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Title: A Phase I/II Trial of Eltanexor (KPT-8602) with Inqovi (Decitabine-Cedazuridine) in High-Risk Myelodysplastic Syndromes

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Drug Name:	Eltanexor (KPT-8602)	Inqovi® (decitabine-cedazuridine)
IND Number:	163958	
Sponsor:	Center for Cancer Research	
Manufacturer:	Karyopharm Therapeutics, Inc.	Generic
Supplier:	Karyopharm Therapeutics, Inc.	CC Pharmacy

PRÉCIS

Background:

- The myelodysplastic syndromes (MDS) are a group of clonal bone marrow neoplasms characterized by ineffective hematopoiesis, cytopenia, and high risk of transformation to acute myeloid leukemia (AML).
- The median survival of patients with newly-diagnosed higher-risk MDS (HR-MDS) according to the Revised International Prognostic Scoring System (IPSS-R) is 1.5 years.
- Hypomethylating agents (HMAs), such as azacitidine and decitabine, are the standard of care therapy for HR-MDS. However, less than half of patients respond to HMAs, and even the best responses are transient and non-curative.
- The only curative treatment for patients with MDS is allogeneic hematopoietic stem cell transplantation (HSCT); however only a small portion are eligible for transplant.
- More effective therapies are needed for patients with HR-MDS.
- A promising approach for improving HMA efficacy in the treatment of MDS is by exploiting therapeutic synergism in combinatorial approaches.
- Inqovi (decitabine-cedazuridine) is an oral formulation of decitabine plus cytidine deaminase inhibitor that was recently FDA-approved for MDS, based on a similar safety and efficacy profile to decitabine for injection.
- KPT-8602 (eltanexor) is an orally-available, second-generation selective inhibitor of nuclear export (SINE) that covalently binds to exportin 1 (XPO1).
- XPO1 is a protein that mediates the nuclear export of molecules from the nucleus to the cytoplasm of the cell. Among affected molecules are tumor suppressor genes, mRNAs encoding oncogenes (including c-MYC), and newly assembled ribosomal subunits.
- By interfering with c-MYC translation, KPT-8602 may diminish rebound methylation after decitabine cessation and improve treatment responses in patients with MDS.
- Preliminary reports from a Phase 1/2 trial of KPT-8602 monotherapy in patients with higher-risk MDS who have failed HMAs show anti-tumor activity and an acceptable toxicity profile.
- Sequential addition of KPT-8602 to Inqovi may improve treatment responses in patients with MDS by acting synergistically to inhibit further DNA methylation.

Objective:

- Phase I: To determine the recommended phase 2 dose (RP2D) of KPT-8602 in combination with Inqovi in adult participants with with higher-risk MDS
- Phase II: To determine overall response rate (ORR) of KPT-8602 in combination with Inqovi in adult participants with with higher- risk MDS

Eligibility:

- Participants must have histologically or cytologically confirmed MDS according to 2016 WHO criteria (1), and for both Phase I and II:
    - have HR-MDS (IPSS-R > 3.5) with inadequate response to hypomethylating agent (HMA) therapy [(received ≥ 4 cycles of the standard dose (35 mg decitabine and 100 mg cedazuridine) without prior dose-reductions, with failure to achieve at least a PR or experienced disease progression prior to completing 4 cycles**)**
- Age ≥ 18 years

- ECOG performance status ≤ 2 (KPS ≥ 60)

Design:

- Participants with HR-MDS will be enrolled in both Phase I and II.
- Participants will be treated with Inqovi at a fixed dose of 1 tablet (35 mg decitabine and 100 mg cedazuridine) daily on Days 1-5 of each 28-day cycle, followed by KPT-8602 at escalating doses (Phase I) or the RP2D (Phase II).
- In Phase I, KPT-8602 will be dose-escalated following a standard 3+3 design, with a starting dose level of 10 mg for 10 days (staggered) within a cycle. If tolerated, the dose will be escalated to 14 days per cycle, or dose de-escalated to 5 mg at 14 or 10 days.
- This study will be done at the NIH Clincal Center with an enrollment of up to 80 planned participants.

TABLE OF CONTENTS

STATEMENT OF COMPLIANCE

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

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

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

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

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- Phase I: To determine the recommended phase 2 dose (RP2D) of KPT-8602 in combination with Inqovi in adult participants with with higher-risk MDS
- Phase II: To determine the overall response rate (ORR) of KPT-8602 in combination with Inqovi in adult participants with higher-risk MDS

1.1.2 Secondary Objectives

- Phase I: To characterize the pharmacokinetic (PK) properties of KPT-8602 in combination with Inqovi (decitabine-cedazuridine) in MDS participants
- Phase II: To further evaluate the PK properties and safety of KPT-8602 in combination with Inqovi (decitabine-cedazuridine) in MDS participants

1.1.3 Exploratory Objectives

- To evaluate the relationship between KPT-8602 exposure (PK) and response
- To evaluate changes in XPO1 mRNA expression and other potential PD markers with treatment
- To assess changes in DNA damage repair by evaluation of gammaH2AX levels
- To evaluate compliance and feasibility of administering PRO in this patient population
- To evaluate tolerability of treatment by assess symptomatic adverse events, physical function and side effect bother
- To longitudinally describe and evaluate disease and treatment-related severity and functional well-being

- To determine meaningful change in disease and treatment-related symptoms and functional well-being by using anchors
- To evaluate changes in DNA methylation status pre- and post-treatment
- To evaluate changes in cell composition in the bone marrow and peripheral blood microenvironment pre- and post-treatment
- To evaluate changes in genetic clonal diversity during treatment
- To evaluate changes in gene expression patterns of tumor suppressor genes and oncogenes (including DNMT3B expression)
- To evaluate the influence of splicing factor mutations (U2AF1, SRSF2, SF3B1, ZRSR2) on nuclear shuttling
- To evaluate the degree of disruption of ribosome biogenesis after XPO1 inhibition
- To evaluate changes in nuclear and cytoplasmic protein composition using mass spectrometry
- To evaluate additional clinical outcomes, such as overall improvement rate (OIR), transfusion-independence (TI), cytogenetic response rate, time to best response (CR, PR, marrow CR + HI, HI), disease-free survival (DFS; definition: time to relapse for participants who achieve CR), progression-free survival (PFS; definition: time to progression or death from MDS), leukemia-free survival (LFS; definition: time to progression to AML or death from any cause), and overall survival (OS; definition: time to death from any cause)

1.2 BACKGROUND AND RATIONALE

1.2.1 Myelodysplastic syndromes

The myelodysplastic syndromes (MDS) are a group of heterogenous clonal neoplasms of hematopoietic stem cells, characterized by dysplastic changes in at least one myeloid lineage, recurrent genetic aberrations, presence of up to 20% myeloblasts in the bone marrow, and high risk of evolution to acute myelogenous leukemia (AML).(1) Myelodysplasia results in ineffective hematopoiesis with consequential peripheral blood cytopenia(s). Anemia is the most common clinical presentation of MDS, but other cytopenias are also often present. Cytopenias, together with ineffective maturation of neutrophils and platelets, often result in severe and/or recurrent infections and/or bleeding episodes, respectively. In general, it is estimated that up to 1/3 of patients with MDS will die from cytopenia-related complications, up to 1/3 have disease progression into a secondary AML with poor prognosis, and the remaining 1/3 may die from causes unrelated to their MDS.(2, 3)

MDS is a disease of the elderly, with a median age at diagnosis of approximately 75 years, with ~80% of patients being ≥65 years.(4) Based on cancer registry data, about 10,000 new MDS cases are diagnosed per year in the United States,(5, 6) but the number is probably underestimated,(7) and may be as high as >40,000 based on Medicare claims analyses.(8) There is a slight predominance of males.(4)

Most MDS patients (~90%) have sporadic disease and the remainder are therapy-related MDS (t-MDS), the latter often presenting in patients younger than 60 years of age. In the last decade,

familial related myeloid neoplasia in persons with germ-line mutations (i.e., *RUNX1, GATA2, DDX41, CEPBA, ANKRD26, ETV6*) is recognized as a predisposing condition for earlier acquisition of additional MDS-related mutations and MDS development.(9) Additionally, MDS can also develop from the rare inherited bone marrow failure disorders, such as Fanconi and Diamond-Blackfan anemia, which can present in childhood and adolescence.(10)

A conceptual model of MDS evolution(11) presumes an initiating somatic driver mutation in the hematopoietic stem cell with subsequent formation of the mutant stem cell clone. The most commonly affected genes involve RNA splicing, DNA methylation, histone modification, transcription regulators, DNA-repair control, signaling and cohesin complex. Six genes are commonly affected and have been reported to be mutant in at least 10% of patients: *SF3B1, TET2, SRSF2, DNMT3A, ASXL1,* and *RUNX1*.(12) In the second phase, the mutant clone expands and when it reaches approximately 4% of the total hematopoiesis, clonal hematopoiesis of indeterminate potential (CHIP) can be diagnosed. The duration of the first phase and potential of further progression to the third phase (MDS or clonal cytopenia of undetermined significance [CCUS] – cytopenia with presence of a clonal population without morphologic evidence of dysplastic changes) seems to be related to the genes affected by mutations and the size of the clonal population.(13) Most patients with CHIP and mutations in *DNMT3A, TET2,* or *ASXL1* will slowly progress to the third phase, while those harboring spliceosome gene mutations (i.e., *SF3B1, SRSF2, U2AF1*) will usually progress faster into MDS.(13) The spliceosome gene mutations are collectively present in more than 50% of the subjects with MDS and are mutually exclusive.(14, 15) They are most commonly present in MDS subjects when compared to the patients with other malignancies. In the third phase, clonal predominance of the mutant clone is established with further acquisitions of additional mutations (median of 3).(16, 17) The fourth phase is initiated with the selection of a clone that usually harbors AML-driving mutations (i.e., *FLT3, PTPN11, WT1, IDH1, NPM1, IDH2* and *NRAS*) leading to progression into secondary AML (s-AML) with ≥20% blasts in the bone marrow.

According to the World Health Organization (WHO) 2016 classification of myeloid neoplasms and acute leukemia,(1) several different MDS-related entities can be discriminated with defined diagnostic criteria such as the number of lineages affected by dysplastic changes, the percentage of blasts in bone marrow, the existence of ring sideroblasts and genetic changes. MDS precursor conditions, such as CHIP and CCUS, are defined by expert panels through a consensus process.(18-21)

The prognosis of MDS depends on disease- and patient-related characteristics. The disease-specific factors with major influence on the prognosis of participants with MDS are the number and depth of cytopenias, the percentage of bone marrow blasts and the cytogenetic aberrations. These factors are incorporated in Revised International Prognostic Scoring System (IPSS-R), currently the most commonly used prognostic index that stratifies MDS patients into 5 prognostic groups predicting overall survival (OS) and time-to-progression to AML.(22) For the purposes of clinical practice, an IPSS-R score of 3.5 is generally accepted as a cutoff for stratifying patients into “higher-risk” MDS (HR-MDS) versus “lower-risk” MDS (LR-MDS) with corresponding median OS of 1.5 versus 5.9 years, respectively.(23) Using this stratification system, about 1/3 of patients with MDS are classified as having HR-MDS and about 2/3 are classified as having LR-MDS.

1.2.2 Current treatment options for patients with HR-MDS

Currently, the only curative treatment modality for patients with MDS is allogeneic hematopoietic stem cell transplantation (HSCT). Since HSCT is associated with high incidence of mortality and morbidity, only a small portion of fit patients are eligible to undergo a transplant.(24, 25) There is an estimate that only 6 of 100 MDS patients will receive HSCT (2 will be cured, 3 will relapse and 1 will die from the HSCT-related complications).(3)

Hypomethylating agents (HMAs), such as 5-azacitidine (AZA) and decitabine (DAC), are the standard of care therapies for HR-MDS. Inqovi is an oral formulation of decitabine, in combination with the cytidine deaminase inhibitor cedazuridine, which was recently FDA approved in July 2020 based on clinical trial results which showed similar drug concentrations between intravenous decitabine and oral decitabine-cedazuridine, with comparable efficacy. In the Phase 3 registrational trial for oral decitabine-cedazuridine, CR rate was 21%; additionally, 53% of patients who were RBC and/or platelet transfusion dependent at baseline achieved transfusion independence during any 56-day post-baseline period.(26)

Unfortunately, less than a half of patients respond to HMAs, and even the best responses are transient, non-durable, and non-curative.(27) Although the benefit on OS was significant in the AZA registrational trial, (27) in real-life practice the impact on OS is not reproducible and prolongs OS for just a few months.(28, 29)

Numerous combination therapies with HMAs have been explored in treatment of MDS and AML. The BCL-2-inhibitor, venetoclax, in combination with HMA has emerged as a promising therapeutic combination with good safety and efficacy in AML,(30) though remains under clinical investigation in MDS.(31-33) Two presentations on early data from ongoing clinical trials of venetoclax in combination with HMA were presented at the 2020 American Society of Hematology conference: (a) a Phase 1b trial by Garcia et al. that explored use of venetoclax plus azacitidine in 57 high-risk MDS participants, and reported an ORR of 77% with a 13 month median follow-up, and high rates of grade 3 AEs in 97% of participants, including febrile neutropenia in 46% and neutropenia and thrombocytopenia in 51% and 30%, respectively;(32) and (b) a Phase 1b trial of venetoclax plus azacitidine by Zeidan et al. for treatment of MDS in the relapsed/refractory setting. Of the 38 participants enrolled, with a median follow up of 6.8 months, there was a clinical response of CR + mCR in 40%, and HI in 25%. Common grade 3-4 AEs included neutropenia and thrombocytopenia in 50% and 42% of participants, respectively.(33) While reported efficacy is promising for this combination, the side effect profile and complications due to cytopenias appear significant based on these preliminarily data and this regimen may require further optimization in the MDS setting.

1.2.3 KPT-8602 (eltanexor)

1.2.3.1 Selective Inhibitors of Nuclear Export (SINE)

Selective inhibitors of nuclear export (SINE) compounds directly bind and block the nucler export protein exportin 1 (XPO1). XPO1 mediates the nuclear export of cargo proteins including tumor suppressor proteins (TSPs) such as p53, p21, and IKB, as well as eIF4E bound messenger ribonucleic acids (mRNAs) encoding oncogenic proteins such as c-MYC, Bcl-2, Bcl-SL, MDM2, and cyclin D1. As a result, XPO1 inhibition leads to nuclear retention and activation of TSPs, a reduction in the level of oncogenic proteins, and down-regulation of drug resistance and pro-inflammatory pathways. The inhibition of XPO1 by SINE compounds and subsequent nuclear

accumulation of TSPs results in selective cytotoxicity to cells with genomic damage (such as tumor cells) both *in vitro* and *in vivo*. All cell types exposed to SINE compounds *in vitro* undergo G1 and/or G2 cell cycle arrest, followed by a "genomic fidelity" review. Cancer cells with damanged genomes fail the review and undergo apoptosis. Normal cells remain in a transient, reversible cell cycle arrest until the export block is relieved. Additionally, through retention of eIF4E-bound oncogenic mRNAs in the nucleus, SINE compounds reduce oncogenic protein expression, contributing to selective induction of apoptosis in malignancies driven by these pathways.

There are 2 SINE compounds currently under clinical development for oncology indications: selinexor and eltanexor.

Selinexor (KPT-330; XPOVIO®) (34) is a first-in-class SINE compound that, in combination with dexamethasone, has regular approval from the US Food and Drug Administration (FDA) for the treatment of adult patients with relaped or refractory multiple myeloma (MM) 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. Selinexor, in combination with bortezomib and dexamethasone, also has regular FDA approval for the treatment of adult pateints with multiple myeloma who have received at least 1 prior therapy. Additionally, selinexor has accelerated approval from the FDA for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified (DLBCL-NOS), including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy. Selinexor is also currently under investigation for the treatment of various other hematologic and solid tumor indications, including further evaluation in MM, DLBCL, endometrial cancer and other gynecological malignancies, non-small cell lung cancer (NSCLC), colorectal cancer (CRC), and advanced unresectable dedifferentiated liposarcoma (DDLS), glioblastoma multiforme (GBM), and recently for patients with COVID-19. Notably, selinexor has also been investigated for the treatment of acute myeloid leukemia (AML) in 2 separate phase I trials and shown some preliminary efficacy in this setting, particularly when given in combination with decitabine.(35, 36) However, toxicity has been an issue. Selinexor can cross the blood-brain barrier (BBB). Neurotoxicity is therefore a common side effect, occurring in 25-30% of patients with MM and DLBCL in clinical trials, with severe (Grade 3-4) events occurring in 3-6%. Other common TEAEs (occurring in ≥ 35%) reported with selinexor have included nausea (66%), fatigue (57%), anorexia (51%), thrombocytopenia (51%), anemia (44%), vomiting (39%), and diarrhea (37%).

Eltanexor (KPT-8602) is a second-generation, slowly reversible, orally bioavailable SINE compound, currently in Phase 1/2 development. It has similar potency to selinexor *in vitro* against XPO1-mediated transport and in cancer cell lines. However, it has a distinct pharmacology related to its unique chemical structure resulting in substantially lower brain penetration when compared with selinexor: ~30-fold lower in monkey studies. In animal models, this resulted in lower levels of anorexia and weight loss and permitted eltanexor once daily dosing for 5 consecutive days each week. It also exhibited superior anti-leukemic activity in in vitro studies of AML cell lines, and was associated with improved survival in a human xenograft model of AML. Preclinical studies also showed that eltanexor is minimally toxic to normal hematopoietic stem and progenitor cells, and eltanexor did not accumulate in plasma after repetitive dosing. The improved tolerability of eltanexor may be due to its reduced brain penetration and improved therapeutic window. The safety, tolerability, and preliminary efficacy of eltanexor is currently under investigation in Study KCP-8602-801 (hereafter referred to as Study 801, NCT02649790) which is an ongoing first-in-human, open-label dose-escalation study in patients with relapsed/refractory multiple myeloma

(R/R MM) followed by a dose-expansion phase in patients with select advanced malignancies, including mCRC, mCRPC, and HR-MDS.

1.2.3.2 Dosing

As of 18 November 2023, a total of 153 patients (39 patients with R/R MM, 30 patients with with RR CRC, 30 patients with mCRPC, and 50 patients with HR-MDS, and 4 with ND MDS) have received eltanexor on Study 801 and have safety data available. In addition, 3 patients have been dosed in Part F Phase 2 (HR-MDS) and 2 patients in Part G (newly diagnosed intermediate or high risk MDS in combination with Inqovi); however, no safety data is available as of the cut-off date in these 5 patients.

In the dose escalation phase, which is now complete, patients with R/R MM were dosed with 5-40 mg eltanexor daily x 5 days (5 days on, 2 days off) per week or 60 mg eltanexor every other day x 3 doses (every other day for 5 days, 2 days off), alone or in combination with dexamethasone. There were 2 DLTs observed (>4 missed doses and Grade 4 thromobcytopenia) in different dose cohorts, however, the protocol-defined MTD was not reached.(37) Therefore, both 20 mg and 30 mg eltanexor daily x 5 + 20 mg dexamethasone twice weekly were selected for further evaluation to clearly define the recommended phase 2 dose (RP2D).

In the dose-expansion phase, patients with mCRC were dosed at 20 or 30 mg eltanexor daily x 5, mCRPC patients were dosed at 20 or 30 mg eltanexor daily x 5 alone or in combination with abiraterone, and HR-MDS patients were dosed at 10 or 20 mg eltanexor x 5 (5 days on, 2 days off, in 28-day cycles).

In patients with HMA-refactory HR-MDS (n = 35) treated with single-agent eltanexor, the median duration of eltanexor (10 mg) was 19.1 weeks (range 2 to 85); however 10 patients treated for ≥ 24 weeks. In 10 mg cohort (n = 5), 3 patients (60%) had marrow complete response (mCR) and 2 patients (40%) had stable disease (SD). In the 20 mg cohort (n = 10), 4 patients (40%) had mCR and 3 (30%) had SD. The overall survival (OS) for all patients was 9.9 months, and 11.9 months for those achieving mCR vs 8.7 months for those who did not achieve mCR (hazard ratio = 0.27, p=0.05). (38)

In the entire safety population, the most frequently occurring TEAEs of any grade were nausea (56.9%), fatigue (64.1%), diarrhea (54.9%), decreased appetite (43.8%), thrombocytopenia (45.8%), weight decreased (42%), neutropenia (42.5%), anemia (38.6%), vomiting (38.6%), and constipation (30.7%). The most frequently occurring ≥ Grade 3 TEAEs were thrombocytopenia (31.4%), anemia (25.5%), and neutropenia (32.7%). However, no clinically significant cumulative toxicities were identified, major organ dysfunction was not observed, and no grade 5 TRAEs were reported. Adverse events leading to discontinuation of eltanexor that occurred in ≥ 3 patients were fatigue (5%), nausea and acute kidney injury (3.4% each), sepsis and weight decreased (2.5% each). There was one patient that did not have a TEAE.

In the MDS cohort (n = 20), the most frequently occurring TEAEs of any grade were diarrhea (70%), nausea (60%), dyspnea (50%), abdominal pain (45%), fatigue (45%), anemia (40%), constipation (40%), dizziness (40%), weight decreased (35%), neutropenia (35%), leukopenia (30%), and thrombocytopenia (30%). The most frequently occurring ≥ Grade 3 TEAEs were anemia (40%), neutropenia (30%), and thrombocytopenia (30%). However, all AEs were reversible and manageable by supportive care and dose modification, and no grade 5 TRAEs were reported. (39) See the Eltanexor Investigator's Brochure (IB) for more information.

Clinicians typically underestimate the symptoms of the toxic effects or adverse events experienced by patients.(40, 41) Patient-centered outcomes assessment starts with an understanding of the impact of a disease and its treatment on patients, and what patients value from a treatment perspective. In cancer-related clinical trials, regulatory agencies and advocacy groups increasingly encourage using patient-reported outcomes (PROs) to describe the clinical benefit of a therapeutic regimen. This includes using information on disease-associated symptoms or functions to help determine treatment efficacy and understand treatment-associated side effects. These measures, which collect information directly from the patient, without interpretation by somebody else, improve researchers' understanding of the patient perspective on the treatment's impact. Standardizing and incorporating PROs into earlier phase trials such as this dose finding in re-irradiation would allow them to be optimized, improve study design and allow more rigorous and systematic assessment of PROs in later-phase trials.

Tolerability and efficacy for KPT-8602 in HR-MDS are being further studied in the Phase 2 portion of Study 801 along with a Phase 1b study in AML. Additional studies in both solid tumors and hematological malignancies are planned. Phase 1 evaluation is also ongoing in newly diagnosed intermediate or high risk MDS.

Additionally, preclinical studies have expored various dosing strategies for KPT-8601 including 5 days/week and continuous daily dosing, and have suggested that either strategy is feasible (42, 43).

1.2.3.3 Pharmacokinetic (PK) and pharmacodynamic (PD) data

In Study 801, the PK profile of KPT-8602 (eltanexor) after oral administration was predictable, dose-proportional, and exhibited moderate inter-patient variability across doses of 5-20 mg in male and female patients with R/R MM, mCRC, mCRPC, and HR-MDS. Following single doses of 5-60 mg at C1D1, the eltanexor PK profile was characterized by rapid absorption (median T_{max} 1-3 hours) and moderate clearance (21-35 L/h), volume of distribution 170-264 L, and terminal half-life 4-6 hours. Interindividual variablility was moderate as evidenced by geometric mean percent coefficient of variation (%CV) values (range) for $AUC_{0-\infty}$ 24-44% and C_{max} 15-53% (Eltanexor IB, version 4.0).

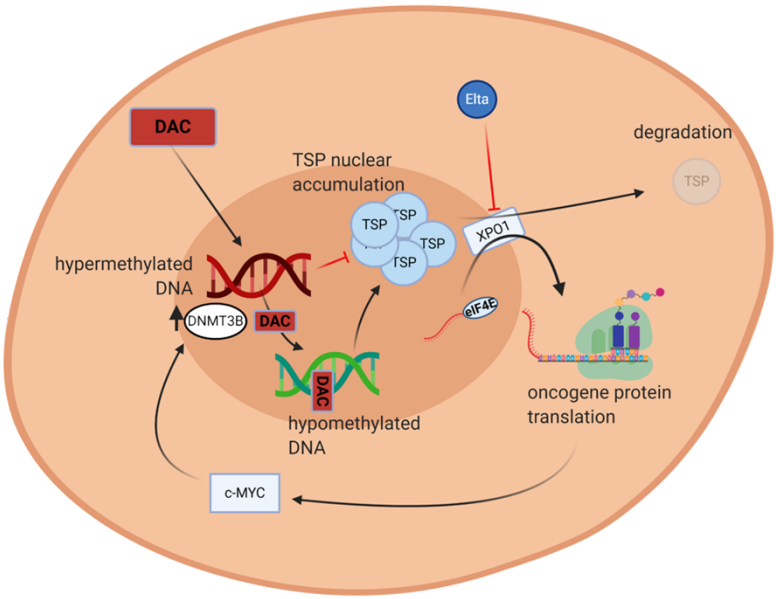
Based on nonclinical and exploratory clinical data from SINE compounds, the change in XPO1 mRNA expression after treatment is an appropriate PD marker and was used to evaluate target engagement across the first 6 R/R MM cohorts treated with single-agent eltanexor on Study 801. Target engagement was assessed from whole blood collected on C1D1 at 2, 4, 8, and 24 hours post dose of eltanexor and was compared to the relative level (i.e., set to 1 at 0 hrs) at pre-dose. The plasma concentration of eltanexor was also calculated and plotted. For all cohorts evaluated, the fold-change maximum (F_{max}) of XPO1 mRNA expression was achieved 4 to 8 hours post-dose. The F_{max} and AUC_{24} for XPO1 mRNA was roughly dose proportional to the Cmax and AUC_{24} of eltanexor in plasma samples from these patients. The plateau for Fmax and AUC24 of XPO1 mRNA in treated patients was 5-fold change and 100-fold change (baseline*hr), respectively, when compared with pre-dose levels. Based on these preliminary data, the maximum dose for these XPO1 changes occurs in patients treated with 60 mg of eltanexor. Although the RP2D of 20-30 mg eltanexor (depending on the indication) does not maximize the F_{max} at C1D1, this reduced response of XPO1 mRNA may correlate with the improved tolerability of eltanexor. Of note, there is currently not enough data for a clinically reliable marker of maximal pharmacologic activity for eltanexor. We will use the MTD to make our RP2D determination and use the totality of data from

this early phase trial, including PK, PD, safety and MTD interpretation to best determine optimal dosing in later trials.

1.2.3.4 Rationale for combining KPT-8602 (eltanexor) and Inqovi

DNMT3B is one protein responsible for *de novo* DNA methylation and fast rebound methylation after HMA cessation in MDS. The proto-oncogene c-MYC directly binds the DNMT3B promoter, causing increased expression of DNMT3B. By interfering with c-MYC translation, KPT-8602 may diminish rebound methylation after decitabine cessation and improve treatment responses in patients with MDS (**Figure 1**). Preliminary reports from Study 801 show anti-tumor activity and an acceptable toxicity profile for KPT-8602 in patients with HR-MDS who have failed HMAs. Additionally, preclinical studies have shown that decitabine priming increases antileukemic effects of selective inhibitors of nuclear transport (SINEs) in AML *in vitro* and *in vivo*. (44) Therefore, sequential addition of KPT-8602 to Inqovi may further improve treatment responses in participants with myeloid malignancies by acting synergistically to inhibit further DNA methylation.

Figure 1: Synergy between eltanexor (KPT-8602) and decitabine



Abbreviations: DAC, decitabine; Elta, eltanexor; TSP, tumor suppressor protein
Figure provided by Dr. Alen Ostojic, NCI

1.2.3.5 Rationale for Myeloid Malignancy Program Investigation

In general, long term treatment outcomes for MDS patients are dismal. It is estimated that of every 100 MDS patients, 4 will be long-time survivors, with the rest of succumbing to either MDS- or treatment-related complications (67) or MDS-unrelated complications (29).(3) There has been no progress in populations based studies in survival of MDS patients during last 2 decades.(29) Novel approaches are needed which do not rely exclusively on cytotoxic therapy and/or intervene earlier in the course of the disease. Current clinical trials for participants with MDS enroll less than 5%

of MDS patients.(28) With better understanding of complex MDS pathophysiology, trials using combination treatments are emerging, especially for those ineligible for HSCT.(11)

A new Clinical and Translational Correlates Facility was recently funded by the *FY20 Directors Challenge Innovation Award* and is physically housed initially within NHLBI space (PI Christopher Hourigan *et al*). This facility will create the ability to perform standardized research correlates proposed on this study and across the growing NIH Myeloid Malignancies Clinical Trials portfolio. Work from intramural investigators has recently demonstrated that high-sensitivity genomic measurements outperform conventional clinical assessments for myeloid malignancy participants in predicting relapse and survival following HSCT and suggest that additional intervention on high-risk subjects can improve clinical outcomes.(45) This sets the stage for a "precision medicine" approach where personalized assessments of clonal disease burden can be used not only to judge the success of therapy, but also as a target for intervention.

In this trial, we hypothesize that sequential addition of KPT-8602 (eltanexor) to Inqovi is safe in treatment of adult MDS participants. For the phase 2 trial, we hypothesize that eltanexor enhances the efficacy of Inqovi in adult MDS participants.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Participants must have histologically or cytologically confirmed MDS by the Laboratory of Pathology, NCI- according to 2016 WHO criteria(1)

AND:

- Cohort 1 (Phase 1) & 2 (Phase 2): have HR-MDS (IPSS-R > 3.5) with inadequate response to hypomethylating agent (HMA) therapy [(received ≥ 4 cycles of the standard dose (35 mg decitabine and 100 mg cedazuridine) without prior dose-reductions, with failure to achieve at least a PR or experienced disease progression prior to completing 4 cycles)

2.1.1.2 Age ≥18 years

2.1.1.3 ECOG performance status ≤ 2 (Karnofsky ≥ 60%, see **Appendix A**)

2.1.1.4 Participants must have adequate organ and marrow function as defined below:

• total bilirubin	≤ 1.5 X institutional upper limit of normal OR ≤ 3 X institutional upper limit of normal in participants with Gilbert's syndrome (except for participants with increased bilirubin levels attributed to intramedullary hemolysis, which will be allowable)
• AST(SGOT)/ALT(SGPT)	≤ 3 X institutional upper limit of normal OR

≤ 5 X institutional upper limit of normal if related to MDS-specific cause

- creatinine clearance (by Cockcroft-Gault) ≥ 60 mL/min/1.73 m^2
- QTc(F) ≤ 470 ms

2.1.1.5 Individuals of child-bearing potential (IOCBP) must have a negative serum test at screening. IOCBP is defined as the following:

- Has not undergone a hysterectomy, tubal ligation, or bilateral oophorectomy
- Has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

2.1.1.6 Individuals of childbearing potential (IOCBP) as well as those able to father a child with an individual able to become pregnant must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) unless they have had a prior vasectomy, hysterectomy, or bilateral oophorectomy, prior to study entry, for the duration of study participation, and for at least 6 months after last dose of HMA.

2.1.1.7 Breastfeeding participants must be willing to discontinue breastfeeding from study treatment initiation through 30 days after the last administration of study drug

2.1.1.8 Any prior therapy must have been completed >4 weeks or, if known, ≥ 5 half-lives of the prior agent (whichever is shorter) prior to treatment (with a minimum of 1 week between prior therapy and study treatment). Note: This does not apply to prior HMA therapy if that therapy is Inqovi per Section **2.1.1.1**.

2.1.1.9 Ability to understand and the willingness to sign a written informed consent document.

2.1.2 Exclusion Criteria

2.1.2.1 Participants with platelet transfusion-refractory thrombocytopenia, with inability to keep platelet threshold above 10K/mcL with transfusions or those with ongoing or uncontrolled hemorrhagic complications.

2.1.2.2 Participants with clinically significant neutropenia, defined as ANC <100 cells/mcL with frequent hospitalizations for infection (average > 1 hospitalization per month in the past 6 months).

2.1.2.3 Participants on treatment with a myeloid growth factor (e.g., G-CSF) within 14 days prior to initiation of study treatment.

2.1.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to HMAs or other agents used in study.

2.1.2.5 Uncontrolled intercurrent illness evaluated by history, physical exam, and chemistries or situations that would limit compliance with study requirements, interpretation of results or that could increase risk to the participant

2.1.2.6 Participants with the following cardiac conditions: symptomatic congestive heart failure, unstable angina pectoris, or uncontrolled cardiac arrhythmia as assessed by electrocardiogram (ECG).

2.1.2.7 Pregnancy (confirmed with β-HCG serum or urine pregnancy test performed in individuals of childbearing potential at screening)

2.1.2.8 Presence of any other malignancy (except basal and squamous cell carcinoma of the skin, or stable chronic cancers on hormone or targeted therapy) for which participant received systemic anticancer treatment (except maintenance therapy) within 24 months prior to treatment.

2.1.2.9 Participants with active/uncontrolled Hepatitis B

2.1.2.10 Participants with active/uncontrolled Hepatitis C

2.1.2.11 Participants with active/uncontrolled HIV infection or AIDS.

2.1.2.12 Participants currently taking contraindicated medications for HIV, Hepatitis B, or Hepatitis C disease control (**Appendix L**)

2.1.3 Recruitment Strategies

This protocol will be advertised on NIH websites (clinicaltrials.gov, future Myeloid Malignancy Program Web Site) and social media platforms, as well as through professional MDS associations.

2.2 SCREENING EVALUATION

2.2.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videos
- Review of existing pathology reports from a specimen obtained for diagnostic purposes

2.2.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the participant has signed the consent for this study for screening. Assessments performed at outside facilities or on another NIH protocol within the timeframes listed below may be used to determine eligibility once a participant has signed the consent for this study.

Assessments and procedures to confirm study eligibility should be completed within 30 days prior to the start of treatment, unless otherwise indicated. See also Section **3.5**, Study Calendar.

Any time prior (no time limit):

- Histologic confirmation: All participants are required to have histologically confirmed MDS. If pathology reports are from outside institutions, outside slides pathologic review of diagnosis by Laboratory of Pathology of NCI is required to determine study eligibility at screening.

Within 30 days:

- History and physical examination: Complete history and physical examination (including height, weight, vital signs, and performance status)
- Laboratory Evaluation:
    - Hematological Profile: CBC with differential, reticulocyte count
    - Biochemical Profile: total bilirubin, BUN, albumin, calcium, creatinine, SGOT [AST], SGPT [ALT], phosphorous, magnesium, potassium, sodium, LDH, uric acid, ferritin, endogenous erythropoietin
    - Vitamin B12, folate, copper, zinc, TSH, free T4- to assess alternative/reversible causes of cytopenias that may confound MDS diagnosis
    - Infectious serologies including HIV, HBV, HCV
    - Urine and/or serum pregnancy test for individuals of childbearing potential (must be performed within 24 hours prior to initating study treatment)
- Cardiac Evaluation: Electrocardiogram (ECG)
- Next Generation Sequencing (as needed): panel of myeloid genes from bone marrow. May be performed during screening evaluation if the MDS diagnosis is in question based on histology alone.
- Bone marrow aspirate and biopsy (as needed): if no prior sample is available for pathology review, a fresh bone marrow aspirate and will be taken at screening to determine diagnosis.

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

2.3.1 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of any specific inclusion/exclusion criteria by discretion of PI may be rescreened.

Circumstances when a participant may be re-screened:

1. If a participant consented to participate and met the eligibility criteria, but there was a delay in starting due to a change in situation (e.g., family issues, individual request for attending a private matter, etc.)
2. If a participant previously failed screening due to an acute event that has now resolved/reversed.

3. If a participant failed screening due to being on a prohibited medication, which has been discontinued.
4. If reversible causes of screen failure have been adequately treated.

2.3.2 Treatment Assignment (for Phase I and II)

Cohorts

Number	Name	Description
1	*Phase I- "Higher-risk" MDS*	*Participants with confirmed MDS and IPSS-R score > 3.5 (high and higher intermediate-risk)*
2	*Phase II- "Higher-risk" MDS*	*Participants with confirmed MDS and IPSS-R score > 3.5 (high and higher intermediate-risk) for phase II dose expansion*

Arms

Number	Name	Description
1	*Phase I- Dose escalation of KPT-8602 for HR-MDS*	*Inqovi for 5 days, followed by escalating doses of KPT-8602*
2	*Phase II- Dose expansion for HR-MDS*	*Inqovi for 5 days, followed by Phase II dose of KPT-8602*

Arm Assignment

Participants in Cohort 1 will be directly assigned to Arm 1; Cohort 2 will be directly assigned to Arm 2;

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

The study consists of two phases:

- Phase I: Safety evaluation with determination of the recommended phase 2 dose (RP2D) of KPT-8602 in combination with Inqovi, and
- Phase II: Efficacy evaluation of KPT-8602 in combination with Inqovi

Participants will be enrolled into one of two cohorts, depending on the phase of study as follows:

- Phase I:
    - **Cohort 1:** Participants with higher-risk MDS that will be treated with Inqovi for 5 days, followed by KPT-8602 at escalating doses.
- Phase II:
    - **Cohort 2:** Participants with higher-risk MDS that will be treated with Inqovi for 5 days, followed by KPT-8602 at the RP2D.

In Phase I, participants enrolled in Cohort 1 will be treated with Inqovi 35 mg/100 mg daily on Days 1-5 of each 28-day cycle, plus KPT-8602 at the corresponding dose level and schedule..

Dose-escalation will follow a standard 3+3 design (see Section **3.1.2**), with DLT assessment during the first 28 days of treatment.

In Phase II, participants enrolled in Cohort 2 will be treated with Inqovi 35 mg/100 mg daily on Days 1-5 of each 28-day cycle, plus KPT-8602 at the RP2D identified in Phase I.

The study drugs will be self-adminstered by the patient, except on days of PK blood draws.

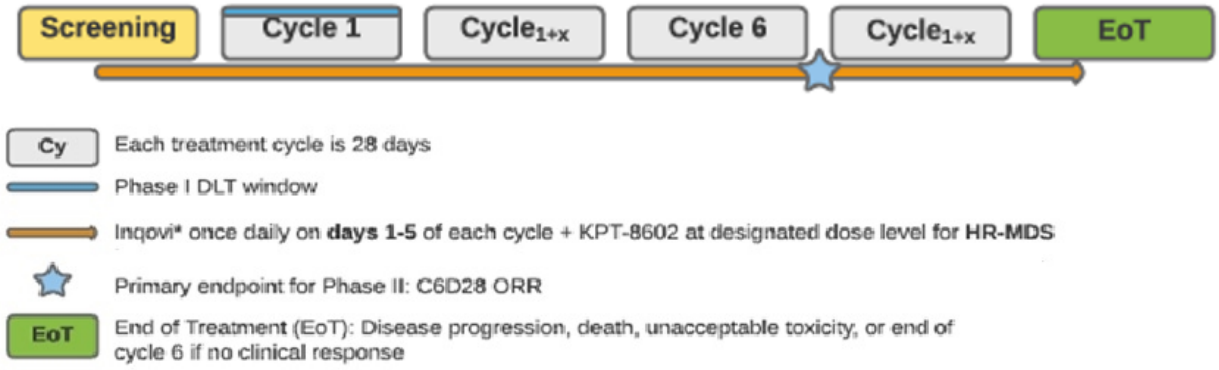
Participants in Cohorts 1 and 2 are eligible to participate in the study if they have received a minimum of 4 cycles of HMA therapy with inadequate response (failure to achieve at least a PR, or experienced disease progression prior to completing 4 cycles). For participants on HMA therapy with Inqovi prior to enrollment, descriptions of initiation of study therapy refer to initiation of KPT-8602 only. Of note, participants receiving Inqovi prior to enrollment must be on the standard dose (35 mg decitabine and 100 mg cedazuridine) without prior dose-reductions.

In both Phase I and Phase II, participants will continue treatment until disease progression, death, unacceptable toxicities as listed in Section **3.3.2**, or another off-treatment criterion is met (see Section **3.7.1**) as long as no other contraindications to further treatment. Participants that do not achieve at least partial remission following cycle 6 will not receive additional treatment.

Blood samples for correlative research will be collected (Section **5.1**). Participants may be admitted on day 8 of cycle 1 for pharmacokinetics (PK) studies to be performed, and on other days if necessary or for convenience.

Upon discontinuation of study treatment, participants will be followed for safety for at least 30 days after the last dose of treatment, and for event-free survival (EFS), progression-free survival (PFS), and overall survival (OS) until study follow-up requirements have been completed. The study will be closed to follow-up when all enrolled participants have been followed for up to 8 years or have died.

Phase I/II Study Schema



3.1.1 Dose Limiting Toxicity (DLT)

The DLT evaluation window will be the first 28 days of study treatment. No dose reductions or interruptions are allowed during the DLT observation period.

A DLT is defined as any of the following treatment-related toxicities (based on CTCAE Version 5.0):

- Any Grade 5 toxicity, unless due to underyling disease, disease progression, or accidental injury.
- Any Grade ≥ 3 non-hematologic toxicity, except:
    - Grade 3 or 4 isolated electrolyte abnormalities that resolve, with or without intervention, to Grade ≤ 2 within 72 hours
    - Grade 3 nausea, vomiting, or diarrhea that does not require/prolong hospitalization, does not require TPN or NGT feeding, and resolves to Grade ≤ 2 within 72 hours
    - Grade 3 fatigue, fever, flu-like symptoms, or headache lasting ≤ 72 hours
    - Grade 3 laboratory abnormalities that are not associated with organ pathology
    - Direct complications of cytopenia(s) due to active myeloid malignancy, such as:

      Grade 3 or 4 febrile neutropenia

      Grade 3 or 4 infection

      Grade 3 or 4 hypotension explained by sepsis

      Grade 3 or 4 hemorrhage/bleeding
- Confirmed Hy's law cases, defined as:
    - AT (ALT or AST) elevation > 3 times upper limit of normal (ULN), AND
    - Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase), AND

  - No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

- In the absence of active MDS, hematologic DLTs for each arm include:
  - any Grade ≥4 decrease ANC or PLTs lasting more than 28 days.
- Any adverse reaction that leads to dose reduction or withdrawal of KPT-8602.

3.1.2 Dose Escalation

In a phase I/II study (NCT 02649790) that evaluated single agent eltanexor in higher-risk MDS, 2 doses were evaluated: 5 patients received 10 mg and 15 patients received 20 mg, every day for 5 days per week of a 28-day cycle. The majority of patients were aged ≥75 and all were treated and refractory to hypomethylating agents. None of the patients experienced dose-limiting toxicities (DLTs) and the RP2D for eltanexor was selected as 10 mg given on days 1-5 of each week of a 28-day cycle in HR-MDS (20/28 days). Given the overlap in toxicities, particularly hematologic, between hypomethylating agents and eltanexor, our starting dose was set at 10 mg PO daily on Days 8-12 and Days 15-19 (total of 10 days per 28-day cycle as opposed to 20 days per 28-day cycle in NCT 02649790).

In Phase I, dose escalation will proceed in cohorts of 3-6 participants. The MTD is the dose level at which no more than 1 of up to 6 participants experience DLT during the first cycle (28 days) of treatment, and the dose below that at which at least 2 (of ≤6) participants have DLT as a result of the drug.

Participants in Cohort 1 will be eligible for the DLT evaluation if ≥90% (9 out of 10 doses) of KPT-8602 and ≥80% (4 out of 5 doses) of Inqovi were taken within the DLT period. Participants not evaluable for toxicity, will be replaced in the dose level.

Dose Escalation Schedule	
Dose Level	Dose of KPT-8602
Level -2	5 mg PO daily on Days 8-12 and Days 15-19
Level -1	5 mg PO daily on Days 8-21
Level 1 (starting dose)	10 mg PO daily on Days 8-12 and Days 15-19
Level 2	10 mg PO daily on Days 8-21

Dose escalation will start at dose level 1 and follow the rules outlined in the Table below.

Number of Participants **with DLT at a Given Dose Level**	**Escalation Decision Rule**
0 out of 3	Enter up to 3 participants at the next dose level
≥ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Up to three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
1 out of 3	Enter up to 3 more participants at this dose level. • If 0 of these 3 participants experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Up to three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is the MTD and is generally the recommended phase 2 dose. At least 6 participants must be entered at the recommended phase 2 dose.

No new participants will initiate study treatment at the current or next higher (or lower) dose level until the required number of participants have completed DLT evaluation. Each dose-escalation or de-escalation decision will be documented in the study file. The report including the supporting safety data and delineation of each criteria met, with the dose-escalation decisions will be provided to the Sponsor (OSROSafety@nih.gov) before additional participants will be enrolled into the study. The Dose Escalation Determination form on the sponsor website: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions may be used for this purpose.

3.1.3 Dose Expansion

If no DLTs are observed at the highest planned dose level for evaluation (dose level 2), dose escalation will stop and this will be considered the recommended phase 2 dose (RP2D) of KPT-8602. Phase II may begin once the RP2D has been identified.

3.1.4 Protocol Stopping Rules

This study will incorporate stopping rules related to safety and response.

For safety stopping rules, see Section **10.4.4**.

For response stopping rules, see Section **10.2**.

3.2 DRUG ADMINISTRATION

Drugs will be self-administered at home except for the days that participants are being seen in clinic for pharmacokinetic blood draws. On those days, participants should be instructed to bring in their medication supply from home, without taking the medication, as they will be instructed when to do so as the blood draws must be timed with drug administration.

3.2.1 KPT-8602

KPT-8602 will be dosed per participant assignment and as outlined in Section **3.1.2**. KPT-8602 tablets are film coated for ease in handling and should be swallowed whole (not crushed). Do not break, crush, or divide the tablets to prevent an increased risk of dermatologic toxicity if the powder comes in contact with skin. Oral KPT-8602 should be taken with or within 30 minutes of eating.

Medication bottles and leftover pills will be collected at the end of each cycle to monitor participant adherence.

Participants will be asked to complete a medication diary (**Appendix K**). If a dose is missed within 12 hours of the time it is usually administered, administer the missed dose as soon as possible and then resume the normal daily dosing schedule. Extend the dosing period by 1 day for every missed dose to complete the total number of daily doses for each cycle. If a dose is vomited, do not administer an additional dose (continue with the next scheduled dose).

3.2.2 Decitabine and Cedazuridine (Inqovi)

In both Phase I and Phase II, the study drug of KPT-8602 will be given in combination with standard-of-care (SOC) FDA-approved PO decitabine and cedazuridine (Inqovi).

- Inqovi will be administered via oral route once daily on Days 1-5 of each treatment cycle, according to guidelines outlined in the FDA product label.

The tablet should be taken on an empty stomach, 2 hours before or 2 hours after meals, and at the same time each day.

Tablet should be swallowed whole, and may not be crushed, cut, or chewed.

Participants will be asked to complete a medication diary. If a dose is missed within 12 hours of the time it is usually administered, administer the missed dose as soon as possible and then resume the normal daily dosing schedule. Extend the dosing period by 1 day for every missed dose to complete 5 daily doses for each cycle. If a dose is vomited, do not administer an additional dose (continue with the next scheduled dose).

3.3 DOSE MODIFICATIONS

Participants may continue study treatment if toxicity can be managed by interruption of the dose of study treatment or dose reductions as explained below. The following outlines dose modifications for study-drug related toxicities.

If toxicity is considered to be due solely to one of the study drugs as defined below, the participant may be taken off this drug and after consulting with a Sponsor may continue treatment with the other drug only if the participant is deriving benefit from treatment in the form of stabilization of disease or response.

When, at the beginning of a treatment cycle, treatment delay related to one drug is indicated, treatment with the other drug will be continued. For the purpose of restaging, cycle number will continue to be defined on the basis of a time of 28 days (+/- 7 days), i.e., cycle number will not change due to one drug being held.

Overlapping toxicities may be attributed solely to KPT-8602 if a participant who was already on Inqovi prior to starting on study treatment develops the toxicity upon addition of KPT-8602. In addition, overlapping toxicities may be attributed solely to one of the drugs if dose modification or delay of one drug (while the other is continued at the same dose) results in resolution of the toxicity.

3.3.1 Dose Levels for Toxicity Management

Dose levels for KPT-8602 (eltanexor) are as follows, for the purposes of toxicity management.

Dose level	KPT-8602 dosage
2	10 mg orally once daily on Days 8-21
1	10 mg orally once daily on Days 8-12 and Days 15-19
-1	5 mg orally once daily on Days 8-21
-2	5 mg orally once daily on Days 8-12 and Days 15-19

Dose levels for Inqovi are as follows, for the purposes of toxicity management.

Dose level	Inqovi dosage
1	1 tablet orally once daily on Days 1 through 5
-1	1 tablet orally once daily on Days 1 through 4
-2	1 tablet orally once daily on Days 1 through 3
-3	1 tablet orally once daily on Days 1, 3, and 5

3.3.2 Dose Modification Guidelines

3.3.2.1 Criteria for initiation of subsequent cycles

The next cycle of therapy may proceed if the following criteria are met:

Non-hematologic criteria to start the next cycle:

- Serum Cr < 2 mg/dL
- Serum bilirubin < 2 x ULN
- AST or ALT < 2 x ULN
- No active or uncontrolled infection

Participants who do not meet these non-hematologic criteria should have the next cycle delayed and labs monitored at least weekly. Once resolved, study treatment may resume at the same dose for the next cycle. If not resolved within 4 weeks, dose-reduce when participant meets criteria (as

noted above) to start the next cycle as noted below (if not resolved within 8 weeks participant will be taken off treatment):

Dose reduction	**Inqovi dosage***	**KPT-8602 dosage***
First	Continue same dose	Reduce by one dose level
Second	Reduce by one dose level	Reduce by one dose level
Third	Reduce by one dose level	Reduce by one dose level
Fourth	Reduce by one dose level	Permanently discontinue

Hematologic criteria to start the next cycle (<u>applies only to participants without active disease by bone marrow</u>):

- ANC ≥ 1000/mcL
- PLT ≥ 50,000/mcL

Participants who do not meet these hematologic criteria (and without active disease by bone marrow) should have the next cycle delayed and CBC monitored at least weekly until ANC is ≥ 1000/mcL and PLT ≥ 50,000/mcL.

- If hematologic recovery (ANC ≥ 1000/mcL and PLT ≥ 50,000/mcL) occurs within 2 weeks of achieving remission by bone marrow, continue Inqovi and KPT-8602 at the same dose for the next cycle.
- If hematologic recovery does not occur within 2 weeks of achieving remission by bone marrow, delay Inqovi and KPT-8602 for up to 2 additional weeks and dose-reduce for the next cycle as noted below:

Dose reduction	**Inqovi dosage***	**KPT-8602 dosage***
First	Continue same dose	Reduce by one dose level
Second	Reduce by one dose level	Reduce by one dose level
Third	Reduce by one dose level	Reduce by one dose level
Fourth	Reduce by one dose level	Permanently discontinue

**Once the lowest dose level has been reached for a given drug, if myelosuppression persists, discontinue drug.*

If not resolved within 8 weeks participant will be taken off treatment.

3.3.2.2 Toxicity Guidelines

In addition, the tables below show general supportive care and dose modification guidelines for toxicities noted at any point during study treatment (other than the scenarios described above). Dose levels of KPT-8602 and Inqovi for the purposes of toxicity management are as noted in Section **3.3.1**.

3.3.2.2.1 Hematologic toxicities

Toxicity	Recommended Action*
Thrombocytopenia	
Grade 2 (PLT ≤ 75,000/mcL)	• Maintain dose of KPT-8602 and Inqovi. • Consider dose reduction of any anti-platelet agents. • Start PPI.
Grade 3 or 4 thrombocytopenia (PLT ≤ 50,000/mcL) *without* bleeding	• In cases where there is still significant disease involvement in the bone marrow: o The treating physician, in consultation with the PI, may continue KPT-8602 and Inqovi at the same dose level • Otherwise, the following guidelines should be followed: o Hold KPT-8602 and Inqovi until improves to ≤ Grade 2 or baseline. ▪ If improves to ≤ Grade 2 or baseline within 72 hours: • Resume KPT-8602 and Inqovi at the same dose ▪ If does not improve to ≤ Grade 2 or baseline within 72 hours: • Hold KPT-8602 and Inqovi for the remainder of the current cycle. • Reduce KPT-8602 by one dose level with the next cycle • Resume Inqovi at the same dose for the next cycle (first occurrence) or reduce Inqovi by one dose level for the next cycle (second or later occurences) • Note: Toxicity must resolve to ≤ Grade 2 or baseline before drugs can be resumed • In addition, the following steps should be taken for all cases: o Consider initiating a platelet growth factor per institutional guidelines. o Monitor platelet counts at least twice weekly and closely monitor for any bleeding signs/symptoms. o Transfuse as per institutional guidelines. o Consider dose reduction of any anti-platelet agents. o Start PPI.
Grade 3-4 thrombocytopenia (PLT ≤ 50,000/mcL) *with* bleeding	• Consider initiating a platelet growth factor per institutional guidelines. • Transfuse as per institutional guidelines. • Start PPI. • Hold KPT-8602 and Inqovi for the remainder of the cycle and until bleeding resolves and platelet count improves to ≤ Grade 2 or baseline, then: o Reduce KPT-8602 by one dose level with the next cycle. o Resume Inqovi at the same dose for the next cycle (first occurrence) or reduce Inqovi by one dose level with the next cycle (second or later occurences).
Neutropenia	
Grade 3 neutropenia (ANC ≤ 1000/mcL) *without* fever	• Maintain dose of KPT-8602 and Inqovi. • Consider use of growth factors per institutional guidelines.
Grade 4 neutropenia (ANC ≤ 500/mcL) *without* fever	• In cases where there is still significant disease involvement in the bone marrow: o The treating physician, in consultation with the PI, may continue KPT-8602 and Inqovi at the same dose level • Otherwise, the following guidelines should be followed: o Hold KPT-8602 and Inqovi until improves to ≤ Grade 3 or baseline.

Toxicity	Recommended Action*
	▪ If improves to ≤ Grade 3 or baseline within 72 hours: • Resume KPT-8602 and Inqovi at the same dose. ▪ If does not improve to ≤ Grade 3 or baseline within 72 hours: • Hold KPT-8602 and Inqovi for the remainder of the current cycle. • Reduce KPT-8602 by one dose level with the next cycle. • Resume Inqovi at the same dose for the next cycle (first occurrence) or reduce Inqovi by one dose level for the next cycle (second or later occurences). • Note: Toxicity must resolve to ≤ Grade 3 or baseline before drugs can be resumed • Consider use of growth factors. • If growth factors are implemented, for participants who achieve neutrophil levels >1000/mcL for >4 weeks, KPT-8602 may be re-escalated with the next cycle of therapy, with frequent monitoring implemented.
Grade 3 or 4 neutropenia with fever	• Implement broad-spectrum anti-microbial agents per institutional guidelines. • Consider use of growth factors. • Hold KPT-8602 and Inqovi for the remainder of the cycle and until fever resolves and the participant is clinically stable, then: o Reduce KPT-8602 by one dose level with the next cycle. o Resume Inqovi at the same dose for the next cycle (first occurrence) or reduce Inqovi by one dose level with the next cycle (second or later occurences). • If growth factors are implemented, for participants who achieve neutrophil levels >1000/mcL for >4 weeks, KPT-8602 may be re-escalated with the next cycle of therapy, with frequent monitoring.

**Once the lowest dose level has been reached, if toxicity persists, discontinue drug.*

3.3.2.2.2 Non-hematologic toxicities

Toxicity	Recommended Action*
Fatigue	
Grade 3	• Interrupt KPT-8602 dosing until fatigue improves to Grade ≤ 2 or baseline. Maintain dose of Inqovi. • If fatigue does not improve to Grade ≤ 2 or baseline within 7 days despite holding KPT-8602, interrupt Inqovi dosing. • Once improved to Grade ≤ 2 or baseline: o If first occurrence: restart KPT-8602 and Inqovi at the same dose. o If second occurrence: restart KPT-8602 one dose level below and Inqovi at same dose. o If third or later occurrence: restart both KPT-8602 and Inqovi one dose level below.
Unintentional weight loss and anorexia	
Grade 3	• Interrupt KPT-8602 dosing until weight loss/anorexia resolves to Grade ≤ 2 or baseline. Maintain dose of Inqovi.

Toxicity	Recommended Action*

	• If weight loss/anorexia does not improve to Grade ≤ 2 or baseline within 7 days despite holding KPT-8602, interrupt Inqovi dosing.
	• Once improved to Grade ≤ 2 or baseline and participant is clinically stable:
	  o If first occurrence: restart KPT-8602 one dose level below and Inqovi at the same dose.
	  o If second or later occurrence: restart both KPT-8602 and Inqovi one dose level below.
	• Provide supportive care, including high-calorie supplements, as needed.

Grade 4 (anorexia only)	• Interrupt KPT-8602 and Inqovi dosing until anorexia resolves to Grade ≤ 2 or baseline. • Once improved to Grade ≤ 2 or baseline, participant is clinically stable, and any other contributing factors have been addressed: restart both KPT-8602 and Inqovi one dose level below. • If anorexia does not improve to Grade ≤ 2 or baseline within 7 days, permanently discontinue treatment.
Nausea or vomiting, acute	

Grade 3	• Interrupt KPT-8602 and Inqovi dosing until resolved to Grade ≤ 2 or baseline.
	• Once improved to Grade ≤ 2 or baseline and participant is clinically stable:
	  o If first occurrence and adequate supportive care resulted in improvement to Grade ≤ 1 within 3 days: restart KPT-8602 and Inqovi at the current dose
	  o If second occurrence or first occurrence not meeting criteria above: restart KPT-8602 one dose level below and Inqovi at same dose.
	  o If third occurrence: restart both KPT-8602 and Inqovi one dose level below.

Diarrhea	
Grade 2	• Rule out infectious causes and institute standard anti-diarrheal therapy • After the first occurrence, consider instituting loperamide 2 mg prophylactically approximately 1-2 hours before the administration of KPT-8602 and repeated every 4 hours for the first 12 hours • Reduce KPT-8602 by one dose level until resolved to Grade ≤ 1 or baseline, then restart at the current dose level. Maintain Inqovi dose.

Grade 3	• Rule out infectious causes and institute standard anti-diarrheal therapy
	• Institute prophylactic loperamide, as above
	• Interrupt KPT-8602 and Inqovi until resolved to Grade ≤ 1 or baseline.
	• Once resolved to Grade ≤ 1 or baseline:
	  o If first occurrence: restart KPT-8602 one dose level below and Inqovi at same dose.
	  o If second or later occurrence: restart both KPT-8602 and Inqovi one dose level below.
	  o If diarrhea stabilizes for at least 4 weeks at Grade ≤ 1 or baseline, then the prior dose of KPT-8602 and Inqovi may be resumed at PI discretion.

Grade 4	• Rule out infectious causes and institute standard anti-diarrheal therapy • Institute prophylactic loperamide, as above • Interrupt KPT-8602 and Inqovi until resolved to Grade ≤ 1 or baseline. • Once resolved to Grade ≤ 1 or baseline: restart both KPT-8602 and Inqovi one dose level below.
Hyponatremia	

Toxicity	Recommended Action*
Grade 3 (sodium level 125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms)	• Consider administration of appropriate saline solution and re-measure serum sodium levels. If (corrected) sodium is Grade ≤1 or baseline, then participant may receive standard dose of KPT-8602. • If immediate sodium correction is not successful, skip 1 dose of KPT-8602 and reassess sodium within 48 hours. Resume KPT-8602 dosing when sodium is Grade ≤1 (≥129 mmol/L) at the same dose level. • Institute salt supplementation 2-3 times per day.
Grade 4 (<120 mmol/L; life-threatening consequences)	• Correct sodium as per institutional guidelines. • Institute salt supplementation 2-3 times per day. • Hold KPT-8602 until sodium resolved to Grade ≤1 (≥129 mmol/L) then reduce KPT-8602 dose by 1 level. Sodium should be reassessed after 1 dose of KPT-8602 is skipped (i.e., within 48 hours) and corrective measures implemented. • If serum sodium stabilizes to Grade ≤1 for at least 4 weeks, original dose of KPT-8602 may be resumed.
Other non-hematologic toxicities at least possibly related to study treatment[a] [a]Follow standard dose-modifications for Inqovi as noted in the USPI for Inqovi	
Grade 1 or 2	• Maintain dose of KPT-8602. • Initiate standard supportive care per institutional guidelines.
Grade 3	• Interrupt KPT-8602 dosing until resolved to ≤ 2 or baseline, then reduce by one dose level. • Initiate standard supportive care per institutional guidelines.
Grade 4	• Interrupt KPT-8602 dosing until resolved to ≤ 2 or baseline, then reduce by two dose levels. • Initiate standard supportive care per institutional guidelines.

**Once the lowest dose level has been reached, if toxicity persists, discontinue drug.Exceptions can be made (i.e., dose reduction not required with the next cycle) for the following adverse events which are not considered clinically significant by the PI: isolated values of ≥ Grade 3 alkaline phosphatase elevation, alopecia*

3.4 On Study Assessments/Evaluations

The following describes all tests and procedures to be conducted on the study and during treatment. Assessments will be performed according to the Study Calendar (Section **3.5**).

3.4.1 Timing of Procedures

For each time period, consider the following order of assessments:

- **Screening:** Refer to Section **2.2**.
- **Baseline:** Baseline assessments to be performed within 7 days prior to initiating study treatment. Tests performed as part of screening do not need to be repeated if they were performed within the specified window prior to initiating treatment.
- **Assessment Windows:** All evaluation days, for flexibility around participant schedules, can be performed within -3 days for a new cycle (day 1, cycle 2-beyond); mid-cycle assessments can be performed with a window of +/- 3 days for cycles 2-beyond. The maximum number of days permitted between the last day of the previous cycle and the start of the next cycle is 28 days.

- **Unscheduled Visits:** In the event of an unscheduled/unplanned visit (e.g., additional clinical assessment(s) due to toxicity), the investigator should use the best clinical judgment as to the necessary assessments. In the event that the decision is made to continue treatment, all tests/assessments as required by the next visit on the Study Calendar (Section **3.5**) should still be conducted (or repeated) within the applicable windows. If a decision is made to discontinue treatment, the participant should have a post-therapy follow-up with tests/assessments completed (or repeated) within the applicable windows.
- **Disease Progression:** When a participant has disease progression on treatment while being evaluated at the NIH, evaluations should be done within +10 days after diagnosis of progression.
- **End of Treatment Visit**: To be done 30 days (+10 day window) after the last dose of study therapy. If participants are not able to come to the Clinical Center for this visit, they will be contacted by a member of the study team for adverse events and further cancer therapy. In these cases, the physical exam will not be required, and laboratory tests performed outside of the Clinical Center may be collected.
- **Post-therapy Follow-up:** Follow up will occur via phone call every 3 months (+/-2 weeks) for first 24 months, then every 6 months (+/-4 weeks) for 3 years, then annually until the end of study. Outside medical records will be requested along with the phone call for the first follow-up visit only and if clinically indicated at a later point.
- **End of Study:** To occur when all participants have been followed for up to 8 years or have died.
- **Telehealth/Remote Visits**: In instances when participant is not able to come, participant may be contact by phone, email or other NIH approved remote platform used in compliance with local policy, including HRPP Policy 303. Only unscheduled/unplanned visits may be conducted by telehealth. Scheduled timepoint visits must be conducted in-person, therefore collection datapoints will not be affected.

3.4.2 Description of Procedures

- Medical history: a review of treatment history, any ongoing medical conditions, and medical history pertaining to eligibility on study and involvement during the study.
- Physical exam: review of organ systems, weight, and vital signs (i.e., temperature, pulse, respirations, blood pressure, and oxygen saturation). After initiation of study drug, symptom-directed physical examinations will be performed as clinically indicated in the investigator's judgment. Note: Height will only be required prior to treatment no later than Cycle 1 Day 1.
- Performance status (ECOG and Karnofsky): an assessment of activities of daily living; see **Appendix A**.
- Laboratory assessments: the following comprises the required tests/analytes. These assessments may be performed at Clinical Laboratory Improvement Amendments (CLIA) (or equivalent) certified laboratories outside the enrolling site and results forwarded to the study team for review and management. Given that the methodologies utilized are similar

across all laboratories, no significant variability is expected and there is no anticipation that study data will be affected.

However, as different laboratories use slightly different kinds of equipment, each laboratory must determine/validate its own reference ranges. Therefore, on this protocol, normal ranges from each lab will be used in reference to terms such as ULN, except in cases where absolute values are appropriate and are specified as such. Note: Panels containing the tests below may be ordered in lieu of individual tests.

- CBC with differential: includes Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, WBC, RBC, Hemoglobin, Hematocrit, RBC Indices, MCV, RDW, Platelet.
- Blood chemistries: includes Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Magnesium total (Mg), Inorganic Phosphorus, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin, Total Protein will be performed to assess organ function for safety
- HIV, HBV, HCV – infectious disease serologies as per section **2.2.2**
- Vitamin B12, Folate, copper, zinc, TSH, free T4- to assess alternative/reversible causes of cytopenias that may confound MDS diagnosis at screening
- Reticulocyte count
- Urinalysis: for safety
- Serum or urine pregnancy test: performed prior to administration of study therapy in individuals of childbearing potential (see Section **2.1.1.5**)

- Electrocardiogram: 12-lead ECGs will be performed to assess cardiac activity
- Bone marrow biopsy and aspiration: to assess response to therapy
- Concomitant medications: a record of all medications including herbal supplements but not including study therapy that a participant has taken during the study will be recorded in order to assess confounding factors in safety and efficacy assessments
- Adverse events: participant reported adverse events will be collected throughout the study in order to assess safety.
- TBNK: for immunologic phenotyping
- Study drug administration, including dispensing and adherence review: Study drug will be dispensed at each cycle and instructed to be self-administered by participants, unless otherwise described, per schedule – see Section **3.1.4**. Participants will be given a dosing diary (see **Appendix K**) to be reviewed at each noted visit for drug dherence/accountability.

3.4.3 Correlative/Exploratory Assessments

- Research blood and tissue samples: refer to Section **5**.
- Clinician tools:

- **Rockwood Frailty Index (Appendix E):** The Rockwood Clinical Frailty Score (CFS) was developed as a deployable tool to be used by clinicians to assess level of vulnerability. It uses clinical descriptors and pictographs to divide participants into 9 levels of vulnerability ranging from 1 (very fit) to 9 (terminally ill). (46) This 9-point scale uses a visual chart to assess frailty classifications; someone with a score of ≥5 is classified as frail. The CFS was validated in a sample of 2305 older Canadian participants who remained alive 5 years after the Canadian Study of Health and Aging (CSHA-2). (47) CFS will be completed in a clinical setting. A member of the study team will observe the participants physical activity and ability and score them.
- **MDS-CI (Appendix F):** MDS-specific comorbidity index (MDS-CI) is a scoring system for MDS participants to be used by clinicians using a time-dependent index to predict the effects of comorbidities on treatment outcomes. (48) Five comorbidities independently predictive for non-leukemic death (cardiac, hepatic, pulmonary, renal, solid tumor) were assigned a score proportional to the regression coefficient of the multivariable Cox's proportional hazards model, the MDS-CI score was calculated as the sum of these weighted scores, and grouped into three risk groups – low, intermediate, and high risk. The MDS-CI was validated in a sample of 840 MDS participants from Pavia, Italy and a validation cohort of 504 participants in Dusseldorf, Germany. (49) A member of the study team will assess clinical information and score by completing the standard form.

- Patient-reported outcomes (PROs): The following PROs will be administered on this study (electronically via a CCR-approved system – Scribe;which is not yet 21 CFR 11 validated, however certification is currently being pursued). Participant questionnaires are only offered in English and are therefore are not required in non-English speaking participants that may be enrolled on the protocol
  - **European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire = EORTC QLQC30 score** (see Study Instrument packet and **Appendix G**): The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire is a participant self-report questionnaire used to assess participants' health-related quality of life in the oncology field. (50) This questionnaire incorporates nine multi-item scales, three symptom scales, a global health scale, and a quality-of-life scale. This questionnaire was validated across three language-cultural groups as well as against different questionnaires. (51) EORTC QLQ-C30 has been the most frequently used participant-reported outcome (PRO)/quality of life questionnaire in published MDS studies to-date and has commonly been a contributory measure of PRO to drug-approval processes for MDS. (52) This questionnaire takes approximately 15 minutes to complete. This will be completed at baseline, at response evaluation, at disease progression, at the end of treatment and post therapy follow-up.
  - **NIH MDS Adult Psychosocial Assessment** (see Study Instrument packet/ **Appendix H**): The psychosocial assessment is a self-report form that was originally developed for the NIH gastrointestinal stromal tumor (GIST) Clinic(53) in order to identify specific psychosocial areas of concern and symptoms not covered in the Patient-Reported Outcomes Measurement Information System (PROMIS) and

other standardized measures. It contains items covering demographic factors, perceived general health, psychosocial concerns, psychiatric history, self-identified needs, and interest in a range of possible psychosocial services. It has now been adapted and is being used with participants at the NIH participating in the Medullary Thyroid Cancer (MTC) and RUNX1 natural history studies. This questionnaires takes approximately 10 minutes to complete.

- **PRO-CTCAE** (see Study Instrument packet/**Appendix H**): The PRO-CTCAE is a participant-reported outcome measurement system developed by the NIH to capture the symptomatic adverse events in participants on cancer clinical trials [1]. It was designed as a companion to the Common Terminology Criteria for Adverse Event (CTCAE), which is often used per medical professionals' evaluation. This instrument will allow us to select, but not be limited to the symptoms that are anticipated based on the previous experiences. It can be a flexible tool for descriptive reporting system, which participants can complete at their own convenience. It also can be used in conjunction with the CTCAE to provide a better understanding of the toxicities of the clinical trial treatments. The PRO-CTCAE predetermined symptoms will consist of 15 symptoms and additional five open text boxes for participants to also add additional symptoms they may be experiencing. Completion of this instrument will take 3-4 minutes on average to complete. This will be completed at baseline, weekly for the first two cycles, at response evaluation, at disease progression, at the end of treatment and post therapy follow-up.
- **PROMIS Physical Function Short Form 10B** (see Study Instrument packet/**Appendix H**): A PROMIS Physical Function (PROMIS-PF) item bank was developed with the goal of measuring a person's ability to carry out various activities that require physical capabilities, ranging from self-care to more vigorous activities that require mobility, strength or endurance [5,6]. The PROMIS Physical Function 10b, a 10-item tool is scored from 1 'unable to do' to 5 'without any difficulty'. Time frame is not provided but current status is inferred. Completion of this instrument will take on average 2-3 minutes. This will be completed at baseline, weekly for the first two cycles, at response evaluation, at disease progression, at the end of treatment and post therapy follow-up.
- **Overall Side Effect Bother** (see Study Instrument packet/**Appendix H**): FACIT Measurement System Item GP5 'I am bothered by the side effects of treatment', is a single item summary index of bother that has demonstrated association with clinician-reported adverse events and with participants' ability to enjoy their lives that can help to adjudicate the variability in adverse effects across treatments being compared with each other [7]. Completion of this item will take less than a minute. This will be completed weekly for the first two cycles, at response evaluation, at disease progression, at the end of treatment and post therapy follow-up.
- **Patient Global Impression of Severity (PGI-S)** (see Study Instrument packet/**Appendix H**): The Patient Global Impression of Severity (PGI-S) is a global index that may be used to rate the severity of a specific condition (a single-state scale). It is a simple, direct, easy to use scale that is intuitively understandable to clinicians. It has been validated in studies of incontinence [8]

and insomnia[9]. For this study, we will ask participants to rate the severity of their symptoms using a 5-point scale (0-none, 1-mild, 2-moderate, 3-severe, 4-very severe) that will take less than a minute on average to complete. This will be completed at baseline, weekly for the first two cycles, at response evaluation, at disease progression, at the end of treatment and post therapy follow-up.

- **Patient Global Impression of Change (PGI-C)** (see Study Instrument packet/**Appendix H**): Patient Global Impression of Change (PGI-C) aims to quantify disease activity relative to an anchor point. Specifically, participants are asked to calculate the difference between their current and previous health state based on a Likert scale. Although PGI-C scales typically comprise between 7 and 11 points which show optimal participant preference, discriminative ability and test–retest ability, they can be tailored to specific conditions and disease parameters as per the clinicians' needs [10]. For this study, we will ask participants to rate their global impression of change in their symptoms since their last visit using a 5-point scale (1-much improved, 2-improved, 3-no change, 4-worse, 5-much worse). Completion of this item will take less than a minute on average. This will be completed weekly for the first two cycles, at response evaluation, at disease progression, at the end of treatment and post therapy follow-up.

3.5 STUDY CALENDAR

3.5.1 Phase I and II – Screening & Cycle 1

Procedure	***Screening***	***Baseline***	***Cycle 1***												
			Day 1	***Days 2-3***	***Days 4-5***	***Day 8***	***Days 9-12***	***Days 13-14***	***Day 15***	***Days 16-19***	***Day 20***	***Day 21***	***Day 22***	***Day 23***	***Day 28***
Window(s):	*≤30 days*	*≤7 days*	*≤7 days*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
Histologic confirmation[1]	*X*														
Medical history	*X*	*X*	*X*												
Physical exam	*X*	*X*	*X*			*X*			*X*				*X*		
Vital signs[2]	*X*	*X*	*X*			*X*			*X*				*X*		
Height	*X*														
Weight	*X*	*X*	*X*			*X*			*X*				*X*		
Performance score	*X*	*X*	*X*												
CBC/differential	*X*	*X*	*X*			*X*			*X*				*X*		
Reticulocyte count	*X*	*X*	*X*												
Chemistries[3]	*X*	*X*	*X*			*X*			*X*				*X*		
Folate, copper, zinc, TSH, free T4, Vitamin B12	*X*														
Ferritin, erythropoietin	*X*	*X*													
HIV HBV and HBC serologies	*X*														
Pregnancy test	*X*	*X*	*X*[4]												
Urinalysis		*X*	*X*												
ECG	*X*	*X*	*X*[5]						*X*[5]						
Bone marrow biopsy and aspirate[6]	*X*[7]	*X*[8]													*X*[9]
TBNK panel[10]		*X*	*X*												
Next gen seq- myeloid panel	*X*[11]	*X*[12]													
*Correlative research studies (see Section **5.1**)*		*X*													*X*[13]
*PK/PD (see Section **5.1**)*						*X*[14]	*X*[15]	*X*				*X*[16]	*X*	*X*	
Inqovi administration[17]			*X*	*X*	*X*										
KPT-8602 administration						*X*	*X*	*X*[18]	*X*	*X*	*X*[19]	*X*[20]			

Procedure	***Screening***	***Baseline***	***Cycle 1***												
			Day 1	***Days 2-3***	***Days 4-5***	***Day 8***	***Days 9-12***	***Days 13-14***	***Day 15***	***Days 16-19***	***Day 20***	***Day 21***	***Day 22***	***Day 23***	***Day 28***
Window(s):	*≤30 days*	*≤7 days*	*≤7 days*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
Transfusion dependency assessment			*X*						*X*						
Adverse event assessment			*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*		*X*	*X*
Concomitant medications		*X*	*X*			*X*			*X*			*X*			
Response Assessment															*X*
Rockwood/CFS and MDS-CI Questionnaires		*X*													
PRO: NIH MDS Adult Psychosocial Assesment		*X*													
PRO: EORTC-QLQC30[21]		*X*	*X*												*X*
PRO: PRO-CTCAE[21]		*X*	*X*			*X*			*X*			*X*			*X*
PRO:Overall Side Effect Bother[21]						*X*			*X*			*X*			*X*
PRO:PROMIS Physical Function[21]		*X*	*X*			*X*			*X*			*X*			*X*
PRO: PGI-S[21]		*X*	*X*			*X*			*X*			*X*			*X*
PRO: PGI-C[21]						*X*			*X*			*X*			*X*

[1]Any time prior to enrollment.
[2]Includes temperature, blood pressure, heart rate, respiratory rate, oxygen saturation
[3]Includes sodium, chloride, potassium, CO2, BUN, creatinine, glucose, AST/ALT, alkaline phosphatase, total bilirubin, direct bilirubin, albumin, total protein, magnesium, phosphorous, calcium, LDH, uric acid
[4]To be performed within 24 hrs prior to initating study treatment, for individuals of childbearing potential.
[5]ECG on C1D1 and C1D15 will be done 2 hours post-dose that day (+/- 20 minutes) for QTc monitoring.
[6]Bone marrow core biopsy will be sent for pathologic evaluation. Bone marrow aspirate will be sent for flow cytometry and additional studies per Section **5.1.**
[7]May be performed during screening evaluation if no prior sample is available to pathology review to determine diagnosis; must be done within 30 days prior to treatment initiation.
[8]Must be done within 30 days prior to treatment initiation. If a fresh sample was taken at screening to determine eligibility, and 30 days have not elapsed, then bone marrow biopsy and aspirate will not be repeated at baseline.
[9]Phase I only. Bone marrow biopsy and aspirate and flow cytometry may be done on C1D28 +/- 3 days.
[10]CD3, CD4, CD8, CD19, CD4:CD8 ratio, NK markers clinical panel.
[11]May be performed during screening evaluation or baseline; must be done within 30 days prior to treatment initiation.

[12]May be performed during screening evaluation or baseline; must be done within 30 days prior to treatment initiation.
[13]Phase I only, on day of bone marrow biopsy (which may be done on C1D28 +/- 3 days).
[14]See Section **5.1** for detailed PK/PD sampling schedule.
[15]On C1D12, blood samples for PK will be collected for participants receiving KPT-8602 at dose level 1 or dose level -2 only (see Section **5.1** for detailed PK/PD sampling schedule).
[16]On C1D21, blood samples for PK will be collected for participants receiving KPT-8602 at dose level 2 or dose level -1 only (see Section **5.1** for detailed PK/PD sampling schedule).
[17]HR-MDS cohorts (Cohorts 1 & 2): administer Inqovi orally once daily on Days 1-5 of each 28-day cycle.
[18]Participants receiving KPT-8602 at dose level 2 or dose level -1 only.
[19]Participants receiving KPT-8602 at dose level 2 or dose level -1 only.
[20]Participants receiving KPT-8602 at dose level 2 or dose level -1 only.
[21]PROs administered at baseline need not be repeasted at C1D1 if within 7 days.

3.5.2 Phase I and II – Cycle 2 – beyond

Procedure	***Cycles 2-3***					***Cycles ≥ 4***			***At Disease Progression***	***End of Treatment***	***Post-therapy follow-up[1]***	***End of Study***
	Day 1	***Day 8***	***Day 15***	***Day 22***	***Day 28***	***Day 1***	***Day 8***	***Day 28***				
Window(s):	*-3 days*	*±3 days*	*±3 days*	*±3 days*	*±3 days*	*-3 days*	*±3 days*	*±3 days*	*±3 days*	*30+7 days*	*See note.*	
Physical exam	*X*		*X*			*X*				*X*		
Vital signs[2]	*X*		*X*			*X*				*X*		
Height												
Weight	*X*		*X*			*X*				*X*		
Performance score												
Chemistries[3]	*X*		*X*			*X*			*X*	*X*		
CBC/differential	*X*		*X*			*X*			*X*	*X*		
Reticulocyte count	*X*					*X*			*X*	*X*		
Pregnancy test	*X*					*X*						
Urinalysis	*X*					*X*				*X*		
Bone marrow biopsy and aspirate [4]					*X[5]*			*X[6]*	*X*			
TBNK panel[7]	*X*					*X*			*X*	*X*		
Peripheral blood flow cytometry									*X[8]*			
Next gen seq- myeloid panel					*X[9]*			*X[10]*	*X*			
*Correlative research studies (see Section **5.1**)*	*X*		*X[11]*		*X[12]*	*X*		*X[13]*	*X*	*X*		
Inqovi administration[14]	*X*					*X*						
KPT-8602 administration[15]		*X*	*X*				*X*					
Response evaluation[16]	*X*					*X*						
Transfusion dependency assessment	*X*		*X*			*X*			*X*	*X*		
Adverse event assessment	*X*	*X*	*X*	*X*	*X*	*X*		*X*	*X*	*X*		
Concomittant-medications	*X*		*X*			*X*				*X*		
PRO: NIH MDS Adult Psychosocial assessment[17]					*X*			*X*		*X*		
PRO: EORTC-QLQC30[18]	*X*				*X*	*X*		*X*	*X*	*X*	*X*	
PRO: PRO-CTCAE[19]	*X*	*X*	*X*	*X*	*X*	*X*		*X*	*X*	*X*	*X*	
PRO: Overall Side Effect Bother[20]					*X*	*X*		*X*	*X*	*X*	*X*	
PRO: PROMIS Physical Function[19]	*X*	*X*	*X*	*X*	*X*	*X*		*X*	*X*	*X*	*X*	
PRO: PGI-S[19]	*X*	*X*	*X*	*X*	*X*	*X*		*X*	*X*	*X*	*X*	

Procedure	*Cycles 2-3*					*Cycles ≥ 4*			*At Disease Progression*	*End of Treatment*	*Post-therapy follow-up[1]*	*End of Study*
	Day 1	*Day 8*	*Day 15*	*Day 22*	*Day 28*	*Day 1*	*Day 8*	*Day 28*				
Window(s):	*-3 days*	*±3 days*	*±3 days*	*±3 days*	*±3 days*	*-3 days*	*±3 days*	*±3 days*	*±3 days*	*30+7 days*	*See note.*	
PRO: PGI-C[20]					*X*	*X*		*X*	*X*	*X*	*X*	
Survival											*X*	*X*

[1]Follow-up will occur via phone call every 3 months (+/-2 weeks) for the first 24 months, then every 6 months (+/- 4 weeks) for 3 years, then annually for up to 8 years. Overall survival, event-free survival, progression-free survival, and treatment status will be assessed at all timepoints.
[2]Includes temperature, blood pressure, heart rate, respiratory rate, oxygen saturation
[3]Includes sodium, chloride, potassium, CO2, BUN, creatinine, glucose, AST/ALT, alkaline phosphatase, total bilirubin, direct bilirubin, albumin, total protein, magnesium, phosphorous, calcium, LDH, uric acid for all timepoints beyond screening and baseline
[4]Bone marrow core biopsy will be sent for pathologic evaluation. Bone marrow aspirate will be sent for flow cytometry and additional studies per Section **5.1.**
[5]Required for Phase II, C2D28 +/- 3 days. Additional timepoints as clinically indicated
[6]Required for Phase II, C6D28 +/- 3 days. Additional timepoints as clinically indicated
[7]CD3, CD4, CD8, C19 clinical panel.
[8]If evidence of peripheral blood blasts
[9]Required for Phase II, C2D28 +/- 3 days. Additional timepoints as clinically indicated
[10]Required for Phase II, C6D28 +/- 3 days. Additional timepoints as clinically indicated
[11]Sparse PK sampling for all participants on C2D15 and C3D15 to be drawn prior to taking dose (trough).
[12]On day of bone marrow biopsy, if being performed.
[13]On day of bone marrow biopsy, if being performed.
[14]HR-MDS cohorts (Cohorts 1 & 2): administer Inqovi orally once daily on Days 1-5 of each 28-day cycle.
[15]Administer KPT-8602 according to dose level assigned to each participant (see Section **3.3**)
[16]Assessment of response to therapy, based on peripheral blood counts +/- bone marrow results (if done).
[17]NIH MDS Adult Psychosocial Assesment to be completed at C12D28 (+/- 1 day), C24D28 (+/- 1 day) and end of treatment.
[18]EORTC-QLQC30 to be completed by participants at C3D28 (+/- 1 day), C6D28 (+/- 1 day), C9D28 (+/- 1 day), C12D28 (+/- 1 day), C24D28 (+/-1 day) and end of treatment. See Section **3.4.3**
[19]PRO_CTCAE, PROMIS PF 10b, and PGI-S will be completed at baseline, weekly for cycles 1 through 3 on D8 (+/- 7 days), D15 (+/- 7 days), D22 (+/- 7 days) and D28 (+/- 7 days), C6D28 (+/- 7 days), C9D28 (+/- 7 days), C12D28 (+/- 7 days), C24D28 (+/- 7 days), at disease progression, and end of treatment. See Section **3.4.3**.
[20]FACIT Bother and PGI-C done weekly for cycles 1 through 3 on D28 (+/- 7 days), D15 (+/- 7 days), D22 (+/- 7 days), D28 (+/- 7 days), C6D28 (+/- 7 days), C9D28 (+/- 7 days), C12D28 (+/- 7 days), C24D28 (+/- 7 days), at disease progression, and end of treatment. See Section **3.4.3**.

3.6 COST AND COMPENSATION

3.6.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures are performed outside the NIH Clinical Center, participants may have to pay for these costs.

3.6.2 Compensation

Participants will not be compensated on this study.

3.6.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.7 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from protocol therapy, effort must be made to have all participants complete a safety visit approximately 30 days after the last dose of study therapy (i.e., End of Treatment Visit – see Study Calendar [Section **3.5**]).

3.7.1 Criteria for removal from protocol therapy

- Progressive disease
- Participant requests to be withdrawn from active therapy
- Toxicities (see Section **3.3.2**)
- Lack of, at least partial remission, after 6 cycles of therapy
- Investigator discretion
- Positive pregnancy test

3.7.2 Off-Study Criteria

- Off treatment and completed follow-up on study (i.e., all participants will be followed for 8 years, or until death, whichever comes first)
- Participant requests to be withdrawn from study
- Death
- Screen failure
- Lost to follow-up
- Study is cancelled for any reason

3.7.3 Lost to Follow-up

A participant will be considered lost to follow-up if they fail to return for 3 scheduled visits or respond to follow-up hpone calls/is unable to be reached by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 30 days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, an IRB-approved certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.

Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4 CONCOMITANT MEDICATIONS/MEASURES

4.1 ALLOWED CONCOMITANT MEDICATIONS/SUPPORTIVE MEASURES

4.1.1 Antimicrobial Prophylaxis

- Per standard of care supportive measures for participants with MDS, standard antimicrobial prophylaxis will be considered for neutropenic participants who exhibit ANC <1000 cells/mcL for ≥7 days prior to study enrollment, either initiation of continuation of prior supportive therapy, including but not limited to:
    - antibacterial prophylaxis with levofloxacin 750 mg daily
    - antiviral prophylaxis with acyclovir 800 mg twice daily
- For participants with clinical indication administration of anti-*Pneumocystis jiroveci* pneumonia prophylactic therapy is allowed.
- For participants with history of fungal infection, or other clinical indication, continuation of antifungal prophylaxis will be allowed.

4.1.2 Hematologic Support

- Due to the hematologic abnormalities associated with MDS, management of hematologic toxicity in MDS participants will be at the discretion of the PI/treating investigator.
- Transfusions of red blood cells and platelets will be allowed per the appropriate participant-specific hematologic parameters.
- G-CSF may be administered for participants with ANC < 500/mcL per the discretion of the treating physician.
- Thrombopoietin agonists may be administered for participants with PLT < 50 x 10^9/L per the discrestion of the treating physician.

- Participants receiving a stable dose of erythropoiesis-stimulating agent (ESA) for at least 1 month at the time of study entry may continue to receive ESA, but changes in dosing of ESA or new start of ESA within <30 days are not permitted.

4.1.3 Other Supportive Care

- In order to minimize nausea, unless contraindicated, all participants will receive a serotonin receptor subtype 3 (5-HT3) antagonist (ondansetron or equivalent) before KPT-8602 dosing. This may be tapered after 1-2 cycles of treatment, per Investigator discretion.
    - 5-HT3 receptor antagonists (ondansetron 8 mg or equivalent) should be started before study treatment dosing and continued for 3 consecutive days.

4.2 DRUG INTERACTIONS

The risk of drug-drug interactions with KPT-8602 is low. However, administration of eltanexor with drugs that undergo substantial GSH conjugation (e.g., acetaminophen) should be minimized. See Section **14.1.7**.

4.3 CONTRAINDICATED AGENTS

- No other antineoplastic, immunomodulatory, or immunosuppressive therapies, including corticosteroids (barring adrenal insufficiency supplementation dosing), should be given concomitantly while on study treatment.

5 CORRELATIVE STUDIES FOR RESEARCH

Participants may submit none, all, or a portion of research specific biospecimens to stay on study. Providing *all* research biospecimens is not a criterion for study inclusion and all samples are optional with the exception of pharmacokinetic (PK) samples. Any unused biological sample or derivative that is obtained from a participant during a clinical procedure on this study may be used for research and/or stored for future research purposes.

Every effort will be made to collect all research samples, including bone marrow aspirates and peripheral blood draws, at the time of a scheduled diagnostic bone marrow aspirate or blood draw for clinical purposes as listed in the study calendar and table below.

If additional tests are done for clinical purposes, additional samples will be collected also at that time(s), if feasible, and used for research.

5.1 BIOSPECIMEN COLLECTION

Test/assay	Volume (approx.)	Type of sample/ tube(s)^	Collection point	Location of specimen analysis
Pharmacokinetics (PK)	4 mL	Blood, SST vacutainer tubes -Serum samples should then be	Dose levels -2 and 1: **C1D8** (1)Pre-dose, (2) 1 hr (± 10 min) post-dose, (3) 2 hr (± 10 min) post-dose, (4) 3 hr (± 10 min) post-dose,	Clinical Pharmacology Program (CPP) ; Figg laboratory

Test/assay	Volume (approx.)	Type of sample/ tube(s)^	Collection point	Location of specimen analysis
		transferred to micronic tubes for shipping to bioanalytical lab.	(5) 4 hr (± 20 min) post-dose, (6) 8 hr (± 20 min) post-dose, (7) 24 hr (± 1 hr) post-dose (8) 24 hr (± 1 hr) post-dose-i.e, C1D9 pre-dose **C1D12** (9) Pre-dose, (10) 2 hr (± 10 min) post-dose, (11) 3 hr (± 10 min) post-dose, (12) 8 hr (± 20 min) post-dose, (13) 24 hr (± 1 hr) post-dose-i.e, C1D13 pre-dose, (14) 48 hrs (± 2hr) post-dose- i.e, C1D14 pre-dose Dose levels -1 and 2: **C1D8** (1)Pre-dose, (2) 1 hr (± 10 min) post-dose, (3) 2 hr (± 10 min) post-dose, (4) 3 hr (± 10 min) post-dose, (5) 4 hr (± 20 min) post-dose, (6) 8 hr (± 20 min) post-dose, (7) 24 hr (± 1 hr) post-dose i.e, C1D9 pre-dose **C1D21** (9) Pre-dose, (10) 1 hr (± 10 min) post-dose, (11) 3 hr (± 10 min) post-dose, (12) 4 hr (± 20 min) post-dose, (13) 8 hr (± 20 min) post-dose, (14) 24 hr (± 1 hr) post-dose-i.e, C1D22 pre-dose, (15) 48 hrs (± 2hr) post-dose- i.e, C1D23 pre-dose **Sparse PK sampling** for all participants: C2D15, C3D15 trough dosing to be drawn prior to taking dose that day.	
Pharmacodynamics (PD):	2.5 mL	Blood, Paxgene RNA tube	**Phase I: C1D8** (1)Pre-dose, (2) 1 hr (± 10 min) post-dose, (3) 2 hr (± 10	Clinical Pharmacology

Test/assay	Volume (approx.)	Type of sample/ tube(s)^	Collection point	Location of specimen analysis
XPO1 mRNA expression (RT-PCR)			min) post-dose, (4) 3 hr (± 10 min) post-dose, (5) 4 hr (± 20 min) post-dose, (6) 8 hr (± 20 min) post-dose, (7) 24 hr (± 1 hr) post-dose	Program (CPP) ; Figg laboratory Larson laboratory
Next generation sequencing/ Myeloid molecular mutation panel: TSO-500 Panel Methylation studies per Section **5.2**	2 mL per tube	Bone marrow, EDTA (lavender top) or ACD (yellow top)	(1) Baseline (2) Phase I: C1D28 (+/-3 days) (3) Phase II: C2D28 (+/-3 days) (4) Phase II:C6D28 (+/-3 days) (5) Any additional timepoints when bone marrow biopsy is done (6) Disease progression	NCI Laboratory of Pathology
Clinical MDS FISH* *only needed if cytogenetic analysis not possible or unrevealing	3 mL per tube if bone marrow 5 mL per tube if whole blood	Blood or bone marrow aspirate, Sodium Heparin green top	(1) Baseline (2) Phase I: C1D28 (+/-3 days) (3) Phase II: C2D28 (+/-3 days) (4) Phase II:C6D28 (+/-3 days) (5) Any additional timepoints when bone marrow biopsy is done (6) Disease progression	Mayo send out test
Clinical Cytogenetics	3 mL	Bone marrow, Sodium Heparin green top	(1) Baseline (2) Phase I: C1D28 (+/-3 days) (3) Phase II: C2D28 (+/-3 days) (4) Phase II:C6D28 (+/-3 days) (5) Any additional timepoints when bone marrow biopsy is done (6) Disease progression	Mayo send out test
Additional samples (e.g., proteomics, cytokines); Section **5.2**	5 mL x 2 tubes	Blood, EDTA tube	(1) Baseline (2) Phase I: C1D28 (+/-3 days) (3) Phase II: C2D28 (+/-3 days) (4) Phase II:C6D28 (+/-3 days)	CPP; Figg laboratory

Test/assay	Volume (approx.)	Type of sample/ tube(s)^	Collection point	Location of specimen analysis
			(5) Any additional timepoints when bone marrow biopsy is done (6) Disease progression	
Additional samples (e.g., proteomics, cytokines); Section 5.2	5 mL x 2 tubes	Bone marrow aspirate, EDTA tube	(1) Baseline (2) Phase I: C1D28 (+/-3 days) (3) Phase II: C2D28 (+/-3 days) (4) Phase II:C6D28 (+/-3 days) (5) Any additional timepoints when bone marrow biopsy is done (6) Disease progression	CPP; Figg laboratory
Research: *Ribosome footprinting; Quantitative mass spectrometry*	10 mL	Bone marrow aspirate, EDTA tube	(1) Baseline (2) Phase I: C1D28 (+/-3 days) (3) Phase II: C2D28 (+/-3 days) (4) Phase II:C6D28 (+/-3 days) (5) Any additional timepoints when bone marrow biopsy is done (6) Disease progression	Larson laboratory

^ *Tubes may be substituted based on availability with the permission of the PI or laboratory investigator.*

5.1.1 Peripheral Blood

Blood samples for research will be collected at time points indicated in the table above and initially processed in Blood Processing Core (BPC) prior to sharing with the research labs for analyses, as indicated below (Section 5.2).

5.1.2 Bone Marrow Samples

Bone marrow for research will be collected at the same time as clinical procedures whenever possible. Samples will be collected distributed per the biospecimen table (Section 5.1), including the Blood Processing Core (BPC) and Larson laboratory. Additional samples than those that would be routinely sent to LP will include aspirate to be tested per TSO 500 and research methylation studies as well as sent to Mayo as a send-out test for Clinical Cytogenetics with reflex to Clinical MDS FISH analyses if cytogenetic analysis is not possible or unrevealing. The results of CLIA approved clinical testing will be made available in the participant's medical record.

5.2 CORRELATIVE ANALYSES

We hypothesize that aberrancies in methylation, molecular shuttling, and ribosome biogenesis in MDS may be corrected by the combination of Inqovi and XPO1 inhibition. As such we propose the following assays to study these phenomena. Not all assays may be performed in each

participant specimen and additional assays not outlined here may be performed to address particular research questions or as technology develops and improved assays are implemented.

Analyses may be performed on banked or fresh tissue dictated by the specifics of the particular assay. In general, correlative assays will be performed using standard techniques on cells or plasma isolated using the Ficoll-Paque™ method. Commercial kits will be used for DNA and RNA isolations, as well as specific assays such as ELISA, LDH assay, and others. Standard procedures will be used for qPCR, mass spectrophotometry, western blotting, flow cytometry, and immunofluorescence. Assays will be performed by an assigned investigator(s) with extensive expertise and supervised by Dr. Larson laboratory with collaboration from NIH cores and field experts.

5.2.1 PK Studies

PK studies of KPT-8602 will be done by Dr. Figg's Clinical Pharmacology Program (CPP). For processing details see **Appendix J**.

Blood draws for PK analysis will be performed relative to in-clinic KPT-8602 dose. The actual date and time (24-hour clock time) of each sample collection and each dose of KPT-8602 will be recorded.

5.2.1.1 Phase I

In Phase I, PK sampling will be done in all participants receiving KPT-8602. The timing of blood sample collection for PK studies are specified in the table in Section **5.1**.

5.2.1.2 Phase II

In Phase II, PK sampling schedules at the RP2D of KPT-8602 will be the same as planned in Phase I.

5.2.2 PD Studies

5.2.2.1 Phase I only

Changes in XPO1 mRNA expression will be assessed by reverse transcription polymerase chain reaction (RT-PCR) in peripheral blood samples from participants treated with KPT-8602. Samples will be collected at the timepoints specified in the table in Section **5.1**.

5.2.3 Methylation Studies

Epigenetic studies including whole methylome analysis using next generation sequencing may be performed on bone marrow mononuclear cells. In general, MDS participants display increased methylation signatures, the foundation for which hypomethylating agents such as AZA and DAC have been used as the standard of care for HR-MDS. However, significant changes in methylation status post-HMA treatment has been inconclusive. Further, the effect of combined HMA and Eltanexor has yet to be studied and will be evaluated here. These studies will be performed by Dr. Aldape.

5.2.4 Proteomics Studies

Bone marrow cells may be used for global mass spectroscopy (MS)-based protein and phospho – protein proteomic analysis. Cells may also be fractioned prior to proteomic and MS analysis. We may also perform quantitative MS and surface MS to determine mechanisms of protein transport

and contribution of XPO1 inhibition to ribosome biogenesis, disease state, and response. These studies will be performed by Dr. Larson.

5.2.5 Cytokine Studies

Peripheral blood and bone marrow plasma will be frozen for chemokine and cytokine analysis. These studies will be performed by Dr. Larson.

5.2.6 Gene Editing

Gene editing may be performed to study specific biological disease processing. Editing may be performed using siRNA, shRNA, and/or CRIPSR editing methods. These may be performed using electroporation or viral transduction. Any cell line created by gene editing will not contain any participant identifying information. As pathways affected specifically by the combination of Inqovi and KPT-8602 are uncovered, specific pathway components may be modulated for validation. These studies will be performed by Dr. Larson.

5.2.7 Microarrays/Immunohistochemistry

Bone marrow aspirates may also be fixed in formalin and embedded in paraffin blocks for later use in tissue microarrays and/or immunohistochemistry.

5.2.8 DNA Damage

Both decitabine and XPO1 inhibition have been shown to increase DNA damage in cells; therefore, we will monitor DNA damage in participants bone marrow cells by evaluating expression of γH2AX before and after treatment via immunofluorescence and flow cytometry. Further, DNA damage repair pathways may also be evaluated by western blotting, immunofluorescence, and flow cytometry.

5.2.9 Additional Studies

In addition to assessing XPO-1 mRNA by RT-PCR, we may also investigate other potential PD markers including decreased expression of oncogenes (i.e., c-Myc), increased expression of tumor suppressor genes (i.e., ARRDC3) and decreased expression of DNA damage repair genes (phenomena that have been observed after XPO1 inhibition by eltanexor). In addition, we may examine protein marker levels including increased XPO1 protein degradation, increased NFkB signaling, nuclear accumulation of tumor suppressors such as p53, as well as plasma levels of proinflammatory cytokines such as IL-6 or IL-8.

Additional assays not described here may be used to validate findings from any of the proposed correlative assays. For example, western blotting, flow cytometry, and/or immunoflorescence may be used to quantitate protein expression or ribosome biogenesis in whole or fractionated cells. Further, validation assays not described here may be used to assess changes in specific cellular pathways (i.e., translation, secretion, and inflammatory pathways).

5.3 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed.

Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

All samples will be barcoded, with data entered and stored in the secure databases. These databases create a unique barcode ID for every sample and sample box, which cannot be traced back to

participants without database access. The data recorded for each sample includes the participant ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Participant demographics associated with the clinical center participant number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in database. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Note: The tracking system for the Blood Processing Core (BPC; Figg lab) is described below. All other CCR lab systems/databases at which samples will be stored/analyzed will follow required CCR requirements for tracking.

5.3.1 Dr. Figg's Blood Processing Core (BPC)

5.3.1.1 Blood and Bone Marrow Collection

Please e-mail NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov

See **Appendix J** for processing instructions.

5.3.1.2 Sample Data Collection

All samples sent to the Blood Processing Core (BPC) will be barcoded, with data entered and stored in Labmatrix utilized by the BPC. This is a secure program, with access to Labmatrix limited to defined Figg lab personnel, who are issued individual user accounts. Installation of Labmatrix is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen.

5.3.1.3 Sample Storage

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

5.3.2 Protocol Completion/Sample Destruction

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a participant withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the participant, if so requested). The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **7.2**.

Sample barcodes are linked to participant demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the Labmatrix. It is critical that the sample remains linked to participant information such as race, age, dates of diagnosis and death, and histological information.

5.4 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.4.1 Description of the scope of genetic/genomic analysis

Genetic analysis will be performed as outlined in section **5.2.2**, **5.2.6**, **5.2.8** and **5.2.9**. Briefly, DNA or RNA may be sequenced on any tissue or derivative and will include analysis of both somatic and germline mutations.

5.4.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

Initially the samples of each participant will be barcoded. At no time will participant's names be used on the blood and tissue samples. In some instances a subject's genetic data will be deposited into a public database such as dbGaP, however. Although there is controlled access to such a database, such a submission carries theoretical risks of revealing the identity of the subject. This is discussed in the consent.

5.4.3 Management of Results

Subjects will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for the purpose of this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists). Subjects will be contacted at this time with a request to provide a blood sample to be sent to a CLIA certified laboratory. If the research findings are verified in the CLIA certified lab, the subject will be offered the opportunity to come to NIH (at our expense) to have genetic education and counseling to explain this result. If the subject does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense).

This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

5.4.4 Genetic counseling

Genetic counseling will be offered in the case of finding a clinically actionable gene variant.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into a 21 CFR Part 11-compliant data capture system provided by the NCI CCR and ensuring data accuracy, consistency and timeliness. Data entry may also be achieved via other systems as permitted by CCR requirements (e.g., Labmatrix, PROs directly via Scribe). The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until resolution or stabilization of event.

Document AEs from the first study intervention, study day 1, through 30 days after the last dose of any study drug. Beyond 30 days, only adverse events which are serious and related to the study investigational agent need to be recorded.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the participant's outcome.

The PI (or designee) evaluation of each AE not captured in the clinical database determining that it meets the criteria above will be documented in the source documents. **Note:** The investigator performing the assessment must be a licensed provider listed on the 1572.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows*:*

_x_ Coded, linked data in an NIH-funded or approved public repository.

_x_ Coded, linked data in another public repository.

_x_ Coded, linked data in BTRIS (automatic for activities in the Clinical Center)

_x_ Coded, linked or identified data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

_x_ An NIH-funded or approved public repository. Insert name or names: ClinicalTrials.gov, dbGaP

_x_ BTRIS (automatic for activities in the Clinical Center)

_x_ Approved outside collaborators under appropriate individual agreements.

_x_ Publication and/or public presentations.

When will the data be shared?

_x_ Before publication.

_x_ At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

Participants will be assessed for response by standard response criteria for MDS.(54) For the purposes of this study, participants will be re-evaluated for response after each cycle by CBC with differential to assess for improvement in cytopenias and by protocol-defined time points for bone marrow evaluation. If results from bone marrow assessment and/or CBC demonstrate progression of disease (as defined by an increase in the number of malignant cells or blasts when compared to pre-treatment bone marrow examination or worsening cytopenias by amounts as defined below in section **6.3.1**), the participant will be taken off treatment. However, the participant will continue to be followed on study for other survival endpoints.

6.3.1 Response Criteria

The table below shows the 2006 International Working Group response criteria for altering the natural history of MDS,(55) with modified definitions for HI-E, HI-P, and HI-N in the suggested 2018 International Working Group response criteria.(54)

Category	**Response criteria** (responses must last at least 4 weeks)

Complete remission	• Bone marrow: ≤5% myeloblasts with normal maturation of all cell lines*
	• Persistent dysplasia will be noted*
	• Peripheral blood†
	  • Hgb ≥11 g/dL
	  • Platelets ≥100 X 10^9/L
	  • Neutrophils ≥1.0 X 10^9/L
	  • Blasts 0%

Category	**Response criteria** (responses must last at least 4 weeks)
Partial remission	All CR criteria if abnormal before treatment except: • Bone marrow blasts decreased by ≥50% over pretreatment but still >5% • Cellularity and morphology not relevant
Marrow CR	• Bone marrow: ≤5% myeloblasts and decrease by ≥50% over pretreatment • Peripheral blood: if HI responses, they will be noted in addition to marrow CR
Stable disease	Failure to achieve at least PR, but no evidence of progression for >8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to more advanced MDS FAB subtype than pre-treatment
Relapse after CR or PR	At least 1 of the following: • Return to pre-treatment bone marrow blast percentage • Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets • Reduction in Hgb concentration by ≥1.5 g/dL or transfusion dependence
Cytogenetic response	Complete • Disappearance of the chromosomal abnormality without appearance of new ones Partial • At least 50% reduction of the chromosomal abnormality
Disease progression	For participants with: • Less than 5% blasts: ≥50% increase in blasts to >5% blasts • 5%-10% blasts: ≥50% increase to 10% blasts • 10%-20% blasts: ≥50% increase to >20% blasts • 20%-30% blasts: ≥50% increase to >30% blasts Any of the following: • At least 50% decrement from maximum remission/response in granulocytes or platelets • Reduction in Hgb by ≥2 g/dL • Transfusion dependence
Survival	Endpoints: • Overall: death from any cause • Event free: failure or death from any cause • PFS: disease progression or death from MDS • DFS: time to relapse • Cause-specific death: death related to MDS

MDS, myelodysplastic syndromes; Hgb, hemoglobin; CR, complete remission; HI, hematologic improvement; PR, partial remission; FAB, French-American-British; AML, acute myeloid leukemia; PFS, progression-free survival; DFS, disease-free

survival.
To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
*Dysplastic changes should consider the normal range of dysplastic changes.
†In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such participants can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

Hematologic Improvement

Category	**Participant pre-trial baseline**	**Response criteria**	
Erythroid response (HI-E)	No Transfusion Dependence at baseline (0 RBC transfusions in 16 weeks)	At least 2 consecutive Hgb measurements ≥1.5 g/dL for a period of minimum 8 weeks in an observation period of 16 to 24 weeks compared with the lowest mean of 2 Hgb measurements (apart from any transfusion) within 16 weeks before treatment onset; only a response duration of at least 16 weeks, however, is considered clinically meaningful	
	Low Transfusion Dependence at baseline (3-7 RBC transfusions in 16 weeks in at least 2 transfusion episodes, maximum 3 in 8 weeks)	Transfusion independence, defined by the absence of any transfusions for at least 8 weeks in an observation period of 16-24 weeks with the same transfusion policy compared with 16 weeks prior to treatment; only a response duration of at least 16 weeks, however, is considered clinically meaningful	
	High Transfusion Dependence at baseline (≥8 RBC transfusions in 16 weeks, ≥ 4 transfusion episodes in 8 weeks)	Major response	Transfusion independence, defined by the absence of any transfusions over a period of minimum 8 weeks in an observation period of 16-24 weeks with the same transfusion policy compared with 16 weeks prior to treatment; only a response duration of at least 16 weeks, however, is considered clinically meaningful
		Minor response	A reduction by at least 50% of RBCs over a minimum of 16 weeks with the same transfusion policy, compared with 16 weeks prior to treatment
Platelet response (HI-P)	Pre-treatment PLT <100 x 10^9/L	• Absolute increase of 30 x 10^9/L for participants starting with >20 x 10^9/L PLTs	

Category	Participant pre-trial baseline	Response criteria
		or • Increase from <20 x 10^9/L to >20 x 10^9/L and by at least 100% In addition: • In addition, evolution of bleeding symptoms is to be taken into account • Increments of platelets also for participants with a pre-treatment PLT count of ≥100 x 10^9 are to be reported
Neutrophil response (HI-N)	Pre-treatment ANC <1.0 x 10^9/L	• At least 100% increase and an absolute increase >0.5 x 10^9/L • Increments of neutrophils also for participants with a pre-treatment ANC of ≥1.0 x 10^9/L are to be reported

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each participant while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements. Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.3 NCI Clinical Director Reporting

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to the Clinical Director/designee at NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH Required Data and Safety Monitoring Plan

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a regular weekly basis when participants are being actively treated on the trial to discuss each participant. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior participants.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each participant to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 SPONSOR PROTOCOL/SAFETY REPORTING

8.1 Definitions

8.1.1 Adverse Event

Any untoward medical occurrence in a participant or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2))

8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see section **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing

condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.

- A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient or subject convenience) is not considered a serious adverse event.
- Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32)

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 5.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.1.6 Adverse Events of Special Interest (AESI)

Neurological toxicity is considered an AESI and should be reported following SAE reporting procedures in Section **8.3** irrespective of temporal relationship to study drug administration and regardless of causality.

8.2 Assessment of Safety Events

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution (or stabilization) of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make

a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to Section **6.1**.

8.3 Reporting of Serious Adverse Events

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form. Any exceptions to the expedited reporting requirements are found in section **8.5**

All SAE reporting must include the elements described in section **8.2**. All serious adverse events recorded from the time of first investigational product administration to 30 days after last investigational product administration must be reported to the sponsor with the exception of any listed in Section **8.4**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 Waiver of Expedited Reporting to CCR

As death due to disease progression is part of the study objectives (PFS), and captured as an endpoint in this study, they will not be reported in expedited manner to the sponsor. However, if there is evidence suggesting a causal relationship between the study drug and the event, the event will be reported in an expedited manner according to Section **8.3**.

8.5 Safety Reporting Criteria to the Pharmaceutical Collaborators

Reporting will be per the collaborative agreement.

8.6 Reporting Pregnancy

All required pregnancy reports/follow-up to OSRO will be submitted to: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. Forms and instructions can be found here: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

8.6.1 Maternal exposure

If a participant becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy becomes known.

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (Section **8.1.2**) should be reported as SAEs.

The outcome of all pregnancies should be followed up and documented until 6 months after last dose of study drug.

8.6.2 Paternal exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 6 months after the last dose of KPT-8602 or Inqovi.

Pregnancy of the participant's partner is not considered to be an AE. However, the outcome of all pregnancies occurring from the date of the first dose until 6 months after the last dose should, if possible, be followed up and documented. Pregnant partners may be offered the opportunity to participate in an institutional pregnancy registry protocol (e.g., the NIH IRP pregnancy registry study) to provide data about the outcome of the pregnancy for safety reporting purposes.

8.7 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected in expedited manner to the FDA in accordance to 21 CFR 31.2.32. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

8.8 SPONSOR PROTOCOL DEVIATION REPORTING

Protocol deviation is defined as any noncompliance with the clinical trial protocol, Manual of Operational Procedures (MOP) and other Sponsor approved study related documents, GCP, or protocol-specific procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial.

It is the responsibility of the study Staff to document any protocol deviation identified by the Staff or the site Monitor in the CCR Protocol Deviation Tracking System (PDTS) online application. The entries into the PDTS online application should be timely, complete, and maintained per CCR PDTS user requirements.

In addition, any deviation to the protocol should be documented in the participant's source records and reported to the reviewing IRB per their guidelines. OSRO required protocol deviation reporting is consistent with E6(R2) GCP: Integrated Addendum to ICH E6(R1): 4.5 Compliance with Protocol; 5.18.3 (a), and 5.20 Noncompliance; and ICH E3 16.2.2 Protocol deviations.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure:

- that the rights of the participants are protected,
- that the study is implemented per the approved protocol, Good Clinical Practice and standard operating procedures; and
- that the quality and integrity of study data and data collection methods are maintained.

Monitoring for this study will be performed by NCI CCR Office of Sponsor and Regulatory Oversight (OSRO) Monitoring and Regulatory Oversight Support (SROS) Services contractor. Clinical site monitoring activities will be based on OSRO standards, FDA Guidance E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) March 2018, and applicable regulatory requirements.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by OSRO. CMPs will be protocol-specific, risk-based and tailored to address human subject protections and integrity of the study data. OSRO will determine the intensity and frequency of monitoring will be based on several factors, including study type, phase, risk, complexity, expected enrollment rate, and any unique attributes of the study and the site. The Sponsor will conduct a periodic review of the CMP to confirm the plan's continued appropriateness. A change to the protocol, significant or pervasive non-compliance with GCP, or the protocol may trigger CMP updates.

OSRO-SROS Monitoring visits and related activities will be conducted throughout the life cycle of each protocol. The first activity is before the study starts, to conduct a Site Assessment Visit (SAV) (as warranted), followed by a Site Initiation Visit (SIV), Interim Monitoring Visit(s) (IMVs), and a study Close-Out Visit (COV).

Some monitoring activities may be performed remotely, while others will take place at the study site(s). Monitoring visit reports will describe visit activities, observations, findings of protocol non-adherence and associated action items or follow-up required for resolution of findings. Monitoring reports will be distributed to the study PI, NCI CCR QA, coordinating center (if applicable) and the OSRO regulatory file.

The site Monitor will inform the study team of any deviations observed during monitoring visits. If unresolved, the Monitor will request that the site Staff enter the deviations in the CCR Protocol Deviation Tracking System (PDTS) for deviation reporting to the Sponsor and as applicable per institutional and IRB guidance.

10 STATISTICAL CONSIDERATIONS

10.1 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Phase I: To determine the recommended phase 2 dose (RP2D) of KPT-8602 in combination with Inqovi in adult participants with with higher-MDS Phase II: To determine the overall response rate (ORR) of KPT-8602 in combination with Inqovi in adult participants with with higher-MDS	- Recommended phase 2 dose (RP2D), as determined by the number of participants with DLTs reported at each dose level studied (Section **3.1.1)** -Any toxicitites identified from Day 1 of study drug through 28 days after the first dose. AEs are reported by type and grade. -ORR (defined as CR+PR+mCR with HI) per each cohort Responses will be assessed after every cyle with CBC and at the end of Cycles 2 and 6 with bone marrow assessment during treatment and every 3-6 months after that until time of disease relapse, disease progression, or death, or 8 years, whichever occurs first.	Standard endpoint for Phase I protocol Efficacy evaluation, standard for Phase II protocol
Secondary		
Phase I: To characterize the PK properties of KPT-8602 in combination with Inqovi in MDS participants	-AUC, half-life, and steady state concentration, measured by the KPT-8602 blood concentration 1, 2, 3, 4, 8, 24 and 48 hours after the product administration on days 8 and 21 of cycle one	PK studies to evaluate for adequate absorption of therapy and further define half-life/AUC and other properties of the study drug, when given in combination with Inqovi
Phase II: To further evaluate the PK properties and safety of KPT-8602 in combination with Inqovi in MDS participants	-Safety, as measured by: Incidence of AEs, SAEs; and AEs leading to discontinuation, death, and laboratory abnormalities, assessed at least weekly through cycle 3 and then at the start and and every cycle after that	Confirm safety of the study drug at the RP2D
Exploratory		
To evaluate the relationship between KPT-8602 exposure (PK) and response	Each of these will be evaluated using descriptive methods and reported as exploratory results. If any statistical	Evaluate mechanism of the study drug, target engagement,

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To evaluate changes in XPO1 mRNA expression and other potential PD markers with treatment	tests are performed in these analyses, the results will be presented without adjustment for multiple comparisons but reported in the context of the number of tests performed. See Section 5 for collection timepoints.	relationship between exposures and response, and treatment impact on quality of life.
To assess changes in DNA damage repair by evaluation of gammaH2AX levels		
To evaluate compliance and feasibility of administering PRO in this patient population		
To evaluate tolerability of treatment by assessing symptomatic adverse events, physical function and side effect bother		
To longitudinally describe and evaluate disease and treatment-related symptom severity and functional well-being		
To determine meaningful change in disease and treatment related symptoms and functional well-being by using anchors		
To evaluate changes in DNA methylation status pre- and post-treatment		
To evaluate changes in cell composition in the bone marrow and peripheral blood microenvironment pre- and post-treatment		
To evaluate changes in genetic clonal diversity during treatment		
To evaluate changes in gene expression patterns of tumor suppressor genes and oncogenes (including DNMT3B expression)		
To evaluate the influence of splicing factor mutations (U2AF1, SRSF2, SF3B1, ZRSR2) on nuclear shuttling		
To evaluate the degree of disruption of ribosome biogenesis after XPO1 inhibition		
To evaluate changes in nuclear and cytoplasmic protein composition by mass spectometry		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To evaluate other clinical outcomes	-Secondary clinical outcomes, including: overall improvement rate (OIR), transfusion-independence (TI), cytogenetic response rate, time to best response (CR, PR, marrow CR + HI, HI), DFS, PFS, LFS, and OS; assessed every 3-6 months	Common set of outcomes reported in MDS therapy studies

10.2 STATISTICAL HYPOTHESIS AND SAMPLE SIZE DETERMINATION

The trial will begin with a phase I dose-escalation phase using a standard 3+3 design which will enroll participants with relapsed/refractory HR-MDS, Up to 18 participants may be enrolled based on the 3+3 design.

Participants will be eligible for the DLT evaluation if ≥90% (9 out of 10 doses) of KPT-8602 and ≥80% (4 out of 5 doses) of Inqovi were taken within the DLT period. Participants not evaluable for toxicity, will be replaced in the dose level.

Phase II will use a Simon's minimal two-stage design, applied separately as noted below:

- Trial will be conducted using a Simon minimax two-stage phase II trial design to rule out an unacceptably low response rate of 25% (p0=0.25) in favor of an improved response rate of 45% (p1=0.45) in order to determine if the combination of KPT-8602 with Inqovi will be able to improve upon an expected 30-40% response rate in participants who have received other agents. With two-sided alpha=0.05 and beta=0.20, the first stage will enroll 21 evaluable participants, and if 0 to 5 of the 21 have a response, then no further participants will be accrued. If 6 or more of the first 21 participants have a response, then accrual would continue until a total of 43 evaluable participants have been treated . If there are only 6-16 participants with a response out of 43 participants, this would be an uninterestingly low response rate. If there were 17 or more of 43 (39.5%) who experienced a response, treatment would be sufficiently interesting to warrant further study in later trials. The probability of early termination under the null (25%) response rate is 56.7%.

It is expected that up to 12-15 participants with MDS may be accrued per year. Thus, in order to accrue up to 18 +43=61 participants (which may be reduced by up to 6 if up to 6 participants in phase I may be included in phase II), and to allow for a small number of inevaluable participants (12), it is expected that 3-4 years may be required to accrue the required 73 participants. Note: To allow for screen failures (7), the accrual ceiling will be set at 80 participants for the purposes of the NIH accrual ceiling.

10.3 POPULATIONS FOR ANALYSES

10.3.1 Evaluable for toxicity

All participants will be evaluable for toxicity from the time of their first treatment with KPT-8602.

10.3.2 Evaluable for objective response

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

10.4 STATISTICAL ANALYSES

10.4.1 General Approach

- Participants in phase I will be evaluated for safety, reporting the toxicities noted per dose level.
- Participants in phase II will have their response rate reported along with a confidence interval.

10.4.2 Analysis of the Primary Endpoints

- Participants enrolled in phase I will have the grades and types of toxicity reported at each dose level. The overall estimate of the fraction of participants who have a DLT at the RP2D will be reported.
- Participants evaluated in phase II will have the fraction with clinical responses reported, with a 95% confidence interval.

10.4.3 Analysis of the Secondary Endpoints

- The secondary objectives for phase I are to describe pharmacokinetic properties of KPT-8602 in MDS participants and to evaluate safety and tolerability of KPT-8602 in combination with Inqovi in MDS participants. The AUC, half-life, and Css of KPT-8602 will be evaluated in participants, by dose level using descriptive statistics.
- The secondary objectives for phase II are to evaluate the safety and tolerability of the agent as measured by the grades and types of toxicity noted for the agent at each dose level and reported descriptively.

10.4.4 Safety Analyses

The safety and tolerability of the agent will be evaluated by reporting the grades and types of toxicity noted for the agent at each dose level.

10.4.4.1 Safety stopping rules

Phase I will follow a 3+3 dose-escalation design, paused for review when the toxicity reaches the criteria in Section **3.1.1**.

For phase II, our goal toxicity rate is less than 20%.

Phase II toxicity assessment will use Bayesian toxicity monitoring with maximum probability of DLT of 0.2, prior distribution (1,1), maximum participants 43, minimum number of participants before stopping 9, cohort size 1, and posterior probability > 80%. Using this approach, the study would be paused for review for toxicities that meet the definition of DLT in 3/9, 4/11, 5/15, 6/20, 7/24, 8/28, and 9/32 participants.

10.4.5 Baseline Descriptive Statistics

Standard sample statistics will be provided for each cohort and overall.

10.4.6 Planned Interim Analyses

As indicated above in Section **10.2**, participants in phase II will be evaluated after 21 participants have been treated, an evaluation will be performed of the responses at that point to determine suitability to enroll the remaining participants. Specifically, the trial will proceed to the second stage if there are least 6 responses out of 21 participants with HR-MDS with a safety follow-up through day 28 required for the interim analysis, enrollment to the cohort will be halted to allow for an analysis by the study investigator. A brief memo will be created by the study investigator to document the number of responses in the first stage and will be reviewed by the PI and study team. The memo will be provided to study sponsor prior to continuation of accrual. Also, if the required number of responses is observed before that time, the memo will be generated, reviewed and provided to the study sponsor at that point without a pause in accrual. Response rates will be calculated using the revised International Working Group (IWG) 2006 response criteria for all responses, except hematologic improvement (HI) responses which will use the IWG 2018 response criteria, as described in the protocol.

10.4.7 Sub-Group Analyses

Results from phase II will be presented according to MDS-subgroup, disease risk category and genomic features.

10.4.8 Tabulation of individual Participant Data

None will be provided.

10.4.9 Exploratory Analyses

All exploratory analyses will be performed with descriptive intent, largely done separately by cohort. In the cases in which a statistical test is performed, the tests will be done without formal adjustment for multiple comparisons, but in the context of the number of tests performed.

10.4.9.1 Anslyses of Patient-Reported Outcomes

Evaluating Compliance and Feasibility of Administering PRO: Received PRO forms will be checked versus the timing schedule and considered as valid if they fall within the specified days of the scheduled assessment window. Compliance rates will be calculated as the number of received valid forms over the number of expected forms. Compliance rates will be described using summary statistics.

We will collectively refer to the symptom scales and functional well-being subscales from the EORTC QLQ C30, individual symptom items from the PRO-CTCAE items, PROMIS physical function T-scores, and the single item overall side effect bother as PRO outcomes. These PRO outcomes will be summarized by descriptive statistics, such as mean, percentages, frequency, standard deviation, and 95% confidence interval. The change in PRO outcomes over time will be evaluated using paired-t test or Wilcoxon signed rank test depending on the distributional assumptions. When appropriate, a linear or generalized linear mixed model will be used to make inferences on the trajectory of PRO outcomes. Error bar graphs for each of the PRO outcomes will be constructed at each time point. Because the PRO-CTCAE complements the CTCAE, we will use the same analysis approach for the PRO-CTCAE. The traditional method of reporting AEs

over the course of a clinical trial is by taking the maximum value. This single value is then reported descriptively. Because many participants enter clinical trials with symptoms at baseline, it is desirable to perform baseline adjustment in the analysis of symptomatic adverse events.(56) The baseline adjustment method consists of two steps. First, determine the maximum AE score for a participant over the study period post baseline. Second, if the maximum AE score is worse than baseline, then use the maximum AE score. However, if the maximum AE score is the same or better than baseline, then assign a value of zero.

Longitudinally describing and evaluating disease and treatment-related symptom severity and functional well-being: We will use two graphical approaches to address this objective. First, Locally weighted regression (LOWESS) curves showing symptom trajectories over time for each symptom scales and functional well-being subscales from the EORTC-QLQ C30 will be constructed. Second, we will also construct individual participant profiles for each of the EORTC QLQ C30 symptom scales and functional well-being subscales to describe the individual participants' patterns of change over time. Effect sizes that standardize the difference in symptom improvement or worsening between two preselected time points will be calculated.

Determining meaningful change in disease and treatment related symptoms and functional well-being by using anchors: In order to determine meaningful change in the EORTC QLQ C30 symptom scales and functional well-being subscales, we will use both clinician-rated (Karnofsky) and patient-rated (PGI-Severity, PGI-Change) anchors. We will stratify patients into 3 change groups (improved, no change, declining) between pre-selected time points (e.g. baseline and end of first disease evaluation). The difference in the EORTC QLQ C30 symptom scale scores and functional well-being subscale scores between the pre-selected time points within each of the change groups provide an estimate of meaningful change.

11 COLLABORATIVE AGREEMENTS

11.1 AGREEMENT TYPE

This study will be conducted under an Umbrella Collaborative Research and Development Agreement (CRADA) with Karyopharm Therapeutics, Inc (#03377).

12 HUMAN SUBJECTS PROTECTIONS

12.1 RATIONALE FOR PARTICIPANT SELECTION

No participants will be excluded from participation based on gender, race or ethnicity. The study will be open to all participants who satisfy the inclusion criteria and provide an informed consent to the protocol.

Participants with active HIV, HCV, or HBV are excluded because study treatment can pose more risks for these participants.

Due to the unknown effects of KPT-8602 on the fetus and infants, and known teratogenicity of Inqovi, women of reproductive age will only be allowed to enroll if they commit to following a strict manner of contraception; Females who are breast-feeding will not be eligible for the trial. Men who are sexually active with women of childbearing age will also have to commit to strict contraceptive practices while on study.

12.2 PARTICIPATION OF CHILDREN

Children will not be eligible for participation in this study due to lack of adequate safety data in children. Biologic rationale and preclinical work were validated in adult population and would need reanalysis in children, where MDS may arise more so from inherited bone marrow failure syndromes than in adults and have a different pathophysiology.

12.3 RISK/BENEFIT ASSESSMENT

12.3.1 Known Potential Risks

All known potential risks associated with KPT-8602 from prior experience in humans has been discussed in Section **14.** In the first-in-human study of KPT-8602 monotherapy, the most frequently occurring AEs were gastrointestinal effects (nausea, fatigue, diarrhea, decreased appetite, weight decreased) and cytopenias (thrombocytopenia, anemia). The potential risks of Inqovi are noted in the USPI for INQOVI and includes myelosuppression and embryo-fetal toxicity. However, there is an unknown element here which is why this is a phase I safety study and participants will be closely monitored for all AEs.

Other risks involved in the study include that of standard MDS procedures, including regular blood draws and bone marrow evaluations. These are invasive procedures that carry with them the risk of infection, bleeding and damage to surrounding tissues/organs. Phlebotomy and bone marrow evaluations will be conducted by well-trained personnel who follow sterile techniques to minimize complications.

12.3.1.1 Risks related to study procedures

12.3.1.1.1 Blood samples

Minor complications including bleeding, pain, and hematoma formation at the site of blood draws, or infections may rarely occur. Up to 82 mL of blood may be collected at one time, no more than 250 mL will be collected over an 8-week period.

12.3.1.1.2 Bone marrow aspiration/biopsy

The bone marrow aspiration and biopsy may cause pain, bruising, bleeding and infection. Soreness near the site may last for a couple of days after the procedure. The subject may have more pain, risk of bleeding and bruising if he/she complete both aspiration and biopsy rather than just the aspiration. The subject should contact the study team immediately if pain is severe or fever develops.

12.3.1.1.3 Electrocardiogram

Other than possibly experiencing some minor skin irritation from the electrodes there are no anticipated risks related to complete the electrocardiogram and/or the echocardiogram.

12.3.1.1.4 Intravenous catheter

The risks of IV insertion include temporary pain and bleeding or bruising at the site where the IV enters the skin. In placing the IV, there is a small chance of fluid leaking into the tissue surrounding the IV and infection, which may cause some swelling and discomfort. Rarely, the IV site may become infected, which might require treatment with antibiotics.

12.3.1.1.5 Questionnaires

Some of the questions in the questionnaire may be upsetting or make subjects feel uncomfortable. Subjects can skip any of the questions he/she does not want to answer, and can stop at any time.

12.3.1.1.6 Urine collection

No physical risks are associated with urine collection.

12.3.1.1.7 Losing data

This includes the risk that data obtained during this study can be released to members of the public, insurers, employers, or law enforcement agencies. Although there are no plans to release results to the participants, family members, or health care providers, this risk will be included in the informed consent document.

12.3.2 Known Potential Benefits

Due to the significant preclinical and prior clinical experience with KPT-8602, this study hypothesis has strong evidence that KPT-8602 may have disease-modifying beneficial therapeutic activity in MDS. If this is confirmed via this trial, participants have the potential for immediate-benefits that include, improved cytopenias, less transfusion- and growth factor-dependence, less complications of cytopenias such as infections and hemorrhagic complications. Transfusion independence also leads to improved quality of life. Long-range potential benefits, should our investigational agent confirm efficacy, include stability of MDS disease with improved quality of life and potential for less progression into AML, which is associated with significant morbidity and mortality.

12.3.3 Assessment of Potential Risks and Benefits

Risks to participants have been minimized in the study and involve no more than that expected from standard of care monitoring of MDS, which includes regular peripheral blood draws and bone marrow evaluations. The potential disease modifying/therapeutic benefit of KPT-8602 as an investigative agent outweighs the risks discussed, which are otherwise mostly standard procedures for participants with MDS.

12.4 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted

remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or on the electronic document. Signatures on electronic documents are described below.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location, but is not required.

Both the investigator and the participant will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 STUDY DISCONTINUATION AND CLOSURE

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

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, Food and Drug Administration (FDA).

13.2 Quality Assurance and Quality Control

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.3 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Cancer Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

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

The study participant's contact information will be securely stored at the/each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure

location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site(s) and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NCI CCR.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL AND INVESTIGATIONAL DEVICE INFORMATION

14.1 KPT-8602 (IND # 163958)

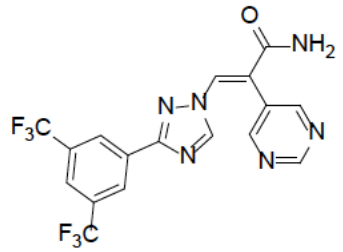
14.1.1 Description

	Current formulations
Dosage form	Tablet
Route of administration	Oral
Strength(s)[a]	5 mg, 10 mg
Manufacturing process	*Roller compaction dry granulation:* *API and inactive excipients are blended before roller compaction to make granules. Granules are further blended with additional excipients and subsequently compressed, then film coated.*
Components[b]	eltanexor (KPT-8602) ~6.25% by weight for 5 mg and 10 mg microcrystalline cellulose mannitol providone croscarmellose sodium colloidal silicon dioxide sodium lauryl sulfate magnesium stearate
Coating	Opadry 200 Clear (sub-coat) and Opadry II Orange (top-coat)
Color	Orange to peach
Packaging	HDPE bottles with desiccant
Shipping	2-25°C
Storage	Store at or below 25°C. Do not freeze.

[a]Tablet strengths are distinguished by tablet size and debossing (5 mg tablets are scored, 10 mg tablets have no debossing)

[b]These tablet components/excipients are common to oral pharmaceuticals and/or compendial.

Chemical structure:
5-Pyrimidineacetamide, α-[[3-[3,5-bis(trifluoromethyl)phenyl]-1*H*-1,2,4-triazol-1-yl]methylene]-, (α*E*)-(*E*)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-1-yl)-2-(pyrimidin-5-yl)acrylamide



$C_{17}H_{10}F_6N_6O$

- **Molecular weight**: 428.30 g/mol
- **Mechanism of action**: selective inhibitor of nuclear export (SINE)

14.1.2 Source/Acquisition and Accountability

KPT-8602 (eltanexor) is manufactured and supplied for by the trial by Karyopharm Therapeutics, Inc.

KPT-8602 will be provided to the clinical trial site by the manufacturer. The investigator or designee (e.g., pharmacist) will maintain an ongoing inventory of the investigational product supply according to standard site procedures. The investigational product will be dispensed at the direction of an investigator for administration to a study participant enrolled on the clinical trial. Disposal of expired or unused product will be returned to the manufacturer or disposed of according to standard site procedures based on agreement between the manufacturer and the site

14.1.3 Toxicity

The key preclinical safety findings in rats and monkeys are as follows:

- In general, the major effects across the toxicology studies was non-adverse, reversible weight loss, some of which also observed for other SINE compounds (selinexor, verdinexor, etc). The effects on body weight were typically associated with lower food consumption, were fully reversible, and considered non-adverse.
- Eltanexor-related effects in male rat reproductive tissues were dependent on dosing frequency and duration, consistent with other SINE compounds. In the 4-week rat GLP study (QDx5/week), non-adverse microscopic findings were reported for thetestes. In rats given 20 doses at ≥4 mg/kg (24 mg/m^2), minimal-mild germ cell degeneration in the testes was accompanied by minimal-mild cellular debris in the epididymis; these findings were non-adverse and fully reversible after a 28-day recovery period. In monkeys, there were no adverse effects observed.
- In the GLP, 4-week study in monkeys (QD×5/week), serum chemistry measures indicated significantly higher serum amylase and lipase. These correlated to microscopic findings in the pancreas including acinar atrophy, acinar hyperplasia (males), individual cell

degeneration/necrosis, interstitial fibrosis, and ductal hypertrophy/hyperplasia (males). Following a 28-day recovery period, effects on the pancreas were fully reversible, except for minimal pancreatic acinar atrophy, interstitial fibrosis, ductal hypertrophy/hyperplasia, and minimally decreased zymogen granules. Based on these results, eltanexor is not considered to pose a risk for pancreatitis.

- Eltanexor was not genotoxic in a GLP *in vitro* bacterial reverse mutation (Ames assay).

The safety, tolerability, and preliminary efficacy of eltanexor in humans is currently under investigation in Study KCP-8602-801 (Study 801) which is an ongoing first-in-human, open-label dose-escalation study in patients with relapsed/refractory multiple myeloma (R/R MM) followed by a dose-expansion phase in patients with select advanced malignancies. As of 18 November 2021, a total of 124 patients have received eltanexor in Study 801, of which 119 patients (39 patients with R/R MM, 30 patients with mCRPC, and 20 patients with HR-MDS) have safety data available. In the entire safety population, the most frequently occurring TEAEs of any grade were nausea (63%), fatigue (63%), diarrhea (58%), decreased appetite (49%), thrombocytopenia (49%), weight decreased (48%), anemia (45%), vomiting (45%). The most frequently occurring ≥ Grade 3 TEAEs were thrombocytopenia (31%), anemia (29%), and neutropenia (25%). However, no clinically significant cumulative toxicities were identified, major organ dysfunction was not observed, and no grade 5 TRAEs were reported. Adverse events leading to discontinuation of eltanexor that occurred in ≥ 3 patients were fatigue (6.7%), nausea (4.2%), sepsis (3.4%), as well as vomiting, acute kidney injury, decreased appetite, and weight decreased (2.5% each). See the Eltanexor Investigator's Brochure (IB) for more information.

14.1.4 Formulation and preparation

Eltanexor is an immediate-release tablet for oral administration. Initial supplies came in 2 strengths: 5 mg and 20 mg of the active pharmaceutical ingredient per tablet. The 20 mg tablet is no longer being used. Current supplies for the clinic are 5 mg and 10 mg tablets, where the 10- mg tablet is weight proportional (2×) with respect to the 5-mg tablet. All inactive ingredients used in the tablets are either compendia or generally recognized as safe. Tablets are film coated for ease of handling. Detailed information related to the manufacturing, components/excipients, packaging, and storage of the drug formulations is provided in the Eltanexor IB.

14.1.5 Stability and Storage

Eltanexor tablets are packaged in white high-density polyethylene bottles with induction seals with polypropylene caps. The eltanexor-containing bottles should be stored at/or below 25°C but not frozen.

14.1.6 Administration Procedures

See Section **3.2.1**.

14.1.7 Incompatibilities

The primary metabolism of eltanexor based on nonclinical studies *in vitro* and *in vivo* appears to involve inactivation by GSH conjugation. This process can be mediated in the absence of proteins, indicating that it is thermodynamically favorable. In vitro studies using human liver microsomes indicate that eltanexor undergoes minimal CYP450 mediated metabolism. There was also minimal to no induction of CYP450 activity observed for CYP1A2, CYP2B6, or CYP3A4.

Therefore, the risk of drug-drug interactions with eltanexor is low; however, administration of eltanexor with drugs that undergo substantial GSH conjugation should be minimized. These drugs include acetaminophen (paracetamol). In the event that GSH depletion is believed to be contributing to patients' symptoms, signs or laboratory findings, replenishment with SAM (S-adenosyl-L-methionine) oral (e.g., 400 mg) or N-acetylcysteine (e.g., up to 140 mg/kg loading dose followed by 70 mg/kg Q4 hours) until symptoms resolve. It should be noted that no studies of eltanexor in combination with acetaminophen have been performed to date and that these recommendations are empirical.

Eltanexor is also a substrate for BCRP and a marginal substrate of P-gp, therefore concomitatnt administration of inhibitors of BCRP and P-gp should be avoided. (Examples can be found at the following link: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-2)

The effect of concomitant administration of gastric acid reducing agents on eltanexor PK cannot be ruled out at this time, therefore concomitant administration of acid-reducing agents, e.g. proton pump inhibitors or H2-receptor antagonists, with eltanexor during the dose finding portion of the study will be avoided.

There are no other known drug interactions.

14.2 INQOVI® (DECITABINE AND CEDAZURIDINE)

INQOVI is a combination of decitabine, a nucleoside metabolic inhibitor, and cedazuridine, a cytidine deaminase inhibitor, indicated for treatment of adult patients with myelodysplastic syndromes (MDS).

14.2.1 Source/Acquisition and Accountability

For participant administration, decitabine and cedazuridine will be purchased by the NIH Clinical Center Pharmacy Department from commercial sources.

14.2.2 Toxicity

Fatal and serious myelosuppression and infectious complications can occur. Can cause fetal harm. Most common adverse reactions (incidence ≥ 20%) are fatigue, constipation, hemorrhage, myalgia, mucositis, arthralgia, nausea, dyspnea, diarrhea, rash, dizziness, febrile neutropenia, edema, headache, cough, decreased appetite, upper respiratory tract infection, pneumonia, and transaminase increased. The most common Grade 3 or 4 laboratory abnormalities (≥ 50%) were leukocytes decreased, platelet count decreased, neutrophil count decreased, and hemoglobin decreased. (57-59)

14.2.3 Formulation and preparation

INQOVI (decitabine and cedazuridine) tablets, for oral use contain 35 mg decitabine and 100 mg cedazuridine. The tablets are biconvex, oval-shaped, film-coated, red and debossed with "H35" on one side. Each film-coated tablet contains the following inactive ingredients: lactose monohydrate, hypromellose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The film coating material contains polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide red.

14.2.4 Stability and Storage

Each tablet should be stored at 20°C to 25°C. Excursions of the tablet are permitted to 15°C to 30°C. Any unused portion of the tablet should be discarded using special handling and disposal procedures.

14.2.5 Administration Procedures

See Section **3.2.2** for details.

14.2.6 Incompatibilities

Avoid coadministration of INQOVI with drugs that are metabolized by cytidine deaminase (CDA) enzymes, such as gemcitabine, cytarabine, and capecitabine.

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16 LIST OF ABBREVIATIONS

Abbreviation	Term
ACAT	Ability to Consent Assessment Team
AE	Adverse Event/Adverse Experience
AESI	Adverse Event/Experience of Special Interest
ANC	Absolute neutrophil count
BTRIS	Biomedical Translational Research Information System
CCR	Center for Cancer Research
CDA	Confidential Disclosure Agreement
CFR	Code of Federal Regulations
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COV	Close-out Visit
CR	Complete Response
CSR	Clinical Study Report
CRADA	Cooperative Research and Development Agreement
CT	Computed Tomography
CTA	Clinical Trials Agreement
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DTA	Data Transfer Agreement
EC	Ethics Committee
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EKG	Electrocardiogram
FDA	Food and Drug Administration
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
GDS	Genomic Data Sharing
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HHS	Health and Human Services
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IBC	Institutional Biosafety Committee
ICD/ICF	Informed Consent Document/Form
ICH	International Council on Harmonisation
IMV	Interim Monitoring Visit
IND	Investigational New Drug
IOCBP	Individuals of childbearing potential

Abbreviation	**Term**
IRB	Institutional Review Board
IRBO	Institutional Review Board Office
IV	Intravenous
LAR	Legally Authorized Representative
MRI	Magnetic Resonance Imaging
MTA	Material Transfer Agreement
MTD	Maximal tolerated dose
N	Number (typically refers to subjects)
NCT	National Clinical Trial (number)
NDA	New Drug Application
NIH	National Institutes of Health
NOS	Not otherwise specified
OHSRP	Office for Human Subjects Research Protections
OHRP	Office for Human Research Protections
OS	Overall survival
OSRO	Office of Sponsor and Regulatory Oversight
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-free survival
PI	Principal Investigator
PR	Partial Response
PS	Performance Status
QA	Quality Assurance
QC	Quality Control
rCR	Revised Common Rule
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II dose
SAE	Serious Adverse Event/Serious Adverse Experience
SAV	Site Assessment Visit
SIV	Site Initiation Visit
SD	Stable Disease
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
ULN	Upper limit of normal
US	United States
WHO	World Health Organization

17 APPENDICES

17.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of 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.

17.2 APPENDIX B: 2016 WHO CLASSIFICATION FOR MYELODYSPLASTIC SYNDROME

Reference: Arber, DA, et al.(1)

Myelodysplastic syndromes (MDS)

- **MDS with single lineage dysplasia (MDS-SLD)**
- **MDS with ring sideroblasts (MDS-RS)**
  - **MDS-RS and single lineage dysplasia**
  - **MDS-RS and multilineage dysplasia**
- **MDS with multilineage dysplasia (MDS-MLD)**
- **MDS with excess blasts**
- **MDS with isolated del(5q)**
- **MDS, unclassifiable**
- ***Provisional entity: Refractory cytopenia of childhood***

17.3 APPENDIX C: REVISED INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS-R) FOR MYELODYSPLASTIC SYNDROMES

Prognostic variable	Score						
	0	0.5	1.0	1.5	2.0	3.0	4.0
Cytogenetics*	Very good		Good		Intermediate	Poor	Very poor
Bone marrow blast (percent)	≤2		>2 to <5		5 to 10	>10	
Hemoglobin (g/dL)	≥10		8 to <10	<8			
Platelets (cells/microL)	≥100	50 to 100	<50				
Absolute neutrophil count (cells/microL)	≥0.8	<0.8					

Risk group	IPSS-R score	Median overall survival (years)	Median time to 25 percent AML evolution (years)
Very low	≤1.5	8.8	>14.5
Low	>1.5 to 3.0	5.3	10.8
Intermediate	>3 to 4.5	3.0	3.2
High	>4.5 to 6	1.6	1.4
Very high	>6	0.8	0.7

AML: acute myeloid leukemia; MDS: myelodysplastic syndromes.
* Cytogenetic definitions:
Very good: –Y, del(11q)
Good: Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate: del(7q), +8, +19, i(17q), any other single, double not including del(5q) or –7/del(7q), or independent clones
Poor: –7, inv(3)/t(3q)/del(3q), double including –7/del(7q), complex: 3 abnormalities.
Very poor: Complex: >3 abnormalities
This research was originally published in Blood. Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System (IPSS-R) for myelodysplastic syndromes. Blood 2012. Copyright © 2012 the American Society of Hematology.

17.4 APPENDIX D: THE 2006 INTERNATIONAL WORKING GROUP RESPONSE CRITERIA WITH MODIFIED DEFINITIONS FOR HEMATOLOGIC IMPROVEMENT BY THE 2018 INTERNATIONAL WORKING GROUP RESPONSE CRITERIA

Reference: Platzbecker, U, et al.(54)

Category	**Response criteria** (responses must last at least 4 weeks)

Complete remission	• Bone marrow: ≤5% myeloblasts with normal maturation of all cell lines*
	• Persistent dysplasia will be noted*
	• Peripheral blood†
	  ◦ Hgb ≥11 g/dL
	  ◦ Platelets ≥100 X 10^9/L
	  ◦ Neutrophils ≥1.0 X 10^9/L
	  ◦ Blasts 0%

Partial remission	All CR criteria if abnormal before treatment except: • Bone marrow blasts decreased by ≥50% over pretreatment but still >5% • Cellularity and morphology not relevant
Marrow CR	• Bone marrow: ≤5% myeloblasts and decrease by ≥50% over pretreatment • Peripheral blood: if HI responses, they will be noted in addition to marrow CR
Stable disease	Failure to achieve at least PR, but no evidence of progression for >8 weeks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to more advanced MDS FAB subtype than pre-treatment
Relapse after CR or PR	At least 1 of the following: • Return to pre-treatment bone marrow blast percentage • Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets • Reduction in Hgb concentration by ≥1.5 g/dL or transfusion dependence
Cytogenetic response	Complete • Disappearance of the chromosomal abnormality without appearance of new ones Partial • At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with: • Less than 5% blasts: ≥50% increase in blasts to >5% blasts • 5%-10% blasts: ≥50% increase to 10% blasts

	• 10%-20% blasts: ≥50% increase to >20% blasts • 20%-30% blasts: ≥50% increase to >30% blasts Any of the following: • At least 50% decrement from maximum remission/response in granulocytes or platelets • Reduction in Hgb by ≥2 g/dL • Transfusion dependence
Survival	Endpoints: • Overall: death from any cause • Event free: failure or death from any cause • PFS: disease progression or death from MDS • DFS: time to relapse • Cause-specific death: death related to MDS

MDS, myelodysplastic syndromes; Hgb, hemoglobin; CR, complete remission; HI, hematologic improvement; PR, partial remission; FAB, French-American-British; AML, acute myeloid leukemia; PFS, progression-free survival; DFS, disease-free survival.
To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
*Dysplastic changes should consider the normal range of dysplastic changes.
†In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

Hematologic Improvement

Category	**Patient pre-trial baseline**	**Response criteria**	
Erythroid response (HI-E)	No Transfusion Dependence at baseline (0 RBC transfusions in 16 weeks)	At least 2 consecutive Hgb measurements ≥1.5 g/dL for a period of minimum 8 weeks in an observation period of 16 to 24 weeks compared with the lowest mean of 2 Hgb measurements (apart from any transfusion) within 16 weeks before treatment onset; only a response duration of at least 16 weeks, however, is considered clinically meaningful	
	Low Transfusion Dependence at baseline (3-7 RBC transfusions in 16 weeks in at least 2 transfusion episodes, maximum 3 in 8 weeks)	Transfusion independence, defined by the absence of any transfusions for at least 8 weeks in an observation period of 16-24 weeks with the same transfusion policy compared with 16 weeks prior to treatment; only a response duration of at least 16 weeks, however, is considered clinically meaningful	
	High Transfusion Dependence at baseline (≥8 RBC transfusions in 16	Major response	Transfusion independence, defined by the absence of any transfusions over a period of minimum 8 weeks in an

	weeks, ≥ 4 transfusion episodes in 8 weeks)		observation period of 16-24 weeks with the same transfusion policy compared with 16 weeks prior to treatment; only a response duration of at least 16 weeks, however, is considered clinically meaningful
		Minor response	A reduction by at least 50% of RBCs over a minimum of 16 weeks with the same transfusion policy, compared with 16 weeks prior to treatment
Platelet response (HI-P)	Pre-treatment PLT <100 x 10^9/L	• Absolute increase of 30 x 10^9/L for patients starting with >20 x 10^9/L PLTs or • Increase from <20 x 10^9/L to >20 x 10^9/L and by at least 100% In addition: • In addition, evolution of bleeding symptoms is to be taken into account • Increments of platelets also for patients with a pre-treatment PLT count of ≥100 x 10^9 are to be reported	
Neutrophil response (HI-N)	Pre-treatment ANC <1.0 x 10^9/L	• At least 100% increase and an absolute increase >0.5 x 10^9/L • Increments of neutrophils also for patients with a pre-treatment ANC of ≥1.0 x 10^9/L are to be reported	

17.5 APPENDIX E: ROCKWOOD FRAILTY INDEX

Reference: Rockwood, K, et al. (47)

Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common symptoms in mild dementia include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In moderate dementia, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In severe dementia, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005; 173:489-495.

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17.6 APPENDIX F: MDS-SPECIFIC COMORBIDITY INDEX (MDS-CI)

Comorbidity	Definition	Variable Weighted Score (to be considered if the specific comorbidity is present)
Cardiac disease	Arrhythmia* Heart valve disease** Coronary artery disease*** or myocardial infarction Congestive heart failure or ejection fraction ≤50%	2
Moderate-to-severe hepatic disease****	Cirrhosis, fibrosis, persistent bilirubin > 1.5 x ULN or AST/ALT > 2.5 x ULN	1
Severe pulmonary disease	DLCO and/or FEV1 ≤65% or dyspnea at rest or requires oxygen	1
Renal disease	Persistent creatinine > 2 mg/dL, renal dialysis, or renal transplant	1
Solid tumor	Malignancy at any time point in the patient's history, excluding non-melanoma skin cancer	1

DLCO indicates diffusion capacity of the lung for carbon monoxide; FEV1: forced expiratory volume in one second; ULN: upper limit of normal; AST: aspartate aminotransferase; ALT: alanine aminotransferase. *Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias; **Except mitral valve prolapse; ***One or more vessel-coronary artery stenosis requiring medical treatment, stent, or bypass graft; ****HCV infection was documented in 7% of patients.

MDS – CI Key

MDS-CI Risk	Sum of Individual Variable Scores
Low risk	0
Intermediate risk	1-2
High risk	>2

Della Porta MG, Malcovati L, Strupp C, Ambaglio I, Kuendgen A, Zipperer E, Travaglino E, Invernizzi R, Pascutto C, Lazzarino M, Germing U and Cazzola M. Risk stratification based on both disease status and extra-hematologic comorbidities in patients with myelodysplastic syndrome. Haematologica 2011;96(3):441-449. doi:10.3324/haematol.2010.033506

17.7 APPENDIX G: EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC) QUALITY OF LIFE QUESTIONNAIRE = EORTC QLQC30 SCORE

Reference: Fayers, P, et al.(50)

See Study Instrument Packet.

17.8 Appendix H: Patient-Reported Outcomes (NIH Adult Psychosocial Assessment for MDS, CTCAE, Overall Side Effect Bother, PROMIS Physical Function, PGI-S, and PGI-C)

See Study Instrument Packet.

17.9 APPENDIX I: DATA ELEMENTS TO CONSIDER FOR CRF ENTRY IN CLINICAL DATABASE

Participant characteristics at protocol entry

- Sex (male, female)
- Age at enrollment (number)
- Ethnicity (white, black, American Indian/Alaskan native, Asian/Pacific islander, Hispanic, other)
- ECOG and Karnofsky performance status
- Diagnosis - MDS (high risk and higher intermediate risk)
- 2016 WHO classification of MDS (MDS with single lineage dysplasia [MDS-SLD], MDS with ring sideroblasts and single lineage dysplasia [MDS-RS-SLD], MDS with ring sideroblasts and multilineage dysplasia [MDS-RS-MLD], MDS with multilineage dysplasia [MDS-MLD], MDS with excess blasts [MDS-EB], MDS with isolated del(5q), MDS unclassifiable [MDS-U],
- Date of MDS diagnosis (month, year)
- Age at MDS diagnosis
- Revised International Prognostic Scoring System (IPSS-R) score at MDS diagnosis
- Cytogenetic profile at diagnosis and enrollment, if available (see Appendix C)- only need overall score (very good, good, intermediate, poor, very poor)
- Bone marrow blasts %, if available (flow/asp and IHC/bx)
- Hemoglobin, if available (at diagnosis and at enrolment) use counts from day of bone marrow for enrollment
- Platelet count, if available (at diagnosis and at enrolment) day of bone marrow for enrollment
- Absolute neutrophil count (ANC), if available (at diagnosis and at enrolment) day of bone marrow for enrollment
- RBC transfusion dependance (transfusion dependent or independent)
- Platelet transfusion dependance (transfusion dependent or independent)
- Average # of transfusions per month (RBCs units and instances of platelets transfusions) in the 3 months leading up to baseline on study
- Laboratory values will be collected from time of screening for duration of trial
- TP53 mutation status at enrollment, if available (TP53 mutation positive or negative)
- Names and # of cycles of prior Lines of therapy for MDS.
- Response to most recent line of therapy: CR (complete response), PR (partial response), HI (hematologic improvement), mCR with HI (marrow CR with hematologic improvement), mCR without HI (marrow CR without hematologic improvement), SD (stable disease), PD (disease progression)
- MDS-CI (low risk, intermediate risk, high risk)
- Rockwood frailty index (see Clinical Frailty Scale)
- Disease status at time of enrollment: CR (complete response), PR (partial response), HI (hematologic improvement), mCR with HI (marrow CR with hematologic improvement), mCR without HI (marrow CR without hematologic improvement), SD (stable disease), PD (disease progression)
- History of prior allogeneic transplantation (yes/no)
    - If history of prior allogeneic transplantation:

    - Date of allogeneic transplant/Day 0
- Patient Reported Outcome Questionnaires (per section 3.5.3)

Data collection during study/treatment

- Cycle number & day of treatment
- Study Drug Administration
- Disease response at assessment timepoints: CR (complete response), PR (partial response), HI (hematologic improvement), mCR with HI (marrow CR with hematologic improvement), mCR without HI (marrow CR without hematologic improvement), SD (stable disease), PD (disease progression)
- Best overall response to study treatment: CR (complete response), PR (partial response), HI (hematologic improvement), mCR with HI (marrow CR with hematologic improvement), mCR without HI (marrow CR without hematologic improvement), SD (stable disease), PD (disease progression)
- Bone marrow percent blasts
- RBC transfusion dependence (transfusion dependent or transfusion independent)
- Platelet transfusion dependence (transfusion dependent or transfusion independent)
- # of transfusions per month (RBCs units and instances of platelets transfusions)
- Adverse events
- Patient Reported Outcome Questionnaires: (per section 3.5.3)

Data collection at post-therapy follow-up visits

- Alive (yes/no)
- Adverse events
- Progression of MDS (if yes, to what and when)
- Diagnosed with sAML (yes/no)
    - If diagnosed with sAML, date of sAML diagnosis (month, year)

Data collection at time of death

- Date of death
- Disease status at time of death: CR or not CR
- Cause of death: disease progression/relapse vs non-relapse mortality (definition of non-relapse mortality: subject in clinical remission at time of death)
- If non-relapse mortality, primary cause of death (per CTCAE)

17.10 APPENDIX J: BLOOD PROCESSING CORE PROCEDURES

Note: The following processing details and supplies may be adjusted as required during the course of the study with approval of the laboratory(ies).

Samples to be Collected:

1. Peripheral Blood:
   a. 2 x 5 mL EDTA tubes (for separation and storage of MNC and plasma, protocol below)
   b. 4 mL SST (or 2 x 2.5ml)Vacutainer tube (for PK analysis)
   c. 1 x 2.5ml Paxgene RNA tube (for storage then pickup by Larson lab)
2. Bone Marrow Aspirate: 2 x 5mL EDTA tubes (for separation and storage of MNC and plasma, protocol below)

Processing Protocols:

Bone Marrow and Peripheral Blood Processing from EDTA Tubes:

1. Spin the bone marrow (BM) aspirate or peripheral blood (PB) at 2500 rpm (1500 rcf) for 5 minutes to isolate neat plasma prior to adding the PBS/Ficoll.
2. Store 5 x 300uL aliquots of plasma at -80deg C.
3. Add 2 volumes of PBS to the PB/BM and be sure to mix well to ensure a good underlay of the Ficoll.
4. Add a 1:1 volume of Ficoll to the diluted BM/PB by carefully dispensing at the bottom of the conical tube. The BM/PB should lay on top of the Ficoll layer. Try not to mix the Ficoll and BM/PB.
5. Spin the tubes at 3000 rpm (2000 rcf) for 15 minutes.
6. The mononuclear layer interface will lay between the Ficoll and plasma/PBS layers and will often appear whitish if there is a larger number of cells. Carefully remove this interface taking as little Ficoll as possible. If you cannot see the layer, just remove several mL from on top of the Ficoll layer, this will contain all the cell. Dilute the interface containing the cells, with 4 volumes of RPMI (supplemented with 10%FBS, and 1% Pen/Strep). The remaining Ficoll and RBCs at the bottom of the tube can be discarded.
7. Spin the mononuclear cells at 1000rpm for 5 min.
8. Resuspend the cell pellet in 10 to 40ml of RBC Lysis Buffer (ie; Qiagen RBC Lysis Buffer). The volume of lysis buffer depends on the cell pellet. For very small pellets use 10mL, for very large pellets, use 40mL RBC lysis .
9. Resuspend the cells in RPMI (supplemented with 10%FBS, and 1% Pen/Strep) and count the cells using a hemacytometer.
10. Freeze the cells in 10% DMSO, 20% FBS, and 70% RPMI with no more than 10million cells per mL and 1 mL per cryotube. Freeze samples either using a cell freezer container in a -80deg C freezer (i.e.; Mr Frosty container) or a controlled rate freezer. Once cells have reached -80deg C, transfer cryotubes to a liquid nitrogen cryounit.

PK Studies, Peripheral Blood Processing from SST Tube

1. Blood samples will be collected by direct venipuncture or through an indwelling catheter. If a catheter is used for blood collection, then approximately 1mL of blood should be withdrawn initially then discarded. Only saline is permitted to keep catheters patent, unless discussed and agreed upon by the Sponsor. If samples are obtained through a heparin lock, sufficient blood (~1mL) must be withdrawn to remove the heparin solution.
2. Immediately after collection, gently invert each tube 5 times and allow blood to clot for 30-45m at room temperature (tube standing upright).
3. Centrifuge samples at 4deg C for 10min (singing buckets) or 15 minutes (fixed buckets) at 100-1300g until clot and serum are well separated. Note: If refrigerated centrifuge is not available, prechill centrifuge tube holders at -20deg C for 20m prior to centrifugation.
4. Transfer 1mL aliquots of serum into 4 appropriately labeled screw cap polypropylene tubes.
5. Store samples at -80deg C until ready for analysis.

PAXgene Tube Storage for BM

1. Tubes will be stored upright at -80deg C until ready for pickup by the Larson Lab.

17.11 APPENDIX K: PARTICIPANT MEDICATION DIARY

Cohort 1 and 2 – Medication Diary

Cycle: _____ Participant's ID: _____

Instructions:

1. Complete one form for each cycle of treatment.
2. You will take Inqovi once daily on Days 1-5 or Days 1-4 , Days 1-3 or Day 1, 3 and 5 depending on the dose level you are assigned,
3. The tablet should be taken on an empty stomach, 2 hours before or 2 hours after meals, and at the same time each day.
4. If a dose of Inqovi is missed within 12 hours of the time it was supposed to be taken, it should be taken as soon as possible. If it is past 12 hours, the dose should not be made up. Extend the dosing period by 1 day for every missed dose to complete the total number of daily doses for each cycle.
5. You will take KPT-8602 once daily on Days 8-12 for all dose levels, and possibly on Days 13-21 or on Days 15-19 dpending on the dose level you are assigned, during a 28-day cycle.
6. If a dose of KPT-8602 is missed within 12 hours of the time it was supposed to be taken, it should be taken as soon as possible. If it is past 12 hours, the dose should not be made up. Extend the dosing period by 1 day for every missed dose to complete the total number of daily doses for each cycle.
7. If you vomit after taking a dose of KPT-8602 and/or Inqovi, do not retake the dose. Take the next dose of KPT-8602 and/or Inqovi at the regular schedule.
8. If you miss any doses please contact us.
9. Record the date, the number of tablets that you took, and when you took them. If you miss a dose, please record this also below.
10. If you have any comments or notice any side effects, please record them in the 'comments' column.
11. On the days you are being seen in clinic, you must bring in your medication supply from home; however, you should not take your medication until instructed, as the blood draws must be timed with when you take your medication.
12. Please bring this form and your bottles (even it is empty) when you come for your clinic visits.

Day	Date	Study Drug				Comments
		KPT-8602		INQOVI		
		Time	# of Tablets	Time	# of Tablets	
1		None	None			
2		None	None			
3		None	None			
4		None	None			

Day	Date	Study Drug				Comments
		KPT-8602		INQOVI		
		Time	# of Tablets	Time	# of Tablets	
5		None	None			
6		None	None	None	None	
7		None	None	None	None	
8				None	None	
9				None	None	
10				None	None	
11				None	None	
12				None	None	
13				None	None	
14				None	None	
15				None	None	
16				None	None	
17				None	None	
18				None	None	
19				None	None	
20				None	None	
21				None	None	
22		None	None	None	None	
23		None	None	None	None	
24		None	None	None	None	
25		None	None	None	None	
26		None	None	None	None	
27		None	None	None	None	
28				None	None	

17.12 APPENDIX L: CONTROLLED MEDICATIONS FOR HIV, HEPATITIS B OR HEPATITIS C DISEASE CONTROL (CYP SUBSTRATES)

Hepatitis C:

- Epclusa (sofosbuvir/velpatasvir), Velpatasvir
- Vosevi (sofosbuvir/velpatasvir/voxilapresvir), Velpatasvir
- Zepatier (Elbasvir/grazoprevir)

Hepatitis B:

- N/A

HIV:

- Efavirenz
- Nevirapine
- Rilpivirine
- Ritonavir
- Dolutegravir