A PHASE 2 STUDY OF IBRUTINIB AS NEOADJUVANT THERAPY IN PATIENTS WITH LOCALIZED PROSTATE CANCER

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Abstract

Title	A phase 2 study of ibrutinib as neoadjuvant therapy in patients with localized prostate cancer
Patient population	Prostate cancer patients scheduled for radical prostatectomy (RP)
Rationale for Study	30-40% of patients who undergo RP with curative intent for their localized prostate cancer experience relapse of their disease. Thus, improved therapeutic approaches are needed in this patient population. Enhancing the patient's anti-tumor immune response prior to surgery may improve long-term outcomes following RP. Tumor-infiltrating B cells are increased in prostate cancer tissue, and high intra-tumoral density of B cells correlate with higher stage of disease and greater potential for recurrence or progression (Woo JR et al, 2014). Unpublished data from UCSF's laboratory have shown that T cells within the prostate that are associated with B cell aggregates lack T cell activation markers. Recently, preclinical studies showed that ibrutinib, a potent inhibitor of Bruton's tyrosine kinase (BTK) but also an inhibitor of interleukin-2 inducible T-cell kinase (ITK) enhances T-cell mediated antitumor immunity when combined with PD-L1 blockade (Sagiv-Barfi I et al, 2015). Btk has also been found to be overexpressed in prostate cancer cells, which correlates with cancer grade, and the knockdown of Btk expression inhibits the growth of prostate cancer cells in vitro (Guo W et al, 2014). Therefore, inhibition of Btk may also have direct anti-tumor activity in prostate cancer. In this study, the immunomodulatory and cytotoxic effects of ibrutinib will be studied in patients with localized prostate cancer in the neoadjuvant setting.
Primary Objective	• To assess safety in patients with localized prostate cancer. • To characterize B and T cell infiltration within prostate tissue of men with localized prostate cancer treated with neoadjuvant ibrutinib, and to compare B and T cell infiltration to a reference population of untreated patients who underwent RP.
Secondary Objectives	• To characterize changes in the frequency and number of circulating B and T cells induced by neoadjuvant ibrutinib in patients with localized prostate cancer. • To determine the cytotoxic effect and clinical benefit (pathologic T0 at time of RP) of neoadjuvant ibrutinib in men with localized prostate cancer.
Exploratory Objectives	• To examine Btk expression in prostate tumor cells and tumor-infiltrating B cells. • To determine the impact of neoadjuvant ibrutinib on PD-L1 expression in prostate cancer cells and tumor-infiltrating lymphocytes (TILs). • To determine the effects of neoadjuvant ibrutinib on T and B cell repertoire within the tumor and blood.

Study Design	This is a phase 2 study of neoadjuvant ibrutinib in men with localized prostate cancer undergoing RP as their initial locally directed therapy with curative intent. In the safety lead-in phase, a cohort of 6 patients will be treated with ibrutinib 840 mg/d x 4 weeks to assess safety and adverse events (AEs). If no more than 2 out of 6 patients experience dose limiting toxicities (DLT), the study will continue accruing. DLTs will be assessed during the safety lead-in phase only, during treatment with ibrutinib and the period prior to RP. To assess the immune response following neoadjuvant treatment, tissue from RP specimen will be compared to tissue from core biopsy specimen obtained prior to treatment, with each subject serving as his own control. Immune infiltration will also be compared to a reference cohort of 12 patients who had undergone RP, matched to the study population using the UCSF CAPRA-S score.
Number of patients	Three patients were enrolled at UCSF in an 840 mg/d x 2 weeks cohort; no DLTs occurred. At WUSM, a safety lead-in of 6 patients will be accrued at the 840 mg/d x 4 week dose level. In the event that no DLTs are encountered, an additional 18 patients will be enrolled for a total of 24 patients at the 840 mg/d x 4 week dose level. A full safety assessment will be carried out after the first 10 patients have completed the phase 2 study (6 in the safety lead-in + 4), and accrual will be suspended if 3 or more of these 10 patients experience grade 3 or 4 treatment-related toxicity. If RP is delayed over 12 days after the last dose of ibrutinib therapy (i.e. from scheduling delay of RP), a replacement patient will be accrued. The maximum number of allowed replacement patients is 4 (see Section 12.4).
Duration of Therapy	All patients will receive ibrutinib for 4 weeks prior to RP. RP will be performed 7 to 12 days after the last dose of ibrutinib.
Duration of Follow up	All patients will be followed for 4 weeks after RP.
Duration of study	The study will conclude when the last patient has completed his 4–week follow-up after RP. The anticipated duration of study is 18-24 months. All treatment related adverse events will be followed until resolution or stabilization to grade $\leq$2.
Study Drugs	Ibrutinib, also known as PCI-32765 and marketed under the name Imbruvica, is a small molecule irreversible Btk inhibitor that has shown clinical efficacy in B cell malignancies by blocking BCR signaling. Btk inhibitors may prove to be efficacious for other cancers where B cells and BTK signaling contribute necessary mechanisms for tumor growth, including immunomodulatory mechanisms. The dose of 840 mg x 4 weeks has been established as safe in solid tumors. The dose level for the phase 2 study is 840 mg/d x 4 weeks. In the event that DLTs are encountered in 2 or more of the initial 6 patients, dose de-escalation with cohort of 6 per dose level are as follows: Level -1: 840mg x 2 weeks Level -2: 560mg x 2 weeks

Safety Assessments	Safety will be assessed by reviewing adverse events (AEs), laboratory evaluations, and by physical examination. The NCI CTCAE v4.03 will be used. All AEs and serious AEs (SAEs) that occur on study drug or within 30 days after the last dose of study drug, will be recorded on case report forms (CRFs) from enrollment through 4 weeks post-surgery. The study will be halted if 4 of the first 4, or 5 of the first 9, or 6 of the first 14, or 7 of the first 18, or 8 of the first 23, or if the 9th non-hematological toxicity is observed before the last patient has completed the trial. Accrual will be stopped and the event will be reviewed by the Data Safety and Monitoring Board if a grade 5 non-hematological toxicity is observed.
Efficacy Assessments	For the primary endpoints, toxicities will be assessed according to NCI CTCAE v.4.03 and changes in B cell infiltration within prostate tissue between core biopsy and RP specimen will be quantified using immunohistochemistry (IHC). A positive result is considered to be $\geq$2 fold decrease in the number of B cell infiltration. For the secondary endpoints, immune subsets including B and T cells will be analyzed in the blood via flow cytometry, and in the core biopsy and RP specimens via IHC.
Unique Aspects of this Study	This is the first study to evaluate the safety of ibrutinib and its effect on B cell infiltration in the neoadjuvant setting for patients with localized prostate cancer. The secondary and exploratory objectives will enhance our understanding of the immunomodulatory and cytotoxic effects of Btk inhibition in prostate cancer. Findings may justify further exploration of ibrutinib in prostate cancer, including combinational therapy in advanced prostate cancer.

List of Abbreviations

5-HT	5-hydroxytryptamine (serotonin)
ADL	activity of daily living
ADT	androgen deprivation therapy
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	area under the curve
B-CLL	B-cell chronic lymphocytic leukemia
BCR	B-cell receptor
Breg	B regulatory cells
BSA	body surface area
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
CAPRA	Cancer of the Prostate Risk Assessment
CBC	complete blood cell (count)
CHR	Committee on Human Research (UCSF IRB)
CpG	cytosine-phosphate-guanine
CNS	central nervous system
CR	complete response
CRC	Clinical Research Coordinator
CrCl	creatinine clearance
CRF	case report form
CSF	cerebral spinal fluid
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTL	cytotoxic T lymphocyte
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTMS	Clinical Trial Management System
CYP	cytochrome P450
DFS	disease-free survival
DL	dose level
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
D2	dopamine receptor D2
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
EC_{50}	median effective concentration
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FCBP	female of childbearing potential
FDA	Food and Drug Administration
FIH	first-in-human
FL	follicular lymphoma
GCP	Good Clinical Practice
g/dL	gram per deciliter
Hb	Hemoglobin
HBcAb	Hepatitis B core antibody
HBeAg	Hepatitis B "e" antigen
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen

List of Abbreviations

HBV	hepatitis B virus
HCT	Hematocrit
HCV	hepatitis C virus
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HED	human equivalent dose
HGB	Hemoglobin
HIV	human immunodeficiency virus
IB	investigator's brochure
IC_{50}	concentration that inhibits a process by 50%
ICH	International Conference on Harmonization
IHC	immunohistochemistry
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
IV	intravenous
LDH	lactate dehydrogenase
LFT	liver function test
LHRH	luteinizing hormone releasing hormone
LLN	lower limit of normal
LMWH	low molecular weight heparin
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute
mL	milliliter
MM	multiple myeloma
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
nM	nanomolar
NOAEL	no-observed-adverse-effect level
NSCLC	non-small cell lung carcinoma
ORR	overall response rate
OTC	over the counter
PBMC	peripheral blood mononuclear cells
PD	disease progression
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PK	pharmacokinetics
Plt	platelet (count)
PML	progressive multifocal encephalopathy
PO	*Per os* (by mouth, orally)
PR	partial response
RP	radical prostatectomy
PRC	Protocol Review Committee (UCSF)
PSA	prostate specific antigen
pT0	pathologic complete response
PT	prothrombin time
PTT	partial thromboplastin time
QOL	Quality of Life
QTc	QT interval corrected for heart rate
RBC	red blood cell (count)

List of Abbreviations

SAE	serious adverse events
SD	stable disease
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIP-T	sipuleucel-T
SLL	small lymphocytic lymphoma
SJS	Stevens-Johnson Syndrome
$t_{1/2}$	half-life
TCR	T-cell receptor
TILs	tumor infiltrating lymphocytes
T_{max}	time to maximum concentration
TPC	Tissue Procurement Core
ULN	upper limit of normal
µL	microliter
WBC	white blood cell (count)
WM	Waldenstrom's macroglobulinemia

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

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1 INTRODUCTION

1.1 Background on Indication

Prostate cancer is the most common malignancy and the second leading cause of cancer-related death in men in Western countries. In the United States, 233,000 new cases were diagnosed and nearly 30,000 men died from prostate cancer in 2014 (Siegel R et al, 2014). While surgery and radiotherapy are potentially curative treatments in patients with localized prostate cancer, treatment failure rates reach 35-40% (Han M et al, 2001; Kuban DA et al, 2003). Neoadjuvant androgen deprivation therapy (ADT) in combination with surgery or radiation have been investigated to reduce treatment failure rates (Goldenberg SL et al, 1996; Van Poppel H et al, 1995). While these studies have shown that neoadjuvant ADT decreases the proportion of patients with positive margins at surgery, neoadjuvant ADT has not translated into significant benefit in meaningful clinical endpoints such as progression-free survival (PFS) or overall survival (Scolieri MJ et al, 2000). Neoadjuvant therapy thus remains an investigational approach.

The clinical efficacy of immunotherapies in the treatment of advanced human malignancies, and the positive impact on survival of sipuleucel-T (Sip-T) in men with advanced prostate cancer (Kantoff PW et al, 2010) has led to the investigation of the role of immunotherapy in the neoadjuvant setting. In a recently completed phase II study of neoadjuvant Sip-T for localized prostate cancer (Fong L et al, 2014), patients received 3 infusions of Sip-T at 2 week intervals beginning 6-7 weeks prior to RP. Neoadjuvant Sip-T was safe and tolerable, and did not impact surgery. Importantly, significant increases in CD3+ and CD4+ T cells were observed in the prostatectomy specimens, suggesting that a tumor-specific immune response can be induced via this approach.

While cancer immunotherapies have largely been focused at inducing T cell mediated anti-cancer immune response, with strategies including cancer vaccines and immune checkpoint blockade, B cells have recently been increasingly appreciated to play an inhibitory role on antitumor immune responses. B regulatory cells (Bregs) secrete the anti-inflammatory cytokine IL-10 and inhibit cytotoxic T lymphocyte (CTL) activity. In addition, a significant role for B cells as promoters of tumorigenesis is their ability to inhibit T_H1 and cytotoxic CD8+ T cell mediated anti-tumor immunity (Gunderson AJ et al, 2013). Targeting B cells in cancers in which B cells contribute necessary mechanisms for tumor growth may therefore prove to be a tractable strategy.

1.2 Ibrutinib

Ibrutinib is a first-in-class, orally administered, potent inhibitor of Bruton's tyrosine kinase (BTK), a mediator of critical B-cell signaling pathways implicated in the pathogenesis of B-cell malignancies. Ibrutinib (IMBRUVICA®) is approved for the treatment of (1) mantle cell lymphoma (MCL) in patients who have received at least one prior therapy, (2) chronic lymphocytic leukemia (CLL) in patients who have received at least one prior therapy, (3) CLL in patients with 17p deletion, (4) Waldenström's Macroglobulinemia, (5) marginal zone lymphoma (MZL) in patients who required systemic therapy and have received at least one prior anti-CD20-based therapy, and (6) adult patients with chronic GVHD after failure of one or more lines of systemic therapy. Ibrutinib covalently binds to the cysteine-481 amino acid of BTK and inhibits various processes, including ERK signaling, NF-κB DNA binding, cytosine-phosphate-guanine (CpG)-mediated CLL-cell proliferation, and tumor-cell migration. At concentrations relevant to exposure levels in patients, ibrutinib demonstrates remarkable selectivity in the inhibition of BCR signaling over TCR signaling.

1.2.1 Nonclinical studies: Ibrutinib

1.2.1.1 Pharmacokinetics and Metabolism

Following oral administration of ibrutinib at doses ranging from 420 to 840 mg/day, exposure to ibrutinib increased proportionally with substantial intersubject variability. The mean terminal plasma elimination half-life ($t_{1/2}$) of ibrutinib ranged from 4 to 6 hours, with a median time to maximum plasma concentration (T_{max}) of 1 to 2 hours. Despite the doubling in mean systemic exposure when dosed with food, the favorable safety profile of ibrutinib allows dosing with or without food. Ibrutinib is extensively metabolized primarily by cytochrome P450 (CYP) 3A4-mediated metabolic pathways. The on-target effects of metabolite PCI-45227 are not considered clinically relevant. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure implying non-clinically relevant accumulation. About 8% of ibrutinib is excreted in the urine. Ibrutinib exposure is not altered in patients with creatinine clearance (CrCl) > 30 mL/min. Patients with severe renal impairment or patients on dialysis have not been studied. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. A higher proportion of Grade 3 or higher adverse reactions were reported in patients with B-cell malignancies (CLL, MCL and WM) with mild hepatic impairment based on NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction compared to patients with normal hepatic function.

For the most up to date and comprehensive pharmacokinetics (PK) and product metabolism information regarding ibrutinib, please refer to the current IB.

1.2.1.2 Toxicology

In safety pharmacology assessments, no treatment-related effects were observed in the central nervous system or respiratory system in rats at any dose tested. Further, no treatment-related corrected QT interval (QTc) prolongation effect was observed at any tested dose in a cardiovascular study using telemetry-monitored dogs.

Based on data from rat and dog including general toxicity studies up to 13 weeks duration, the greatest potential for human toxicity with ibrutinib is predicted to be in lymphoid tissues (lymphoid depletion) and the gastrointestinal tract (soft feces/diarrhea with or without inflammation). Additional toxicity findings seen in only one species with no observed human correlate in clinical studies to date include pancreatic acinar cell atrophy (rat), minimally decreased trabecular and cortical bone (rat) and corneal dystrophy (dog).

In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. In a rat embryo-fetal toxicity study ibrutinib administration was associated with fetal loss and malformations (teratogenicity) at ibrutinib doses that result in approximately 6 times and 14 times the exposure (AUC) in patients administered the dose of 560 mg daily, respectively.

1.2.1.3 Pharmacology

Ibrutinib was evaluated in vitro for its ability to inhibit purified BTK and selected members of the closely related Tec and Src/Ab1 family kinases. The concentration that inhibits kinase activity by 50% (IC50) for BTK and other kinases are listed in Table 1.2.1. With only a few exceptions, a 10-fold or greater selectivity was demonstrated for BTK relative to the off-target kinases.

Table 1.2.1 Median IC_{50} Values of Ibrutinib toward Selected Tec and Src/Ab1 Family Kinases

Kinase	Median IC_{50} (nM)	Selectivity for BTK
Btk*	0.39	1.0
ErbB4/HER4*	0.64	1.6
Blk*	0.94	2.4
Bmx/Etk*	1.10	2.8
Fgr	2.86	7.3
Txk*	2.87	7.4
Lck	3.49	9.0
Yes/YES1	3.94	10
Tec*	5.49	14
Csk	6.17	16
EGFR*	7.80	20
Brk	10.10	26
Itk*	11.70	30
Hck	16.98	44
ErbB2/HER2*	21.57	55
JAK3*	21.90	56

*Kinases labeled with an asterisk (*) have a cysteine in the active site representing a possible target for covalent binding with ibrutinib.

A cellular signal transduction assay conducted to investigate ibrutinib inhibition of BCR signaling showed concentration-dependent inhibition of autophosphorylation of BTK by ibrutinib (IC_{50} = 11nM), phosphorylation of the physiological substrate of BTK, PLCγ (IC_{50} = 29nM), and phosphorylation of a further downstream kinase, ERK (IC_{50} = 13nM). The phosphorylation of Syk, which functions upstream or in parallel to BTK, was not affected (Honigberg et al, 2010).

Ibrutinib inhibited the proliferation of DLBCL patient derived cell lines with a median effective concentration (EC_{50}) of 1 or 2nM. Ibrutinib reduced proliferation of primary CLL cells at concentrations of 500nM and 1000nM. Nonclinical primary pharmacodynamics studies have shown that orally administered ibrutinib inhibits tumor growth in human tumor xenograft murine models. Maximum ibrutinib growth inhibition of OCI-Ly10 xenograft tumors (81% to 140%) occurred with a once-daily oral gavage dose of 12mg/kg/day.

Based on preclinical data, the blockade of BCR signaling pathway by ibrutinib in CLL has 2 major effects: (1) direct induction of apoptosis and (2) inhibition of cell homing and migration to chemokines and subsequent adhesion to cellular substrates (Herman et al, 2011; de Rooij et al, 2012). In preclinical models, ibrutinib caused a transient early lymphocytosis and profoundly inhibited CLL progression, as assessed by weight, development of hepatomegaly, and survival. Similarly, in human subjects with CLL, ibrutinib clinical activity (resolution of lymphadenopathy and/or organomegaly) was accompanied by a transient increase in lymphocyte counts, which presumably is due to an egress of tissue-resident CLL cells into the blood.

No treatment-related effects were observed in rat in vivo central nervous system (CNS) and respiratory safety pharmacology studies. No treatment-related QT interval corrected for heart rate (QTc) prolongation effect was observed in a cardiovascular study in telemetry-monitored dogs. However, oral administration of ibrutinib in dogs at dose levels of 24mg/kg or more was associated with increased PR interval, lowered heart rate and QTc shortening, with a no-observed-adverse-effect level (NOAEL) of 24 mg/kg/day.

1.2.2 Clinical studies: Ibrutinib

In healthy subjects and in patients with B-cell malignancies, ibrutinib is readily absorbed, with a median time to maximum concentration (T_{max}) of 1 to 2 hours and half-life of 4 to 6 hours. Exposure increases proportionally with dose. Ibrutinib is primarily metabolized by cytochrome P450, CYP3A. Strong and moderate inhibitors of CYP3A, as well as strong CYP3A inducers should be avoided (See Section 7.6 for restricted medications). Ibrutinib is rapidly cleared mainly in the form of metabolites, and is eliminated primarily via feces with ~80% recovered mostly within 2 days.

In the current clinical development program, ibrutinib is being evaluated in over 26 ongoing and 9 completed company-sponsored clinical studies in healthy volunteers and in subjects with recurrent B-cell lymphomas, including chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), multiple myeloma (MM), Waldenstrom’s macroglobulinemia (WM), and marginal zone lymphoma (MZL). As of data cutoff date of April 6, 2014, safety data from nonrandomized studies are available for 1,204 subjects treated with single agent ibrutinib (1,061 subjects plus 143 healthy volunteers) and for 136 subjects treated with ibrutinib combinations with immunotherapy and/or chemotherapy. In addition, one randomized comparator-controlled phase 3 study of ibrutinib monotherapy in subjects with CLL/SLL has undergone primary analysis in which 195 subjects received ibrutinib and 191 subjects received ofatumumab. Seven additional phase 3 trials (1115, CLL3001, CLL3002, MCL3001, MCL3002, DBL3001 and FLR3001) in subjects with CLL/SLL or non-Hodgkin's lymphoma (NHL) are ongoing.

The clinical benefit of ibrutinib was first demonstrated in a phase 1 dose-escalation study of ibrutinib in subjects with recurrent B-cell lymphomas with overall response rates (ORRs) ranging from 85.7% in subjects with CLL/SLL and MCL to 33.3% in subjects with DLBCL. These findings were further demonstrated in subsequent phase 2 studies in subjects with previously treated MCL or CLL/SLL, and a randomized, comparator-controlled phase 3 pivotal study in subjects with previously treated CLL/SLL. Activity was also demonstrated in other histologies (FL, DLBCL, WM, FL, MZL, MM) and with combination therapy (fludarabine, cyclophosphamide, rituximab; bendamustine + rituximab; and ofatumumab).

In pooled safety data for subjects treated with ibrutinib monotherapy in 11 nonrandomized studies (1102, 1117, 1112 [crossover only], 1104, MCL2001, MCL4001, 1106, 1111, FLR2002, 04753, and JPN-101) with a median duration of treatment of 5.1 months (range 0.0 to 30.3 months), the most frequently reported treatment-emergent adverse events in >10% of subjects were diarrhea (35.9%), fatigue (28.6%), nausea (20.2%), cough (17.5%), and anemia (15.2%). The most frequently reported treatment-emergent adverse events related to ibrutinib in >5% of subjects were diarrhea (25.5%), fatigue (16.0%), nausea (11.7%), neutropenia (9.1%), and thrombocytopenia (8.2%). The most common treatment-emergent grade 3 or 4 AEs in >2% of subjects were neutropenia (10.7%), thrombocytopenia (6.2%), pneumonia (5.7%), anemia (5.5%), fatigue (2.9%), hypertension (2.7%) and atrial fibrillation (2.6%). Among the 1,061 subjects in the pooled analysis of monotherapy studies, 9.4% discontinued ibrutinib therapy due to an adverse event. The most frequently reported AEs leading to treatment discontinuation included infection (e.g., pneumonia [0.9%] and septic shock [0.4%]), disease progression (0.6%), acute renal failure (0.4%), respiratory failure (0.4%), and thrombocytopenia (0.4%). No subjects discontinued ibrutinib treatment due to diarrhea. Fatal AEs were reported in 9.9% of subjects. The most frequently reported fatal AEs included progressive disease, pneumonia (1.2%), sepsis (0.6%), respiratory failure (0.5%), cardiac arrest (0.4%), and plasma cell myeloma (0.4%).

Safety data are available for one phase 3 randomized comparator controlled (ibrutinib vs. ofatumumab) study of ibrutinib monotherapy in subjects with CLL/SLL (ibrutinib: 195 subjects, ofatumumab: 191 subjects). As of Nov 6, 2013 data cutoff, the median exposure of ibrutinib was 8.6 months (range: 0.2 to 16.1). The most frequent treatment-emergent adverse events in >10% subjects were diarrhea (47.7%), fatigue (27.7%), nausea (26.2%), pyrexia (23.6%), anemia (22.6%), and neutropenia (21.5%). The most common treatment-emergent adverse events in >5% subjects were diarrhea (32.8%), nausea (15.9%), neutropenia (13.3%), arthralgia (11.3%), petechiae (11.3%), and fatigue (9.7%). The most common treatment-emergent grade 3 or 4 AEs in >2% subjects were neutropenia (16.4%), pneumonia (6.7%), thrombocytopenia (5.6%), and anemia (4.6%). In this study, 8.2% of subjects receiving ibrutinib discontinued study treatment due to an adverse event. The most frequently reported AE leading to study discontinuation in the ibrutinib arm was pneumonia. Fatal AEs were reported for 6.2% of subjects receiving ibrutinib. The most common AEs leading to death were pneumonia (1.5%), CLL disease progression (1.0%), and sepsis (1.0%).

In pooled safety data for 143 healthy subjects receiving ibrutinib monotherapy in 7 clinical studies (CLL1001, CLL1002, CLL 1004, CLL 1006, CLL 1008, CLL 1010, and CLL 10113), treatment-emergent adverse events were reported by 26.6% of subjects. The most frequently reported AEs by preferred term were headache (8.4%), diarrhea (6.3%), and abdominal pain (3.5%). No treatment-emergent grade 3 or 4 adverse events, SAEs, or fatal AEs were reported in healthy subjects. No healthy subjects discontinued study treatment due to AEs.

Based on currently available data, ibrutinib has an acceptable safety profile as monotherapy and when combined with chemoimmunotherapy or immunotherapy. No maximum tolerated dose (MTD) was reached in the first-in-human (FIH) study (04753) using intermittent dosing cohorts up to 12.5mg/kg/day and continuous dosing of 560mg or with combination therapies (up to 560mg). Data from the randomized, comparator-controlled phase 3 pivotal study also demonstrated the safety and tolerability of ibrutinib in subjects with previously treated CLL/SLL when compared with ofatumumab.

Based on positive early phase 1 and 2 data, the FDA granted Breakthrough Therapy Designation to ibrutinib as monotherapy for previously treated MCL, for WM and for CLL/SLL. In June 2014, ibrutinib (Imbruvica) was approved in the United States for the treatment of patients with MCL, and those with CLL, who have received at least 1 prior therapy.

A full list of completed and ongoing clinical studies with ibrutinib as well as investigator sponsored trial studies with ibrutinib can be found in the investigator's brochure (IB).

Integrated safety data from a total of 1,523 subjects with B-cell malignancies treated with ibrutinib monotherapy in 17 studies that have completed primary analysis or final analysis included in the CSR as of the 31 July 2017 cutoff date for the current IB update in B-cell malignancies are summarized below.

The most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N = 1,523):

Most frequently reported TEAEs >10% [a]	Most frequently reported Grade 3 or 4 TEAEs >2% [a]	Most frequently reported Serious TEAEs >1% [b]
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Pyrexia
Cough	Anemia	Febrile neutropenia
Pyrexia	Hypertension	Sepsis
Anemia	Diarrhea	Cellulitis
Upper respiratory tract infection	Atrial fibrillation	Pleural effusion
Neutropenia	Fatigue	Dyspnoea
Oedema peripheral	Neutrophil count decreased	Urinary tract infection
Thrombocytopenia	Febrile Neutropenia	Lung infection
Muscle spasms	Hyponatraemia	Abdominal pain
Constipation	Hypokalaemia	Acute kidney injury
Arthralgia		Amaemia
Vomiting		Respiratory failure
Decrease appetite		
Dyspnoea		
Headache		
Pneumonia		
Rash		
Hypertension		
Abdominal pain		
Back pain		
Contusion		
Dizziness		

[a] Source is Table 5 of IB (v11), [b] Source is Table 6 of IB (v11)

1.2.2.1 Risks

Bleeding-related Events
There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria.

Initially, subjects were excluded from participation in specific ibrutinib Phase 2 and 3 studies if they required warfarin or other vitamin K antagonists. Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib unless specified in the protocol. Supplements such as fish oil and vitamin E preparations should be avoided In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. See Section 7.3.1 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery, depending upon the type of surgery and the risk of bleeding. See Section 7.7 for guidance on ibrutinib management with surgeries or procedures. Patients with congenital bleeding diathesis have not been studied.

Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib. Some of these infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) and hepatitis B reactivation have occurred in subjects treated with ibrutinib. Subjects should be monitored for signs and symptoms (fever, chills, weakness, confusion, vomiting and jaundice) and appropriate therapy should be instituted as indicated.

Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib. Monitor complete blood counts monthly.

Interstitial Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Monitor subjects for pulmonary symptoms indicative of ILD. If symptoms develop, interrupt ibrutinib and manage ILD appropriately. If symptoms persist, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines as needed.

Atrial Fibrillations

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor subjects clinically for atrial fibrillation. Subjects who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset of dyspnea should be evaluated clinically, and if indicated, have an ECG performed. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines.

Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with ibrutinib therapy. Subjects at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Monitor subjects closely and take appropriate precautions.

Non-melanoma Skin Cancer

Non-melanoma skin cancers have occurred in subjects treated with ibrutinib. Monitor subjects for the appearance of non-melanoma skin cancer.

Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe and are generally managed with supportive therapies including antidiarrheals and antiemetics. Subjects should be monitored carefully for gastrointestinal AEs and cautioned to maintain fluid intake to avoid dehydration. Medical evaluation should be made to rule out other etiologies such as *Clostridium difficile* or other infectious agents. Should symptoms be severe or prolonged follow the protocol dose modification guidelines.

Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. Most rashes were mild to moderate in severity. Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) have been reported in subjects treated with ibrutinib. Subjects should be closely monitored for signs and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events including erythema, urticaria, and angioedema have been reported.

Hypertension

Hypertension has been commonly reported in subjects treated with ibrutinib. Monitor subjects for new onset of hypertension or hypertension that is not adequately controlled after starting ibrutinib. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

1.3 Rationale for the Proposed Study

Immunotherapy is an attractive strategy in the treatment of advanced human malignancies due to its potential to induce durable clinical responses and its low toxicity profile. Sipuleucel-T is the first FDA approved cancer vaccine for the treatment of patients with metastatic castrate resistant prostate cancer (CRPC) (Kantoff PW et al, 2010). Immune checkpoint antibodies targeting PD-1 and/or CTLA-4 have gained approval for the treatment of advanced melanoma and squamous NSCLC, and shows promise in a variety of other solid malignancies. While cancer immunotherapies have largely been focused at inducing T cell mediated anti-cancer immune response, B cells have recently been increasingly appreciated to play an inhibitory role on antitumor immune responses.

Ibrutinib is a potent inhibitor of BTK, which mediates critical B-cell signaling pathways and is critical to the survival of malignant B cells. Tumor-infiltrating B cells are increased in prostate cancer tissue, and high intra-tumoral density of B cells correlates with higher stage of disease and greater potential for recurrence or progression (Woo JR et al, 2014). Unpublished data from our laboratory have shown that T cells within the prostate that are associated with B cell aggregates lack T cell activation markers. BTK also has inhibitory activity on other kinases including ITK, and essential enzyme in T_H2 cells. Inhibition of BTK can therefore not only inhibit B cells but also potentially shift the balance between T_H1 and T_H2 cells and enhance antitumor immune response. Indeed, Ibrutinib has recently been shown to enhance anti-PD-L1 mediated antitumor activity in preclinical models of lymphoma, breast and colon cancer (Sagiv-Barfi I et al, 2015). **We hypothesize that intratumoral B cells suppress anti-tumor immune responses in prostate cancer, and predict that ibrutinib reduces the frequency of intratumoral B cells and enhances**

the recruitment and expansion of tumor-reactive T cells into the prostate.

BTK has also been found to be overexpressed in prostate cancer cells, and its expression level correlates with cancer grade. Furthermore, knockdown of BTK expression inhibits the growth of prostate cancer cells in vitro (Guo W et al, 2014). **We hypothesize that BTK not only has immunomodulatory effects but also may have direct anti-tumor activity in prostate cancer that overexpress BTK.** The goals of this study are to study the immunomodulatory and cytotoxic effects of ibrutinib in patients with localized prostate cancer in the neoadjuvant setting. These findings may justify further exploration of ibrutinib in prostate cancer, including combination therapy in advanced prostate cancer.

1.4 Rationale for Study Design

This study will evaluate the immunologic and cytotoxic changes induced by ibrutinib in prostate tissues compared to pretreatment biopsies. Three patients were enrolled at the 840 mg/d x 2 weeks dose level at UCSF and no DLTs were seen. A safety lead-in consisting of 6 patients will be enrolled at the 840 mg/d x 4 weeks dose level to evaluate the safety and tolerability of ibrutinib administered for 4 weeks preoperatively in patients scheduled for RP. If fewer than 2 DLTs are seen, an additional 18 patients will be treated with ibrutinib at the 840 mg/d x 4 weeks dose level before undergoing RP.

The safety profile of ibrutinib is well established from multiple studies in subjects treated with single agent ibrutinib (1061 subjects with B cell malignancies, 143 healthy subjects). Ibrutinib is generally well tolerated, and treatment related adverse events are generally manageable. The rationale for studying ibrutinib at dose of 840mg is that the dose of ibrutinib required for activity in solid malignancies via immune modulation and/or direct cytotoxicity may be higher than 560mg, the dose currently approved for hematologic malignancies. In the phase 1 study of ibrutinib in relapsed or refractory B-cell NHL and B-cell CLL, MTD was not reached after dose escalation form 2.5mg/kg/day to 12.5mg/kg/day (Advani RH et al. J Clin Oncol 2012). The phase 1b/2 study of ibrutinib in relapsed/refractory CLL or small lymphocytic lymphoma showed similar efficacy and toxicity profiles of ibrutinib administered at 420mg and 840mg (Byrd JC, et al. N Engl J Med 2013). Recently, interim data from an open label phase 2 study of ibrutinib combined with dexamethasone in relapsed/refractory multiple myeloma showed manageable toxicities at a dose up to 840mg (Vij R et al. ASH 2014). We therefore believe that the dose of ibrutinib 840mg will be well tolerated in patients with localized prostate cancer.

1.5 Correlative Studies

This study aims to evaluate the immunomodulatory and cytotoxic effects of ibrutinib in prostate cancer patients by comparing their pre-treatment prostate biopsy tissue to post-treatment prostatectomy tissue. Specifically, immunohistochemistry and genomic analysis will be carried out to analyze the following:

1. Characterize the tumor and immune cell subsets
2. Explore the location of tumor infiltration lymphocytes (e.g., tumor center, tumor and benign tissue interface)
3. Characterize BCR and TCR clonality and diversity
4. Examine PD-L1 expression in tumor and immune-infiltrating immune cells
5. Examine Btk expression in B cells and tumor cells
6. Assess rate of downstaging and pT0 rate
7. Assess rate of PSA decline

In addition, serum and blood will be analyzed to characterize circulating immune cell subsets in response to treatment.

2 OBJECTIVES AND ENDPOINTS OF THE STUDY

2.1 Objectives

2.1.1 Primary Objectives

1. To assess safety in patients with localized prostate cancer.
2. To characterize B and T cell infiltration within prostate tissue of men with localized prostate cancer treated with neoadjuvant ibrutinib, and to compare B and T cell infiltration to a reference population of untreated patients who underwent RP.

2.1.2 Secondary Objectives

1. To characterize changes in the frequency and number of circulating B and T cells induced by neoadjuvant ibrutinib in patients with localized prostate cancer.
2. To determine the cytotoxic effect and clinical benefit of neoadjuvant ibrutinib in men with localized prostate cancer.

2.1.3 Exploratory Objectives

1. To examine Btk expression in prostate tumor cells and tumor-infiltrating B cells at baseline before neoadjuvant ibrutinib treatment and at RP after treatment.
2. To determine the impact of neoadjuvant ibrutinib on PD-L1 expression in prostate cancer cells and tumor-infiltrating lymphocytes (TILs).
3. To determine the effects of neoadjuvant ibrutinib on T and B cell repertoire within the tumor and blood.

2.2 Endpoints of the Study

2.2.1 Primary Endpoints

The primary endpoint of the safety-run in part is adverse events (AEs), especially dose limiting toxicity (DLT), as defined in Section 6.1.4.

The primary endpoint of the phase II study include: the change in infiltration of CD20+ B cells, IL-10+ B cells, CD3+ T cells, CD8+ cytotoxic T cells, effector CD4+FOXP3- T cells, and CD4+FOX3+ T regulatory cells in pre-treatment biopsy, RP tissue, and reference RP tissue quantitated by immunohistochemistry (IHC). Patients will be considered to have a positive response if there is $\geq$2 fold decrease from pre-treatment to post-treatment, or considered to have a negative response if there is <2 fold decrease. The proportion of patients who have “positive” responses will be evaluated.

2.2.2 Secondary Endpoints

The changes in the frequency and number of circulating CD19+ B cells, $CD25^{high}CD27^{high}CD86^{high}$ B regulatory cells, and CD3+, CD8+, CD4+FOXP3- and CD4+FOXP3+ T cells induced by neoadjuvant ibrutinib in patients with localized prostate cancer by flow cytometry. Patients will be considered to have a positive response if there is >2 fold decrease from pre-treatment to post-treatment, or considered to have a negative response if there is <2 fold decrease. The proportion of patients who have "positive" responses will be evaluated.

The proportion of patients who achieve >50% PSA decline, pathologic down-staging and/or pathologic T0 at RP after neoadjuvant ibrutinib in men with localized prostate cancer.

2.2.3 Exploratory Endpoints

To examine Btk expression in prostate tumor cells and tumor-infiltrating B cells in pre-treatment and post-RP tissue via immunohistochemistry with anti-Btk antibody.

To examine the change in PD-L1 expression in prostate cancer cells and tumor-infiltrating lymphocytes induced by neoadjuvant ibrutinib via immunohistochemistry with anti-PD-L1 antibody.

To determine the change in T and B cell repertoire within the tumor and blood with neoadjuvant ibrutinib via deep sequencing of VDJ regions of TCRs and BCRs.

3 STUDY DESIGN

3.1 Characteristics

This is a single center phase 2 open label study starting with a safety lead-in ibrutinib administered as neoadjuvant therapy in patients with localized prostate cancer. We believe that the dose of ibrutinib 840mg x 4 weeks will be well tolerated in patients with localized prostate cancer based on current trial data on ibrutinib but to ensure safety, we will start with a safety run-in. Previously at UCSF, 3 patients were enrolled to the 840 mg/d x 2 weeks dose level. No DLTs were observed. Beginning at WUSM, patients will be enrolled at the dose level of 840 mg/d x 4 weeks. If there are fewer than 2 DLTs, the Phase II dose expansion study will open and enroll up to an additional 18 patients to be treated with ibrutinib 840mg PO daily for 4 weeks.

If there are ≥2 DLTs in the safety lead-in, dosing will be de-escalated as follows:
- Level -1: 840 mg/d x 2 weeks, followed by de-escalation if ≥ 2 DLTs to Level -2
- Level -2: 560 mg/d x 2 weeks

In each enrolled patient, neoadjuvant ibrutinib therapy will be followed by radical prostatectomy (RP) performed 7 to 12 days after the last dose of ibrutinib. Pre-treatment and RP tissue will be evaluated for immunologic characterization, Btk expression and pathologic response. The proportion of patients achieving ≥ 50% PSA decline will be assessed. Serum will also be obtained to characterize circulating immune response. All patients will be followed clinically for 4 weeks after RP to monitor for adverse events.

3.2 Number of Subjects

The safety lead-in part requires 6 patients at the 840 mg/d x 4 weeks dose level. The phase II study will require a total of 24 patients (6 in the safety lead-in plus an additional 18). A sequential stopping rule is in place during Phase II (see Section 12.5).

If RP is delayed to over 12 days after the last dose of ibrutinib therapy (i.e. from scheduling delay of RP), a replacement patient will be accrued. The maximum number of allowed replacement patients is 4 (see Section 12.4).

To date, 3 patients have been enrolled and treated at UCSF (PI: L Fong) in Phase I/Cohort I (840 mg x 2 weeks) with no DLTs noted to date.

3.3 Eligibility Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

3.3.1 Inclusion Criteria

1. 18 years of age or older
2. ECOG performance status 0 or 1
3. Histologically documented adenocarcinoma of the prostate
4. Patients must be suitable for and willing to undergo a radical prostatectomy at the completion of study therapy.
5. Adequate bone marrow function, defined as:
    - o WBC >2,500 cells/mm^3
    - o ANC >1,500 cells/mm^3
    - o Hemoglobin >9 mg/dL
    - o Platelet count >100,000 cells/mm^3
6. Adequate renal function, defined as serum creatinine <2 mg/dL or CrCl >30 mL/min
7. Adequate liver function, defined as:
    - o AST and ALT <2.5x institutional ULN
    - o Serum bilirubin <1.5x institutional ULN
8. Adequate coagulation function, defined as normal PT/INR and PTT
9. Ability to understand and willingness to sign a written informed consent document
10. Available evaluable archival tumor tissue for correlative studies including assessment of immune infiltration and Btk expression is required. If archival tissue is unavailable, patients must be willing to undergo repeat prostate biopsy. Tissue is considered sufficient for correlative endpoint analyses if they are obtained from at least 2 prostate cores and consist of at least 15 unstained slides from the largest tumor volume and/or highest Gleason score. The availability of archival tissue or consent for repeat prostate biopsy is required for study eligibility; determination of tissue sufficiency is not required for study

eligibility.
11. The effects of ibrutinib on the developing human fetus is unknown. Men treated or enrolled on this protocol must agree to use adequate contraception prior to the study, for the duration of the study participation, and for 3 months after completion of treatment.

3.3.2 Exclusion Criteria

1. Patients with neuroendocrine or small cell features are not eligible.
2. Any evidence of metastatic disease. Pre-operative staging will be undertaken per urologic standard of care.
3. Any prior use of hormonal therapy, including:
    - GNRH agonists or GNRH antagonists (e.g., leuprorelin, degarelix)
    - Antiandrogens (e.g., bicalutamide, flutamide, nilutamide)
    - Novel androgen-directed therapies (e.g., abiraterone, enzalutamide)
    - Any estrogen containing compounds
    - 5-alpha reductase inhibitors (e.g., finasteride, dutasteride)
    - PC-SPES or PC-x products. Other herbal therapies or supplements will be considered by the Principle Investigator on a case by case basis based on their potential for hormonal or anti-cancer therapies.
4. Chemotherapy ≤ 21 days prior to first administration of study treatment and/or monoclonal antibody ≤ 6 weeks prior to first administration of study treatment
5. Prior radiation therapy for prostate cancer
6. Prior exposure to BTK inhibitors
7. Prior investigational therapy for prostate cancer
8. Patients may not receive any other concurrent investigational agents while on study.
9. Use of systemic steroid therapy within 28 days of study screening. Patients on inhaled or topical steroids are eligible.
10. Concurrent systemic immunosuppressive therapy within 21 days of the first dose of study drug.
11. Major surgery requiring the use of general anesthetic within 4 weeks of study enrollment
12. HIV, active hepatitis B (HBV) or active hepatitis C (HCV)
    - Patients with past HBV infection or resolved HBV infection, defined as the presence of hepatitis B core antibody (HBc Ab) and absence of hepatitis B surface antigen (HBsAg) are eligible. HBV DNA must be obtained in these patients prior to day 1 of ibrutinib therapy, but detection of HBV DNA in these patients will not exclude study participation.
    - Patients positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
13. Inability to swallow capsules or presence of malabsorption syndromes, disease significantly affecting gastrointestinal function, history of resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete small obstruction.
14. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Function Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to screening.
15. Uncontrolled concurrent illness, or any underlying medical condition, which in

the Principal Investigator's opinion will make the administration of ibrutinib hazardous or obscure the interpretation of adverse events.

16. Recent infection requiring systemic treatment that was completed within 14 days prior to the first dose of study drug
17. Concurrent active malignancy other than non-melanoma skin cancers. Patients are considered to be free of active malignancy if they have completed curative therapy and have a <30% risk of relapse.
18. History of congenital bleeding diathesis.
19. Known bleeding disorders (e.g. von Willebrand's disease or hemophilia).
20. Concomitant use of anticoagulants including warfarin, other Vitamin K antagonists, and enoxaparin.
21. Subjects who received a strong or moderate cytochrome P450 (CYP) 3A4 inhibitor within 7 days prior to the first dose of ibrutinib or patients who require treatment with a strong or moderate cytochrome P450 (CYP) 3A inhibitor.
22. Vaccination with live, attenuated vaccines within 4 weeks of first dose of study drug.
23. Patients on anti-platelet agents including clopidogrel and glycoprotein IIb/IIIa inhibitors. Aspirin is allowed, but should be held before surgery according to standard practices.
24. Currently active, clinically significant hepatic impairment Child-Pugh class B or C according to the Child-Pugh classification
25. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.
26. Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to CTCAE v 4.03 grade 0 or 1 or to the levels dictated in the eligibility criteria with the exception of alopecia.

3.3.3 Inclusion of Minorities

Members of all races and ethnic groups are eligible for this trial.

3.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until:

- Administration of all planned doses is completed
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- Significant patient non-compliance with protocol
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

3.5 Duration of Follow Up

Patients will be followed for 4 weeks after radical prostatectomy. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related adverse events to grade 2 or lower.

4 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name, and your institution name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

4.4 UCSF Patients

The 3 patients enrolled at UCSF will be registered to the Siteman Cancer Center OnCore database, and UCSF will provide study data to the Washington University study team.

5 STUDY DRUGS

5.1 Ibrutinib

Ibrutinib capsules are provided as a hard gelatin capsule containing 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib Investigator's Brochure for a list of excipients.

The ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All study drug will be dispensed in child-resistant packaging.

Refer to the Pharmacy Manual/site investigational product manual for additional guidance on study drug storage, preparation and handling.

Study drug labels will contain information to meet the applicable regulatory requirements.

5.1.1 Classification

Cytotoxic drug: molecular targeted cytotoxic drug

5.1.2 Mechanism of Action

Ibrutinib is a potent (IC_{50} 0.39nM) orally bioavailable small-molecule inhibitor of Bruton's tyrosine kinase (BTK). With only a few exceptions, a 10-fold or greater selectivity was demonstrated for BTK relative to off-target kinases. Upon oral administration, Ibrutinib binds to cysteine 481 of BTK and irreversibly inhibits BTK activity, thereby preventing both B-cell activation and B-cell mediated signaling. BTK is a member of the src-related BTK/Tec family of cytoplasmic tyrosine kinases that is required for B cell receptor signaling, plays a key role in B cell maturation, and is overexpressed in a number of B-cell malignancies. The expression of BTK in other tumors has also been associated with increased proliferation, including prostate cancer and breast cancer (Guo W et al, 2014; Eifert C et al, 2013).

5.1.3 Contraindications

Ibrutinib is contraindicated in subjects with clinically significant hypersensitivity, including anaphylactic and anaphylactoid reactions to the compound itself or to the excipients in its formulation.

5.1.4 Availability

Ibrutinib will be supplied by Pharmacyclics Inc.

5.1.5 Storage and handling

Ibrutinib capsules should be stored according to the storage conditions indicated on the label. The recommended storage condition for ibrutinib capsules is 15°C to 25°C (59°F to 77°F) with excursions permitted to 30°C (86°F).

6 TREATMENT PLAN

6.1 Dosage and Administration

Ibrutinib is administered orally once daily on an outpatient basis at a dose of 840 mg. The capsules are to be taken around the same time each day with 8 ounces (approximately 240 mL) of water, with or without food. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study. Examples of inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/

If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose.

The first dose will be delivered in the clinic on Day 1, after which subsequent dosing is typically on an outpatient basis. Ibrutinib will be dispensed to subjects in bottles at each visit. Study drug may not be shipped to the subject without approval from PCYC and may not be dispensed to anyone other than the subject. Unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records updated at each visit. Returned capsules must not be redispensed to anyone.

6.1.1 Overdose

There is no specific experience in the management of ibrutinib overdose in patients. No maximum tolerated dose (MTD) was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1,400 mg/day). Healthy subjects were exposed up to single dose of 1680 mg. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Subjects who ingest more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

Refer to Section 10 for further information regarding special reporting situations as a result of overdose.

6.1.2 Regimen Description

Study Drug	Premedication; precautions	Route	Schedule
Ibrutinib	No premedication required	Oral	Days 1-28

Ibrutinib is supplied in 140mg capsules. Patients in the safety lead-in will be treated at a dose of 840 mg PO daily x 4 weeks. If fewer than 2 DLTs are observed, patients will continue to be treated at that dose level. If ≥ 2 DLTs are observed, dose de-escalation is required. The first reduction will be to Level -1 (840 mg/d x 2 weeks) and the second reduction (if ≥ 2 DLTs are observed at Level -1) will be to Level -2 (560 mg/d x 2 weeks).

6.1.3 Other Modalities or Procedures

Blood samples for PSA and for immune assays will be collected at baseline, before RP, and after RP. Radical prostatectomy will be performed at Washington University, at least 7 days but not more than 12 days following the last scheduled dose of ibrutinib (Day 36 to 41; See Table 6.1). Information including WBC count prior to surgery, amount of blood loss during surgery and/or any post-operative complication(s) will be included in the safety analysis. As there is a potential for loss of immune cell infiltration within the prostate tissue after >12 days of not receiving ibrutinib, any patient who undergoes RP after 12 days from the last dose of ibrutinib will be included in the final analysis; however, an additional patient will be accrued as replacement. This will keep the treatment uniform in order to evaluate for immune response. The maximum number of allowed replacement patients is 4.

Standard institutional practices for the care and treatment of surgical patients will be followed before, during, and after each patient's RP. Patients will be informed in the written consent that radical prostatectomy may be delayed due to adverse events resulting from study treatment, at the discretion of the investigator and performing surgeon.

6.1.4 Dose Limiting Toxicities

Each patient in the safety lead-in will be assessed periodically for the development of any toxicity as outlined in Section 7 Study Procedures and Observations. Toxicity will be assessed according to the NCI CTCAE v4.0. Dose adjustments will be made according to the system showing the greatest degree of toxicity.

Dose de-escalation in this study will be based on the occurrence of dose-limiting toxicities (DLTs) that occur during the duration of ibrutinib therapy and the period after the last dose of ibrutinib until the day of surgery. DLTs will be defined as any of the following that are attributable to ibrutinib.

- Any grade 4 toxicity, including hematologic toxicities with the exception of lymphocytosis. Lymphocytosis, in the absence of clinical symptoms, is excluded from DLT, as this may be considered an on-target pharmacodynamics effect of BTK inhibition.
- Any grade 3 toxicity.
- Any recurrence of the same grade 3 toxicity.
- Any delay of RP due to study-drug related toxicity.
- Any complications of RP (e.g., bleeding, delayed wound healing) deemed to be related to study drug.

The dose of study drug should be modified according to the dose modification guidelines, including any of the following toxicities:

- Grade 4 ANC (<500/mm^3) for more than 7 days.
- Grade 3 thrombocytopenia (<50,000/mm^3) in the presence of clinically significant bleeding events.
- Grade 4 thrombocytopenia (<25,000/mm^3)).
- Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and/or anti-diarrheal therapy.

Patients who experience a DLT may be removed from protocol therapy and undergo RP at the discretion of the operating surgeon.

6.2 Dose Modifications for an Individual Patient Regardless of Dose Cohort

If a patient experiences any CTCAE v4.0 grade 4 toxicity attributed to treatment, ibrutinib must be discontinued. If a patient experiences any CTCAE v4.0 grade 3 toxicity attributed to treatment, ibrutinib must be held until resolution of the toxicity to grade 1 or the patient's baseline, at which time the patient may resume ibrutinib at 50% of the starting dose. If the patient experiences recurrence of the same grade 3 toxicity while on 50% reduced dose, ibrutinib must be discontinued. If a grade 3 toxicity does not resolve to grade 1 or the patient’s baseline within 2 weeks of holding therapy, ibrutinib must be discontinued.

Ibrutinib Dose Modifications According to Toxicity

Event	Management
Any grade 4 toxicity attributed to treatment	Discontinue ibrutinib
Any grade 3 toxicity attributed to treatment	Hold ibrutinib until ≤ grade 1, then resume ibrutinib at 50% starting dose
Recurrence of the same grade 3 toxicity while on half dose	Discontinue ibrutinib
Grade 3 toxicity not resolving to ≤ grade 1 within 2 weeks	Discontinue ibrutinib

Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessments.

6.2.1 Dose Modification for Hepatic Impaired Subjects

Subjects who develop acute hepatic toxicity with liver enzymes Grade 3 or higher while on study should be managed per standard dose modification guidelines. Ibrutinib is metabolized in the liver and therefore subjects with clinically significant chronic hepatic impairment at the time of Screening (Child- Pugh class C) are excluded from study participation. Concomitant use of strong CYP inhibitors is not permitted in subjects with chronic hepatic impairment. Refer to Appendix D for Child-Pugh classification. Please refer to the table below for dose modifications due to hepatic impairment.

Dose Modification Guidance for Hepatic Impaired Subjects

	Child Pugh class A (Mild hepatic impairment) *		**Child Pugh Class B (Moderate hepatic impairment) ****	**Child Pugh class C (Severe hepatic impairment)**
	Ongoing at time of enrollment	Develops during study	Develops during study	Develops during study
Ibrutinib Dose (daily)	280 mg	280mg	140 mg	Hold until improves to moderate [Class B] or better)

* If further reduction is needed due to non-hepatic toxicity, dose may be reduced to 140 mg. In the event that additional reduction is needed, ibrutinib should be held for non-hepatic toxicity until resolution.
** If further reduction is needed due to non-hepatic toxicity, ibrutinib should be held until resolution.

6.3 Monitoring and Toxicity Management

Each patient receiving ibrutinib will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical findings, and spontaneous reports of adverse events reported to the investigator by patients.

We will monitor for potential adverse effects including but not limited to fatigue, dehydration, cytopenias, leukocytosis, diarrhea, nausea, vomiting, signs and symptoms of infection including pneumonia, as well as skin disorders including rash.

Acute toxicity will be managed by supportive care and/or delay of dose. Further management will depend upon the judgment of the treating clinician and may include dose reduction. Guidelines for dose modification and management of anticipated adverse events are summarized in Table 5.3.1.

Criteria for dose adjustments and management of ibrutinib related toxicities

Toxicity and Intensity	**Dose Modification and Suggestions for Management**
Fatigue (very common)	
Grade 1 (relieved by rest)	Ensure adequate caloric intake and assess volume status. Rule out other causes of fatigue including anemia. Avoid prescription of steroids (e.g., Prednisone or Dexamethasone) which has immunomodulatory effects and may affect study endpoints.
Grade 2 (not relieved by rest, limiting instrumental ADL)	Ensure adequate caloric intake and assess volume status. Rule out other causes of fatigue including anemia. Avoid prescription of steroids (e.g., Prednisone or Dexamethasone) which has immunomodulatory effects and may affect study endpoints. If fatigue is not resolved to ≤ grade 1 with supportive management, reduce the starting dose of ibrutinib by 140mg.
Grade 3 (not relieved by rest, limiting self care ADL)	Ensure adequate caloric intake and assess volume status. Rule out other causes of fatigue including anemia. Avoid prescription of steroids (e.g., Prednisone or Dexamethasone) which has immunomodulatory effects and may affect study endpoints. Hold ibrutinib dosing until fatigue is resolved to ≤ grade 2, at which time restart dose at 50% of the starting dose.
Diarrhea (very common)	
Grade 1 (increase of <4 stools per day over baseline)	Consider *Clostridium difficile* testing if clinically indicated. The patient should be monitored carefully to ensure maintenance of fluid intake to avoid dehydration. Manage with supportive therapy including antidiarrheals.
Grade 2 (increase of 4-6 stools per day over baseline)	Patient should be evaluated by the treating clinician or other physicians including history and physical exam. Infectious work-up include *Clostridium difficile* and other suspected organisms should be obtained. The patient should be monitored carefully to ensure maintenance of fluid intake to avoid dehydration. If infectious work-up is negative, patient should be managed with supportive therapy including antidiarrheals. If symptoms are prolonged (e.g.,, >2 weeks) and do not improve with supportive management, reduce the starting dose of ibrutinib by 140mg.
Grade 3 (increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated)	Hospitalization with management per standard institutional practices. Rule out *Clostridium difficile*. Hold ibrutinib until diarrhea ≤ grade 1, then resume ibrutinib at 50% of the starting dose.
Grade 4 (Life-threatening consequences; urgent intervention indicated)	Urgent hospitalization and medical management per standard institutional practices. Discontinue ibrutinib therapy.
Nausea/Vomiting (very common)	
Grade 1 (loss of appetite without alteration in eating habits; 1-2 episodes of vomiting in 24 hours)	5-HT3 antagonists (e.g., Ondansetron), D2 antagonists (e.g., Prochlorperazine), or other antiemetic, alone or in combination can prevent nausea in the majority of patients. Avoid prescription of steroids (e.g., Prednisone or Dexamethasone) which has

Toxicity and Intensity	Dose Modification and Suggestions for Management
	immunomodulatory effects and may affect study endpoints.
Grade 2 (oral intake decreased without significant weight loss, dehydration or malnutrition; 3-5 episodes of vomiting in 24 hours)	Implement one or more combinations of antiemetics. Avoid prescription of steroids (e.g., Prednisone or Dexamethasone) which has immunomodulatory effects and may affect study endpoints.
Grade 3 (inadequate oral caloric or fluid intake; tube feeding, TPN or hospitalization indicated; ≥6 episodes of vomiting in 24 hours)	Hospitalization and supportive management including hydration and caloric intake per standard institutional practices. Hold ibrutinib until nausea ≤ grade 1, then resume ibrutinib at 50% of the starting dose after adequate fluid and caloric intake are achieved. Avoid steroids (e.g., Prednisone or Dexamethasone) which has immunomodulatory effects and may affect study endpoints.
Cough (very common)	
Grade 1 (mild symptoms, nonprescription intervention indicated)	Symptomatic management with OTC cough suppressants (e.g., Robitussin).
Grade 2 (moderate symptoms, medical intervention indicated; limiting instrumental ADL)	Chest imaging as clinically indicated to rule out pneumonia. Trial of prescription cough suppressants (e.g., Benzonatate). If symptoms are prolonged (e.g., >2 weeks) and do not improve, reduce the starting dose of ibrutinib by 140mg.
Grade 3 (severe symptoms; limiting self care ADL)	Chest imaging as clinically indicated to rule out pneumonia. Hospitalization if clinically indicated. Hold ibrutinib until cough ≤ grade 1, and any reversible causes (e.g., pneumonia) are fully treated. Then resume ibrutinib at 50% of the starting dose.
Pneumonia (very common)	
Grade 2 (moderate symptoms; oral intervention indicated)	Oral antibiotic, antifungal or antiviral as clinically indicated. Chest imaging if clinically indicated. If symptoms are prolonged (e.g., >2 weeks) and do not improve, reduce ibrutinib starting dose by 140mg.
Grade 3 (IV intervention indicated; radiologic, endoscopic or operative intervention indicated)	Hospitalization for infectious work-up and management including imaging and endoscopic or operative intervention per standard institutional practices. IV antibiotic, antifungal and/or antiviral per standard institutional practices. Hold ibrutinib until pneumonia is fully treated, then resume at 50% of the starting dose.
Grade 4 (life-threatening consequences; urgent intervention indicated)	Hospitalization and management including IV antibiotics, antifungal and/or antiviral per standard institutional practices. Discontinue ibrutinib.
Maculopapular rash (very common)	
Grade 1 (<10% BSA covered with or without symptoms)	Continue dose level of ibrutinib. Review medications for other potential drug etiologies and discontinue agent(s) as appropriate. Use topical or oral antihistamines for symptomatic relief. Topical corticosteroids may be used if clinically indicated. Avoid systemic corticosteroids which has systemic immunomodulatory effects and may affect study endpoints.
Grade 2 (10-30% BSA covered with or without symptoms; limiting instrumental ADL)	Review medications for other potential drug etiologies and discontinue suspected agent(s) as appropriate. Use topical or oral antihistamines for symptomatic relief. Topical corticosteroids may be used if clinically indicated. Avoid systemic corticosteroids which has systemic immunomodulatory effects and may affect study endpoints. If symptoms are prolonged (e.g., >2 weeks) and do not improve, reduce the starting dose of ibrutinib by 140mg.

Toxicity and Intensity	Dose Modification and Suggestions for Management
Grade 3 (>30% BSA covered with or without symptoms; limiting self care ADL)	Review medications for other potential drug etiologies and discontinue suspected agent(s) as appropriate. Use topical or oral antihistamines for symptomatic relief. Topical corticosteroids may be used if clinically indicated. Avoid systemic corticosteroids which has systemic immunomodulatory effects and may affect study endpoints. Hold ibrutinib until rash $\leq$ grade 1, and then resume at 50% of the starting dose.
Anemia (very common)	
Grade 1 (Hb <LLN-10.0 g/dL)	Maintain ibrutinib dose level. Assess for evidence of gastrointestinal bleeding.
Grade 2 (Hb <10.0-8.0 g/dL)	Assess for evidence of gastrointestinal bleeding. Hold ibrutinib until anemia is resolved to $\leq$ grade 1, at which time resume ibrutinib at 140mg lower than the starting dose.
Grade 3 (Hb <8.0 g/dL, transfusion indicated)	Transfuse PRBC per standard institutional practices. Hold ibrutinib until anemia $\leq$ grade 1, and then resume at 50% of the starting dose. Red blood cell growth factors (erythropoietin) are permitted per institutional policy and in accordance with the ASCO guidelines. Short doses of steroids for autoimmune cytopenias are permitted for <14 days at doses that do not exceed 100 mg per day of prednisone or equivalent.
Thrombocytopenia (very common)	
Grade 1 (Plt <LLN- 75,000/mm^3)	Check manual blood smear to rule out pseudothrombocytopenia. Maintain ibrutinib dose level.
Grade 2 (Plt <75,000-50,000/mm^3)	Check manual blood smear to rule out pseudothrombocytopenia. Hold ibrutinib until thrombocytopenia is resolved to $\leq$ grade 1, at which time resume at 140mg lower than the starting dose.
Grade 3 (Plt <50,000-25,000/mm^3)	Check manual blood smear to rule out pseudothrombocytopenia. Hold ibrutinib until thrombocytopenia $\leq$ grade 1, and then resume at 50% of the starting dose. Platelet transfusions may be given if clinically indicated (e.g., bleeding).
Grade 4 (Plt <25,000/mm^3)	Check manual blood smear to rule out pseudothrombocytopenia. Discontinue ibrutinib. Platelet transfusions may be given if clinically indicated (e.g., bleeding or Plt <10,000/mm^3). Short courses of steroids for autoimmune cytopenias are permitted for <14 days at doses that do not exceed 100mg per day of prednisone or equivalent.
Neutropenia (very common)	
Grade 1 (ANC <LLN-1,500/mm^3)	Maintain ibrutinib dose level. Avoid the use of growth factors due to potential interference with immune effects of ibrutinib and study endpoints.
Grade 2 (ANC <1,500-1,000/mm^3)	Hold ibrutinib until neutropenia is resolved to $\leq$ grade 1, at which time resume at 140mg lower than the starting dose. Avoid the use of growth factors due to potential interference with immune effects of ibrutinib and study endpoints.
Grade 3 (ANC <1000-500/mm^3)	Hold ibrutinib until neutropenia is resolved to $\leq$ grade 1, at which time resume at 50% of the starting dose. Avoid the use of growth factors due to potential interference with immune effects of ibrutinib and study endpoints.
Grade 4 (ANC <500/mm^3)	Discontinue ibrutinib. Growth factors such as filgrastim or

Toxicity and Intensity	Dose Modification and Suggestions for Management
	pegfilgrastim may be used per institutional policy and in accordance with the ASCO guidelines.
Febrile neutropenia (common)	
Grade 3 (ANC <1000/mm^3 with a single temp >38.3°C (101 F) or a sustained temp of >38°C (100.4 F) for >1 hour	Urgent admission and management including IV antibiotics per standard institutional practices. Hold ibrutinib until neutropenia is resolved to < grade 1 and any evident infection is adequately treated, then resume ibrutinib at 140mg lower than the starting dose. Avoid the use of growth factors due to potential interference with immune effects of ibrutinib and study endpoints.
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue ibrutinib. Urgent admission and management including IV antibiotics per standard institutional practices. Growth factors may be used if clinically indicated.
Leukocytosis (common)	
Grade 3 (ANC >100,000/mm^3)	Admit patient for close monitoring including CBC and signs and symptoms of leukostasis. Hold ibrutinib until ANC normalizes, at which time resume ibrutinib at 50% of the starting dose.
Grade 4 (clinical manifestations of leukostasis; urgent intervention indicated)	Discontinue ibrutinib. Supportive care including hydration and/or cytoreduction per standard institutional practices.
Other ibrutinib-related AEs	
Grade 1 or 2	Maintain dose level and initiate standard supportive care. If grade 2 toxicity does not improve to < grade 1 with optimal supportive care, reduce ibrutinib dose by 140mg.
Grade 3	Hold ibrutinib until resolve to < grade 1, then reduce dose by 50%.
Grade 4	Discontinue ibrutinib.
Frequency category is based on the following: • Very common: anticipated >10% • Common: anticipated >1% and <10% Notes: • All dose modifications should be based on the worst preceding toxicity. • If a patient requires a dose interruption of >14 days due to a study drug related toxicity, the patient must be discontinued from the study. • Patients who discontinue the study for a study related AE must be followed at least once a week for 28 days and subsequently at 28 day intervals until resolution or stabilization of the event, whichever comes first.	

7 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below. Please refer to Appendix 5 for definitions and Appendix 6 for a grid of reporting timelines.

Adverse events will be tracked from the start of study treatment through 30 days after the end of treatment. All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF
- Adverse events related to prostatectomy

Refer to the data submission schedule in Section 11 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in Section 7.1.

7.1 Sponsor-Investigator Reporting Requirements

7.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

7.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The Sponsor-Investigator is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

7.1.3 Reporting to Pharmacyclics

All SAEs and AESIs (initial and follow-up information) will be reported on a MEDWATCH form 3500A or Suspect Adverse Event Report (CIOMS Form 1, IRB Reporting form) and sent via email (AEintakePM@pcyc.com) or fax (408) 215-3372 to Pharmacyclics Drug Safety, or designee, within 15 days of the event. Pharmacyclics may request follow-up and other additional information from the sponsor Investigator.

Pharmacyclics Inc.
995 E Arques Ave
Sunnyvale, CA 94085
Fax (408) 215-3372
EMAIL: drugsafety@pcyc.com

Significant new information regarding an ongoing SAE and the resolution must be provided promptly to Pharmacyclics Inc. on the SAE form MEDWATCH 3500A.

7.1.3.1 Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy of a sexual partner. However, should a pregnancy occur in the partner of a study subject, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.

A subject must immediately inform the Investigator if his partner becomes pregnant from the time of consent to 90 days after the last dose of study drug. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a subject's partner from the time of first dose up until to 90 days after the last dose of study drug must be reported. Any occurrence of pregnancy must be reported to Pharmacyclics Drug Safety, or designee, per SAE reporting timelines of learning of the event. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. For pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing the Pregnancy Report Form Part II and this must be reported to Pharmacyclics Drug Safety, or designee, per SAE reporting timelines. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

7.1.3.2 Other Malignancies

All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

7.1.3.3 Adverse Events of Special Interest (AESI)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities by the Sponsor. These events (regardless of seriousness) should be reported on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 15 days of awareness.

7.1.3.1.3 Major Hemorrhage

Major hemorrhage is defined as any of the following:

1. Any treatment-emergent hemorrhagic adverse events of Grade 3 or higher*.
2. Any treatment-emergent serious adverse events of bleeding of any grade
3. Any treatment-emergent central nervous system hemorrhage / hematoma of any grade

*All hemorrhagic events requiring transfusion of red blood cells should be reported as grade 3 or higher AE per CTCAE v4.03.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 10.4.3 above.

7.1.4 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the Washington University principal investigator to report to the FDA as follows:

- Report any unexpected fatal or life-threatening suspected adverse reaction (refer to Appendix 5 for definitions) no later than **7 calendar days** after initial receipt of the information.
- Report a suspected adverse reaction that is both serious and unexpected (SUSAR, refer to Appendix 5) no later than **15 calendar days** it is determined that the information qualifies for reporting. Report an adverse event (refer to Appendix 5) as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:
    - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
    - One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug
    - An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group
- Report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies that suggest a significant risk in humans exposed to the drug no later than 15 calendar days after it is determined that the information qualifies for reporting.
- Report any findings from animal or in vitro testing that suggest significant risk in humans exposed to the drug no later than 15 calendar days after it is determined that the information qualifies for reporting.
- Report any clinically important increase in the rate of a serious suspected adverse reaction of that listed in the protocol or IB within 15 calendar days after it is determined that the information qualifies for reporting.

Submit each report as an IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. Study teams must notify the Siteman Cancer Center Protocol Development team of each potentially reportable event within 1 business day after initial receipt of the information, and must bring the signed 1571 and FDA Form 3500A to the Siteman Cancer Center Protocol Development team no later than 1 business day prior to the due date for reporting to the FDA.

Each notification to FDA must bear prominent identification of its contents (“IND Safety Report”) and must be transmitted to the review division in the Center for Drug Evaluation and Research (CDER) or in the Center for Biologics Evaluation and Research (CBER) that has responsibility for review of the IND. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such (“Follow-up IND Safety Report”).

7.2 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 7.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

8 STUDY PROCEDURES AND OBSERVATIONS

8.1 Schedule of Procedures and Observations

The study-specific assessments are detailed in this section. Screening assessments must be performed within 28 days prior to the first dose of investigational product. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All on-study visit procedures are allowed a window of +/- 3 days unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

8.1.1 Pretreatment Period

8.1.1.1 Informed Consent

Before initiation of any screening procedures, each prospective subject will be provided a verbal, in-depth explanation of the study, requested to read the Institutional Review Board (IRB) approved informed consent form (ICF), and encouraged to ask questions. The Investigator must ensure that each subject understands how the study will be conducted and how they will participate if they so choose. The subject shall be given sufficient time to properly consider the information and to make an informed decision regarding consent. Once all questions have been answered and the Investigator is assured that the subject understands the implications of study participation, the subject will be asked to provide written consent to participate in the study by signing the ICF. The Investigator will document the informed consent process in the subject's medical chart or progress notes and will provide a copy of the signed ICF to the subject.

8.1.1.2 Screening Assessments

The Screening procedures and assessments must be completed within 28 days of the first day of ibrutinib.

- Physical examination
- Vital signs
- Complete medical history
- Documentation of disease assessment
- ECOG Performance status
- Baseline concomitant medications taken within 28 days of Day 1
- Complete blood count (CBC) with differential and platelet count
- Blood chemistry assessment, including alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate, lactate dehydrogenase (LDH)
- Coagulation assessment, including prothrombin time, partial thromboplastin time, international normalized ratio (PT/PTT/INR)
- PSA
- Hepatitis B surface antigen, anti-HBc antibody and anti-HBs antibody. In patients who have positive serology for the anti-HBc antibody, HBV DNA should be collected prior to Cycle 1, Day 1.
- HCV serology (anti-HCV antibody)
- HIV screening in accordance with national and/or institutional guidelines
- Serum collection in eight 10mL EDTA tubes for immune analyses to be sent to the TPC at Washington University
- Electrocardiogram (ECG)
- Pre-treatment tissue for correlative studies. If adequate tissue is available from a prior biopsy or surgery, samples will be requested from the hospital or clinic pathology department. If adequate tissue from a prior biopsy is not available, a prostate biopsy is required to participate in the study. There must be a minimum of 3 days between prostate biopsy and start of study drug.

8.1.2 Treatment Period

8.1.2.1 Study Procedures, Week 1, Day 1

- Physical examination
- Vital signs

- ECOG performance status
- Evaluation of adverse events
- Concomitant medications
- CBC with differential and platelet count
- Blood chemistry assessment, including alkaline phosphatase, AST, ALT, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate, LDH
- PSA

8.1.2.2 Study Procedures, Week 2, Day 8

- Telephone Visit
  - Evaluation of adverse events
  - Concomitant medications
  - Other pertinent interval history
- CBC with differential and platelet count (not required to be completed at Washington University, but results must be communicated to the CRC within protocol window)

8.1.2.3 Study Procedures, Week 3, Day 15

- Physical examination
- Vital signs
- ECOG performance status
- Evaluation of adverse events
- Concomitant medications
- CBC with differential and platelet count
- Blood chemistry assessment, including alkaline phosphatase, AST, ALT, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate, LDH

8.1.2.4 Study Procedures, Week 4, Day 22

- Telephone visit
  - Evaluation of adverse events
  - Concomitant medications
  - Other pertinent interval history
- CBC with differential and platelet count (not required to be completed at Washington University, but results must be communicated to the CRC within protocol window)

8.1.2.5 Study Procedures, Week 5, Day 29

- Physical examination
- Vital signs
- ECOG performance status
- Evaluation of adverse events

- Concomitant medications
- CBC with differential and platelet count
- Blood chemistry assessment, including alkaline phosphatase, AST, ALT, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate, LDH
- PSA
- Serum collection in eight 10mL EDTA tubes for immune monitoring to be sent to the TPC at Washington University

RP will be performed 7 to 12 days after the last dose of ibrutinib (between Week 6, Day 36 and Day 41).

8.1.3 Post-RP/Follow Up Visit (Week 10, Day 64):

Patients will be followed approximately 4 weeks after RP. The following procedures will be performed at the follow up Visit:

- Physical examination
- Vital signs
- ECOG performance status
- Evaluation of adverse events
- Concomitant medications
- CBC with differential and platelet count
- Blood chemistry assessment, including alkaline phosphatase, AST, ALT, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate, LDH
- PSA
- Serum collection in eight 10mL EDTA tubes for immune monitoring to be sent to the TPC at Washington University

8.1.4 Long Term Follow-up Procedures

The study will conclude when all enrolled patients have been followed 4 weeks after RP. All treatment related adverse events will be followed until resolution or stabilization to grade $\leq$2.

8.1.5 Discontinuation of Therapy

The Investigator will withdraw a patient whenever continued participation is no longer in the patient’s best interests. Reasons for withdrawing a patient include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a patient’s request to end participation, a patient’s non-compliance or simply significant uncertainty on the part of the investigator that continued participation is prudent. There may also be administrative reasons to terminate participation, such as concern about a patient’s compliance with the prescribed treatment regimen.

8.2 Schedule of Study Procedures and Assessments

Study Day/Visit Day	Screening D-28 to 0 +/- 3 days	Week 1 D1 +/- 3 days	Week 2 D8 +/- 3 days	Week 3 D15 +/- 3 days	Week 4 D22 +/- 3 days	Week 5 D29 +/- 3 days	RP D36 to D41[7]	Post-RP Follow Up Visit +/- 3 days[8]
Informed consent	X						Radical Prostatectomy	
AE assessment		X	X[6]	X	X[6]	X		X
Concomitant medications	X	X	X[6]	X	X[6]	X		X
Pre-treatment prostate biopsy tissue available	X							
Treatment/Drug Administration								
Ibrutinib		Oral daily, D1 to D28						
Clinical procedures								
Telephone visit			X[6]		X[6]			
Physical exam	X	X		X		X		X
Vital signs	X	X		X		X		X
Medical history	X							
Disease assessment	X[9]							
ECOG performance status	X	X		X		X		X
Laboratory procedures								
CBC with differential	X	X	X[6]	X	X[6]	X		X
Blood chemistry + LDH[1]	X	X		X		X		X
Glucose	X	X		X		X		X
Coagulation[2]	X							
PSA	X	X				X		X
Hepatitis B and C[3]	X							
HIV[4]	X							
Immune monitoring[5]	X					X		X
Urinalysis	X							
Imaging procedures								
ECG	X							

1. Blood chemistry assessment includes alkaline phosphatase, AST, ALT, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, potassium, sodium, chloride, bicarbonate, and LDH.
2. Coagulation assessment includes PT, PTT and INR.
3. Serum hepatitis assessment includes HBsAg, HBsAb, HBcAb, and anti-HCV antibody.
4. HIV screening with ELISA based assay.
5. Refer to Appendix 3.
6. Obtained during telephone visits; CBC may be done at a local lab.
7. 7-12 days after the last dose of ibrutinib
8. Week 10, Day 64
9. Window for disease assessment is up to 60 days prior to enrollment

8.3 Usage of Concurrent/Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) is permitted per institutional policy and in accordance with the ASCO guidelines (Smith 2006). Transfusions may be given in accordance with institutional policy.

Short courses (≤14 days) of steroid treatment for non-cancer related medical reasons (e.g, joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that do not exceed 100 mg per day of prednisone or equivalent are permitted.

Treatment for autoimmune cytopenias are permitted for <14 days at doses that do not exceed 100 mg per day of prednisone or equivalent.

Concomitant use of ibrutinib and drugs that inhibit or induce CYP3A should be recorded on the CRF. Use of medications that inhibit platelet function and may increase the risk of bleeding (e.g. Aspirin) should be recorded on the CRF. Use of any medications that may have immunosuppressive effects should be recorded on the CFR.

All AEs and serious AEs (SAEs) that occur on study drug or within 30 days after the last dose of study drug, will be recorded on case report forms (CRFs) from enrollment through 4 weeks post-surgery.

8.3.1 Antiplatelet Agents and Anticoagulants

Use ibrutinib with caution in subjects requiring anticoagulants or medications that inhibit platelet function. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed. Supplements such as fish oil and vitamin E preparations should be avoided during treatment with ibrutinib. Bleeding events of any grade, including bruising and petechiae, occurred in subjects treated with ibrutinib. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding (see Section 7.7). Subjects with congenital bleeding diathesis have not been studied.

Subjects requiring the initiation of therapeutic anticoagulation therapy (e.g., atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

8.4 Dietary Restrictions

Ibrutinib can be taken with or without food at approximately the same time each day. Avoid grapefruit and Seville oranges during ibrutinib treatment as these contain moderate inhibitors of CYP3A. Patients should also avoid supplements such as fish oil and vitamin E preparations as they can cause an interaction with ibrutinib.

8.5 Prohibited Medications/Therapies

The following should not be administered at any time during the study.

- Any investigational product other than ibrutinib.
- Systemic corticosteroid with the exception of a short course of steroids for the management of treatment related autoimmune cytopenias). Topical and inhaled steroids are allowed.
- Anticoagulant including warfarin or other vitamin K antagonists and lower molecular weight heparin (LMWH) including enoxaparin.
- With the exception of aspirin, anti-platelet agents (e.g., clopidogrel, glycoprotein IIb/IIIa inhibitors) are not allowed.
- Vaccine therapy including influenza vaccination. However, COVID-19 vaccines may be allowed at discretion of investigator.
- Hormone therapy including LHRH agonists, antiandrogens (e.g., bicalutamide, flutamide, nilutamide), and 5-α-reductase inhibitors (e.g., finasteride, dutasteride)
- Radiation therapy may not be initiated until after RP.

Should subjects receive one or more of the above medications or therapies, they will remain on study and will continue to receive safety evaluations. Following RP, subjects may receive hormone therapy or radiation therapy as deemed appropriate by their medical professional.

8.6 Restricted Medications

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A.

Concomitant use of ibrutinib and drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure and should be avoided. Strong inhibitors of CYP3A (e.g., ketoconazole, intraconazole, clarithromycin, telithromycin, nefazadone) and moderate inhibitors (e.g., voriconazole, erythromycin, aprepitant, ciprofloxacin, Diltiazem, fluconazole, verapamil) should be avoided. If the benefit outweighs the risk and a strong CYP3A inhibitor must be used, reduce the ibrutinib dose to 140mg or withhold treatment temporarily (for 7 days or less). If a moderate CYP3A inhibitor must be used, reduce ibrutinib treatment to 140mg for the duration of the inhibitor use. No dose adjustment is required in combination with mild inhibitors. Monitor patient closely for toxicity and follow dose modification guidance as needed.

After discontinuation of a CYP3A inhibitor, resume previous dose of ibrutinib.

Administration of ibrutinib with rifampin, a strong CYP3A inducer, decreases ibrutinib plasma concentrations by approximately 90%. Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's wort). Consider alternative agents with less CYP3A induction. For further information, please refer to the current version of the IB and examples of inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

Any medications known to cause QT prolongation should be used with caution; periodic ECG and electrolyte monitoring should be considered.

A standard list of prohibited and restricted medications is provided in Appendix 2.

8.7 Guidelines for Ibrutinib Management with Surgeries and Procedures

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. The following guidance should be applied to the use of ibrutinib in the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib.

8.7.1 Minor Surgical Procedures

For minor procedures (such as a central line placement, skin or needle biopsy, lumbar puncture (other than shunt reservoir access), thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib. A minimum of 3 days between prostate biopsy and start of study drug is required for patients who undergo prostate biopsy.

8.7.2 Major Surgical Procedures

For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention (except for emergency procedures) and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.

9 REPORTING AND DOCUMENTATION OF RESULTS

9.1 Evaluation of Activity

9.1.1 Characterization of PBMCs using flow cytometry

The number and frequency of immune cell subsets in the peripheral blood, before, during and after ibrutinib therapy will be assessed. Fluorochrome-labeled antihuman antibodies, including antibodies to CD19, CD25, CD27, CD86, CD3, CD8, CD4, CD25, and FOXP3 will be used. Flow cytometry will be performed in either the Immunomonitoring Lab (IML) or Pachynski Lab in the Center for Human Immunology and Immunotherapy Programs (CHiiPs) at Washington University.

9.1.2 Characterization of immune infiltration within prostate tissue

The effect of ibrutinib on the number of infiltrating B cells and T cells will be assessed by immunohistochemistry with antibodies to CD20, IL-10, CD3, CD8, CD4, and FoxP3. Prostate tumor tissue from diagnostic core biopsy specimens and post-treatment prostatectomy tissue specimens will be analyzed. Infiltrate will be scored by the number of cells/μm^2; thus, the number of inflammatory cells will be normalized to the unit area. For each patient, the change in the number of immune cell infiltration from the pre-treatment biopsy to post-treatment prostatectomy tissue specimens will be represented by the ratio of post-treatment prostatectomy versus pre-treatment biopsy tissue specimen. IHC for immune infiltration will be performed in the Pachynski Lab at Washington University.

9.1.3 Characterization of Circulating and Intratumoral T and B cells via TCR and BCR sequencing

Next-generating sequencing (NGS) of the VDJ region of T-cell receptors (TCRs) and B-cell receptors (BCRs) will be utilized to define the TCR and BCR repertoire in the blood and tumor tissue before and after ibrutinib therapy. This approach allows the tracking of T and B cell clones in the blood and tissue over time to assess their expansion and migration. TCR and BCR sequencing will be carried out by Sequenta, Inc.

9.1.4 PD-L1 Expression in Tumor and Tumor-Infiltrating Lymphocytes

The expression level of PD-L1 on tumor and tumor-infiltrating lymphocytes (TILs) will be examined using immunohistochemistry on diagnostic core biopsy specimens and post-treatment prostatectomy tissue specimens. The expression level of PD-L1 will be graded by an expert pathologist to determine the impact of neoadjuvant ibrutinib on PD-L1 expression in prostate cancer cells and TILs. IHC for PD-L1 will be performed in the Pachynski Lab at Washington University.

9.1.5 Btk expression

The expression level of Btk on prostate cancer tissue from core biopsy before surgery will be examined using immunohistochemistry with anti-Btk antibody (Santa Cruz Inc., Santa Cruz, CA, USA; sc-1107). IHC for total Btk and phospho-Btk will be performed in or the Pachynski Lab at Washington University.

9.1.6 PSA

The utility of a decline in PSA as a marker of response to neoadjuvant therapies is not well defined. However, the proportion of patients with PSA response, defined as $\geq$50% PSA decline, will be reported.

9.1.7 Pathologic Response

The proportion of patients with down-staging of disease by Gleason score will be reported. The proportion of patients with pathologic complete response (pT0) at the time of prostatectomy will be reported.

9.2 Evaluation of Safety

The following will be collected to evaluate safety:

- Adverse events (including SAEs and deaths)
- Physical examinations
- Vital signs
- ECOG performance status
- Laboratory test results

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE v4.03 for reporting of non-hematologic adverse events and modified criteria for hematologic adverse events.

10 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least one patient has been enrolled) or one year after accrual has opened (if no patients have been enrolled at the six-month mark).

For phase I dose escalation studies, Principal Investigator will review all patient data at least monthly (or before each dose-escalation if occurring sooner than monthly), and provide a semi-annual report to the Quality Assurance and Safety Monitoring Committee (QASMC). For phase II or dose expansion cohorts of a phase I study, the Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy (phase I studies only if efficacy is objective of the protocol)
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Power analysis and/or interim analysis (if described in the protocol)
- Summary of toxicities separated by cohorts with the number of dose-limiting toxicities indicated
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

11 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form Medical and Surgical History	Prior to starting treatment
Concomitant Medications Form Toxicity Form	Continuous
PSA Form	Baseline, Week 1, Week 5, Post-RP Follow-Up Visit
Research Blood Form	Baseline, Week 5, Post-RP Follow-Up Visit
Treatment Summary Form	Completion of treatment
RP Form	Time of surgery
Progression Form	Time of disease progression
MedWatch Form	See Section 7.0 for reporting requirements
Death Form	At time of death

11.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 7.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

12 STATISTICAL CONSIDERATIONS AND EVALUATION OF RESULTS

12.1 Study Endpoints

See Section 2.4 for study endpoints.

12.2 Study Design

This is a single center phase 2 open label study of neoadjuvant ibrutinib in patients with localized prostate cancer.

12.3 Sample Size and Power Estimate

For this phase 2 study, the primary endpoint is the change of B cells between the pre-treatment biopsy and post-treatment RP specimen. Each patient’s response to neoadjuvant ibrutinib will be a binary classification. Patients will be considered to have a "positive" response if there is ≥2 fold decrease in the number of B cells, or considered to have a "negative" response if there is <2 fold decrease in the number of B cells. The accrual of 18 patients to the phase 2 trial and incorporation of 6 patients who received ibrutinib at MTD in the safety lead-in (a total of 24 evaluable subjects) will be sufficient to determine whether 20% or more of the cohort achieves this 2 fold decrease in B cells, compared to a null response of 5% or less of a reference group of patients who underwent RP without neoadjuvant treatment. This comparison has a power of 0.818 at a significance level of 0.044 based on a one-sided binomial exact test. If 4 more evaluable patients show a "positive" response, the treatment achieves the expected "response" rate of 20%.

The safety-run in will require 6 patients (with a potential for 6-12 more if dose de-escalation is required). The Phase II study will require a total of 24 patients on MTD and thus 18 additionally enrolled patients besides the 6 on MTD during the safety lead-in.

12.4 Replacement Policy

All patients who receive a dose of ibrutinib will be analyzed for safety and efficacy. Subjects who discontinue from study participation prior to receiving any dose of study therapy may be replaced. Subjects who have received any dose of study therapy will not be replaced for the safety and efficacy endpoints. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related AEs to grade 2 or lower. However, they will not be replaced. Patients enrolled during the safety lead-in who discontinue treatment during the DLT observation period for reasons other than a DLT will need to be replaced for DLT purposes.

Because there is a potential for loss of immune cell infiltration within the prostate tissue after >12 days of not receiving ibrutinib, any patient who undergoes RP after 12 days from the last dose of ibrutinib (i.e. from scheduling delay of RP) will be included in the final analysis; however, an additional patient will be accrued as replacement. This will keep the treatment uniform in order to evaluate for immune response. The maximum number of allowed replacement patients for delayed RP is 4.

12.5 Stopping Rules

If ≥2 patients experience DLTs during the safety lead-in, then the dose of ibrutinib will be reduced as follows:

- Level -1 840 mg/d x 2 weeks; if ≥ 2 of 6 DLTs are observed at Level -1, dosing will be de-escalated to Level -2
- Level -2 560 mg/d x 2 weeks

If ≥2 patients experience DLTs at Level -2, then the study will be terminated for lack of safety.

Toxicity is continuously monitored for all patients.

12.5.1 Non-hematological Toxicity and plans for data and safety monitoring

Early stopping of the Phase II phase of the trial will be based on unacceptable non-hematological toxicity. Approximately less than 15% of patients are expected to experience grade 3 and up toxicity and a non-hematological toxicity rate of 30% or more would definitely be unacceptable. Based on the sequential probability ratio test (SPRT) with 80% power and a 0.05 significance level, the study will be halted if 4 of the first 4, or 5 of the first 9, or 6 of the first 14, or 7 of the first 18, or 8 of the first 23, or if the 9th non-hematological toxicity is observed before the last patient has completed the trial. Accrual will be stopped and the event will be reviewed by the Data Safety and Monitoring Board if a grade 5 non-hematological toxicity is observed.

12.6 Analyses Plans

12.6.1 Analysis Population

All patients who receive a dose of ibrutinib will be analyzed for safety and efficacy. Subjects who discontinue from study participation prior to receiving any dose of study therapy may be replaced after discussion with the Study Monitor. Subjects who have received any dose of study therapy will not be replaced.

Demographic and baseline characteristics will be summarized by each cohort and overall. In general, frequency distribution and percentage will be used to summarize categorical measurements, while mean with standard deviation and median with range will be used to describe symmetric and skewed continuous measurements, respectively. Univariate analysis among variables will be assessed using the two-sample t-test, Wilcoxon-rank-sum test, Chi-square test, as appropriate.

12.6.2 Analysis of Primary Endpoints

12.6.2.1 Safety

SAEs and non-SAEs will be summarized by descriptive statistics.

12.6.2.2 Intratumoral Immune Infiltration

For all subjects, immune cell subsets and localization will be summarized by changes from baseline to after treatment. Patients will be considered to have a positive response if there is $\geq$2 fold decrease in the number of B cells, or considered to have a negative response if there is <2 fold decrease in the number of B cells. The proportion of patients who have "positive" responses will be reported, with 95% confidence intervals. Descriptive statistics will be used to describe pre-treatment biopsy immune infiltration, post-treatment RP immune infiltration, and immune infiltration of reference RP tissue.

12.6.3 Analysis of Secondary Endpoints

12.6.3.1 Circulating immune subsets

For each patient, flow cytometry of circulating immune cell subsets will also be performed on pre-treatment blood and again after RP. Established flow cytometry panels will examine B cell and T cell populations. Immune cell quantification will be summarized by changes from baseline to after treatment using descriptive statistics. Furthermore, paired Wilcox on signed-rank test will be applied to test the pre-post treatment changes. When available, immune cells digested from resected tumor tissues will also be assessed by flow cytometry.

12.6.3.2 Cytotoxic effects and clinical benefits: rate of downstaging, pT0 rate, ≥50% PSA decline (phase II)

Point estimates and 95% confidence intervals of pathologic T0 rate at the time of RP will be obtained for phase 2 subjects treated with ibrutinib. Pathologic T0 rate at the time of RP will be compared with the null hypothesis rate separately by using binomial test.

12.6.4 Analysis of Exploratory Endpoints

12.6.4.1 Assessment of Btk expression

Btk expression on tumor tissue from pre-treatment biopsies, RP specimens, and any other tumor biospecimens obtained will be evaluated immunohistochemically and graded as low, intermediate or high. Frequency distribution and percentage will be used to summarize Btk expression by pre- and post- treatment. In addition, Kappa statistics will be used to test if there is any change of Btk expression from pre-treatment biopsy to post-treatment RP tissue.

12.6.4.2 Assessment of PD-L1 expression

PD-L1 protein expression on tumor tissue from pre-treatment biopsies, RP specimens, and any other tumor biospecimens obtained will be evaluated immunohistochemically and scored on a scale of 0, 1, 2, or 3. We will categorize tumors based on the frequency of tumor cells or of immune cells staining positively for PD-L1 as follows: IHC 0: <1%, IHC 1: 1-<5%, IHC 2: 5-<10% and IHC 3: ≥10%. Frequency distribution and percentage will be used to summarize PD-L1 protein expression by pre- and post- treatment. Furthermore, McNemar's test will be used to assess the impact of the treatment on PD-L1 expression by considering IHC estimates of ≥10% as being positive.

12.6.4.3 TCR and BCR deep sequencing

For each individual dose level, and for the phase II cohort the change in tumor-infiltrating BCR and TCR between pre-treatment and post-RP after treatment will be assessed by calculating the number of unique clonotypes, read depth and Shannon diversity index. Repertoire overlap and change between sequencing experiments will be measured using Baroni-Urbani and Buser overlap index and Morisita's distance, respectively.

12.7 Reference Population

As discussed in the introduction (Section 1.1), in a prior study of neoadjuvant Sipuleucel-T, a negative control was felt to be important to be confident that the observed changes in the study population were due to treatment effect since the effect of systemic Sip-T administration on localized prostate cancer was unknown. Therefore, a group of 12 patients who had undergone RP at UCSF without any neoadjuvant therapy, were selected prior to undergoing any tissue analyses, and were matched to the study population using the UCSF CAPRA-S score for preoperative risk stratification - were used as a negative control. These patients were selected from the surgical population at UCSF who provided separate, written consent to the use of their RP specimens for research purposes.

Similarly, in this study, a cohort of 12 patients not treated with any neoadjuvant therapy will be used as a negative control, since the effect of neoadjuvant ibrutinib in prostate cancer tissue is unknown. Patients will be selected from the RP population at UCSF or Washington University who provided separate, written consent to the use of their RP specimens for research purposes, and will be matched to the phase II study population using the UCSF CAPRA-S score for preoperative risk stratification. This analysis will provide confidence that the changes observed in the prostates of treated patients are due to neoadjuvant treatment effect. These 12 patients will not otherwise be included in the analyses as delineated in 12.6.

12.8 Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the NCI CTCAE v4.0.

12.9 UCSF's Data

Data from the first three patients enrolled at UCSF will be shared with Washington University under a Data Use Agreement and analyzed under the auspices of this study.

13 REFERENCES

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APPENDIX 1: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*,, light housework, office work)
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair
5	Dead

APPENDIX 2: Prohibited and Restricted Medications

Generic name	Trade/Brand name (if applicable)
Bicalutamide	Casodex
Carbamazepine	Tegretol
Celecoxib	Celebrex
Ciprofloxacin	Cipro
Clarithromycin	Biaxin
Clopidogrel	Plavix
Dexamethasone	Decadron
Diltiazem	Cardizem
Enoxaparin	Lovenox
Finasteride	Proscar
Fluconazole	Diflucan
Flutamide	Eulexin
Itraconazole	Onmel, Sporanox
Ketoconazole	
Nilutamide	Nilandron
Phenytoin	Dilantin
Prednisone	Sterapred
Rifampin	Rifadin
Telithromycin	Ketek
Verapamil	Calan
Warfarin	Coumadin

Notes:

1. This list is not meant to be all-inclusive.
2. Any medications known to cause QT prolongation should be used with caution. Periodic ECG and electrolyte monitoring should be considered.

APPENDIX 3: SPECIMEN COLLECTION

A: For tissue analyses:

Paired pre- and post- treatment tumor tissue specimens will be collected in all patients and analysis will be performed per section 8. Specimens will be processed initially through the Tissue Procurement Core Facility.

B: For blood analyses:

All patients will have 8 (eight) 10mL tubes of blood specimens collected at baseline, at the end of ibrutinib therapy, and after RP. The collection will be divided into 60 mL in 6 EDTA tubes for PBMCs for immune monitoring and 20 mL in 2 EDTA tubes for plasma for cytokines.:

These specimens will be transported at room temperature to the Tissue Procurement Core Facility where they will processed using their SOPs to obtain plasma and PBMCs.

APPENDIX 4: CHILD-PUGH SCORE

Measure	1 point	2 points	3 points
Total bilirubin, µmol/L (mg/dL)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/L (g/dL)	>35 (>3.5)	28-35 (2.8-3.5)	<28 (<2.8)
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points	Class
5-6	A
7-9	B
10-15	C

Source:

1. Child CG, Turcotte JG. “Surgery and portal hypertension”. In Child CG. *The liver and portal hypertension.* Philadelphia:Saunders. 1964. pp. 50-64.
2. Pugh RN, Murray-Lyon IM, Dawson L, Pietroni MC, Williams R . “Transection of te oesophagus for bleeding oesophageal varices”. *The British journal of surgery*, 1973;60: 646-9.

APPENDIX 5: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/adevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX 6: Reporting Timelines

Expedited Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Pharmacyclics**
Serious AND unexpected suspected adverse reaction			Report no later than 15 calendar days after it is determined that the information qualifies for reporting	Report no later than 15 calendar days after the event
Unexpected fatal or life-threatening suspected adverse reaction			Report no later than 7 calendar days after initial receipt of the information	Report no later than 15 calendar days after the event
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment		
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.			
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.			

Expedited Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Pharmacyclics**
Protocol exception	Approval must be obtained prior to implementing the change			
Clinically important increase in the rate of a serious suspected adverse reaction of that list in the protocol or IB			Report no later than 15 calendar days after it is determined that the information qualifies for reporting	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.			
Breach of confidentiality	Within 10 working days.			
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days.			

Expedited Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Pharmacyclics**
	If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.			
Pregnancy/Other Malignancies/AESIs				Report no later than 15 days of learning of the event

Routine Reporting Timelines			
Event	**HRPO**	**QASMC**	**FDA**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.	The most current toxicity table from the DSM report is provided to the FDA with the IND's annual report.
Minor deviation	Report summary information at the time of continuing review.		
Complaints	If the complaint reveals an		

	unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.		
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.		