be documented as soon and as completely as possible in the EDC. Follow-up information must be entered as soon as available. The causality assessment must be assigned by the Investigator.

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its

duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study, and actions taken.

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior investigational agent exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

10.10 EXPECTED AND UNEXPECTED ADVERSE EVENTS

Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure.

Unexpected adverse events are those not listed in the current Investigator Brochure (IB). This includes adverse events for which the specificity or severity is not consistent with the description in the IB. (For example, under this definition, hepatic necrosis would be unexpected if the IB only referred to elevated hepatic enzymes or hepatitis.)

10.11 ADDITIONAL ADVERSE EVENT CONSIDERATIONS

Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

Deaths

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

Death due to disease progression will not be considered a serious adverse event

Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When

reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

Hospitalizations for Medical or Surgical Procedures
Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

10.12 SERIOUS ADVERSE EVENT REPORTING

The Investigator must report all SAEs promptly to Dr. Michael Lilly (via the SIS Unit, HCC/MUSC) and RedHill Biopharma (via redhill107_safety@mwbconsulting.com) **within 24 hours of first becoming aware of the event**. This report will be accomplished by completing a study-specific SAE form available in the REDCap system. The submitted report will be transmitted simultaneously and immediately to RedHill Biopharma and MUSC.

For all **possibly related and unexpected** SAEs, sites will complete a Medwatch 3500A form and submit to MUSC via REDCap.

MUSC will be responsible for submission of SAE reports to the FDA, either on a routine basis or as expedited reports, as required by FDA regulations.

At the time of first notification of an SAE, the following information should be provided by the site, if available:

- Patient's study number and initials
- Treatment regimen including date of first & last dose of test article, as applicable
- Protocol description (and number, if assigned)
- Adverse event term and grade
- Date of occurrence of the event
- A brief description of the event, severity, outcome to date and any actions taken
- The seriousness criteria(on) that were met
- Concomitant medication at onset of the event
- Relevant past history information
- Relevant laboratory test findings
- Investigator's assessment of the relationship to test article

Any missing or additional relevant information concerning the SAE should be provided in a written follow-up report.

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the subject's removal from treatment. If the subject is permanently withdrawn from the study due to an SAE, this information must be included in either the initial or follow-up SAE Report Form.

The Investigator is required to comply with applicable regulations regarding the notification of his/her IRB or Ethics Committee. A copy of any SAE submissions to the IRB should also be submitted to MUSC.

11 MONITORING

The SIS Unit (Hollings Cancer Center CTO) will be responsible for the monitoring of study patient data and records. Each patient case will have their eligibility criteria audited prior to patient registration. The eligibility reviews will be conducted by the SIS Unit. The procedure for submitting registration documents for eligibility review is outlined in the operations manual for this study.

11.1 PROTOCOL DEVIATIONS

A Protocol Deviation is any variance from the protocol involving a subject or subjects that is not approved by the IRB prior to its initiation or implementation, and occurs when a member of the study team departs from the IRB-approved protocol in any way without the investigator first obtaining IRB approval. Any protocol deviation will be reported by the site within 10 days of notification. The procedure for submitting protocol deviations is outlined in the operations manual for this study.

11.2 SAFETY REPORTING

All toxicities, serious and non-serious, that meet the AE reporting criteria will be reported in the EDC. In addition, Serious Adverse Events have special reporting requirements.

11.3 DATA SAFETY MONITORING COMMITTEE (DSMC)

The Hollings Cancer Center DSMC will have oversight of the protocol. The DSMC will meet at a minimum on a semi-annual to discuss this investigator-initiated trial.

In addition, all protocol deviations and SAEs as defined above will be reviewed by the DSMC at monthly meetings. As new protocol deviations or serious adverse events are reported, the SIS Unit will review these reports for form completion and follow up if more information is warranted. The SIS Unit will forward the event report to the DSMC so that the information can be reviewed at the next available meeting. During the DSMC review, the DSMC can make recommendations for any further study action.

12 ADMINISTRATIVE STRUCTURE

This trial will be a multi-institution, investigator-initiated study. Potential sites will be identified by Dr. Michael Lilly as the lead Principal Investigator.

12.1 INVESTIGATOR REQUIREMENTS

Dr. Michael Lilly will be responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation, ensuring that the investigation is conducted in accordance with the general investigational plan and protocol, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug.

12.2 STUDY INITIATION

Centers participating in this study cannot begin enrollment until an initiation letter has been issued from the SIS Unit. Each center is required to participate in an initiation conference call.

Before the start of this study and the shipment of opaganib to a participating center, the following documents must be on file at the SIS Unit. Participating centers will be responsible for submitting the initiation documents to the SIS Unit.

These documents are required to be submitted by each participating center:

1. U.S. Food and Drug Administration (FDA) Form 1572, signed by the Principal Investigator at the participating center.
2. The names of any sub-investigators at the participating center must appear on this form. Investigators must also complete all regulatory documentation as required by local regulations. This includes any required human subjects training required by the site's local IRB.
3. Current curricula vitae and documentation of professional licensure of the Principal Investigator and co-Investigators listed on the 1572.
4. Resumes and human subject protections documentation (e.g. NIH, CITI) for all research personnel (e.g. study coordinators, data managers and other research personnel).
5. A signed and dated investigator brochure acceptance form.
6. A signed and dated protocol signature page.
7. Written documentation of IRB approval of protocol (identified by title, protocol version and date of approval) for each site.
8. IRB approved study informed consent and HIPAA consent form. HIPAA consent language can be included within the study informed consent. Please note that all informed consent forms should be reviewed and approved by the Sis Unit prior to submission to the site's designated IRB.
9. A signed Confidentiality Agreement.

10. A signed Clinical Trial Agreement for each site.
11. Laboratory certifications (CAP, CLIAs) and laboratory reference value ranges for each laboratory listed on the site's 1572.
12. Any other site specific forms as specified in the investigator-initiated multicenter manual.

12.3 STUDY COMPLETION

The following data and materials are required by MUSC before a study can be considered complete or terminated:

1. Copies of protocol amendments and IRB approval/notification, if appropriate.
2. Copies of the IRB final report, documentation of submission to the IRB.
3. A summary of the study prepared by the Principal Investigator (Study report, manuscript and/or abstract).
4. All regulatory documents (e.g., updated curriculum vitae for each Principal Investigator, updated U.S. FDA Form 1572 for each site).

12.4 RECORD RETENTION

The Sponsor-Investigator must ensure maintenance of all study records per applicable federal regulations and institutional requirements set forth in MUSC HRPP 5.2.

12.5 INFORMED CONSENT

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Informed consent will be obtained by personnel who are qualified by education, training and experience to perform the task. The Sponsor-Investigator will not use the services of study personnel for whom sanctions have been invoked where there has been scientific misconduct or fraud.

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical studies in which they volunteer to participate. The approved consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

12.6 INSTITUTIONAL REVIEW BOARD APPROVAL

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. In addition, any advertising materials, if applicable, must be approved by the IRB. The study

will be conducted in accordance with U.S. FDA, applicable national and local health authority, and IRB requirements.

The Principal Investigator at each site is responsible for keeping his/her IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case the IRB must be updated at least once a year. The Principal Investigator must also keep the IRB informed of any significant adverse events.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to serious adverse events that are not already identified in the Investigator Brochure and that are considered possibly or probably related to the study drug by the investigator. Some IRBs may have other specific adverse event requirements to which investigators are expected to adhere. If a center's IRB does not require the review of all external adverse events, a written policy or statement outlining the IRB's reporting requirements must be provided to the SIS Unit.

12.7 QUALITY ASSURANCE

Steps to assure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the Investigator and associated personnel prior to the study, remote monitoring visits by and ongoing data quality reviews of the EDC. Data will be reviewed for accuracy and completeness and any discrepancies will be resolved with the Investigator or designees as appropriate.

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APPENDIX A: SCHEDULE OF INTERVENTION

Procedure[j]	**Screening**[a]	**Day 1**[g]	**Day 29**	**Day 57**	**Day 85**	**Day 113**[d]	**Day 141** *and every 28 days post Day 113*	**Day 169** *and every 56 days post Day 113*	**End Rx**[m]	**Off-Study**[e, l, m]
Informed consent	x									
Vital signs, weight	x	x	x	x	x	x	x	x	x	
Performance status	x	x	x	x	x	x	x	x	x	
Concomitant medications	x	x	x	x	x	x	x	x	x	
Focused history & physical exam	x	x	x	x	x	x	x	x	x	
FACT-P	x	x				x			x	
Likert pain score, pain med use	x	x		x		x			x	
Pill count			x	x	x	x	x	x	x	
Mini-mental status exam	x	x		x		x			x	
Adverse event assessment			x	x	x	x	x	x	x	x
12-Lead ECG	x									
CBC + differential	x	x	x	x	x	x	x	x	x	
CMP	x	x	x	x	x	x	x	x	x	
PSA	x	x	x	x	x	x	x	x	x	
LDH	x	x	x	x	x	x	x	x	x	
CEA	x	x	x[i]	x[i]	x[i]	x[i]	x[i]	x[i]	x[i]	
PT, PTT, INR	x	x				x			x	
Plasma magnesium	x	x				x			x	
Urinalysis + Urine Protein + Urine Creatinine	x	x	x	x	x	x	x	x	x	
Research blood samples for Dr. S. Mehrotra's lab[h]	x			x		x			x	
Guardant 360 genomic profile[k]	x					x			x	
Radiographic Assessment [b]	x					x		x	x	

Tumor response assessment[f, n]						x		x	x	
Abiraterone/prednisone or enzalutamide[c]		x								
Opaganib		x								
Pharmacokinetics[o]	x		x							
Procedure	**Screening[a]**	**Day 1[g]**	**Day 29**	**Day 57**	**Day 85**	**Day 113[d]**	**Day 141** *and every 28 days post Day 113*	**Day 169** *and every 56 days post Day 113*	**End Rx[m]**	**Off-Study[e, l, m]**

Items highlighted yellow are considered research specific procedures

a. Procedures done at screening do not need to be repeated at week 1 unless there is more than 21 days (28 days for imaging studies) between screening and the start of treatment.
b. Radiographic tumor measurements. Investigator's choice of CT scans of chest/abdomen/pelvis with contrast, MRI scan of abdomen/pelvis with or without contrast, fluciclovine PET scan, technetium bone scan. Abdomen, pelvis CT imaging should be done with contrast unless there is a contraindication (allergy, renal insufficiency). MRI may be substituted for abdominal, pelvic CT if the physician wishes. The same imaging modality should be used throughout the study.
c. Subject should continue their previous dose of abiraterone (plus prednisone) or enzalutamide throughout the study unless new toxicity from those agents develops.
d. Subjects who show disease control at day 113 should continue on protocol treatment, with clinical assessments every 4 weeks, and radiographic assessment every 56 days.
e. Approximately 30 days after the last dose of opaganib, can be done via phone call
f. Tumor response should be assessed at day 113, and if there is disease control, every 56 days thereafter.
g. All times are +/- 5 days.
h. Research sample = 1 x up to 10 mL EDTA blood delivered to Dr. Shikar Mehrotra's lab.
i. Only if elevated at screening or Day 1.
j. Deviations from standard of care procedures will not be considered protocol deviations
k. When feasible, Guardant 360 genomic profile will be obtained as standard of care procedure
l. Patients will be followed for survival by clinic visit, review of medical record, and/or telephone call every 3 months from treatment discontinuation date for a maximum of 30 months after the last patient has been registered to the trial or until at least 80% of patients treated on study in both arms have died, whichever comes first.
m. Patients that come off study for PSA progression can re-initiate study therapy if their PSA comes back down below what would be considered progression within two months of treatment discontinuation – see section 8.1 for specific criteria for treatment re-initiation. Patients should still complete all End Rx procedures per the study calendar.
n. Patients are also assessed for PSA disease control at these time points; however, it is up to the treating investigator to determine whether they think the patient's PSA is progressing prior to Day 113.
o. PKs are optional – the patient must elect to participate

APPENDIX B: DEFINITION OF DISEASE CONTROL

Parameter	Disease Control	Not Disease Control
PSA level	**Less than a 25% increase in PSA level above baseline level (if no PSA decrease) or nadir level (if there is a PSA decrease)**	**25% or more increase in PSA level above baseline (if no PSA decrease) or nadir level (if there is a PSA decrease). The absolute level of PSA increase must be at least 2ng/mL.**
RECIST-evaluable lesions	• **Complete disappearance of lesion;** • **Less than a 30% increase in the shortest diameter (lymph nodes) or longest diameter (all other lesions)**	**30% or more increase in the shortest diameter (lymph nodes) or longest diameter (all other lesions)**
Bone scan	• **One or no new lesions compared with baseline scan** • **Two or more new lesions compared with baseline scan, but without two additional lesions on followup scan in 8 weeks**	**Two or more new lesions compared with baseline scan, confirmed with another scan showing two additional lesions in 8 weeks (2+2)**

Patients with *disease control* at an assessment point must demonstrate at least one of the findings in each category (PSA, RECIST, bone scan) under the disease control category. If the findings in the "not disease control" column are found for any category, the patient will have failed to show disease control, and should be removed from study. Criteria for disease control are from PCWG3 (Scher, et al., 2016).

APPENDIX C: LIST OF CYP SUBSTRATES AND INHIBITORS

List of commonly used drugs that are sensitive substrates of CYP450 1A2, 3A4, 2B6**,** 2C8, 2C9, 2C19 or 2D6, **or strong inhibitors or inducers of all major CYP450 isozymes**

This table was developed using information published on the University of Indiana, School of Medicine, Department of Medicine, Division of Clinical Pharmacology website http://www.medicine.iupui.edu/clinpharm/ddis/table.asp. This list in not inclusive; therefore, please refer to the FDA-approved package insert to review drug interactions for medications not listed in this appendix.

In determining the half-life, where a time range was provided, the upper end of the range was used to provide the largest margin of safety. Additionally, for a few drugs, half-lives were provided for "fast" and "slow" metabolizers. In those cases, the longer value is given below.

Drug	**Half-life (hr)**	**5 x half-life (hr)**	**Reference**
alprazolam	12	60	Goodman & Gilman 11th edition
amiodarone	600	3000	Goodman & Gilman 11th edition
amitriptyline	21	105	Goodman & Gilman 11th edition
amlodipine	39	195	Goodman & Gilman 11th edition
aripiprazole	47	235	Goodman & Gilman 11th edition
astemizole	24	120	http://en.wikipedia.org/wiki/ Astemizole (accessed 09/03/2010)
atorvastatin	19.5	97.5	Goodman & Gilman 11th edition
bupropion	11	55	Goodman & Gilman 11th edition
buspirone	2.4	12	Goodman & Gilman 11th edition
carbamazepine	15	75	Goodman & Gilman 11th edition
celecoxib	11.2	56	Goodman & Gilman 11th edition
chlorpheniramine	20	100	Goodman & Gilman 11th edition
cimetidine	2	10	Goodman & Gilman 11th edition
cisapride	10	50	http://en.wikipedia.org/wiki/ Cisapride (accessed 09/03/2010)
clarithromycin	3.3	16.5	Goodman & Gilman 11th edition

clomipramine	50	250	http://en.wikipedia.org/wiki/ Clomipramine (accessed 09/03/2010)
clopidogrel	8	40	http://en.wikipedia.org/wiki/ Clopidogrel (accessed 09/03/2010)
clozapine	12	60	Goodman & Gilman 11th edition
codeine	2.9	14.5	Goodman & Gilman 11th edition
cyclobenzamideprine	18	90	http://en.wikipedia.org/wiki/ Cyclobenzamideprine (accessed 09/03/2010)
cyclophosphamide	7.5	37.5	Goodman & Gilman 11th edition
cyclosporine	10.7	53.5	Goodman & Gilman 11th edition
dabrafenib	8	40	http://online.lexi.com Dabrafenib (accessed 1/6/20)
desipramine	23	115	http://en.wikipedia.org/wiki/ Desipramine (accessed 09/03/2010)
dextromethorphan	29.5	147.5	Goodman & Gilman 11th edition
diazepam	43	215	Goodman & Gilman 11th edition
diclofenac	1.1	5.5	Goodman & Gilman 11th edition
diltiazem	4.4	22	Goodman & Gilman 11th edition
doxepin	18	90	Goodman & Gilman 11th edition
duloxetine	12.1	60.5	http://en.wikipedia.org/wiki/ Duloxetine (accessed 09/03/2010)
efavirenz	76	380	http://online.lexi.com Efavirenz (accessed 1/6/20)
erythromycin	1.6	8	Goodman & Gilman 11th edition
felodipine	14	70	Goodman & Gilman 11th edition
flecainide	11	55	Goodman & Gilman 11th edition
fluconazole	32	160	Goodman & Gilman 11th edition
fluoxetine	53	265	Goodman & Gilman 11th edition
fluvastatin	2.5	12.5	http://en.wikipedia.org/wiki/ Fluvastatin (accessed 09/03/2010)

fluvoxamine	15.6	78	http://en.wikipedia.org/wiki/ Fluvoxamine (accessed 09/03/2010)
glipizide	3.4	17	Goodman & Gilman 11th edition
haloperidol	18	90	Goodman & Gilman 11th edition
ibuprofen	2	10	Goodman & Gilman 11th edition
ifosfamide	15	75	http://online.lexi.com Ifosfamide (accessed 1/6/20)
imatinib	40	200	http://en.wikipedia.org/wiki/ Imatinib (accessed 09/03/2010)
imipramine	16	80	Goodman & Gilman 11th edition
indinavir	1.8	9	http://en.wikipedia.org/wiki/Indinavir (accessed 09/03/2010)
indomethacin	2.4	12	Goodman & Gilman 11th edition
irbesartan	13	65	Goodman & Gilman 11th edition
isoniazid	3.1	15.5	Goodman & Gilman 11th edition
itraconazole	21	105	Goodman & Gilman 11th edition
ketoconazole	3.3	16.5	Goodman & Gilman 11th edition
lansoprazole	0.9	4.5	Goodman & Gilman 11th edition
losartan	5.4	27	Goodman & Gilman 11th edition
lovastatin	4	20	Goodman & Gilman 11th edition
meperidine	4	20	http://online.lexi.com Meperidine (accessed 1/6/20)
methadone	27	135	Goodman & Gilman 11th edition
mexiletine	12	60	http://en.wikipedia.org/wiki/Mexiletine (accessed 09/03/2010)
mibefradil	25	125	http://www.drugs.com/mmx/ mibefradil-dihydrochloride.html (accessed 09/03/2010)
midazolam	1.9	9.5	Goodman & Gilman 11th edition
nambutone	23	115	http://www.drugbank.ca/drugs/DB00461 (accessed 09/03/2010)
naproxen	14	70	Goodman & Gilman 11th edition

nefazodone	4	20	http://en.wikipedia.org/wiki/ Nefazodone (accessed 09/03/2010)
nelfinavir	5	25	Goodman & Gilman 11th edition
nevirapine	45	225	http://online.lexi.com Nevirapine (accessed 1/6/20)
nifedipine	1.8	9	Goodman & Gilman 11th edition
nisoldipine	12	60	http://en.wikipedia.org/wiki/ Nisoldipine (accessed 09/03/2010)
nitrendipine	24	120	http://adisonline.com/drugs/Abstract/1987/33020/Nitrendipine__A_Review_of_its_Pharmacodynamic_and.3.aspx (accessed 09/03/2010)
olanzapine	33.1	165.5	Goodman & Gilman 11th edition
olodaterol	7.5	37.5	http://online.lexi.com Olodaterol (accessed 1/6/20)
omeprazole	1.2	6	http://en.wikipedia.org/wiki/ Omeprazole (accessed 09/03/2010)
ondansetron	3.5	17.5	Goodman & Gilman 11th edition
paclitaxel	20	100	http://online.lexi.com Paclitaxel (accessed 1/6/20)
pantoprazole	1	5	http://en.wikipedia.org/wiki/ Pantoprazole (accessed 09/03/2010)
paroxetine	17	85	Goodman & Gilman 11th edition
phenobarbital	99	495	Goodman & Gilman 11th edition
phenobarbitone	120	600	http://www.webhealthcentre.com/drugix/Phenobarbitone_di0110.aspx (accessed 09/03/2010)
phenytoin	24	120	Goodman & Gilman 11th edition
pimozide	72	360	http://en.wikipedia.org/wiki/ Pimozide (accessed 09/03/2010)
pioglitazone	11	55	Goodman & Gilman 11th edition
piroxicam	86	430	http://en.wikipedia.org/wiki/ Piroxicam (accessed 09/03/2010)

ponatinib	24	120	http://online.lexi.com Pontini (accessed 1/6/20)
progesterone	55.1	275.5	http://en.wikipedia.org/wiki/ Progesterone (accessed 09/03/2010)
propafenone	10	50	http://en.wikipedia.org/wiki/ Propafenone (accessed 09/03/2010)
quinidine	6.2	31	Goodman & Gilman 11th edition
quinine	18	90	Goodman & Gilman 11th edition
rabeprazole	1.5	7.5	http://en.wikipedia.org/wiki/ Rabeprazole (accessed 09/03/2010)
repaglinide	1	5	http://online.lexi.com Repaglinide (accessed 1/6/20)
rifabutin	62	310	http://en.wikipedia.org/wiki/ Rifabutin (accessed 09/03/2010)
rifampin	3.5	17.5	Goodman & Gilman 11th edition
riluzole	14	70	Goodman & Gilman 11th edition
risperidone	3.2	16	Goodman & Gilman 11th edition
ritonavir	5	25	Goodman & Gilman 11th edition
rosiglitazone	4	20	Goodman & Gilman 11th edition
saquinavir	15	75	http://en.wikipedia.org/wiki/ Saquinavir (accessed 09/03/2010)
secobarbital	40	200	http://en.wikipedia.org/wiki/ Secobarbital (accessed 09/03/2010)
selegiline	10	50	http://online.lexi.com Selegiline (accessed 1/6/20)
selexipag	2.5	12.5	http://online.lexi.com Selexipag (accessed 1/6/20)
sildenafil	2.4	12	Goodman & Gilman 11th edition
simvastatin	3	15	Goodman & Gilman 11th edition
S-metoprolol	3.2	16	Goodman & Gilman 11th edition
sorafenib	48	240	http://online.lexi.com Sorafenib (accessed 1/6/20)
sulfamethoxazole	10.1	50.5	Goodman & Gilman 11th edition

tacrine	4	20	http://en.wikipedia.org/wiki/ Tacrine (accessed 09/03/2010)
tacrolimus (FK506)	12	60	Goodman & Gilman 11th edition
tamoxifen	264	1320	Goodman & Gilman 11th edition
telithromycin	23	115	Goodman & Gilman 11th edition
theophylline	9	45	Goodman & Gilman 11th edition
thioridazine	20	100	http://en.wikipedia.org/wiki/ Thioridazine (accessed 09/03/2010)
ticlopidine	120	600	http://en.wikipedia.org/wiki/ Ticlopidine (accessed 09/03/2010)
timolol	2.7	13.5	Goodman & Gilman 11th edition
tizanidine	2.5	12.5	http://en.wikipedia.org/wiki/ Tizanidine (accessed 09/03/2010)
tolbutamide	5.9	29.5	Goodman & Gilman 11th edition
torsemide	8	40	http://en.wikipedia.org/wiki/ Torsemide (accessed 09/03/2010)
tramadol	7.5	37.5	Goodman & Gilman 11th edition
trazodone	5.9	29.5	Goodman & Gilman 11th edition
triazolam	5.5	27.5	http://en.wikipedia.org/wiki/ Triazolam (accessed 09/03/2010)
troglitazone	34	170	http://en.wikipedia.org/wiki/ Troglitazone (accessed 09/03/2010)
troleandomycin	4.2	21	Roger G. Finch, 2003 http://books.google.com/books?id=PQW4kz6rQDEC&printsec=frontcover&dq=inauthor:%22Roger+G.+Finch%22&hl=en&ei=3lqGTNLJIcT48Aau652eAg&sa=X&oi=book_result&ct=result&resnum=2&ved=0CDIQ6AEwAQ#v=onepage&q&f=false
velpatasvir	15	75	http://online.lexi.com Velpatasvir (accessed 1/6/20)
venlafaxine	4.9	24.5	Goodman & Gilman 11th edition
verapamil	4	20	Goodman & Gilman 11th edition

vincristine	22.6	113	Goodman & Gilman 11th edition
warfarin	37	185	Goodman & Gilman 11th edition
zileuton	2.5	12.5	http://en.wikipedia.org/wiki/ Zileuton (accessed 09/03/2010)
zolmitriptan	3	15	http://en.wikipedia.org/wiki/ Zolmitriptan (accessed 09/03/2010)

APPENDIX D: ECOG PERFORMANCE STATUS SCALE

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

APPENDIX E. STUDY SCHEMATIC DIAGRAM