A Phase II Study to Evaluate the Efficacy and Safety of Selinexor in Patients with Myelofibrosis Refractory or Intolerant to JAK1/2 Inhibitors (ESSENTIAL)

CTO # HCI-17-HEM-13 – IRB # 114354

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LIST OF ABBREVIATIONS

Abbreviation or Term[1]	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AV	Atrioventricular
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
BSA	Body Surface Area
BUN	Blood urea nitrogen
Ca^{++}	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
Cl-	Chloride
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
D/C	Discontinue
ECOG	Eastern Cooperative Oncology Group

Abbreviation or Term[1]	**Definition/Explanation**
eCRF	Electronic case report form
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
Eg	Exempli gratia (for example)
ET	Essential thrombocytosis / thrombocythemia
FACS	Fluorescence Activated Cell Sorting
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose (FDG)-positron emission tomography (PET)
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GLP	Good laboratory practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCO_3^-	Bicarbonate
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
hr	Hour or hours
IC_{50}	Half maximal inhibitory concentration
i.e.	Id est (that is)
IEC	Independent ethics committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional review board
IU	International unit
IV	Intravenous, intravenously
LDH	Lactate dehydrogenase
LLQ	Lower limit of quantitation
MedRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic resonance imaging
MRSD	Maximum recommended starting dose
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level

Abbreviation or Term[1]	**Definition/Explanation**
NOEL	No-observed-effect-level
PDn	Pharmacodynamic(s)
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QC	Quality control
RBC	Red blood cell
QD	Once daily
QTc	QT interval corrected
QTcF	QT interval corrected using Fredericia equation
QTcB	QT interval corrected using Bazett's formula
SAE	Serious adverse event
SD	Standard deviation or stable disease
$T_{1/2}$	Terminal elimination half-life
T_3	Triiodothyronine
T_4	Thyroxine
T_{max}	Time of maximum observed concentration
TID	Three times daily
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
ULQ	Upper limit of quantitation
UV	Ultraviolet
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of nonchildbearing potential

[1] All of these abbreviations may or may not be used in protocol.

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during 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 will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

This document is signed electronically through submission and approval by the Principal Investigator at Huntsman Cancer Institute in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system. For this reason, the Principal Investigator at Huntsman Cancer Institute will not have a hand-written signature on this signature page.

Instructions to multisite Principal Investigators at locations other than Huntsman Cancer Institute: SIGN and DATE this signature page and PRINT your name. Return the original, completed and signed, to the HCI Research Compliance Office. Retain a copy in the regulatory binder.

_____ _____

Signature of Principal Investigator **Date**

_____

Principal Investigator Name (Print)

_____

Name of Institution

STUDY SUMMARY

Title	A Phase II Study to Evaluate the Efficacy and Safety of Selinexor in Patients with Myelofibrosis Refractory or Intolerant to JAK1/2 Inhibitors
Short Title	Selinexor in myelofibrosis refractory or intolerant to JAK 1/2 inhibitors
Protocol Identifiers (IRB – internal)	IRB # 114354 – CTO # HCI-17-HEM-13
IND number	140746
Phase	II
Design	Open label, non-randomized, prospective, single-arm study
Study Duration	Up to 30 months
Study Center(s)	Multisite
Objectives	To evaluate the efficacy, safety, and tolerability of selinexor in primary myelofibrosis (PMF), post-essential thrombocytosis myelofibrosis (PET-MF), or post-polycythemia vera myelofibrosis (PPV-MF) patients refractory or intolerant to ruxolitinib and/or any other experimental JAK1/2 inhibitors
Number of Subjects	Up to 24 subjects
Diagnosis and Main Eligibility Criteria	**Inclusion:** • Diagnosis of PMF or PET-MF or PPV-MF • Refractory or intolerant to ruxolitinib and/or any other experimental JAK1/2 inhibitors • Age ≥ 18 years, ECOG ≤ 2 • Life expectancy ≥ 6 months • Adequate hepatic, renal, and hematopoietic function **Exclusion:** • Prior exposure to a SINE compound, including selinexor • Radiation, chemotherapy, immunotherapy, or any other anticancer therapy within 2 weeks of C1D1. • Major surgery within 4 weeks of C1D1 • Uncontrolled active infection requiring treatment, active hepatitis A, B, or C infection • Active gastrointestinal dysfunction affecting absorption or ability to swallow
Study Product, Dose, Route, Regimen	Selinexor, 40-80 mg orally once weekly depending on cohort
Duration of administration	Until IWG-MRT progressive disease criteria for leukemic transformation have been met (appendix 5), subject experiences an intolerable toxicity, or is no clinical benefit per treating physician's discretion, whichever occurs first
Reference therapy	None

Statistical Methodology	Primary Objective: Response is defined as a 35% or greater reduction in spleen volume as measured by MRI or CT abdomen from baseline to after 6 cycles of treatment. A sample size of 18 evaluable subjects will provide 83% power at one-sided alpha = 0.05 to reject a response rate of 15% (the null hypothesis) using a one sample exact test for a binomial proportion provided the true response rate is 42%. The null hypothesis will be rejected if 6 or more out of 18 subjects respond. The planned sample size is 24 to allow for up to a 25% dropout rate. Change and percentage change in radiographic spleen volume as well as radiographic spleen response rates will be summarized using descriptive statistics. The mean, range, standard deviation and 95% confidence interval will be reported for change and percent change in spleen volume. Secondary Objectives: adverse events will be evaluated and graded as per the CTAEv5.0 and safety endpoints will be analyzed by descriptive statistics. Additional efficacy endpoints will be analyzed descriptively: response rates (overall response and symptoms response by IWG-MRT criteria) will be determined by tabulating the number and proportion of subjects that respond. The mean, standard deviation, minimum, and maximum time to response will be computed for the subset of patients that have a response.

1 OBJECTIVES

1.1 Primary Objective

To assess the efficacy of selinexor on spleen volume reduction in subjects with myelofibrosis (PMF, PET-MF, or PPV-MF) refractory or intolerant to ruxolitinib and/or any other experimental JAK1/2 inhibitors.

Primary Endpoint:
Response rate defined as the proportion of subjects with ≥ 35% reduction in spleen volume as measured by MRI or CT abdomen from baseline to after six cycles of treatment. Patients who do not complete six cycles of therapy will be considered non-responders, but their data will still be reported. Patients who do not complete six cycles of treatment will receive an MRI at cycle 7 day 1, or at discontinuation of therapy (see section 11.4.2).

1.2 Secondary Objectives

1.2.1 To assess the safety/tolerability and further characterize the safety profile of selinexor in PMF, PET-MF, or PPV-MF patients refractory or intolerant to ruxolitinib and/or any other experimental JAK1/2 inhibitors.

Secondary Endpoints: rate of adverse events (AEs) and serious adverse events (SAEs).

1.2.2 To further assess the efficacy and clinical activity of selinexor (by means of reduction in symptoms, overall response, and overall survival) in subjects with myelofibrosis (PMF, PET-MF, or PPV-MF) refractory or intolerant to ruxolitinib and/or any other experimental JAK1/2 inhibitors.

Secondary Endpoints:

- Percent change of spleen volume as measured by MRI or CT abdomen.
- Proportion of patients with ≥ 50% reduction of total symptoms score as measured by the MPN-Symptoms Assessment Form (MPN-SAF) from baseline to after 6 cycles of treatment. Patients who do not complete six cycles of therapy will be considered non responders, but their data will still be reported. Patients who do not complete six cycles of treatment will receive the MPN-SAF assessment at cycle 7 day 1, or at discontinuation of therapy (see section 11.4.2).
- Overall response rate according to the 2013 IWG-MRT consensus criteria for treatment response in primary and secondary MF (post-PV and post-ET).
- Overall survival at 24 months from the initiation of study therapy

1.3 Exploratory Objective(s)

1.3.1 To assess the effects of selinexor on MF bone marrow fibrosis grade.

Exploratory Endpoints: changes in bone marrow fibrosis grade and cytogenetic abnormalities from baseline.

1.3.2 To assess the effects of selinexor on duration of spleen volume reduction.

Exploratory Endpoints: Duration of ≥ 35% reduction in spleen volume as measured by MRI or CT abdomen.

1.3.3 To assess the effects of selinexor on levels of circulating inflammatory cytokines.

Exploratory Endpoints: change in circulating inflammatory cytokine profile including but not limited to IL-6, IL-1β, tumor necrosis factor (TNF), TNFRII.

1.3.4 To assess the effects of selinexor on JAK2 or CALR or MPL mutant allele burden.

Exploratory Endpoints: change in allele burden of JAK2V617F, MPLW515 and S505 and CALR exon 9.

1.3.5 To assess the effects of selinexor on genetic mutations by NGS.

Exploratory Endpoints: changes in genetic mutations by NGS from baseline.

1.3.6 To assess the effects of selinexor on other pharmacodynamic markers.

Exploratory Endpoints: change in other pharmacodynamic markers levels from C2D1 pre dose to 4 hours post dose.

1.3.7 To explore whether a customized tool can be developed to estimate spleen volume based on MRI or CT abdomen.

Exploratory Endpoints: correlation between spleen volumes calculated using the standard institutional method and a new experimental method.

1.3.8 To find predictive marker of selinexor response, from DNA and RNA sequencing.

Exploratory Endpoints: to identify predictive markers of selinexor response from DNA and RNA sequencing.

2 BACKGROUND

2.1 Myelofibrosis

The classic *BCR-ABL* negative myeloproliferative neoplasms (MPNs) encompass polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (MF). MF is characterized by clonal hematopoietic stem cell proliferation and bone marrow reticulin fibrosis, leading to ineffective erythropoiesis, elevated inflammatory cytokines, and marked extramedullary hematopoiesis.[1] The prevalence of MF in the United States is estimated to be 4-6 cases per 100,000 people with a median age of 60 to 65 years at diagnosis.[2] MF can present de novo (primary MF) or as secondary from PV (post-PV MF or PPV-MF) or ET (post-ET MF or PET-MF). Cytopenias, thromboembolism, symptomatic splenomegaly, and leukemic transformation account for the major morbidity of MF patients. The survival of MF patients is significantly reduced compared to age-matched controls as well as PV and ET patients. In addition, many MF patients have low quality of life (QoL) and experience debilitating constitutional symptoms including fatigue, anorexia, night sweats and weight loss.[3,4] Various tools have been developed and validated in large cohorts of MPN patients for

the assessment of disease-related symptoms. The MPN symptom assessment form (MPN-SAF) is a 27-item tool that allows for objective assessment of MPN symptoms and is validated in large cohort of MPN patients (including MF). A short abbreviated tool, the MPN-SAF Total Symptom Score (MPN-SAF TSS), includes the 10 most common symptoms in patients with MPN and is also a validated tool to assess symptom burden in MF patients.[5,6] A ≥ 50% reduction in the total symptoms score is considered to be a valid end point in clinical trials of MF patients.[7-10]

A number of prognostic scoring systems have been developed for MF and are currently used in the clinic to estimate overall survival, risk of leukemic transformation, and also guide treatment decisions. The International Prognostic Scoring System (IPSS) was developed based on certain clinical features at diagnosis including age > 65 years, presence of constitutional symptoms, hemoglobin < 10 g/dL, white blood cell count > 25,000/μL and peripheral blood blasts > 1%.[11] IPSS stratifies patients to low, intermediate-1, intermediate-2, and high risk based on the presence of 0, 1, 2 or ≥ 3 of the variables. The Dynamic International Prognostic scoring system (DIPSS) is a time-dependent risk model which takes into account the development of anemia over time in addition to the IPSS variables (as shown in Table 1).[12,13]

Constitutive activation of JAK/STAT signaling through mutations in *JAK2* (*JAK2*^{V617F}, 50% to 60%), calreticulin (*CALR*, 20-30%), or *MPL* (W515L and others, 5-7%) is characteristic of MF.[14] Several co-existing mutations are reported, most commonly involving genes associated with epigenetic regulation such as *EZH2*, *ASXL1*, *TET2* and *DNMT3A*. *ASXL1* mutations are shown to be independently associated with inferior overall survival, and in one study, *CALR* mutations were found to be associated with a more indolent phenotype.[15] So far, none of the molecular abnormalities outside of those involving JAK/STAT activation (*JAK2*, *MPL* and *CALR*) have led to therapeutic advances.

Table 1: Risk stratification of myelofibrosis by Dynamic International Prognostic Scoring System (DIPSS)

Total risk score	Risk category	Median overall survival
0	Low	not reached
1 to 2	Intermediate-1	14.2 years
3 to 4	Intermediate-2	4 years
5 to 6	High	1.5 years

Until 2012, MF treatment was limited to chemotherapy to control myeloproliferation (hydroxyurea, busulfan), supportive care measures such as cytokines to improve cytopenias (erythropoietin, G-CSF), and prednisone or immunomodulatory drugs (thalidomide and lenalidomide).[16] The discovery of *JAK2*^{V617F} mutations in MF patients led to the development of ruxolitinib (RUX), a JAK1/2 inhibitor, which was approved in 2012 for high-risk and intermediate-2 risk MF patients. Two large randomized Phase 3 studies conducted in the United States and Europe showed superiority of RUX over placebo or best available therapy (BAT) in major endpoint (spleen volume reduction) and improvement in constitutional symptoms and QoL.[17,18] In a more recent update, a trend toward improved overall survival was reported. However, some patients demonstrate inadequate response to RUX or develop progressive increase in spleen size after an initial response (refractory disease). Additionally, thrombocytopenia frequently limits dose intensity and renders many patients ineligible for

RUX. More importantly, the effect of RUX treatment on the natural history of MF is minimal. Except in few rare patients, RUX does not significantly affect the *JAK2*^{V617F} mutant allele burden.[19] Pacritinib, a JAK2-specific inhibitor with less myelosuppressive effects than RUX, has been found to be superior to best available therapy (BAT) but has not yet been approved due to increased bleeding and cardiovascular events.[7,9] Momelotinib, another JAK1/2 inhibitor, showed responses in term of spleen volume reduction and anemia response, but failed to show superiority over BAT in patients previously treated with ruxolitinib.[8,10] Further studies are currently ongoing to evaluate the clinical benefits of momelotinib in comparison to danazol in symptomatic and anemic MF patients (NCT04173494). Fedratinib, a JAK2-selective inhibitor is recently approved for intermediate-2 or high risk MF patients based on JAKARTA study, which showed superiority of fedratinib over placebo in major end points (spleen volume reduction and symptoms). However similar to RUX, no meaningful changes were observed in *JAK2* mutant allele burden indicating minimal effect of fedratinib on the disease clone (Pardanani JAMA oncology 2015). Anemia and thrombocytopenia were common with fedratinib. More importantly, serious and fatal encephalopathy has occurred in some patients leading to a Boxed warning and treating physicians are advised to assess thiamine levels prior to starting fedratinib and periodically during treatment. Allogeneic stem cell transplant is the only available therapy for patients who are refractory or intolerant to RUX but is limited by significant transplant-related morbidity and mortality and many MF patients are ineligible.[20] Although some studies reported high success rates with allogeneic stem cell transplantation in MF, subsequent studies failed to replicate similar level of success. Therefore, novel therapeutic approaches are needed to improve outcomes.

2.2 Selinexor

Selinexor (also known as KPT-330) is a small molecule, oral, first-in-class, potent, slowly reversible, covalent-binding Selective Inhibitor of Nuclear Export (SINE) that specifically blocks the karyopherin protein exportin 1 (XPO1), also called chromosome region maintenance 1 (CRM1). XPO1 is overexpressed 2-4 fold in all cancers studied to date and overexpression is frequently correlated with poor prognosis and/or reduced survival, suggesting that XPO1 could have a direct role in the etiology of the malignant phenotype. XPO1 is the exclusive nuclear transporter for shuttling the major tumor suppressor proteins (TSPs) and other growth regulators out of the nucleus. Since TSPs require nuclear localization to mediate their deoxyribonucleic acid (DNA) damage assessment/tumor suppressing functions, nuclear export leads to their functional inactivation and/or proteasome-dependent cytoplasmic degradation. In addition, XPO1 mediates the nuclear-to-cytoplasmic transport of the mRNAs for several oncoproteins (associated with the carrier molecule eIF4E) including c-Myc, Cyclin D, BTK, Flt3 and Bcl2 family proteins leading to increased cytoplasmic ribosomal translation and higher levels of these pro-survival proteins. Blockade of XPO1 leads to marked accumulation of TSPs in the nucleus of all cells, leading to cell cycle arrest at the G1±G2 checkpoints, inhibition of DNA damage repair (DDR), inhibition of the NF-κB pathway, and modulation of the immune checkpoint response. Cells with damaged genomes (i.e., cancer cells) undergo apoptosis, whereas undamaged normal cells remain in cell cycle arrest until the XPO1 block is released. Blockade of XPO1 similarly leads to decrease in the nuclear-to-cytoplasmic transport of mRNAs for several oncoproteins with consequent reductions in their protein levels.

2.3 Study rationale

2.3.1 Nuclear-cytoplasmic transport and oncogenesis

Chromosomal maintenance 1 (CRM1), also known as exportin-1 (XPO-1), promotes the energy-dependent directional transport of cargo proteins with a leucine-rich nuclear export signal (NES) through the nuclear pore complex (NPC) into the cytoplasm. NES-containing cargo proteins in the nucleus form a trimeric complex with CRM1 and the GTP-bound form of the small GTPase Ran. This complex is shuttled through the NPC into the cytoplasm, where the GTP bound to Ran is hydrolyzed to GDP (facilitated by RanGTPase activating protein, RanGAP), which in turn lowers the affinity for cargo, causing its release. CRM1 is then shuttled back into the nucleus, where the transport cycle resumes. The RanGTP/RanGDP gradient provides the energy for the directional cargo transport. CRM1 cargos include a number of cancer-relevant proteins such as p53, p21, p27, PP2A and surviving.[21] Some cancer cells rely on effective NCT to inactivate nuclear tumor suppressors (e.g., p53) or to activate cytoplasmic oncogenes (e.g., survivin). For example, it has been shown that CML cells with BCR-ABL1 – independent imatinib resistance are sensitive to inhibition of NCT by knockdown of Ran.[22] The potential of inhibiting CRM1 for cancer therapy has been recognized for some time. A series of compounds (selective inhibitors of nuclear export, SINE) are recently developed that inhibit XPO-1 mediated NCT. The most advanced compound, selinexor (KPT-330), is active in pre-clinical cancer models; early clinical trials at several cancer indications are ongoing.

2.3.2 Nuclear-cytoplasmic transport and myelofibrosis

Aberrant JAK/STAT pathway activation is central to the pathogenesis of myelofibrosis. However, JAK inhibitors, such as ruxolitinib, only reduce symptoms, but are not curative. To identify novel targets in myelofibrosis, irrespective of somatic mutation status, a short hairpin RNA library screen was performed on *JAK2*^{V617F} mutated HEL cells. HEL cells were subjected to a lentiviral shRNA library (Human Module 1, Cellecta, Inc.) containing 27,239 noncontrol shRNAs targeting 5,034 genes involved in cell signaling, with 5-6 shRNAs per gene as described before.[22] Candidate genes were selected on the basis of 10-fold depletion ≥ 3 shRNAs and reduction in ≥ 3 shRNAs targeting the same gene. (See Table 2). Nuclear-cytoplasmic transport (NCT) proteins, RAN and RANBP2 were amongst the top 20 candidate genes, suggesting that HEL cells may be highly dependent on NCT.[23]

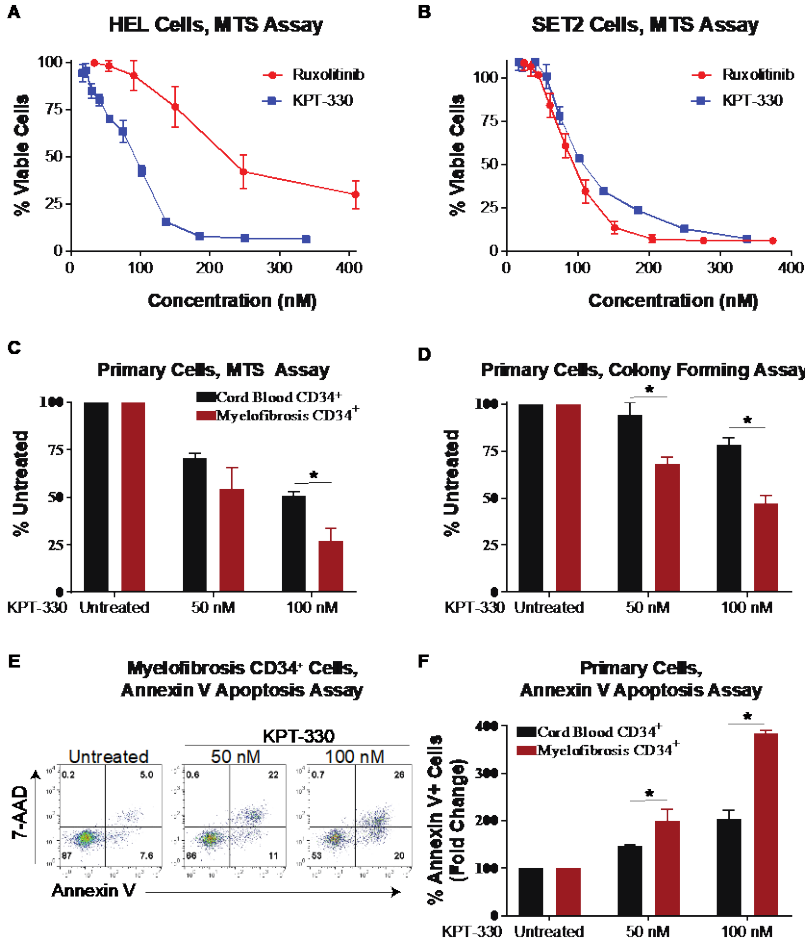
Table 2: Top 20 candidate genes from the shRNA library screen in HEL cells

Rank	Gene Symbol	Median Fold Depletion	Gene Name
1	PSMB2	59	proteasome subunit beta 2
2	RAN	50	RAN family GTPase, Ras superfamily GTPase
3	SHFM1	45	26S proteasome complex subunit
4	IL28B	43	interferon lambda 3
5	PSMD13	41	proteasome 26S subunit, non-ATPase 13
6	POLR2F	40	RNA polymerase II subunit F
7	RPL11	40	ribosomal protein L11

8	PSMD2	38	proteasome 26S subunit, non-ATPase 2
9	SSRP1	36	structure specific recognition protein 1
10	RPL12	36	ribosomal protein L12
11	HMGCR	35	3-hydroxy-3-methylglutaryl-CoA reductase
12	RPL6	34	ribosomal protein L6
13	HNRNPC	34	heterogeneous nuclear ribonucleoprotein C (C1/C2)
14	ITK	33	IL2 inducible T-cell kinase
15	SIN3A	33	SIN3 transcription regulator family member A
16	RANBP2	33	RAN binding protein 2
17	PSMA3	33	proteasome subunit alpha 3
18	PSMB7	33	proteasome subunit beta 7
19	LOC402057	32	unknown gene, NM_001080499.1
20	PSMB3	32	proteasome subunit beta 3

To validate the screen results, HEL and another *JAK2*^{V617F} mutant SET-2 cells were stably transduced with doxycycline (DOX)-inducible shRAN. DOX-induced knockdown of RAN, reduced cell viability, strongly increased apoptosis and reduced colony formation (data not shown). Inhibition of XPO-1 by selinexor was found to phenocopy the results of RAN knockdown in HEL and SET-2 cells (Figure 1 A and B). Selinexor selectively decreased proliferation of primary MF CD34+ cells (Fig. 1C), decreased colony formation ability (Figure 1D), and increased apoptosis (Figure 1E and F). To evaluate the role of NCT in vivo, selinexor was tested in a mouse model of *JAK2*^{V617F} driven myeloproliferative neoplasm. BALB/c mice were infected with pMIG-*JAK2*^{V617F} containing retrovirus after lethal total body irradiation. Animals develop advanced MPN characterized by severe myeloid expansion, bone marrow reticulin fibrosis and splenomegaly in 3-4 weeks. Animals were treated with vehicle, selinexor alone or in combination with RUX. Selinexor decreased white blood cell counts and granulocytes and MPN clone as measured by GFP positive fraction in peripheral blood, spleen and bone marrow both as single agent and in combination with RUX (animal data not shown). These data provide a strong rationale for targeting NCT in MF. [23]

Figure 1: Preclinical data.



Analysis of the efficacy of KPT-330 against JAK2^{V617F}-positive human cell lines shows that KPT-330 is comparable to ruxolitinib (A, B). KPT-330 prevents the growth of primary myelofibrosis cells (red bars) at 50 and 100 nM, while these doses are less effective against cord blood cells (black bars; C). KPT-330 is effective at reducing colony formation by MF cells and shows minimal effect against cord blood cells (D). Analysis of apoptosis by Annexin V and 7-AAD labeling revealed selectivity for myelofibrosis cells over cord blood cells (E, F). * denotes p value below 0.05.

2.3.3 Dose Schedule Rationale

Selinexor Dosing

Selinexor is approved for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies and whose disease is refractory to at least 2 proteasome inhibitors, at least 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody.

In addition, selinexor is currently under investigation in ongoing Phase 1-3 trials in patients with various hematologic malignancies. In the phase 1 study dosing has safely reached 60 mg/m^2 (~100 mg) twice weekly (cleared DLT; total weekly dose 120 mg/m^2 [~200 mg]). The MTD has not been reached in this study, but two DLTs were observed at a dose of 85 mg/m^2 in a parallel ongoing study (KCP-330-002) of selinexor in patients with advanced solid tumors. Based on these findings, the MTD for selinexor in patients with B-cell malignancies

is 60 mg/m^2 twice weekly (120 mg per week or 480 mg per cycle). Among heavily pretreated patients enrolled in this ongoing Phase 1 trial, selinexor-related Grade 3-4 thrombocytopenia has been observed primarily at total weekly doses of ≥ 46 mg/m^2 and Grade 3-4 neutropenia at total weekly doses ≥ 60 mg/m^2. Overall, increased rates of infection associated with selinexor have not been reported, however greater incidences of sepsis were seen with selinexor vs. PC in elderly patients with RR AML receiving doses > 60 mg of selinexor in study KCP-330-008. Going forward, selinexor will be administered primarily as fixed milligram doses, as analyses of Phase 1 PK data indicated that exposure is not strongly correlated with BSA. Based on tolerability, safety, efficacy, and DLT evaluations, the following doses are recommended as a single agent for current and future Phase 2 and 3 studies: 60 mg BIW in elderly AML, 60 mg BIW in NHL, and 80 mg BIW in multiple myeloma (in combination with dexamethasone 20 mg BIW). Selinexor in combination however is administered on a weekly schedule and at doses of 60-100 mg.

To date, 12 patients with myelofibrosis were dosed with selinexor in this study. The starting dose of selinexor was 80 mg weekly in the first six patients. After 3 out 6 patients required dose reduction due to grade 2 weight loss. The starting dose of selinexor was decreased to 60 mg weekly for subsequent patients. Additional six patients were enrolled at starting dose of 60 mg weekly. Of all the 12 patients, 7 required dose reduction to 40 mg weekly. Grade 2 weight loss occurred in 5 of 7 patients that required dose reduction to 40 mg weekly. At this time, 4 patients remain on selinexor treatment, 2 on 60 mg weekly dose and 2 on 40 weekly dose. The starting dose of selinexor will be decreased to 40 mg weekly for the remaining 12 expected patients.

3 DRUG INFORMATION

3.1 Selinexor

Selinexor is a Selective Inhibitor of Nuclear Export (SINE) compound. Selinexor specifically blocks nuclear export by binding to the nuclear export protein XPO1.

Refer to the most recent IB for detailed background information on selinexor. The following information is taken from the IB

3.1.1 Pharmacology

Selinexor is a Selective Inhibitor of Nuclear Export (SINE) compound that binds and inactivates Exportin 1 (XPO1), thereby forcing the nuclear retention of key tumor suppressor proteins (TSPs). Transient retention of TSPs in the nucleus at high levels via XPO1 blockade activates their cell cycle checkpoint and genome surveying actions. This leads to the death of nearly all types of malignant cells, whereas normal cells undergo transient cell cycle arrest and recovery when the export block is released. The reactivation of multiple tumor suppressor pathways and inhibition of translation of key pro-survival proteins through inhibition of a non-redundant, single protein represents a novel approach to the treatment of neoplastic diseases including those with multiple genomic alterations and resistance mechanisms.

Selinexor has shown broad activity in a variety of in vitro and animal cancer studies.

3.1.2 Physical and Chemical Properties

Selinexor, also known as KPT-330, has a molecular weight of 443.31 g/mol and a molecular formula of $C_{17}H_{11}F_6N_7O$. Its chemical name is (Z)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)-*N*′-(pyrazin-2-yl)acrylohydrazide.

3.1.3 Pharmaceutical Properties and Formulation

20 mg tablets for oral administration will be supplied in blister packs of 12.

Selinexor 20 mg tablets are manufactured via roller compaction dry granulation (RCDG) and contain 1.25% by weight of the API as well as microcrystalline cellulose ([Avicel PH101], binder/filler); croscarmellose sodium ([Ac-Si-Sol], disintegrant); Kollidon 30 powder ([polyvinylpyrrolidone povidone], solubilizing agent); colloidal silicon dioxide ([M5-P], anti-caking agent); magnesium stearate (lubricant). Additional inactive excipients include microcrystalline cellulose [Avicel 102], croscarmellose sodium, colloidal silicon dioxide, sodium lauryl sulphate, and magnesium stearate are blended with the granulated material, and compressed to make tablets. The compressed tablet cores are coated with Opadry II clear (undercoat) and blue (topcoat) to provide product formulation.

3.1.4 Clinical Safety

To date, more than 3226 patients with hematologic or solid tumors have received selinexor in clinical studies (including Karyopharm-sponsored studies and Investigator-sponsored studies) in > 10 disease indications. The majority of patients were treated with selinexor as a single agent but > 300 patients received selinexor in combination with a diverse array of other anticancer agents. Single-agent Phase 1 studies with oral selinexor have been conducted in advanced hematological malignancies including MM, acute myeloid leukemia (AML), NHL, and chronic lymphocytic leukemia; in solid tumors; and in soft tissue and bone sarcomas. Broad antitumor activity has been observed in all of these studies. In addition, Phase 2 studies are ongoing in MM, AML, diffuse large B-cell lymphoma, Richter's transformation, glioblastoma, gynecological malignancies, and dedifferentiated liposarcoma (Phase 2 and 3). Additional information about clinical studies of selinexor is available in the selinexor IB.

Pharmacokinetics

Oral selinexor pharmacokinetics (PK) are predictable, approximately dose-proportional, and exhibit moderate- to moderately-high inter-patient variability across a wide range of doses in male and female patients with advanced hematological malignancies or solid tumors.

Additional details are available in the selinexor IB.

Safety and Efficacy

To date, 3226 patients with hematologic or solid tumors had received at least one dose of selinexor in Company Sponsored (CSTs), Investigator Sponsored (ISTs) or Compassionate Use Trials and are included in the preliminary safety analyses provided in the UB in this IB. These 3226 patients include 2076 patients from CSTs, 1016 patients from ISTs, and 130 patients from compassionate use trials. Safety data from all CSTs, ISTs and compassionate use trials are reviewed at least quarterly by Karyopharm at Safety Review Committee meetings.

In ongoing clinical studies, the most common AEs reported as at least possibly related to selinexor (incidences in parentheses) have been low-grade nausea (65.1%), fatigue (57.9%), anorexia (51%), thrombocytopenia (52.1%), vomiting (38.2%), and diarrhea (36%). Most of these AEs can be managed effectively with dose modification and/or supportive care initiated prior to first dose.

Since clinical trials began with selinexor, 3 acute cerebellar syndrome (ACS) cases have been reported in 1 adult (pancreatic cancer, index case) and 2 pediatric (refractory AML) patients in the selinexor development program to date (including CSTs and ISTs). Symptoms of ACS can include a sudden loss of coordination, balance, difficulty walking or abnormal speech. All of these cases occurred in dose escalation studies at high doses of selinexor (85 mg/m^2 in the adult and 70 mg/m^2 in the children and were reversible. The maximum doses in adults (70 mg/m^2) and children (55 mg/m^2) have been established based largely on these events.

Reproductive Risks
Macroscopic and microscopic changes in reproductive organs were noted during rat and monkey toxicology studies, most of which partially or fully resolved during the recovery period. The long-term effects of these changes on reproductive potential are unknown. Secondary developmental effects due to reduced maternal body weights were also noted during a study on rat embryo/fetal development.

It is unknown whether similar effects may occur or whether selinexor might have reproductive toxicity in humans and as such, patients must agree to use effective contraception (refer to Section 7.3 for details) during the study and for 3 months following the last dose of study treatment.

Nursing Mothers
It is not known whether selinexor is excreted in human milk. Because many drugs are excreted in human milk, and the effect of selinexor on newborns is unknown, selinexor should not be administered to women who are nursing.

Pediatric Use
ISTs of selinexor in pediatric patients with leukemia and solid tumors are ongoing as of 31 March 2017, and additional studies in pediatric patients with other malignancies are planned.

Geriatric Use
Many of the patients who participated in selinexor clinical studies have been > 65 years old, however no formal studies on the use of selinexor in geriatric patients have been performed.

4 STUDY DESIGN

4.1 Description

This is a phase II, open label, prospective, single-arm study evaluating the efficacy and safety of selinexor in patients with PMF or secondary MF (PPV-MF or PET-MF) who are refractory or intolerant to ruxolitinib and/or any other experimental JAK1/2 inhibitors. As of protocol version 7, Selinexor will be administered orally at a starting dose of 40 mg once weekly due to previous toxicity rates. Prior to protocol version 7, 6 patients were treated with a starting

dose of 80 mg once weekly and an additional 6 patients were treated with a starting dose of 60 mg once weekly.

4.2 Number of Patients

The study will enroll up to 24 patients. The power calculation for efficacy is based on a sample size of 18 response-evaluable patients. The sample size was set to 24 to allow for enrollment of up to 6 patients who are not evaluable.

4.3 Number of Study Centers

This is a single-center study to be conducted at Huntsman Cancer Institute at the University of Utah, Salt Lake City, Utah.

4.4 Study Duration

The estimated duration of enrollment will be 30 months. The primary objective will be evaluated after 6 cycles of selinexor (cycle 7 day 1) treatment. Selinexor treatment will continue thereafter as long as the study drug is tolerated and subject does not meet discontinuation criteria. After discontinuation of the study drug, patients will be followed for survival. It is estimated that each patient will participate in the study for approximately 24 months. Therefore, the estimated study duration is about 60 months.

5 ELIGIBILITY CRITERIA

This eligibility checklist is used to determine patient eligibility and filed with enrolling investigator's signature in the patient research chart.

Patient No. _____
Patient's Initials: (L,F,M) _____

5.1 Inclusion Criteria
Yes/No (Response of "no" = patient ineligible)

5.1.1 _____ Male or female subject aged ≥ 18 years.

5.1.2 _____ Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2

5.1.3 _____ Diagnosis of primary myelofibrosis (PMF), post-essential thrombocytosis myelofibrosis (also known as thrombocythemia) (PET-MF) or post-polycythemia vera myelofibrosis (PPV-MF).

5.1.4 _____ Life expectancy ≥ 6 months.

5.1.5 _____ Prior treatment with ruxolitinib or any experimental JAK1/2 inhibitor with any one or more of the following:

a. Inadequate response after being on ≥ 3 months of treatment defined by:
   i. Palpable spleen ≥ 10 cm below the left subcostal margin on physical examination at the screening visit OR
   ii. Palpable spleen ≥ 5cm below the left subcostal margin on physical examination at the screening visit AND active symptoms of MF at the screening visit defined presence of 1 symptom score of ≥ 5 or two symptom scores each of ≥ 3 using the Screening Symptoms Form (Appendix 6)

b. Intolerant to ruxolitinib and/or other JAK1/2 inhibitors due to any grade ≥ 3 non-hematologic AEs of or any grade ≥ 2 AEs requiring treatment discontinuation AND palpable spleen ≥ 5cm below the left subcostal margin on physical examination at the screening visit.

5.1.6 _____ Adequate organ function as defined as:

- **Hematologic** (≤ 28 days prior to C1D1):
  - Total white blood cell (WBC) count ≥ 1000/mm^3
  - Absolute neutrophil count (ANC) ≥ 500/mm^3
  - Hemoglobin ≥ 7 g/dL
  - Platelet count ≥ 30,000/mm^3

For patients receiving transfusion and growth factor support, the following delays must be observed between the last administration and hematologic laboratory screening assessments:

- For hematopoietic growth factor support (including erythropoietin, darbepoetin, granulocyte-colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], and platelet stimulators [e.g., eltrombopag, romiplostim, or interleukin-11]): at least 2 weeks.

Growth factor support, RBC and/or platelet transfusions are allowed as clinically indicated per institutional guidelines during the study.

- **Hepatic** (≤ 28 days prior to C1D1):
  - Total bilirubin < 1.5 × ULN except in patients with indirect hyperbilirubinemia due to hemolysis or gilbert's syndrome where total bilirubin should be <5X ULN
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.5 × ULN.

- **Renal** (≤ 28 days prior to C1D1):
  - Estimated creatinine clearance (CrCl) ≥ 20 mL/min using the Cockcroft and Gault formula *[(140-Age) × Mass (kg)/(72 × creatinine mg/dL), multiply by 0.85 if the patient is female]* OR

5.1.7 _____ Female patients of childbearing potential must have a negative serum pregnancy test (≤ 3 days prior to C1D1).

5.1.8 _____ Female patients of childbearing potential must agree to use 2 methods of contraception throughout the study and for 3 months following the last dose of study treatment (including 1 highly effective and 1 effective method of contraception as defined in section 7.4)

5.1.9 _____ Male patients must use an effective barrier method of contraception if sexually active with a female of childbearing potential.

5.1.10 _____ Recovery to baseline or ≤ Grade 1 CTCAE v. 5.0 from toxicities related to any prior treatments including ruxolitinib or other experimental agents unless AE(s) are clinically nonsignificant and/or stable on supportive therapy.

5.1.11 _____ Able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

5.2 Exclusion Criteria
Yes/No (Response of "yes" = patient ineligible)

5.2.1 _____ Prior exposure to a SINE compound, including selinexor.

5.2.2 _____ Patients who are below their ideal body weight and would be unduly impacted by changes in their weight, in the opinion of the investigator, will be excluded.

5.2.3 _____ Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals ≤ 1 week prior to C1D1. Patients on prophylactic antibiotics or with a controlled infection ≤ 1 week prior to C1D1 are eligible.

5.2.4 _____ Radiation, chemotherapy, immunotherapy, or any other anticancer therapy (including investigational therapies) ≤ 2 weeks

5.2.5 _____Ruxolitinib or other JAK1/2 inhibitors ≤ at least 3 days or 5 half-lives prior to C1D1.

5.2.6 _____ Major surgery ≤ 4 weeks prior to C1D1.

5.2.7 _____ Known active hepatitis A, B, or C infection; or known to be positive for hepatitis C virus ribonucleic acid (RNA) or hepatitis B virus surface antigen.

5.2.8 _____ Any active gastrointestinal dysfunction interfering with the patient's ability to swallow tablets, or any active gastrointestinal dysfunction that could interfere with absorption of study treatment.

5.2.9 _____ Any life-threatening illness, organ system dysfunction, or serious psychiatric, medical, or other conditions/situations which, in the investigator's opinion, could compromise a patient's ability to give informed consent, safety, or compliance with the protocol.

5.2.10 _____ Contraindication to any of the required concomitant drugs or supportive treatments.

5.2.11 _____ Subjects taking prohibited medications as described in Section 6.3. Following discontinuation of prohibited medications, a washout period is required prior to initiating study treatment (the duration of the washout must be as clinically indicated, e.g., at least five half-lives).

5.2.12 _____ Subjects who are breastfeeding and unwilling to stop while on study.

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

Investigator Signature	**Date**	**Time**

5.3 Recruitment Strategies

Potential patients will be identified by Investigators in the setting of their outpatient clinics.

6 TREATMENT PLAN

6.1 Administration Schedule

The schedule is based on 28-day cycles.

For patients enrolled after protocol version 7, Selinexor will be administered by oral route, beginning at 40 mg once weekly. Prior to protocol version 7, the starting dose of selinexor was 60 mg and 80 mg once weekly.

In case of toxicity at the starting dose level, dose modifications will be implemented as described in Section 7.1. Treating investigators may consider increasing the dose to 60 mg once weekly after 12 weeks of treatment in the absence of grade 2 or higher weight loss. The dose increase must be done after documented consultation with PI and medical monitor.

6.2 Selinexor

6.2.1 How Supplied, Stored, Packaged and Labeled

Selinexor will be provided by Karyopharm Therapeutics Inc. as coated, immediate-release oral tablets in strengths of 20 mg in wallet-sized blister packs which will be maintained by site Investigational pharmacy.

Selinexor 20 mg tablets are to be stored in a locked and secured area with access restricted to the site staff at room temperature (below 30 °C) in clear blister strips that are composed of either polyvinyl chloride (PVC)/polyethylene (PE)/polychlorotrifluoroethylene (PCTFE) clear film blister with a foil paper backing or (PVC)/(PCTFE)/(PVC) clear film blister with a foil paper backing. Room temperature storage is recommended, refrigerated is acceptable. Tablets should not be stored frozen.

The blistered packaged product will be placed in paperboard secondary packaging, to which labeling materials will be affixed.

All labels will include conditions for storage, lot number, and other information required by the Food and Drug Administration (FDA), International Council for Harmonisation (ICH), and/or Annex 13, as well as all local regulations for investigational medication.

Selinexor tablets are currently in on-going stability studies. The expiry will be based on concurrent stability studies and extended during the course of the study as further stability data becomes available.

6.2.2 Preparation and Administration

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the handling and safe disposal of selinexor in a self-contained and protective environment No special preparation is required.

Selinexor should be taken with at least 120 mL (4 ounces) of fluids (water, juice, etc.) at approximately the same time each dosing day.

Selinexor tablets should be swallowed whole (not crushed) to prevent an increased risk of dermatologic toxicity if the powder comes in contact with skin. For doses of oral medications to be taken on non-clinic days, patients will be provided with medication to take home.

Missed Doses
If a dose was missed, the dose can be made up and the schedule should be altered to maintain at least 36 hours between two consecutive doses.

If a dose must be skipped (e.g., due to recommendation of treating physician), the next dose will be taken as per schedule. Doses should not be administered less than 36 hours apart and all missed and delayed doses should be documented.

Vomited Doses
If a dose is vomited within 1 hour of ingestion, it will be replaced. If vomiting occurs more than 1 hour after dosing, it will be considered a complete dose.

6.2.3 Accountability and Compliance

Selinexor must be requested by submitting an order form directly to the drug depot and will be shipped directly to site's Investigational Drug Services.

The investigator, or a responsible party designated by the investigator, must maintain an adequate record of receipt, distribution, and return of all study drugs in the form of a Drug Accountability Form. Such records must be provided to the drug supplier upon request.

Subjects are required to bring all used packs and any unused investigational product (IP) when they visit to the site at the end of each cycle. Compliance will be assessed by discussion with the patient and confirmed by pill count. Any deviations and missed doses (including reasons for the deviation or missed doses) will be recorded in the site's internal database and drug accountability logs with the reasons for subsequent verification.

The IP returned by subjects or any unused IP (that is, never dispensed to any subject) must be destroyed after accountability has been performed and only after written authorization from Karyopharm Therapeutics, Inc. has been received.

Subject compliance with the treatment and protocol includes willingness to comply with all aspects of the protocol. The investigator will try to ensure complete compliance with the dosing schedule by providing timely instructions to the patients. In case of non-compliance, the patients will be instructed again. At the discretion of the principal investigator, a subject may be discontinued from the trial for non-compliance with follow-up visits or study drug.

Selinexor should not be used for any purpose outside the scope of this protocol, nor may selinexor be transferred or licensed to any party not participating in the clinical study. Data for selinexor are confidential and proprietary and shall be maintained as such by the investigators.

6.3 Concomitant Medications and Therapies

Concomitant medications include any prescription or over-the-counter preparation, including vitamins, dietary supplements, over-the-counter medications, and oral herbal preparations taken during the study. Patients may continue their baseline medication(s). Any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure(s), and any clinical findings, if applicable.

6.3.1 Allowed Therapy

Any medication which is considered necessary for a subject's welfare is permitted and may be given at the discretion of the investigator. Medications for treatment of underlying disease and symptomatic treatment of adverse events are permitted. Exceptions are listed in the section below.

Use of Blood Products
During treatment, patients may receive red blood cell (RBC) or platelet transfusions, if clinically indicated, per institutional guidelines.

Appropriate anti-coagulation is allowed during the study (e.g., low molecular weight heparin, direct factor Xa inhibitors, etc.). Warfarin is allowed during the study provided patients are monitored for INR twice a week during the first two cycles of therapy, then weekly to biweekly. Patients may receive supportive care with erythropoietin, darbepoetin, granulocyte-colony stimulating factor or granulocyte macrophage-colony stimulating factor, pegylated growth factors, and platelet stimulatory factors, in accordance with clinical practice or institutional guidelines prior to entry and throughout the study.

6.3.2 Prohibited Therapy

Concurrent therapy
Concurrent therapy with any approved or investigative anticancer therapeutic outside of those included in this study is not allowed except hydroxyurea. Hydroxyurea is allowed after consultation with medical monitor and PI. Use of any immunosuppressive agents during the study must be confirmed by the Sponsor-Investigator. Treatment that could increase selinexor concentration should be prohibited.

Diet
There are no dietary restrictions on this study. Patients on selinexor should maintain adequate caloric and fluid intake.

Medications
Patients should not take glutathione (GSH)-, S-adenosylmethionine (SAM)-, or N-acetylcysteine (NAC)-containing products during their participation in this study as these products may enhance the metabolism of selinexor. However, they are permitted if the patient has elevated liver function tests.

Given the theoretical potential for GSH depletion, the total dose of acetaminophen should be ≤ 1 gram per day on days of selinexor dosing.

6.4 Duration of Therapy

Study subjects may remain on treatment until they experience intolerable toxicities, stop receiving clinical benefit in the opinion of the investigator, or experience IWG-MRT disease progression. Patients who experience IWG-MRT disease progression may continue treatment at the discretion of the investigator if they meet any of the following criteria:

- Subjects are continuing to receive clinical benefit (i.e. symptom improvement and/or anemia response).

- Subject meets progression criteria based solely on spleen size without leukemic transformation (appendix 5).

6.4.1 Criteria for Discontinuation of Study Intervention

In addition to the drug-specific discontinuation criteria listed in section 7.2, the following will result in treatment discontinuation:

- Subject withdraws consent from the study treatment and/or study procedures. A subject must be removed from the trial at his/her own request. At any time during the trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Any AE that requires a dose interruption > 28 days.
- Unacceptable AE or toxicity that cannot be managed by supportive care.
- Other AEs or intercurrent illnesses which, in the opinion of the investigator, would be injurious to the health or well-being of the subject and warrant their withdrawal from study treatment.
- Necessity for prohibited treatment (as defined in section 6.3) of sufficient dose and duration to confound the study results.
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (as defined in section 7.4) during the course of the study and for 3 months after discontinuation of study treatment.
- Women who become pregnant or are breastfeeding.
- Significant non-compliance with the protocol schedule or treatment in the opinion of the investigator.
- Subject is lost to follow-up or dead.
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol.

Any patient who does not withdraw from the study but who stops attending study visits and does not respond to 3 documented contact attempts will be considered lost to follow-up.

All patients will be followed until disease progression, withdrawal of consent, occurrence of any withdrawal criteria, loss of clinical benefit or intolerable toxicity precluding further treatment with study treatment, death or loss to follow up.

6.4.2 Criteria for Withdrawal from the Study

Subjects will be taken off study for the following:

- Completed study follow-up period
- Participant requests to be withdrawn from study
- Death

- Screen failure
- The study is discontinued at the discretion of the PI or drug manufacturer for any reason, including medical or ethical reasons affecting the continued performance of the study, or difficulties in the recruitment of patients

7 TOXICITIES AND DOSAGE MODIFICATION

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for adverse event and serious adverse event reporting.

While drug-related major organ toxicities are not prominent, selinexor treatment can lead to a number of constitutional and other side effects. Therefore, patients should be treated aggressively with supportive care to reduce toxicities and prevent the need for dose modifications.

Based on preliminary observations from the ongoing Phase 1 studies in patients with advanced hematological and solid tumors, selinexor shows a reasonably wide therapeutic range with activity observed at doses ranging from ~6 mg/m^2 to ≥ 60 mg/m^2 (approximately 10 mg to 120 mg orally).

Therefore, in order to optimize specific anti-tumor activity and tolerability, dose modifications and treatment delays will be allowed as described below. Each dose modification or treatment delay must be documented (including the reason for the modification or delay).

7.1 Dose Modifications

For patients enrolled after protocol version 7, alternate dosing schedules, dose reductions, and/or treatment delays in response to AEs are allowed as defined in Table 3 below.

Dose interruptions are due to non-resolving adverse events lasting > 28 days are prohibited and will result in permanent discontinuation from treatment.

Refer to Section 7.2 and Table 4 for dose reduction and interruption recommendations for specific AEs.

Table 3: Pre-specified Dose Modifications for AEs Related to Selinexor

	Dose Level	Dose of Selinexor
Dose Escalation	1	60 mg once weekly
Starting Dose	0	40 mg once weekly
Dose reduction	-1	20 mg once weekly

Dose escalation for selinexor is allowed after 12 weeks if no grade 2 or higher weight loss occurred. Dose escalation is at the discretion of the treating physician and requires documented consultation with the PI and medical monitor.

7.2 Guidelines for Management of Adverse Events

Patients who are experiencing tolerable low-grade symptoms and are deriving clinical benefit from selinexor treatment may receive a dose reduction at the discretion of the enrolling

physician and after consultation with the PI (with subsequent re-escalation allowed as described in Section 7.1). Of note, the constitutional side effects associated with selinexor often attenuate over the first 4 to 6 weeks of treatment; nearly all are reversible with dose modification and/or supportive care.

Supportive care per institutional guidelines and/or National Comprehensive Cancer Network® Clinical Practice Guidelines in Oncology (NCCN) should be used as clinically indicated at the discretion of the treating physician.

Prophylactic therapy with 5-HT3 antagonists or other anti-nausea agents prior to each dose and as needed thereafter is required for all patients initiating selinexor treatment. Additional anti-nausea agents such as olanzapine, dopamine 2 antagonists, neurokinin 1 receptor antagonists, or others should be considered in any patients with insufficient response to initial therapy.

Particular attention should be also paid to anorexia with poor caloric intake which is often accompanied by poor fluid intake. This can lead to weight loss, dehydration, and fatigue. Nutritional consultation, frequent body weight assessments, and appetite stimulants (e.g., olanzapine or megesterol acetate) can mitigate anorexia and weight loss.

Some patients with rapid tumor responses experience significant fatigue, nausea, malaise and/or asthenia after 1 or more doses of selinexor. This effect has not been associated with typical markers of tumor lysis syndrome, but if suspected, assessment of tumor response is strongly recommended in order to better inform treatment recommendations.

Thrombocytopenia

Selinexor may induce reductions in platelet counts, with minimal effects on numbers of megakaryocytes. The effects of selinexor on platelet generation are related to a slowing of maturation of megakaryocytes and a reduction in their average ploidy. There is no known effect on platelet function, and bleeding associated with low platelets has been uncommon.

Interruption of selinexor therapy, when appropriate, may lead to return of platelet counts in 1 to 3 weeks. See Table 4 for specific guidance for managing Grades 1 through 4 thrombocytopenia. Thrombopoietin agonists, particularly romiplostim at moderate to high doses, have improved platelet counts in heavily pretreated patients receiving selinexor, permitting continued dosing and maintaining anti-neoplastic effects.

Neutropenia

Standard granulocyte growth factors are highly effective for the treatment of neutropenia observed during treatment with selinexor and should be used early in patients whose neutrophil counts decline during treatment. Patients should be instructed to report any symptoms or signs of infection such as fever, pain, sweating, and redness to their physician immediately. If infection during neutropenia is suspected, then standard treatment for febrile neutropenia may be instituted. Selinexor should be interrupted until the patient is clinically stable on appropriate antimicrobial agents. No known interactions with selinexor and antimicrobial agents have been reported, and selinexor may be restarted when the patient's condition has clinically stabilized.

Anemia

Selinexor-induced anemia may contribute to dizziness, confusion, syncope and/or fatigue, particularly in elderly patients and patients who are at greater risk of cognitive sequelae. As per NCCN Guidelines, treatment with red blood cell (RBC) transfusions and/or growth factors, per institutional guidelines, should be considered for patients with symptomatic anemia.

Nausea

In order to minimize nausea, all patients should receive 5-hydroxytryptamine (5-HT3) antagonists (8 mg or equivalent) unless contraindicated, starting on C1D1 before the first dose of study treatment and continued 2 to 3 times daily, as needed. Additionally, olanzapine (2.5 mg or higher) may be given prior to the first dose of selinexor and continued once daily (QD), up to 4 days, as per NCCN Guidelines. Patients with breakthrough nausea or vomiting should receive additional anti-emetic agents.

Infection

No prophylactic antimicrobial agent is recommended for most patients initiating therapy with selinexor. Patients with a history of recurrent infections or those at high risk for specific infections may continue their prophylactic antimicrobial regimens without modification when initiating selinexor therapy.

Selinexor should be withheld in patients with suspected or active uncontrolled infections, grade 4 infections, or clinical sepsis (in the absence of documented infection). Selinexor treatment can be resumed after initiation of appropriate antimicrobial therapy and when the infection has clinically resolved and/or the patient is clinically stable. When ready to resume selinexor, treatment may continue at the original dose, even in the setting of continued antimicrobial agents.

Diarrhea

Diarrhea associated with selinexor is typically watery and low-grade and usually responds to treatment with standard anti-diarrheal agents (e.g., loperamide) and/or dose modification. Careful assessment of the patient's volume status is essential. Fluid replacement is important to prevent dehydration, fatigue and electrolyte abnormalities (e.g., hyponatremia).

Fatigue

Prevention of anorexia, vomiting, and dehydration may reduce fatigue. Also, as per NCCN Guidelines, the use of methylphenidate 5 mg QD each morning may be helpful. Hemoglobin levels must be optimized as anemia appears to contribute substantially to fatigue, particularly in patients with heavily pretreated hematologic malignancies. In patients with adequate antitumor control on selinexor, QW dosing is often associated with improvement in fatigue and other side effects.

Decreased Appetite

In patients with problematic food/liquid/caloric intake secondary to anorexia, a patient log of food and drink, as well as body weights, should be considered and monitored by site staff. Nutritional counseling is important. Dysgeusia may contribute to the anorexia, and dietary

adjustments can be helpful. Fresh juices and simple carbohydrates, as well as ginger-containing foods and beverages, can improve appetite; ginger-containing foods may also improve dysgeusia. Administration of high caloric beverages (e.g., Boost®, Ensure®) and appetite stimulating agent(s) should be instituted aggressively in patients who develop significant anorexia.

A combination of appetite stimulating agents, particularly olanzapine (2.5 to 5.0 mg every morning), and standard anti-emetics is usually effective in managing selinexor associated anorexia that does not respond to the above interventions. Megesterol acetate 400 mg daily may also be effective. Additional information on the management of anorexia is provided in the NCCN Guidelines.

Hyponatremia

Investigators should rule out the possibility of pseudo-hyponatremia due to elevated glucose (or monoclonal protein) levels. Abnormal serum sodium levels should be corrected. Adequate fluid and caloric intake, including electrolyte-rich beverages instead of plain water, has led to reversal of hyponatremia. Diuretic use should be addressed and possibly stopped, and salt supplements should be considered if hyponatremia persists

Confusional State

Confusion is usually multifactorial with associated events including older age, dehydration, electrolyte abnormalities, anemia, diarrhea, infection, concomitant medications, other comorbidities and/or high tumor burden. Optimization of fluid status, electrolytes, hemoglobin levels, thyroid function, and concomitant medications should be undertaken. Glucocorticoids should be suspected and splitting the glucocorticoid dose over 2 days may be helpful. Other CNS-active agents should also be evaluated. However, confusion can be an isolated and dose-dependent event and thus a direct role for selinexor, which crosses the blood brain barrier, cannot be ruled out. Dose reduction of selinexor may be undertaken when other causes have been ruled out. If confusion resolves and patient returns to at least baseline status, cautious re-escalation of selinexor may be attempted.

Renal Insufficiency

Baseline renal insufficiency does not appear to affect tolerability of selinexor and renal dysfunction should not preclude continued dosing with selinexor, even for patients on dialysis. If a patient is undergoing dialysis, selinexor should be given after the dialysis procedure because the effect of dialysis on selinexor plasma levels has not yet been studied. Selinexor can lead to increased creatinine, and the majority of these cases are associated with hypovolemic conditions (i.e., represent “pre-renal” azotemia). Dose modifications or interruptions and appropriate hydration typically reverse the increased creatinine.

Vision Blurred and Cataracts

Patients reporting blurry vision or other visual changes should be evaluated by an ophthalmologist. Nearly all cases of treatment-emergent visual changes have not been associated with objective findings. Changes in lens prescriptions and/or wetting drops may improve vision. Blurred vision associated with selinexor use is typically self-limited, and dosing can usually be maintained at the same level and frequency.

Patients who are at risk of cataract formation, or have cataracts present at baseline, should be monitored for changes in lens opacity. If changes in lens opacity are observed, the patient should be evaluated by an ophthalmologist. In selinexor clinical studies, several patients have undergone cataract surgery with minimal to no interruption of selinexor dosing and without complications.

The relationship between cataract and selinexor is confounded by multiple contributing factors which are known risk factors for cataracts: the heavily pretreated nature of the patients' cancers, older age, pre-existing lens disease, and concomitant (and prior) medications including glucocorticoids.

The incidence and severity of occurrence of ocular AEs following treatment with selinexor was evaluated in a large, pooled-population of patients treated in all CSTs (N = 1458). These results show that new onset, clinically significant ophthalmological abnormalities following initiation of selinexor treatment were not commonly associated with objective findings upon ophthalmological examination

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is rarely observed in patients treated with selinexor (see Section 5.5.2.3.1). It has been reported in 5 patients with MM, 2 patients with ALL, and 1 patient with AML. It has not been reported in any patient with NHL or solid tumor to date. All protocols require assessment of relevant screening laboratories and patient status (e.g., adequate hydration) to mitigate the risks for TLS.

Early recognition of signs and symptoms in patients at risk for TLS, including identification of abnormal clinical and laboratory values, is key and Investigators must ensure that patients being treated with selinexor maintain adequate caloric and fluid intake. Close monitoring and management of patients with hematological malignancies, including MM, for potential signs and symptoms of TLS are most relevant.
Based on the data received during the interval, evidence of a causal relationship between TLS and selinexor is not available at this point. Hence, it will remain as an important potential risk and Karyopharm will continue to monitor this event.

Overdose
As selinexor is metabolized by glutathione (GSH) conjugation, it is possible, but not demonstrated, that hepatic GSH depletion might occur in case of extreme overdose. Therefore, in patients who develop liver function test abnormalities, supportive measures such as S-adenosylmethionine (SAM) or other drugs that can replace GSH might be considered as part of the overall management plan.

Management guidelines for other selinexor-related AEs are provided in Table 4 below.

Table 4: Supportive Care and Selinexor Dose Adjustment Guidelines for AEs related to Selinexor[a,b,c]

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines
Fatigue	
Grade 1	Maintain dose. Rule out other causes. If found to be anemic and symptomatic, consider transfusing even with hemoglobin >8 g/dL (anemia Grade <3). Patients with significant fatigue after several doses of selinexor may have an antitumor response. Consider an unscheduled assessment of tumor response as part of the patient's evaluation.
Grade 2 lasting ≤7 days	As per the NCCN guidelines, consider stimulants such as methylphenidate 5mg QD in the morning only.
Grade 2 lasting >7 days or Grade 3	Rule out other causes. If found to be anemic and symptomatic, consider transfusions for hemoglobin >8 g/dL (Grade <3); transfusions usually indicated for Hb <8 g/dL (Grade ≥3). Interrupt selinexor dosing until resolved to Grade 1 or baseline. For first occurrence, restart selinexor at current dose. For ≥ second occurrence, reduce selinexor by 1 dose level. Patients with significant fatigue after several doses of selinexor may have an antitumor response. Consider an unscheduled assessment of tumor response as part of the patient's evaluation. As per the NCCN guidelines, consider stimulants such as methylphenidate 5mg QD in the morning only.
Anorexia or Weight loss	
Grade 1 anorexia	Maintain dose. Rule out other causes. Consider nutritional consultation and use nutritional supplements (e.g., Ensure®, Boost®). For persistent symptoms, start appetite stimulants, such as olanzapine (2.5 to 5 mg PO every morning) or megesterol acetate (400 mg QD), per NCCN guidelines.
Grade1 weight loss Grade 2 anorexia	Initiate appetite stimulants, such as olanzapine (2.5 to 5 mg PO every morning) or megesterol acetate (400 mg QD), as per NCCN guidelines.
Grade 2 weight loss Grade 3 anorexia, or Grade 3 weight loss	Interrupt selinexor dosing until improved to Grade 1 or baseline and weight stabilizes. Reduce selinexor by 1 dose level. Rule out other causes. Consider nutritional consultation and use nutritional supplements (e.g., Ensure®, Boost®) Start appetite stimulants as above
Grade 4 anorexia	Permanently discontinue selinexor

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines
Nausea, Acute	
Grade 1 or 2	Maintain dose. Rule out other causes. Use standard additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonists. If persistent, use additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonist(s). Olanzapine 2.5 to 5 mg PO every morning, per NCCN guidelines, can mitigate nausea and anorexia.
Grade 3	Rule out other causes. Use additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonist(s). Olanzapine 2.5 to 5 mg PO every morning, per NCCN guidelines, can mitigate nausea and anorexia. Interrupt selinexor dosing until resolved to Grade ≤2 or baseline and reduce selinexor by 1 dose level. Patients with significant nausea/vomiting after several doses of selinexor may have an antitumor response. Consider an unscheduled assessment of tumor response as part of the patient's evaluation.
Hyponatremia	
Grade 1 (sodium levels < Normal to 130 mmol/L)	Maintain dose. Rule out other causes including drug (e.g., diuretic) effects. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose >150 mg/dL). Treat hyponatremia per institutional guidelines including dietary review. Provide supplemental oral and/or intravenous fluids if dehydration is present. Consider addition of salt tablets to patient's diet.
Grade 3 with sodium levels <130-120 mmol/L without symptoms	Rule out other causes including drug (e.g., diuretic) effects. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose >150 mg/dL). If (corrected) sodium is Grade ≤3 and continues to be asymptomatic, then patient may continue current dosing without interruption provided that IV saline and/or salt tablets are provided and patient is followed closely. If Grade 3 is persistent or worsens or does not respond to treatment, interrupt selinexor dosing until resolved to Grade 1 or baseline and reduce selinexor by 1 dose level.
Grade 3 with sodium levels <130-120 mmol/L with symptoms or Grade 4 (<120 mmol/L)	Rule out other causes including drug (e.g., diuretic) effects. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose > 150 mg/dL). Interrupt selinexor dosing until resolved to Grade 1 or baseline and without symptoms. Reduce selinexor by 1 dose level.
Diarrhea	
Grade 1	Maintain dose. Rule out other causes including drug effects. Treat per institutional guidelines with anti-diarrheals, such as loperamide.
Grade 2	Rule out other causes including drug effects. Treat per institutional guidelines with anti-diarrheals. Interrupt selinexor dosing until resolved to Grade 1 or baseline. For first occurrence, restart selinexor at current dose. For ≥ second occurrence, reduce selinexor by 1 dose level.
Grade 3	Interrupt selinexor dosing until resolved to Grade 1 or baseline and patient is clinically stable. Reduce selinexor dose by 1 dose level.
Grade 4	Permanently discontinue selinexor
Thrombocytopenia	
Grade 1 or 2	Maintain dose. Rule out other causes including drug effects.
Grade 3 without bleeding	Maintain dose. Rule out other causes including drug effects.

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines
Grade 4 without bleeding	Rule out other causes including drug effects. Platelet transfusion is allowed if clinically indicated at the discretion of the principal investigator. For first occurrence: skip 1 dose and reduce selinexor by 1 dose level. If recurrent, the investigator in consultation with the Medical Monitor may decide to continue selinexor dosing without dose reductions and/or interruptions as specified above, provided that platelet counts and bleeding symptoms/signs are closely monitored. Treatment with moderate to high doses of thrombopoietin stimulating agents such as romiplostim 5 to 10 μg/kg SC weekly or eltrombopag 100 to 150 mg QD can be considered at the discretion of the principal investigator. Platelet transfusion is allowed if clinically indicated at the discretion of the principal investigator.
Grade ≥3 with bleeding	Interrupt selinexor dosing and check platelet counts weekly until the bleeding has stopped, patient is clinically stable and the platelets have recovered to Grade ≤3 or baseline. Platelet transfusion is allowed if clinically indicated at the discretion of the principal investigator. When resuming selinexor, reduce by 1 dose level. If recurrent, unless contraindicated, start treatment with moderate to high doses of thrombopoietin stimulating agents as above.
Neutropenia	
Grade 4 neutropenia (afebrile) OR Febrile neutropenia	Institute colony stimulating factors and prophylactic antibiotics as clinically indicated per institutional guidelines. Interrupt selinexor and check neutrophils at least weekly until recovers to Grade 3 or baseline and without fever (if febrile) and the patient is clinically stable. Colony stimulating factors per institutional guidelines or at the discretion of the principal investigator. When resuming selinexor, reduce by 1 dose level. If recurrent, continue colony stimulating factors, interrupt selinexor until neutrophil counts improve to Grade ≤3 or baseline levels. Investigator in consultation with the Medical Monitor may decide to continue selinexor dosing without dose reductions as specified above, provided that CBC and infection symptoms/signs are closely monitored.
Anemia	
Treat per institutional guidelines including blood transfusions and/or erythropoietins. Consider transfusing for symptoms with hemoglobin >8 g/dL (Grade <3) or for any Grade 3 (hemoglobin <8 g/dL). If possible, maintain selinexor dose as long as patient is clinically stable, but if a dose reduction or interruption is desired, it should be done at the discretion of the treating physician and requires authorization from the principal investigator and consultation with the medical monitor if indicated.	
Other clinically significant selinexor-related adverse events	
Grade 1 or 2	Rule out other causes. Maintain dose. Start treatment and/or standard supportive care per institutional guidelines.
Grade 3	Rule out other causes. Interrupt selinexor until recovers to Grade 2 or baseline and reduce selinexor by 1 dose level. Isolated values of Grade 3 alkaline phosphatase do NOT require dose interruption. Determination of liver versus bone etiology should be made, and evaluation of gamma-glutamyl transferase, 5'-nucleotidase, or other liver enzymes should be performed.
Grade 4	Permanently discontinue selinexor

[a]For all Grade ≥3 hematologic or Grade 3 non-hematologic AEs that are NOT selinexor related, after consultation with the principal Investigator, selinexor, dosing may be maintained.

[b]For all selinexor-related AEs, if the below prescribed dose reductions/interruptions result in a stabilization of ≥4 weeks, a re-escalation may be considered at the discretion of the treating physician, and consultation with the medical monitor if indicated, and requires authorization from the principal investigator.
All dose modifications should be based on the worst preceding toxicity.
[c]For all Grade 4 non-hematologic AEs that are NOT selinexor related, selinexor should be permanently discontinued.
Note: When toxicities due to selinexor have returned to baseline levels or the patient has stabilized, the dose of selinexor may be re-escalated at the discretion of the treating physician, and consultation with the medical monitor if indicated, and requires authorization from the principal investigator.

7.2.1 Conditions Not Requiring Selinexor Dose Reduction

The following conditions are exceptions to the dose-modification guidelines and do not require a dose reduction or delay:

- Alopecia of any grade
- Electrolyte or serum analyte (e.g., urate) abnormalities that are reversible with standard interventions
- Isolated values of Grade ≥ 3 alkaline phosphatase. Determination of liver versus bone etiology should be made, and evaluation of gamma-glutamyl transferase, 5'-nucleotidase, or other liver enzymes should be performed.

In addition, selinexor dosing may be maintained in case of grade ≥ 3 hematological or non-hematological AEs not listed above (in Section 7.2) at the discretion of the enrolling physician and after consultation with the Sponsor-Investigator and the DSMC medical monitor.

7.3 Contraception

Patients should not become pregnant or father a child while on this study as selinexor can affect an unborn baby.

Female patients of childbearing potential must agree to use two methods of contraception (one highly effective and one effective) and have a negative serum pregnancy test at Screening

Male patients must use an effective barrier method of contraception if sexually active with a female of childbearing potential.

Highly effective methods of contraception include:

- Hormonal contraceptives (e.g., combined oral contraceptives, patch, vaginal ring, injectables, and implants)
- Intrauterine device or intrauterine system
- Vasectomy or tubal ligation

Effective methods include:

- Barrier methods of contraception (e.g., male condom, female condom, cervical cap, diaphragm, contraceptive sponge)

Notes:

- No barrier method by itself achieves a highly effective standard of contraception
- The proper use of diaphragm or cervical cap includes use of spermicide and is considered one barrier method.

- The cervical cap and contraceptive sponge are less effective in parous women.
- The use of spermicide alone is not considered a suitable barrier method for contraception.
- When used consistently and correctly, "double barrier" methods of contraception (e.g., male condom with diaphragm, male condom with cervical cap) can be used as an effective alternative to the highly effective contraception methods described above.
- Male and female condoms should not be used together as they can tear or become damaged.

Alternatively, the following fulfill the contraception requirements:

- A sexual partner who is surgically sterilized or post-menopausal.
- Total (true) abstinence (when this is in line with the preferred and usual lifestyle of the patient), is an acceptable method of contraception.

  NOTE: periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- The method of acceptable contraception must be explained to both male and female potential patients. In order to be eligible for the study, patients must agree to use the methods of birth control described above throughout the study and for 3 months following the last dose of study treatment at the time of consent for the study.

Breastfeeding
Women should not breastfeed while on this study.

8 STUDY CALENDAR

1 cycle = 28 days (± 3 days unless otherwise specified)

Some study visits may be conducted remotely when remote telehealth visits do not present increased risk to the participant and all necessary data for the trial can be collected. The method of telehealth should be documented in the participants' charts. Visits that require study-related imaging, research lab samples, and/or pathology should be conducted in person.

Activity/Assessment	**Screening**	**Baseline**	**Cycle 1**					**Cycles 2 to 6**		**Cycle 7** [27]	**Cycle 10 +**[27]	**End of Treatment Visit (EOT)**	**Survival Follow-up**[23] **(Every 3 mo.)**
	Day -28 to Day -1	**Day -7 to Day -1**	**D1**	**D3**[22]	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**	**D1**	**7 Days Post-Last Dose**	
			± 1 day					***± 2 days***		***± 2 days***	***± 3 days***	***± 2 days***	***± 14 days***
Informed consent[1]	X												
Eligibility criteria	X												
Demographics	X												
Medical history[2]	X												
Medication history[2]	X												
Screening symptom evaluation[3]	X												
Height[4]	X												
Weight	X		X					X		X	X	X	
Body Surface Area (BSA)[4]	X												
Body Mass Index (BMI)[4]	X		X					X		X	X	X	
Vital signs[5]	X		X					X		X	X	X	
Physical examination[6]	X		X					X		X	X	X	
DIPSS risk assessment[7]	X												
ECOG performance status[8]	X							X		X	X	X	
Optional Ophthalmic exam[9]	X		ACI									X	
12-lead ECG[10]	X		ACI									X	
CBC with differential[11]	X	X[11]			X	X	X	X	X	X	X	X	

Activity/Assessment	**Screening**	**Baseline**	**Cycle 1**					**Cycles 2 to 6**		**Cycle 7** [27]	**Cycle 10 +**[27]	**End of Treatment Visit (EOT)**	**Survival Follow-up**[23] **(Every 3 mo.)**
	Day -28 to Day -1	**Day -7 to Day -1**	**D1**	**D3**[22]	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**	**D1**	**7 Days Post-Last Dose**	
			± 1 day					***± 2 days***		***± 2 days***	***± 3 days***	***± 2 days***	***± 14 days***
Thyroid stimulating hormone (TSH)	X		ACI										
Complete serum chemistry[12]	X							X		X	X	X	
Limited serum chemistry[13]					X	X							
Coagulation tests[14]	X											X	
MRI (or CT abdomen)[15]		X						X[15]		X	X[15]	X[15]	
Chest radiograph[16]	X		ACI										
Serum pregnancy test[17]		X											
Bone marrow and peripheral blood for local pathology review[18]	X									X	X[18]	X	
Bone marrow and peripheral blood for central pathology review[18]	X									X		X	
Bone marrow aspirate for CD34 section and testing,	X									X		X	
Selinexor administration[19]			See administration table below										
Blood draw for PDn testing[20]								X[20]					
Adverse events			X										
Concomitant medication		X											
Nutritional consultation[21]	X		ACI										
Telephone contact[22,23]				X[22]									X[23]
MPN-SAF TSS[24]		X			X	X		X		X	X	X	
IWG-MRT assessment[25]		X						X[25]		X	X	X	
Peripheral blood sample for cytokine profile[26]		X						X[26]		X[26]		X	
Peripheral blood sample for JAK2 V617F, MPL and		X						X[26]		X[26]		X	

Activity/Assessment	Screening	Baseline	Cycle 1					Cycles 2 to 6		Cycle 7 [27]	Cycle 10 +[27]	End of Treatment Visit (EOT)	Survival Follow-up[23] (Every 3 mo.)
	Day -28 to Day -1	Day -7 to Day -1	D1	D3[22]	D8	D15	D22	D1	D15	D1	D1	7 Days Post-Last Dose	
			± *1 day*					± *2 days*		± *2 days*	± *3 days*	± *2 days*	± *14 days*
CALR exon 9 mutations allele burden[26]													

Procedure	Day 1 of each cycle	Day 8 of each cycle	Day 15 of each cycle	Day 22 of each cycle
Selinexor administration[19]	In clinic	In clinic for C1 At home for C2+	In clinic for C1 At home for C2+	At home for all cycles

ACI = As clinically indicated

1 Prior to the first study-specific measures.

2 Review of medical history and medication history, from the 12 months before screening, but incorporating, in full, prior lines of therapy regardless of date of occurrence. Including details of all therapies for myelofibrosis (start/stop dates, best response, disease progression during/after therapy, discontinuations due to intolerability/toxicity, etc.).

3 Using Screening Symptoms Form, see Appendix 6

4 Body Surface Area (BSA) and height will be collected at screening only. Screening height will be used to calculate BMI at all future visits.

5 To include blood pressure, pulse, temperature, and oxygen saturation.

6 All physical examinations (PE) must include spleen palpation. Symptom-directed limited PE can be performed outside of screening and EOT.

7 See Appendix 8

8 ECOG performance status assessments will be done on D1 of each Cycle, however the assessment for C1D1 may be done during Screening or pre-dose C1D1.

9 Full ophthalmic examination is optional at baseline and the final visit, and, if clinically indicated, during the study. Prior to dilation, best corrected visual -– acuity, slit lamp examination including tonometry, following dilation; fundoscopy and slit lamp to document lens clarity – if a cataract/lens opacity is seen during the examination, the cataract/lens opacity will be graded according to a Grade 1-4 system (see Appendix 2)

10 ECG will be performed during Screening (or pre-dose C1D1) and the EOT Visit and as clinically indicated throughout the study.

11 CBC with differential includes hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell (WBC) count, WBC differential, RBC count, lymphocytes, monocytes, neutrophils, band neutrophils, eosinophils, basophils, platelets. WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated. The baseline CBC need not be repeated if the screening CBC is performed within 7 days of C1D1.

12 Complete serum chemistry includes limited serum chemistry (as defined below) as well as, phosphate, magnesium, LDH, amylase, lipase, and uric acid. It is due at Screening or C1D1, then D1 of each subsequent Cycle, and EOT visit.

13 Limited chemistry includes sodium, potassium, chloride, calcium, bicarbonate, BUN, creatinine, glucose, total protein, albumin, ALT, AST, alkaline phosphatase, and total bilirubin. It is due at C1D8 and C1D15.

14 Includes prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT).

15 Spleen volume will be measured by MRI (or CT abdomen if MRI is contraindicated) at screening, at C4D1 after completion of 3 cycles and at C7D1 after completion of 6 cycles, allowing up to 4 weeks after cycle 7 D1. Additional MRIs will be performed for patients continuing on study treatment at cycle 10 D1, cycle 13 D1, cycle 19 D1, C25D1 to assess spleen volume. Imaging modality should remain consistent throughout study for each patient. Screening MRI should be completed ≤14 days prior to C1D1. An additional MRI will be performed at the End of Treatment for all patients including those who do not complete at least 6 cycles of study treatment unless death occurs. CT abdomen is acceptable if MRI is contraindicated for estimation of spleen volume.

16 Both posteroanterior and lateral films should be obtained at baseline. Note that this test does not need to be repeated if results are available from a test performed within 30 days prior to start of therapy. This test serves as a baseline in the event that patients develop any adverse events during the study.

17 For women of childbearing potential; negative serum β-hCG pregnancy test within 3 days of C1D1.

18 Bone marrow biopsies and aspirates will be obtained at ≤ 42 days before C1D1, C7D1 (± 7 days), and EOT. Additional bone marrow biopsies will be performed at C19D1 and then every 12 cycles after that until treatment discontinuation.

19 Study drug administration will take place on a weekly basis and will be done in clinic at C1D1, and on the first day of each subsequent cycle. Patients will be instructed to take their dose of study drug at home on D8, D15, and D22 of each subsequent cycle.

20 Blood draws for PDn analysis will be collected at either C2D1 or C3D1 pre-dose (within 10 minutes prior to dose) and 4 hours post-dose (± 10 min)

21 It is strongly recommended that patients be given nutritional consultation to discuss food recommendations and strategies for managing potential nausea and appetite changes experienced with selinexor. Nutritional consultation can be done by study nurse/clinician face-to-face or by the HCI Wellness Center or site equivalent or over the telephone. These consultations should be continued during study therapy as clinically indicated.

22 Telephone call (or visit) with patient to evaluate supportive care medications and adverse events, and to adjust supportive care as appropriate. The telephone contact with the patient must take place on Day 3 (± 1 day) following the C1D1 selinexor dosing. If available, survival follow up data may be collected from patient medical record review in lieu of a telephone call.

23 After study discontinuation, a telephone call will be made to the patient (or the patient's family) every 3 months to inquire about the patient's disease status, well-being, and information on any antineoplastic therapies utilized since discontinuation of selinexor study treatment until 24 months after initiation. If available, survival follow up data may be collected from patient medical record review in lieu of a telephone call

24 MPN SAF TSS evaluation will be performed at baseline and at each subsequent clinic visit (C1D8, C1D15, C2D1 and D1 of every subsequent cycle up to cycle 7 and every 3 cycles thereafter and EOT. Patients will be given copies of the evaluation form for time points which do not coincide with a study visit and will be asked to return the forms at their next visit.

25 Disease status and/or response by IWG-MRT will be assessed at C4D1, C7D1, C10D1, C13D1, C19D1, C25D1 and EOT.

26 Peripheral blood sample for cytokine profile, mutation allele burden will be collected at baseline, C4D1, C7D1, and at the EOT visit.

27 Starting with Cycle 7, patients only need to return to clinic every three months unless earlier follow up is necessary per treating physician's discretion.

9 STUDY PROCEDURES

Some study visits may be conducted remotely when remote telehealth visits do not present increased risk to the participant and all necessary data for the trial can be collected. The method of telehealth should be documented in the participants' charts. Visits that require study-related imaging, research lab samples, and/or pathology should be conducted in person.

9.1 Screening Evaluations

All screening procedures must be completed ≤ 28 days of C1D1. Screening procedures include:

- Informed consent
- Demographics
- Inclusion and exclusion criteria
- Review of medical history and medication history, from the 12 months before screening, but incorporating, in full, prior lines of therapy regardless of date of occurrence.
- Vital signs, height, weight, BSA, and BMI
- Physical examination including spleen size by palpation
- ECOG performance status (Appendix 1)
- DIPSS risk assessment (Appendix 8)
- Screening symptoms assessment (Appendix 6)
- Nutritional consult
- Optional Ophthalmologic exam (Appendix 2)
- Laboratory assessments:
  - CBC with differential (including reticulocytes if clinically indicated)
  - Complete serum chemistry to include:
    - CMP: sodium, potassium, chloride, carbon dioxide, alkaline phosphatase, AST, ALT, BUN, glucose, creatinine, calcium, total protein, albumin, total bilirubin (direct and indirect bilirubin must be obtained if total bilirubin is ≥ 1.5 × ULN)
    - Phosphorus, magnesium, uric acid, LDH, amylase, lipase
  - Thyroid stimulating hormone
  - Coagulation tests to include PT, INR, and aPTT
- Serum pregnancy test (for women of childbearing potential, see Section 7.4)
- 12-lead ECG
- Chest X-ray
- Bone marrow biopsy and aspiration ≤ 42 days before cycle one day one (can also be performed during the baseline visit). The study team will follow instructions in the lab manual for shipping tissue for central review.
- Standard of care procedures (e.g., blood count, serum chemistry) performed during this period should not be repeated and will be used for study purposes.

9.2 Baseline Evaluations

All baseline procedures must be completed ≤ 7 days of C1D1. Baseline procedures include:

- Laboratory assessments:
  - CBC with differential (including reticulocytes if clinically indicated) – does not need to be repeated if screening CBC test has been performed within that same timeframe.
  - Serum pregnancy test ≤ 72 hours prior to treatment initiation (for women of childbearing potential, see Section 7.4) – does not need to be repeated if screening pregnancy test has been performed within that same timeframe.
- MRI (or CT abdomen if MRI is contraindicated) ≤14 days of C1D1 for estimation of spleen volume. Imaging modality should remain consistent throughout study for each patient.
- IWG-MRT assessment.
- MF symptom burden evaluation using the MPN-SAF TSS questionnaire (Appendix 7)
- Peripheral blood samples for cytokine profiling
- Peripheral blood samples for evaluation of *JAK2*, *MPL,* and *CALR* mutant allele burden

9.3 On Treatment Evaluations

9.3.1 Cycle 1 Day 1

- Concomitant medication review
- Vital signs, weight, BMI
- Physical examination including spleen size by palpation
- Selinexor dosing (level 0)

9.3.2 Cycle 1 Day 3

- Telephone call (or visit) to evaluate and/or adjust supportive care medications and adverse events

9.3.3 Cycle 1 Days 8 and 15

- Adverse events assessment and concomitant medication review
- Laboratory assessments:
  - Limited serum chemistry to include a CMP as defined in Section 9.1
  - CBC with differential (including reticulocytes if clinically indicated)
- MF symptom burden evaluation using the MPN-SAF TSS questionnaire (Appendix 7)
- Selinexor dosing (patients will be instructed to take their C1D8, C1D15, and C1D22 selinexor dose at home)

9.3.4 Cycle 1 Day 22

- Selinexor dosing (at home)
- Laboratory assessments:
  - CBC with differential (including reticulocytes if clinically indicated)

9.3.5 Cycle 2 Day 1 – Cycle 6 Day 1

- Adverse events assessment and concomitant medication review
- Vital signs, weight, BMI
- Physical examination including spleen size by palpation
- ECOG performance status (see Appendix 1)
- Optional Ophthalmologic exam (Appendix 2) *as clinically indicated*
- MF symptom burden evaluation using the MPN-SAF TSS questionnaire (Appendix 7)
- Laboratory assessments:
  - CBC with differential (including reticulocytes if clinically indicated)
  - Complete serum chemistry as defined in Section 9.1
- Peripheral blood sample for PDn analysis pre-dose and 4 hours post-dose (± 10 min) *at either C2D1 or C3D1.*
- Spleen volume will be measured by MRI (or CT abdomen if MRI is contraindicated) at the completion of 3 cycles and 6 cycles, allowing up to 4 weeks after cycle 7 D1. Imaging modality should remain consistent throughout study for each patient. Screening MRI should be completed ≤14 days prior to C1D1.
- 12-lead ECG *as clinically indicated*
- Selinexor dosing

9.3.6 Day 8 and 22 of each cycle from Cycle 2 through Cycle 6 (not clinic visit days)

- Selinexor dosing (at home)

9.3.7 Day 15 of each cycle from Cycle 2 through Cycle 6

- Selinexor dosing (at home)
- Laboratory assessments:
  - CBC with differential (including reticulocytes if clinically indicated)

9.4 Cycle 7 Day 1

- Adverse events assessment and concomitant medication review
- Vital signs, weight, BMI
- Physical examination including spleen size by palpation
- ECOG performance status (see Appendix 1)
- Optional Ophthalmologic exam (Appendix 2) *as clinically indicated*
- Bone marrow biopsy and aspiration: local testing for pathology reporting takes sample priority. However, when possible bone marrow biopsy and aspirate samples should be taken for correlative tests per Section 14.1.1. The study team will follow instructions in the lab manual for shipping tissue for central review.
- MF symptom burden evaluation using the MPN-SAF TSS questionnaire (Appendix 7)
- Laboratory assessments:
  - CBC with differential (including reticulocytes if clinically indicated)
  - Complete serum chemistry as defined in Section 9.1

- MRI (or CT abdomen if MRI is contraindicated) for estimation of spleen volume. Imaging modality should remain consistent throughout study for each patient.
- IWG-MRT response assessment.
- 12-lead ECG *as clinically indicated*
- Selinexor dosing
- Peripheral blood samples for cytokine profiling
- Peripheral blood samples for evaluation of JAK2, MPL, and CALR mutant allele burden

Starting with cycle seven, patients will need to return to clinic every three months.

9.5 Cycle 10 + (every three months)

- Adverse events assessment and concomitant medication review
- Vital signs, weight, BMI
- Physical examination including spleen size by palpation
- ECOG performance status (see Appendix 1)
- Optional Ophthalmologic exam (Appendix 2) *as clinically indicated*
- MF symptom burden evaluation using the MPN-SAF TSS questionnaire (Appendix 7)
- Laboratory assessments:
  - CBC with differential (including reticulocytes if clinically indicated)
  - Complete serum chemistry as defined in Section 9.1
- 12-lead ECG *as clinically indicated*
- Selinexor dosing
- MRI (or CT abdomen if MRI is contraindicated) and IWG-MRT assessments will be performed for patients continuing on study treatment at cycle 10 D1, cycle 13 D1, and then every 6 cycles thereafter until treatment discontinuation to assess spleen volume and disease status.

9.6 End of Treatment Evaluations

The end of treatment visit will take place 7 days (+ 2 days) after the last dose of study drug and will include the following:

- Adverse events assessment and concomitant medication review
- Vital signs, weight, BMI
- Physical examination including spleen size by palpation
- ECOG performance status (see Appendix 1)
- Optional Ophthalmologic exam (Appendix 2)
- Laboratory assessments:
  - CBC with differential (including reticulocytes if clinically indicated)
  - Complete serum chemistry as defined in Section 9.1

  - Coagulation tests to include PT, INR, and aPTT
- MRI (or CT abdomen if MRI is contraindicated) for estimation of spleen. Imaging modality should remain consistent throughout study for each patient. MRI need not be repeated at the EOT visit if one has been performed ≤ 6 weeks
- IWG-MRT assessment
- 12-lead ECG
- MF symptom burden evaluation using the MPN-SAF TSS questionnaire (Appendix 7)
- Bone marrow biopsy and aspiration: local testing for pathology reporting takes sample priority. However, when possible bone marrow biopsy and aspirate samples should be taken for correlative tests per Section 14.1.1. The study team will follow instructions in the lab manual for shipping tissue for central review.
- Peripheral blood samples for cytokine profiling
- Peripheral blood samples for evaluation of JAK2, MPL, and CALR mutant allele burden

9.7 Survival Follow Up

After treatment discontinuation, a telephone call will be made to the patient (or the patient's family) every 3 months to inquire about the patient's myelofibrosis disease status, general health, and information on any subsequent therapies utilized since discontinuation of study treatment for 24 months since the initiation of treatment. If available, medical records may be reviewed in lieu of a telephone call to the patient.

10 CRITERIA FOR EVALUATION AND ENDPOINT

10.1 Safety

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, and clinical laboratory test results. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator.

Physical Examination
Complete and symptom-directed physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner).

Vital Signs
Vital signs (blood pressure, pulse rate, and temperature) will be obtained. Height, weight, and BMI will be obtained. ** Note: Height will be collected at the screening visit only. Screening height will be used to calculate BMI at all future visits.

Safety Laboratory Determinations
Laboratory evaluations will be performed as noted in the Study Calendar.

10.2 Efficacy

10.2.1 Radiographic Assessment of Efficacy

Volumetric measurements of the spleen will be obtained by MRI (or CT scans if MRI is contraindicated) as indicated on the Study Calendar.

A radiographic spleen response is defined per IWG-MRT criteria[26] as a ≥ 35% volume reduction in the spleen (by MRI or CT), regardless of what is reported with physical examination. See Appendix 5 for details.

10.2.2 Efficacy Based on Patient Reported Outcomes

Subjects will complete the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF, see Appendix 7) at baseline and at each subsequent clinic visit (C1D8, C1D15, D1 of each subsequent cycle, EOT). Their Total Symptoms Score (TSS) will be calculated at each time point.

A symptoms response is defined per IWG-MRT criteria[26] as a ≥ 50% reduction in the MPN-SAF TSS. See Appendix 5 for details.

10.2.3 Overall Response

Overall response criteria are based on the 2013 International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) Criteria for myelofibrosis (listed in Appendix 5).[26]

The overall response rate (CR, PR, CI) from after six cycles of treatment is defined in Appendix 5.

10.2.4 Overall Survival

Patients will be followed for 24 months from the initiation of study treatment. Overall survival will be assessed from initiation of study therapy to 24 months or death from any cause. Patients will be censored at 24 months.

10.3 Stopping Rules

10.3.1 Original Design

Up to 24 patients will be treated with the maximum tolerated dose of selinexor. Subjects will be enrolled in treatment cohorts of 8 subjects each and there will be a safety evaluation after each cohort has completed 1 cycle of treatment. Initially, 8 subjects will be enrolled in Cohort 1 and treated at a starting dose of 80 mg once weekly. The starting dose will be reduced by 1 dose level for all future patients after more than 2 patients in Cohort 1 require dose reduction for excess toxicity defined in section 7. Another set of up to 8 patients will be enrolled in Cohort 2. If more than 2 of 8 subjects in Cohort 2 (alone) require dose reduction for excess toxicity, then the starting dose will be reduced by 1 dose level in Cohort 3. Regardless of dose reduction, no cohort will ever contain more than 8 patients. The study will be discontinued if the starting dose for treatment cohorts is reduced more than 2 dose levels. Transition from dose level 1a to dose level -1 will not be considered a dose reduction.

10.3.2 **Version 7 Update**

After accrual of 12 patients, 7 patients required dose reduction to 40 mg once weekly. The decision was made to accrue the remaining patients at the lowest starting dose of 40 mg once weekly. Stopping rules do not apply after protocol version 7.

11 STATISTICAL CONSIDERATIONS

11.1 Statistical hypothesis

We hypothesize that treatment with selinexor will produce a clinically meaningful effect on the radiographic spleen response rate after six cycles of treatment.

11.2 Sample size determination

Response is defined as a 35% or greater reduction in spleen volume from baseline to after 6 cycles of treatment. A sample size of 18 evaluable subjects will provide 83% power at one-sided alpha = 0.05 to reject a response rate of 15% (the null hypothesis) using a one sample exact test for a binomial proportion provided the true response rate is 42%. The null hypothesis will be rejected if 6 or more out of 18 subjects respond. Patient who discontinued treatment and failed to receive 6 cycles of treatment would be considered as non-responders. The planned sample size is up to 24 to allow for up to a 25% dropout rate.

The alternative hypothesis is based on the known radiographic spleen response rate of ruxolitinib in MF patients and would indicate comparable efficacy.[17,18] The radiographic spleen response rate of the standard therapy for patients who fail or can't tolerate ruxolitinib is unknown, and 15% was chosen as a response rate below the minimum clinically meaningful response rate.

11.3 Statistical Analysis of Dose de-escalation

11.3.1 **Original Design**

Study was originally designed to enroll in treatment cohorts of 8 subjects each with a planned safety evaluation after each cohort has completed at least 3 cycles of treatment. Initially, up to 8 subjects would be enrolled in Cohort 1 and treated at a starting dose of 80 mg once weekly. The starting dose will be reduced by 1 dose level for all future patients after more than 2 patients in cohort 1 required dose reduction for excess toxicity as defined in section 7. Another set of up to 8 patients will be enrolled in Cohort 2. If more than 2 of 8 subjects in cohort 2 (alone) required dose reduction for excess toxicity, then the starting dose would be reduced by 1 dose level in Cohort 3.

To date of protocol version 7, 12 patients were dosed with selinexor in this study. The starting dose of selinexor was 80 mg weekly in the first six patients. 3 out 6 patients required dose reduction due to grade 2 weight loss after at least 1 cycle of treatment. The starting dose of selinexor was decreased to 60 mg weekly for subsequent patients. Additional six patients were enrolled at starting dose of 60 mg weekly. Of all the 12 patients, 7 patients required

dose reduction to 40 mg weekly. The starting dose of selinexor will be decreased to 40 mg weekly for the remaining 12 patients.

11.3.2 Dose Reduction

After the initial enrollment of 6 patients, 2 patients required dose reduction by at least 1 dose level (60 mg). As per the protocol, at that time all subsequent patients, including the remaining 2 patients in cohort 1, were started at 60 mg weekly.

11.3.2.1 Version 7 Update

After enrollment of 12 patients, 7 patients required dose reduction to 40 mg weekly. The decision was made to enroll the remaining 12 patients at the starting dose of 40 mg weekly.

11.4 Population for analyses

11.4.1 Evaluable for toxicity

The safety population includes all enrolled patients who received at least 1 dose of the study drug.

11.4.2 Evaluable for efficacy

The intent-to-treat population evaluable for efficacy includes all enrolled patients who received at least 1 dose of study medication.

11.5 Statistical Analyses

11.5.1 Primary endpoint

The primary endpoint is defined as the proportion of subjects with ≥ 35% reduction in spleen volume as measured by MRI or CT abdomen from baseline to after six cycles of treatment. A one sample test of binomial proportions will be performed at the one sided 0.05 significance level to test this hypothesis. The null hypothesis will be a response rate of 15% or less. Counts, proportions and 95% exact binomial confidence intervals (Clopper-Pearson) will be reported for each response category.

11.5.2 Secondary endpoints

Safety and tolerability

Adverse events, serious adverse events

AEs will be coded using the MedDRA dictionary and displayed in tables and listings using System/Organ/Class (SOC) and Preferred Term. AEs will be summarized by patient incidence rates. In all tabulations, a patient may contribute only once to the count for a given AE preferred term. The number and percentage of patients AEs will be summarized along with the number and percentage of AEs assessed by the Investigator as at least possibly related to treatment. The number and percentage of patients with any Grade ≥ 3 AEs will be tabulated in the same manner. In the event a patient experiences repeated episodes of the same AE, the event with the highest severity and/or strongest causal relationship to study treatment will be used for purposes of tabulations. Serious AEs (SAEs) will also be tabulated.

All AEs will be listed in patient data listings. Separate by-patient listings will be provided for the following: patient deaths, SAEs, and AEs leading to withdrawal.

No formal hypothesis-testing analysis of AE incidence rates will be performed.

Laboratory Data

The actual value and change from baseline for each on-study evaluation will be summarized for each clinical laboratory parameter, including hematology and clinical chemistry, by arm, and for all study patients combined. In the event of repeat values, the last non-missing value per study day/time will be used.

Severity of select clinical lab measures will be determined using CTCAE criteria (i.e., those measures that have a corresponding CTCAE grade classification). Labs with CTCAE Grades ≥ 3 will be presented in a data listing. Shift tables that present changes from baseline to worst on-study values relative to CTCAE classification ranges will be produced.

Vital signs and physical examinations

The actual value and change from baseline to each on-study evaluation will be summarized for vital signs for all study patients combined. By-patient listings of vital sign measurements will be presented in data listings.

Physical examination results at screening will be summarized; all other abnormal physical examination data will be recorded. All examination findings will be presented in a data listing.

Additional Efficacy Analysis

Change and percentage change in radiographic spleen volume, as well as radiographic spleen response rates, will be summarized using descriptive statistics. The mean, range, standard deviation and 95% confidence interval will be reported for change and percent change in spleen volume.

The proportion of patients with ≥ 50% reduction of total symptoms score will be summarized by observed proportion and exact 95% binomial confidence interval.

The number and proportion of patients with responses per the IWG-MRT criteria will be tabulated and an exact 95% binomial confidence interval for response will be calculated. Overall survival from initiation of therapy to 24 months will be estimated using Kaplan-Meier methods and associated 95% confidence intervals.

11.5.3 **Exploratory endpoints**

A statistical plan will be determined for exploratory endpoints prior to the initiation of the statistical evaluation.

12 REGISTRATION GUIDELINES

Study related screening procedures can only begin once the patient has signed a consent form.

Patients must meet all of the eligibility requirements listed in Section 5 prior to registration.

Patients must be registered before receiving any study treatment and must begin treatment as soon as logistically possible after registration.

To register eligible patients on study, complete a Clinical Trials Office Patient Registration Form and submit to CTORegistrations@hci.utah.edu or multisiteregistrations@hci.utah.edu.

13 DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) are a set of (electronic or paper) forms for each patient that provides a record of the data generated according to the protocol. CRFs should be created prior to the study being initiated and updated (if applicable) when amendments to the protocol are IRB approved. These forms will be completed on an on-going basis during the study. The medical records will be source of verification of the data. During the study, the CRFs will be monitored for completeness, accuracy, legibility and attention to detail by a member of the Research Compliance Office. The CRFs will be completed by the Investigator or a member of the study team as listed on the Delegation of Duties Log. The data will be reviewed no less than annually by the Data and Safety Monitoring Committee. The Investigator will allow the Data and Safety Monitoring Committee or Research Compliance Office personnel access to the patient source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose. The Investigator further agrees to assist the site visitors in their activities.

Data capture should be restricted to endpoints and relevant patient information required for planned manuscripts.

14 CORRELATIVE STUDIES

14.1.1 Bone Marrow

Bone marrow aspirates (5 mL) will be collected at the time points indicated on the Schedule of Events of for CD34 selection and testing.

Bone marrow aspirates and biopsies will be collected at the time points indicated on the Schedule of Events for local and central pathology review.

Instructions for processing and shipping will be detailed in the lab manual.

14.1.2 Blood

Peripheral blood (20 mL) will be collected at the time points indicated on the Schedule of Events for pharmacodynamics studies.

Peripheral blood (34 mL) will be collected at the time points indicated on the Schedule of Events for analysis that may include but are not limited to plasma proteins and cytokines as well as for evaluation of changes in mutant allele burden of *JAK2*, *MPL,* and *CALR* RNA.

Peripheral blood will be collected at the time points indicated on the Schedule of Events for local and central pathology review.

Instructions for processing and shipping will be detailed in the lab manual.

15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Informed consent

Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB-approved version.

15.2 Human Subjects Protections

15.2.1 Participation of Children

Patients must be at least 18 years of age to participate.

15.2.2 Participation of Subjects Unable To Give Consent

Patients must be able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

15.3 Institutional Review

This study will be approved by the Institutional Review Board of the University of Utah.

15.4 Data and Safety Monitoring Plan

A Data and Safety Monitoring Committee (DSMC) is established at Huntsman Cancer Institute (HCI) to ensure the well-being of patients enrolled on Investigator Initiated Trials that do not have an outside monitoring review. The roles and responsibilities of the DSMC are set forth in the NCI-approved Data and Safety Monitoring (DSM) plan. The activities of the committee include reviewing adverse events (including SAEs), deviations, important medical events, significant revisions or amendments to the protocol, and approving cohort/dose escalations. If the DSMC and/or the PI have concerns about unexpected safety issues, the study will be stopped and will not be resumed until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

This is a Phase II, multisite study classified as high risk per the NCI-approved DSM plan.

Each high-risk study may be assigned a physician member of the DSMC as medical monitor, or in rare cases, an external medical monitor. The medical monitor will be notified of all serious adverse events (SAEs). Specific notifications will also be issued when a dose-limiting toxicity is encountered and when the MTD dose is defined. Approval by the medical monitor is required for all dose escalations. All serious adverse events (SAEs) occurring in patients treated at HCI or its affiliates will also be reviewed by the full DSMC monthly. The full committee will also review all toxicities for patients on treatment and within 30 days of their last treatment on a quarterly basis.

Each high-risk study will be assigned a dedicated research compliance officer who will monitor the trial. High-risk trials will be monitored by RCO personnel after the first patient is enrolled and every three months thereafter during active enrollment. The RCO monitor will

review the study status and summarize enrollment, toxicities, SAEs, dose escalation, statistical endpoints (e.g., stopping rules), deviations, etc. for the full DSMC membership at the regularly scheduled meetings. Amendments that increase risk, change dosing, or impact study objectives will be reviewed by the DSMC and approved by the PRMC and IRB. High-risk trials will be formally reviewed by the DSMC after the first patient is enrolled and then quarterly thereafter.

An initial audit of high-risk studies will be conducted by the RCO approximately one year after enrollment begins and annually thereafter. Audits of high-risk studies may be conducted more frequently as requested by the DSMC, IRB, PRMC, RCO management, or the PI.

15.5 Adverse Events and Serious Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for AE and SAE reporting.

15.5.1 Adverse Events (AEs)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Collection of adverse events will begin after the subject's first dose and end 30 days after the last dose of study drug or until a new cancer treatment is initiated, whichever happens soonest.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit or phone contact during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade based on CTCAE v.5.0 (grade 1-5)
2. Its relationship to the study drug(s) (definite, probable, possible, unlikely, not related)
3. Its duration (start and end dates or if continuing at final exam)
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. Whether it constitutes an SAE

All adverse events will be treated appropriately. Such treatment may include changes in study drug treatment as listed in the dose modification section of this protocol (see section 8

for guidance). Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about selinexor are described in the Drug Information (Section 3.1) and in the investigator brochure (Selinexor IB v.11). This information will be included in the patient informed consent and will be discussed with the patient during the study as needed.

All adverse events will be immediately recorded in the patient research chart.

15.5.2 Adverse Events of Special Interest (AESI)

AESIs for selinexor include cataracts and acute cerebellar syndrome. All cases of cerebellar toxicity, Grade 3 or higher must be reported as described below in a manner similar to SAEs (section 15.6).

All cases of Grade 3 or higher cerebellar toxicities occurring in patients enrolled in the study from the informed consent signature and up to 30 days after the last drug administration, or after if related to study drug, must be immediately reported as SAE (even if not meeting the definition of a SAE) to the drug supplier, within 24 hours of first knowledge of the event, following reporting rules for SAE in section 15.6).

15.5.3 Reporting of Cataracts

The drug supplier is closely monitoring the occurrence of cataracts during treatment with selinexor as adverse events of special interest. Optional ophthalmic examinations are planned on regular basis to identify cataracts or worsening of existing cataracts. Any cataracts or worsening of existing cataracts has to be reported as an AE irrespectively of grade.

15.5.4 Serious Adverse Event (SAE)

A serious adverse event is defined as any untoward event that is:

- Fatal;
- Life-threatening;
- Results in persistent or significant disability/incapacity;
- Medically significant;
- Causes a congenital abnormality or birth defect;
- Requires or prolongs inpatient hospitalization.

Investigator judgment must be used to assess an event as medically significant. The event may not be life-threatening or cause disability but may jeopardize the subject and require intervention to prevent the other SAE outcomes.

The following situations should not be reported as an SAE:

- Hospital admission not associated with a precipitating AE such as:
    - Treatment for a preexisting condition not associated with a new AE or the worsening of a preexisting condition;
    - Admission for social or administrative reasons;
    - Optional admission or elective surgery;
    - Observation;
    - Preplanned treatments or surgical procedures as noted at baseline;
    - Admission for the administration of blood products.

15.6 SAE Reporting Requirements

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All serious adverse events should be reported as soon as possible but no later than one business day after the Investigator becomes aware. All SAEs must be reported via the HCI CTMS (OnCore) and submitted to HCI-RCO@utah.edu and Karyopharm. The HCI Clinical Site Monitor will in turn, submit the report to the Medical Monitor. The RCO will summarize and present all reported SAEs according to the Data and Safety Monitoring Plan at the monthly DSMC meeting.

At a minimum, initial SAE reports must include a description of the event, assessment of event causality, event grade, and the expectedness of the event. Although the Investigator may not know all the information at the time of the event, the available information should be reported. An SAE follow-up may be submitted at a later date once more information is known. It is required that follow-up reports be submitted until the SAE is resolved.

Follow-Up Information
It is recommended that follow-up reports be submitted as new information becomes available, however, a follow-up report should be submitted within 3 days of knowledge of event resolution. Follow-up information will be added to the SAE in OnCore and submitted to the DSMC via RCO.

15.6.1 FDA Notifications

Per 21 CRF 312.32 adverse events and serious adverse events will be reported on a MedWatch 3500A form to the FDA. Reportable events will be reported by the RCO according to the following guidelines:

MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic (Section A) and suspect medication information (Section C & D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)

- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication
- Expectedness of the event (i.e., expected or unexpected event).

FDA Reporting Timelines:

- 7 Calendar Day Report:

  Any event that is fatal or life-threatening, unexpected, and definitely, probably or possibly related to study medication will be reported to the FDA by telephone or fax within seven calendar days of first learning of the event.

- 15 Calendar Day Report:

  Any event that is serious, unexpected, and definitely, probably or possibly related to study medication will be reported to the FDA in an IND safety report within 15 calendar days of first learning of the event.

  In accordance with 21 CFR 312.32, an Analysis of Similar Events should be included in the IND Safety Report. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

  FDA fax number for IND Safety Reports:

  Fax: 1 (800) FDA 0178

15.6.2 **IRB Notification**

The University of Utah IRB requires any unanticipated problems that may increase the risk to research participants be promptly reported. All study-therapy related, unexpected adverse events whose nature, severity, or frequency is not consistent with either:

- The unknown or foreseeable risk of adverse events that are described in the protocol related-documents, such as the IRB-approved research protocol, applicable investigator brochure, the current IRB-approved informed consent document, and/or other relevant sources of information, such as product labeling and package inserts; or
- The expected natural progression of any underlying disease or condition of the subject(s) experiencing the adverse event.

Adverse events meeting this criterion must be promptly reported to the IRB within 10 business days of awareness.

15.6.3 **Drug Manufacturer Notifications**

All SAEs must be reported to Karyopharm Pharmacovigilance within 24 hours of awareness. Reports must be emailed or faxed to:

Pharmacovigilance Department
Karyopharm Therapeutics Inc.
Email: pharmacovigilance@karyopharm.com
Fax: +1-617-334-7617

Any SAE observed after the 30-day follow-up period should only be reported to Karyopharm if the Investigator suspects that the SAE has causal relationship to study treatment

In addition to reporting SAEs as described above, the PI will report all AEs (including non-serious events) to Karyopharm Pharmacovigilance twice per year in the form of line-listings. Karyopharm will supply the cut-off dates. The line listings will contain the following information: study ID, unique subject ID, adverse event term, serious event (yes or no), onset date (complete or partial), end date (complete or partial), action taken with selinexor, causality to selinexor, event ongoing (yes or no), outcome of AE, severity CTCAE Grade (1-5), subject dosed with selinexor (yes or no), date of first dose of selinexor, preferred term, system organ class (optional).

For multisite studies the HCI DSMC will notify all participating sites of all unexpected and related SAEs via the Research Compliance Office. The RCO will also notify all investigators at remote clinical sites participating in a multisite trial of any other safety update, including manufacturer's reports and updates to the investigator's brochure.

15.7 Reporting of Pregnancy

Although pregnancy is not considered an adverse event, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject, including the pregnancy of a male subjects' female partner as an SAE. Pregnancies or lactation that occurs during the course of the trial or within 90 days of the last administration of selinexor or starting another new anticancer therapy, whichever is earlier, must be reported to the DSMC, IRB, FDA, and the drug manufacturer as applicable. All subjects and female partners who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events.

15.8 Overdose

An overdose is a deliberate or accidental administration of any Karyopharm treatment to a study patient, at a dose greater than that which was assigned to that patient per the study protocol. If an overdose occurs, Karyopharm should be notified immediately, and the patient should be observed closely for AEs. Resulting symptoms should be treated, as appropriate, and the incident of overdose and related AEs and/or treatment should be recorded. Overdose is to be reported on an FDA 3500A MedWatch form to the DSMC and Karyopharm pharmacovigilance regardless of whether or not an AE or SAE has occurred due to the overdose. If the overdose is associated with an SAE, the SAE report form must be submitted to the DSMC and Karyopharm pharmacovigilance within 24 hours of awareness. If there is no AE or SAE, the overdose report must be submitted within 24 hours of awareness. In all cases, the IRB and the FDA must be notified as applicable.

15.9 Abuse, Misuse, or Medication Error

Abuse is the persistent or sporadic, intentional excessive use of the study drug which is accompanied by harmful physical or psychological effects.

A medication error is any preventable incident that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care

professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including prescribing; order communication; and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.'

All occurrences of abuse, misuse or medication error with Karyopharm drug are to be reported on an FDA 3500A MedWatch form to the DSMC and Karyopharm pharmacovigilance regardless of whether or not an AE or SAE has occurred due to the abuse, misuse or medication error. If the abuse, misuse or medication error is associated with an SAE, the SAE report form must be submitted to the DSMC and Karyopharm pharmacovigilance within 24 hours of awareness. If there is no AE or SAE, the report must be submitted as soon as possible. In all cases, the IRB and the FDA must be notified as applicable.

15.10 Occupational Exposure

Occupational exposure is the exposure to a study drug as a result of one's professional or non-professional occupation.

All occurrences of occupational exposure with Karyopharm drug are to be reported on an FDA 3500A MedWatch form to the DSMC and Karyopharm pharmacovigilance regardless of whether or not an AE or SAE has occurred due to the occupational exposure. If the occupational exposure is associated with an SAE, the SAE report form must be submitted to the DSMC and Karyopharm pharmacovigilance within 24 hours of awareness. If there is no AE or SAE, the report must be submitted as soon as possible. In all cases, the IRB and the FDA must be notified as applicable.

15.11 Protocol Amendments

Any amendments or administrative changes in the research protocol during the period, for which the IRB approval has already been given, will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all subjects included in the trial.

Any amendments to the protocol that significantly affect the safety of subjects, scope of the investigation, or the scientific quality of the study are required to submit the amendment for FDA review.

15.12 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The IRB requires the **prompt reporting** of protocol deviations which are:

- Exceptions to eligibility criteria.
- Intended to eliminate apparent immediate hazard to a research participant or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or
- Possible serious or continued noncompliance

15.13 FDA Annual Reporting

An annual progress report will be submitted to the FDA within 60 days of the anniversary of the date that the IND went into effect. (21 CFR 312.33).

15.14 Clinical Trials Data Bank

The study will be registered on **http://clinicaltrials.gov** and the NCI CTRP (Clinical Trials Reporting Program) by the Clinical Trials Office.

15.15 Record Keeping

Per 21 CFR 312.57, the Investigator records shall be maintained for a period of 2 years following the date a marketing application is approved; or, if no application is filed or the application is not approved, until 2 years after the investigation is discontinued and the FDA is notified.

16 APPENDICES

16.1 Appendix 1 - Eastern Cooperative Oncology Group Performance Status Criteria (ECOG) & Karnofsky Performance Scale Index (KPS) equivalency

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

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2. Karnofsky D, Burchenal J, The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. *Evaluation of Chemotherapeutic Agents*. New York, NY: Columbia University Press; 1949:191–205.

16.2 Appendix 2 - Ophthalmic Exam

An ophthalmic examination by an optometrist or ophthalmologist is optional at screening and if clinically indicated during the study (e.g., monitoring of pre-existing cataracts, visual disturbances).

The optional examination is to include the following:

Prior to dilation:

- Best corrected visual acuity
- Slit lamp examination
- Tonometry

Following dilation:

- Fundoscopy
- Slit lamp examination to document lens clarity

If a cataract/lens opacity is seen during the examination, the cataract/lens opacity will be graded according to a Grade 1-4 system (modified from Optometric Clinical Practice Guideline: Care of the Adult Patient with Cataracts: available on the American Optometric Association website: www.aoa.org).

Grading of Cataracts*				
Cataract Type	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Nuclear Yellowing and sclerosis of the lens nucleus	Mild	Moderate	Pronounced	Severe
Cortical Measured as aggregate percentage of the intrapupillary space occupied by the opacity	Obscures 10% of intrapupillary space	Obscures 10% - 50% of intra-pupillary space	Obscures 50% - 90% of intra-pupillary space	Obscures >90% of intrapupillary space
Posterior subcapsular Measured as the aggregate percentage of the posterior capsular area occupied by the opacity	Obscures 10% of the area of the posterior capsule	Obscures 30% of the area of the posterior capsule	Obscures 50% of the area of the posterior capsule	Obscures >50% of the area of the posterior capsule
*Designation of cataract severity that falls between grade levels can be made by addition of a + sign (e.g., 1+, 2+). Grading of cataracts is usually done when pupil is dilated.				

16.3 Appendix 3 - NCCN Clinical Practice Guidelines in Oncology: Antiemesis

Available at http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf.

Available at http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf.

16.4 Appendix 4 - NCCN Clinical Practice Guidelines in Oncology: Anorexia/Cachexia

16.5 Appendix 5 - International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) Criteria for myelofibrosis

Response Categories	Required Criteria (for All Response Categories, Benefit Must Last for ≥ 12 Weeks to Qualify as a Response)
CR	Bone marrow[1]: Age-adjusted normocellularity; <5% blasts; ≤Grade 1 MF[2] and
	Peripheral blood: Hemoglobin ≥ 100 g/L and < UNL; neutrophil count ≥ 1 × 10^9/L and < UNL;
	Platelet count ≥ 100 × 10^9/L and < UNL; < 2% immature myeloid cells[3] and
	Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
PR	Peripheral blood: Hemoglobin ≥ 100 g/L and < UNL; neutrophil count ≥ 1 × 10^9/L and < UNL; platelet count ≥ 100 × 10^9/L and < UNL; < 2% immature myeloid cells[3] and
	Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH or
	Bone marrow:[1] Age-adjusted normocellularity; < 5% blasts; ≤ Grade 1 MF[2]; and peripheral blood: hemoglobin ≥ 85 g/L but < 100 g/L and < UNL; neutrophil count ≥ 1 × 10^9/L and < UNL; platelet count ≥ 50 × 10^9/L but < 100 × 10^9/L and < UNL; < 2% immature myeloid cells[3] and
	Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
CI	The achievement of anemia, spleen or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia[4]
Anemia Response	Transfusion-independent patients: a ≥ 20 g/L increase in hemoglobin level[5]
	Transfusion-dependent patients: becoming transfusion-independent[6]
Spleen Response[7]	A baseline splenomegaly that is palpable at 5-10 cm, below the LCM, becomes not palpable[8] or
	A baseline splenomegaly that is palpable at > 10 cm, below the LCM, decreases by ≥ 50%[8]
	A baseline splenomegaly that is palpable at < 5 cm, below the LCM, is not eligible for spleen response
	A spleen response requires confirmation by MRI or CT showing ≥ 35% spleen volume reduction
Symptoms response	A ≥ 50% reduction in the MPN-SAF TSS[9]
Progressive disease[10]	Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM or
	A ≥ 100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm or
	A 50% increase in palpable distance, below LCM, for baseline splenomegaly of > 10 cm or
	Leukemic transformation confirmed by a bone marrow blast count of ≥ 20% or A peripheral blood blast content of ≥ 20% associated with an absolute blast count of ≥ 1 × 10^9/L that lasts for at least 2 weeks
Stable Disease	Belonging to none of the above-listed response categories
Relapse	No longer meeting criteria for at least CI after achieving CR, PR, or CI, or
	Loss of anemia response persisting for at least 1 month or
	Loss of spleen response persisting for at least 1 month

Abbreviations: LCM = left costal margin; MF = myelofibrosis; MPN-SAF TSS = Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; MRI = magnetic resonance imaging; PR = partial response; PRBC = packed red blood cell; UNL = upper normal limit.

1. Baseline and post-treatment bone marrow slides are to be interpreted at 1 sitting by a central review process. Cytogenetic and molecular responses are not required for CR assignment.
2. Grading of MF is according to the European classification.[a] It is underscored that the consensus definition of a CR bone marrow is to be used only in those patients in which all other criteria are met, including resolution of leukoerythroblastosis. It should also be noted that it was a particularly difficult task for the working group to reach a consensus regarding what represents a complete histologic remission.
3 Immature myeloid cells constitute blasts + promyelocytes + myelocytes + metamyelocytes + nucleated red blood cells. In splenectomized patients, < 5% immature myeloid cells is allowed.
4. See above for definitions of anemia response, spleen response, and progressive disease. Increase in severity of anemia constitutes the occurrence of new transfusion dependency or a ≥ 20 g/L decrease in hemoglobin level from pretreatment baseline that lasts for at least 12 weeks. Increase in severity of thrombocytopenia or neutropenia is defined as a 2-grade decline, from pretreatment baseline, in platelet count or absolute neutrophil count, according to the CTCAE version 5.0. In addition, assignment to CI requires a minimum platelet count of ≥ 25,000 × 10^9/L and absolute neutrophil count of ≥ 0.5 × 10^9/L.
5. Applicable only to patients with baseline hemoglobin of < 100 g/L. In patients not meeting the strict criteria for transfusion dependency at the time of study enrollment (see as follows), but have received transfusions within the previous month, the pretransfusion hemoglobin level should be used as the baseline.
6. Transfusion dependency before study enrollment is defined as transfusions of at least 6 units of PRBCs, in the 12 weeks prior to study enrollment, for a hemoglobin level of < 85 g/L, in the absence of bleeding or treatment-induced anemia. In addition, the most recent transfusion episode must have occurred in the 28 days prior to study enrollment. Response in transfusion-dependent patients requires absence of any PRBC transfusions during any consecutive "rolling" 12-week interval during the treatment phase, capped by a hemoglobin level of ≥ 85 g/L.
7. In splenectomized patients, palpable hepatomegaly is substituted with the same measurement strategy.
8. Spleen or liver responses must be confirmed by imaging studies where a ≥ 35% reduction in spleen volume, as assessed by MRI or CT, is required. Furthermore, a ≥ 35% volume reduction in the spleen or liver, by MRI or CT, constitutes a response regardless of what is reported with physical examination.
9. Symptoms are evaluated by the MPN-SAF TSS. The MPN-SAF TSS is assessed by the patients themselves and this includes fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers. Scoring is from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be) for each item. The MPN-SAF TSS is the summation of all the individual scores (0-100 scale). Symptoms response requires ≥ 50% reduction in the MPN-SAF TSS.
10. Progressive disease assignment for splenomegaly requires confirmation by MRI or CT showing a ≥ 25% increase in spleen volume from baseline. Baseline values for both physical examination and imaging studies refer to pretreatment baseline and not to post-treatment measurement.

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16.6 Appendix 6 - Screening Symptoms Form

Patient Initials: _____ ***Patient Study ID:*** _____

Please fill out all questions reflecting how these symptoms affected you at their worst moment over the past 7 days. Please give the answer that best reflects your opinion.

Symptom	1 to 10 (0 if absent) ranking 1 is most favorable and 10 least favorable
1. During the past 7 days, how severe were your worst night sweats (or feeling hot or flushed) due to MF?	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
2. During the past 7 days, how severe was your worst itchiness due to MF?	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
3. During the past 7 days, how severe was your worst abdominal discomfort (feel uncomfortable, pressure or bloating) due to MF?	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
4. During the past 7 days, how severe was your worst pain under the ribs on the left side due to MF?	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
5. During the past 7 days, how severe was your worst fullness (early satiety) you had after beginning to eat, due to MF?	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
6. During the past 7 days, how severe was your worst bone or muscle pain due to MF (not joint or arthritis pain)?	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
7. During the past 7 days, what was the worst degree of inactivity (work or social activities) you had due to MF (not joint or arthritis pain)?	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

For Investigators/site staff:

Please confirm the criterion based on assessment of subject's active symptoms of myelofibrosis.

Criterion Review	Confirmation
A symptoms score of at least 5 on at least 1 of the symptoms	☐Yes ☐ No
A symptoms score of 3 or greater on at least 2 of the symptoms	☐Yes ☐ No

Investigator signature: _____ **Date:** _____

16.7 Appendix 7 - Myeloproliferative Neoplasms Symptom Assessment Form- Total Symptom Score (MPN-SAF TSS) Form

Patient Initials: _____ ***Patient Study ID:*** _____

Study Time Point (cycle/day): _____ ***Date:*** _____

Please fill out all questions by circling the one number that best describes your symptoms at their worst moment. Please give the answer that best reflects your opinion.

Symptom	**1 to 10 (0 if absent) ranking 1 is most favorable and 10 least favorable**
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your **WORST** level of fatigue during **past 24 hours**	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Circle the one number that describes how, during the PAST WEEK how much difficulty you have had with each of the following symptoms	
Filling up quickly when you eat (Early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration (compared to prior to my MPD)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Numbness/ Tingling (in my hands and feet)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse, not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss **(last 6 months)**	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

What is your Overall Quality of Life?	(As good as it can be) 0 1 2 3 4 5 6 7 8 9 10 (As bad as it can be)

Patient signature: _____ **Date:** _____

16.8 Appendix 8 – Primary Myelofibrosis Dynamic International Prognostic Scoring System (DIPSS)

The DIPSS score assigns points for the following five variables:

Prognostic Variable	Point per Factor
Age > 65 years	1
Hemoglobin < 10 g/dL	2
White Blood Cells > 25 K/uL	1
Circulating Blasts ≥ 1%	1
Constitutional Symptoms*	1

Total risk score	Risk category	Median overall survival
0	Low	not reached
1 to 2	Intermediate-1	14.2 years
3 to 4	Intermediate-2	4 years
5 to 6	High	1.5 years

- *Constitutional symptoms include:
  - Weight loss>10% of the baseline value in the year preceding PMF diagnosis
  - Unexplained fever or excessive sweats persisting for more than one month.

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