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Herbert Irving Comprehensive Cancer Center Protocol

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Columbia University Medical Center
Herbert Irving Comprehensive Cancer Center
Version Date: 27 Jul 2023

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TITLE: A Multi-Center Phase II study of Ruxolitinib in Solid Organ Transplant Recipients with Advanced Cutaneous Squamous Cell Carcinoma

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1. Protocol Signature Page

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practices, and the applicable federal, state, and local laws, rules, and regulations relating to the conduct of the protocol. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I will promptly submit the protocol to the applicable IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modification made during the course of the study must first be approved by the IRB, prior to implementation except when such modification is made to remove an immediate hazard to the subject. I certify that I, and the study staff, have received the requisite training to conduct this research protocol. I agree to maintain adequate and accurate records in accordance with Columbia University and Herbert Irving Comprehensive Cancer Center policies, Federal, state and local laws and regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Instructions to Principal Investigator: Sign and Date this signature page and print your name. Return the original, completed and signed to the Clinical Protocol & Data Management Office. Retain a copy in the regulatory binder.

_____ _____
Signature of Principal Investigator Date

_____
Principal Investigator Name (Print)

_____
Name of Institution

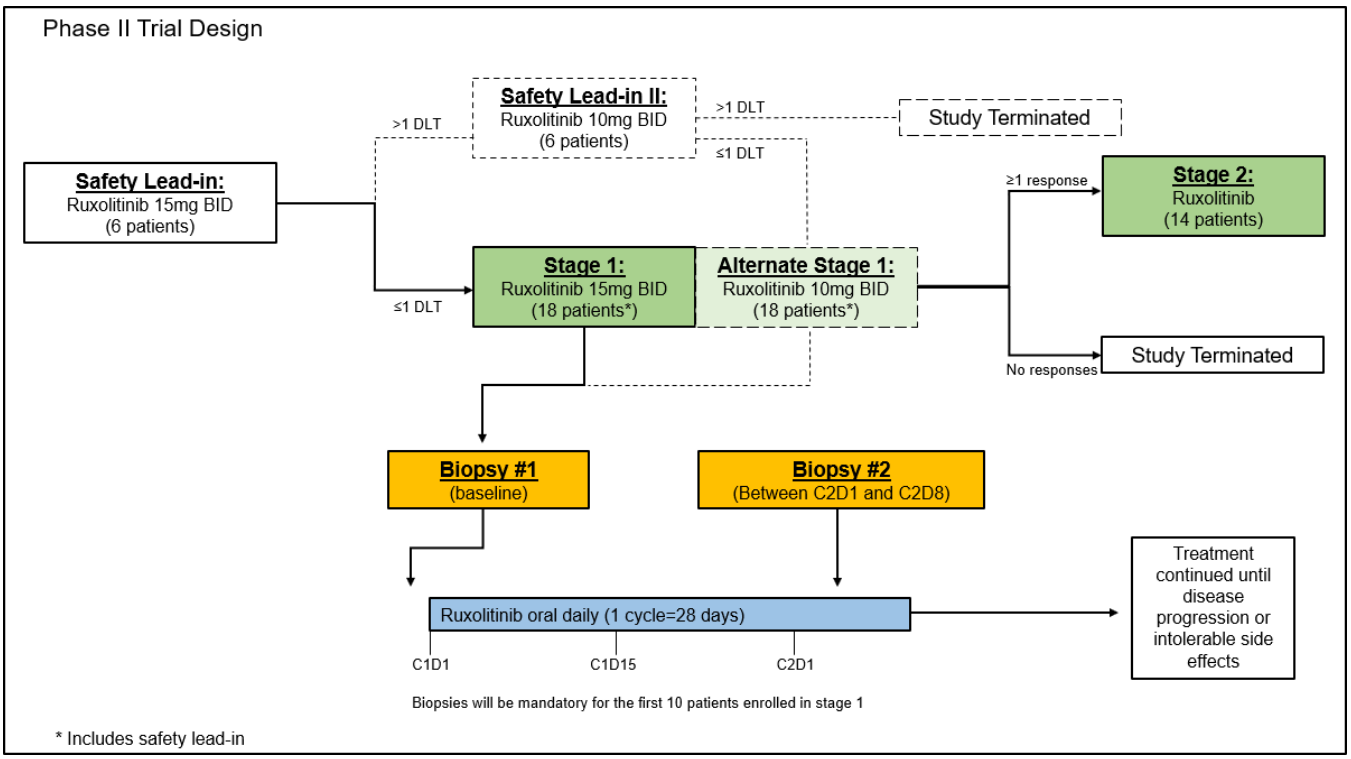
Protocol Synopsis

Title	Multi-Center Phase II Study of the JAK1/2 inhibitor, Ruxolitinib, in Solid Organ Transplant Recipients with Advanced Cutaneous Squamous Cell Carcinoma
Short Title	Ruxolitinib for Advanced Cutaneous Squamous Cell Carcinoma
Protocol Number	AAAT5353
Phase	Phase II
Methodology	This is an open-label, multi-center, phase II clinical trial with a primary endpoint of overall response rate by RECIST v 1.1.
Study Duration	36 months
Study Center(s)	1. Columbia University Irving Medical Center 2. Winship Cancer Institute of Emory University 3. Robert H. Lurie Cancer Center of Northwestern University
Objectives	**Primary Objectives:** • To determine the efficacy of ruxolitinib in post-transplant patients with advanced cutaneous squamous cell carcinoma as determined by overall response rate. **Secondary Objectives:** • To evaluate the clinical benefit of ruxolitinib as determined by progression free survival and overall survival. • To determine the safety and tolerability of ruxolitinib in post-transplant patients with advanced cutaneous squamous cell carcinoma • To assess the pharmacodynamics of ruxolitinib in post-transplant patients with advanced cutaneous squamous cell carcinoma. **Exploratory Objectives:** • To explore the association between clinical benefit/response and changes in expression of phosphorylated STAT3 and Cyclin D1 using pre- and post-treatment tumor biopsies. • To explore the effect of ruxolitinib on the tumor immune microenvironment. • To explore the effect of ruxolitinib on circulating immune cell populations • To explore mechanisms of sensitivity and resistance using RNA-Seq analysis of tumor biopsies from responding and non-responding patients.

Number of Subjects	Thirty-five patients will be enrolled across all 3 sites Each site will plan to accrue 1 patient every 2 months and we anticipate that the last patient will be enrolled approximately 24 months after the anticipated start date.
Diagnosis and Main Inclusion Criteria	**Main Inclusion Criteria:** • Histopathologically confirmed diagnosis of metastatic advanced cutaneous squamous cell carcinoma. • History of solid-organ transplant requiring immunosuppression • Age ≥ 18 yrs • Measurable disease by RECIST v1.1 • KPS ≥60%, ECOG ≤2 • No prior JAK Inhibitor therapy • Adequate organ function • All clinically significant toxicities from prior systemic therapy must be ≤ Grade 1 (with the exception of alopecia, and peripheral neuropathy, which may be ≤ grade 2). • Subjects must agree to undergo tumor biopsies until biopsies have been obtained from 10 subjects (i.e., biopsies are required in at least the first 10 enrolled subjects, or until a goal of 10 study biopsies are obtained). Subjects in whom a biopsy is technically not feasible or in whom would result in unacceptable risk in the opinion of the investigator, may be exempted from the biopsy requirement with discussion with the principal investigator. • Negative pregnancy test for women of child bearing potential • Ability to take oral medications • Adequate marrow function: - ANC ≥1000 /mm3 - Platelet count ≥50,000/mm3 - Hemoglobin ≥8.0g/dL (not requiring transfusion in the past 2 weeks)
Study Product, Dose, Route, Regimen	Ruxolitinib will be administered orally twice daily during the entirety of each 28-day cycle. There will be a safety lead-in cohort of 6 patients who receive the starting dose of 15mg twice daily (BID). If dose limiting toxicities (DLT) are seen in 1 or fewer patients, the starting dose for all remaining patients will be 15mg BID. If DLT's are seen in >1 patient, another 6 patients will be enrolled at 10mg BID. If DLT's are seen in 1 or fewer patients, the starting dose for the remaining patients will be 10mg BID. Otherwise the study will be terminated. Individual subjects may have dose reductions of ruxolitinib during the course of treatment, based upon safety laboratory assessments.

Duration of administration	Treatment with ruxolitinib will commence following enrollment and continue until objective disease progression as confirmed by RECIST v1.1, intolerable toxicity or the occurrence of another discontinuation criterion.
Reference therapy	Historical response rates to chemotherapy in advanced cutaneous squamous cell carcinoma in transplant recipients (reference respone rate 5-10%)
Statistical Methodology	**Definition of primary outcome/endpoint:** The primary endpoint is the overall response rate as defined as the best response, confirmed at ≥4 weeks, within the first 24 weeks of the start of study therapy, using RECIST v1.1 criteria. **Definition of secondary outcomes/endpoints:** PFS is defined as time from registration to time of clinical or radiographic disease progression as defined by RECIST v1.1 criteria, or death. OS is defined as time from registration to time of death from any cause. **Analytic plan for primary objective:** We will estimate the response rate to ruxolitinib using the exact 95% confidence interval based on the binomial distribution. **Analytic plan for secondary and exploratory objectives:** • We will estimate the survival distribution for both PFS and OS endpoints using the Kaplan Meier method. The log rank test will be used to examine differences between survival curves. • For correlative studies we will apply either the Fisher's exact test or Wilcoxon rank sum test to examine the correlation between response status and markers for categorical and continuous variables, respectively. **Sample size justification:** We will utilize a Simon mini-max two-stage design in which a 5% RR is considered not promising, a 20% RR is considered promising, and the probabilities of a type I error (falsely accepting a non-promising therapy) and type II error (falsely rejecting a promising therapy) are set at 0.10 and 0.10, respectively. Eighteen patients with advanced cSCC will be accrued in the first stage. If 1 or more patients achieve a response, then an additional 14 will be accrued. If 4 or fewer responses are seen, the study will be declared negative.

Protocol Schema:



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1. INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is a common malignancy in patients receiving immunosuppressive therapy, including solid organ transplant recipients (SOTRs). These patients have an estimated 60- to 250-fold increased risk of cSCC development and are particularly vulnerable to the development of highly aggressive or catastrophic cSCC [1-4]. Post-transplant cSCC occurs at a younger age and is more aggressive than in non-transplant cohorts, with 30% recurring within 1 year and up to 8% of disease associated with metastasis [5]. The median survival after diagnosis of metastasis is 3 years [6]. Cemiplimab, an anti-PD1 antibody, recently became the first agent to achieve FDA approval for the treatment of advanced cSCC [7, 12]. However, due to the risk of graft rejection, the role of checkpoint blockade in the SOTR population is extremely limited. In retrospective series, the rate of graft rejection has ranged between 37-41% with a significant percentage of these patients dying as a result [8]. There is a dearth of data to guide decision making in patients who cannot receive cemiplimab. Two small phase II studies investigating epidermal growth factor receptor (EGFR) antagonists have demonstrated response rates of 28 and 31%, however it is unclear if these agents have any survival benefit and it is unknown if these response rates are seen in SOTR [13, 14]. Thus, there remains a large unmet medical need for novel strategies in these patients.

The Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway plays a critical role in tumorigenesis and has been implicated in cSCC. STAT proteins regulate the transcription of genes involved in cytokine signaling, cell proliferation, and tumorigenesis [9]. Elevated levels of STAT3 have been observed in a number of human epithelial cancers [10, 11]. Pre-clinical data from our group supports the role of JAK1/2 co-inhibition as a potential therapeutic strategy in cSCC. We propose to evaluate the efficacy of ruxolitinib, an orally administered inhibitor of JAK1/2, in solid organ transplant recipients with advanced cSCC. Paired pre-treatment and on-treatment biopsies will also be obtained to further define the mechanism of response and resistance to JAK1/2 inhibition in this population.

2. STUDY OBJECTIVES

2.1 Primary Objective

- To determine the efficacy of ruxolitinib in post-transplant patients with advanced cutaneous squamous cell carcinoma as determined by overall response rate.

2.2 Secondary Objectives

- To evaluate the clinical benefit of ruxolitinib as determined by upon progression free survival and overall survival.
- To determine the safety and tolerability of ruxolitinib in post-transplant patients with advanced cutaneous squamous cell carcinoma
- To assess the pharmacodynamics of ruxolitinib in post-transplant patients with advanced cutaneous squamous cell carcinoma.

2.3 Exploratory Objectives

- To explore the association between clinical benefit/response and changes in expression of phosphorylated STAT3 and Cyclin D1 using pre- and post-treatment tumor biopsies.
- To explore the effect of ruxolitinib on the tumor immune microenvironment
- To explore the effect of ruxolitinib on circulating immune cell populations
- To explore mechanisms of sensitivity and resistance using RNA-Seq analysis of tumor biopsies from responding and non-responding patients.

3. BACKGROUND

3.1 Cutaneous Squamous Cell Carcinoma

Approximately 5.4 million individuals in the United States are diagnosed with non-melanoma skin cancers (NMSC) annually, with the incidence increasing over time. Twenty-five percent are cutaneous squamous cell carcinomas (cSCC), which affect up to 1,350,000 individuals and result in up to 12,000 deaths annually in the US alone.[1, 2] Immunosuppressed patients are particularly vulnerable to the development of highly aggressive or catastrophic cSCC.[3, 4] Patients receiving immunosuppressive therapy, such as solid organ transplant recipients (SOTRs), and HIV/AIDS patients have an estimated 60 to 250-fold increased risk of cSCC development. In renal SOTRs, cSCC represents over 70% of all malignancies that develop, with an incidence up to 200 times that of the general population. Post-transplant cSCC occurs at a younger age and is more aggressive than in non-transplant cohorts, with 30% of cSCC recurring within 1 year and up to 8% of disease associated with metastasis. The median survival from diagnosis of metastasis is 3 years.[5] Cemiplimab, an anti-PD1 antibody, recently became the first agent to achieve regulatory approval for the treatment of advanced cSCC;[6, 7] however, due to the risk of graft rejection, the role of immunological checkpoint blockade in the SOTR population is extremely limited. Thus, although surgical excision is effective for sporadic cSCC, there remains a large unmet medical need for novel strategies for treatment and/or prevention of multiply recurrent, locally advanced and metastatic cSCC, particularly in immunosuppressed patients

3.2 Rationale for JAK inhibition in advanced cutaneous squamous cell carcinoma

The Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway plays a critical role in the downstream signaling of inflammatory cytokines and various growth factors, and has emerged as an important therapeutic target in inflammatory and immunologic diseases.[8] Upon nuclear translocation, STAT proteins regulate the transcription of genes involved in cytokine signaling, cell proliferation, and tumorigenesis. Elevated levels of STAT3 have been observed in a number of human epithelial cancers ranging from head and neck SCC to breast cancer.[9, 10] In murine models of cSCC, genetic disruption of STAT3 confers resistance to cSCC, while forced expression of constitutively active STAT3 sensitizes to cSCC formation.[11] Previous analysis of human cSCC specimens positively correlated levels of phosphorylated (activated) STAT3 with increased depth of tumor invasion and metastasis.[10, 12]

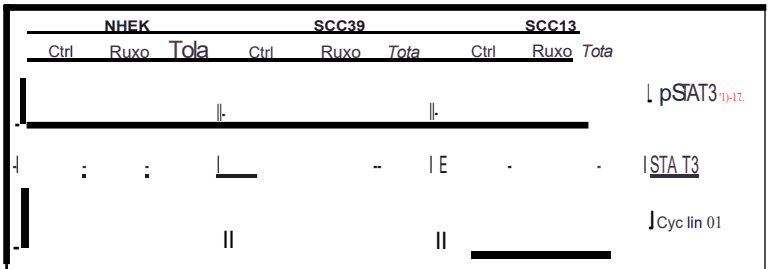
3.3 Preliminary data supporting JAK inhibition in cutaneous squamous cell carcinoma

To es tab lish releva nce for the JAK-STAT pathway in cSCC pathogenesis, we first examined protein levels for all four JAK family members, JAK.l , JAK.2, JAK.3, and TYK2, in n01mal human epide1mal keratinocytes (NHEK) and cSCC. We examined primaiy cultures ofNHEKs (NHEKI, 2, and 3) and cSCC (SCC13, SCC35, and SCC39) previously established **in** our laborato1y [13] from patients seen at CUIMC. Whole cell protein lysates were generated from primaiy NHEK (n=3) or cSCC (n=3) and analyzed by irmnunoblot analysis using commercially available antibodies (Cell Signaling). We observed expression of JAK I, JAK2, and TYK2 protein in all NHEK and cSCC cultures; JAK.3 was undetectable **(Figure 1).** Interestingly, variable levels for each JAK family protein were observed between NHEK and cSCC - JAKI and TYK2 were down-regulated approximately two-fold in cSCC compai·ed to NHEK, while JAK.2 prote in levels were significantly upregulated in cSCC **(Figure 1).** Thus, multiple JAK proteins ai·e prese nt in cSCC and JAK2 upregulation is present in cSCC.

Fi gure 1. JAK family protei n levels in NHEK and cSCC. Left: micrographs show immunodetection of JAK1, JAK2, JAK3, TYK2 and p-ACTIN (loading control) in 3 independent NHEK and cSCC samples (SCC13, SCC35, SCC39). Right: bar graphs show relative densitometric units of blots normalized to P-ACTIN using ImageJ software. (*)- Student's t-test; Error bars- Std. Dev.

Cutaneous SCC cells show upregulated JAK-STAT signaling and ai·e respons ive to phannacological JAK inhibitors:

To assess the role of JAK signaling in the tumorigenic properties of cSCC, NHEK and cSCC cultures were senun-starved for 4hr followed by treatment with lmM of either selective JAK inhibitors rnxolitinib (JAK.1/2) or tofacitinib (JAK.1/3) for 1hr. Ce lls were then treated with 1Ong/ml EGF for 30min to stimulate entiy into the cell cycle and harvested to generate protein lysates. Lysates were exainined by immunoblot analysis for total and activated levels of STAT3, a major downstream tai·get of JAK activity. While total levels of STAT3 were similar between nonnal and cSCC keratinocytes, constitutive levels of pSTAT3 yr[705] we re dramat ica ll y highe r in two of thr ee cSCC cultures compared to NHEKs **(Figure 2).** Levels of pSTAT3Tyr[705] were dramatically decreased in NHEK and cSCC cultures ti·eated with either JAK inhibitor. However, levels of cyclin Dl, a mai·ker of cell proliferation that is associated with increased JAK-STAT signaling in a number of tumor types,[14] were decreased only with rnxolitinib (JAK 1/2) treatment **(Figure 2).**



Fi g ur e 2 . J A K/STAT signaling in cSCC cells. Immunoblot analysis of protein lysates from vehicle (Ctrl) and drug-treated NHEK and cSCC cultures using antibodies against active (pSTAT3Tyr[705]), total STAT3 and cyclin D1. Similar results were observed in SCC35 (not shown). Ruxo, ruxolitinib; Tofa, tofacitinib.

The differential effects of rnxolitinib versus tofacitinib (JAK 1/3) on cyclin Dl protein levels provide insight into which JAK family members may be critical for cSCC growth. First, these findings largely exclude a role for JAK3, which is not detectable in NHEK or cSCC lysates **(Figure 1).** Second, the reductions in pSTAT3Tyr[705] and cyclin D1 levels following rnxolitinib, which targets JAK2, but not tofacitinib treatment suggests that JAKl and JAK2 co-inhibition may be 11ec e ss aly to block cyclin D1 induction and, therefore, cSCC proliferation. We further tested this idea with larger panels of JAK/STAT inhibitors, siRNAs and cSCC cultures shown below.

Phaim acological JAK inhibition blocks cSCC growth:

Since rnxolitinib (JAKl/ 2 inhibitor), but not tofacitinib (JAKl/ 3 inhibitor), treatment decreased cyclin D1 levels in cSCC primaiy cultures, we hypothesized that i) JAK inhibition could attenuate cSCC growth, and ii) co-inhibition of JAK l and JAK2 may be necessaiy to effectively block cSCC growth. To test our hypothesis, three independent cSCC cultures were plated at equal numbers in the presence of a panel of JAK inhibitors: baricitinib (JAKl/ 2), rnxolitinib (JAKl /2), tofacitinib (JAKl/ 3), fedratinib (JAK2), or vehicle (DMSO). Total cell numbers were counted at 3, 6 and 8 days. While little to no difference in cSCC numbers was observed between vehicle-, tofacitinib-, or fedratinib-treated cultures, 35-45% growth inhibition was observed in baricitinib- and rnxolitinib-treated cultures **(Figure 3).** Collectively, these results suggest that JAK l and JAK2 co-inhibition may be a relevant therapeutic strategy for cSCC.

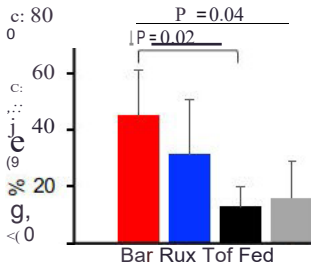


Figure 3. JAK inhibition blocks cSCC growth. Growthinhibition of cSCC13, cSCC35 or cSCC39 cells plated each of four different JAK inhibitors (baricitinib (JAK1/2), ruxolitinib (JAK1/2), tofacitinib (JAK1/3), fedratinib (JAK2). Data are averaged across all three cultures; n = 3 replicates per time point. The maximum inhibition value was selected for each inhibitor at the 500 nM dose. Error bars represent standard deviation. P value- Student's t-test.

JAK l /2 RNA silencing blocks cSCC growth:

To exclude potential off-target effects of the JAK inhibitors above, we perfo1med mRNA silencing of JAK members using pooled siRNAs (Origene). cSCC39 cells were transfected with pooled siRNAs (three per pool) targeting JAKl, JAK2, TYK.2 or sc ram bled (Se r) con trol. Kn ockdown of each JAK family protein compai·edto SCR-transfected cells was confnm ed by immunoblot (data not shown). JAK3 was excluded as a target due to lack of irmmmodetectab le protein in cSCC cultures **(Figure 1).** As outlined above, cell numbers were counted at 3, 6 and 8 days later (n=3 replicates per group and time point). Approximately 30% growth inhibition was observed in cSCC39 cells transfected with JAKl or JAK2 siRNAs compared to SCR siRNA control cells **(Figure4A).** TYK2 siRNA-transfected cells also demonstrated abrogated growth albeit to a lesser

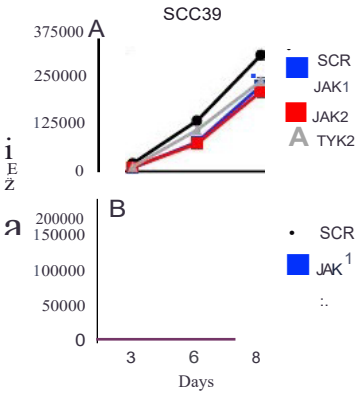


Figure 4. JAK1/2 co-silencing blocks cSCC growth. Line plots showing average cell numbers of cSCC39 cultures transfected with (A) Sa- (ctrl), JAK1, JAK2, JAK3 or TYK2 pooled siRNAs or co-transfected with JAK1+JAK2 pooled siRNAs (B). For each JAK family member, three independent siRNAs were used for each pool (Origene). (*)- P values compared to SCR-transfected cells in A: JAK1, P < 0.05; JAK2, P < 0.04; and in B: JAK1+JAK2, P < 0.001. P values calculated by Student's t-test, n = 3 replicates per group. Error bars represent standard deviation.

extent compared to JAKl or JAK2 siRNA cells **(Figure 4A).** In a repeat experiment, cells co-transfected with pooled JAKl and JAK2 siRNAs (equivalent total siRNA levels were used compared to individual pooled siRNA cells) showed dramatically reduced growth (two- to three-fold) compared to cells transfected with JAK1 or JAK2 siRNA alone **(Figure 4B).** Collectively, these findings indicate that the JAK-STAT pathway is effectively blocked by inhibitors such as baricitinib and ruxolitinib that target both JAKl and JAK2 and indicate therapeutic relevance for co-targeting JAKl and JAK2 in human cSCC.

3.4 Study Rationale and Hypothesis

We propose a multicenter, open-label, phase II clinical trial to evaluate the efficacy of ruxolitinib, an orally active kinase inhibitor of JAKl and JAK2, in post-transplant patients with advanced cutaneous squamous cell carcinoma. The analysis of pre- and post-treatment tumor biopsies collected from patients treated on this study will be used for phannacodynamic analysis to assess the biological activity of ruxolitinib in human tumor samples. We hypothesize that JAKl/2 co-inhibition will achieve clinical efficacy as deten nined by increased radiographic responses compared to historical response rates seen with chemotherapy and other agents in patients with advanced cutaneous squamous cell carcinoma. We anticipate that inhibition of STAT3 and cyclin D1 will con elate with response to therapy

4. INVESTIGATIONAL AGENT

Ruxolitinib (INCB018424 phosphate, INC424, ruxolitinib phosphate) represents a well established, potent and selective inhibitor of Janus kinase (JAK)1 (inhibition concentration 50% [IC50]=3.3 ± 1.2 nanomolar (nM)) and JAK2 (IC50=2.8 ± 1.2 nM), with modest to marked selectivity against tyrosine kinase (TYK)2 (IC50=19 ± 3.2 nM) and JAK3 (IC50=428 ± 243 nM), respectively. Ruxolitinib interferes with the signaling of a number of cytokines and growth factors that are impo1tant for hematopoiesis and immune function.

JAK signaling involves recruitment of signal transducers and activators of transcription (STATs) to cytokine receptors, activation, and subsequent localization of STATs to the nucleus leading to modulation of gene expression. Dysregulationof the JAK./ST AT pathway has been associated with several types of cancers and increased proliferation as well as smvival of malignant cells. In paiticular, this pathway may be dysregulated in majority of patients with Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs), including myelofibrosis (MF) and polycytheinia vera (PV), demonstrating that JAK inhibition may be

efficacious in these diseases.

Ruxolitinib (JAKAVI®) is currently approved in the European Union (EU) for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (PMF) (also known as chronic idiopathic MF), post-polycythemia vera myelofibrosis (PPV-MF) or post-essential thrombocythemia myelofibrosis (PET-MF) and for the treatment of adult patients with PV who are resistant to or intolerant of hydroxyurea (HU). In the USA ruxolitinib (JAKAFI®) is approved for the treatment of intermediate or high-risk MF, including PMF, PPV-MF and PET-MF and for treatment of patients with PV who have had an inadequate response to or are intolerant of HU. Ruxolitinib is currently under further development for the treatment of MF, PV, essential thrombocytopenia (ET), Graft versus Host Disease (GvHD) and other hematologic malignancies.

4.1 Mechanism of Action

Ruxolitinib (INCB018424 phosphate, INC424, ruxolitinib phosphate) represents a potent, and selective inhibitor of JAK1 (Janus kinase 1) (inhibition concentration 50% [IC50]=3.3 ± 1.2 nM) and JAK2 (IC50=2.8 ± 1.2 nM) with modest to marked selectivity against TYK2 (tyrosine kinase 2) (IC50=19 ± 3.2 nM) and JAK3 (IC50=428 ± 243 nM), respectively. Ruxolitinib interferes with the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of signal transducers and activators of transcription (STATs) to cytokine receptors, activation, and subsequent localization of STATs to the nucleus leading to modulation of gene expression. Dysregulation of the JAK-STAT pathway has been associated with several types of cancer and increased proliferation and survival of malignant cells.

4.2 Non-Clinical Pharmacology

Ruxolitinib has high aqueous solubility and high permeability *in vitro* based on Caco-2 cell culture study. In single oral dose PK studies, ruxolitinib was absorbed rapidly with mean Tmax values ranging from 0.5 to 2 h. In mice, dogs, minipigs and humans, there were minimal gender differences in the exposure of ruxolitinib and its metabolites. In rats, the Cmax and AUC (area under the concentration-time curve) values were several-fold higher in females compared to males, due to metabolism by male rat specific isozymes 2C11, 2C13 and CYP3A2. The terminal half-life, routes and rate of excretion for ruxolitinib-derived radioactivity and metabolites observed between male and female rats were similar. The oral bioavailability was variable across species, ranging from 22% in male monkeys to virtually complete in female rats consistent with the species dependent clearance observed following IV dosing.
Following IV administration of ruxolitinib, the plasma clearance was species-dependent and ranged from moderate in male dogs (0.48 L/h/kg) to very high in male rats (9.4 L/h/kg). Based on the apparent steady-state volume of distribution, ruxolitinib was not distributed extensively beyond body water in dogs (1.1 L/kg) and monkeys (0.81 L/kg), but may be distributed to a greater degree in rats (1.6-3.8 L/kg) and minipigs (6.4 L/kg). The terminal elimination half-life ranged from 0.4 h (rat) to 2.5 h (dog). In monkeys, the PK parameters of ruxolitinib were comparable with and without the pretreatment of agents that increase gastric pH, indicating that elevated gastric pH is not likely to affect the oral exposure of ruxolitinib.

4.3 Animal Toxicity

Ruxolitinib was evaluated in several in animal based toxicology studies and did not exhibit significant toxicities at target concentrations. Cardiovascular evaluation in dogs demonstrated lowered blood pressure and increased heart rate at the highest dose of ruxolitinib (30 mg/kg). Effects noted in multiple-dose toxicity studies in mice (up to 4 weeks), rats (up to 6 months), and dogs (up to 12 months) were primarily those associated with the mechanism of action of ruxolitinib, a potent and reversible inhibitor of JAK-STAT signaling. Decreases in red blood cells, reticulocytes, eosinophils and lymphocytes have been observed along with lymphoid depletion in bone marrow and lymphoid organs. In addition, in dogs, demodectic mange, bacterial pneumonia and viral-induced papillomas, expected consequences of the pharmacology of JAK inhibition, were noted.
Embyro-fetal assessments in rat and rabbit, maternal toxicity and minimal embryo-fetal toxicity were noted at the highest doses. No teratogenicity was noted in rat or rabbit animal models. There were no reported effects on fertility or early embryonic development. In an evaluation of fertility and early embryonic development, no effects were noted on reproductive performance or fertility in male or female rats. Increases in post-implantation loss were noted at the higher doses. In a pre- and post-natal development and maternal function study in rats there were no adverse findings for fertility indices or for maternal and embryo-fetal survival, growth, and developmental parameters. Ruxolitinib passed into the milk of lactating rats with an exposure that was 13-fold higher than maternal plasma exposure.

4.4 Absorption, bioavailability, and pharmacokinetics

Ruxolitinib is a potent and selective inhibitor of the JAKs with selectivity for JAK1 and JAK2 (Quintás-Cardama et al, 2010). Ruxolitinib potently inhibits JAK1 and JAK2 (IC50<5nM), yet it does not significantly inhibit a broad panel of 28 kinases (<30% inhibition) when tested at 200 nM (approximately 100 × the average IC50 value for JAK1 and JAK2 enzyme inhibition). In cell-based assays relevant to the pathogenesis of MPNs (myeloproliferative neoplasms), such as JAK/STAT signaling and the growth of cytokine-dependent tumor cell lines, ruxolitinib demonstrates IC50 values of 80-300 nM. This effect is not due to general cytotoxicity, because ruxolitinib (up to 25 μM) had no significant effect on the growth of a cytokine-independent, BCR-ABL-driven cell line. In addition, ruxolitinib inhibited JAK/STAT signaling and growth of a cell line expressing the constitutively active JAK2 mutant (JAK2V617F) that has been implicated in the pathogenesis of the majority of Philadelphia chromosome negative MPNs. Ruxolitinib was also tested in cell-based assays relevant to the increased inflammatory cytokine levels observed in MPNs that contribute to MPN-related systemic symptoms. Ruxolitinib potently inhibited IL-23 stimulated IL-22 production in human T cells (IC50=50 nM), as well as IL-6, GM-CSF and TPO induced STAT3 phosphorylation in human peripheral blood mononuclear cells with IC50 values < 100 nM. Ruxolitinib also inhibited GCSF stimulated STAT3 phosphorylation in human neutrophils (IC50=28 ± 9 nM), as well as TPO induced STAT3 phosphorylation in human whole blood (IC50=281 ± 62 nM). Finally, ruxolitinib inhibited the production of IL-17 in response to IL-23 in T cells, and the production of monocyte chemotactic protein-1 in response to IL-6 in peripheral blood mononuclear cells with IC50 values of ≤120 nM (Fridman et al, 2011).
Ruxolitinib inhibited splenomegaly in mice resulting from intravenous (IV) inoculation of cells expressing the clinically relevant JAK2V617F mutation (Quintás-Cardama et al, 2010). After 3 weeks of treatment, more than 90% of vehicle-treated mice had succumbed to disease while more than 90% of ruxolitinib -treated mice survived. Treatment with ruxolitinib also reduced inflammatory

cytokine levels in these mice. The effects of ruxolitinib were also tested in a mouse disease model of polycythemia vera-like disease, based on transplantation of a 1:1 ratio of JAK2 wild type green fluorescent protein (GFP)-expressing murine bone marrow cells with JAK2V617F-positive murine bone marrow cells, which have a repopulation advantage. In this model, oral ruxolitinib treatment at doses of 30 or 90 mg/kg twice a day for 21 consecutive days reduced levels of phosphorylated STAT5 (pSTAT5) in the spleen, as well as the spleen size. Ruxolitinib also effectively reduced the red cell parameters (RBC count, Hgb, Hct and reticulocyte count) and neutrophil count. The treatment was well tolerated as assessed by monitoring body weight, and histological assessments of spleen and bone marrow samples post-therapy revealed a decrease of hypercellularity (erythroid and myeloid lineages) in ruxolitinib treated groups as compared to vehicle treated animals. However, no significant decrease in the mutant allele burden surrogate readout (percentage of GFP-negative cells, i.e. cells expressing JAK2V617F) was observed, as assessed by flow cytometry. Treatment of mice with ruxolitinib in a cytokine-dependent multiple myeloma (MM) xenograft model resulted in a dose-dependent suppression of phosphorylated STAT3 (pSTAT3) and tumor growth. Efficacy was also observed in additional preclinical tumor models representing both hematologic and solid tumors. Taken together, these data indicate that ruxolitinib will be able to inhibit wild-type and mutant JAKs in the clinical setting and are consistent with its observed efficacy in patients with MPNs.

4.5 Clinical Trials

To date, more than 9,400 patients have received ruxolitinib in Novartis and Incyte sponsored interventional clinical trials. The clinical experience of ruxolitinib in humans is mainly based on data obtained in patients with myelofibrosis (MF), polycythemia vera (PV), and graft versus host disease (GVHD). Limited data are available in healthy volunteers, essential thrombocytosis, multiple myeloma, prostate cancer, pancreatic cancer, thalassemia and rheumatoid arthritis.

The clinical database (safety set) in solid tumor and hematologic malignancies consists of 787 patients treated in 6 studies evaluating patients with myelofibrosis (MF) (n=679), prostate cancer (n=22), MM (n=13), essential thrombocythemia (ET), and polycythemia vera (PV) (n=73), of whom 617 patients received ruxolitinib. Hematologic events are the most frequently reported adverse events (AEs) and include thrombocytopenia and anemia. The majority of these AEs are of Grades 1-2, seldom led to study drug discontinuation (<1% of patients), and can be usually managed through dose reduction or interruption. Increased rates of anemia resulted in an increase in packed red blood cell (PRBC) transfusion requirements for some ruxolitinib-treated patients. Platelet transfusions while on ruxolitinib were rare. Biochemistry laboratory abnormalities of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and cholesterol were reported. The majority of these increases were Grade 1 or 2. No Grade 4 events were reported.

Safety in clinical pharmacology studies
The safety profile for ruxolitinib in the Phase I development program was assessed in over 145 healthy subjects for single doses from 5 mg to 200 mg, and in 53 healthy subjects for repeat doses from 15 mg to 50 mg b.i.d. and 50 to 100 mg q.d. Ruxolitinib has also been administered to 32 subjects with various degrees of renal impairment, 24 subjects with various degrees of hepatic impairment, and 50 subjects with RA (rheumatoid arthritis). AEs were, in general, mild and resolved without interventions. In the first in human study one subject had hyponatremia after receiving 5 mg ruxolitinib. The hyponatremia was assessed as severe in intensity, unrelated

to study medication, reversed within 5 days, and was reported as a serious adverse event (SAE). A Phase I dose escalation study and a study to evaluate food effect in Japanese healthy volunteers showed that administration of ruxolitinib with a high-fat meal led to results that were in line with results from the North American study. A Phase I dose escalation study in Chinese healthy volunteers showed similar overall results over a dose range of 10-50 mg. The pharmacokinetics of ruxolitinib was linear in the dose range studied, with a short half-life of 2-4 hours resulting in no notable drug accumulation following multiple doses.
In the repeat-dose study in healthy subjects, the intensity of an adverse event was graded according to the protocol-defined toxicity criteria based on Rheumatology Common Toxicity Criteria V 1.0. The dose-limiting AE was neutropenia, which occurred at a dose of 50 mg b.i.d. Neutropenia as an AE was noted in three subjects, all receiving the highest dose of ruxolitinib, 50 mg b.i.d. Neutropenia at the Grade 4 level, assessed as severe, led to study drug discontinuation on Day 5 in one subject, and was reported as a SAE. Neutrophil count returned to a normal level 12 days after the final dose of study medication. In two other subjects, neutropenia was Grade 1 or 2, and resolved with dose interruption or during continued dosing. The AE profile was similar for single- and multiple-dose studies, and no differences were observed between males and females. The most frequent (≥2 subjects) treatment-emergent AEs (TEAEs) occurring in the Phase I multiple-dose study were: neutropenia (4.2%), dizziness (2.8%), headache (2.8%) and nausea (2.8%). Overall, in healthy volunteer studies where frequent sampling of the neutrophil count was performed, a transient, reversible decrease in neutrophil count was frequently seen following dosing, which reversed after 12-24 hours off drug.
Two clinical pharmacology studies are ongoing to evaluate the effect of ruxolitinib on the pharmacokinetics of orally administered midazolam in healthy males subjects and of monophasic oral contraceptives in health female subjects.

The first Periodic Safety Update Report (PSUR) for ruxolitinib covered the reporting period from 16 Nov 2011 to 22 Feb 2013. A critical analysis of the efficacy and safety data revealed that the overall benefit-risk assessment of ruxolitinib remains favorable. Based on a single confirmed case of PML in an MF patient treated with ruxolitinib, this condition has been identified as an important potential risk. Reports of tuberculosis continue to be received in ruxolitinib-treated subjects in clinical trials. While the cumulative incidence of these tuberculosis reports appears to decline since the original Phase III trials, given the potential impact of JAK1/JAK2 inhibition upon immune defense, the risk tuberculosis will be monitored closely in subsequent PSURs.

Phase III studies in patients with myelofibrosis
The Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment I, (COMFORT-I) was a randomized, double-blind, placebo-controlled, multicenter study comparing the efficacy and safety of ruxolitinib tablets to a matched placebo in 309 patients with MF. The primary objective was to evaluate the efficacy, safety and tolerability of ruxolitinib given b.i.d. compared to placebo in patients with MF. Patients were randomized in a 1:1 ratio of ruxolitinib: placebo with no stratification. Ruxolitinib starting dose was based on baseline platelet count as follows: patients with baseline platelet count >200 x109/L started at 20 mg b.i.d. and patients with baseline platelet count >100 x 109/L to ≤200 x 109/L started at 15 mg b.i.d. The primary endpoint for this study was the percentage of patients with ≥35% reduction in spleen volume

assessed by imaging (MRI or CT) from baseline, at Week 24. The Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment II (COMFORT II) was an open-label, randomized, active-comparator, multicenter study comparing the efficacy and safety of ruxolitinib tablets versus best available therapy as selected by the investigators in 219 adults patients with myelofibrosis. Key eligibility criteria were as follows: adult MF patients, not candidates for stem cell transplantation, with two or more risk factors identified by IPSS, palpable spleen length ≥5 cm below the left costal margin, peripheral blast count <10%. The primary endpoint for this study was the percentage of patients with ≥35% reduction in spleen volume assessed by imaging (MRI or CT) from baseline, at Week 48. These trials identified statistically significantly larger proportion of patients randomized to ruxolitinib achieved a ≥35% reduction from baseline in spleen volume compared to patients randomized to control. This effect was seen at both Week 24 (primary endpoint in COMFORT-I) and Week 48 (primary endpoint in COMFORT-II). For patients who remained on study, the median percent reduction from baseline in spleen volume in both ruxolitinib arms was approximately 30%, was reached as early as Week 12 and was maintained throughout the study. The control arms had a median percent increase from baseline in spleen volume throughout the study.

Phase III studies in patients with polycythemia vera
The RESPONSE Trial was a global, randomized, open label phase III pivotal study comparing ruxolitinib (starting dose of 10 mg b.i.d.) with best available therapy (HU, pipobroman, immunomodulatory drugs, pegylated interferon or interferon, anagrelide, observation only) in PV patients. The protocol was designed for patients with evidence of need for phlebotomy and splenomegaly, either resistant or intolerant to HU. The primary endpoint was a composite one with phlebotomy control (absence of phlebotomy from Week 8 to 32) and reduction in spleen volume by MRI (or CT if MRI is clinically contraindicated) of at least 35% measured at 32 weeks. Two key secondary endpoints included durability of the primary endpoint and complete hematologic remission. The primary efficacy objective was based on a composite endpoint consisting of Hct control (absence of phlebotomy eligibility) and of at least 35% spleen volume reduction as assessed by central radiologic evaluation. Significantly more patients randomized to ruxolitinib met the primary endpoint at Week 32 when compared to patients randomized to BAT, 22.7% vs. 0.9%, respectively ($p<0.0001$). Significantly more patients randomized to ruxolitinib maintained primary response (Hct control and spleen volume reduction) at Week 48 when compared to patients randomized to BAT, 20.0% vs. 0.9%, respectively, ($p<0.0001$). Among the 25 patients randomized to ruxolitinib who had achieved primary response (Hct control and ⩾35% reduction in spleen volume), 23 maintained the response through data cutoff (15-Jan-2014). The probability of maintaining primary response for 48 weeks and longer after the start of response was 0.90. Longer follow-up to Week 80 showed that no further patients had lost the primary response.

Ruxolitinib for the treatment of inadequately controlled PV without splenomegaly (RESPONSE-2) followed the pivotal RESPONSE study which demonstrated that ruxolitinib was superior to BAT at controlling Hct and improving splenomegaly and symptoms in PV patients with splenomegaly who were inadequately controlled with HU. In the RESPONSE-2 study, the efficacy and safety of ruxolitinib was assessed in controlling disease in patients with PV without splenomegaly who need second-line therapy. The primary endpoint was the proportion of patients

achieving Hct control at week 28. Analyses were done according to an intention-to-treat principle, including data from all patients randomly assigned to treatment. Hct control was durable for a higher proportion of patients in the ruxolitinib arm compared to the BAT arm at Week 52 (59.5% vs 6.7%, respectively) and at Week 80 (47.3% vs 2.7%, respectively). The median duration of Hct control was not achieved in the ruxolitinib and the BAT arm. The estimated proportion of patients without an event at 72 weeks was 80.7% in the ruxolitinib arm. The proportion of patients without event at 72 weeks in the BAT arm was not reported due to very small number of patients responding to BAT. CHR was durable for a higher proportion of patients in the ruxolitinib arm compared to the BAT arm at Week 52 (23.0% vs 4.0%, respectively) and at Week 80 (24.3% vs 2.7%, respectively). In the ruxolitinib arm, the median duration of CHR was 34.0 weeks. The median duration of CHR in the BAT arm was not reported due to very small number of patients responding to BAT.

Phase I/II study in patients with prostate cancer
A Phase II, open label study of ruxolitinib administered orally to patients with androgen independent metastatic prostate cancer (AIPC) was performed. The primary endpoint was PSA50 (prostate-specific antigen) response rate, a clinically validated endpoint associated with clinical benefit in patients with metastatic prostate cancer. This endpoint is defined as a PSA decline from baseline of 50% or greater, confirmed by measurement on two occasions at least 4 weeks apart. The study used a Simon 2-stage optimal design. The first stage of the trial (Part 1) was designed to enroll 21 patients. If fewer than two PSA50 responses were observed in the first 21 patients (no later than 10 weeks after the last patient in the first stage is enrolled), the trial would be closed and the agent will be declared inactive as a monotherapy. If two or more PSA50 responses are seen in the first stage, an additional 20 patients would be enrolled in the second stage (Part 2) for a total of 41 patients. The study in patients with advanced prostate cancer completed enrollment of 22 subjects in the first stage of the study. The study endpoint permitting advancement to a second stage of the study was not reached. Seventeen of 22 subjects enrolled experienced death or protocol-defined progressive disease while on study.

Given that all patients discontinued the study due to protocol-specified lack of efficacy, the primary efficacy endpoint of PSA50 response rate was not assessed. Similarly, the secondary endpoints of median time to progression and tumor response rates were not assessed. All patients provided samples for the secondary endpoints of evaluating population PK and plasma PD markers; however, the samples were not assessed as part of this analysis.

The primary endpoint of safety and tolerability was assessed in this analysis. All patients experienced at least one TEAE, and the majority of patients (16 patients; 72.7%) experienced treatment-related TEAEs. The events associated with ruxolitinib treatment included anemia, fatigue, diarrhea, nausea, leukopenia and peripheral edema, all of which were not unexpected events in this patient population of metastatic androgen AIPC, as were the most frequently reported severe or life-threatening TEAEs (anemia, thrombocytopenia, peripheral edema, increased blood alkaline phosphatase, bone pain).

Treatment with ruxolitinib was generally well-tolerated. Among the 11 SAEs reported by nine patients, the only SAE that was reported by more than one patient was anemia (two patients), and

only two SAEs were considered to be possibly or definitely related to study medication by the investigator (cardiac arrest and anemia, respectively). Further, only one patient discontinued treatment as a result of an AE (anemia). Among the four deaths, cardiac arrest was deemed by the investigator as possibly related to study medication in one patient, but the patient had other risk factors that may have also contributed to the event; the other three deaths were likely associated with medical history and metastatic AIPC.

Eight patients had laboratory abnormalities that resulted in serious, severe, or life-threatening AEs, which included the following events: anemia, increased blood alkaline phosphatase, increased γGT, thrombocytopenia, hyperuricemia, and leukopenia. There was no specific trend among patients with regards to laboratory abnormalities or ECG values out of the normal range. Overall, there were no specific safety concerns associated with ruxolitinib.

4.6 Other Agent(s)
Not applicable

5. STUDY DESIGN
5.1 General Design
This is an open-label, multi-center, Phase II study to evaluate the efficacy of ruxolitinib in post-transplant patients with advanced cutaneous squamous cell carcinoma.

Study Intervention: In a safety lead-in of 6 patients, subjects will receive ruxolitinib 15mg BID. After 4 weeks, if dose-limiting toxicities (DLT) are observed in 1 or fewer patients, the study will enter stage 1 of the Simon two-stage design where all subsequent patients will receive a starting dose of ruxolitinib 15mg BID. If more than 1 DLTs are observed, another cohort of 6 patients will be treated at a dose of 10mg BID. If less than 2 DLTs are observed at the new dose of 10mg, then the study will proceed to stage I using this dose; otherwise the study will stop.

Individual subjects may have dose reductions of ruxolitinib during the course of treatment, based upon safety laboratory assessments.

Schedule of Evaluations: Subjects will have regularly scheduled study visits at the clinical site on Day 1 and Day 15 (± 3 days) of the first cycle, then on Day 1 (± 3 days) of every subsequent cycle (starting cycle 2), where safety assessments, including laboratory assessments, vital signs, and physical examinations will be performed (see Section 12 for study calendar).

Response to treatment will be determined by CT scans of the chest, abdomen, and pelvis with contrast. The overall response rate for the primary endpoint evaluation will be determined by RECIST v1.1 criteria. In patients who are unable to get a CT scan w/ contrast due to renal function (or any other reason), an MRI with and without contrast may be used instead. Imaging will be performed at the following time points:

Baseline scan	Baseline scan within 4 weeks prior to first treatment
Weeks 1 – 32	Every 8 weeks +/- 1 week (at weeks 8, 16, 24, 32)
Weeks 33 – until disease progression	Every 12 weeks +/- 1 week (at weeks 44, 56, 68, 80, 92, 104)
2 years	If subjects achieve ongoing disease control at 2 years, patients will be continued on study treatment and observed with imaging every 12 weeks +/- 2 weeks.

Duration of treatment: Subjects will continue treatment until confirmed radiographic disease progression, intolerable toxicity or side effects (Section 6.5.1).

Correlative studies: A minimum of 10 enrolled subjects must undergo paired biopsies for correlative studies. CT-guided biopsies will be collected at baseline and between C2D1 and C2D8 of therapy for correlative studies. A biopsy at the time of disease progression is optional in all subjects. Subjects in whom a biopsy is technically not feasible or in whom would result in unacceptable risk, in the opinion of the investigator, may be exempted from the biopsy requirement with discussion with the principal investigator.

Whole blood will be requested as outlined in section 13.2 for peripheral blood mononuclear cell (PBMC) and circulating tumor DNA (ctDNA) collection to evaluate the effect of ruxolitinib on circulating immune cell populations before and during treatment and to further evaluate ctDNA as a potential biomarker of disease response.

Duration of follow-up: Adverse events and laboratory tests will be graded using the NCI CTCAE v5.0 scoring system. Adverse events will be assessed continuously during the study and for **90 days** after the last dose of treatment. Subjects will be followed for at least **90 days** post-study, or until all treatment related adverse events have recovered to baseline or are deemed irreversible by the investigator. Subjects who are removed from study for reasons other than progression of disease will be followed every 3 months with imaging to evaluate disease status and survival analysis while the study remains open.

5.2 Number of Patients

Utilizing a Simon Two-Stage Mini-Max design, 18 patients with advanced cSCC will be accrued in the first stage. If 1 or more patients achieve a response, then an additional 14 will be accrued. If 3 or fewer responses are seen, the study will be declared negative. If the initial safety lead-in does not result in advancement to stage I, an additional 6 patients will need to be accrued for a second safety lead-in. Assuming a 10% drop-out rate, we anticipate a total accrual of 35 patients with a maximum potential accrual of 41 patients (see Statistical Considerations).

5.3 Correlative Studies

5.3.1 Tumor biopsies for pharmacodynamic assessment

The biological activity of ruxolitinib will be assessed by performing paired tumor biopsies

at baseline, and between Cycle 2 Day 1 and Cycle 2, Day 8 of study therapy. These biopsies will be mandatory in the first 10 patients enrolled on Stage I of the study (first 18 enrolled subjects), and optional in subsequent patients. A biopsy at the time of disease progression is optional in all patients. (Note: If sufficient flash frozen tumor material is available from a prior tumor biopsy performed within 3 months of registration with no intervening therapy, then a repeat baseline biopsy will not be necessary.)

A goal of at least 3 cores and up to 8 cores from the patient's tumor biopsy specimen, if safe to obtain, will be obtained for research purposes. The first core will be placed in buffered formalin and paraffin-embedded as standard of care. Subsequent cores will be flash frozen.

5.3.2 Blood Collection

Whole blood will be requested as outlined in section 13.2 for peripheral blood mononuclear cell (PBMC) and circulating tumor DNA (ctDNA) collection to evaluate the effect of ruxolitinib on circulating immune cell populations before and during treatment and to further evaluate ctDNA as a potential biomarker of disease response.

Detailed specimen processing and shipping information can be found in the laboratory manual.

Correlative analysis may include some or all of the following studies:

- IHC and/or Western blot and qRT-PCR to evaluate changes in STAT3, Cyclin D1, and other proteins
- Multiplex immunohistochemistry to assess changes in the immune microenvironment
- Bulk and single cell RNA-Seq analysis may be performed on paired tumor biopsies to assess mechanisms of disease response and resistance
- Additional studies may be performed in the future.

Samples will be stored on-site and shipments will be sent to the Owens laboratory by batch shipments when requested to the address listed below:

Owens Laboratory
Columbia University Medical Center
1130 St. Nicholas Avenue
ICRC Room 207
New York, NY 10032

The analyzing laboratories will be notified by email (AAAT5353@columbia.edu) the day the samples are sent. The email will contain the following information:

- Subject ID

- Subject Initials
- Date of collection
- Time point (e.g. baseline, cycle 2 day 1, end of treatment, etc)
- Name of study center
- Shipment date
- Contents of shipment

Samples should be shipped via courier so that the package is tracked appropriately (specifically Federal Express or UPS). The samples should be shipped for morning delivery, Monday through Thursday for optimal processing.

Samples will be tracked through a Microsoft Excel tracker.

6. SUBJECT SELECTION AND WITHDRAWAL

6.1 Inclusion Criteria

1. Histologically confirmed diagnosis of cSCC.
2. Unresectable or metastatic cSCC.
3. History of solid-organ transplant requiring immunosuppression
4. Allowable prior therapies:
    a. A maximum of 4 prior therapies for metastatic disease are allowed.
5. Male or female subjects, age 18 years or older.
6. ECOG performance status ≤ 2 (Appendix A)
7. Life expectance of ≥ 3 months.
8. Laboratory parameters within the following Protocol-defined range. All screening laboratory tests should be performed within 28 days of treatment initiation and must be independent of hematopoietic growth factor support.
    - Absolute neutrophil count ≥ 1.5 x 10^9/L.
    - Platelets ≥ 100 x 10^9/L.
    - Hemoglobin ≥ 9 g/dL (transfusion is acceptable to meet this criteria)
    - Serum creatinine ≤ 1.5 x institutional upper limit of normal (ULN) OR calculated creatinine clearance ≥ 50 mL/min for subjects with creatinine levels > 1.5 x institutional ULN.
    - Aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase ≤ 2.5 x ULN, or ≤ 5 x ULN in subjects with liver metastases.
    - Total bilirubin ≤ 1.5 x ULN
        - **Note**: patients with hyperbilirubinemia clinically consistent with an inherited

disorder of bilirubin metabolism (eg, Gilbert syndrome) will be eligible at the discretion of the principal investigator.

- International normalized ratio (INR) or prothrombin time (PT) < 1.5x ULN unless subject is receiving anticoagulation therapy as long as PT or INR is within therapeutic range of intended use of anticoagulant.
- Activated partial thromboplastin time (aPTT) < 1.5 x ULN unless subject is receiving anticoagulant therapy, as long as PTT is within therapeutic range of intended use of anticoagulants.

9. Presence of baseline measureable disease by RECIST v1.1 for solid tumors, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan, MRI, or calipers by clinical exam. (See Section 15.4 for the evaluation of measurable disease).

10. The effects of ruxolitinib on the developing human fetus are unknown, and thus female subjects of childbearing potential (defined as women who have not undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy, and are not postmenopausal (defined as ≥ 12 months of amenorrhea)) must have a negative pregnancy test at screening and must agree to use adequate contraception (complete abstinence, or two methods of birth control (Appendix B)) prior to study entry and until at least 4 months after the last dose of study treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

11. Fertile men must also agree to use adequate contraception (2 barrier methods or abstinence) during the study and for up to 4 months after the last dose of study drug.

12. Subjects must agree to pre- and on-treatment tumor biopsies. Subjects in whom biopsy is technically not feasible or in whom would result in unacceptable risk, in the opinion of the investigator, may be exempted from the biopsy requirement with discussion with the principal investigator. Use of outside archived tumor tissue for a baseline biopsy is not permitted.

13. Willingness and ability to provide written informed consent prior to any study-related procedures and to comply with all study requirements.

6.2 Exclusion Criteria

1. At least 21 days must have elapsed since the last dose of systemic chemotherapy or immunotherapy and the first dose of study drug.
2. At least 14 days must have elapsed since the last dose of radiation therapy and the first dose of study drug.
3. Patients who have previously been treated with a JAK inhibitor.

4. Patients who are receiving any other investigational agents concurently.
5. Patients who have had recent major surgery within a minimum 4 weeks prior to
6. starting study treatment, with the exception of surgical placement for vascular access.
7. Patients with a history of allergic reactions attributed to compounds of similar chemical or biologic composition to ruxolitinib.
8. Patients with symptomatic or growing brain metastases. Patients with brain metastases that have been treated and have remained stable for at least one month prior to initiation of study therapy are eligible.
9. Concurrent use of strong CYP3A4 or CYP3A4 substrate drugs with a narrow therapeutic range within 14 days or 5 drug half-lives, whichever is longer, before start of study drug. A list of strong CYP3A4 and 2C8 inhibitors and inducers can be found in Appendix C.
10. HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with ruxolitinib. In addition, these patients are at increased risk of lethal infections when treated with marrow- suppressive therapy.
11. Subjects with known active hepatitis B or C, or chronic hepatitis B or C requiring treatment with antiviral therapy.
12. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
13. Patients being actively treated for a second malignancy.

6.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

6.4 Subject Recruitment

A member of the patient's treatment team, the protocol investigator, or research team at the multi-center sites will identify potential research participants. If the investigator is a part of the treatment team, s/he will screen the patient as to eligibility, and will discuss the study and the possibility of enrollment in the research study with the patient. The preliminary screen of eligibility will be confirmation for the diagnosis of advanced cutaneous squamous cell carcinoma.

Potential subjects that meet these basic criteria will be referred by their treatment physician to the investigator, co-investigators, or research staff of the study. Minority and women are well represented in cutaneous oncology clinics, and we expect that they will be well represented in the trial accrual. The principal investigator, Richard Carvajal, MD, will be available to all patients for further questions and information through a contact number will be provided on the consent form.

During the initial conversation between the investigator/research staff and the patient, the patient

may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patients during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

6.5 Early Withdrawal of Subjects

When and How to Withdraw Subjects

Patients may withdraw from study at any time. Patients who discontinue early should return within 30 days of the last dose of the study drugs for a follow up evaluation. Any assessments listed for the final visit should be performed at that time.

In addition, any of the following conditions require withdrawal of the subject from study treatment:

- Disease progression defined by RECIST 1.1
- Severe, unexpected toxicities/side effects
- Lost to follow up or non-compliance with the protocol schedule
- An AE or current illness that in the opinion of the investigator or sponsor warrants the subject's withdrawal from treatment
- Necessary treatment with other investigational drug or other anticancer medications prohibited by protocol
- Participation in another clinical study using anti-cancer agents
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under this protocol
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception during the course of the study and for 3 months following discontinuation of study treatment
- Women who are pregnant or are breast feeding
- If the patient withdraws consent for continued participation, he/she will be removed from study.

The reason for study treatment discontinuation will be documented. For subjects who discontinue or are withdrawn from study treatment, every effort must be made to undertake protocol specified follow up procedures and end of treatment assessments, if possible unless consent to participate in the study is also withdrawn.

If a subject is discontinued from study treatment because of an AE considered to be related to study treatment and the event is ongoing 30 days after the last dose of study treatment, the event

must be followed until resolution or determination by the investigator that the event has become stable or irreversible.

If a subject withdraws consent to participate in the study the reason for withdrawal will be documented, no further study procedures or assessments will be performed, and no further study data will be collected for this subject other than the determination of survival status from public records such as governmental vital statistics or obituaries.

Data Collection and Follow-up for Withdrawn Subjects

Even though subjects may be withdrawn prematurely from the study, it is imperative to collect at least survival data on such subjects throughout the protocol defined follow-up period for that subject (though careful thought should be given to the full data set that should to be collected on such subjects to fully support the analysis). Such data is important to the integrity of the final study analysis since early withdrawal could be related to the safety profile of the study drug. If a subject withdraws consent to participate in the study, attempts will be made to obtain consent from the subject to record at least survival data up to the protocol-described end of subject follow-up period. It must be a high priority to try to obtain at least survival data on all subjects lost to follow-up and to note what methods should be used before one can state the subject is truly lost to follow-up (e.g. number of phone calls to subject, phone calls to next-of-kin if possible, certified letters, etc.). Subjects withdrawn because of unacceptable adverse events will be followed-until resolution or stabilization of the adverse event.

7. REGISTRATION PROCEDURES

7.1 CUMC Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures, along with applicable institutional policies and federal regulations.

Only Investigators/Research personnel properly trained and delegated to consent subjects for this protocol will participate in the consenting process. Furthermore, properly delegated/trained Physician Investigators (e.g., MD, MD PhD) are required to sign/verify a protocol specific Eligibility Checklist for each subject enrolled on the study, in addition to providing the relevant source documentation confirmation subject eligibility.

All participants must be centrally registered through the Central Registration Office within Herbert Irving Comprehensive Cancer Center at CUMC prior to initiation of study treatment.

Registration hours are available Monday through Friday from 9:00am – 5:00pm EST (excluding holidays and weekends). Same day patient registrations (and after hour registrations) will be accommodated on a case by case basis provided that the study team has expressed all time sensitive registration concerns/cases in a timely manner to the Central Registration Office.

CPDM Central Registration Procedures:
Within 48 hours of obtaining consent (excluding holidays and weekends), a completed/signed IRB approved informed consent HIPAA form, and demographics forms must be submitted to the CPDM Central Registration Office via an email to CPDMRegistration@columbia.edu or fax to 212.305.5292, with the subject line "AAAT5353 Pending Subject Registration Request (PHI)". Upon receipt, applicable subject information as well as a "pending eligibility" status will be entered into HICCC's institutional database. This status will remain until further source documentation is made available to confirm overall patient eligibility. Required materials for all

pending registration submissions are as follows:

- Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable.
- The completed/signed IRB approved HIPAA Authorization form
- Completed/signed CPDM ICF checklist
- Completed/signed HICCC personal census form
- Completed/signed CPDM Demographics Note to File

In order to confirm eligibility status, Investigators/designees (e.g., study specific Clinical Research Coordinator/Research Nurse, etc.) must submit the following documentation to the Central Registration Office via email or fax:

- The completed/signed study specific Eligibility Checklist (signed by an Physician level Investigator)
- Copies of source documentation necessary for each item to be verified on the CPDM specific Eligibility Checklist, including but not limited to:
    - Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)
    - Copy of pathology and surgical reports
    - Copy of clinic note(s) or other appropriate medical records capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)
    - Protocol deviation/waiver approvals (if applicable)

- **Please note**: subject line of email or fax should include the following: "AAAT5353 Complete Subject Registration Request (PHI)".

Upon receipt of the above mentioned documentation, participant eligibility information will be verified by a qualified Central Registration Registrar. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable study team personnel for clarification prior to enrollment. .All applicable finalized registration/eligibility information will then be entered into HICCC's institutional CTMS database by the Central Registration Registrar. Upon completion, an official subject registration notification email will be sent to the PI/research team which will include eligibility/enrollment status, as well as subject ID information. Protocol therapy may not be initiated prior to receipt of this notification from the Central Registration Office.

All screen fail/ineligible subjects, as well as subject's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

7.2 Informed Consent Procedures

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

8. TREATMENT PLAN

8.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for ruxolitinib are described in Section 10. Appropriate dose modifications for ruxolitinib are described in Section 9. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

If all eligibility criteria are met, study participants will initiate ruxolitinib twice daily. One cycle will consist of 4 weeks of therapy.

- Patients will be provided with a Medication Diary for ruxolitinib (Appendix D), instructed in its use, and asked to bring the diary with them to each appointment.
- Doses of ruxolitinib will be taken orally with approximately 8 oz. of water. Subjects should fast at least 1 hour before administration and 1 hour after administration

of the drug. Study drug should be taken at approximately the same time each day. Study drug should be swallowed whole and not crushed, chewed, or dissolved in water.

- Missed doses (outside of a 2 hour dosing window) should be skipped and not administered as a double dose at the next administration. Missed doses should be recorded on the Medication Diary but will not be considered violations of the protocol.
- Subjects who vomit their dose should be instructed NOT to make up that dose. Doses that are vomited should not be replaced.
- Patients will be instructed that ruxolitinib can be stored at room temperature.
- No premedication or other supportive medications are required.

8.1.1 Investigational Agent(s)

Ruxolitinib will be administered twice daily, in the morning and evening, approximately 12 hours apart, without regard to food. If a dose is late but within 4 hours of its scheduled administration time it should be taken; if more than 4 hours have passed, the dose should be omitted and the patient should continue treatment with the next scheduled dose. If vomiting occurs while taking dose, no redosing is allowed before the next rescheduled dose.

Patients will not require any premedications, however supportive medications to control symptoms such as nausea, emesis, diarrhea, and pain will be provided for symptom control.

Doses will be self-administered. Subjects will be required to keep a pill diary (Appendix D). Each cycle of treatment will last 28 days.

8.1.2 Other Agent(s)

Not applicable

8.1.3 Other Modality(ies) or Procedures

Not applicable

8.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of IND Agent with other concomitantly administered drugs through the CYP3A4 pathway, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect CYP3A4 pathways.

8.3 Treatment Compliance

Treatment compliance with all study-related medications should be emphasized to the subject by the site personnel. Subjects will bring all bottles of unopened, empty, and unused study drug with

them to each study visit. The appropriate study personnel will maintain records of study drug receipt and dispensing. Any discrepancy regarding the dose administered and the reason for the discrepancy will be recorded in the electronic case report form (eCRF). At each clinic visit, patients will be questioned about their compliance with study drug administration, and their dosing diary should be reviewed. Bottles of study drug, including all bottles of unopened, partially opened, or empty bottles cannot be destroyed or returned to the depot until a monitor reviews and verifies all tablet counts for compliance.

8.4 Randomization and Blinding

Not applicable.

8.5 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

8.6 Duration of Follow Up

Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Patients who are taken off therapy for any reason other than death or disease progression will continue to undergo reimaging studies every 8 weeks (+/- 1 week) until disease progression, start of a new anticancer therapy, or death. After disease progression or start of a new anticancer therapy, patients will be followed in clinic or by telephone on an approximately every 12 weeks schedule (+/- 2 weeks) until death for the purposes of survival follow-up.

8.7 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 6.5 applies. The reason for study removal and the date the patient was removed will be documented in the Case Report Form.

9. DOSING DELAYS/DOSE MODIFICATIONS

9.1 Required Laboratory Parameters for Initiation of a Treatment Cycle

A cycle of therapy may be initiated provided that the patient meets the following criteria on Day

1 of each cycle:

- ANC ≥ 1,000/mcL
- Platelets ≥ 50,000/mcL
- Hemoglobin ≥ 8 g/dL
- Non-hematologic toxicity recovered to ≤ tolerable grade 2 (or baseline)
- No evidence of progressive disease

9.2 Dosing Delays/Dose Modifications for Ruxolitinib

Patients may continue ruxolitinib for Grade 1 or tolerable Grade 2 toxicity without a dose reduction (graded according to NCI CTCAE v5.0). For intolerable Grade 2, Grade 3 or Grade 4 toxicity, ruxolitinib must be withheld until the toxicity has resolve to Grade 1 or tolerable Grade 2. At the discretion of the treating physician, ruxolitinib may then be resumed as per following guidelines (Table 1-6). If an adverse event is not covered in the table, doses may be reduced or held at the discretion of the investigator for the subject's safety. The tables are intended to serve as guidance and cases in which the management is unclear should be discussed with the principal investigator or study medical monitor as appropriate.

Subjects with adverse events that are manageable with supportive therapy may not require dose reductions (e.g., nausea/vomiting may be treated with antiemetics, diarrhea may be treated with loperamide, and electrolyte abnormalities may be corrected with supplements rather than by dose reduction).

Subjects will be withdrawn from the study treatment if they fail to recover to Grade 0, Grade 1 or tolerable grade 2 (or within 1 grade of starting values for pre-existing laboratory abnormalities) from a treatment-related adverse event within 21 days unless the principal investigator agrees that the subject should remain on he study because of evidence that the patient is/may continue deriving benefit from continuing study treatment.

Table 1. Dose Modifications

Dose Level	**Dose**
1	15mg twice daily
0	10mg twice daily
-1	5mg twice daily
-2	5mg once daily

Table 2. Management recommendations for decreased neutrophil count:

Neutropenia	**Management/Next Dose for *Ruxolitinib***
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	

Table 3. Management recommendations for decreased platelet count:

Thrombocytopenia	**Management/Next Dose for *Ruxolitinib***
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	

Table 4. Management recommendations for anemia:

Anemia	**Management/Next Dose for *Ruxolitinib***
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3	Transfuse PRBC as clinically indicated. Hold* until ⩽ Grade 2. Resume at one dose level lower, per investigator discretion**
Grade 4	Transfuse PRBC as clinically indicated. Hold* until ⩽ Grade 2. Work up for alternative causes of blood loss. First occurrence: Resume at one dose level lower. Second occurrence: off therapy.
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	

Table 5. Management recommendations for febrile neutropenia:

Febrile Neutropenia	**Management/Next Dose for *Ruxolitinib***
≤ Grade 1	N/A
Grade 2	N/A
Grade 3	Hold* until ⩽ Grade 2. Resume at one dose level lower **
Grade 4	Hold* until ⩽ Grade 2. First occurrence: Resume at one dose level lower. Second occurrence: off therapy.
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	
Grade 3: ANC <1.0 X 109/L with a single temperature of >38.3 ° C (101° F) or a sustained temperature of ≥ 38 ° C (100.4 ° F) for more than 1h Grade 4: Life-threatening consequences; urgent	

Febrile Neutropenia	**Management/Next Dose for *Ruxolitinib***
intervention indicated	

Table 6. Management recommendations for non-hematologic toxicities:

Non-Hematologic Toxicities (non-Cardiac)	**Management/Next Dose for Ruxolitinib**
≤ Grade 1	No change in dose
Grade 2	Hold* until ⩽ Grade 1. Recommend resume at same dose level, but per investigator discretion. If the toxicity is deemed possibly, probably, or definitely related to ruxolitinib – and not reduced after the first occurrence - a dose reduction should be considered after a second recurrence, if still deemed possibly, probably, or definitely related.
Grade 3	Hold* until ⩽ Grade 1. Resume at one dose level lower **
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	
Recommended management if diarrhea: loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used. Recommended management if nausea/vomiting: anti-emetics	

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

10.1 Adverse events

Anemia

In Phase III MF clinical studies, median time to onset of first CTCAE Grade 2 or higher anemia was 1.5 months. One patient (0.3%) discontinued treatment because of anemia. In patients receiving ruxolitinib mean decreases in Hgb reached a nadir of approximately 15 to 20 g/L below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 10 g/L below baseline. This pattern was observed in patients regardless of whether they had received transfusion during therapy. In the randomized, placebocontrolled
COMFORT-I study, 59.4% of ruxolitinib treated patients and 37.1% of patients receiving placebo received RBC transfusions during randomized treatment. In the COMFORTII study, the rate of PRBC transfusions was 51.4% in the ruxolitinib arm and 38.4% in the BAT arm.
Over the randomized period in the RESPONSE and RESPONSE-2 studies, anemia was less frequent in PV patients (40.8%) versus 82.4% in MF patients. In the PV population, the CTCAE Grade 3 or Grade 4 events were reported in 2.7%, while in the MF patients, the frequency was of 42.5%.

Thrombocytopenia

In the Phase III MF clinical studies, in patients who developed Grade 3 or Grade 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50 x 109/L was 14 days. Platelet transfusions were administered to 4.5% of patients receiving ruxolitinib and to 5.8% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving ruxolitinib and 0.9% of patients receiving control regimens. Patients with a platelet count of 100 x 109/L to 200 x 109/L before starting ruxolitinib had a higher frequency of Grade 3 or Grade 4 thrombocytopenia compared to patients with platelet count >200 x 109/L (64.2% versus 35.4%).
Over the randomized period in the RESPONSE and RESPONSE-2 studies, the rate of patients experiencing thrombocytopenia was lower in PV (16.8%) compared to MF (69.8%) patients. The frequency of severe (i.e. of CTCAE Grade 3 or Grade 4) thrombocytopenia was lower in PV (2.7%) than in MF (11.6%) patients.

Neutropenia

In the Phase III MF clinical studies, in patients who developed Grade 3 or Grade 4 neutropenia, the median time of onset was 12 weeks. During the randomized period of the studies dose holding or reductions due to neutropenia were reported in 1% of patients and 0.3% of patients discontinued treatment because of neutropenia.
Over the randomized period in the RESPONSE and RESPONSE-2 studies in PV, neutropenia was observed in 3 patients (1.6%) of which one patient developed CTCAE Grade 4 neutropenia

Urinary tract infections
In Phase III MF clinical studies Grade 3 or Grade 4 urinary tract infection was reported for 1.0% of patients. Urosepsis was reported in 1.0% of patients and kidney infection was reported in one patient.
Over the randomized period in the RESPONSE and RESPONSE-2 studies in PV, one (0.5%) Grade 3 or Grade 4 urinary tract infection was observed.

Herpes zoster
The rate of herpes zoster was similar in PV (4.3%) patients and MF patients (4.0%). There was one report of Grade 3 or Grade 4 post herpetic neuralgia amongst the PV patients.

Tuberculosis
In Phase III MF clinical studies tuberculosis (TB) (any grade) was reported in 0.7% of patients. Epidemiological data suggests hematological malignancies, corticosteroid use, diabetes, emphysema, body mass index (BMI) below 20 kg/m2, bronchitis, smoking and asthma are risk factors for TB in a general population (Jick et al 2006, Kamboj and Sepkowitz 2006).
Although limited epidemiological data on the incidence of TB in the targeted population are available, the immune function of MF patients is known to be compromised due to disease and therapeutic measures, including corticosteroid therapy.
The Phase III clinical trial sample size did not allow detection of a statistically significant difference in the incidence of TB between the treatment and control arms.
Reports of TB continue to be received in ruxolitinib-treated patients in clinical trials. While the cumulative incidence of these TB reports appears to have declined since the original Phase III trials, given the potential impact of JAK1/JAK2 inhibition upon TB immune defense, the risk of TB is closely monitored.
No cases of TB were seen in the RESPONSE and RESPONSE 2 studies in patients with PV. However, a case of TB was observed in a patient with PV in a non-interventional study.

Increased blood pressure
In the Phase III pivotal clinical studies in MF an increase in systolic blood pressure of 20 mmHg or more from baseline was recorded in 31.5% of ruxolitinib-randomized patients on at least one visit compared with 18.5% in the placebo arm and 21.7% in the BAT arm. In COMFORT-I the mean increase from baseline in systolic blood pressure was 0-2 mmHg on ruxolitinib versus a decrease of 2-5 mmHg in the placebo arm. In COMFORT-II mean values showed little difference between the ruxolitinib-treated and the control-treated patients.
In the randomized period of Phase III clinical studies in PV (RESPONSE and RESPONSE-2), hypertension was noted to occur at 6.5% compared with 2.7% in BAT arm of RESPONSE and 4.0% with the BAT arm of RESPONSE-2.

Withdrawal effects
Following interruption or discontinuation of ruxolitinib, symptoms of MF may return over a period of approximately one week. There have been cases reported of patients discontinuing ruxolitinib who sustained more severe events, particularly in the presence of acute intercurrent illness.

Warnings and precautions

Decrease in blood cell count
Treatment with ruxolitinib can cause hematologic adverse reactions, including thrombocytopenia, anemia and neutropenia. A complete blood count must be performed before initiating therapy with ruxolitinib. Complete blood counts should be monitored every 2-4 weeks until doses are stabilized, and then as clinically indicated and dose adjusted.
It has been observed that patients with low platelet counts (<200 x 109/L) at the start of therapy are more likely to develop thrombocytopenia during treatment. Thrombocytopenia was generally reversible and was usually managed by reducing the dose or temporarily withholding ruxolitinib. However, platelet transfusions may be required as clinically indicated.
Patients developing anemia may require blood transfusions. Dose modifications or interruption for patients developing anemia may also be considered.
Neutropenia (ANC <0.5 x 109/L) was generally reversible and was managed by temporarily withholding ruxolitinib.

Infections
Serious bacterial, mycobacterial, fungal, viral and other opportunistic infections have occurred in patients treated with ruxolitinib. Patients should be assessed for the risk of developing serious infections. Physicians should carefully observe patients receiving ruxolitinib for signs and symptoms of infections and initiate appropriate treatment promptly. Ruxolitinib therapy should not be started until active serious infections have resolved.
Hepatitis B viral load (HBV-DNA titer) increases, with and without associated elevations in ALT and AST, have been reported in patients with chronic HBV infections taking ruxolitinib. The effect of ruxolitinib on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines.

Tuberculosis
TB has been reported in patients receiving ruxolitinib for MF. Before starting ruxolitinib therapy, patients should be evaluated for latent or active TB as per local recommendations. This can include medical history, possible previous contact with TB, and/or appropriate screening such as lung x-ray, tuberculin test and/or interferon-gamma release assay, as applicable. Physicians are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

Withdrawal effects
Following interruption or discontinuation of ruxolitinib, symptoms of MF may return over a period of approximately one week. There have been cases reported of patients discontinuing ruxolitinib who sustained more severe events, particularly in the presence of acute intercurrent illness.

Hepatic impairment
In patients with any hepatic impairment the recommended starting dose based on platelet count should be reduced by approximately 50% (or as specified in country specific product labels).

Patients diagnosed with hepatic impairment while receiving ruxolitinib should be carefully monitored and may need to have their dose reduced to avoid ADRs.

Dose adjustment with concomitant CYP3A4 inhibitors/inducers/substrates
When ruxolitinib is administered with strong CYP3A4 inhibitors (such as, but not limited to, boceprevir, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole) as well as fluconazole (a dual inhibitor of CYP3A4 and CYP2C9, see also Section 5.1.5.4), the dose should be reduced to approximately 50% of the dose rounding to the nearest dosage strength. The concomitant use of ruxolitinib with fluconazole doses of greater than 200 mg daily should be avoided. More frequent monitoring of hematology parameters and clinical signs and symptoms of ruxolitinib related adverse reactions is recommended upon initiation of a strong CYP3A4 inhibitor. No dose adjustment is necessary when a mild or moderate CYP3A4 inhibitor is used concomitantly with ruxolitinib. No dose adjustment is necessary when a CYP3A4 inducer (such as, but not limited to, avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifampicin, St. John's) is used concomitantly with ruxolitinib. No dose adjustment is necessary when ruxolitinib is administered with a CYP3A4 substrate. Patients should be closely monitored and the ruxolitinib dose titrated based on safety and efficacy.

Women of child-bearing potential
Women of child-bearing potential must take appropriate precautions to avoid pregnancy during treatment. In case pregnancy occurs, risk-benefit evaluations must be carried out on an individual basis with careful counseling regarding potential risk to the fetus using the most recent data available.
Embryo-fetal development studies with ruxolitinib in rats and rabbits did not indicate teratogenicity. Ruxolitinib was embryotoxic and fetotoxic in rats (increases in post-implantation loss and reduced fetal weights). The potential risk for humans is unknown.

Breast-feeding
Women taking ruxolitinib should not breast-feed.

Overdosage
There is no known antidote for overdoses with ruxolitinib. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression including leukopenia, anemia and thrombocytopenia. Appropriate supportive treatment should be given. Hemodialysis is not expected to enhance the elimination of ruxolitinib.

10.2 Definitions

Adverse Event:
An adverse event (AE) is any untoward or unfavorable medical occurrence in a human subject, including abnormal sign, symptom or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the

research. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event:
Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires inpatient hospitalization/prolongation of existing hospitalization, unless:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above/below and not resulting in hospital administrations
    - social reasons and respite care in the absence of any deterioration in the patient's general condittion
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious events should be regarded as non-serious adverse events.

Unanticipated Problem:
An unanticipated problem is any incident, experience or outcome involving risks to subjects or others in any human subjects research that meets all of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approval protocol and informed consent document, and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in such research (e.g., there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in such research); and

- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures (e.g., after the first dose of study treatment) to the end of the study treatment (e.g., last dose of study treatment) and/or follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment, **or** 30 days **following the decision to remove the subject from study treatment, whichever is earliest.**

Baseline/Preexisting Condition
A baseline/preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or if the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management (e.g., change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.).

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.
Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

10.3 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

Reporting of Serious Adverse Events

10.4.1 IRB Notification by Sponsor-Investigator

Reports of all events (including follow-up information) that meet the definition of an unanticipated problem posing risk to subjects or others must be submitted to the IRB within one week (5 business days) following the occurrence of the unanticipated problem or the principal investigator's acquiring knowledge of the unanticipated problem in accordance with IRB policy. Additionally, the sponsor-investigator will submit a summary of all Unanticipated problems that occurred since the beginning of the study at the time of continuing review. Copies of each report and documentation of IRB notification and receipt will be kept in the Regulatory binder.

10.4.2 FDA Notification by Sponsor-Investigator

The Columbia University Medical Center Sponsor-Investigator, as holder of the IND, will be responsible for all communication with the FDA. Columbia University Medical Center Sponsor-Investigator will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and there is evidence to suggest a causal relationship between the drug and the adverse event. These must be reported to the FDA and any affiliate sites as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting. The Sponsor-Investigator will also submit an IND annual report to the

FDA in accordance with 21.CFR 312.33.

The Columbia University Medical Center Sponsor Investigator must report to the FDA and any affiliate site investigators as follows:

- Any unexpected fatal or life-threatening event must be reported as soon as possible, but no later than 7 calendar days after the sponsor investigator initial receipt of the information
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND, and whether or not conducted by the sponsor-investigator, that suggest a significant risk in humans exposed to the drug must be reported as soon as possible but no later than 15 calendar days after the sponsor-investigator determines that the information qualifies for reporting
- Any findings from animal or in vitro testing whether or not conducted under an IND, and whether or not conducted by the sponsor-investigator, that suggest a significant risk in humans exposed to the drug must be reported as soon as possible but no later than 15 calendar days after the sponsor-investigator determines that the information qualifies for reporting
- Any clinically important increase in the rate of a serious suspected adverse reactions over that listed in the protocol or Investigator Brochure
- Expected SAEs and AEs will be included in the IND Annual Reports.

Follow-up information to a safety report should be submitted as soon as the relevant information is available. However, if the results of a sponsor's investigation show that an adverse drug experience not initially determined to be reportable are so reportable, the sponsor investigator must report such experience as soon as possible, but no later than 15 calendar days after the determination is made.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

10.4.3 DSMC Reporting by the Sponsor Investigator

Serious adverse events not constituting unanticipated problems are to be reported to the HICCC DSMC. Reporting should occur within 24 hours of knowledge of the SAE occurring at our institution or affiliate sites.

Participating investigators must report each serious adverse event to the Columbia University Medical Center Overall Principal Investigator within 24 hours of learning of the occurrence using the SAE Report Form. In the event that the participating investigator does not become aware of the serious adverse event **immediately** (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Richard D. Carvajal, MD

177 Fort Washington Avenue, MHB 6GN-435
New York, NY 10032
Telephone: 646-317-6354
Fax: 212-305-3035
Email address: CPDM_T5353@lists.cumc.columbia.edu

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

10.4.4 Reporting to Drug Manufacturer by Sponsor-Investigator

SAE Reporting to Incyte

The Sponsor-Investigator must report all Serious Adverse Events (SAEs) to Incyte within 24 hours of learning of an event, regardless of the PIs causality assessment. This notification should be provided on a completed Serious Adverse Event (SAE) form. SAE reporting for each subject begins the day the informed consent is signed by the patient and within 30 days after subject has completed or discontinued from the study or has taken last dose of the study drug, or as described in the protocol.

SAEs, occurring using Incyte Study drug, are reported in accordance with the effective protocol. SAEs occurring with any other commercial drug are reported to the manufacturer of that drug in accordance with regulations and protocol.

Initial SAEs and/or subsequent follow-up reports should be reported via email to SafetyReporting@Incyte.com or fax (+) 1-866-981-2057. SAE reports should be for a single subject. SAE forms should be sent with a cover sheet and any additional attachments.

All adverse event information is reported to Incyte on the Principal Investigator's/Institution's Adverse Event Report Form, or a CIOMS-I or MedWatch Form FDA 3500A, or on an Adverse Event Report Form which may be provided by Incyte upon request. The Principal Investigator does not provide medical records (e.g., discharge summary) to Incyte, unless specifically requested.

Reporting of Pregnancy to Incyte

An "Initial Pregnancy Report" or equivalent must be completed in full and emailed to SafetyReporting@Incyte.com or faxed to (+) 1-866-981-2057 within 24 hours of discovery of a pregnancy of a subject who has taken the Incyte product or the pregnancy of a partner for a subject who has taken the Incyte product. The "Follow-up Pregnancy Report Form" or equivalent must be completed and emailed to SafetyReporting@Incyte.com or faxed to (+) 1-866-981-2057 within 30 days after delivery, so that Incyte is provided with information regarding the outcome of the pregnancy. If the pregnancy results in any events which meet the serious criteria (i.e., miscarriage or termination), the SAE reporting process needs to be followed and the timelines associated with a SAE should be followed.

The Sponsor-Investigator will report to investigational agent manufacturer any serious adverse events that meet the reporting criteria to the Institutional Review Board as described in section 10.4and/or to the FDA as described in section 10.4 within 24 hours of becoming aware of it, so that these reports can be evaluated and included in the Investigator's Brochure and for IND safety submissions per regulations. Reporting will occur by sending the reporting form along with any additional documentation sent to the regulatory authorities.

At the time of IRB renewal or at the request of the manufacturer, the Sponsor- Investigator will submit a summary of all Serious Adverse Events that have occurred inclusive of all sites to manufacturer.

10.4 Reporting Process

Adverse events may be submitted on FDA Form 3500A, the HICCC DSMC Serious Adverse Event Reporting Form, or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 10.

11. PHARMACEUTICAL INFORMATION

11.1 Description

Ruxolitinib phosphate is a kinase inhibitor with the chemical name (R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate and a molecular weight of 404.36.

Ruxolitinib phosphate is a white to off-white to light pink powder and is soluble in aqueous buffers across a pH range of 1 to 8. Ruxolitinib tablets are for oral administration. Each tablet contains ruxolitinib phosphate equivalent to 5 mg, 10 mg, 15 mg, 20 mg and 25 mg of ruxolitinib free base together with microcrystalline cellulose, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, sodium starch glycolate, povidone and hydroxypropyl cellulose.

11.2 Treatment Regimen

Ruxolitinib is an orally-administered tablet. Patients with adequate hematologic counts will be started on a dose of 10mg twice daily. Dosing will be adjusted for safety as delineated. Treatment will consist of 28-day cycles. Treatment will continue until disease progression or severe toxicity requiring cessation.

11.3 Method for Assigning Subjects to Treatment Groups

Not applicable

11.4 Preparation and Administration of Study Drug

Doses will be taken orally with approximately 8 oz. of water. Study drug should be taken at approximately the same times of day. Study drug should be swallowed whole and not crushed, chewed, or dissolved in water.

Missed doses (outside of a 4 hour dosing window) should be skipped and not administered as a double dose at the next administration. Subjects who vomit their dose should be instructed not to make up that dose. Doses that are vomited should not be replaced.

11.5 Subject Compliance Monitoring

Subject compliance will be monitored with the aid of a "Patient Pill Diary" (Appendix D) which will be reviewed by the study team at each visit. Subjects who are non-compliant with protocol schedule or filling out the pill diary will be removed from the study at the discretion of the study investigator.

11.6 Packaging

Ruxolitinib tablets (5 mg) are manufactured, packaged, and labeled according to GMP and GCP at the following address:

DSM Pharmaceuticals, Inc.
Greenville, NC 27834

11.7 Blinding of Study Drug

Not applicable

11.8 Receiving, Storage, Dispensing and Return

11.8.1 Receipt of Drug Supplies

Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify agent manufacturer of any damaged or unusable study treatments that were supplied to the investigator's site.

11.8.2 Storage

Ruxolitinib tablets should be stored at room temperature or as described in detail in the current Investigator's Brochure. Subjects should be requested to store the study drug at the recommended storage conditions noted on the label.

11.8.3 Dispensing of Study Drug

Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.

11.8.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation

form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of the study drug.

11.9 Other Agent(s)

Not applicable

12. STUDY EVALUATIONS

12.1 Screening Phase

The screening phase will be up to 28 days. Screening is the interval between the signing of the informed consent form (ICF) and the day the subject receives the first dose of treatment in the study (Cycle 1 Day 1). Informed consent must be obtained before performing any study-specific procedures not considered standard of care. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during this phase.

Results from the screening visit evaluations will be reviewed to confirm subject eligibility before enrollment or the administration of study drug. Tests with results that fail eligibility requirements may be repeated during the screening phase if the investigator believes the results to be in error. Additionally, a subject who fails screening may repeat the screening process 1 time if the investigator believes there has been a change in eligibility status (eg, after recovery from an infection).

See **Section 13** for detailed list of screening procedures.

12.2 Treatment Phase

The treatment period will continue every 28 days and may continue as long as subjects are receiving benefit from treatment and have not met any criteria for study withdrawal.

See **Section 13** for list and schedule of procedures while on treatment.

12.2.1 Clinic Visits

During Cycle 1, patients will be seen every 2 weeks for vitals, physical exam, assessment of adverse effects, and appropriate laboratory tests and procedures (**Section 13**) Starting Cycle 2 and onward, patients will be seen on Day 1 of each cycle for vitals, physical exam, assessment of adverse effects, and appropriate laboratory tests and procedures. Patients may be seen for additional unscheduled visits as needed at the discretion of the investigator.

12.2.2 General laboratory assessment

See Section 13 for detailed laboratory tests and timing of these tests.

12.2.3 Schedule of Disease monitoring

A CT scan of the chest, abdomen, and pelvis with contrast will be obtained to evaluate disease status. A scan will be obtained at baseline (within 28 days of first study drug dose), then every 8 weeks for the first 32 weeks. After week 32, a CT chest, abdomen, pelvis with contrast will be performed every 12 weeks until disease progression, withdrawal from study, or ongoing disease control at 2 years (defined as at least stable disease at this point). For patients who achieve ongoing disease control at 2 years, subjects will be observed with a CT chest, abdomen, pelvis with contrast every 12 weeks. In patients who are unable to get a CT scan with contrast due to renal function (or any other reason), an MRI with and without contrast may be used instead. If the patient develops disease progression during this observation time, they will have the option of restarting study treatment at that time.

Table 7: Schedule of Disease Monitoring.

Baseline scan	Baseline scan within 4 weeks prior to first treatment
Weeks 1 – 32	Every 8 weeks +/- 1 week (at weeks 8, 16, 24, 32)
Weeks 33 – until disease progression	Every 12 weeks +/- 1 week (at weeks 44, 56, 68, 80, 92, 104)
2 years	If subjects achieve ongoing disease control at 2 years, patients will be continued on study treatment and observed with imaging every 12 weeks +/- 2 weeks.

12.2.4 Collection of Tumor Biopsies and Blood for Correlative Studies

A minimum of 10 subjects must undergo pre- and on-treatment research tumor biopsies. Subjects in whom biopsy is technically not feasible or in whom would result in unacceptable risk, in the opinion of the investigator, may be exempted from the biopsy requirement with discussion with the principal investigator. Use of outside archived tumor tissue for a baseline biopsy is not permitted. Biopsies will be collected at baseline and between C2D1 and C2D8 of therapy for correlative studies. An optional research biopsy at the time of progression will also be discussed with these patients, however, is not mandatory.

Whole blood will be requested as outlined in section 13.2 for peripheral blood mononuclear cell (PBMC) and circulating tumor DNA (ctDNA) collection to evaluate the effect of ruxolitinib on circulating immune cell populations before and during treatment and to further evaluate ctDNA as a potential biomarker of disease response.

12.2.5 Adverse Events Monitoring

Adverse events will be monitored from the time the subject receives the first dose of study treatment. Subjects will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study. All AEs (serious and nonserious) must be recorded on the source documents and eCRFs regardless of the assumption of a causal relationship with the study drug. The definition, reporting, and recording requirements for AEs are described in

Section 10.

All AEs of unknown etiology associated with ruxolitinib exposure should be evaluated to determine if it is possibly an irAE.

12.3 End of Treatment

If a decision is made that the subject will permanently discontinue study drug, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT page in the eCRF. The subject should be encouraged to return for the follow-up visits.

12.4 Follow-up Phase

12.4.1 Safety Follow-up

The safety follow-up phase is the interval between the last dose of study treatment and the scheduled safety follow-up visits, which should occur on days 30 (+/- 7 days) after the EOT visit. Adverse events and SAEs must be reported up until at least 90 days after the last dose of study drug, or until study drug-related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. If a subject initiates a new anti-cancer therapy within 90 days after the last dose of study treatment, the next scheduled safety follow-up visit must occur before the first dose the new therapy. Once new anti-cancer therapy has been initiated, the subject will move into the survival follow-up phase.

12.4.2 Follow-up (patients taken off treatment for reasons other than POD)

Subjects who discontinue study treatment for a reason other than disease progression (including patients who achieve stable disease control at 2 years) will move into the follow-up phase and will be assessed every 12 weeks by radiologic imaging to monitor disease status.

For patients who achieved stable disease at 2 years, re-treatment on study may be allowed at the time of disease recurrence or progression with permission of the study PI.

Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, and end of the study.

12.4.3 Survival Follow-up

Once a subject has confirmed disease progression or starts a new anticancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone, email, or visit every 12 weeks (+/- 2 weeks) to assess survival status. Clinical notes for patients currently being treated at Columbia University Medical Center (or collaborating medical center) will also suffice

as follow up. Overall survival will be followed until death, withdrawal of consent, or the end of the study, whichever occurs first.

12.5 Unscheduled Visits

Unscheduled study visits may occur at any time if medically warranted. Any assessments performed at those visits should be recorded in the eCRF.

13. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

13.1 Safety Lead-In Calendar:

	Screening	C1D1	C1D15 +/- 3d	C2D1 +/- 3d
Ruxolitinib (daily)		X	X	X
Informed consent	X			
Demographics	X			
Medical history	X			
Concurrent meds	X	X	X	X
Physical exam	X	X	X	X
Vital signs	X	X	X	X
Height	X	X		
Weight	X	X	X	X
Performance status	X	X	X	X
CBC w/diff, plts	X	X	X	X
Serum chemistry[a]	X	X	X	X
Serum Liver Function Tests[b]	X	X	X	X
EKG (as indicated)	X			
Adverse event evaluation		X	X	X
Tumor measurements	X			
Radiologic evaluation	X			
Serum B-HCG[c]	X			
Tumor Biopsy (10 patients)		X		X
Research blood collection		X		X
Survival Follow-up				X

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride,

creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium
b: Albumin, alkaline phosphatase, total bilirubin, AST, ALT
c: Perform only in women of child-bearing potential

13.2 Study Calendar

	Screening	C1D1	C1D15 +/- 3d	C2D1 +/- 3d	C3D1 ± 3d (and D1 ± 3d of every subsequent cycles)	End of Treatment (Within 30d of last treatment)	Survival follow-up
Ruxolitinib		X		X	X		
Informed consent	X						
Demographics	X						
Medical history	X						
Concurrent meds	X	X	X	X	X	X	
Physical exam	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	
Height	X	X					
Weight	X	X	X	X	X	X	
Performance status	X	X	X	X	X	X	
CBC w/diff, plts	X	X	X	X	X	X	
Serum chemistry[a]	X	X	X	X	X	X	
Serum Liver Function Tests[b]	X	X	X	X	X	X	
EKG (as indicated)	X						
Adverse event evaluation		X	X	X	X	X	
Tumor measurements	X				X (every other cycle)	X	
Radiologic evaluation	X				X (every other cycle)	X	
Serum B-HCG [c]	X[b\]						
Tumor Biopsy (10 patients	X			X (between D1 and D8)			
Research blood collection		X		X	X	X	
Survival Follow-up							X

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium
b: Albumin, alkaline phosphatase, total bilirubin, AST, ALT
c: Perform only in women of child-bearing potential

14. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

14.1 Collection of samples for correlative studies

14.1.1 Tumor biopsy samples

Pre- and on-treatment tumor biopsies are mandatory in a minimum of 10 subjects. Subjects in whom biopsy is technically not feasible or in whom would result in unacceptable risk, in the opinion of the investigator, may be exempted from the biopsy requirement, with discussion with the principal investigator.

Timing of Biopsy Samples:

A fresh biopsy must be obtained at the following time-points:

- Prior to treatment (anytime during the screening period) (mandatory)
- On-treatment (between C2D1 and C2D8 treatment dose)) (mandatory)
- At the time of disease progression (optional)

Collection & Processing Instructions:

Collection and processing instructions are the same for all of the specified tumor biopsy time points.

A goal of at least 3 cores and up to 8 cores, if safe to obtain, will be obtained at each collection time point.

14.1.2 Blood samples

Whole blood will be requested as outlined in section 13.2 for peripheral blood mononuclear cell (PBMC) and circulating tumor DNA (ctDNA) collection to evaluate the effect of ruxolitinib on circulating immune cell populations before and during treatment and to further evaluate ctDNA as a potential biomarker of disease response.

See laboratory manual for detailed processing and shipping instructions for all correlative study specimens.

Shipping Instructions:

Shipments will be sent to the Schwartz laboratory by batch shipments when possible.

Owens Laboratory
1130 Saint Nicholas Avenue
ICRC Room 207
New York, NY 10032

The analyzing laboratories should be notified by email (Study listserv email: CPDM_T5353@lists.cumc.columbia.edu) the day the samples are sent. The email wirell contain the following information:

- Subject ID number
- Subject Initials
- Date of collection
- Time point (e.g. baseline, Cycle 2 Day 1, end of treatment, etc)
- Name of study center
- Shipment date
- Contents of shipment

All samples should be directed to the address listed above. Samples should be shipped via courier so that the package is tracked appropriately (specifically Federal Express or UPS). The samples should be shipped for morning delivery, Monday through Thursday for optimal processing.

Samples will be tracked through a Microsoft Excel tracker.

15. MEASUREMENT OF EFFECT

15.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4 of weeks weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

15.2 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with ruxolitinib.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

15.3 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as $\geq$20 mm by chest x-ray, as $\geq$10 mm with CT scan or MRI, or $\geq$10 mm with

calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).
Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan or MRI (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

15.4 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and

never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ³10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the

next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
Endoscopy/Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology/Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

15.5 Response Criteria

15.5.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

15.5.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

15.5.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 8. Response Criteria for Patients with Measurable Disease (e.g., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (e.g., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

15.6 Duration of Response

Duration of overall response: The duration of overall response is measured from the time

measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

15.7 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

15.8 Response Review

All responses will be reviewed by an expert independent of the study at the study's completion. All imaging will be stored at Columbia University Irving Medical Center

15.9 Unblinding Procedures

Not applicable

15.10 Stopping Rules

Not applicable

16. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10.0 (Adverse Events: List and Reporting Requirements).

16.1 Data Collection

The Herbert Irving Comprehensive Cancer Center has an electronic clinical trials and data management system (CTMS) that will be used for data collection. CRFs for the study will be built into the CTMS for data entry. The system has full auditing capabilities which is web-based and housed on a server in a fully HIPAA compliant server room with restricted access and video camera monitoring. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials. Users are only able to see study information if they are indicated as study personnel in our electronic IRB system. Users are limited to access based on the role assigned in their corresponding protocol. Subject data is entered directly into the system, which (in the case of Columbia subjects) confirms the correct identity of patients via an interface with the electronic medical patient index. Staff with the

appropriate IRB defined roles can run reports within the system for reporting purposes.

16.2 Data Reporting

Case Report Forms will be completed for each subject enrolled into the clinical study through the CTMS. It is the investigator's responsibility for ensuring that all clinical and laboratory data entered on the corresponding CRFs are complete, accurate and authentic.

16.3 Data and Safety Monitoring Committee

The NCI-approved Data Safety and Monitoring Committee (DSMC) of the Herbert Irving Comprehensive Cancer Center (HICCC) will monitor every subject who receives treatment on this protocol for toxicity. This protocol will adhere to the policies of the currently approved HICCC Data and Safety Monitoring Plan (DSMP), which is in accordance with NCI and CUMC-IRB policy and guidelines. The committee is chair is appointed by the HICCC Director. The committee consists of HICCC faculty and staff with expertise in oncology, research pharmacy, research nursing, and data management. The DSMC convenes twice a month to review patient safety and the conduct of the trial. The PI will submit data and safety monitoring reports to the DSMC at a frequency to be determined by the DSMC based on risk to the subjects.

At the time of renewal, the study team will submit the most recent DSMC approval letter for safety review to the CUMC IRB. Any modifications that are required by the DSMC to ensure patient safety will be submitted to the IRB. All protocol deviations, violations, and eligibility waivers will be submitted to and approved by the DSMC prior to being reported to the IRB. All study data reviewed and discussed during these meetings will be kept confidential.

For multicenter research, the principal investigator will assure that there is a mechanism in place to distribute the report to all participating investigators for submission to their local IRB. The report will document that a review of data and outcomes across all centers took place on a given date. It will summarize the DSMC's review of the cumulative toxicities reported from all participating sites without specific disclosure by treatment arm. It will also inform site investigators of the study the DSMC's conclusion with respect to progress or need for modification of the protocol.

16.4 Quality Control and Quality Assurance

Independent monitoring of the clinical study for protocol and GCP compliance will be conducted periodically by the CPDM Compliance Core on behalf of the HICCC DSMC. Additionally, the Compliance Oversight Committee of the IRB at Columbia University Medical Center may audit the study at any time per institutional policies and procedures. The investigator-sponsor and Columbia University Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

A risk-based approach will be used by the Compliance Core to determine the frequency, number of subject charts, and data elements to be monitored. The Compliance Coordinator will review the study status and summarize enrollment, toxicities, SAEs/UPs, statistical endpoints (e.g., stopping

rules), etc. for the full DSMC membership at the regularly scheduled meetings.

Internal On-site Monitoring:

- Initial, recurrent, and close-out on-site monitoring visits will also be conducted at remote clinical sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).

    - The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.

- The Compliance Coordinator will communicate with the site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.

- The assigned Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

16.5 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject

authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (e.g., that the subject is alive) at the end of their scheduled study period.

The subject binders will be maintained with in the CPDM offices, a secured floor within the Herbert Irving Pavilion and only the investigator and study staff will have access to the file.

16.6 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

16.7 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A".

16.8 Records Retention

Records relating to a specific research activity, including research records collected by investigators, must be maintained for at least three years after completion of the research (45 CFR 46.115(b); 21 CFR 56.115(b); 21 CFR 312.62). This minimum retention period applies whether or not any subjects were enrolled in the study.
If the research is FDA regulated, records should be retained for at least two years after approval of the investigational agent by FDA; if it is not approved, records should be retained at least two years after the study is terminated and FDA is notified (note the additional requirement below for clinical research studies);
Clinical records, including consent forms that document clinical intervention or clinical diagnostic procedure research-related procedures, must be retained in medical records by the institution for at least seven years, per CUMC and NYP policy which is based on state law.

17. STATISTICAL CONSIDERATIONS

17.1 Study Design and Sample Size

This is a multi-center, non-randomized, open-label phase 2 trial to evaluate the efficacy and safety of ruxolitinib in post-transplant patients with advanced cutaneous squamous cell carcinoma. The primary endpoint is overall response rate, defined as the best response confirmed

within the 24 weeks of the start of study therapy.

We will use a Simon Two-Stage Min-Max design with a target overall response rate of 20% (alternative hypothesis), compared to a historical response rate of 5% (null hypothesis) with chemotherapy, with one-sided probability of a type I error set at 0.10 and power of 90%. In the first stage, 18 patients will be accrued. If less than 1 patient achieves a response among the initial 18 patients, the study will be declared negative and terminated. If at least 1 patient achieves a response, an additional 14 patients will be accrued to the second stage for a total of 32 evaluable patients. Overall, if 4 or fewer responses are seen, the study will be declared negative. If at least 5 total patients achieve a response, that treatment will be declared positive for attaining the primary endpoint. There is a 40% chance of stopping at Stage 1 if the true confirmed response rate is at most 5% (null hypothesis). Accounting for 10% dropout, we will plan to enroll a total of 35 patients unless a second safety lead-in is required, in which case the the maximum potential accrual will be 41 patients.

17.2 Study Endpoints and Analytic Plan

All subjects who receive at least one dose of study drug will be considered evaluable and included in the efficacy and safety analysis.

Definition of primary outcome/endpoint:
The primary endpoint is the overall response rate defined as the best response within the first 24 weeks of the start of study therapy using RECIST v. 1.1 that has been confirmed at a subsequent time point (≥4 weeks).

Definition of secondary outcomes/endpoints:
PFS is defined as time from enrollment to time of clinical or radiographic disease progression as defined by RECIST v.1.1 criteria. OS is defined as time from enrollment to time of death from any cause.

Analytic plan for primary objective:
The overall response rate will be summarized using point estimates and 95% confidence intervals.

Analytic plan for secondary and exploratory objectives:

- We will estimate the survival distribution for both PFS and OS endpoints using the Kaplan Meier method. The log rank test will be used to examine differences between survival curves using prognostic markers.
- For correlative studies we will apply either the Fisher's exact test or Wilcoxon Rank Sum test to examine the associations between response status and changes in markers expression for categorical and continuous variables, respectively. Because of the limited sample size, the biomarker data analysis is for exploratory research only.
- Toxicity data will be summarized by type, frequency, and severity according to the NCI CTCAE criteria v4.0.

- Pharmaocokinetic and pharmacodynamic parameters will be summarized using descriptive statistics and graphical methods (individual profile plots).

17.3 Size/Accrual Rate

The planned accrual size is 35 patients. Each participating site will aim to accrue 1 patient every 2 months month.

17.4 Stratification Factors

Not applicable

17.5 Reporting and Exclusions

17.5.1 Evaluation of toxicity

All patients will be evaluable for toxicity from the time of their first treatment with the study drug.

17.5.2 Evaluation of response

All patients included in the study will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) will be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions will be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

18. PROTECTION OF HUMAN SUBJECTS

This study is to be conducted in accordance with applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the

study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be obtained before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, as outlined in the IRB approved protocol, and the investigator-designated research professional obtaining the consent.

19. STUDY FINANCES

19.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the Columbia University Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved prior to participation in this study. All CUMC investigators will follow the University conflict of interest policy.

20. PUBLICATION PLAN

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor-investigator. Any investigator involved with this study is obligated to provide the sponsor-investigator with complete test results and all data derived from the study.

21. GUIDELINES FOR AFFILIATE INSTITUTIONS IN MULTICENTER STUDIES

21.1 Multi-site Communication

The CPDM Office at CUMC provides administration, data management, and organizational support for the affiliate sites in the conduct of a multicenter clinical trial. The CPDM Office will coordinate regularly scheduled conference calls with affiliate sites.

The following issues will be discussed, as appropriate:

- Enrollment information
- Response assessments
- Adverse events (e.g., new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

21.2 New Protocol Distribution, IRB Submission, Modifications, and Annual Renewals

- Protocol specific documents are distributed to affiliate sites once CUMC IRB approval has been obtained.
- The affiliate site must submit a draft of site specific revisions to protocol and/or consent form documents for review and approval by the sponsor-investigator prior to submission to the local IRB. Draft documents should be sent to the study specific email address. The site will be provided confirmation that they are approved to submit to their local IRB.
- Protocol amendments must be approved by the affiliate site's local IRB within 90 days of distribution to the site by the sponsor-investigator.

21.3 Regulatory Documents

Prior to Site Initiation:
Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected, prior to the initiation of an affiliate site.

- CV of PI, Co-I's and other research staff listed on FDA 1572 (signed and dated copy within 2 years)
- Medical Licenses of PI and Co-I's (current copy)
- Human subjects training certificates for PI and Co-I's
- CLIA/Laboratory Certifications for Local Laboratories listed on FDA 1572
- Local Laboratory Director's CV and License
- Local Laboratory Reference Ranges
- IRB roster or statement of compliance
- FDA Form 1572, if applicable (wet ink originals required)
- Financial Disclosure forms for all members listed on FDA 1572 (wet ink originals required)

Ongoing Regulatory Documentation: Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected throughout the course of the study.

- IRB approval letters for all protocol modifications and all renewals
- IRB-approved consent forms
- Current IRB roster, if statement of compliance is not provided as part of site initiation
- FDA Form 1572, if applicable as updates are required
- Updated investigator and site information where relevant (e.g., CV, medical licensure and Financial Disclosure for new sub-investigator, local laboratory information)

Regulatory documents may be sent to CPDM_T5353@lists.cumc.columbia.edu or to the following address:

Clinical Protocol & Data Management Office
161 Fort Washington Ave.
Herbert Irving Pavilion

Mezzanine Level, M-203
New York, NY 10032

21.4 Site activation

Columbia University will schedule a site initiation visit once IRB approval has been submitted from the affiliate site.

21.5 Central Registration Procedures- Affiliate Institution Research Participant Registration Process

All Affiliate Institutions **must** register subjects with the coordinating center (CUMC) **prior** to any administration of study drug/intervention/local institution registration. Please see instructions below:

1. Within 48 hours of obtaining consent (excluding holidays and weekends), the Affiliate Institution CRN and/or CRC is required to submit the following documents to the coordinating center's designee (CUMC Multicenter Core) via the study listserv CPDM_T5353@lists.cumc.columbia.edu. The coordinating center's designee will review the documents for accurateness, and subsequently submit the documents to the CPDM Central Registration Office via email at CPDMRegistration@columbia.edu (or via fax at 212.305.5292), with a request to register the patient "pending eligibility." The title of the email should read, "Pending Subject Registration Request (PHI)". The following documents should be submitted with the pending registration request, as applicable:
    a. Redacted Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable
    b. Redacted Signed HIPAA (or institutional equivalent)
    c. MCT CPDM Velos Note to File form

2. The Affiliate Institution's investigator/research nurse/data manager/coordinator must contact the coordinating center's designee (CUMC Multicenter Core) via telephone or email to communicate the following:
    a. Notify of pending registration request
    b. Confirm method of registration request submission (email or fax)
    c. Communicate expected time-line of registration request submission (e.g., same day, next day, within the hour, etc.)

3. To complete registration, the Affiliate Institution's investigator/research nurse/data manager/coordinator should then submit the following documents to the CUMC study specific designee:
    a. A signed Affiliate Site Eligibility Checklist (signed by the investigator)
    b. Copies of redacted source documentation necessary for each item to be verified on the CUMC specific Eligibility Checklist, including but not limited to:
        i. Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)

ii. Copy of pathology and surgical reports
iii. Copy of clinic note(s) capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms. (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)
iv. Protocol deviation/waiver approvals (if applicable)

c. **Please note**: subject line of email or fax should include the following: "AAAT5353 Complete Subject Registration Request (PHI)".

4. Upon receipt of the above mentioned documents, the designated study specific Clinical Research Coordinator will review all documents and verify patient eligibility. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable affiliate site study team personnel for clarification prior to enrollment. Upon verification, the CUMC Multicenter Core will then forward all documents to the CPDM Central Registration Office for central registration (as described above). The CPDM Central Registration Registrar will review all applicable documents and communicate to the CUMC study specific designee in order to clarify any items. The CUMC study specific designee will communicate with the applicable site study team personnel for additional clarifications necessary prior to enrollment.

5. Upon receipt of the subject registration notification email, the CUMC Multicenter Core will forward the notification email (which will include the study specific patient ID) to the affiliate site's Principal Investigator, Consenting Professional, and applicable research personnel. This notification should be filed in the patient research binder accordingly. Protocol therapy **may not** be initiated prior to receipt of this notification from the coordinating center.

6. All screenfail/ineligible subjects, as well as subject's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration Office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

21.6 Protocol Deviation/Subject Waiver request for Affiliate Sites:

The Affiliate site MUST submit a prospective deviation request to the CUMC lead PI for review and submission to the HICCC DSMC and CUMC IRB. Approvals must be obtained from all entities prior to implementation at the Affiliate site. If a prospective protocol deviation request is submitted for review (from an Affiliate site), the PI/site memo(s), HICCC DSMC approval(s) and correspondence and CUMC IRB approval letter(s)/equivalent should be forwarded to the Affiliate site for documentation. The Affiliate site is also required to obtain prospective local IRB approval as per institutional policies/procedures prior to implementing the proposed deviation and registering/enrolling the subject via CUMC Central Registration. All documents and determinations must be clearly documented in the study subject's medical record, research chart and regulatory binder, as described. Please note that the HICCC DSMC and PRMC do not approve

eligibility deviations. If eligibility deviations are submitted, they will not be approved.

21.7 Guidelines for Affiliate Site Monitoring

On-Site MCT Monitoring:

1. Initial, recurrent, and close-out on-site monitoring visits will also be conducted at Affiliate sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).
    a. The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.
2. The Compliance Coordinator will communicate with the Affiliate site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.
3. The Compliance Coordinator will monitor Investigator Initiated Trial (IIT) within 1 month after the first subject is enrolled at the Affiliate site and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the participating site PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to Coordinating Center, local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

4. An SIV (or) teleconference will be scheduled and conducted prior to study drug being made available (if applicable) and before any subjects are enrolled on a study at the Affiliate site.

Remote MCT Monitoring:

- When necessary (due to logistical constraints), Affiliate sites will be monitored remotely by a designated Compliance Coordinator. Sites will be informed of this remote monitoring process on a site by site basis.
- Affiliate sites will be monitored by the Compliance Coordinator on both a regulatory level, as well as a clinical data/source documentation review level.
- Redacted source documents (applicable to supporting the protocol specific CRF data requirements) will be sent to the designated Compliance Coordinator via fax or secure email for all subjects enrolled at Affiliate sites. Timelines for submission procedures will be defined on a case by case basis.
- The Compliance Coordinator will review all submitted redacted source documents against the data entered on the protocol specific CRFs. The Compliance Coordinator will issue queries when/if necessary.

- The Affiliate site research staff will respond to queries within 30 days. If queries remain outstanding, the Compliance Coordinator will send a delinquent query reminder for the outstanding items.
- The remote monitoring procedures will include review of applicable redacted source documentation and supporting applicable documents to determine compliance regarding:
    a. Informed consent procedures
    b. Eligibility criteria
    c. Protocol specific treatment compliance
    d. Protocol specific toxicity/outcome documentation/compliance
    e. Protocol specific schedule of events (e.g., baseline visits, pre-treatment, on study, follow-up)
    f. Participating site IRB documents (e.g., IRB amendment approvals, annual renewals, SAE/UP submissions, violation/deviation submissions, INDSR submissions, etc).
    g. Required specimen submissions (e.g., tissue specimens, research blood specimens, etc.)
    h. Pharmacy accountability records
    i. Adherence to the CRF submission timeframes to CUMC (within the protocol specified timeframes)
- Affiliate site remote monitoring reports will be sent to the lead PI, HICCC DSMC, and Affiliate sites after each remote monitoring review. Reports will include information regarding data submission timeliness/accuracy, protocol adherence items, query resolution status, regulatory status, and overall Affiliate site performance. These reports will be generated by the Compliance Coordinator and reviewed with the Compliance Core Manager prior to dissemination.

21.8 Adverse event reporting

Sponsor reporting: Notifying participating investigators at affiliate sites of adverse events

It is the responsibility of the study sponsor-investigator to notify all affiliate sites, in a written IND safety report, of any adverse event associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects. Additionally, sponsor-investigators are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Serious Adverse Event Reporting

Each participating investigator is required to abide by the reporting requirements set by Columbia University Irving Medical Center. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Participating investigators must report each serious adverse event to the Columbia University

Medical Center Overall Principal Investigator within 24 hours of learning of the occurrence using the SAE Report Form. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Richard D. Carvajal, MD
177 Fort Washington Avenue
New York, NY 10032
Telephone: 212-305-2055
Fax: 212-305-3035
Email: CPDM_T5353@lists.cumc.columbia.edu

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation or if study drug was interrupted or discontinued.

If the SAE is not previously documented in the Investigator's Brochure for the study drug (new occurrence) and is thought to be related to the investigational agent, the sponsor-investigator may urgently require further information from the investigator for reporting to Health Authorities.

Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the Columbia University Medical Center Overall Principal Investigator on the toxicity Case Report Forms.

Reporting to the Institutional Review Board (IRB) and the Data and Safety Monitoring Committee:

All Unanticipated Problems (UPs) will be reported to the CUMC IRB. SAEs not constituting UPs will reported to the HICCC DSMC.

Each affiliate site will be responsible for safety reporting to their local IRB. Investigators are responsible for complying with their local IRB's reporting requirements, though must submit the required reports to their IRB no later than 7 calendar days following the occurrence of the UP or the Principal's Investigator's acquiring knowledge of the UP. Copies of each report and

documentation of IRB notification and receipt must be included in the regulatory binder.

Expected or unexpected AEs must be reported at the time of continuing review of a protocol.

Guidelines for Processing IND Safety Reports

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. The CUMC Principal Investigator will review all applicable IND Safety Reports and has the responsibly for forwarding the IND Safety Reports to the Affiliate Institutions. The Affiliate Institution investigators are to review, send a copy to their IRB according to their local IRB's policies and procedures, and file a copy with their regulatory documents. All Affiliate site INDSR submissions, along with IRB acknowledgment (per local policies and procedures) are to be forwarded to CUMC for placement within the trial master file.

Reporting to Hospital Risk Management

Affiliate Site investigators will report to their local Risk Management Office any subject safety reports or sentinel events that require reporting according to institutional policy.

21.9 Efficacy analysis/ correlative analysis

Efficacy analysis:
Imaging will be reviewed by a site radiologist and interpreted according to response criteria detailed in section 12.4 for primary and secondary endpoint analysis. Imaging studies may be requested from participating centers for central radiology review.

Correlative analysis:
All tissue and blood samples collected at each site will be sent to Columbia University Medical Center for storage and correlative studies described above.

21.10 Confidentiality

Each affiliate site will be assigned a site number. Each subject that signs consent should be assigned a unique code number consisting of site number followed by a number with each new subject being assigned the next sequential number (e.g., 04-10). All sites will be required to enter their data in the Velos eResearch, the Clinical Trial Management System used for all Cancer-related clinical research at CUMC. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials.

Subject confidentiality must be maintained according to HIPAA regulations and GCP recommendations.

Except when required by law, study information shared with persons and organizations outside of Columbia University Medical Center must not identify the patient by name, social security number, address, telephone number, or any other direct personal identifier.

If the results of this research project are published or presented at a scientific or medical meeting, the patient not be identified. Otherwise, all results will be kept confidential and will not be divulged (except as required by law) without permission.

21.11 Data Reporting Plan

Columbia University Medical Center (CUMC) is deeply committed to research integrity and strong credibility when it comes to the discovery of new treatment concepts, implementation of new clinical research techniques, and acceptance of its researcher's findings by the medical establishment. In accord with these ethics, CUMC encourages and supports its investigators in the sharing of final research data and/or details of newly developed clinical treatments.

CUMC's policies that pertain to patient data sharing conform to CUMC IRB rules, local and state laws, and HIPAA privacy regulations. The primary reason for this is to protect the privacy of patients who participate in clinical trials. The data can be made available for continuing review by federal agencies upon request and for ongoing study safety reviews by the Principal Investigator, Statistician, Data Safety and Monitoring Board (DSMC), and, in other instances, the CUMC IRB.

Data collected during the course of this clinical trial will primarily be shared with other investigators and University staff, the IRB, FDA, and other reporting agencies, and/or transferred to other collaborators. Prior to transfer, the data collected must comply with, and must be limited by, the CUMC's guidelines for Protecting the Rights and Privacy of Human Subjects.

21.12 Data Acquisition and Submission

Informed consent, including HIPPA authorization, must be obtained on all subjects prior to their participation. Always keep the original signed and dated consent form, with the redacted source documents and eligibility checklist. Velos eResearch will be used as the electronic clinical trials and data management system. Affiliate sites will enter data directly into Velos eResearch via customized case report forms for the study. The research staff will generate reports from Velos eResearch to ensure timely submission of data by affiliate sites. This resource allows for the timely analysis of particular data sets for safety analysis.

21.13 Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

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 on each individual

administered the investigational drug or employed as a control in 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, CHR 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.
In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

22. REFERENCES

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23. APPENDIX

23.1 Appendix A: ECOG Performance Status Criteria.

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

23.2 Appendix B: Appropriate contraceptive methods for study subjects.

The following methods have been determined to be more than 99% effective (<1% failure rate per year) when used consistently and correctly[35] and are permitted under this Protocol for use by the subject and his/her partner:

- Complete abstinence from sexual intercourse
- A barrier method (male or female condom) in addition to one of the following:
    - Diaphragm or cervical cap with spermicide
    - Intrauterine device (IUD)
    - Birth control patch or vaginal ring
    - Oral, injectable, or implanted contraceptives

23.3 Appendix C: Strong CYP3A4 and 2C8 Inhibitors and Inducers

Strong Inhibitors	**Strong Inducers**
Protease Inhibitors: • Ritonavir • Indinavir • Nelfinavir	Anticonvulants, mood stabilizers: • Phenytoin • Carbamazepine • Oxcarbazepine
Macrolide antibiotics: • Erythromycin • Telithromycin • Clarithyromycin	Non-nucleoside reverse transcriptase inhibitors: • Efavirenz • Nevirapine • Etravirine
Azole antifungals: • Fluconazole • Ketoconazole • Itraconazole	Others: • Phenobarbital • Rifampicin • Modafinil • Hyperforin (constituent of St Johns Wort) • Cyproterone (antiandrogen, progestin)
Others: • Chloramphenicol • Nefazodone • Bergamottin (constituent of grapefruit juice) • Aprepitant • Verapamil • Gemfibrozil • Trimethoprim	

• Thiazolidinedione • Montelukast • Quercetin	

23.4 Appendix D: Pill Diary

An Open-label, Multi-center, Phase II Study of Janus-Associated Kinase 1 and 2 (JAK1/2) Inhibition with Ruxolitinib in Solid Organ Transplant Recipients with Advanced Cutaneous Squamous Cell Carcinoma

Patient Name:_____Study ID:_____MRN:_____
(To be Completed by RN)
Number of Ruxolitinib Tablets Given:_____Pill Bottle(s) returned: Circle **Yes** or **No**
Total Daily Dose of Ruxolitinib:_____Number of Ruxolitinib Tablets **returned**:_____

PLEASE FILL OUT AND BRING THIS SHEET AT YOUR NEXT VISIT.

SPECIAL INSTRUCTIONS

1. Ruxolitinib should be taken at approximately the same time twice daily with a full glass (8 oz.) of water. Ruxolitinib should not be crushed, chewed, or dissolved in water.
2. If you forget to take a dose, you can take that dose up to 2 hours after the scheduled dosing time. However, if it is greater than 2 hours after your scheduled dosing time, t he dose should be skipped and considered a missed dose. Missed doses should be skipped and not taken as a double dose at the next dosing time. If you vomit your dose, DO NOT make up that dose.
3. Ruxolitinib tablets should be **stored at room temperature**.

WEEKS **CYCLE #:** **# of**

Day	Medication	Date	Time		# Capsules taken	Comments
Example	Ruxolitinib	1/1/2020	9:00AM	9:00PM	1	
1	Ruxolitinib					
2	Ruxolitinib					
3	Ruxolitinib					
4	Ruxolitinib					
5	Ruxolitinib					
6	Ruxolitinib					
7	Ruxolitinib					
8	Ruxolitinib					
9	Ruxolitinib					
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27	Ruxolitinib					
28	Ruxolitinib					

Patient Signature: **Date:**
Consenting Professional/Research RN Signature: **Date:**
Consenting Professional/Research RN Comments: