Official title: Pacritinib for Biochemical Relapse After Definitive Treatment for Prostate Cancer

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MEDICAL COLLEGE OF WISCONSIN
CANCER CENTER

A Single-Arm, Open-Label, Phase 2 Study Evaluating PacritiniB for Patients with BiochemicaL RelApse after Definitive Treatment for ProStaTe Cancer

Short Title:

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Marja Nevalainen, MD (CO-PI)

Current Version Number and Date
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Title: A Phase 2 Study of Pacritinib for the Management of Patients with Biochemical Relapse after Definitive Treatment for Prostate Cancer

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MCW Cancer Center

Drug supply
CTI BioPharma

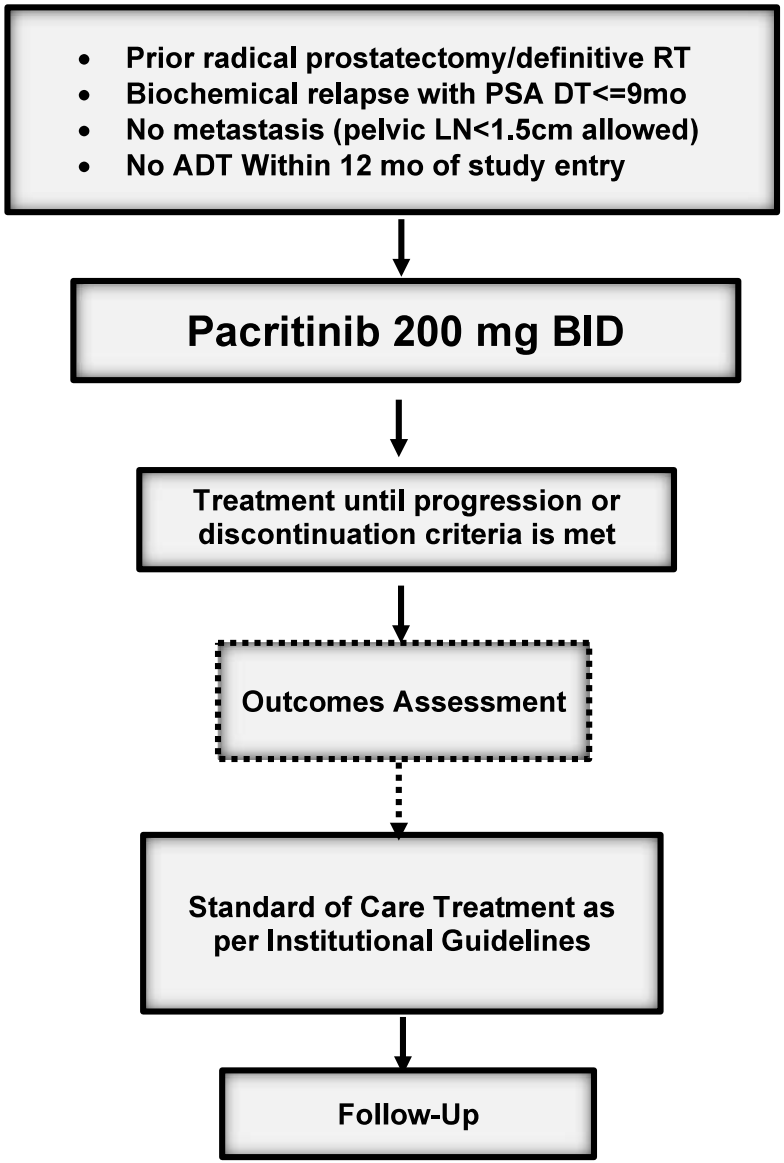
PROTOCOL SUMMARY

Title	A Phase 2 Study of Pacritinib for the Biochemical Relapse after Definitive Treatment for Prostate Cancer
IND Sponsor	Investigator-Sponsor
Principal Investigator	Deepak Kilari, MD
Clinical Trial Phase	Phase 2
Study Population	Patients with histologically or cytologically confirmed prostate adenocarcinoma, status post definitive treatment and biochemical recurrence.
Primary Objectives	To determine the effect of pacritinib on the time to PSA progression in patients with biochemical relapse of prostate cancer (defined as the length of time that a given subject will be alive and free from PSA progression per PCWG3 guidelines).
Secondary Objectives	1. To evaluate the absolute PSA nadir as a result of treatment. 2. To determine the time to PSA nadir from the start of treatment. 3. To determine the time to subsequent antineoplastic therapy 4. To determine the effect of investigational treatment on testosterone levels 5. To determine the safety and toxicities of the study drug.
Explorative Objectives	1. To determine the effect of study drug on comprehensive geriatric assessment domains. 2. To determine the effect of the study drug on short-term and long-term health-related quality of life (HRQOL) 3. To evaluate if positive status for Stat5 activation in the paraffin-embedded tissue sections of the most recent biopsy specimen has a trend to predict biochemical response to pacritinib treatment
Study Design	Single-arm, open-label study.
Study Agent	Pacritinib 200 mg BID.
Number of Subjects	N= 46. The first cohort of the study will enroll 10 patients. Enrollment to the second cohort(n=36) would be dependent on the response noted in the first cohort and funding.
Estimated Time to Complete Enrollment:	Approximately 12 months for the first 10 patients and 36 months for total study.

Inclusion criteria	▪ Histologically or cytologically confirmed prostate adenocarcinoma. ▪ Prior radical prostatectomy or definitive radiation therapy. ▪ Biochemically recurrent prostate cancer with PSA doubling time ≤ 9 months at the time of study entry. ▪ Prior adjuvant or salvage radiation or not a candidate for radiation based upon clinical assessment of disease. characteristics and patient comorbidities. ▪ Screening PSA > 0.5 ng/mL. ▪ No definitive evidence of metastases on screening imaging per the judgment of the investigator. Pelvic lymph nodes measuring 1.5 cm or less in short axis diameter are allowed. ▪ Screening serum testosterone > 50 ng/dL. ▪ Eastern Cooperative Oncology Group (ECOG) Performance Status grade 0-1 or Karnofsky Performance Status ≥ 70. ▪ Age ≥ 18 years. ▪ Absolute neutrophil count ≥ 500/ µL, ▪ Agrees to use a condom (even men with vasectomies) and another effective method of birth control if he is having sex with a woman of childbearing potential. ▪ Adequate organ function. ▪ Left ventricular cardiac ejection fraction of ≥ 50% by echocardiogram or multigated acquisition scan. ▪ Adequate coagulation defined by prothrombin time/international normalized ratio and partial thromboplastin time ≤ 1.5x ULN.
Exclusion criteria	▪ Prior systemic treatment with androgen deprivation therapy and/or first-generation anti-androgen (e.g. bicalutamide, nilutamide, flutamide) for biochemically recurrent prostate cancer (prior systemic treatment in the neoadjuvant, setting with definitive and/or salvage RT allowed as long as the interval between completion of systemic treatment and the start of pacritinib ≥12 months) ▪ Prior treatment with CYP17 inhibitor (e.g., ketoconazole, abiraterone acetate, galeterone) or next-generation androgen receptor antagonist including apalutamide or enzalutamide. ▪ Prior chemotherapy for prostate cancer ▪ Use of 5-alpha reductase inhibitor within 42 days before randomization. ▪ Use of investigational agent within 28 days before randomization. ▪ Use of other prohibited medications within seven days before Cycle 1 Day 1 on study. ▪ Prior bilateral orchiectomy. ▪ Uncontrolled hypertension. ▪ Gastrointestinal disorder affecting absorption or the ability to swallow tablets. ▪ Baseline severe hepatic impairment (Child-Pugh Class B & C) ▪ Intercurrent illness that is not controlled, such as active infection, psychiatric illness/social situations that would limit compliance with study requirements.

	▪ Any chronic medical condition requiring a higher dose of corticosteroid than the equivalent of 10-mg prednisone /prednisolone per day.
Statistics	A two-stage design based on the methods of Huang et al (2010) will be used. The null hypothesis that the median PSA-progression-free survival is six months will be tested against a one-sided alternative by for the six-month PSA-progression-free survival probability exceeding 50%. The study is designed to have 80% power to obtain a result significant at a one-sided 10% level if the experimental treatment has a six-month PSA-progression-free probability of 66%, which corresponds to a median of 10 months if the time to PSA progression is exponentially distributed. The design is based on a modification of a binomial two-stage design that allows the incorporation of data from subjects with less than six months of follow-up at the interim analysis. The study will enroll up to 46 subjects with an interim analysis performed when 10 patients have been treated and followed for six months.
Pacritinib Dosage Modifications	Pacritinib dosage may be interrupted or modified for pacritinib-related hematologic toxicities, hemorrhage, severe infections, cardiac toxicities (including QTcF interval prolongation and reduction in ejection fraction), diarrhea, and other pacritinib-related nonhematologic toxicities. Pacritinib dosage may also be held for invasive procedures or at the discretion of the investigator. Refer to Section 5.2 for pacritinib dosage management guidelines.
Safety	Safety and tolerability will be assessed primarily by the incidence, severity, and change from baseline in safety parameters, such as treatment-emergent AEs (TEAEs; including SAEs), laboratory values, cardiac assessments, and vital signs.

STUDY SCHEMA



RT–radiation therapy
BID- twice a day
ADT-androgen deprivation therapy
LN-lymph node
DT-doubling time

STUDY CALENDAR

Study Assessments	Screening[1]	Cycle 1[2]		Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6 and beyond (Treatment till progression)	Progression +/- 7[14]	End of treatment[1] [2] (EOT) visit	Follow-up (2 years)[3]
		Each Cycle (28 days)								30-day post-last dose Safety Visit (±7 days)	Every 6 months post EOT visit (±21days)
	Day – 30 to -1	(in Days)						Every 2 months (± 7 days)			
		1	15±3	±3	±3	±3	±3				
Informed consent	X										
Medical History[11]	X										
AE reporting		Recorded from Day 1 through 30 days after the last dose of study drug.									
Concomitant Medications		Recorded from the signing of the ICF through 30 days after the last dose of study drug.									
Physical Exam	X	X		X	X	X	X	X	X	X	X
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[5]	X	X		X			X	X[5]			
Transthoracic echocardiogram (TTE)[6]	X			X			X	X[6]			
Comprehensive Geriatric Assessment	X					X					
Tissue for STAT 5 analysis [10]	X										
Serum PSA	X	X		X	X	X	X	X	X	X	X
Serum Testosterone	X					X					
CBC w/ Diff	X	X	X	X	X	X	X	X	X	X	
Blood Chemistry[8]	X	X	X	X				X	X	X	

Study Assessments	Screening[1]	Cycle 1[2]		Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6 and beyond (Treatment till progression)	Progression +/- 7[14]	End of treatment[1] [2] (EOT) visit	Follow-up (2 years)[3]
		Each Cycle (28 days)								30-day post-last dose Safety Visit (±7 days)	Every 6 months post EOT visit (±21days)
	Day – 30 to -1	(in Days)						Every 2 months (± 7 days)			
		1	15±3	±3	±3	±3	±3				
Coagulation (PT/PTT) and Hb A1C	X										
Research blood draw		X		X		X			X		
CT of Abdomen and Pelvis. /CT urogram/MRI abdomen and pelvis/PET [9, 13,15]	X					X			X		
Bone scan[9, 13, 15]	X					X			X		
Chest Imaging[9,15]	X								X		
Pacritinib dispense		X[7]		X[7]	X	X	X[7]	X[7]			
Patient-reported outcome instrument: - FACT-P	X					X			X		

1. All screening procedures must occur within 30 days prior to treatment initiation.
2. Day 1 assessments are required to be performed prior to initiation of study treatment and can be performed up to 24 hours prior to initiation of study treatment. Study days are to be counted based on the start of treatment.
3. If a subject has disease progression or subject withdrawal, then they will be followed as per follow-up requirements. Patients will be in follow up for 2 years from EOT visit.
4. Vital signs include systolic and diastolic blood pressure, pulse, respiratory rate, temperature, and body weight.
5. A 12-lead ECG (collected in triplicate), including QTcF, will be performed at Screening, and then predose at C1D1, C2D1,, C5D1, C7D1, and every four months (every other cycle/odd cycles) thereafter provided normal QTcF.. if QTc is prolonged, more frequent monitoring will be done after discussion with sponsor. For patients who have discontinued treatment, ECGs are to be performed at the End-of-Treatment Visit but are not otherwise required
6. TTE will be performed at screening, C2D1, C5D1, C8D1, and every six months thereafter (every 3 cycles) provided normal LVEF and no

clinical evidence of heart failure. Window for all TTEs is -14 days from Day 1 of the cycle it is due for.

7. On days when ECGs are to be obtained, Pacritinib will be administered in the clinic to facilitate the performance of pre-dose assessments
8. Serum chemistry values will include ALT/SGPT, AST/SGOT, alkaline phosphatase, bilirubin (total, direct, and indirect) creatinine, LDH, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, BUN/urea, albumin, glucose, cholesterol (fasting not required), and uric acid. Serum chemistry results obtained from unscheduled visits should be entered into the electronic database. Additional serum chemistry testing should be done as clinically indicated.
9. Unscheduled visits should include physical examination, laboratory tests, and radiographic evaluations as clinically indicated in the judgment of the investigator and these results must be entered into the clinical database (e.g., electronic data capture). Additional visits may be required for patients who have pacritinib dose modifications due to hematologic, cardiac, diarrhea, or other non-hematologic toxicities. Results of clinical laboratory assessments at unscheduled visits should be entered into the electronic database.
10. Core biopsy or surgical specimens from primary prostate cancer prior to administration of Jak2 inhibitor as well as other archive tissue (if available) will be used for study biomarker assessments. Tissue from surgical specimen will be preferred over core biopsy specimens when available. One hematoxylin and eosin slide and five unstained slides from formalin-fixed, paraffin-embedded pathology blocks with cancer will be reserved for study labs/biomarkers. If adequate tissue is not available, the patient would still qualify and be enrolled to the study.
11. Including demographics form
12. Treatment duration is expected to be 2 years. Patients may continue drug beyond 2 years, if in the opinion of the treating physician, the patient is benefitting from treatment and benefits outweigh the risks of therapy.
13. imaging due at Cycle 4 has a 14-day window
14. If any of the required progression assessments have already been completed in the last 30 days, at the treating physician's discretion, they do not need to be repeated.
15. If PSMA/Axumin PET imaging is performed at baseline, other imaging is not required in addition to PET. Different modalities may be used at each imaging timepoint based on treating provider and insurance preference.

LIST OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BUN	Blood Urea Nitrogen
CBC	Complete Blood Cell (Count)
CDK	Cyclin-Dependent Kinases
CQ	Chloroquine
CR	Complete Response
CRC	Clinical Research Coordinator
CRF	Case Report Form
CSF	Cerebral Spinal Fluid
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T Cell
CTO	Clinical Trials Office
DFS	Disease-Free Survival
DLT	Dose-Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ER	Estrogen Receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GVHD	Graft-Versus-Host Disease
HCT	Hematopoietic Cell Transplantation
HGB	Hemoglobin
IP	Investigational Product
IRB	Institutional Review Board
LDH	Lactate Dehydrogenase
MCWCC	Medical College of Wisconsin Cancer Center
MTD	Maximum-Tolerated Dose

NCI	National Cancer Institute
ORR	Overall Response Rate
PBMC	Peripheral Blood Mononuclear Cells
PD	Disease Progression
PK	Pharmacokinetics
PSGL-1	P-selectin Glycoprotein Ligand-1
PR	Partial Response
RBC	Red Blood Cell (Count)
ROS	Reactive Oxygen Species
SAE	Serious Adverse Event
SD	Stable Disease
SD	Standard Deviation
SRC	Scientific Review Committee
ULN	Upper Limit of Normal
UP	Unanticipated Problem
UPIRSO	Unanticipated Problems Involving Risks to Subjects or Others

TABLE OF CONTENTS

1 BACKGROUND

1.1. Prostate cancer

Prostate cancer (PC) is the most common non-cutaneous malignancy among elderly men, with more than 60% of all PC cases diagnosed in men over 65 years of age. (1) The estimated prevalence of PC in men aged 75 years and older is currently more than a million and expected to quadruple by 2030, given the long natural history of the disease and aging of the population. (2, 3) Systemic disease from prostate cancer includes biochemical recurrence (a rise in PSA after definitive treatment with no radiographic evidence of disease elsewhere), as well as overt metastatic disease confirmed by imaging. Once the disease is systemic, the goal of treatments is palliative, and physicians should take into account therapy-related side effects, which can adversely affect the quality of life.

Recurrent PC with a short PSA doubling time (≤ 9 months) represents a high-risk subpopulation with a significant risk of PC-related mortality. The median PC-specific survival for patients with rapidly rising serum PSA is approximately five years, which is comparable to patients with limited metastatic castration-sensitive disease (< 4 bone metastases and/or node-only soft tissue involvement).

Intermittent androgen deprivation therapy (ADT) achieved with GnRH agonist or antagonist is considered the standard of care for biochemical relapse. Side effects of ADT include but are not limited to weakness, osteoporosis, muscle wasting, metabolic syndrome, hot flashes, increased risk of diabetes, cardiovascular disease, depression, impotence, falls, and cognitive/mood disorders. (4-7) While these untoward effects are tolerable in the young fit population, they lower the quality of life significantly. Importantly, they can have significant adverse consequences in elderly cancer patients with preexisting comorbidities and functional impairment. (5, 7, 8) Once ADT is initiated for systemic disease, it is usually continued for life.

Given the mechanism of ADT, it is postulated that these effects are a direct result of low testosterone. In many elderly men, their testosterone levels do not return to pre-ADT levels after ADT is discontinued. Therefore, even a limited trial of ADT may leave them at risk for long-lasting adverse effects from hypogonadism. Approximately one-third of patients are deemed high risk for side effects and toxicities from ADT. (5) Despite often being asymptomatic from systemic cancer and in the absence of a clear survival benefit with early initiation of ADT, older patients continue to be subjected to substantial side effects from ADT with a decline in quality of life, falls (due to muscle weakness) and exacerbation of underlying chronic diseases (such as heart disease); **hence there is an urgent and unmet need to explore alternate non-hormonal options for PC therapy.**

*Our data that are described in the next section support a **novel concept** that Stat5 is a driver of androgen receptor(AR) gene expression in PC, and the Jak2-Stat5 pathway represents a target to inhibit expression of diverse AR and AR-V species and thereby control of hormone-sensitive and castrate-resistant PC (CRPC) growth.*

1.2 Jak2-Stat5 signaling pathway

The Janus kinases (JAKs) are a family of cytoplasmic tyrosine kinases (TYKs) consisting of JAK1, JAK2, JAK3, and TYK2. They play a pivotal role in the signaling pathways of numerous cytokines, hormones, and growth factors. Their intracellular substrates include the signal transducer and activator of transcription (STAT) family of proteins.

The JAK/STAT pathways, through the proper actions of the ligands, regulate important physiological processes, such as the immune response to viruses, hematopoiesis, lactation, and lipid homeostasis. However, dysfunctional signaling caused by a myriad of factors results in pathological conditions, such as allergies, asthma, rheumatoid arthritis, severe combined immune deficiency, and hematological malignancies. In particular, mutations in the JAK2 gene have been associated with myeloproliferative disorders (MPDs), including polycythemia vera (PV), essential thrombocythemia (ET), and idiopathic myelofibrosis (MF).

The incidence of the JAK2V617F mutation, as determined by an allele-specific polymerase chain reaction in granulocytes from patients with MPDs, occurs in 35% to 50% of patients with primary MF (PMF), 32% to 57% of patients with ET, and 74% to 97% of patients with PV. This mutation, however, can also be found on rare occasions in patients with other chronic myeloid diseases, including myelodysplastic syndrome (MDS), MDS/MPDs, and unclassifiable MPD. There is strong evidence that the JAK2 mutation (and corresponding continuously active JAK2 tyrosine kinases) significantly contributes to the existence and progression of the disease. Its inhibition thus presents a suitable target for drug development. Even in patients without JAK2 mutation, the JAK/STAT pathway may be deregulated, and these patients may also benefit from JAK2 inhibitor therapy.

Stat5 comprises two highly homologous isoforms Stat5a (94 kDa) and Stat5b (92 kDa) (referred to as Stat5) which are nucleocytoplasmic proteins acting both as signaling proteins and nuclear transcription factors.(9-13) Stat5 becomes activated by phosphorylation of a conserved C-terminal tyrosine residue(11) by Jak2 tyrosine kinase in PC(14-18) and forms functional dimers that translocate to the nucleus and bind to specific Stat5 DNA response elements.(11) Jak2, in turn, has a catalytically active kinase domain (JH1) located at the C-terminus juxtaposed to the regulatory pseudokinase domain (JH2).(19, 20) Upon cytokine activation, amino acid residues Tyr1007/1008 in the activation loop of the JH1 are rapidly autophosphorylated in *trans*, leading to full catalytic activity of Jak2 kinase.(19, 20)

1.3 Transcription factor Stat5 and PC Growth:

Numerous studies by our team and others have provided the *proof-of-concept* that Stat5 is an inducer of PC growth.(17, 18, 21-41) The blockade of Stat5 signaling induces the apoptotic death of PC cells. Conversely, overexpression of active Stat5 induces the proliferation of PC cells in culture and promote robustly the growth of PC tumors in mice.(29) In 30–40% of advanced CRPCs, the chromosome 17 locus encompassing *STAT5A* and *STAT5B* genes undergoes amplification, resulting in increased Stat5 protein levels.(29) Notably, high nuclear Stat5 protein expression in clinical PCs, at the time of the initial treatment, predicted recurrence of the disease in three independent cohorts totaling 1,035 patients.(40, 41) Our recent study shows that combined positive status for ***both*** Stat5 gene locus amplification and protein expression indicated 55–60% disadvantage in recurrence-free survival at seven years after radical prostatectomy (RP) in univariate analysis and was independently associated with shorter progression-free survival (HR=3.62, p=0.021, 95%CI=1.22-10.78) in multivariate analysis, including the CAPRA-S nomogram variables(42) in a cohort of 300 PC patients treated with RP only.(41) These findings demonstrating the predictive value of active Stat5 for clinical PC progression to castrate-resistant lethal state(40, 41) **illustrate the significance of Stat5 in PC growth and progression in patients and corroborate the results in preclinical PC models.(17, 18, 21-38)**

While the significance of Stat5 in promoting the growth of PC has been well demonstrated, the mechanisms underlying how Stat5 sustains PC cell viability are largely unclear. The effects of

active Stat5 signaling on inducing PC cell proliferation, antagonizing apoptosis, and promoting CRPC growth mimic closely those of AR effects on PC cells. Our data support a new paradigm of Stat5 critically sustaining AR mRNA and protein expression in PC. These data indicate that Stat5 signaling represents a significant driver of AR signaling network and its phenotypic effects on PC. **Inhibitors of Jak2-Stat5 signaling may serve as a new class AR- antagonists for PC therapy.**

1.4 Genetic Stat5 inhibition suppresses AR protein and mRNA expression in PC

To investigate whether AR is a Stat5 target gene in PC, Stat5 was inhibited in a comprehensive panel of six PC cell lines by lentiviral expression of Stat5a/b targeting shRNA (Stat5 shRNA), and the mRNA levels of FL-AR, AR-V7 and AR-V9 were evaluated by quantitative RT-PCR. Stat5 knockdown downregulated mRNA levels of both full-length-AR and the AR splice variants ARV-7 and ARV-9. Noteworthy, the degree of AR and AR-V inhibition achieved by Stat5 knockdown was at the same level or higher than direct depletion of AR with lentiviral expression of AR shRNA in all PC cell lines tested (***Figure 1***). Stat5 knockdown reduced the mRNA levels of full-length AR, AR-V7, and AR-V9 by 80-90% in eight days after lentiviral Stat5 shRNA expression, shown in ***Figure 1***.

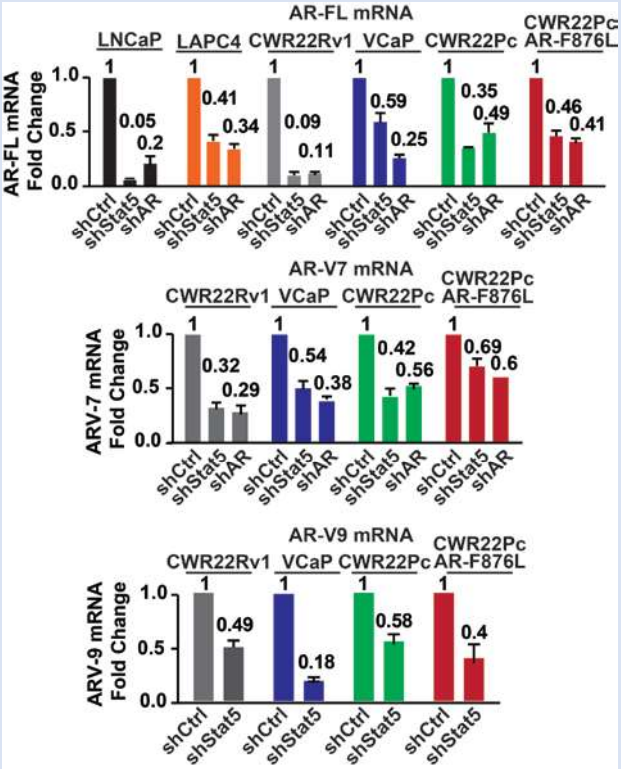


Fig.1. Stat5 knock-down depletes AR mRNA expression in PC cells. Stat5a/b was inhibited by lentiviral expression of Stat5a/b shRNA (shStat5a/b) or non-target shRNA (shCtrl) in PC cell lines for 72 h, followed by RNA extraction and quantification of FL-AR, AR-V7 and AR-V9 mRNA levels by qRT-PCR.

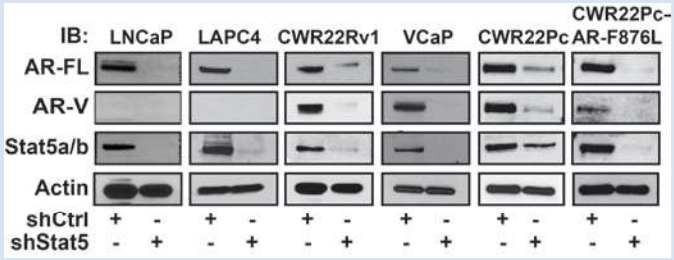


Fig. 2. Stat5 drives AR protein expression in PC cells. Immunoblotting (IB) of AR in PC cells 72 h after lentiviral expression of Stat5 shRNA (shStat5a/b) vs. control shRNA (shCtrl). Effective genetic depletion of Stat5a/b and equal loading are demonstrated by IB with anti-Stat5a/b and anti-actin antibodies of whole cell lysates (WCLs), as indicated.

We further evaluated whether Stat5 suppression of AR mRNA levels leads to downregulation of AR protein levels in PC. ***Figure 2*** shows that genetic depletion of Stat5a/b by lentiviral expression of Stat5 shRNA resulted in reduced AR protein expression in all PC cell lines tested. Genetic knockdown of Stat3 did not affect AR mRNA levels (data not shown), indicating this effect is specific to Stat5.

Given that inhibition of Stat5 in PC resulted in downregulation of AR expression in PC, we next tested whether activation of Stat5, in turn, upregulates AR expression in PC. Constitutively active mutants of Stat5a/b (CAStat5a/b; Stat5aS710F, Stat5bS715F)(18) were lentivirally expressed in

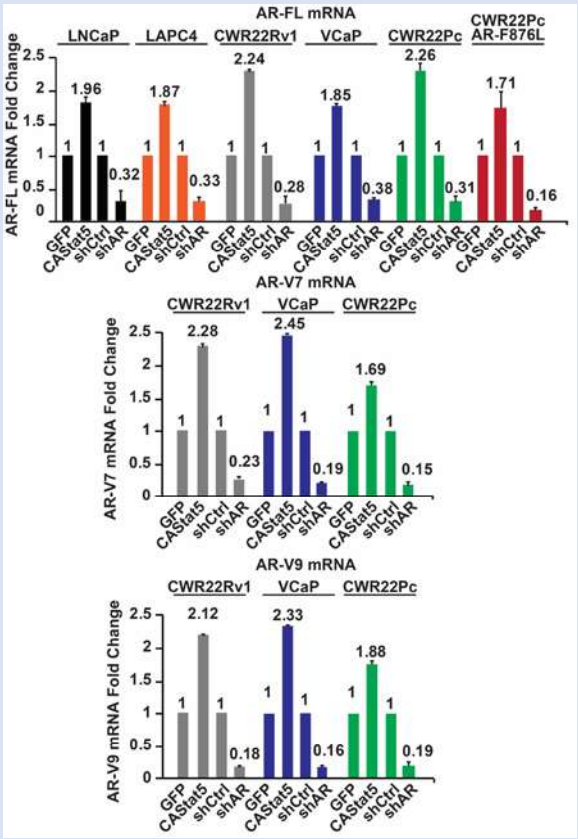


Fig. 3. Active Stat5 induces a robust increase in AR mRNA levels in both androgen sensitive and CRPC cells. Stat5a/b signaling was increased by lentiviral expression of constitutively active (CA) Stat5a/b or GFP (control) for 72 h in PC cell lines followed by RNA extraction and quantification of FL-AR, AR-V7 and AR-V9 mRNA levels by qRT-PCR.

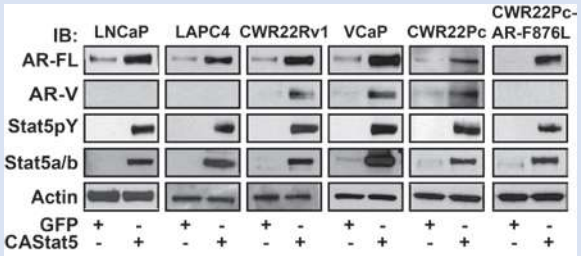


Fig.4. Active Stat5 induces a robust increase in AR protein levels in PC cells. Stat5a/b signaling was increased by lentiviral expression of constitutively active (CA) Stat5a/b or GFP (control) for 72 h in PC cell lines followed by IB analysis of AR protein levels. Increased active Stat5a/b levels and equal loading are demonstrated by IB with anti-Stat5pY mAb and anti-actin pAb of WCLs.

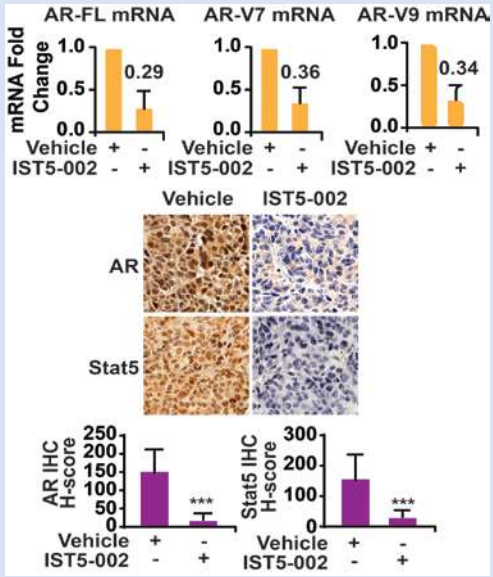


Fig.5. Pharmacological Stat5 inhibition decreases AR protein and mRNA levels in PC xenograft tumors in nude mice. Nuclear AR and Stat5 levels were detected by immunostaining of paraffin-embedded tissue sections of CWR22Pc tumors from mice treated with IST5-002 (IST5) (40 mg/kg; i.p.) for 40 days. AR mRNA levels were evaluated by qRT-PCR.

a panel of six PC cell lines, and mRNA levels of full-length AR and AR splice variants (AR-V7, AR-V9) were determined by quantitative RT-PCR. Expression of CAStat5a/b resulted in a uniform increase in mRNA levels of full-length AR, AR-V7, and AR-V9 in all PC cell lines tested, as shown in ***Figure 3.*** Furthermore, expression of CAStata/b resulted in a robust increase in AR protein expression in all PC cell lines tested, shown by immunoblotting in ***Figure 4. In summary, our data show that active Stat5 induces FL-AR and AR-V mRNA levels resulting in robustly increased AR protein expression in both androgen sensitive and CRPC.***

We next sought to evaluate if Stat5 regulation of AR mRNA and protein levels is evident in an *in vivo* setting where PC cells were grown as xenograft tumors in mice. CWR22Pc cells (1.5×10^7) were inoculated subcutaneously (s.c.) into the flanks of nude mice. After tumors reached ~100 mm^3 in size (12 d), mice were treated with a specific Stat5 inhibitor IST5-002(24) (40 mg/kg; i.p.) or vehicle (0.3% hydroxypropyl cellulose/H_2O) (5 mice/group). AR mRNA and protein levels were evaluated by q-RT-PCR(43) and by immunohistochemistry (IHC), as previously described.(39-41, 44, 45) As shown in ***Figure 5***, suppression of Stat5 by IST5-002 resulted in a marked decrease in AR mRNA and protein expression in PC xenograft tumors *in vivo*.

In conclusion, these data indicate that Stat5 is a critical inducer of full-length AR and AR-V7 mRNA expression not only in cell culture models of PC but also in PC xenograft tumors grown in vivo in mice.

Pharmacological Jak2 inhibition:

The discovery and identification of the Jak2V617F mutation causing constitutive activation of Jak2 in patients with myeloproliferative disorders (MPDs)(46-50) triggered the development of small-molecule Jak2 inhibitors to specifically target hyperactive Jak2 signaling. Predominantly utilizing structure-based drug design, the current Jak2 inhibitors target both wild-type Jak2 and the mutated Jak2 in an ATP-competitive manner occupying the ATP-binding pocket.(51) This is termed Type I mode of inhibition which stabilizes the kinase in its active conformation.(52) Numerous Type I Jak2 inhibitors differing in structure, specificity against wild-type vs. mutated Jak2, and selectivity for different Jak family members, are at different stages of clinical development.(51) CHZ686 is a Type II Jak2 inhibitor, which binds Jak2 in the inactive conformation, where the inhibitor occupies the ATP binding site and an induces hydrophobic pocket stabilizing the conformation.(52) CHZ686 is not in clinical development.

Ruxolitinib (53-55) is a first-in-class, orally available Type I inhibitor of Jak1 and Jak2 which is FDA approved for MPDs and is currently being tested for efficacy in rheumatoid arthritis (RA) and psoriasis.(51) AZD1480 (56) is a potent early Jak1/2 inhibitor which, unfortunately, was withdrawn from clinical development because of neurotoxicity. Baricitinib (57) is another first-generation Jak1/2 inhibitor, which is structurally related to RUXO with predominant indication for RA and psoriasis (58). New generation Type I Jak2 inhibitors include momelotinib, (59) gandotinib,(60) fedratinib, (61-65) and pacritinib (66-72). Fedratinib is currently FDA approved for MPDs, and pacritinib (NCT03165734), momelotinib (NCT04173494) and gandotinib (NCT01594723) are being tested in phase III trials for MPDs.

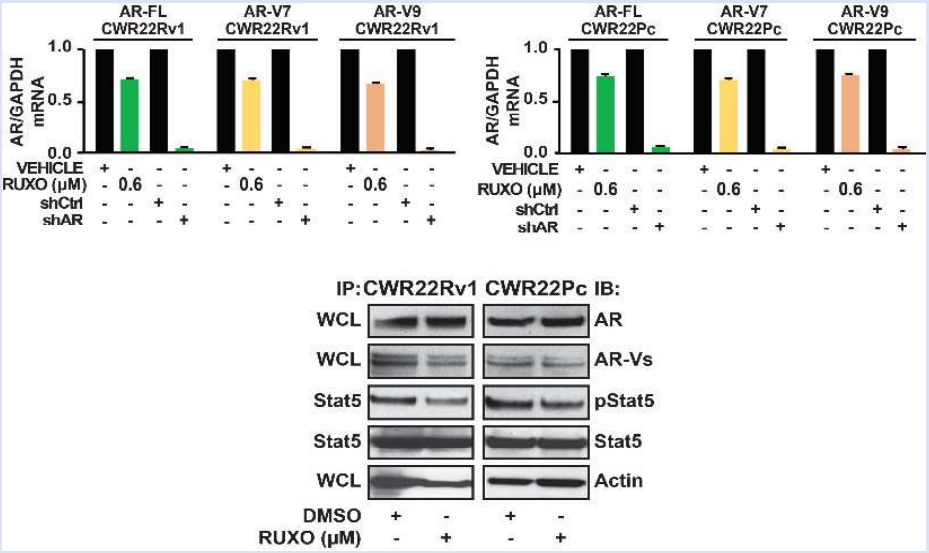


Fig.6a. Ruxolitinib (RUXO) does not effectively suppress Jak2-Stat5 signaling, AR levels and PC cell viability in PC cells. CWR22Rv1 and CWR22Pc PC cells were treated with RUXO at 0.6 μM for 3 days followed by RNA extraction and quantification of FL-AR, AR-V7 and AR-V9 mRNA levels by qRT-PCR. PC cells with lenti-viral expression of shAR were used as control for the q-PCR of AR regulation. Analysis of the Stat5 activation was analyzed by immunoprecipitation of Stat5 followed by immunoblotting with anti-pYStat5 ab and the AR protein levels were evaluated by immunoblotting of whole cell lysates (WCL) with anti-AR ab. Equal loading is demonstrated by IB with anti-Stat5a/b and anti-actin antibodies of whole cell lysates (WCLs).
AR protein levels was conducted by immunoprecipitation (IP) and immunoblotting (IB). Equal loading is demonstrated by IB with anti-Stat5a/b and anti-actin antibodies of whole cell lysates (WCLs).

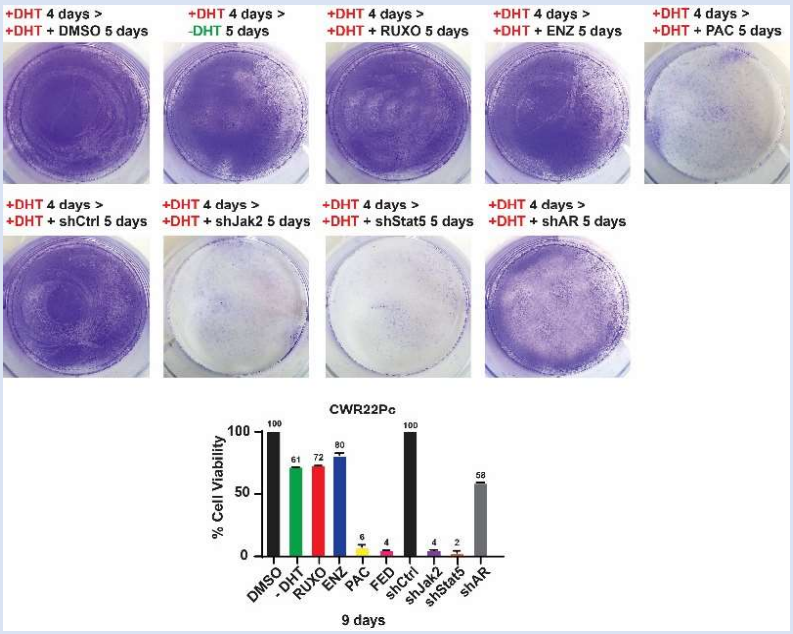


Fig.6b. Treatment of PC cells with Ruxolitinib (RUXO) (600 nM) did not affect PC cell viability when compared to treatment of the cells with Pacritinib (PAC) (600 nM), which decreased the fraction of viable CWR22Pc PC cells more effectively than androgen deprivation (-DHT), lenti-shJak2, lenti-shStat5 or lenti-shAR. Attached viable cells were visualized by crystal violet staining and counting (graphs).

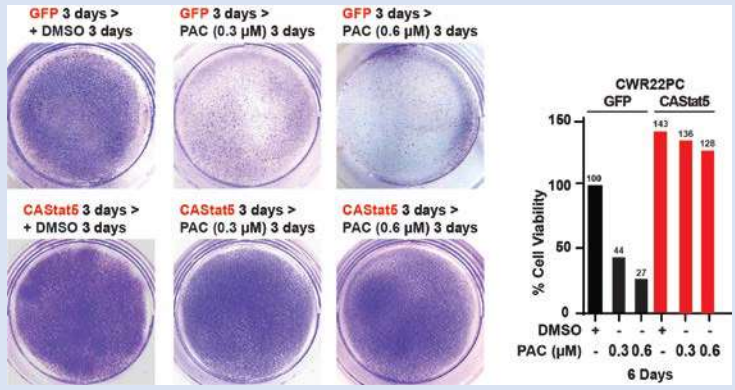


Fig.7. Expression of constitutively active Stat5 (CASTat5) counteracts the effect of Pacritinib in reducing PC cell viability. CAStat5 was lentivirally expressed in CWR22Pc PC cells for 3 days prior to treatment of the cells with Pacritinib at 300 or 600 nM concentrations for 3 days. Attached viable cells were visualized by crystal violet staining and counting (graphs).

Pacritinib was tested for efficacy in non-small cell lung cancer (NSCLC) (NCT02342353), but the trial was terminated because of drug shortage. In addition, Pacritinib has been tested in phase II trial for refractory colorectal cancer (NCT02277093) but the trial was terminated because of lack of efficacy(73).

The key adverse effects noted in this trial included nausea, abdominal discomfort, constipation and fatigue.(73) Of the other Type I Jak2 inhibitors, both ruxolitinib and momelotinib have been tested for efficacy in solid tumors (NCT0063878;03274778; 03878524;02711137; 02101021;02244489; 02206763; 02258607); these were terminated due to lack of efficacy. Specifically, ruxolitinib displayed no efficacy in a phase II trial in metastatic CRPC (NCT0063878). However, it is important to note that the potency of ruxolitinib and momelotinib against cells expressing wild-type Jak2 vs. the mutated Jak2V617F is largely unclear. Clinical PC does not to harbor the Jak2V617F mutation,(74) which explains our findings showing that both ruxolitinib and momelotinib (data not shown) are very weak inhibitors of Jak2-Stat5 pathway in PC (***Figure 6 a and b***). At the same time, ***our data show potent suppression of Jak2-Stat5 pathway in PC by pacritinib (Figures 7–10), which makes pacritinib an excellent candidate for therapy development for recurrent PC.***

As shown in ***Figure 6b***, we compared the efficacy of pacritinib vs. ruxolitinib to suppress PC cell viability vs. androgen deprivation (-DHT), lenti-shStat5, lenti-shJak2 or lenti-shAR. Treatment of CWR22Pc PC cells with 600 nM pacritinib (PAC) led to remarkable decrease in the fraction of viable PC cells after five days of exposure to pacritinib (PAC). At the same time, similar treatment

of the PC cells with ruxolitinib (600 nM) did not affect the viability of the cells. Importantly, pacritinib, lentiviral expression of shStat5 or shJak2 (vs. shCtrl) were all significantly more robust inducers of cell death than androgen deprivation itself (-DHT) or lentiviral expression of shAR in PC cells (***Figure 6b***). At the same time, lentiviral expression of constitutively active Stat5 (CAStat5) abolished the growth suppression induced by pacritinib in PC cells (***Figure 7***).

To evaluate the efficacy of PAC in suppressing AR in PC models, PC cell lines were treated with different concentrations of PAC. Jak2 activity was inhibited by Jak2 inhibitor pacritinib (PAC) in PC models. (71, 72, 75, 76). Pharmacological Jak2 inhibition by pacritinib caused a dose-dependent reduction in both FL and AR-V AR mRNA and protein levels in CWR22Rv1 and CWR22Pc PC cell lines (***Figure 8***). Furthermore, we compared the potency of research grade pacritinib (MedChem Express) vs. clinical grade pacritinib in suppressing AR mRNA and protein expression in PC cells lines. The clinical grade pacritinib showed greater potency in suppressing AR mRNA and protein expression in PC cells compared to the research grade pacritinib, likely due to the purity level of the compound (***Figure 8***). Of note, similar to pacritinib, other Jak2 inhibitors, such as AZD1480, gandotinib and baricitinib, all suppress Stat5 and AR levels in PC cells (data not shown).

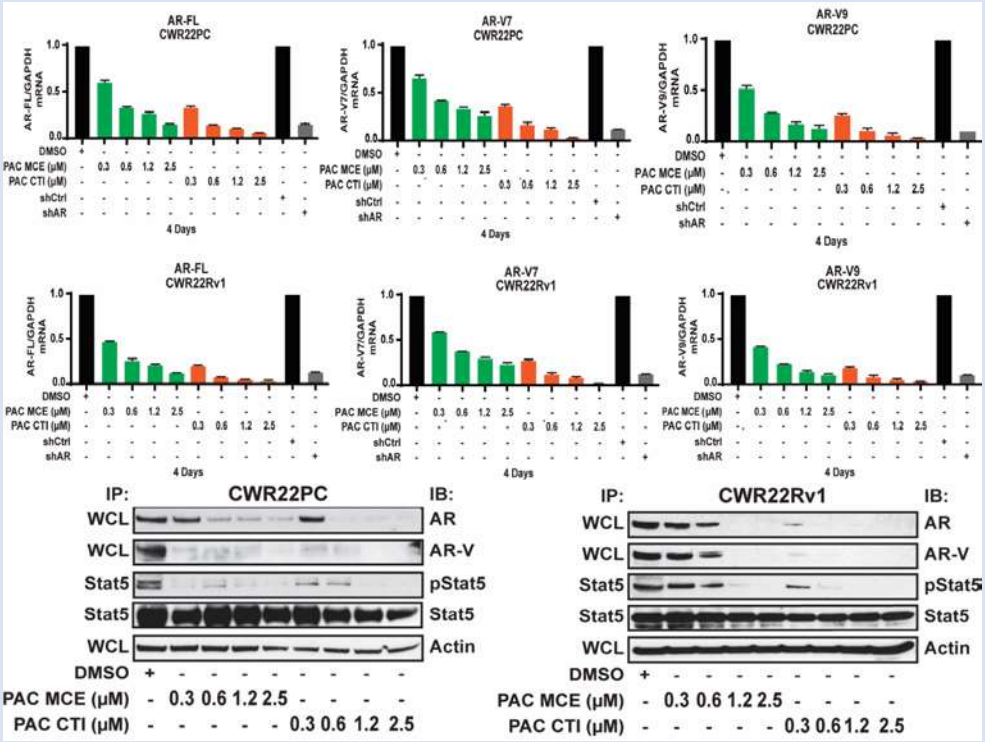


Fig. 8. Pharmacological inhibition of Jak2-Stat5 by Pacritinib suppresses AR mRNA and protein levels in PC cells. The clinical grade Pacritinib (PAC) (from CTI-BioPharma; CTI) is more potent in suppressing androgen receptor (AR) mRNA and protein expression in prostate cancer (PC) cells than the research grade PAC from MedChem Express (MCE). CWR22Pc and CWR22Rv1 cells were treated with PAC (CTI vs. MedChem Express) for 3 days at indicated concentrations followed by RNA extraction and quantification of FL-AR, AR-V7 and AR-V9 mRNA levels by qRT-PCR. PC cells with lenti-viral expression of shAR were used as control for the q-PCR of AR regulation. Analysis of the AR protein levels was conducted by immunoprecipitation (IP) and immunoblotting (IB). Equal loading is demonstrated by IB with anti-Stat5a/b and anti-actin antibodies of whole cell lysates (WCLs).

To evaluate if Jak-Stat5 inhibition suppresses AR mRNA and protein levels in clinical patient-derived PCs, we utilized *ex vivo* PC tumor explant culture model we have previously established. (17, 18, 39, 77-83) In essence, the finding of Stat5 regulating AR mRNA in PC cell lines was recapitulated in patient-derived PC tissues cultured *ex vivo* in 3D tumor explant cultures for seven days in the presence or absence of the Stat5 inhibitor IST5-002(24) or the Jak2 inhibitor PAC. As shown in ***Figure 8***, both FL-AR and AR-V7 mRNA levels were decreased in 3D tumor explants by either IST5-002 (patients nos. 1 and 2) or

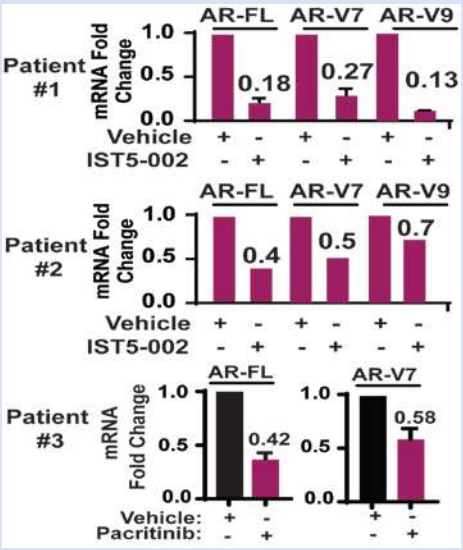


Fig.8. Inhibition of Stat5 by IST5-002 or PAC suppress AR mRNA levels in patient-derived PCs cultured *ex vivo*. Clinical PCs (n=3) obtained from prostatectomies were cultured for 7 days *ex vivo* in 3D tumor explant cultures in the presence of Stat5 inhibitor IST5-002 (12.5 μM) or PAC (1 μM) vs. vehicle. AR mRNA levels were analyzed by q-PCR.

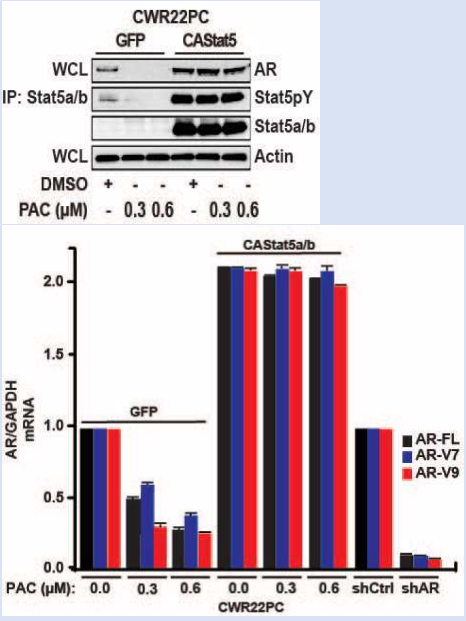


Fig. 10. Expression of constitutively active Stat5 (CAStat5) counteracted the Pacritinib-induced suppression of AR mRNA and protein expression in prostate cancer cells. CAStat5 vs. GFP were lentivirally expressed in PC cells for 72 h prior to treatment of the cells with PAC at indicated concentrations for 72 h. Stat5 and AR protein levels were evaluated by IP and immunoblotting. FL-AR, AR-V7 and AR-V9 mRNA levels were determined by qRT-PCR.

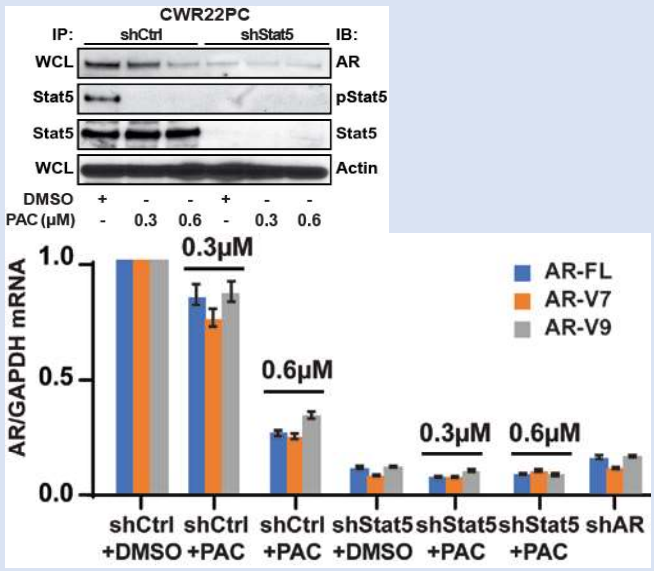


Fig. 9. Pacritinib does not further reduce AR mRNA and protein levels in PC cells after genetic depletion of Stat5. Stat5 was genetically down-regulated by lentiviral expression of shStat5 vs. shCtrl for 48 h followed by Pacritinib treatment of the cells for 72 h. Immunoblotting (IB) of AR in PC cells 72 h after lentiviral expression of Stat5 shRNA (shStat5a/b) vs. control shRNA (shCtrl). Stat5 and AR protein levels were evaluated by IP and immunoblotting. FL-AR, AR-V7 and AR-V9 mRNA levels were determined by qRT-PCR.

PAC (patient no. 3). Collectively, these data indicate that Jak2-Stat5 axis is critical for FL- AR and AR-V7 mRNA expression not only in cell culture or xenograft PC tumor models of androgen sensitive and CRPC, but also in clinical patient-derived PCs.

In order to investigate whether the regulatory effect of pacritinib on AR mRNA and protein expression is mediated by Stat5, we first overexpressed constitutively active Stat5 (CAStat5) vs. GFP by lentivirus in PC cells for three days followed by pacritinib treatment of the cells for three days. As shown in ***Figure 9***, expression of active Stat5 entirely abolished the suppressive effect of pacritinib on AR protein and mRNA expression in PC cells. In parallel experiments, we evaluated if pacritinib is able to further reduce AR protein and mRNA expression after genetic depletion of Stat5. In these experiments, Stat5 levels were suppressed by lentiviral expression of shStat5 for three days followed by pacritinib treatment for three days (***Figure 10***). The data show that pacritinib did not further reduce AR levels after genetic depletion of Stat5 in PC cells (***Figure 10***). ***In summary, these data indicate that the regulatory effects of pacritinib on the AR mRNA and protein levels in PC cells are mediated by Stat5.***

In conclusion, pharmacological inhibition of Jak2-Stat5 signaling by pacritinib results in extensive

death of PC cells. Specifically, pacritinib-induced loss of PC cell viability is greater than that of androgen deprivation. These data provide a solid scientific background for the clinical trial described here.

1.5 Pacritinib

Pacritinib is a novel JAK2/fms-like receptor tyrosine kinase 3 (FLT3) inhibitor that has demonstrated promising antitumor activity in two mouse models of human malignancies. Preclinical toxicology studies have identified a safe starting dosage for clinical studies. The potential indications that may be targeted include (i) PV, ET, and MF, all of which are MPDs with a high frequency of a *JAK2V617F* mutation;(ii) certain leukemias and lymphomas where other forms of JAK aberrations have been reported; and (iii) acute myeloid leukemia, in which FLT3 inhibitors have shown preliminary clinical promise.

1.5.1 Pharmacology

Pacritinib is a potent, selective inhibitor of JAK2 and FLT3 kinase activities (50% inhibitory concentration.[IC50=23 nM and 22nM respectively) as well as JAK2V617F mutant kinase activity (IC50=19 nM). Pacritinib is also a potent inhibitor of cellular proliferation in human leukemia and lymphoma cell lines selected for their dependence on the target kinases. Consistent with these activities, exposure to pacritinib resulted in the reduction of phospho-JAK2, phospho-STAT3, or phospho-STAT5 in the relevant cell lines.

Pharmacokinetics in Animals
Pharmacokinetics (PK) following single intravenous (i.v.) or oral administration of pacritinib were evaluated in mice, rats, and dogs. Following oral administration, pacritinib showed rapid absorption in mice (time of maximum concentration [Tmax] from 0.5 to 1.3 hours) and moderately fast absorption in rats and dogs (Tmax ~4 hours). The oral terminal half-lives were 2.2, 5.7, and 4.4 hours in mice, rats, and dogs, respectively. As measured by liver blood flow, the systemic clearance of pacritinib from plasma was high in mice (8 L/h/kg) and dogs (1.6 L/h/kg) and moderate in rats (1.6 L/h/kg). The i.v. terminal half-lives were 5.6, 6, and 4.6 hours in mice, rats, and dogs, respectively. The oral bioavailability of pacritinib was 39% in mice, 10% in rats, and 24% in dogs

1.5.2 Preclinical Toxicology

The adverse effects of pacritinib were evaluated in 30-day repeated oral dose toxicity studies with 14-day recovery in both mice and dogs, and in 26- and 39-week chronic toxicity studies in mice and dogs, respectively. Key findings included dose-dependent leukopenia accompanied by neutropenia (dog) and neutrophilia (mice) that partially reversed during recovery. Mice also showed dose-dependent but reversible thrombocytosis and anemia. In the chronic toxicity studies, low magnitude decreases in neutrophils and RBC parameters were observed. No treatment-related hepatic changes were observed. with the exception of increased aspartate transaminase (to +109%, male dogs) and increased triglycerides (to +57%, male and female dogs).

In the 30-day study in dogs, animals receiving mid and high dosages of pacritinib experienced vomiting and diarrhea that increased in severity despite treatment with antiemetic and antidiarrheal medication. Similarly, in the 39-week study in dogs, an increased incidence of

nausea and vomiting was observed at dosages of 20 mg/kg/day and higher. Periods of low food consumption in individual animals receiving 40 and 50 mg/kg/day were accompanied by rapid weight loss (which was controlled and reversed with subcutaneous fluid and supplemental food) and were considered treatment related and adverse. Based on these studies, the no observed adverse effect level was determined to be 100 mg/kg BID in mice and 10 mg/kg BID in dogs.

1.5.3 Summary of Clinical Pharmacology and Phase 1 Studies with Healthy Volunteers with Pacritinib

To date, the Sponsor has completed two PK studies for pacritinib in healthy volunteers, including a food effect study (SB1518-2010-006) characterizing the effects of a high calorie, high-fat meal on the bioavailability and PK of pacritinib and a study assessing inter- and intra-individual variability of oral pacritinib in healthy volunteers under fasted conditions at 100 mg, 200 mg and 400 mg doses (SB15182010-004). Also, the single and multiple-dose population PK of pacritinib has been characterized following multiple-dose administration of pacritinib in two studies (SB1518-2007-001 and SB1518-2008-003) in patients with advanced myeloid malignancies.

After the administration of single doses of pacritinib in a randomized, three-treatment, three-period crossover study (SB1518-2010-004) in healthy volunteers under fasting conditions, peak plasma concentrations were reached at a median Tmax ranging from 4.5 to 5.5 hours across the 100 to 400 mg dose range. While between-patient variability was relatively high (28% to 45%), the within-patient variability was low (13% to 15%), highlighting the consistent systemic exposure for pacritinib in individual patients. The mean elimination half-life was approximately 34 hours and was not dependent on dose. The systemic exposure of pacritinib in healthy volunteers was comparable to that in patients. After oral administration of single 200-mg doses (2×100 mg capsules) of pacritinib under fed and fasted conditions in study SB1518-2010-006, the 90% confidence intervals for the geometric mean ratios (fed to fasted) for maximum concentration observed (Cmax), area of the curve up to the last measurable concentration (AUC0-t), and area under the curve to infinite time (AUCinf) were between 80% and 125%, demonstrating lack of an effect of food on absorption. Given this data, pacritinib can be orally administered without regard to timing of meals.

Pooled analyses of PK assessments from the two completed clinical studies in patients at pacritinib dosages up to 600 mg once daily (QD) showed slow absorption (Tmax four to six hours) and dose-related increases in systemic exposure up to 400 mg QD. The rate of absorption was linear at doses up to 300 mg and thereafter appeared to be rate limited. Therefore, modeling suggested that, at doses of over 200 mg per day, divided doses would yield increased steady study blood levels. Beyond the 400 mg QD dosage, there was a minimal increase in exposure with doses up to 600 mg QD suggesting an involvement of a saturable process in oral absorption of pacritinib. In addition, the results demonstrated a prolonged elimination half-life (mean Day 1 half-life=47 hours), supporting a QD regimen of pacritinib in clinical development. Comparison of systemic exposure of pacritinib on Days 1 and 15 showed a 1.5- to 2-fold increase in systemic exposure at steady state.

1.5.4 Overview of Clinical Studies of Pacritinib in Patients with Myelofibrosis

Approximately 967 individuals have received pacritinib in 15 completed studies, which includes 552 patients with myelofibrosis who were assigned to a pacritinib arm. Completed studies include two controlled studies in myelofibrosis, four uncontrolled clinical studies in cancer patients, and

nine clinical pharmacology/pharmacokinetic studies. The summary below describes efficacy and safety observations from across the completed controlled (phase 3) studies in myelofibrosis.

Phase 3 Myelofibrosis Study

PERSIST-1 was the first phase 3 study of pacritinib, comparing the efficacy of 400 mg QD with best available therapy (not including ruxolitinib) in patients with PMF, PPV-MF, or PET-MF. Patients previously treated with JAK2 inhibitors were excluded. There were no exclusion criteria based on platelet count. Three hundred twenty-seven patients (327) were randomized in a 2:1 allocation to pacritinib or best available therapy (BAT). PERSIST-1 demonstrated a statistically significant improvement in the primary endpoint of percent of pacritinib-treated patients achieving a ≥35% reduction in spleen volume at Week 24 compared to baseline, as assessed by centrally read MRI or computed tomography [CT] imaging), compared to best available therapy. Pacritinib efficacy in SVR response was not affected by baseline thrombocytopenia (<50,000/μL or <100,000/μL platelets), compared to BAT (prespecified subgroup intent-to-treat [ITT] <50,000/μL: 22.9% versus 0% SVR response, respectively; <100,000/μL: 16.7% versus 0% SVR response, respectively), although statistical significance could not be determined in accordance with the pre-specified statistical analysis plan. More patients treated with pacritinib had improved MF-related symptomatology, meeting the predefined TSS response definition (≥50% reduction at Week 24 compared to baseline, as assessed by Myeloproliferative Neoplasm-Symptom Assessment Form Total Symptom Score version 2.0 (MPN-SAF TSS 2.0) than those treated with BAT, but this trend was not statistically significant. In general, safety was similar to that seen in early phase studies, although interim OS results were consistent with a negative trend in survival in pacritinib-treated patients, and there were imbalances in fatal and life-threatening events, including intracranial hemorrhage, and arrhythmias including sudden death.

PERSIST-2 was the second phase 3 study of pacritinib, comparing the efficacy of 400 mg QD and 200 mg BID with the best available therapy, including ruxolitinib, in patients with PMF, PPV-MF, or PET-MF and thrombocytopenia (baseline platelet count ≤100,000/μL). Patients previously treated with JAK2 inhibitors were included. There were no exclusion criteria based on platelet count. Three hundred eleven patients (311) were randomized in a 1:1:1 ratio to the three treatment arms. Due to Full Clinical Hold on February 8, 2016, only 211 of the accrued patients were evaluable in the ITT (efficacy) population, having been randomized with sufficient time to reach the Week 24 evaluation window, thus limiting the power to detect differences in the efficacy endpoints.

PERSIST-2 demonstrated a statistically significant improvement in the coprimary endpoint comparing the pooled pacritinib arms with the BAT arm for the percent of pacritinib-treated patients achieving a ≥35% reduction in spleen volume at Week 24 compared to baseline (SVR response), as assessed by centrally read MRI or CT imaging, compared to best available therapy (18.1% vs. 2.8%, p=0.0011). More patients in the pooled pacritinib had improved MF-related symptomatology, meeting the predefined TSS response definition (≥50% reduction at Week 24 compared to baseline, as assessed by MPN-SAF TSS 2.0, TSS response) than those treated with BAT, but this trend in the second co-primary endpoint was not statistically significant (24.8% vs. 13.9%, p=0.791). Comparing the individual pacritinib treatment arms to BAT, SVR response was nominally significant for BID (21.6%) vs. BAT (p=0.0007), and for QD (14.7%) vs. BAT (p=0.0173).

Unlike the pooled coprimary analysis, the BID arm had nominal significance for TSS response vs. BAT (32.4% vs. 13.9%, p=0.0106), but the QD arm did not (17.3%, p=0.6524). Exploratory analyses most relevant to the current study showed that in comparison with the ruxolitinib-treated

BAT patients, more pacritinib-treated patients achieved the SVR response than patients treated with either ruxolitinib or other BAT agents (QD 11/75, 14.7%; BID 16/74, 21.6%; ruxolitinib 1/32, 3.1%; other BAT 1/40, 2.5%). Similarly, more pacritinib 200 mg BID (but not 400 mg QD) patients achieved the MPN-SAF TSS2.0 response (pacritinib 24/74, 32.4% vs. ruxolitinib 6/32, 18.8%), despite the increased effect of ruxolitinib compared to all other BAT patients (4/40, 10%).

Interim analyses of the PERSIST-2 study led to Full Clinical Hold due to interim OS results in which the pooled pacritinib treatment arms (QD + BID) were compared with BAT and concerns about fatal intracranial hemorrhage, cardiac failure, and cardiac arrest. Updated analyses based on the locked database demonstrated that the QD dosing arm had a survival decrement compared to BAT (hazard ratio [HR]=1.18; p=0.6615), but the BID dosing arm had a trend for survival benefit (HR=0.68; p=0.3458).

In general, the safety observed in PERSIST-2 was similar to that observed in PERSIST-1, although differences were seen between the QD and BID pacritinib dosing arms. Except for hemorrhage, BID dosing generally was associated with lower rates of adverse events (AEs), including grade 3/4 and fatal events. The pacritinib BID arm had greater apparent efficacy for both SVR and reduction in TSS than either pacritinib dosed at 400 mg QD or BAT. Based on these efficacy data, the dose of 200 mg BID has been selected as the upper-level dosage regimen for the current dose-ranging study.

Most relevant to the current study, the safety impacts of prior JAK2 inhibitor treatment in PERSIST-2 were compared to patients who did not have such prior treatment. Incidences of treatment-emergent AEs (TEAEs) overall followed a similar pattern in the prior JAK2 inhibitor treatment and no prior JAK2 inhibitor treatment subgroups in the pacritinib and BAT treatment arms (pacritinib, 98.1%, and 96.3%, respectively; BAT, 90.4% and 87.0%, respectively), with a comparable incidence in the QD and BID dosing arms. While thrombocytopenia showed similar rates between subgroups, anemia was increased in the no prior treatment group (pacritinib, 15.5% [13.5% QD and 17.6% BID] and BAT, 11.5% in the prior treatment group, and pacritinib, 35.5% [42.3% QD and 29.1% BID] and BAT, 19.6% in the no prior treatment group). Diarrhea, nausea, and vomiting had increases in incidence in the prior treatment group compared to the no prior treatment group.

The percentages of patients who experienced TEAEs of CTCAE grade 3 in the pacritinib QD + BID pooled arms and BAT arms were 35.9% and 26.9%, respectively, in patients with prior treatment and 36.4% and 28.3%, in patients with no prior treatment. When comparing the incidence of grade 3 events in the QD and BID arm in each subgroup, there was an increased incidence of events in the QD arm in the prior treatment subgroup (44.2% compared to 27.5%) and an increased incidence of events in the BID arm in the no prior treatment subgroup (40.0% compared to 32.7%). The percentage of patients who experienced TEAEs of CTCAE grade ≥3 in the pacritinib and BAT arms were 70.9% and 42.3%, respectively, in patients with baseline prior treatment and 74.8% and 56.5% respectively, in patients with baseline no prior treatment.

The rates of grade 3/4 TEAEs in the QD and BID pacritinib groups were similar to those observed in the pacritinib QD + BID pooled arms. The rates of grade 3/4 thrombocytopenia and more notably, anemia events were decreased in the prior treatment group (prior treatment: pacritinib, 12.6% [QD 11.5% and BID 13.7%] and BAT, 9.6%; no prior treatment: pacritinib, 35.5% [QD 42.3% and BID 29.1%] and BAT, 19.6%). Fatal TEAEs occurred at modestly higher rates in the prior treatment group compared to the no prior treatment group in the pacritinib arms, particularly in the pacritinib QD arm, (12.6% [QD 17.3% and BID 7.8%] compared to 9.3% [QD 11.5% and

BID 7.3%]). The BAT arm showed a reverse pattern, with fatal events increased in the no prior treatment group compared to the prior treatment group (13.0% versus 5.8%).

Adverse Events in the Myelofibrosis Population

Overall, amongst the MF subjects treated with pacritinib in the completed controlled and uncontrolled studies, 96% experienced a treatment-emergent AE. The most common TEAEs (> 10% of subjects) occurred in the SOCs of gastrointestinal disorders (including diarrhea [66%], nausea [37%], vomiting [24%], abdominal pain [16%] and constipation [13%]), blood and lymphatic system disorders (including anemia [28%] and thrombocytopenia [25%]) and general disorders (fatigue [22%], pyrexia [12%] and decrease appetite [13%]). Events of dizziness (10%), dyspnea, epistaxis, and pruritus (all 11%) were also observed.

The most commonly (>10% of all subjects) reported treatment-related TEAEs by the preferred term, were in the SOC of gastrointestinal disorders including diarrhea (62%), nausea (31%) and vomiting (18%), and the SOC of blood and lymphatic system disorders, including thrombocytopenia (16%) and anemia (15%). While GI-related events were common, they were generally reversible, of low grade, and rarely led to treatment discontinuation. The potential risk of hypersensitivity reaction with pacritinib is low. Pacritinib is contraindicated in patients with a known hypersensitivity to the active substance or any of the excipients. Potential mechanisms include an immune-mediated response to pacritinib or any of the excipients of the product.

Summary of the PAC203 Phase 2 Dose-Finding Study in Myelofibrosis

The fully enrolled phase 2 component of Study PAC203 is a dose-finding study in patients with primary or secondary MF (Dynamic International Prognostic Scoring System [DIPSS] risk score of Intermediate-1 to High Risk) who experienced intolerance or treatment failure with ruxolitinib. The patient population in Study PAC203 was selected in recognition of safety concerns concerning pacritinib that were brought to light during the PERSIST-1 and -2 studies to balance the potential for risk with the unmet medical need in patients who failed to achieve or maintain benefit from the only approved agent for MF.

Patients who are refractory to ruxolitinib are likely to have high molecular risk disease and poor survival (median: 13 to 14 months) (Newberry et al 2017; Kuykendall et al 2018; Pacilli et al 2018). As such, these patients have a lower likelihood of achieving SVR and overall poor prognosis. Enrollment was not restricted based on platelet count. The primary objective of the study is to determine the optimal dosage of pacritinib, spanning the dose-response curve for safety and efficacy established in previous phase 1/2 clinical studies and the phase 3 PERSIST-1 and -2 studies.

Patients were randomized 1:1:1 to 200 mg pacritinib BID, 100 mg pacritinib BID, or 100 mg pacritinib QD, and randomization was stratified by geographic region and baseline platelet count. A total of 165 patients were randomized in the phase 2 portion of Study PAC203, and 161 (97.6%) patients received any treatment with pacritinib. Median platelet count was 55,000//µL and 76% met criteria for ruxolitinib failure, 73% for ruxolitinib intolerance, and 50% for both.

PAC203 Phase 2 Safety Observations

The most common treatment-emergent non-hematologic AEs were GI, including diarrhea (23.6%) and nausea (23.6%), and were distributed similarly across treatment arms. The most common hematologic AEs were thrombocytopenia and anemia, both occurring at higher frequencies in the

200 mg pacritinib BID group (35.2% and 24.1%, respectively); this did not, however, lead to higher rates of grade 3 /4 hemorrhage at higher doses (200 mg pacritinib BID: 5.6%; 100 mg pacritinib BID: none; and 100 mg pacritinib QD: 7.7%). A slightly higher percentage of patients in the 200 mg pacritinib BID group had grade 3 or 4 TEAEs (74.1%) compared with the other treatment groups, possibly due to higher rates of thrombocytopenia and anemia at baseline in the 200 mg pacritinib BID group compared with the other treatment groups. Across the treatment groups, no notable shifts from Baseline to a higher worst post-baseline grade were observed for hemoglobin, platelets, leukocytes, neutrophils, lymphocytes, or partial thromboplastin time (PTT). The incidence of clinically significant laboratory abnormalities was low across the treatment groups.

Overall, 19.3% of patients had a TEAE leading to study drug interruption, and the incidence was higher in the 200 mg pacritinib BID group compared with the other treatment groups. The most common TEAE leading to study drug interruption was thrombocytopenia (3.7%). The most common type of TEAE leading to study drug interruption was in the system organ class of infections and infestations (5.6% overall); the incidence was higher in the 200-mg pacritinib BID group (11.1%) compared with the other treatment groups (100-mg pacritinib BID group: 5.5%; 100 mg pacritinib QD group: none). One of the infections was an opportunistic infection (herpes esophagitis in the 200 mg pacritinib BID group). Altogether, 17.4% of patients had a TEAE leading to study drug discontinuation, and the incidence was higher in the 100 mg pacritinib BID group compared with the other treatment groups. The most common TEAE leading to study drug discontinuation was thrombocytopenia (3.7% overall).

Grade 3 or 4 TEAEs were reported by 104 patients (64.6%), and the most common TEAEs (>10%) by worst grade 3 or 4 were thrombocytopenia (20.5%) and anemia (12.4%). The incidence of grade 3 or 4 thrombocytopenia and anemia was higher in the 200 mg pacritinib BID group compared with the other treatment groups. However, dose modifications due to thrombocytopenia and anemia occurred in all arms; rates of discontinuation due to these events were low overall but slightly more common at higher doses:

Overall, 39.8% of patients had an SAE and the incidence was higher in the 200-mg pacritinib BID group (46.3%) compared with the other treatment groups (100-mg pacritinib BID: 36.4%; 100-mg pacritinib QD: 36.5%). Overall, the most common SAEs were pneumonia (5.6%), pyrexia (5.0%), dehydration (3.1%), sepsis (2.5%), and urinary tract infection (2.5%). The most common SAEs in the 200-mg pacritinib BID group were in the system organ class of infections and infestations. A total of 15 patients (9.3%) died on the study, of which 10 deaths (6.2%) occurred on treatment or within 30 days of treatment discontinuation. On-treatment deaths were due to cardiac failure, disease progression, general physical health deterioration, sepsis, tuberculosis, subdural hematoma, subdural hemorrhage, myeloproliferative disorder, and respiratory failure.

Adverse Events of Interest

Hemorrhage AEs of special interest (AESIs) were reported in 56 patients (34.8%), of which the incidence was higher in the 200-mg pacritinib BID group (42.6%) compared with the other treatment groups (100-mg pacritinib BID: 25.5%; 100-mg pacritinib QD: 36.5%). The most common hemorrhage AESI was epistaxis (10.6% overall). Most of the hemorrhage events (37 of 56; 66.1%) were reported within the first eight weeks of treatment. Overall, grade 3 or 4 treatment-emergent hemorrhage was reported in seven patients (4.3%): three patients (5.6%) in the 200-mg pacritinib BID group (GI hemorrhage, epistaxis, and hematoma), no patients in the 100-mg pacritinib BID group, and four patients (7.7%) in the 100-mg pacritinib QD group (muscle hemorrhage, epistaxis, and two events of hematuria). Two grade 5 bleeding events were reported,

one in the 200-mg pacritinib BID group (subdural hematoma/injury) and one in the 100-mg pacritinib BID group (subdural hemorrhage/injury). Study drug was discontinued for three patients due to hemorrhage events (subdural hemorrhage, hematoma, and one patient with both epistaxis and hematuria). The study drug was interrupted for two patients due to hemorrhage events (epistaxis and mouth hemorrhage). All other patients with bleeding events continued treatment without any dose reduction or interruption.

Cardiac AESIs were reported in 45 patients (28.0%) and the incidence was higher in the 200-mg pacritinib BID group (40.7%) compared with the other treatment groups (100-mg pacritinib BID: 21.8%;100-mg pacritinib QD: 21.2%). The most common cardiac AESI was peripheral edema (13.0% overall). Most of the cardiac events (27 of 45; 60.0%) were reported within the first eight weeks of treatment. Overall, grade 3 or 4 treatment-emergent cardiac events were reported in nine patients (5.6%): two patients (3.7%) in the 200-mg pacritinib BID group (supraventricular arrhythmia, cardiac failure, and peripheral edema),4 patients (7.3%) in the 100-mg pacritinib BID group (splenic infarction, cardiac failure, and two events of ejection fraction decreased), and three patients (5.8%) in the 100-mg pacritinib QD group (syncope and two events of ejection fraction decreased). One grade 5 cardiac failure was reported for a patient in the 100-mg pacritinib BID group.

The mean change in the QT interval corrected by the Fridericia method (QTcF) from baseline across the treatment groups was approximately 10 ms and no patient had QTcF >500 ms at any time point. No patients had left ventricular ejection fraction (LVEF) <20%. Overall,15 % had LVEF≤ 50% with the incidence being highest in the 100-mg pacritinib BID group (12.7%) compared with the other treatment groups (200-mg pacritinib BID: 9.3%; 100-mg pacritinib QD:5.8%). Overall, the median worst LVEF change post-baseline ranged from 2.0% to 2.5% across the treatment groups.

PAC203 Phase 2 Benefit/Risk Conclusion

Administration of 200-mg pacritinib BID was generally well tolerated. The most common treatment-emergent non-hematologic AEs were GI, including diarrhea and nausea, which were distributed similarly across treatment arms. The most common hematologic AEs were thrombocytopenia and anemia, both occurring at higher frequencies in the 200-mg pacritinib BID group, however, this did not lead to higher rates of grade 3/4 hemorrhage at higher doses.

The benefit/risk profile of 200-mg pacritinib BID supports continued investigation of this dose in the Phase 3 PACIFICA study comparing pacritinib with physician's choice (P/C) therapy for patients with MF and severe thrombocytopenia.

1.5.5 Rationale for Dosage Selection

The early clinical development program for pacritinib consisted of two-phase 1/2 dose-escalation studies (Studies 001 and 003) spanning a dose range of 100 to 600 mg QD in patients with advanced myeloid malignancies and chronic idiopathic MF. The maximum-tolerated dose in both studies was determined to be 500 mg QD. Based on favorable observations from both studies, the 400-mg QD dose level was advanced into the first phase 3 (PERSIST-1) clinical study in patients with MF. The most common AE observed in phase 1, phase 2, and PERSIST-1 was diarrhea, which was effectively managed with administration of anti-diarrheal agents and/or study drug interruption or dose reduction.

Population pharmacokinetic (PPK) analysis suggested that a higher steady-state and daily exposure to pacritinib could be achieved by dividing the 400-mg QD dose into a 200-mg BID dosing regimen. Informed by these results, the second phase 3 (PERSIST-2) study evaluated the efficacy and safety of a 200-mg BID regimen as well as the 400-mg QD regimen. Observationally, the results of PERSIST 2 demonstrated that the 200-mg BID regimen showed better efficacy relative to BAT for both SVR and TSS as compared to the 400 mg QD regimen.

To identify an optimal dosage of pacritinib for further clinical development in MF, a phase 2 dose-ranging study (PAC203) was initiated, and enrollment was completed in January 2019. Three dosage levels (100 mg QD, 100 mg BID, and 200 mg BID) were selected to allow adequate characterization of dose-response relationships for the efficacy and safety of pacritinib. PPK and exposure-response analysis utilizing clinical PK/PD data from all completed clinical studies along with data from 54 patients and 109 patients from Week 24 and Week 12, respectively, in the PAC203 study showed that systemic exposure (area under the curve [AUC], Cmax, and minimum concentration observed [Cmin]) of the 100-mg QD and 100-mg BID regimens is, as originally predicted, well below that of the 400-mg QD and 200-mg BID regimens. Simulation results indicate that AUC and Cmin are similar between 200 mg BID and 400 mg QD while the median peak concentration (Cmax) is higher with 200 mg QD; however, there is considerable overlap.

Pacritinib exposure and the occurrence of the most common AEs of interest (diarrhea, vomiting, nausea, thrombocytopenia, hemorrhage, anemia, and cardiovascular events) were evaluated using clinical data from PERSIST-1, PERSIST-2, and the interim data from PAC203. The exposure-safety analysis showed no correlation between pacritinib exposure and the occurrence of the most common AEs of interest except for GI AEs (including diarrhea, vomiting, and nausea) and cardiovascular (CV) AEs. The model predicted the probability of GI AEs for the 200-mg BID dose was approximately 14% and approximately 7% for CV AEs.

Taken together, the exposure-efficacy and exposure-safety analyses based on the PERSIST studies and the safety and efficacy observations from the PAC203 Phase 2 study indicate that the 200 mg BID is an appropriate dose for investigation in a phase 3 study.

2 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

Jak2-Stat5 signaling pathway sustains the expression of androgen receptor (AR) and AR variants (AR-Vs) in PC cells. Inhibition of Jak2-Stat5 signaling depletes expression of AR and AR-Vs in PC cell lines, in xenograft tumors grown in nude mice and in patient-derived clinical PCs grown in tumor explant cultures ex vivo. We hypothesize that pacritinib through inhibition of the JAK2-STAT 5 signaling pathway would induce biochemical responses in men with systemic PC by depleting expression of AR and AR-V.

2.1 Primary Objectives

To establish the effect of pacritinib on the time to PSA progression in patients with biochemical relapse of prostate cancer by assessing the length of time that a given subject will be alive and free from PSA progression.

2.2 Secondary Objectives

1. To evaluate the absolute PSA nadir as a result of treatment which is expressed for each subject in the absolute value and as a percentage, change from baseline.
2. To determine the time to PSA nadir from the start of treatment. which is the lowest PSA on treatment.
3. To determine the time to next subsequent antineoplastic therapy.
4. To determine the effect of investigational treatment on testosterone levels which is assessed by the change of testosterone from baseline to cycle 4.
5. To determine the safety and toxicities of the study drug as assessed by CTCAE version 5.

2.3 Exploratory Objectives

1. To determine if the study drug affects comprehensive geriatric assessment domains.
2. To determine if the study drug combination affects the quality of life.
3. To evaluate if positive status for Stat5 activation in the paraffin-embedded tissue sections of the diagnostic biopsies has a trend to predict biochemical response to pacritinib treatment.

2.4 Primary Endpoint

Six-month PSA-progression free survival

2.5 Secondary Endpoint(s)

1. Absolute PSA nadir.
2. Time to PSA nadir.
3. Time to next subsequent antineoplastic therapy.
4. Effect of investigational treatment on testosterone levels.
5. Safety and toxicities of the study drug.

2.6 Exploratory Endpoints

1. Effect of pacritinib on CGA domains.
2. Effect of pacritinib on FACT-P score.
3. Effect of levels of Stat5 transcription factors in prostate cancer cells determined by fluorescence-based immunohistochemistry on biochemical responses response to pacritinib.
4. Identify biomarkers of response/resistance.

3 STUDY DESIGN

3.1 General Description

This is a single-arm, open-label phase 2 study to evaluate the role of pacritinib for patients with biochemical relapse after definitive treatment for prostate cancer. Patients will receive pacritinib 200 mg twice daily. To be eligible, patients are not allowed to have been treated with a JAK2

inhibitor. Assigned treatment will continue until the patient experiences progressive disease or intolerable adverse events (AEs), withdraws consent, initiates new PC-directed therapy, or the study is terminated. In addition to the above, patients will be considered to have discontinued treatment if pacritinib is held for >28 consecutive days due to treatment toxicity, or if treatment is discontinued for lack of efficacy, or at the request of the principal investigator or the patient. This study will be monitored by an Independent Data Monitoring Committee (IDMC).

3.2 Study Completion

The study will reach study completion approximately 36 months from the time the study opens to accrual.

4 SUBJECT PARTICIPATION, DISCONTINUATION, AND WITHDRAWAL

Investigators must follow all MCW IRB requirements and policies regarding subject participation, found here:

https://www.mcw.edu/HRPP/Policies-Procedures.htm

4.1 Subject Status

Subject statuses throughout the trial are defined as follows:

- Prescreening: preconsent (subject considering trial or study staff considering a patient for the trial per institutional recruitment methods).
- Screening: the period after the consent, but prior to eligibility confirmation.
- Consented: consented, prior to eligibility confirmation.
- Eligible: the local investigator confirms all eligibility criteria apply.
- On study/enrolled: date eligibility is confirmed.
- On arm: date of enrollment.
- On treatment: first-day treatment was given to the last day treatment was given.
- Off treatment: the last day treatment was given.
- On follow-up: from the last day of treatment to the end of the follow-up period.
- Off study: follow-up period completed, with no additional data gathered.
- Withdrawn: subject fully withdraws consent (i.e., refuses ALL follow-up, even survival) or is taken off the study by the local principal investigator.

4.2 Prescreening and Screening Log

The MCW study principal investigator regularly reviews screen failure reasons to understand barriers to accrual and consider amending eligibility criteria. Screen failures are defined as participants who were considered for the trial to participate in the clinical trial with or without consent but are not subsequently assigned to the study intervention or enrolled in the study. MCWCC CTO will follow its SOPs regarding prescreening and screening tracking.

4.3 Consent

Investigators or their appropriate designees will identify potentially eligible subjects from their clinics, subject self-referrals, referrals from other clinicians, and/or other IRB-approved recruitment methods. No study conduct, including subject prescreening, can occur until after IRB approval.

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 signed ICF copy will be given to the subject and a copy will be filed in the medical record (per local IRB policies and SOPs). The original will be kept on file with the study records.

4.4 Screening Procedures

Refer to the study calendar of events.

Visit procedures that were performed as standard of care before consent (without the specific intent to make the subject eligible for the trial), may count toward screening tests and eligibility if they are within the screening window.

4.5 Biospecimen studies and procedures

Archived tissue samples will be requested and are required if available. Tumor and blood biomarkers to be evaluated to support the exploratory objectives of the study may be evaluated per study calendar. Biomarker assessments that may have the potential to identify patients likely to respond to treatment with investigational agents will be investigated to determine a patient's biomarker status and for possible correlation with efficacy endpoints.

All samples collected for biomarker analyses will be stored and analyzed at Dr. Nevalainen's and Dr. Rui's laboratory and may be used for subsequent research relevant to evaluating biological and/or clinical response to pacritinib.

Quantitative fluorescence-based immunohistochemistry will be used to determine levels of nuclear localized Stat5 in prostate cancer cells, to provide pilot data to explore the hypothesis that high levels of nuclear localized Stat5 in cancer cells prior to Jak2-inhibitor treatment correlate with responsiveness to pacritinib treatment.

Specimens to be provided:
One H&E and five unstained sections from formalin-fixed, paraffin-embedded prostate cancer samples from before initiation of pacritinib treatment (biopsy or resected specimen) will be required if available. Surgical specimens would be preferred over biopsy specimens when available. All archived tissue samples available may be used, not just the most recent sample.

Blood (2x10ml EDTA tube) will be collected per calendar and processed as below. Plasma will be isolated for cell-free DNA extraction and exosome isolation. The cell-free DNA will be tested for genetic and epigenetic changes. The exosomes will be tested to quantify their microRNA contents. Correlative analyses will be performed to associate the genetic and epigenetic

changes with treatment responses. These analyses will include (but not limited to) Cox regression, Kaplan-Meir and area under the curve (AUC)

Blood will be stored in Dr. Nevalainen's laboratory. If a response is detected after the first 10 patients, a protocol amendment will occur to allow for analysis of blood specimens. .Tissue and blood will be sent to:

Marja Nevalainen's laboratory,
TBRC C4960, Medical College of Wisconsin,
8701 Watertown Plank Road, Milwaukee, WI 53226
(office 414-955-2103, mobile 301-219-6689; mnevalainen@mcw.edu)

Laboratory staff:
Vindhya Udhane, PhD (Research Scientist; 414-955-2938; mobile: 234-706-8384; vudhane@mcw.edu));
Cristina Maranto PhD (Research Scientist; office 414-955-2115; mobile 414-897-6211; cmaranto@mcw.edu)

Either Dr. Nevalainen or laboratory staff can be contacted for any questions regarding specimen (tissue and blood) handling.

1. Biomarkers to be assessed include Signal Transducer and Activator of Transcription-5a/b (Stat5a/b) and will be correlated with response to treatment.
2. If adequate tissue is not available for all study biomarkers to be done, the patient would still qualify and be enrolled to the study.

Pathologic Evaluation and Handling of Tissue Specimens:
1. Tissue for analysis will be subject to routine pathological analysis. Routine hematoxylin and eosin (H&E) stain will be used for morphological analysis and for the determination of carcinoma diagnosis. The samples will be assessed by our GU pathologists.
2. One H&E slide and five unstained slides will be reserved for study labs/biomarkers and will be sent to Dr. Marja Nevalainen's laboratory (suite C4960) at the Medical College of Wisconsin Translational and Biomedical Research Center (TBRC).
3. Cancer cell levels of Stat5a/b protein will be quantified on slides, using optimized fluorescence-based multiplexed immunohistochemical protocols.

Handling of Blood Specimens
1. Collect blood in 2x10ml K2EDTA venous blood collection tubes.
2. Gently invert sample(s) eight to 10 times and process within 30 minutes, but no longer than two hours after blood draw.
3. Centrifuge specimens at approximately 3000 rpm in a standard clinical centrifuge for 10 minutes at RT.
4. Being careful to not disturb the buffy coat, transfer the platelets-rich plasma to a 15-ml conical tube and spin again at 3000 rpm to separate platelets from platelets-poor plasma.
5. Transfer buffy coat layer into a 2-ml cryovial tube. Some red blood cell contamination is expected.
6. Once finished with the second spin, transfer platelets-poor plasma to 1-ml cryovial tubes, being careful not to disturb pellet.

7. Label all aliquots with study, patient ID, date/time of collection, timepoint, and specimen (i.e. PPP – platelet poor plasma, BC – buffy coat, PL - platelet).
8. Immediately freeze samples at -80°C.

4.5 Eligibility Confirmation

Study staff must adhere to MCWCC CTO SOPs regarding eligibility review/confirmation.

No waivers of protocol eligibility will be granted. When clinical factors relating to an eligibility item are unclear or questionable, the MCW PI can only provide guidance or clarification on eligibility. Any eligibility questions should be directed to Dr. Kilari at dkilari@mcw.edu.

Inclusion Criteria

1. Patients aged ≥ 18 years.
2. Histologically or cytologically confirmed prostate adenocarcinoma.
3. Prior radical prostatectomy or definitive radiation.
4. Biochemically recurrent prostate cancer with PSA doubling time ≤ 9 months at the time of study entry(calculated per MSKCC prostate nomogram: https://www.mskcc.org/nomograms/prostate/psa_doubling_time). Calculation of PSA doubling time should include the use of all available PSA values obtained within the past 12 months prior to randomization, with a minimum of three values separated by at least two weeks apart. The PSA values used to calculate the PSA doubling time must all be ≥ 0.1 ng/mL and should be measured in the same laboratory whenever feasible.
5. Prior adjuvant or salvage radiation or not a candidate for radiation based upon clinical assessment of disease characteristics and patient comorbidities. (N/A for patients who underwent definitive radiation therapy).
6. Screening PSA > 0.5 ng/mL.
7. No definitive evidence of metastases on screening imaging per the judgment of the investigator. Pelvic lymph nodes measuring 1.5 cm or less in short axis diameter are allowed. Lesions identified on imaging modalities (e.g. PSMA or choline PET) that are not visualized on CT and/or MRI or radionuclide bone scan are allowed. Equivocal lesions on bone scan should be followed up with additional imaging as clinically indicated.
8. Screening serum testosterone > 50 ng/dL.
9. Eastern Cooperative Oncology Group (ECOG), Performance Status grade 0-1 or Karnofsky Performance Status ≥ 70.
10. No prior JAK2 inhibitor treatment.
11. Male patients, even if surgically sterilized (i.e., status post-vasectomy), must agree to one of the following:
    - Practice effective barrier contraception and another effective method of birth control if he is having sex with a woman of childbearing potential during the entire study period and through 90 calendar days after the last dose of study agent
12. Ability to understand a written informed consent document, and the willingness to sign it.
13. Left ventricular cardiac ejection fraction of ≥50% by echocardiogram or multigated acquisition (MUGA) scan.
14. Willing to provide blood and tissue for research analysis. (encouraged but not necessary for inclusion in trial).
15. Adequate organ function as defined by the following laboratory values at screening:
    - Serum aspartate transaminase (AST), serum glutamic oxaloacetic transaminase [SGOT]) and serum alanine transaminase (ALT; serum glutamic pyruvic transaminase [SGPT]) < 2.5 x upper limit of normal (ULN).
    - Total serum bilirubin ≤1.5 x ULN. In subjects with Gilbert's syndrome, if total bilirubin is >1.5 × ULN, measure direct and indirect bilirubin and if direct bilirubin is ≤1.5 × ULN, the subject may be eligible).

- Serum potassium ≥ 3.5 mmol/L. Supplementation and re-screening is allowed.
- Estimated GFR > 45 ml/min using Cockroft-Gault equation.
- Platelets ≥ 100,000/mL independent of transfusion and/or growth factors within three months prior to randomization.
- Hemoglobin ≥ 9.0 g/dL independent of transfusion and/or growth factors within three months prior to randomization.
- Absolute neutrophil count ≥500/μL.
- Serum albumin ≥ 3.0 g/dL.
- Adequate coagulation defined by prothrombin time (PT)/international normalized ratio (INR) and PTT≤ 1x.5 ULN.

Exclusion Criteria

A potential subject who meets any of the following exclusion criteria is ineligible to participate in the study.

1. Previously treated with pacritinib.
2. Prior systemic treatment with androgen deprivation therapy and/or first-generation anti-androgen (e.g. bicalutamide, nilutamide, flutamide) for biochemically recurrent prostate cancer. Prior ADT and/or first-generation anti-androgen in the (neo)adjuvant, definitive and/or salvage setting in conjunction with radiation or surgery is allowed provided last effective dose of ADT and/or first-generation anti-androgen is ≥ 12 months prior to the date of randomization and the total duration of prior therapy is ≤ 36 months.
3. Prior treatment with CYP17 inhibitor (e.g., ketoconazole, abiraterone acetate, galeterone) or next-generation androgen receptor antagonist including apalutamide or enzalutamide.
4. Prior chemotherapy for prostate cancer
5. Use of 5-alpha reductase inhibitor within 42 days prior to randomization.
6. Use of investigational agents within 28 days prior to randomization.
7. Use of other prohibited medications within seven days prior to Cycle 1 Day 1 on study (see Appendix 3 and 4 for list of prohibited medications).
8. Systemic treatment with a strong CYP3A4 inhibitor or a strong CYP450 inducer within 14 days prior to treatment Day 1 (Appendix 3 and Appendix 4, respectively)
9. Prior bilateral orchiectomy.
10. Uncontrolled hypertension.
11. Baseline severe hepatic impairment (Child-Pugh Class B & C).
12. An intercurrent illness that is not controlled, such as active infection, psychiatric illness/social situations that would limit compliance with study requirements.
13. Any chronic medical condition requiring a higher dose of corticosteroid than an equivalent of 10 mg prednisone/prednisolone per day.
14. Significant recent bleeding history, as defined as NCI CTCAE grade≥2 within three months prior to treatment Day 1, unless precipitated by an inciting event (e.g., surgery, trauma, or injury)
15. Systemic treatment with medications that increase the risk of bleeding, including anticoagulants (warfarin, direct oral anticoagulant, etc.), antiplatelet agents (except for aspirin dosages of ≤ 100mg/day), vascular endothelial growth factor (anti-VEGF) agents, and daily use of COX-1 inhibiting nonsteroidal anti-inflammatory agents (NSAIDs) within 14 days prior to treatment Day 1.
16. Systemic treatment with medications that can prolong the QT interval within 14 days prior to treatment Day 1. Shorter washout periods may be permitted with the approval of the PI, provided that the washout period is at least five half-lives of the drug prior to treatment Day 1.
17. Any history of CTCAE grade ≥2 cardiac conditions within six months before

treatment Day 1. Patients with asymptomatic grade 2 non-dysrhythmia cardiovascular conditions may be considered for inclusion, with the approval of the PI, if stable and unlikely to affect patient safety.

18. QT corrected by the Fridericia method (QTcF) prolongation >450 ms or other factors that increase the risk for QT interval prolongation (e.g., heart failure, hypokalemia [defined as serum potassium <3.0 mEq/L that is persistent and refractory to correction]), or history of long QT interval syndrome.
19. New York Heart Association Class II, III, or IV congestive heart failure (Appendix 7).
20. Any active GI or metabolic condition that could interfere with absorption of oral medication.
21. Active or uncontrolled inflammatory or chronic functional bowel disorder such as Crohn's disease, inflammatory bowel disease, chronic diarrhea, or chronic constipation.
22. Other malignancy within three years prior to treatment Day 1, other than curatively treated basal cell or squamous cell skin or corneal cancer; curatively treated carcinoma in situ of the cervix; or in situ breast carcinoma after complete surgical resection.
23. Uncontrolled intercurrent illness, including, but not limited to, ongoing active infection, psychiatric illness, or social situation that, in the judgment of the treating physician, would limit compliance with study requirements.
24. Known seropositivity for human immunodeficiency virus.
25. Known active hepatitis A, B, or C virus infection.

I have reviewed all inclusion and exclusion criteria and confirm the subject is eligible."

_____ _____

(CRC Signature) (Date)

_____ _____

(Investigator/Enrolling Physician Signature) (Date)

4.6 Discontinuation of Study Treatment, Withdrawal, and Compliance

Treatment duration is 2 years. Patients may continue drug beyond two years if, in the opinion of the treating physician, the patient is benefitting from treatment and benefits outweigh any risks of therapy

Discontinuation from the study treatment does not mean discontinuation from the study. The subject will be considered in follow-up, study procedures should still be completed as indicated by the study protocol, and AEs/SAEs will continue to be reported according to this protocol.

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

- Disease progression per PCWG3 guidelines
- General or specific changes in the subject's condition renders the subject unacceptable for further treatment in the investigator's judgment.
- An inter-current illness that prevents further treatment administration.
- The subject decides to withdraw from the study.
- The subject has significant noncompliance with the protocol (see below).
- Unacceptable adverse event(s) and/or dose level reduction beyond requirements as detailed in this protocol.
- The clinical need for concomitant therapy that is not permitted in the study.
- Subjects who sign the informed consent form, enroll and receive the study intervention, but subsequently withdraw, or are withdrawn or discontinued from the study will not be replaced.

Progression of disease

Progression of disease per PCWG3 is defined as one or more of the following:

PSA progression

Recognize that a favorable effect on PSA may be delayed for ≥ 12 weeks, even for a cytotoxic drug. Monitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progression.

If there is a decline in PSA from baseline: record time from baseline to the first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value ≥ 3 weeks later (i.e., a confirmed rising trend).

If there is no decline in PSA from baseline but stable PSA at 12 weeks: PSA progression will be defined as ≥ 25% and ≥ 2 ng/mL from PSA at 12 weeks .

Radiographic progression

Radiographic progression will be assessed per RECIST 1.1. Any new unequivocal bone lesion is considered progression, except if that lesion appears in the first post-treatment scan; in that

case, document the event, continue treatment until two additional new lesions appear, and record both events.

Consent Withdrawal

A subject may decide to withdraw from the study at any time. MCWCC CTO will follow their IRB of record's SOPs regarding consent withdrawal.

If a subject intends on withdrawing consent, staff should confirm which of the following options the subject chooses and document the discussion:

- Full consent withdrawal, with no study follow-up.
- Selective consent withdrawal from the interventional portion of the study but agree to continued follow-up of associated clinical outcome information.

Investigator-initiated Withdrawal

The investigator will withdraw a subject whenever continued participation is no longer in the subject's best interests. Reasons for withdrawing a subject include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a subject's request to end participation, a subject's noncompliance, or simply significant uncertainty on the part of the investigator that continued participation is prudent. The reason for study withdrawal and the date the subject was removed from the study must be documented.

4.7 Lost to Follow-up

The following actions must be taken if a participant fails to return to the clinic for a required study visit and/or is unable to be reached for follow-up:

- The investigator or designee must make every effort to regain contact and/or reschedule a missed visit with the participant.
- A participant is deemed lost to follow-up if his/her status cannot be obtained after *all* of the following occurs at two consecutive scheduled protocol calendar timepoints:
    - Three telephone calls (at least one day apart) from the study team are unanswered, **AND**
    - A letter (Appendix 2) to the participant's last known mailing address goes unanswered, **AND**
    - These contact attempts must be documented in the participant's medical record or study file.
- Update OnCore® (Follow-up tab and eCRF) when a participant is officially considered lost to follow-up.
- If a subject is considered lost to follow-up, but subsequently contacts the study team, the subject should be considered in follow-up again.

4.8 Accrual Suspension and Closure

The MCW PI facilitates the suspension and closing of accrual in the following manner:

- OnCore® tracks accrual throughout the study.

- If the study must be suspended, OnCore® is updated to 'suspended' status.
- When the accrual number is reached, OnCore® notifies staff of study closure.

4.9 End of Study Definition

A participant is considered to have completed the study if he or she completed all phases of the study, including the last visit or the last scheduled procedure shown in the calendar of events or has been discontinued.

4.10 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause (as determined by the MCW study PI, DSMC, sponsor, and/or IRB). Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) sponsor, and regulatory authorities. If the study is prematurely terminated or suspended, the MCW principal investigator (PI) will promptly inform the MCW Institutional Review Board (IRB), and the sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes.

5 TREATMENT PLAN

5.1 Pacritinib

5.1.1 Study Treatment Description and Storage

Pacritinib for oral administration is supplied in capsules containing 100 mg (as the free base) in red cap/gray body size 0 opaque hard gelatin capsules. The inactive ingredients are microcrystalline cellulose, magnesium stearate, and polyethylene glycol 8000.

Each capsule contains 146-mg of pacritinib citrate, which is equivalent to 100-mg pacritinib free base. Pacritinib capsules should not be opened or crushed. Direct contact of the powder in pacritinib capsules with the skin or mucous membranes should be avoided. If such contact occurs, affected areas should be washed thoroughly with water. Pacritinib capsules should be stored at controlled room temperature 20°C to 25°C or 68°F to 77°F, with excursions allowed from 15°C to 30°C or 59°F to 86°F. All pacritinib supplies must be kept in a restricted-access area.

5.1.2 Dosage, Route, and Mode of Administration

Patients assigned to pacritinib will be supplied with 100-mg capsules of pacritinib. Patients will take two 100-mg capsules of pacritinib BID, orally, at the same time of day, with or without food. On days when ECGs are to be obtained, pacritinib will be administered in the clinic to facilitate the performance of predose assessments. Any missed or vomited doses should not be retaken or replaced.

Regimen Description				
Study agent	**Route**	**Premedication; precautions**	**Dose**	**Duration**
Pacritinib	Oral	None	200 mg b.i.d	Continue treatment until progression of disease (at least 12 weeks) or meeting discontinuation criteria.

5.2 Dose Adjustment

5.2.1 Treatment Interruption and Discontinuation

Safety parameters including AEs, hematology, and serum chemistry will be monitored according to the protocol. Pacritinib treatment may be withheld for up to four weeks due to drug-related toxicities. A longer recovery period may be allowed based on the toxicity but must be agreed upon between the investigator and study PI.

Pacritinib should be withheld seven days prior to planned invasive procedures and concurrently with any unplanned invasive procedure. Pacritinib may be restarted after two days without active signs or symptoms of active bleeding. Pacritinib dosage may also be held at the discretion of the investigator. The PI must be notified of such dose holds. After treatment interruption, patients may resume pacritinib treatment per the dose management guidelines below.

After treatment interruption, patients may resume the pacritinib treatment at the same dose level or at a reduced dose level. No dose re-escalation is allowed.

Pacritinib dose levels for dose adjustments only:

1. Dose level -1: Pacritinib 100 mg BID
2. Dose level -2: Pacritinib 100 mg QD

Any Grade 2 events with duration ≥90 days should prompt dose modification, with reduction to 50% of current pacritinib dose.

Additional drug discontinuation criteria include any treatment-related grade ≥3 toxicity, except for
•Grade 3 nausea/vomiting or diarrhea that resolves within 72 hours with supportive care
•Grade 3 fatigue that lasts more than 1 week
•Grade 3 electrolyte abnormality that is asymptomatic and resolves within 72 hours.

Study can be terminated early for multiple reasons including.

1. Poor adherence to protocol and regulatory requirements
2. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
3. Plans to modify or discontinue the development of the study drug.
4. Events that meet Hy's law criteria

Should the study be terminated at the interim analysis due to futility, patients with ongoing responses will be allowed to continue with treatment at the discretion of PI and CTI BioPharma.

5.2.2 Dosage Management Guidelines for Hematologic Toxicity and Related Complications

Hematology parameters, including CBC, differential, will be evaluated at regular intervals during the study. These parameters should be monitored more frequently if clinically required. Unscheduled local laboratory test results may be used for the assessment and management of patients in real-time.

Table 1 indicates the required dose interruptions and modifications for hematologic toxicities and complications such as hemorrhage and febrile neutropenia that are treatment related . Of note, if more than one toxicity is experienced simultaneously, the higher-grade toxicity should determine the dose interruption/modification. Treatment-related toxicities are those that are considered at least possibly related to study drug.

Table 1. Treatment Toxicity and Dosage Management: Hematologic Toxicities and Related Complications

Event	CTCAE Grade	Management/Action
Thrombocytopenia	For patients starting treatment with baseline (Day 1) grade 1 thrombocytopenia who have treatment-related ≥ 1 grade decrease in platelets	Hold pacritinib for up to 10 days until recovery of platelet count to grade ≤1 or baseline. After recovery, restart at 50% of the prior dose. If thrombocytopenia recurs at the 100 mg BID dose level, discontinue pacritinib.
Hemorrhage	Treatment-emergent hemorrhage Grade 2	Hold pacritinib for up to seven days until hemorrhage resolves. Restart with a 50% dose reduction. If event recurs, discontinue pacritinib
	Grade 3	Discontinue pacritinib.
	Grade 4	Discontinue pacritinib.
Neutropenic infections, including neutropenic sepsis	Grade 2	Hold pacritinib for up to seven days and start at 50% of the dose once

		resolved (100 mg BID). If toxicity recurs discontinue pacritinib
	Grade 3	Discontinue pacritinib
	Grade 4	Discontinue pacritinib

Coagulation Testing

Coagulation testing will include PT, INR, PTT, at screening. Additional coagulation testing should be done as clinically indicated.

These results will be taken into account, together with baseline platelet counts and prior medical history of bleeding, to help guide ongoing hematologic monitoring of platelet counts and clinical monitoring for bleeding. Pacritinib dosage modifications will be implemented for clinically significant AEs identified with this testing per the guidelines in Table 5.

5.2.3 Pacritinib Dosage Management Guidelines for QTc Interval Prolongation, Reduction in Ejection Fraction, and Other Cardiac Toxicities

A 12-lead ECG (collected in triplicate), including QTcF calculation, will be performed during Screening and at Cycle 1 Day 1,, Cycle 2 Day 1, Cycle 5 Day 1, Cycle 7 Day 1, and every four months thereafter provided there is normal QTcF.

Treatment should be modified as shown in Table 2, as recommended by the FDA in case of QTcF interval prolongation. Dose levels referenced in the following tables refer to the following available doses: 200 mg BID, 100 mg BID, and 100 mg QD.

Table 2. Pacritinib-Related QTc Prolongation, Clinically Significant Decreases in Cardiac Ejection Fraction and Other Cardiac Toxicities

CTCAE v5 Toxicity Grade	Management/Action
1	No change.
2 (First occurrence) For patients with grade 2 LVEF decreased at baseline (LVEF 45%-50%) and further decreases in LVEF on the study, see Table 3)	• Hold pacritinib. • If the toxicity resolves to grade ≤1 within 14 days, treatment may be resumed at the next lower dosage level (or discontinued, if toxicity occurred while taking 100 mg QD). • Toxicity that does not resolve to grade ≤1 within 14 days requires treatment discontinuation.
2 (second occurrence)	Discontinue treatment.
3	Discontinue treatment.
4	Discontinue treatment.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; LVEF = left ventricular ejection fraction; QD = once daily; QTc = corrected QT interval.

A transthoracic echocardiogram will be performed at screening, Cycle 2 Day 1, Cycle 5 Day 1, Cycle 8 Day 1, and every six months thereafter provided there is normal LVEF and no clinical evidence of heart failure. The window for all TTEs is -14 days from Day 1 of the cycle it is due at.

Pacritinib dosage modifications will be implemented for clinically significant cardiac ejection fraction changes as per Table 2 and Table 3.

For patients with a grade 2 decreased cardiac ejection fraction at baseline (left ventricular ejection fraction [LVEF]=50% Table 3 should be used for any further decreases in LVEF.

If pacritinib treatment is resumed after holding for ejection fraction abnormality, ejection fraction should be reassessed approximately seven days later, then again within 12 weeks following the seven-day reassessment. If stable, ejection fraction will be checked every six months during the follow-up period and at the End of Treatment Visit. Additional ejection fraction testing shall be done as clinically indicated.

Table 3. Pacritinib-related Clinically Significant Decreased Cardiac Ejection Fraction for Patients with Grade 2 Ejection Fraction (LVEF 45%-50%) at Baseline

CTCAE v5 Toxicity Grade	Management/Action
Worsening of grade 2; 10-19% drop from bassline	Hold pacritinib for one to two weeks and reassess LVEF. If LVEF returns to baseline, the patient may resume treatment at the next lower dose level; if does not resolve, pacritinib should be discontinued.
3	. Discontinue treatment.
4	Discontinue treatment.

In patients who resume pacritinib treatment after holding treatment for grade 2 QTc interval prolongation, follow-up ECGs (in triplicate) are recommended on Days 1, 7, 14, 28, and 56 after pacritinib restart. After the restart of pacritinib, QTc monitoring should follow this schedule with ECGs obtained in triplicate:

- Restart Day 1 at four hours (± one hour) after ingestion of the first reduced dosage
- Restart Day 7 (± two days) four hours after dosing (± one hour)
- Restart Day 14 (± two days) four hours after dosing (± one hour)
- Restart Day 28 (± two days) at any time relative to dosing
- Restart Day 56 (± seven days) at any time relative to dosing

If grade 2 toxicity does not resolve to grade ≤1 within seven days, discontinue all treatment with pacritinib. If grade 2 toxicity recurs despite dosage reduction discontinue all treatment with pacritinib. For grade 3 and 4 QTc prolongation, discontinue all treatment with pacritinib.

Other Cardiac Toxicities

Discontinue treatment with pacritinib for all other grade 3 and 4 cardiac toxicities.

5.2.4 Pacritinib Dosage Management Guidelines for Diarrhea

The need for managing GI effects of pacritinib, particularly diarrhea, should be anticipated. A careful baseline evaluation of bowel habits (frequency and consistency of bowel movements) should be obtained at baseline for all patients. At the baseline visit, all patients in the pacritinib arm will be provided with a prescription (and instructions to fill that prescription) for loperamide (Imodium®) or a similarly effective antidiarrheal drug. Patients will be instructed to start taking the prescribed loperamide or other antidiarrheal drugs per package and physician instructions as soon as they notice any changes in frequency or consistency of bowel movements after starting study treatment. Early intervention for diarrhea should be initiated for patients in the pacritinib arm with increases of one grade or more in diarrhea (Appendix 7). At the investigator's discretion, prophylactic use of antidiarrheals may be initiated for patients or populations in whom it is judged necessary to enhance patient safety. Standard supportive care measures to control symptoms of GI toxicity such as diarrhea, constipation, and nausea should be provided.

Treatment with antidiarrheals is advised for all patients who experience new-onset diarrhea (Table 4). Dose modifications for patients with diarrhea, nausea, and vomiting that is considered at least possibly related to study drug are described in Table 4.

Table 4. Treatment Toxicity and Dosage Management for drug-related Diarrhea, Nausea, Vomiting

CTCAE v5 Toxicity Grade	Management/Action
1	No Change
2	• Hold pacritinib for up to seven days • If the toxicity resolves to grade ≤1 or the baseline grade within seven days, treatment will be resumed at the same level • If the toxicity recurs after the restart at the same dosage level, treatment may only be resumed at the next lower dosage level start at 50% of the dose once resolved (100 mg BID)
3	• Hold treatment. • If the toxicity resolves to grade ≤1 or the baseline grade within seven days, treatment may be resumed at the same level or the next lower dosage. Concomitant antidiarrheal treatment is required for patients restarting pacritinib at the 100 mg QD dosage level. • If the toxicity recurs after the restart at the same dosage level, treatment may only be resumed at the next lower dosage level. • If the toxicity resolves to grade ≤1 or the baseline grade after more than seven days, treatment may be resumed only at the next lower dosage level. Discontinuation is required if on hold from the 100 mg QD dosage level. Concomitant antidiarrheal treatment is required for patients restarting pacritinib at the 100 mg QD dosage level.

CTCAE v5 Toxicity Grade	Management/Action
	• If the toxicity recurs after the restart at the lower dosage level, pacritinib treatment must be discontinued.
4	• Discontinue pacritinib

5.2.5 Pacritinib Dosage Management Guidelines for Pacritinib-Related Nonhematologic Toxicities Other than QTc Prolongation, Decreased Cardiac Ejection Fraction, Other Cardiac Toxicities or Diarrhea

As defined in Table 5, a maximum of two dosage reductions are allowed for pacritinib-related nonhematologic toxicities other than QTc prolongation, decreased cardiac ejection fraction, or diarrhea.

Table 5. Treatment Toxicity and Dosage Management: Pacritinib-Related Nonhematologic Toxicities Other than **QTc Prolongation, Decreased Cardiac Ejection Fraction, Other Cardiac Toxicities or nausea, vomiting and Diarrhea**

CTCAE v5 Toxicity Grade	Management/Action
1 or 2	No change.
3	• Hold treatment. • If the toxicity resolves to grade ≤1 or to the baseline grade within seven days, treatment may be resumed at the same level or the next lower dosage, at the discretion of the investigator after discussion with the Sponsor. • Toxicity that does not resolve to grade <1 or to the baseline grade within seven days requires dosage reduction to the next lower dosage.
4	• Hold treatment. • If the toxicity resolves to grade <1 or to the baseline grade within seven days, treatment may be resumed, but the dosage will be reduced by one dosage from the level at which the toxicity was observed. • If grade 4 toxicity occurs at the lowest dosage of 100 mg QD, the patient should be discontinued from the study.

5.3 Concomitant and Excluded Therapies

Patients should receive full supportive care, including transfusions of blood and blood products, antidiarrheal and antiemetic agents, and antibiotics when appropriate.

Patients may not receive other investigational agents during the study.

Patients must not receive treatment with any potent CYP3A4 inhibitors for one week prior to the administration of pacritinib and during treatment with pacritinib.

The following therapies and procedures are prohibited for all patients during the washout period and throughout the treatment phase of the study.:

- Strong CYP3A4 inhibitors (Appendix 3) and strong CYP450 inducers (Appendix 4), except as needed to treat AEs, with Medical Monitor approval.
- Any drugs with significant potential for QTc prolongation (Appendix 6), except as needed to treat AEs, with PI approval.

5.4 Dietary Restrictions

None.

6 ADVERSE EVENTS: DEFINITIONS, COLLECTION AND REPORTING REQUIREMENTS

6.1 Definitions

6.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. (International Conference on Harmonisation [ICH], E2A, E6).

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, located on the CTEP web site:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures.

6.1.2 Serious Adverse Event (SAE)

Serious Adverse Event (SAE) means any untoward medical occurrence that results in any of the following outcomes:

- **Death.** Results in death.

- **Life-threatening**. Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).

- **Hospitalization**. Requires inpatient hospitalization or prolongation of an existing hospitalization.

- **Disability/incapacity**. Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).

- **Pregnancy**

- **Medically important event**. This refers to an AE that may not result in death, be immediately life-threatening, or require hospitalization, but may be considered serious when based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

6.1.3 Attribution of an Adverse Event

An assessment of the relationship between the adverse event and the medical intervention, using the following categories:

Definitely Related: *The AE is clearly related to the intervention*. There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

Probably Related: *The AE is likely related to the intervention.* There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

Possibly Related: *The AE may be related to the intervention.* There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events).

Unlikely: *The AE is doubtfully related to the intervention.* A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).

Unrelated: *The AE is clearly NOT related to the intervention.* The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology.

6.1.4 Expectedness of an Adverse Event

Study Investigator or treating Physician will be responsible for determining whether an AE is expected or unexpected as indicated in the protocol, informed consent form, and/or drug information brochure. An AE will be considered unexpected if the nature, severity, or frequency

of the event is NOT consistent with the risk information previously described for the study intervention.

6.2 Collection and Reporting Requirements for Adverse Events and Serious Adverse Events

6.2.1 Collection of Adverse Events

All (or specify if only certain grade AE needed) adverse events (including SAEs) must be recorded in OnCore® and/or an adverse event log. All AEs required to be collected must be graded according to the CTCAE v5. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. The investigator's or treating physician's assessment of AE attributions must also be documented.

AEs will be collected from the time the subject signs the consent form through 30 days post last dose of study drug(s). AEs will be tracked and followed until resolution, subject withdraws consent, or is lost to follow-up (including subjects who discontinue early). All adverse events collected per the protocol will be followed with appropriate medical management until they are resolved, if they are related to the study treatment, or until the investigator deems the event to be chronic.

Please see section 6.2.2 and table 6 to identify the adverse events that need to be reported.

6.2.2 Reporting of Adverse Events and Serious Adverse Events

Please refer to table 6 below to identify adverse events that meet reporting requirements.

All serious adverse events (SAEs) that occur after the subject has signed the consent form through 30 days post last dose of study drug(s) will be reported. All SAEs will be followed until satisfactory resolution, or until the investigator deems the event to be chronic.

All serious adverse events (SAEs) must also be documented in OnCore®.
SAEs (regardless of attribution) will be reported to CTI within 24 hours after the lead investigator learns of the event.

Attribution	SAE				AE		
	Grade 1, 2 & 3		Grade 4 and 5		Grade 3	Grade 4	
	Expected	Unexpected	Expected	Unexpected	Unexpected	Expected	Unexpected

<table>
<tr><td>Unrelated
Unlikely</td><td rowspan="2">IRB[1] and DSMC[2]-Routine Review[3]

CTI Biopharma</td><td>IRB[1] and DSMC[2]-Routine Review[3]</td><td rowspan="2">IRB[1]-Routine Review[3]

DSMC[2]-Within 5 calendar days

CTI Biopharma</td><td>IRB[1]-Routine Review[3]

DSMC[2]-Within 5 calendar days</td><td rowspan="2">DSMC[2]-Routine Review[3]</td><td rowspan="2">DSMC[2]-Within 5 calendar days</td><td rowspan="2">DSMC[2]-Within 5 calendar days</td></tr>
<tr><td>Possible
Probable
Definite</td><td>IRB[1] and DSMC[2]-Within 5 calendar days

FDA[4]

CTI Biopharma</td><td>IRB[1] and DSMC[2]-Within 5 calendar days

FDA[4]

CTI Biopharma</td></tr>
</table>

Table 6

1. Guidance on adverse event reporting to the IRB is available online at MCW IRB Policies and Procedures.
2. For expedited DSMC reporting, the study coordinator/research nurse must notify the DSMC via email including the subject ID, date of event, grade, relatedness, expectedness, and a short narrative. The DSMC will review data entered into OnCore®.
3. For routine reporting, the events will be reported to IRB as part of the annual continuing progress report and the DSMC will review data entered into OnCore® at the time of scheduled monitoring.
4. Fatal or life-threatening SAEs meeting the criteria indicated in the above table will be reported to FDA no later than seven calendar days after study staff's initial awareness of the event. If the SAE is not fatal or life-threatening and meets the above criteria, the timeline for submitting an IND safety report to FDA is no later than 15 calendar days after study staff's initial awareness of the event. See section 6.2.3 for detailed reporting instructions.

6.2.3 Reporting Instructions

- **Food and Drug Administration**

  An IND safety report will be submitted for any adverse event that meets all three definitions: possibly related to the study drug, unexpected, and serious. If the adverse event does not meet one of the above definitions, it should not be submitted as an expedited IND safety report.

  Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

  Suggested Reporting Form:

US FDA MedWatch 3500A:
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

- **CTI BioPharma**

  All serious adverse events (SAEs) must also be faxed to CTI BioPharma's local safety representative at 1-866-660-8967 within 24 hours of study staff awareness. The report should include deidentified Oncore® SAE report along with MedWatch form. It may also be emailed to pv@ctibiopharma.com.

  All pacritinib-related non-serious adverse events (any grade) should be reported to CTI at the end of the study.

  SAEs (regardless of attribution) should be reported to CTI within 24 hours after the lead investigator learns of the event.

  Sponsor-Investigator shall report investigational drug product quality complaints to CTI within 24 hours after the lead investigator learns of the event, or if the event or reporting time frame occurs during a weekend or holiday, the quality complaints will be submitted to CTI the following business day. This includes any instances wherein the quality or performance of a CTI product (marketed or investigational) does not meet expectations (e.g., color, odor, appearance, quality, safety, effectiveness, suspected contamination) or that the product did not meet the specifications defined in the application for the product (e.g., unexpected labeling or contents). The product quality also includes quality of the drug delivery device (in this case, the capsule). As such, device defects should be reported according to the instructions on the PQC Form provided by CTI.

6.3 Unanticipated Problem Involving Risk to Subject or Other (UPIRSO)

The investigator and his or her team will follow the Medical College of Wisconsin policies related to unanticipated problems involving risks to subjects or others. This information may be found on the Human Research Protection Program website.

6.4 Subject Complaints

If a complaint is received by anyone on the study staff, it will be discussed with the study staff and will be addressed on a case-by-case basis. The PI will be notified of any complaints. Complaints will be reported to the IRB if indicated.

If the subject has questions about his or her rights as a study subject, wants to report any problems or complaints, obtain information about the study, or offer input, the subject can call the Medical College of Wisconsin/Froedtert Hospital research subject advocate at 414-955-8844. This information is provided to the subject in their consent.

6.5 Product Complaint

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact the Drug Manufacturer and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Drug Manufacturer representative. Product complaints in and of themselves are not Reportable Events. If a product complaint results in an SAE, an SAE form should be completed. All product complaints must be reported to CTI within 24 hours of study staff awareness at productcomplaints@ctibiopharma.com

7 PHARMACEUTICAL INFORMATION

7.1 Product Description

Pacritinib for oral administration is supplied in capsules containing 100 mg (as the free base) in red cap/gray body size 0 opaque hard gelatin capsules. The inactive ingredients are microcrystalline cellulose, magnesium stearate, and polyethylene glycol 8000. Each capsule contains 146 mg of pacritinib citrate, which is equivalent to 100-mg pacritinib free base.

Pacritinib capsules should not be opened or crushed. Direct contact of the powder in pacritinib capsules with the skin or mucous membranes should be avoided. If such contact occurs, affected areas should be washed thoroughly with water.

7.2 Mechanism of Action

Pacritinib is a macrocyclic Janus kinase inhibitor that is being developed for the treatment of myelofibrosis. It mainly inhibits Janus kinase 2 (JAK2) and Fms-like tyrosine kinase 3 (FLT3).

7.3 Product Supply

Pacritinib will be supplied in 100-mg capsules by CTI BioPharma.

7.4 Storage Conditions

The drug product should be stored in the pharmacy, hospital, clinic, or warehouse at controlled room temperature, 20°C to 25°C (68°F to 77°F), with excursions between 15°C and 30°C (59°F and 86°F) allowed. Patients should be instructed that storage temperatures for pacritinib in the home should be below 30°C (86°F).

7.5 Handling and Drug Accountability

The investigator is fully responsible for the investigational products at the trial site. Dispensing of investigational products will be delegated to delegated site staff. The person responsible for dispensing the investigational products will be responsible for maintaining adequate control of the investigational products and for documenting all transactions with them.

The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of all agents. Each participating site investigator, or authorized designee, is responsible for maintaining a careful record of inventory and disposition of all investigational agents received at the site. Use of the NCI Drug Accountability Record Form is recommended, but sites may use their own accountability logs per institutional standards. Sites

must ensure accountability records capture the same information as the NCI Drug Accountability Record Form and in addition, capture the preparation time. Any used or partially used vials may be destroyed on-site per the institutional standard of practice. Expired vials remaining at the end of the study may be destroyed onsite per institutional standards.

At every study visit, patients will return bottles in which pacritinib is supplied with all remaining untaken pacritinib capsules, if any. Patient compliance will be evaluated by pill count and through pill diary provided at each visit. (Appendix 10)

Patients on the study will maintain a "Subject Diary" to record the number of tablets/pills/capsules of study medications they take daily. On this diary, they will also record any side effects related to the study medications.

7.6 Contraindications

Supportive care therapies, except when prohibited by any of the below provisions, are permitted, including the use of low-dose aspirin. Corticosteroids (up to 20 mg/day of prednisone or equivalent) and/or hydroxyurea may be used for up to two weeks during the first month of treatment with pacritinib.

The following therapies and procedures are prohibited throughout the study:

- Antiplatelet or anticoagulation agents, with the exception of ≤ 100 mg/day of aspirin.
- Growth factor therapies, including erythropoietin and thrombopoietin.
- Strong CYP3A4 inhibitors and strong CYP450 inducers, except as needed to treat AEs, with study PI approval.
- Any drugs with significant potential for QTc prolongation (Appendix 6), except as needed to treat AEs, with medical monitor approval.
- Splenic irradiation or splenectomy.

Ongoing Hemorrhage: Patients with active bleeding should not begin or continue treatment with pacritinib. Reports of serious bleeding events, including life-threatening and fatal events, have been reported in association with pacritinib use. Pacritinib should be discontinued before planned surgery.

Hypersensitivity: Patients with a known hypersensitivity to the active ingredient or any of the excipients of the drug product should not take pacritinib.

7.7 Known Adverse Events

Based on the adverse effects observed in nonclinical toxicity studies, as well as data from clinical studies in patients with advanced MF, AML, and lymphoma, the investigator is advised to observe the following precautions:

Gastrointestinal: Diarrhea has been reported during treatment with pacritinib and generally occurs within the first eight weeks of treatment. Pacritinib-related diarrhea is usually low grade, with severe diarrhea (grade 3 or 4) occurring in 5.8% of patients. Early identification and intervention are critical for the optimal management of diarrhea. Antidiarrheal medications should be given to patients starting on pacritinib, with instructions to start taking to control symptoms at the first sign of diarrhea. Pre-existing diarrhea should be adequately controlled before beginning

therapy. Nausea, vomiting, and abdominal pain have also been reported in relation to pacritinib administration. Most cases were reported to be of low severity, and symptoms improved with supportive management without requiring discontinuation of treatment. Patients with significant GI symptoms despite optimal supportive care may have pacritinib interrupted or have the dose of pacritinib reduced per protocol.

Platelet Count Reduction: Clinically relevant decreases in platelet count have been observed in patients treated with pacritinib. Prior to initiating treatment, patients should undergo laboratory testing to establish their baseline hematology profile, including complete blood count with a white blood cell count differential, platelet count, and coagulation testing, including prothrombin, international normalized ratio, partial thromboplastin time, and thrombin time. While on pacritinib, patients should be monitored as specified in the protocol for severe thrombocytopenia. For clinically significant decreases in platelet count, the dose of pacritinib should be reduced or interrupted in accordance with protocol guidelines.

Bleeding: Pacritinib may increase the risk of bleeding. Reports of serious bleeding events, including life-threatening and fatal events, have been reported. These bleeding events were generally without lasting sequelae, although life-threatening and fatal events of hemorrhage, including intracranial hemorrhage, were observed more frequently in pacritinib-treated patients compared with BAT patients. Risk factors for bleeding with pacritinib may include prior bleeding events and anti-platelet and anti-coagulant medications in addition to severe thrombocytopenia. Concomitant use of drugs affecting hemostasis, such as aspirin and other antiplatelet agents, other anticoagulants, heparin, and thrombolytic agents, may increase the risk of bleeding. Refer to the protocol for guidance on dose modifications for pacritinib-related bleeding events.

Cardiac: QTc prolongation has been observed in patients treated with pacritinib. Prior to initiating treatment with pacritinib, patients should undergo an ECG to establish baseline QTc and an echocardiogram (or other appropriate methodology) to establish baseline left ventricular ejection fraction; patients should be monitored periodically for changes in their QTc. Pacritinib should not be used in patients with uncontrolled cardiac dysrhythmias, QTc prolongation >450 ms, or other factors that increase the risk for QT prolongation (e.g., heart failure, hypokalemia, hypomagnesemia, or a history of long QT interval syndrome). Caution should be used when co-administering other medicinal products with the potential to elongate QT interval. Ejection fraction should be monitored at baseline, after one month on treatment, after three and six months on treatment, and every six months thereafter; pacritinib dose should be modified if significantly reduced ejection fraction is detected. Additional ECG and ejection fraction assessments should be performed as clinically indicated. Refer to the protocol for guidance on dose modifications for pacritinib-related QTc prolongation.

General: Additional AEs commonly (>10% of patients) reported during pacritinib administration include fatigue, peripheral edema, pyrexia, decreased appetite, and pruritus. Adverse events and SAEs in the SOC of infections and infestations have been frequently reported, but none of these events were considered atypical for this population. Neoplasms, typically nonmelanoma skin cancers, have been reported in patients treated with pacritinib and were clustered in patients with geographic and other risk factors for skin malignancy, making further conclusions difficult. Participants in clinical studies of pacritinib will be monitored closely for these AEs.

8 STATISTICAL CONSIDERATIONS

8.1 Study Populations

Efficacy population — all enrolled subjects who received at least one dose of the study drug and have either died or have at least one evaluation of PSA after the initiation of study treatment.

Safety population — all enrolled subjects who received at least one dose of the study drug.

8.2 Study hypotheses

The null hypothesis that the median PSA-progression-free survival is six months will be tested against a one-sided alternative by for the six-month PSA-progression-free survival probability exceeding 50%. The study is designed to have 80% power to obtain a result significant at a one-sided 10% level if the experimental treatment has a six-month PSA-progression-free probability of 66%, which corresponds to a median of 10 months if the time to PSA progression is exponentially distributed.(84)

8.3 Study design and sample size

A two-stage single-arm design based on the methods of Huang et al (2010) will be used.

The design is based on a modification of a binomial two-stage design that allows the incorporation of data from subjects with less than six months of follow-up at the interim analysis. The study will enroll up to 46 subjects with an interim analysis performed when 10 patients have been treated and followed for 6 months. The underlying binomial design would stop for futility if there are four or fewer patients alive without PSA progression at six months among these 10 patients. The modified futility decision will use the Kaplan-Meier estimate of the six-month PSA-progression-free survival using the data from the first 10 subjects and any subject who have been enrolled during the six-month follow-up period of the tenth subject. If the six-month PSA-progression-free survival is significantly lower at a one-sided 10% significance level than the clinically meaningful value of 66% defined by the alternative hypothesis, the study will be stopped for futility. If no new patients would be enrolled during the follow-up period, this decision rule is equivalent to the one defined by the binomial design.

If the study is not stopped for futility, study enrollment continues until 46 subjects are enrolled. The final analysis will be performed when all subjects have been followed for at least six months. The null hypothesis will be rejected, and the study drug will be considered promising if 27 or more patients are alive without PSA progression at six months among the 46 patients. The underlying binomial design yields a type I error rate of 10% if the underlying six-month PSA-progression-free probability is 50% (and the median PSA-progression-free survival is 6 months), and power of 80% when the six-month PSA-progression-free probability is 66%, which corresponds to a median of 10 months if the time to PSA progression is exponentially distributed. Simulation studies confirmed that the design with the modified futility stopping method maintains these properties. If the median PSA-progression-free survival is six months, then the binomial design would stop at the interim analysis with 38% probability. Assuming an enrollment rate of 1.5 subjects/month, the modified futility stopping rule increases this probability of stopping at the interim analysis to 45%.

8.4 Analysis of primary endpoint

The probability of PSA-progression-free survival over time will be estimated using the Kaplan-Meier method and shown with 80% pointwise confidence limits. The six-month PSA-progression-free survival will be compared to the null-value of 50% using a z-test at a one-sided 10% significance level.

8.5 Analysis of secondary endpoints

The PSA nadir values will be summarized with mean and standard deviation as absolute values and as percent change from baseline PSA value. The time to PSA nadir and time to subsequent antineoplastic therapy will be summarized using Kaplan-Meier (KM) curves. The median will be estimated using the inverse-KM method and shown with 95% confidence intervals. The change in testosterone levels from baseline to cycle 4 will be shown graphically using box-plots and reported with mean and standard deviation.

8.6 Analysis of exploratory endpoints

The analysis of Comprehensive Geriatric Assessment domains will be descriptive and will describe mean, median, standard deviations of scores at baseline and at follow up time points. CGA deficits over 6 months will be captured. Each domain will be evaluated individually, and scores will be compared between baseline and 6 months. Overall CGA deficits will be examined and the proportion of patients who decline in more than 1 domain will be determined for these time points.

For each of the 27 core items and 12 site-specific items of the FACT-P tool, mean score for the study cohort will be computed at baseline and at specified follow-up visits (Section 8). These means will be plotted against follow-up time and visually assessed for evidence of an upward or a downward trend. For each item, an upward or a downward trend in mean scores over time will indicate improvement or deterioration in a given dimension of quality of life (i.e., the dimension measured by that item). Changes in mean scores from baseline will be calculated at three months and six months after therapy initiation and will be reported with 95% confidence intervals.

8.7 Safety analyses

Safety and toxicities of the study drug will be examined by documenting the type and grade of each adverse event (as defined by CTCAE v5, at baseline, and each follow-up visit). These data will be summarized with counts and percentages. In addition, each grade 3 or 4 adverse event will be described separately, and the plausibility of its causation by the study drug combination will be discussed.

8.8 Other analyses

Demographic and clinical characteristics of the patient population will be reported using appropriate descriptive statistics such as frequencies and percentages with standard errors for categorical variables, mean with standard error or median with quartiles for continuous variables. The disposition of each subject will be reported as a listing.

8.9 Interim analyses

An interim analysis for futility will be performed when 10 patients have been treated and followed for six months. The Kaplan-Meier estimate of the six-month PSA-progression-free survival using the data from the first 10 subjects and any subject who have been enrolled during the six-month follow-up period of the tenth subject will be computed and compared to 66% using a z-test at a one-sided 10% significance level. The study will be stopped for futility if the hypothesis is rejected for the alternative of the 6-month PSA-progression-free survival being lower than 66%.

8.10 Missing data

For all outcomes, summary statistics will include the count of missing and non-missing values. Patients with missing value for the primary outcome, PFS, will be censored at the time when last known to be alive and without progression. A similar approach will be used for other time-to-event outcomes, such as time to PSA nadir. Secondary outcomes requiring numeric values, such as geriatric assessments, PSA and testosterone levels will be analyzed among patients with non-missing values as required for each analysis (e.g., non-missing value at specific time point for cross-sectional analysis, and non-missing values at two time points for change analyses). The limitations of extensive missingness, if present, will be clearly noted in all reports and any related findings will be interpreted with caution.

9 DATA AND SAFETY MONITORING PLAN (DSMP)

9.1 Data and Safety Management Overview

The Medical College of Wisconsin (MCW) Data Safety Monitoring Committee (DSMC) and the MCW Institutional Review Board (IRB) will approve protocol-specific DSM plans. A local, investigator-initiated trial will be required to be continuously monitored by the principal investigator of the study with safety and progress reports submitted to the DSMC.

The DSMP for this study will involve the following entities:

9.2 Study Team

The study team minimally consists of the principal investigator, the clinical research coordinator, regulatory specialist, and the study biostatistician. While subjects are on study, the principal investigator will meet regularly with the research coordinator and the study biostatistician to review study status. This review will include but not be limited to reportable SAEs and UPIRSOs and an update of the ongoing study summary that describes study progress in terms of the study schema. The appropriateness of further subject enrollment and the specific intervention for the next subject enrollment is addressed. All meetings including attendance are documented.

9.3 Quality Assurance

The MCWCC Clinical Trials Office provides ongoing quality assurance audits. This protocol was classified as intermediate risk and will be reviewed internally by the MCW Cancer Center Clinical Trials Office Quality Assurance Staff according to the MCWCC Data and Safety Monitoring Plan and current version SOP, 6.5.2 Internal Quality Assurance Reviews.

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9.4 Clinical Trials Office

The MCWCC Clinical Trials Office [CTO] provides administrative assistance and support to the DSMC.

9.5 DSMC

The Medical College of Wisconsin Cancer Center places the highest priority on ensuring the safety of patients participating in clinical trials. Every cancer interventional trial conducted at MCW includes a plan for safety and data monitoring.

More information can be found related to the MCWCC Data and Safety Monitoring Plan at the MCWCC website (Data and Safety Monitoring Plan).

This study will be reviewed by the Medical College of Wisconsin Cancer Center Data and Safety Monitoring Committee (MCWCC DSMC). A summary of the MCWCC DSMC activities are as follows:

- Review the clinical trial for data integrity and safety
- Review all DSM reports
- Submit a summary of any recommendations related to study conduct
- Terminate the study if deemed unsafe for patients

A copy of the MCWCC Data and Safety Monitoring Plan and membership roster will be maintained in the study research file and updated as membership changes. The committee will review reports from the study PI twice annually (or more frequently if needed) and provide recommendations on trial continuation, suspension, or termination as necessary.

Any available DSMC letters will be submitted to the IRB of record as required.

10 REGULATORY COMPLIANCE, ETHICS, AND STUDY MANAGEMENT

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

10.1 Regulatory Compliance

This study will be conducted in compliance with:

- The protocol
- Federal regulations, as applicable, including 21 CFR 50 (Protection of Human Subjects/Informed Consent); 21 CFR 56 (Institutional Review Boards) and 45 CFR 46 Subparts A (Common Rule), B (Pregnant Women, Human Fetuses and Neonates), C (Prisoners), and D (Children), GCP/ICH guidelines, and all applicable regulatory

requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

10.2 Prestudy Documentation

Prior to implementing this protocol at MCWCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MCW IRB.

The clinical investigation will not begin until the Investigator has received a letter from the FDA stating that the study is exempt from IND requirements.

10.3 Institutional Review Board

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by the MCW Institutional Review Board. Before obtaining MCW approval, the protocol must be approved by the Medical College of Wisconsin Cancer Center Scientific Review Committee. The initial protocol and all protocol amendments must be approved by the IRB before implementation.

Informed Consent Process

Informed consent is a process that is initiated prior to the individuals agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product.

Consent forms will be IRB-approved and the subject (and Legally Authorized Representative, if necessary) will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. In accordance with 46 CR 46.111, the subject will sign and date the informed consent document prior to any procedures being done specifically for the study.

A witness should only sign when required, per FH/MCW IRB policy. If a witness signs the document when not required, the study staff should document in the legal medical record (or note to file) the relationship to the patient and why a witness signed. (i.e., "Although not required, the subject's spouse was present during the consenting process and signed as the witness." Or "Although not required, the hospital staff was present for the consenting process and signed as a witness.")

The subjects will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial.

A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. If there are changes to the consent form, all revisions will be reviewed with the study subject at the next appropriate opportunity. Patients that require reconsenting will be defined in the IRB approved

amendment submission. The process for obtaining informed consent will again be performed. Study subjects will not be reconsented for continuing reviews. The MCWCC CTO will follow the MCW/FH IRB's policy for subjects who demonstrate limited English proficiency or limited literacy.

After the subject's visit in which the consent is signed, it is documented in the clinic chart that the consent has been signed and that all questions have been answered to the subject's satisfaction after adequate time for the review of the consent. It is also documented that a copy of the consent is given to the subject. The original consent is kept with the subject's study file, and a copy of the consent is sent to the OCRICC office, which will then submit to HIM a copy of the signed consent to be scanned into EPIC, the legal medical record.

10.4 Subject Confidentiality and Access to Source Documents/Data

Subject confidentiality is strictly held in trust by the sponsor-investigator, participating investigators, and any staff, [and the sponsor(s) and their agents] (include bracketed portion if applicable). This confidentiality includes clinical information relating to participating subjects, as well as any genetic or biological testing.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the principal investigator.

The conditions for maintaining the confidentiality of the subjects' records are required for the life of the data. These rules apply equally to any and all MCWCC projects.

One risk of taking part in a research study is that more people will handle the personal health information collected for this study. The study team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass the subject or affect his/her ability to get insurance.

While data are being collected and after all data have been collected but are still in the process of being analyzed, the subject's data/PHI are stored in the locked Clinical Research office in the Clinical Trials Office. Databases in which the study subject information is stored and accessed are password-protected, allowing for limited access by authorized personnel only. Data/PHI kept in the Case Report Forms contain the study identifiers, subject initials, date of birth and date of service.

The principal investigator will allow access to all source data and documents for the purposes of monitoring, audits, IRB review, and regulatory inspections.

The study monitor/s or other authorized representatives of the principal investigator may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

10.5 Protection of Human Subjects

10.5.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the informed consent process. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study to ensure that the consent document accurately and communicates the nature of the research to be done and its associated risks and benefits.

10.5.2 Protection of Privacy

As noted, patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document.

10.5.3 Changes in the Protocol

Once the protocol has been approved by the MCW IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the investigator and approved by IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five working days after implementation.

The IRB may provide, if applicable regulatory authority(ies) permit, expedited review, and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB. The investigator will submit all protocol modifications to the sponsor and the regulatory authority(ies) in accordance with the governing regulations.

Changes to the protocol may require approval from the sponsor.

Any departures from the protocol must be fully documented in the source documents.

10.6 Investigator Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies).

<u>Onsite Audits</u>

Auditing is essential to ensure that research conducted at the Medical College of Wisconsin (MCW) Cancer Center is of the highest quality and meets MCW and regulatory agency standards.

Regulatory authorities, the IRB and/or sponsor may request access to all source documents, data capture records and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

11 DATA HANDLING AND RECORD KEEPING

11.1 Overview

Every effort is made to uphold the integrity of the project, the research, the institution, and the researchers involved. Data collection guidelines and methodologies are carefully developed before the research begins. Investigators focus on the following to ensure data integrity: well-trained data collectors/recorders to ensure consistency and quality, well-designed data collection protocols and ongoing monitoring. In this way, study rigor and validity are maintained. Data is protected from physical damage as well as from tampering, loss, or theft. This project's data management is a multidisciplinary activity that includes investigators, research coordinators and nurses, data mangers, support personnel, biostatisticians, and database programmers. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

11.2 Data Management Responsibilities

Principal Investigator
The principal investigator oversees the management of patient records/case report forms and ensures that a) complete and accurate data will be obtained and provided to the sponsor; b) patient records are maintained to include history, prescribed medication, and investigational product(s), measurements, exams, evaluations, and adverse events; c) corrections are applied to clinical research data according to principles of good research practice (i.e., single-line delete, date and initial). He or she will ensure that there is a correlation between the case report forms and the source documents**.**

Research Coordinator
A research coordinator creates, collects, and organizes clinical trial documentation. He or she ensures that source documentation and data abstraction and entry are being done at protocol-specified time points.

Research Nurse/Medical Staff
The research nurse and medical staff documents protocol-required care or assessment of the subject's outcomes, adverse events, and compliance to study procedures.

Biostatistician
The biostatistician may assist in CRF development (content and design), dataset specifications (annotation of CRFs and record layout) and validation.

11.3 Source Documents

Source documents for clinical information (patient history, diagnosis, clinical and diagnostic test reports, etc.) are maintained in the patient's clinical file.

All source documents will be written following ALCOA standards:

ALCOA Attribute	Definition
Attributable	Clear who has documented the data.
Legible	Readable and signatures identifiable.

Contemporaneous	Documented in the correct time frame along with the flow of events. If a clinical observation cannot be entered when made, chronology should be recorded. Acceptable amount of delay should be defined and justified.
Original	Original, if not original should be exact copy; the first record made by the appropriate person. The investigator should have the original source document.
Accurate	Accurate, consistent and real representation of facts.
Enduring	Long-lasting and durable.
Available and accessible	Easily available for review by treating physicians and during audits/inspections. The documents should be retrievable in reasonable time.
Complete	Complete until that point in time.
Consistent	Demonstrate the required attributes consistently.
Credible	Based on real and reliable facts.
Corroborated	Data should be backed up by evidence.

11.4 Case Report Forms

The principal investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study-specific Case Report Forms (CRFs) will document outcomes. All study data will be entered into OnCore® via standardized CRFs, in accordance with the study calendar, using single data entry with a secure access account. The Clinical Research Coordinator will complete the CRFs as soon as possible upon completion of the study visit; the investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by MCWCC personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The principal investigator will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and data will be available for review/monitoring by the MCWCC DSMC and regulatory agencies.

11.5 Study Record Retention

The principal investigator is required to maintain adequate records.

The principal investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation.

Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, sponsor-investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

APPENDIX 1. PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of the disease
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)	80	Normal activity with effort; some signs or symptoms of the disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

APPENDIX 2. LOST TO FOLLOW-UP LETTER

Date: _____

Dear _____,

The research study team has been unable to contact you regarding the clinical trial (A Phase 2 Study of Pacritinib for the Management of Patients with Biochemical Relapse after Definitive Treatment for Prostate Cancer) you participated in.

We would like to discuss how you are doing and if we may continue contacting you.

Please contact us at _____

Sincerely,

_____

APPENDIX 3. SELECTED STRONG INHIBITORS OF CYP3A4

Boceprevir	ciprofloxacin	clarithromycin
Conivaptan	erythromycin	fluconazole
Grapefruit	grapefruit juice	indinavir
Itraconazole	ketoconazole	lopinavir
Mibefradil	nefazodone	nelfinavir
Norfloxacin	posaconazole	Quinidine
Ritonavir	saquinavir	Seville oranges
star fruit	telaprevir	telithromycin
troleandomycin	voriconazole	

This list is not comprehensive. When considering using an agent that could be a potential CYP3A4 inhibitor, please discuss this with the pharmacy team.

Source: http://medicine.iupui.edu/clinpharm/ddis/table.asp and http://www.pharmacytimescom/issue/pharmacy/2008/2008-09/2008-09-8687.

APPENDIX 4. SELECTED STRONG INDUCERS OF CYP450

carbamazepine
efavirenz
nevirapine
phenobarbital
phenytoin
pioglitazone
rifabutin
rifampin
St. John's Wort
Troglitazone

This list is not comprehensive. When considering using an agent that could be a potential CYP450 inducer, please discuss this with the pharmacy team.
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Source: http://medicine.iupui.edu/clinpharm/ddis/table.asp and
http://www.pharmacytimescom/issue/pharmacy/2008/2008-
09/2008-09-8687.

APPENDIX 5. THE STAGES OF HEART FAILURE, NEW YORK HEART ASSOCIATION CLASSIFICATION

To determine the best course of therapy, physicians often assess the stage of heart failure according to the New York Heart Association (NYHA) functional classification system. This system relates symptoms to everyday activities and the patient's quality of life.

Class	Patient Symptoms
I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less-than-ordinary activity causes fatigue, palpitation, or dyspnea.
IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased

Source: Dolgin M, Fox AC, Devereaux RB. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston: Little Brown and Company; 1994. p. 253-256

APPENDIX 6. MEDICATIONS WITH SIGNIFICANT ARRHYTHMOGENIC POTENTIAL

Use of the following drugs is prohibited due to the potential for QT interval prolongation.[a]	
Alkylating agent	Bendamustine (Treanda, Treakisym, Ribomustin, Levact)
Alpha 1 blocker	Alfuzosin (Uroxatral)
Analgesic	Hydrocodone-ER (Hysingla™ ER, Zohydro ER); Tramadol (Crispin, Ralivia ER, Ralivia Flashtab, Tramadolum, Tramal, Tramodol, Tridural, Ultram, Ultram ER, Zydol)
Anesthetic	Propofol (Diprivan, Propoven); Sevoflurane (Ultane, Sojourn)
Antianginal	Bepridil (Removed from Market) (Vascor)
Antiarrhythmic	Amiodarone (Cordarone, Pacerone, Nexterone); Disopyramide (Norpace); Dofetilide (Tikosyn); Dronedarone (Multaq); Flecainide (Tambocor, Almarytm, Apocard, Ecrinal, Flécaine); Ibutilide (Corvert); Procainamide (Pronestyl, Procan); Quinidine (Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora); Sotalol (Betapace, Sotalex, Sotacor); Pilsicainide (Only on Non-US Market) (Sunrythm)
Antibiotic	Azithromycin (Zithromax, Zmax); Bedaquiline (Sirturo); Ciprofloxacin (Cipro, Cipro-XR, Neofloxin); Clarithromycin (Biaxin, Prevpac); Delamanid (Only on Non US Market) (Deltyba); Erythromycin (E.E.S., Robimycin, EMycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth); Gatifloxacin (Removed from Market) (Tequin); Gemifloxacin (Factive); Grepafloxacin (Removed from Market) (Raxar); Levofloxacin (Levaquin, Tavanic); Moxifloxacin (Avelox, Avalox, Avelon); Norfloxacin (Removed from Market) (Noroxin, Ambigram); Ofloxacin (Floxin); Roxithromycin (Only on Non US Market) (Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig, Roxar, Roximycinv, Roxomycin, Rulid, Tirabicin, Coroxin); Sparfloxacin (Removed from Market) (Zagam); Telavancin (Vibativ); Telithromycin (Ketek);
Anticancer	Arsenic trioxide (Trisenox); Capecitabine (Xeloda); Lenvatinib (Lenvima); Tamoxifen (Nolvadex [discontinued 6/13], Istubal, Valodex); Vandetanib (Caprelsa); Cabozantinib (Cometriq); Epirubicin (Ellence, Pharmorubicin, Epirubicin Ebewe); Fluorouracil (5-FU) (Adrucil, Carac, Efudex, Efudix, others); Midostaurin (Rydapt); Necitumumab (Portrazza); Tipiracil and Trifluridine (Lonsurf)
Anticoagulant	Betrixaban (Bevyxxa)
Anticonvulsant	Ezogabine (Retigabine) (Potiga, Trobalt); Felbamate (Felbatol)

Antidepressant	SNRI: Venlafaxine (Effexor, Efexor) SSRI: Citalopram (Celexa, Cipramil); Escitalopram (Cipralex, Lexapro, Nexito, Anxiset-E [India], Exodus [Brazil], Esto [Israel], Seroplex, Elicea, Lexamil, Lexam, Entact [Greece], Losita [Bangladesh], Reposil [Chile], Animaxen [Colombia], Esitalo [Australia], Lexamil [South Africa]) Tetracyclic: Mirtazapine (Remeron) Tricyclic: Clomipramine (Anafranil); Desipramine (Pertofrane, Norpramine); Imipramine (melipramine) (Tofranil); Nortriptyline (Pamelor, Sensoval, Aventyl, Norpress, Allegron, Noritren, Nortrilen); Trimipramine (Surmontil, Rhotrimine, Stangyl)
Antiemetic	Dolasetron (Anzemet); Granisetron (Kytril, Sancuso, Granisol); Ondansetron (Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax); Palonosetron (Aloxi); Tropisetron (Only on Non US Market) (Navoban, Setrovel)
Antifungal	Fluconazole (Diflucan, Trican); Pentamidine (Pentam)
Antihistamine	Astemizole (Removed from Market) (Hismanal); Terfenadine (Removed from Market) (Seldane)
Antihypertensive	Isradipine (Dynacirc); Ketanserin (Only on Non US Market) (Sufrexal); Moexipril/HCTZ (Uniretic, Univasc); Nicardipine (Cardene)
Antilipemic	Probucol (Removed from Market) (Lorelco)
Antimalarial	Artenimol+piperaquine (Only on Non-US Market) (Eurartesim); Chloroquine (Aralen); Halofantrine (Only on Non-US Market) (Halfan); Primaquine phosphate
Antimania	Lithium (Eskalith, Lithobid)
Antimycobacterial	Clofazimine (Only on Non-US Market) (Lamprene)
Antinausea	Domperidone (Only on Non-US Market) (Motilium, Motillium, Motinorm Costi, Nomit)
Antineoplastic agent	Inotuzumab ozogamicin (Besponsa); Oxaliplatin (Eloxatin)
Antipsychotic	Cyamemazine (cyamepromazine) (Only on Non-US Market) (Tercian); Haloperidol (Haldol [US & UK], Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol [Germany], Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol); Levomepromazine (methotrimeprazine) (Only on Non-US Market) (Nosinan, Nozinan, Levoprome); Levosulpiride (Only on Non-US Market) (Lesuride, Levazeo, Enliva [with rabeprazole]; Mesoridazine (Removed from Market) (Serentil); Perphenazine (Trilafon, Etrafon/Triavil, Decentan); Pimozide (Orap); Pipamperone (Only on Non-US Market) (Dipiperon [E.U], Propitan [Japan], Dipiperal, Piperonil, Piperonyl); Prothipendyl (Only on Non-US Market) (Dominal, Largophren, Timoval, Timovan, Tumovan); Thioridazine (Mellaril, Novoridazine, Thioril); Benperidol (Only on Non-US Market)

	(Anquil, Glianimon)
Antipsychotic/antiemetic	Chlorpromazine (Thorazine, Largactil, Megaphen); Droperidol (Inapsine, Droleptan, Dridol, Xomolix); Promethazine (Phenergan)
Antipsychotic, atypical	Aripiprazole (Abilify, Aripiprex); Asenapine (Saphris, Sycrest); Clozapine (Clozaril, Fazaclo, Versacloz); Iloperidone (Fanapt, Fanapta, Zomaril); Melperone (Only on Non-US Market) (Bunil, Buronil, Eunerpan); Paliperidone (Invega, Xepilon); Pimavanserin (Nuplazid); Risperidone (Risperdal); Sertindole (Only on Non-US Market) (Serdolect, Serlect); Sulpiride (Only on Non-US Market) (Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor); Sultopride (Only on Non-US Market) (Barnetil, Barnotil, Topral); Zotepine (Only on Non-US Market) (Losizopilon, Lodopin, Setous and Zoleptil)
Antiretroviral	Efavirenz (Sustiva and others)
Antisense oligonucleotide	Nusinersen (Spinraza)
Antiviral	Rilpivirine (Edurant, Complera, Eviplera); Saquinavir (Invirase [combo])
Beta-3 adrenergic antagonist	Mirabegron (Myrbetriq)
Cholinesterase inhibitor	Donepezil (Aricept)
Cyclin dependent kinase inhibitor	Ribociclib (Kisqali)
Dopamine 2 and 5HT2a antagonist	Flupentixol (Only on Non-US Market) (Depixol, Fluanxol)
Dopamine agonist	Apomorphine (Apokyn, Ixense, Spontane, Uprima)
Estrogen agonist/antagonist	Toremifene (Fareston)
GI stimulant	Cisapride (Removed from Market) (Propulsid)
Glucosylceramide synthase inhibitor	Eliglustat (Cerdelga)
Gonadotropin receptor agonist/antagonist	Leuprolide (Lupron, Eligard, Viadur, Carcinil, Enanton, Leuplin, Lucrin, Procren, Prostap and others)
Gonadotropin releasing hormone agonist/antagonist	Degarelix (Firmagon, Ferring)
Histone deacetylase inhibitor	Panobinostat (Farydak); Romidepsin (Istodax); Vorinostat (Zolinza)
Imaging contrast agent	Perflutren lipid microspheres (Definity, Optison)

Imunosuppressant	Tacrolimus (Prograf, Advagraf, Protopic)
Kinase inhibitor	Ceritinib (Zykadia); Crizotinib (Xalkori); Dabrafenib (Tafinlar); Lapatinib (Tykerb, Tyverb); Nilotinib (Tasigna); Sunitinib (Sutent); Vemurafenib (Zelboraf)
Local anesthetic	Cocaine
Microtubule inhibitor	Eribulin mesylate (Halaven)
Muscle relaxant	Terodiline (Only on Non-US Market) (Micturin, Mictrol [not bethanechol]); Tizanidine (Zanaflex, Sirdalud); Tolterodine (Detrol, Detrusitol)
Norepinephrine reuptake inhibitor	Atomoxetine (Strattera)
Opioid agonist	Levomethadyl acetate (Removed from Market) (Orlaam); Methadone (Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon)
Opioid receptor modulator	Buprenorphine (Butrans, Belbuca, Bunavail, Buprenex, Suboxone, Zubsolv)
Oxytocic	Oxytocin (Pitocin, Syntocinon)
Phosphodiesterase 3 inhibitor	Anagrelide (Agrylin, Xagrid); Cilostazol (Pletal)
Phosphodiesterase 5 inhibitor	Vardenafil (Levitra)
Progesterone antagonist	Mifepristone (Korlym, Mifeprex)
Proteasome inhibitor	Bortezomib (Velcade, Bortecad)
Psychedelic	Ibogaine (Only on Non-US Market)
Sedative	Dexmedetomidine (Precedex, Dexdor, Dexdomitor)
Selective D2, D3 dopamine antagonist	Tiapride (Only on Non-US Market) (Tiapridal, Italprid, Sereprile, Tialaread, Tiaryl, Tiaprim, Tiaprizal, Sereprid, Tiapridex)
Somatostatin analog	Pasireotide (Signifor)
Sphingosine phosphate receptor modulator	Fingolimod (Gilenya)
Tyrosine kinase inhibitor	Bosutinib (Bosulif); Dasatinib (Sprycel); Osimertinib (Tagrisso); Pazopanib (Votrient); Sorafenib (Nexavar)
Vasoconstrictor	Terlipressin (Only on Non US Market) (Teripress, Glypressin, Terlipin, Remestyp, Tresil, Teriss and others)
Vasodilator, Coronary	Papaverine HCl (Intra-coronary)
Vesicular monoamine transporter 2 inhibitor	Deutetrabenazine (Austedo); Valbenazine (Ingrezza); Tetrabenazine (Nitoman, Xenazine)

Viral protease inhibitor	Lopinavir and ritonavir (Kaletra, Aluvia)
Source: CredibleMeds Filtered QT Drug List Rev March 01 2018 (AZCERT.ORG)	

APPENDIX 7. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS: DIARRHEA (VERSION 5.0)

	Definition: A Disorder Characterized by Frequent and Watery Bowel Movements.
1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline.
2	Increase of 4 – 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL
3	Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL,
4	Life-threatening consequences; urgent intervention indicated.
5	Death

APPENDIX 8. INVESTIGATOR RESPONSIBILITIES, REQUIRED DOCUMENTATION, AND SIGNATURE

- Obtain Institutional Review Board (IRB), Research Ethics Board (REB), or Independent Ethics Committee (IEC) approval of the protocol and amendments to the protocol and Informed Consent Form before initiation of the protocol or any amendments for the study, and obtain annual IRB or IEC renewal, as required. Ensure that current FDA and/or ICH-E6 regulations are followed.
- Select all patients per the selection criteria outlined in the study protocol.
- Treat and follow patients as described in this research protocol. Complete all electronic case report forms (eCRFs) promptly and review eCRFs for accuracy and completeness. Provide the original clinical source documents to verify all data entered on eCRFs or SAE reports and all data that document the course of the patient throughout their participation in the study. Provide a clinical summary to the Sponsor's clinical research monitor.
- Report all adverse events to CTI BioPharma Corp. or designee, as required by the protocol.
- Ensure that the investigational drug is kept in a secured, limited access area and stored under proper conditions. Ensure that all investigational drug receipt and dispensing information is recorded and all drug can be accounted for at all times.
- Before initiation of the study, each participating investigator will submit to CTI:
  - FDA Form 1572 and, if applicable,
  - Copies of the medical licenses of principal investigators and sub investigators
  - Addresses and descriptions of all clinical laboratory facilities to be used
  - Laboratory certification and expiration dates
  - Normal ranges and effective dates for all required laboratory tests
  - IRB/REB/IEC approval letter referencing the protocol (and amendments, if applicable).
  - IRB/REB/IEC Membership List: A list of the IRB/REB/EC members, their respective titles or occupations, and their institutional affiliations.
  - A sample copy of the IRB/REB/IEC-approved Informed Consent Form
  - Curricula vitae: Curricula vitae for the principal investigator and all sub investigators
  - Financial disclosure for the principal investigator and all sub investigators
  - Protocol signature page, signed by the principal investigator

Investigator Statement and Signature

I attest that I have read this protocol, understand and agree to the provisions of the protocol, and accept the responsibilities listed above in my role as principal investigator for the study.

Principal Investigator Signature Date

Principal Investigator Name, Printed

APPENDIX 9. COMPRESSIVE GERIATRIC ASSESSMENT FORMS

Please click the below PDF file.

cga.pdf

APPENDIX 10. PILL DIARY

Please click the below Word file.

SUBJECT DIARY[75814].docx

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