MSK PROTOCOL COVER SHEET

A Phase II clinical trial of E7820 for patients with relapsed/refractory myeloid malignancies with mutations in splicing factor genes.

Principal Investigator/Department:
Dr. Eytan Stein, Department of Medicine

Glossary:

Acronym	Definition
ACS	Acute coronary syndrome
AE	Adverse event
AESI	Adverse Events of Special Interest
AML	Acute myeloid leukemia
AST	Serum aspartate aminotransferase
ALT/SGPT	Alanine aminotransferase
CMML	Chronic myelomonocytic leukemia
CR	Complete remission
CRi	Complete remission with incomplete hematologic recovery
CRh	Complete remission with partial hematologic recover
CR (MRD-)	Complete remission without minimal residual disease
CR (MRD+)	Complete remission with minimal residual disease
DLT	Dose limiting toxicity
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EFS	Event free survival
ESA	Erythropoiesis-stimulating agents
FLT3	Flms-like tyrosine kinase 3
GFR	Glomerular filtration rate
HBV	hepatitis B virus
HCV	hepatitis C virus
HI	Hematologic improvement
HIDAC	High-dose cytarabine
HMA	Hypomethylating agents
HSCT	Hematopoietic stem cell transplantation
IDH1	Isocitrate dehydrogenase 1
IDH2	Isocitrate dehydrogenase 2
IPSS-R	Revised International Prognostic Scoring System
IWG	International working group
LDAC	Low dose cytarabine
LVEF	Left ventricular ejection fraction
MDS	Myelodysplastic syndromes
MEC	Mitoxantrone, etoposide and cytarabine
MLFS	Morphologic leukemia free state
MPN	Myeloproliferative neoplasm

MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PR	Partial remission
RBM39	RNA-binding protein 39
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
ULN	Upper limit of normal
VAF	Variant allele frequency

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Name & contact information	**Principal Investigators**	**Alternate Contact**
	Dr. Eytan M. Stein	**<u>Co-Investigators</u>** **Dr. Aaron Goldberg**
Institution(s)	Memorial Sloan Kettering Cancer Center University of Miami Sylvester Cancer Center	
Study Title	A Phase II clinical trial of E7820 for patients with relapsed/refractory myeloid malignancies with mutations in splicing factor genes.	
Study Objective(s)	***<u>Primary Objective</u>*** • To evaluate the efficacy of E7820 in patients with relapsed/refractory myeloid malignancies with mutations in splicing factor genes as measured by the response rate within 6 cycles of therapy AML: complete remission (CR) + complete remission with partial hematologic recovery (CRh) MDS: CR + partial remission (PR) CMML: CR+ PR ***<u>Secondary Objectives</u>*** • To evaluate the efficacy of E7820 as measured by overall response rate within 6 cycles of therapy, which includes CR (MRD-), CR (MRD+), marrow CR, CRi, MLFS, PR and hematologic improvement. • To assess the Event free survival (EFS). Events are defined as failure to respond within 6 cycles of therapy, relapse after achieving a response or death • To assess the 1 year Overall Survival (OS). ***<u>Exploratory Objectives:</u>*** • To assess drug effects on RBM39 protein levels in patients pre- and on-treatment • To assess E7820 effects on splicing of key target splicing events (as well as on splicing globally in vivo in patients). • To assess the effects of E7820 on variant allele frequency of splicing factor mutant clones.	

	• To assess the evaluation of DCAF15 mRNA levels and response to therapy.
Study Design	**Methodology** This is a phase II study exploring the efficacy of E7820 in patients with relapsed and refractory myeloid malignancies with mutations in splicing factors. The study will treat patients with the sulfonamide E7820 at a dose of 100mg once daily based on two previous Phase 1 trials in solid tumors with dose modification allowed if excessive toxicity is encountered. An optimal Simon two-stage design will be used to differentiate between a null unpromising ORR of 10% and a promising rate of 30%. In the first stage of the study 12 patients will enroll. If no more than one patient achieves a response, the study will close due to a lack of efficacy; otherwise, an additional 23 patients will accrue. If at the end of study, at least 6 of the 35 patients achieve a response, the study will be considered promising for further investigation. The type I and type II errors are both set at 0.10. **Clinical Activity Assessments:** All participants will have the extent of their disease assessed, including bone marrow biopsies and/or aspirates and peripheral blood, at screening, cycle 1 days 1 and 15 (peripheral blood only), cycle 2 day 1 and then every 2 months thereafter while on study drug and before the patient has achieved a remission independent of dose delays and/or dose interruptions, and/or at any time when progression of disease is suspected. Response to treatment and treatment decisions in all participants will be determined based on the 2017 ELN criteria for AML [2] and the International Working Group 2006 criteria for MDS [3] and 2015 for CMML [4]. Patients will be assessed weekly in cycle 1 then bimonthly of all subsequent cycles for toxicity assessment, limited physical and performance status evaluation. Patients will remain on E7820 until confirmed progression, unacceptable toxicity, withdrawal of consent, or if the study physician feels removal from the study is in the patient's best interest.
Number of participants	• Up to 38 patients will be enrolled in the study consisting of two stages In the first stage of the study 12 patients will enroll. If >1 patient achieves a response, an additional 23 will accrue. In the event of early drop out, up to 3 additional patients can be enrolled.
Timeframe for study start-up & duration of study	Study startup will be approximately 3 months Study accrual duration will be 1.5 years

	Entire study duration will be up to 3 years

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective

- To evaluate the efficacy of E7820 in patients with relapsed/refractory myeloid malignancies with mutations in splicing factor genes as measured by the response rate within 6 cycles of therapy
  AML: complete remission (CR) + complete remission with partial hematologic recovery (CRh)
  MDS: CR + partial remission (PR)
  CMML: CR+ PR

Secondary Objectives

- To evaluate the efficacy of E7820 as measured by overall response rate within 6 cycles of therapy, which includes CR (MRD-), CR (MRD+), marrow CR, CRi, MLFS, PR and hematologic improvement.
- To assess the Event free survival (EFS). Events are defined as failure to respond within 6 cycles of therapy, relapse after achieving a response or death
- To assess the 1 year Overall Survival (OS).

Exploratory Objectives:

- To assess drug effects on RBM39 protein levels in patients pre- and on-treatment
- To assess E7820 effects on splicing of key target splicing events (as well as on splicing globally in vivo in patients).
- To assess the effects of E7820 on variant allele frequency of splicing factor mutant clones.
- To assess the evaluation of DCAF15 mRNA levels and response to therapy.

3.0 BACKGROUND AND RATIONALE

3.1 Background

3.1.1 Novel therapeutic approaches for relapsed and treatment refractory myeloid malignancies are needed

Acute myeloid leukemia (AML) and Myelodysplastic Syndromes (MDS) are hematologic malignancies characterized by a block in myeloid differentiation leading to the accumulation of immature myeloblasts and/or pancytopenia and its sequelae. Patients with de novo AML younger than age 60 have a 40% overall survival at five years. Recently several novel agents such as CPX-351 and venetoclax in combination with the hypomethylating agents azacitidine, decitabine and low dose ara-C were approved for patients older than age 60 years, however, long-term outcomes of these patients remain worse than for younger patients [5, 6]. The response to therapy for relapsed/refractory myeloid diseases is historically very low and survival is very poor. There is currently no standard of care

therapeutic approach to relapsed or refractory AML (after therapy with chemotherapy, venetoclax based therapy and targeted therapy), MDS (after therapy with hypomethylating agents) or CMML (after therapy with hypomethylating agents). Response rates and survival achieved to multiple different salvage therapies is slightly heterogenous (and therefore difficult to report one uniform response rate) but overall very poor.

The complete remission rate in relapsed or refractory AML is 10% [7] for patients who receive hypomethylating agent monotherapy and 4% for patients who receive salvage therapy (a variety of different agents) after not responding or relapsing after prior venetoclax-based therapy [8]. Median OS is 6.7 months for relapsed refractory AML patients who receive hypomethylating agent monotherapy and 2.5 months for patients who have received prior venetoclax-based therapy [8].

Multiple agents have been tested for MDS after failure to respond to hypomethylating agents but no therapy has been approved for this treatment indication given the overall very poor outcomes in this patient population. The median OS after hypomethylating agent treatment failure in MDS is 5.6 months[9]. For CMML patients who are refractory to or relapse after prior hypomethylating agent therapy outcomes are equally poor with median OS reported at 4-8 months [10]. Response rates to a multitude of salvage therapy approaches (none of them approved or standard of care) are uniformly low but slightly varied and therefore examples are given. For instance, patients who received low-dose chemotherapy (including hydroxyurea, mercaptopurine, low-dose cytarabine, low-dose melphalan) after hypomethylating agent failure had a response rate of 0% [9]. In another study, of 65 patients with hypomethylating agent refractory MDS, the response rate was 9% to a variety of different salvage treatment regimens [11]. Similarly, treatment of hypomethylating agent refractory MDS patients with lenalidomide resulted in absent (0% response rate at 15 mg dose) or very scarce responses (11% response at 50 mg dose), respectively [12]. In summary, outcomes for patients with relapsed or treatment refractory AML, MDS and CMML is very poor with complete response rates with salvage therapy after prior intensive chemotherapy or lower intensity therapy with venetoclax based therapy ranging from 0-10% depending on the specific agent and disease [7-12].

3.1.2 Mutations in RNA splicing factor as a potential therapeutic target in myeloid malignancies

RNA splicing is the process in which a newly made precursor messenger RNA (pre-mRNA) transcript is transformed into a mature messenger RNA (mRNA). During splicing, introns (non-coding regions) are removed and exons (coding regions) are joined together [13]. RNA splicing is a nuclear enzymatic process accomplished by a macromolecular machine composed of a large constellation of RNA binding proteins (RBP) and additional splicing proteins combined with five small nuclear RNAs (snRNA) in complexes known as small nuclear ribonucleoproteins (snRNP) [13]. There is increased recognition that genetic alterations affecting RNA splicing are common in cancer and may generate novel therapeutic opportunities [13]. Mutations in genes encoding RNA splicing factors such as *SRSF2, SF3B1, U2AF1, U2AF2* and *ZRSR2* occur in 40-70% of patients with MDS and CMML and are enriched (up to 30%) in a subset of patients with AML including patients older than 60 year and patients with AML with myelodysplasia related changed (Figure 1A and B) [14-16].

In theory, these mutations represent therapeutic vulnerability as leukemia cells who have a splicing factor mutation are dependent on residual wild type splicing. Although hotspot mutations in oncogenes such as *BRAF, RAS, PIK3CA*, and other signaling proteins commonly undergo allelic imbalance in a manner that increases the dosage of the mutant allele, this conspicuously does not occur with hotspot mutations in *SRSF2, SF3B1,* or *U2AF1* [17, 18]. Instead, cells bearing mutations in

these genes consistently retain expression of thewild type allele and never undergo loss of heterozygosity or become hemizygous. These data indicate haploessentiality of mutations in *SF3B1, SRSF2,* and *U2AF1*, and suggest that increased expression of the mutant allele is negatively selected in cells. Consistent with this genetic requirement for the WT allele in splicing factor–mutant cells, spliceosomal gene mutations are also highly mutually exclusive with one another [16, 19]. In MDS, where mutations in the three most commonly mutated splicing factors, SF3B1, SRSF2, or U2AF1, are present in >50% of patients, fewer than 1% of patients harbor a mutation in >1 of these genes simultaneously [18]. These data argue for the strong requirement of a certain level of normal splicing catalysis in splicing factor–mutant cells.

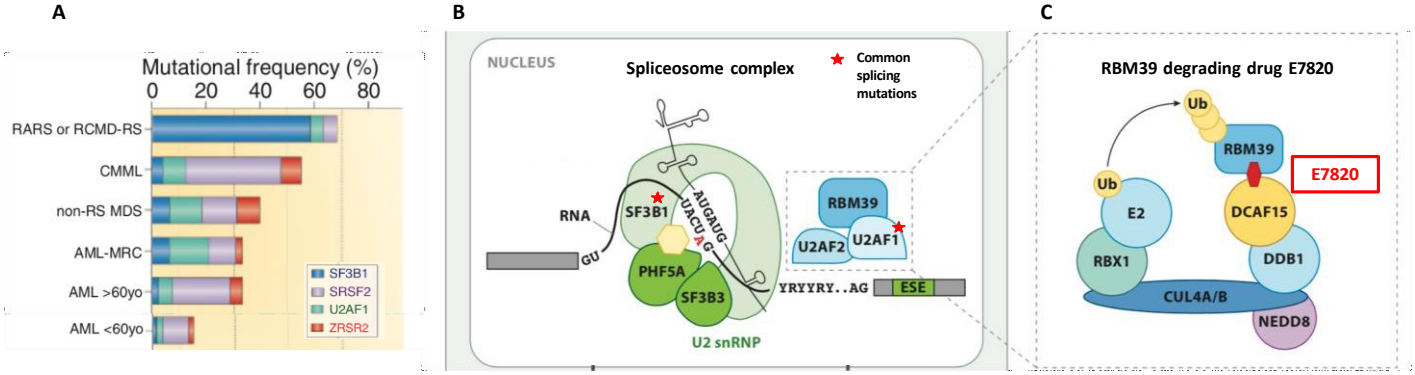
However, despite their high prevalence in myeloid malignancies, there is currently no therapy approved to directly target splicing factor mutations in myeloid malignancies.

3.2. Study Rationale

3.2.1 Perturbation of RNA splicing by proteasomal degradation of the accessory splicing factor RBM39

Until recently, few chemical means to perturb splicing were known. In 2017, Han and colleagues and investigators from Eisai discovered that a series of sulfonamide-containing compounds induce proteasomal degradation of the accessory RNA-splicing factor RBM39 [20-23.]. RBM39 is an RBP that interacts with the splicing factors SF3B1 and U2AF2 and RBM39 degradation *in vitro* results in inhibition of splicing catalysis [1].These sulfonamide-containing compounds, which include the molecules indisulam and E7820 had been known for decades to have anticancer properties *in vitro*,

Figure 1: Splicing factor mutations in myeloid malignancies and targeting of RBM39 as an essential component of the spliceosome complex by inducing proteasomal degradation of RBM39.
(A) Splicing mutation are common in MDS, CMML and AML. Histogram depicting frequency of mutations in *SF3B1, SRSF2, U2AF,*



and ZRSR2 in hematopoietic malignancies. In addition to these four genes (which are the most frequently mutated in hematopoietic malignancies), a host of additional splicing factors affected by hotspot as well as presumed loss-of-function muta- tions are also mutated in cancer and not shown here. RARS, refractory anemia with ring sideroblasts; RCMD-RS, refractory cytopenias with multilineage dysplasia and ring sideroblasts (Obeng Cancer Discovery 2019) **(B) Spliceosome complex and essential function of the splicing factor RBM39**. Several splicing factors within the spliceosome complex are recurrently mutated in myeloid malignancies including *SF3B1* and U2AF1 (marked by red star). RBM39 is an essential component of the spliceosome complex and genetic or pharmacological depletion of RBM39 results in a dysfunctional spliceosome complex and mis-splicing (Hoyos Annu. Rev. Cancer Biol. 2019). **(C) Pharmacological targeting of RBM39.** Anticancer sulfonamides such as Indisulam and E7820 bridge the cellular CUL4-DDB1-DDA1 E3 ubiquitin ligase complex to RBM39 via the adaptor protein DCAF15, resulting in polyubiquitination and subsequent proteosomal degradation of RBM39 (Hoyos Annu. Rev. Cancer Biol. 2019).

but the cellular mechanism of action was not fully understood. However, a chemical genetic

approach to identify indisulam-resistant cells and an expression proteomics effort identified RBM39 as the cellular target of these compounds. This led to the discovery that the anticancer sulfonamides bind a substrate receptor of the CRL4 E3 ubiquitin ligase complex known as DCAF15 and direct ubiquitin-mediated degradation of RBM39 (Figure 1C). Targeting RBM39 through linkage to the DCAF15 CUL4 E3 ubiquitin ligase was most effective in cells derived from the hematopoietic system and specifically those with high DCAF15 mRNA expression [20-23].

3.2.2 Preclinical data showing potent antileukemic activity associated with pharmacological RBM39 degradation in both *in vitro* and *in vivo* leukemia model

Through our own preclinical investigations in the Abdel-Wahab Laboratory at MSKCC we have discovered that the splicing factor RBM39 is required for survival of malignant myeloid cells [1]. Both genetic deletion of RBM39 (Figure 2A-B) and pharmaceutical degradation of RBM39 by anti-neoplastic sulfonamides leads to reduction in leukemia burden and survival in AML carrying mice (Figure 2C-D) [1]. Mechanistically, RBM39 degradation induced by anti-neoplastic sulfonamides leads to altered splicing of genes involved in essential oncogenic pathways [1]. The predominant change in

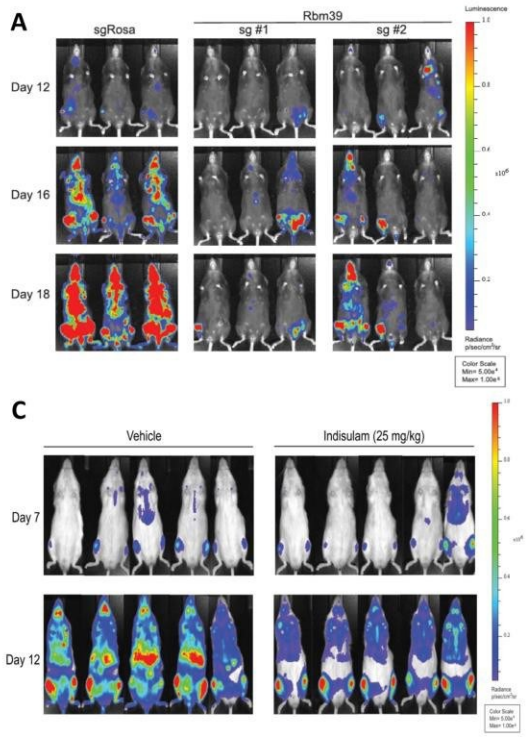


Figure 2: Preclinical evidence supporting RBM39 degradation as a potential antileukemic strategy for myeloid malignancies
A-B: RBM39 is Required to Sustain AML Growth in vivo. (A) Bioluminescent images of mice transplanted with MLL-AF9 NrasG12D cells transduced with sgRosa (n = 4) or two independent sgRbm39 (n = 7/group). (B) Kaplan-Meier survival curves of recipient mice transduced with sgRosa-negative control and two independent Rbm39 sgRNAs. **p < 0.01, ***p < 0.001
C-D: Degradation of RBM39 with anti-cancer sulfonamide Indisuluam reduces AML burden and prolongs survival in an in vivo AML model. (C) Bioluminescent imaging of mice transplanted with MOLM-13 luciferase cells and treated with vehicle or 25 mg/kg indisulam. (D) Kaplan-Meier overall survival of indisulam-treated AML mice. ***p < 0.001
Data from Wang Cancer Cell 2019 [1]

RNA splicing upon RBM39 depletion is a change in cassette exon event splicing with approximately equal proportions of exon inclusion and exclusion [1].

Induction of mis-splicing induced by E7820 induced RBM39 results in preferential lethality of AML cells bearing spliceosomal gene mutations, thereby providing a strategy for treating AML patients bearing splicing factor mutations (Figure 3A-C) [1]. Measurement of cell viability upon E7820 exposure revealed broad anti-leukemic effects with potent inhibitory activity across many AML subtypes, with most cell lines exhibiting submicromolar sensitivity (Figure 3A). Importantly, leukemia cells bearing mutations in leukemia-associated mutations in splicing factors were among the most sensitive cells to sulfonamides. The preferential effects of E7820 on leukemia cells bearing spliceosomal gene mutations was further confirmed in a series of isogenic AML lines (e.g. K562, Figure 3B) and B cell acute lymphoblastic leukemia cell lines (e.g. NALM-6 cells; Figure 3C) engineered to express hotspot mutations in SF3B1, SRSF2, and U2AF1 from their endogenous loci with exposure to E7820. In each instance, spliceosomal mutant cells were preferentially sensitive to growth inhibition to E7820 over spliceosomal wild-type cells (Figure 3B-C).

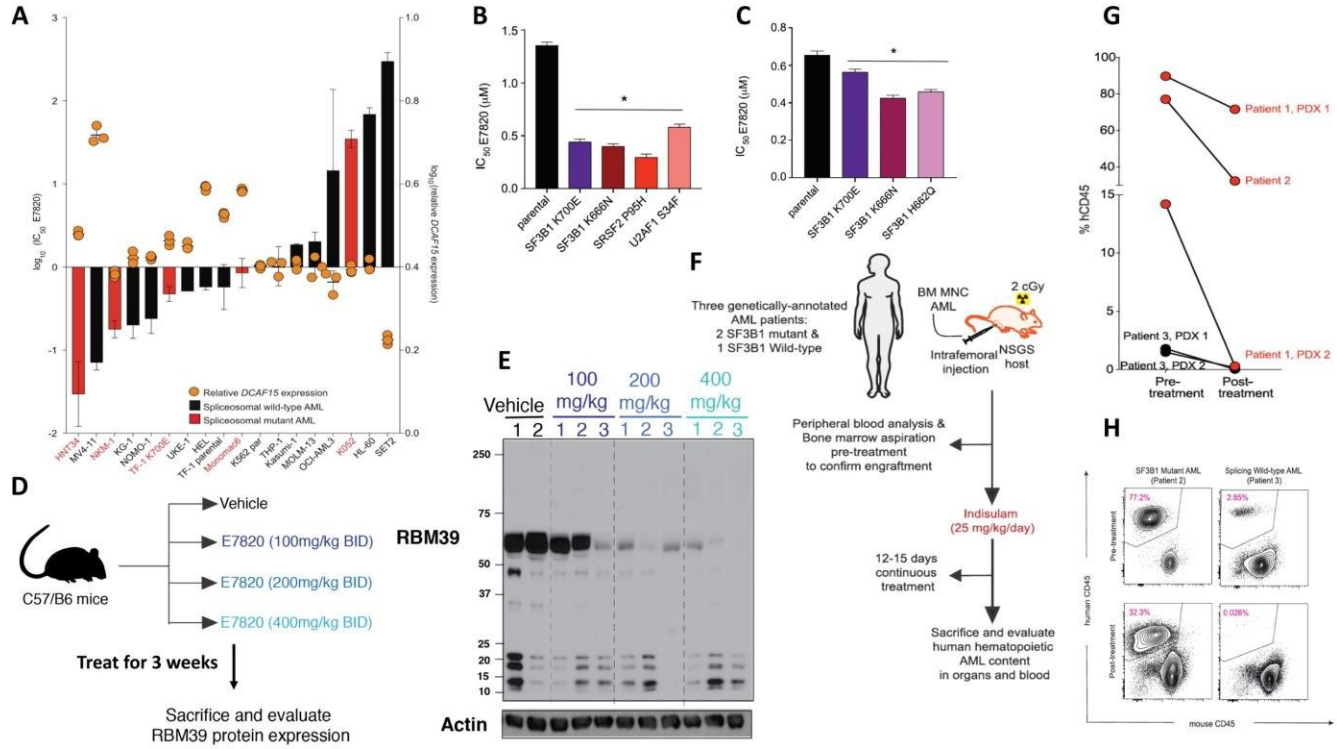


Figure 3: Preclinical evidence of antileukemic activity of of RBM39 degrading sulfonamides (E7820, Indisulam) in *in vitro* and *in vivo* AML models carring RNA splicing factor mutations.
A-C: Preferential effect of E7820 on splicing factor mutated leukemia. Log10 of IC50 values of a panel of human AML cell lines to E7820 annotated for spliceosomal gene mutation status (red versus black bars indicate spliceosomal mutant or wild-type cells, respectively). Also shown are log10 relative *DCAF*15 mRNA expression levels for each cell line (A). Bar plots of IC50 values of isogenic K562 (B) and NALM-6 (C) cells with or without knockin of spliceosomal gene mutations to E7820. **D-E: In vivo efficacy of E7820 in degrading RBM39.** Schematic of C57/B6 mice were treated with different doses of E7820 (D).Doses were well tolerated and led to potent *in vivo* degradation of RBM39 in PBMC as assessed by Western blot (E). **F-H: In vivo anti-leukemic effect in a patient-derived xenograft (PDX) model:** Schematic of generation of the PDX and treatment with indisulam (25 mg/kg/day) (F). Percentage of human CD45+ (hCD45) cells among total live bone marrow mononuclear cells by flow-cytometry analysis of bone marrow aspirate pre- and post-treatment with indisulam in five primary AML PDX models from three patients. Red indicates *SF3B1* mutant patients (G). Representative flow-cytometry plots of CD45 in patient 2 and patient 3 bone marrow aspirates before and after indisulam treatment (H). Data from Wang Cancer Cell 2019 [1]

In addition, evaluation of relative *DCAF15* mRNA expression revealed that the highest and lowest relative levels of *DCAF15* mRNA correlated with the greatest and worst response to E7820, respectively, arguing for incorporating *DCAF15* expression levels as a biomarker of response to E7820 (Figure 3A).

Importantly, E7820 leads to potent *in vivo* degradation of RBM39 when mice were treated with different doses of E7820 and RBM39 protein levels in peripheralblood monon culear cells were assessed by Westn blot (Figure 3 D-E). In addition, treatment with the anti-cancer sulfonamide indisulam demonstrated reduced leukemia burden with indisulam treatment in each case of five patient-derived xenografts (PDX) generated from three distinct patients (Figure 3 F-H) [1].

3.2.3 Rationale for testing E7820 in a clinical trial of patients with splicing factor mutated myeloid malignancies

Degrading the key accessory splicing factor RBM39 with E7820 exploits an inherent genetic dependency in splicing factor mutated myeloid neoplasms. While splicing factor wild type cells are able to compensate for degradation of RBM39, splicing factor mutant cells are unable to compensate to further perturbation of the spliceosome machinery caused by RBM39 degradation. Therefore, we hypothesize that in a biomarker selected population of patients with splicing factor mutated AML, MDS and CMML E7820 will results in a potent antileukemic effect (Figure 4).

Importantly, the safety of these sulfonamides has been established in previous clinical trials in solid tumor and leukemia patients. For E7820 specifically, a Phase 1 study to determine the maximum tolerated dose was performed in patients with advanced solid tumors (NCT00078637)[24].

At 100 mg daily, 1 patient experienced a DLT consisting of grade 3 neutropenia, thrombocytopenia, and elevated liver enzymes. At the 200-mg daily dose level, 2 patients experienced grade 4 thrombocytopenia and neutropenia. Therefore, the MTD and RP2D was determined to be 100mg daily. A separate Phase I study of E7820 to study the effect of food and to determine the maximum tolerated dose following twice daily administration was performed (NCT01773421) and found that the MTD was 50mg twice daily[25].

Based on our preclinical data and previous safety data established with Phase 1 trials of E7820 in solid tumors, we propose to conduct a phase 2 study to assess the efficacy of E7820 in myeloid malignancies with splicing factor mutations. The study population will include patients with relapsed, refractory myeloid malignancies with splicing factor mutations. We hypothesize that perturbing splicing by E7820 mediated RBM39 degradation will be synthetically lethal to cells carrying a splicing factor mutation therefore leading to higher likelihood of clinical response in patients with myeloid malignancies carrying splicing factor mutation (Figure 4).

It is important to note that we do not yet know whether splicing factor mutated AML, MDS, CMML will be responsive to E7820 and that we also do not know whether certain splicing factor mutations (e.g. *SF3B1* mutations) or histologic disease subtypes (e.g. AML) will be more responsive to E7820 compared to other splicing factor mutations (e.g. *SRSF2* mutations) or histologic disease subtypes (e.g. MDS or CMML). The trial will evaluate overall effect of proposed treatment on myeloid malignancies. If this trial is successful, disease specific studies will be conducted to confirm efficacy

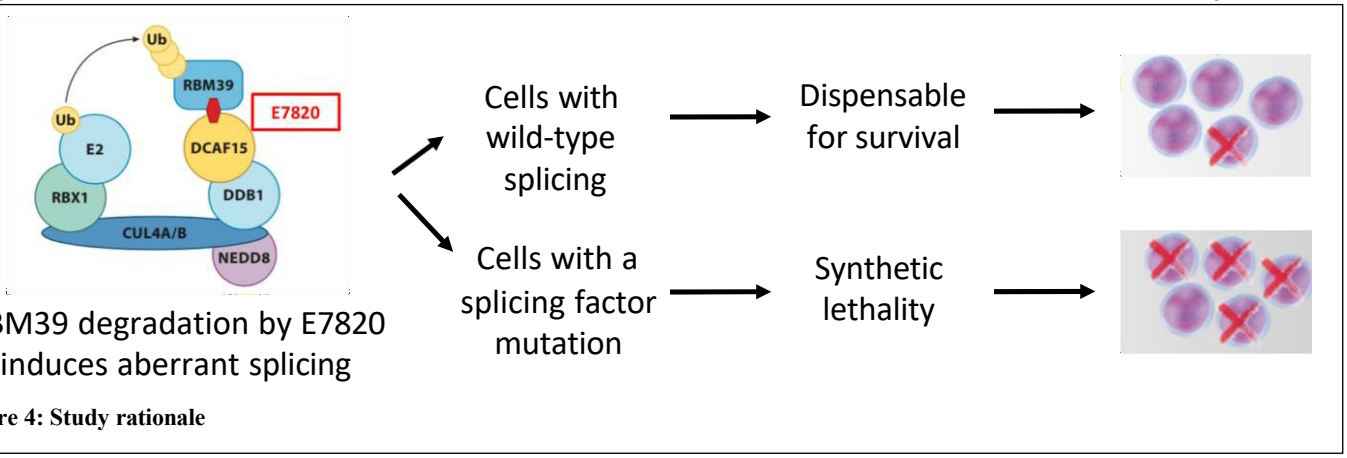


Figure 4: Study rationale

for each histologic disease subtype.

3.3 Rationale for doses selected

A Phase 1 study to determine the maximum tolerated dose of E7820 was performed in patients with advanced solid tumors [24]. At 100 mg daily, 1 patient experienced a DLT consisting of grade 3 neutropenia, thrombocytopenia, and elevated liver enzymes. At the 200-mg daily dose level, 2 patients experienced grade 4 thrombocytopenia and neutropenia. Therefore, the MTD and RP2D was determined to be 100mg daily. A separate Phase I study of E7820 to study the effect of food and to determine the maximum tolerated dose following twice daily administration was performed and found that the MTD was 50mg twice daily [25]. There was no difference in objective response rate among all doses of E7820. The recommended dose was 100mg daily.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a phase II study exploring the efficacy of E7820. Patients will consist of patients with relapsed and refractory myeloid malignancies with mutations in splicing factors. Patients will receive 100mg of E7820 QD until relapse, progression, development of unacceptable toxicity, hematopoietic stem cell transplantation (HSCT), or death. Patients will be followed for survival every 3 months for 1 year. An optimal Simon two-stage design will be used to differentiate between a null unpromising ORR of 10% and a promising rate of 30%[7-9, 26]. In the first stage of the study 12 patients will enroll. If no more than one patient achieves a response, the study will close due to a lack of efficacy; otherwise, an additional 23 patients will accrue for the second stage of the study. If at the end of study, at least 6 of the 35 patients achieve a response, the study will be considered promising for further investigation. The type I and type II errors are both set at 0.10.

It is anticipated that the study will be conducted in up to 2 study centers in the United States. The schedule of assessments is provided in Table 2.

4.2 Intervention

Each patient will receive daily administration of E7820. The starting dose for every patient will be 100 mg daily but the dose can subsequently be reduced if excessive toxicity is encountered (Section 10.1).

Participants will continue treatment with E7820 until relapse, progression, development of unacceptable toxicity, hematopoietic stem cell transplantation (HSCT), or death provided that the patient is deriving clinical benefit at the discretion of the Investigator with study Sponsor (MSKCC) approval. If after 6 cycles of therapy AML and CMML patients have not achieved at least a partial remission (PR), and MDS patients have not at least achieved hematologic improvement (HI), they will discontinue the study drug.

Participants who achieve an adequate response and are eligible for HSCT may proceed with HSCT after discontinuation of E7820. After discontinuing study treatment, participants will be followed for survival for up to 1 year If patients relapse after HSCT, restarting study treatment will be considered with study Sponsor (MSKCC) approval.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS & NON-THERAPEUTIC ASSESSMENTS

The study is cross referencing Eisai Pharmaceuticals IND # 066,803. Please reference study pharmacy manual and IB for additional details regarding investigational product.

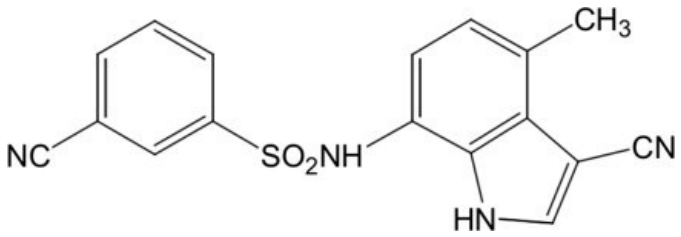
Information pertaining to the investigational product is as follows:

Active Ingredients:
N-(3-Cyano-4-methyl-1H-indol-7-yl)-3- cyanobenzenesulfonamide (developmental Code: E7820)

Excipients:
Core: D-Mannitol, Corn Starch, Low-substituted Hydroxypropyl Cellulose, Hydroxypropyl Cellulose, Magnesium Stearate
Film-Coat (Yellow): Hypromellose 2910, Talc, Polyethylene Glycol 8000, Titanium Dioxide, Ferric Oxide
Film-Coat (White): Hypromellose 2910, Talc, Polyethylene Glycol 8000, Titanium Dioxide

Pharmacological Class:
E7820, a sulfonamide derivative, is both:

(i) an angiogenesis inhibitor
(ii) a protein degrading drug leading to the degradation of the protein RBM39 through linkage to the DCAF15-CUL4 E3 ubiquitin ligase
(iii) Structural Formula:



Molecular Formula: $C_{17}H_{12}N_4O_2S$
Molecular Weight: 336.37

Dose Formulation:
E7820 drug products contain 10 or 50 mg of E7820 drug substance. The 10 mg dosage strength is a white or yellow round, biconvex film-coated tablet that is 7.6 mm in diameter. The 50 mg dosage strength is a yellow round, biconvex film-coated tablet that is 7.6 mm in diameter. All dosage strengths are manufactured using a wet granulation process.
Source of Supply: Investigational. E7820 will be suppled as 10mg and 50 mg tablets by Eisai in 30 count bottles. All study drug products will be supplied by Eisai. Eisai will ship E7820 directly to participating sites.

5.1 Study Drug Packaging and Labeling

E7820 will be supplied in appropriate containers with child-resistant closures and will be labeled as an investigational product for this study. E7820 tablets will be supplied in high density polyethylene (HDPE) bottles with a desiccant (silica gel) canister, a polyester coil, and child resistant closures with heat induction seal. Packaging and labeling will be prepared to meet all regulatory requirements

5.2 Study Drug Storage

Bottles of E7820 tablets must be stored according to the package label: Tablets are packaged in high-density polyethylene (HDPE) bottles. Store at room temperature. Do not store above 30°C. All study drug products must be stored in a secure, limited-access location and may be dispensed only by the Investigator or by a member of the staff specifically authorized by the Investigator.

5.3 Study Drug Preparation and Administration

Subjects will receive a single daily dose of E7820 100mg starting on Cycle 1 Day 1. E7820 100mg daily will continue until the end of study treatment.

Subjects will be instructed to take their daily dose at approximately the same time each day. Each dose should be taken with a glass of water and consumed over as short a time as possible. Subjects should be instructed to swallow tablets whole and to not chew the tablets. E7820 will be dispensed on Day 1 of each treatment cycle and a quantity of E7820 only sufficient for one treatment cycle will be dispensed. Subjects should be instructed to open the E7820 packaging as close as possible to when they are going to take E7820, inspect each E7820 tablet and only take tablets that are totally intact (subjects should be instructed to return any tablet not totally intact to the clinic). All subjects are advised to avoid grapefruit and grapefruit products and Seville oranges during treatment with study drug. Subjects may take study drugs with or without food. Subjects should be advised that if study drugs are taken with food, they should avoid consuming a high-fat meal.

Study drugs must be taken within ± 4 hours of the scheduled dose at approximately the same time each day. If the subject forgets to take the daily dose at the scheduled time, then they should take the study drug dose within four hours after the missed dose. If more than four hours have elapsed, then that dose should be omitted, and the subject should resume treatment with the next scheduled dose.

5.4 Study drug compliance

At the day of a scheduled visit to the clinic, the patient will take the study drugs under supervision of the Investigator or designee. The time of dose administration must be recorded by the patient in the pill diary. For all other study days, the patient will take the study drugs at home. Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit. Study drug interruptions should be noted in the Dose Administration Record eCRF.

5.5 Study drug accountability

The Investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment (including Lot numbers) according to local institutional drug accountability procedures. Any discrepancies should be noted on the drug accountability log(s). Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

5.6 Disposal and destruction

At study close-out and as appropriate during the course of the study, the study drugs will be destroyed as per local site's SOP and records will be sent to Eisai for documentation.

6.0 CRITERIA FOR PARTICIPANT ELIGIBILITY

6.1 Participant Inclusion Criteria

Patients must meet the following criteria in order to be eligible for study entry:

1. Subject is ≥ 18 years of age at the time of signing informed consent
2. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
3. Subject has relapsed or refractory MDS, AML or CMML with a previously defined hotspot splicing factor mutation in *SF3B1*, *SRSF2*, *U2AF1* or *U2AF2* (with hotspot mutations as defined by OncoKB) or a nonsense or frameshift mutation in *ZRSR2*. A splicing factor mutation is required to be detected on next generation sequencing from bone marrow aspirate or peripheral blood at any timepoint within the 6 months prior to screening for the study.
    a. Relapsed AML is defined as:
        i. The appearance of 5% or greater myeloblasts in the bone marrow or peripheral blood after achieving a CR (MRD positive or negative), CRh, or CRi
            1. Patients with mutations in FLT3, IDH1 or IDH2 must have failed or been intolerant of an FDA approved FLT3, IDH1 or IDH2 inhibitor before enrolling on study.
    b. Refractory AML is defined as failure to achieve a CR, CRh, or CRi after one of the following regimens:
        i. Two cycles of intensive induction chemotherapy with a cytarabine containing regimen (e.g. 7+3, MEC, HIDAC, etc.)
        ii. Two cycles of HMA/venetoclax or LDAC/glasdegib
        iii. 4 cycles of HMA monotherapy
    c. Relapsed MDS is defined as:
        i. Any relapse after achieving an IWG defined response.
    d. Refractory MDS is defined as:
        i. For patients with intermediate, high or very high risk disease by IPSS-R, the failure to achieve a response (as per IWG 2006 criteria) after 4 cycles of HMA monotherapy or 2 cycles of HMA + venetoclax.
        ii. For patients with very low and low risk disease by IPSS-R failure to achieve hematologic improvement or loss of hematologic improvement after treatment with standard of care agents such as ESAs, Luspatercept (for MDS with ringed sideroblasts) and lenalidomide (for pts with a 5q-).
    e. Relapsed CMML is defined as:
        i. Any relapse after achieving an IWG defined response.
    f. Refractory CMML is defined as:
        i. Failure to achieve a response (as per IWG 2006 criteria) after 4 cycles of HMA monotherapy or 2 cycles of HMA + venetoclax.
4. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status of 0-3
5. Subject has adequate organ function defined as:
    a. Serum aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) ≤ 3 x ULN, unless considered due to organ involvement by the patient's myeloid malignancy (in that case a cut off of ≤ 5 x ULN will be used)
    b. Serum direct bilirubin < 1.5 x ULN.
    c. Creatinine clearance ≥ 60 mL/min based on the Cockroft-Gault glomerular filtration rate (GFR) estimation.

   d. Females of childbearing potential may participate provided they have a negative serum pregnancy test at screening and a negative serum OR urine pregnancy test within 72 hours of starting on treatment. Females and male participants with female partnersof childbearing potential also must agree to either abstain from sexual intercourse or use a highly effective method of contraception while on study and for 4 months after completing the study treatment.
6. There are no limits on transfusion and/or growth factor support for enrollment.
7. In case of leukemic organ involvement, patients with creatinine clearance > 30 ml/min and bilirubin ≤ 2.0 x ULN will be eligible to be included.

6.2 Participant Exclusion Criteria

1. Patients with acute promyelocytic leukemia
2. Subject has immediate life-threatening, severe complications of their myeloid malignancy such as uncontrolled bleeding, pneumonia with hypoxia or shock, and/or disseminated intravascular coagulation
3. Subject has significant active cardiac disease within 6 months prior to the start of study treatment, including New York Heart Association (NYHA) class III or IV congestive heart failure; acute coronary syndrome (ACS); and/or stroke or left ventricular ejection fraction (LVEF) <40% by echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan obtained within 28 days prior to the start of study treatment.
4. Subject has active viral infection with human immunodeficiency virus (HIV), or active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV). Patients with HIV that is controlled with HAART are eligible to participate.
5. Subject is known to have dysphagia, short-gut syndrome, gastroparesis, or other conditions that limit the ingestion or gastrointestinal absorption of drugs administered orally.
6. Subject has active uncontrolled systemic fungal, bacterial, or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment).
7. Subject has QTc interval (i.e., Fridericia's correction [QTcF]) ≥ 480 ms or other factors that increase the risk of QT prolongation or arrhythmic events (e.g., heart failure, family history of long QT interval syndrome) at screening. Patients with left bundle branch block or right bundle branch block with prolonged QTc will be allowed to enroll on the trial with medical monitor approval.
8. Female subject who is pregnant or lactating.
9. Subject with known hypersensitivity to sulfa medications

7.0 RECRUITMENT PLAN

7.1 Subject Identification and Registration

Patients potentially eligible for enrollment will be identified by their primary leukemia physician or may be identified at the weekly protocol meeting discussions. Patients will be approached in clinic by their leukemia physician. Participants who are candidates for enrollment into the study will be evaluated for eligibility by the Investigator to ensure that the inclusion and exclusion criteria been satisfied and that the subject is eligible for participation in this clinical study.

7.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

8.0 INFORMED CONSENT PROCEDURES

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

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

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

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

9.0 PRE-TREATMENT/INTERVENTION

After informed consent has been completed, all participants will undergo screening procedures within 28 days prior to the start of study drug treatment to determine eligibility. All subjects are required to undergo a bone marrow aspirate and biopsy. If the participant is inaspirable, a biopsy alone is sufficient. Bone marrow biopsy will also be used for pathologic confirmation of myeloid malignancy and as a baseline specimen for correlative studies. Additional screening procedures include medical, surgical and medication history, physical exam, vital signs, ECOG PS, 12-lead ECG, laboratory assessments (hematology, chemistry, coagulation, HIV, Hepatitis), and serum pregnancy test.

9.1 Prior and Concomitant Therapy

All red blood cell and platelet transfusions within 8 weeks prior to starting study drug treatment are to be recorded on the electronic case report form (eCRF) for enrolled subjects. In addition, all prior treatments for the underlying malignancy should be recorded. There should be a 14 day washout

period prior to Induction Day 1 for any chemotherapy, biologic therapy or investigational therapy that subjects may have received, with the exclusion of Hydroxyurea.

9.2 Prohibited Concomitant Therapy

Antineoplastic therapy other than the treatment outlined in the protocol is not permitted during the study. If alternative therapy is required for treatment of the subject's disease, the subject should be discontinued from the study drug treatment. An exception to this rule is hydroxyurea, which may be used on study with the intent for initial cytoreduction.

10.0 TREATMENT/INTERVENTION PLAN

Each patient will receive daily administration of E7820. The starting dose for every patient will be 100 mg daily but the dose can subsequently be reduced if excessive toxicity is encountered (Section 10.1)

Participants will continue treatment with E7820 until relapse, progression, development of unacceptable toxicity, hematopoietic stem cell transplantation (HSCT), or death provided that the patient is deriving clinical benefit at the discretion of the Investigator with study funder approval. If after 6 cycles of therapy AML and CMML patients have not achieved at least a partial remission (PR), and MDS patients have not at least achieved hematologic improvement (HI), they will discontinue the study drug.

Participants who achieve an adequate response and are eligible for HSCT may proceed with HSCT after discontinuation of E7820. After discontinuing study treatment, participants undergoing HSCT will be followed for survival. If patients relapse after HSCT, restarting study treatment will be considered with the PI's (Dr. Stein) approval.

10.1 Dose modification based on toxicity

The study will evaluate at E7820 at a starting dose of 100 mg daily (dose level 1).

Patients with relapsed and refractory myeloid malignancies, who have yet to respond, commonly have toxicities related to their underlying disease. For this reason, the criteria for dose holds, dose reduction and drug discontinuation only apply where the toxicity is thought to be possibly, probably or definitely related to the drug under study and not as a consequence of the disease itself. For patients requiring dose reductions, step decreases occur in single dose level reductions and up to two dose reductions are allowed. No dose reductions are allowed below dose level -2, and if required, E7820 is to be discontinued.

Table 1: Dose levels for treatment with E7820

Dose level	E7820 dose	Tables taken by patient
1 (starting dose for every patient)	100mg daily	Two 50 mg tablets
-1	70 mg daily	One 50 mg tablet and Two 10 mg tablets

-2	50 mg daily	One 50 mg tablet

Dose Modification for Non-hematologic Toxicity:

The rules outlined below are to be followed for the management of non-hematologic toxicities that are definitely or possibly due to E7820, with toxicities graded by the Investigator according to the NCI, CTCAE, Version 5.0.

Dose interruptions for the management of other toxicities ≥ grade 3 as per CTCAE version 5.0 (excluding fever or infection) that are at least possibly related to E7820 with the following exceptions:
- Grade 3 nausea that persists for less than 3 days and is controlled with oral anti-emetics
- Grade 3 diarrhea that persists for less than 3 days and is controlled with anti-diarrheal medication
- Grade 3 electrolyte abnormalities that correct within 48 hours with appropriate electrolyte repletion.

Resume E7820 upon recovery to Grade 1 or baseline, under the following directions:

1) If recovered in ≤7 days of treatment interruption, restart E7820 at dose level 1
2) If recovered in >7 to 14 days of treatment interruption, restart E7820 at dose level -1
3) If recovered in >14 days of treatment interruption, treatment should be discontinued.
4) If the same toxicity recurs within 60 days of dose reduction (i.e., second episode) and recovers within 14 days of treatment interruption, one additional dose reduction to dose level -2 may occur for patients on dose level -1. For patients on dose level -2, E7820 should be discontinued.

Discontinue treatment for all ≥ grade 4 non-hematologic events

Dose Modification for Hematologic Toxicity

The rules outlined below are to be followed for the management of hematologic toxicities that occur in patients who have achieved CR with complete blood count recovery (ANC ≥1.0 × 10^9/L and platelet count ≥100 × 10^9/L).

If ANC decreases to <1.0 × 10^9/L and/or if platelet count decreases to <50 × 10^9/L, withhold E7820. Resume E7820 upon recovery to ANC ≥1.0 × 10^9/L and platelet count ≥50 × 10^9/L, under the following directions:

First Occurrence of ANC <1.0 × 10^9/L and/or Platelet Count <50 × 10^9/L

If recovery to ANC ≥1.0 × 10^9/L L and platelet count ≥50 × 10^9/L occurs within 14 days of withholding E7820, resume E7820 at the same dose the patient was taking prior to the episode of myelosuppression.

Second Occurrence of ANC <1.0 × 10^9/L and/or Platelet Count <50 × 10^9/L

If recovery to ANC ≥1.0 × 10^9/L and platelet count ≥50 × 10^9/L occurs within 14 days of withholding, resume E7820 at the next lower dose level (dose level -1). If after 4 weeks from resuming treatment, the ANC ≥1.0 × 10^9/L and platelet count ≥50 × 10^9/L, increase E7820 to the next highest dose level.

Third Occurrence of ANC <1.0 × 10^9/L and/or Platelet Count <50 × 10^9/L
If recovery to ANC ≥1.0 × 10^9/L and platelet count ≥50 × 10^9/L occurs within 14 days of withholding, resume E7820 at the next lower dose level (dose level -2). If after 4 weeks from resuming treatment, the ANC ≥1.0 × 10^9/L and platelet count ≥50 × 10^9/L, increase E7820 to the next highest dose level.

Fourth Occurrence of ANC <1.0 × 10^9/L and/or Platelet Count <50 × 10^9/L
Discontinue treatment

Discontinue treatment for ≥ grade 3 neutropenia and thrombocytopenia of ≥ 14 days in the absence of evidence of active AML.

11.0 EVALUATION DURING TREATMENT/INTERVENTION

11.1 Study Assessments

11.1.1 Schedule of Assessments
The schedule of assessments for this study is provided in Table 2.

11.1.2 Informed Consent
A complete description of the study is to be presented and discussed with each potential subject, and a signed and dated informed consent form is to be obtained before any study specific procedures are performed.

11.1.3 Demographic Data and Medical, Surgical, and Medication History
Subject demographic data, including biological sex, date of birth, age, race, and ethnicity will be obtained during Screening. A complete medical history, including the date of diagnosis of the myeloid malignancy and current stage, will be obtained during Screening. The medical history is to include all relevant prior medical and surgical history as well as all current medical conditions. All medications administered and procedures conducted within 28 days prior to the start of induction therapy should be reported in the eCRF.

11.1.4 Safety Assessments

11.1.4.1. Physical Examination and ECOG Performance Status
A complete physical examination will be obtained at Screening and at the EOT visit or as determined by the Investigator. An abbreviated physical examination will be completed on weekly visits during C1 and on bimonthly visits thereafter. Determination of ECOG PS will be performed at Screening, on Day 1 of the cycle(s).

11.1.4.2 Vital Signs
Vital signs (including systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature) and weight will be obtained at Screening at each assessment visit. Blood pressure assessments should be conducted after the subject has been in a seated position for five minutes. Height will be obtained at the Screening visit only. Body surface area (BSA) calculation should be conducted on Day 1 of each cycle.

11.1.4.3 Electrocardiogram

A single 12-lead ECG will be taken at screening to support eligibility determination. A single 12-lead ECG should also be obtained at any time as clinically indicated during the study.

11.1.4.4 Safety Laboratory Assessments

Clinical laboratory evaluations are to be conducted by the site's local laboratory. All clinically significant laboratory abnormalities will be followed by repeat testing and further investigated according to the judgment of the Investigator. The following safety laboratory parameters are to be evaluated by the Investigator:

- Hematology: hematocrit, hemoglobin, red blood cell (RBC) count, WBC count with differential (WBC differential may be omitted if total WBC count is too low to run differential, according to local laboratory standards), ANC, platelet count, and peripheral blasts
- Serum Chemistry: sodium, potassium, chloride, calcium, magnesium, phosphorus, CO2, albumin, total protein, glucose, blood urea nitrogen (BUN), creatinine, uric acid, lactate dehydrogenase, ALP, ALT, AST, total bilirubin, and direct bilirubin

Blood for hematology and chemistry is to be obtained at Screening and at each assessment visit. Creatinine clearance should be calculated at Screening using the Cockcroft-Gault GFR.
Pregnancy Test: Females of childbearing potential may participate provided they have a negative serum pregnancy test at screening and a negative serum OR urine pregnancy test within 72 hours of starting on treatment.

11.1.4.5 Adverse Events

All AEs will be graded using the NCI CTCAE version 5 grading system.AEs and concomitant therapy should be assessed weekly for the first cycle and then bimonthly on Cycle 2, then monthly thereafter on the same day as physical examination assessments.

11.1.4.6 Collection timepoint of bone marrow samples and peripheral blood samples

A bone marrow aspirate and biopsy are required at Screening. If the participant is inaspirable, a biopsy alone is sufficient. If a bone marrow aspirate and biopsy cannot be performed during the Screening period, the PI of the study (Dr. Stein) should be consulted. Additionally, a bone marrow aspirate and biopsy are required at C2D1 and every 2 months until a patient achieved a remission or comes of study. If a patient achieved a complete remission, subsequent bone marrow biopsies will only be performed at the time that progression or relapse is suspected.

Bone marrow aspirates/biopsies should be performed according to standard of care and analyzed at the local site's laboratory in accordance with the International Council for Standardization in Hematology (ICSH) Guidelines (Lee, et al., 2008).

Peripheral blood for the evaluation of leukemic blast cells and neutrophils will be drawn at the following time points: C1D1, C1D15, C2D1, and the first day of every subsequent cycle thereafter until study discontinuation or any time that disease progression is suspected.

11.1.4.7 Pharmacodynamic Assessments

Bone marrow samples will be evaluated for RBM39 levels for PD analyses. Bone marrow, peripheral blood, and processed bone marrow and peripheral blood samples, including neutrophils, will also be subject to exploratory biomarker analyses, including global splicing, changes and variant allele frequency of mutations.

11.1.4.8 Bone marrow samples

Bone marrow samples will be collected at time points indicated above (section 11.1.4.6) to assess disease status and immunophenotype by flow cytometry.

Next-generation DNA gene mutation analysis by next generation sequencing (utilizing MSK IMPACT Hem at MSKCC and local next generation sequencing technology at other centers), as per standard of care, will be sent from each bone marrow aspirate sample. Matched normal sample (nail sample) will be sent at the time of screening only. For patients enrolling at Memorial Sloan Kettering Cancer Center, nail samples will be collected only if the patient is enrolled in protocol 12-245. For patients not enrolled in protocol 12-245, nail sample collection is optional.

A Pax-gene RNA preservation tube will be sent from each bone marrow aspirate sample as part of a biospecimen research protocol that will be associated with this study. Global splicing changes and DCAF15 mRNA levels will be measured by RNA-sequencing.

Bone marrow mononuclear cells will be drawn from each bone marrow aspirate sample and will be viably frozen and then used for protein extraction in batches to test for RBM39 levels by western blot. Patients will also be consented to specimen collection protocol 06-107 so that research samples can be used for future analysis.

11.1.4.9 Blood samples

Peripheral blood analysis will be collected at time points indicated above (section 11.1.4.6) Viably frozen peripheral blood mononuclear cells as well as plasma will be stored in liquid nitrogen for as backup to bone marrow samples that fail analysis.

11.1.5 Correlative Research Assessments

Much of the preclinical research that serves as the basis for this clinical trial was performed at MSKCC in the Abdel-Wahab laboratory and we will leverage the research assays that are available in the lab to perform detailed correlative studies with the goal of informing biological markers that can potentially predict response to therapy with E7820. Given the mechanistic role of RBM39 in splicing and the requirement of the DCAF15 adapter protein for E7820 activity, we identified that both the presence of spliceosomal gene mutations and levels of DCAF15 expression are important predictors of response in preclinical models. We will extend this by looking for spliceosomal gene mutations by MSKCC Heme-IMPACT. We will evaluate DCAF15 protein levels by western blot and RNA levels by RT-PCR. We will test our hypothesis of the mechanism of action of E7820 and its selective therapeutic efficacy in the following correlative analyses:

1) Assessment of E7820 effects on RBM39 protein levels in patients pre- and post-treatment.
2) Assessment of E7820 effects on splicing of key target splicing events and on splicing globally
3) Effects of E7820 on variant allele frequency of splicing factor mutant clones.
4) Evaluation of *DCAF15* mRNA levels and response to therapy.

SPECIFIC AIM 1: To assess the effects of E7820 on RBM39 protein levels in patients pre- and post-treatment.

Rationale: Consistent with the genetic requirement of RBM39 in AML, pharmacologic selective targeting of RBM39 by E7820 via ubiquitin-mediated degradation induced broad anti-leukemic effects in vitro and potent single agent activity in vivo PDX AML cell lines. These effects were dependent on the ability of E7820 to cause decreased amounts of RBM39 protein.

Procurement/Methods: Bone marrow and peripheral blood samples will be collected, processed for mononuclear cells and viably frozen for later lysis and assessment of RBM39 protein levels by western blot.

SPECIFIC AIM 2: Assessment of E7820 effects on splicing of key target splicing events and on splicing globally

Rationale: Mechanistically, RBM39 promotes the splicing of genes involved in essential oncogenic pathways. The effects of RBM39 loss on alteration of splicing further resulted in preferential lethality of AML cells bearing spliceosomal gene mutations over spliceosomal wildtype counterparts, thereby providing a strategy for targeted treatment of AML patients bearing RNA splicing mutations.

Procurement/Methods: RNA sequencing will be on bone marrow biopsy mononuclear cells at screening, at regular intervals on treatment as specified, and at time of progression. We will isolate poly(A) mRNA using magnetic isolation method using ~1 ug of total mRNA. To generate RNA-sequencing libraries, we used NEXTflex Rapid Directional protocol and NEXTflex RNA-seq barcodes according to manufacturer's protocol. RNA-seq barcoded libraries will then be sequenced using Illumina Hi-Seq 4000 (150 cycles paired end).

SPECIFIC AIM 3: Evaluate the effects of E7820 on variant allele frequency of splicing factor mutant clones.

Rationale: If E7820 is selectively targeting spliceosomal mutant cells the variant allele frequency of splicing factor mutations should decrease with therapy.

Procurement/Methods: DNA sequencing with MSKCC Heme-IMPACT panel will be performed on bone marrow aspirates at screening C2D1 and at time of response and progression to evaluate changes in variant allele frequency, which will be in line with the clinical standard of care at MSKCC.

SPECIFIC AIM 4: Evaluate *DCAF15* mRNA levels and response to therapy.
Rationale: Given that decreased DCAF15 protein levels are required for therapeutic effect of E7820 and preclinical evidence shows that cells with higher expression of *DCAF15* have higher rates of response to E7820, we hypothesize that *DCAF15* mRNA levels will positively correlate with response.

Procurement/Methods: RNA sequencing being performed for Aim 2 can also be used to evaluate this question but for a quicker turnaround and as an orthogonal validation we will perform RT-PCR to quantitate levels of DCAF15 in patients on the trial and then correlate with response to E7820.

Sample Processing, Storage, and Shipment:

Instructions for the processing, storage, and shipment of all study samples for will be provided in a separate laboratory manual.

Table 2. Study calendar

Assessment Period	Screening	Cycles 1 (+/- 3 days)				Cycle 2 (+/- 3 days)		Cycles 3 and beyond (+/- 3 days)	End of Treatment [8] (+/-7 days)	Follow up HSCT	Survival Follow-Up
Study Days	**within 28 days of study initiation**	**D1**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**Every 3 months**	**Every 3 months**
Informed consent	X										
Review Entry Criteria	X										
Demographics	X										
Medical and Surgical History	X										
Medication History	X										
Complete Physical Examination	X	X							X	X	X
Limited Physical Exam						X	X	X			
Height and Weight	X	X				X		X			
Vital Signs [1]	X	X				X	X	X	X	X	X
ECOG/KPS	X	X				X	X	X	X	X	X
12-lead ECG	X										
Gene Mutation Analysis	X	X				X					
Laboratory Evaluations											
Hematology [2]	X	X	X	X	X	X	X	X	X		
Chemistry [3]	X	X	X	X	X	X	X	X	X		
Coagulation studies	X										
HIV, Hepatitis B and Hepatitis C	X										
Pregnancy test [4]	X	X				X		X	X		

Bone Marrow Biopsy and/or Aspirate for molecular and functional studies of blasts and plasma[5,7]	X					X		X	X		
Peripheral blood for molecular and functional studies of blasts, plasma and neutrophils[6,7]	X	X		X		X		X	X		
Evaluate extent of disease and response to treatment[5]	X					X		X	X		
Compliance Assessment		X	X	X	X	X	X	X	X		
Adverse Events	X	X	X	X	X	X	X	X	X		
Concomitant Medications/ Procedures	X	X				X		X	X	X	X
Survival Status										X	X

1. Vital signs include: pulse, blood pressure, temperature, respiratory rate, and oxygen saturation.
2. Hematology must include CBC with differentials and lymphocyte and eosinophil count.
3. Chemistry must include comprehensive metabolic panel (albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, magnesium, phosphorus), LDH, uric acid, amylase, and lipase.. PT (or INR) and aPPT should be tested for screening only.
4. Females of childbearing potential may participate provided they have a negative serum pregnancy test at screening and a negative serum OR urine pregnancy test within 72 hours of starting on treatment.
5. Bone marrow aspirate and biopsies at screening, C2D1 and every 2 months until a patient achieved a remission or comes of study. If a patient achieved a complete remission, subsequent bone marrow biopsies will only be performed at the time that progression or relapse is suspected. A bone marrow biopsy will also be performed at the time of progression. DNA gene mutation analysis by next generation sequencing (utilizing MSK IMPACT Hem at MSKCC and local next generation sequencing technology at other centers) will be sent from each bone marrow aspirate sample. Matched normal sample (nail sample) will be sent at the time of screening only.
6. Peripheral blood collection at screening, C1D1, C1D15, C2D1, and the first day of every subsequent cycle thereafter until study discontinuation or any time that disease progression is suspected.
7. Research BM and blood tests will be performed at the same time of routine bone marrow and peripheral blood sampling as detailed in 6. and 7.
8. End of Treatment visit, should be within 30 days (± 7 days) of last dose of study drugs

12.0 CRITERIA FOR REMOVAL FROM STUDY

Participants may continue treatment with E7820 until disease progression, development of other unacceptable toxicity, confirmed pregnancy, undergoing a hematopoietic stem cell transplant (HSCT), death, withdrawal of consent, lost to follow-up, or study team ending the study, whichever occurs first. Subjects who experience disease progression per the applicable response criteria who are, in the opinion of the Investigator, benefiting from treatment may be allowed to continue on study drug with approval of the MSK PI (Dr. Stein).

Patients, who are able to receive a HSCT, will stop the study drug prior to HSCT and will not restart the study drug after HSCT. Participants who relapse after HSCT and have recurrent splicing factor-mutant positive disease may be eligible to restart treatment with MSK PI (Dr. Stein).

All subjects, including those who relapse following HSCT and elect not to restart treatment, will enter survival follow-up and will be contacted every 3 months for assessment of survival status and BMT conditioning or other new antineoplastic therapies since discontinuation of study drug for 1 year, withdrawal of consent, lost to follow-up, or end of study .

12.1 Participant withdrawal criteria and replacement of subjects

Participants have the right to withdraw from the study at any time for any reason.
Participants may withdraw or be withdrawn from study treatment for any of the following reasons:

- Withdrawal of consent
- Experiences with unacceptable toxicity
- Any medical condition, which, in the opinion of the Investigators, would put the patient at risk with continuing treatment
- Disease Progression
- Confirmed pregnancy
- Investigator removes the subject from the trial in the best interest of the patient
- Protocol violation: non-adherence to study drug regimen or protocol requirements
- Lack of efficacy

Lost to follow up Patients withdraw or are withdrawn from study treatment will not be replaced.

13.0 CRITERIA FOR OUTCOME ASSESSMENT AND ENDPOINT EVALUABILITY

13.1 Criteria for Therapeutic Response/Outcome Assessment

The clinical activity of E7820 will be evaluated by assessing response to treatment according to the International Working Group for AML, MDS and CMML.

Disease response to treatment will be assessed through the evaluation of bone marrow biopsies and/or aspirates, along with complete blood counts and examination of peripheral blood smears. Treatment decisions will be based on Investigator’s assessment.

Participants will have the extent of their disease assessed and recorded at screening, on C2D1, and then every 2 months thereafter while on study treatment, independent of dose-delays and/or dose interruptions. Disease will also be assessed when progression of disease is suspected and at the End of Treatment visit for participants, who discontinue treatment for reasons other than disease progression.

Participants will have absolute neutrophil, hemoglobin and platelet levels recorded and well as any RBC and platelet transfusions required at baseline and at each disease assessment. The following criteria outlined in the table below will be used to assess response to treatment.

Tables: Response criteria

AML: 2017 European Leukemia Network (ELN) response criteria [2]

Category	Definition
Response	
CR without minimal residual disease (CR_{MRD-})	If studied pretreatment, CR with negativity for a genetic marker by RT-qPCR, or CR with negativity by MFC
Complete remission (CR)	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥1.0 × 10^9/L (1000/μL); platelet count ≥100 × 10^9/L (100 000/μL)
CR with incomplete hematologic recovery (CR_i)	All CR criteria except for residual neutropenia (<1.0 × 10^9/L [1000/μL]) or thrombocytopenia (<100 × 10^9/L [100 000/μL])
Morphologic leukemia-free state (MLFS)	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%
Additional response criterium not included in 2017 ELN AML response criteria: Complete remission with partial hematologic recovery (CRh)	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; and partial recovery of peripheral blood counts (platelets > 50 × 10^9/L and ANC > 0.5 × 10^9/L).
Treatment failure	
Primary refractory disease	No CR or CR_i after 2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause

Death in aplasia	Deaths occurring ≥7 d following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 d of death, without evidence of persistent leukemia
Death from indeterminate cause	Deaths occurring before completion of therapy, or <7 d following its completion; or deaths occurring ≥7 d following completion of initial therapy with no blasts in the blood, but no bone marrow examination available
Response criteria for clinical trials only	
Stable disease	Absence of CR_{MRD-}, CR, CR_i, PR, MLFS; and criteria for PD not met
Progressive disease (PD)	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood:
	• >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 mo; without at least a 100% improvement in ANC to an absolute level (>0.5 × 10^9/L [500/μL], and/or platelet count to >50 × 10^9/L [50 000/μL] nontransfused); or
	• >50% increase in peripheral blasts (WBC × % blasts) to >25 × 10^9/L (>25 000/μL) (in the absence of differentiation syndrome)†; or
	• New extramedullary disease
Relapse	
Hematologic relapse (after CR_{MRD-}, CR, CR_i)	Bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease
Molecular relapse (after CR_{MRD-})	If studied pretreatment, reoccurrence of MRD as assessed by RT-qPCR or by MFC

ANC, absolute neutrophil count; IDH, isocitrate dehydrogenase; MLFS, morphologic leukemia-free state; WBC, white blood cell.

Category	Definition
Response	
Complete Remission (CR)	Bone marrow blasts < 5% with normal maturation of all cell lines. Persistent dysplasia will be noted; Peripheral blood (Response must be maintained for at least 4 weeks): Hgb ≥ 11g/dL; ANC ≥ 1.0 x 10^9 /L (1000/μL); platelet count ≥100 x 10^9 /L (100,000/μL), Blasts 0%
Marrow CR	Bone marrow blasts <5% and decrease by ≥50% over pretreatment; Hematologic Improvement (HI) responses will be noted in addition to marrow CR (see below).
Partial Remission (PR)	All hematologic criteria of CR; except decrease of pretreatment bone marrow blast percentage by at least 50% but still >5%.
Hematologic improvement (HI)	Erythroid (HI-E): - Hb increase of > 1.5 g/dL - decrease of ≥4 RBC transfusions/8weeks in patients with baseline transfusion burden of ≥4 RBC transfusions/8weeks only RBC transfusions given for a pretreatment Hgb of < 9.0 g/dL count Platelet (HI-P): - increase of platelets > 30,000/mL (starting with > 20,000/mL) - increase from < 20,000/mL to >20,000/mL by > 100% Neutrophil (HI-N): - increase of > 100% and ANC > 500/uL
Transfusion independence (TI)	≥ 8 weeks (during weeks 1-24) without - Red blood cell transfusion (RBC-TI) - Platelet transfusion (PLT-TI)
Treatment Failure	
Disease Progression	For patients with: Less than 5% blasts: ≥50% increase in blasts to >5% 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
Failure	Death during treatment or disease progression characterized by worsening of cytopenia, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment

Relapse	
Relapse (after CR or PR)	At least 1 of the following: Return to pretreatment 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
Additional Clinical Trial Response Criteria	
Stable Disease (SD)	Failure to achieve at least a PR, but no evidence of progression for >8 weeks.

MDS: 2006 International Working Group (IWG) response criteria [3]

CMML: 2015 International Working Group (IWG) response criteria [4]

Category	Definition
Response	
Complete Remission (CR)	Bone marrow: blasts < 5% (including monocytic blast equivalent); ≤ Grade 1 fibrosis; Peripheral blood: Hgb ≥ 11g/dL; ANC ≥ 1.0 x 10^9 /L (1000/μL); platelet count ≥100 x 10^9 /L (100,000/μL); WBC ≤ 10 x 10^9 /L; Monocytes <1.0 x 10^9 /L, Blasts 0%.
Marrow response	Optimal: Bone marrow blasts <5% and decrease by ≥50% over pretreatment without normalization of peripheral blood indices as presented above; Partial: Decrease of blasts by ≥50% over pretreatment but still above 5%.
Partial Remission (PR)	All hematologic criteria of CR; except decrease of pretreatment bone marrow blast percentage by at least 50% but still >5%.
Treatment Failure	
Disease Progression (Combination of 2 major criteria, 1 major and 2 minor criteria, or 3 minor criteria from list)	Major Criteria: Increase in blast count - Less than 5% blasts: ≥50% increase in blasts to >5% - 5%-10% blasts: ≥50% increase to >10% blasts - 10%-20% blasts: ≥50% increase to >20% blasts - 20%-30% blasts: ≥50% increase to >30% blasts Evidence of cytologic evolution New extramedullary disease Worsening splenomegaly Minor Criteria: At least 50% decrement from maximum remission/response in granulocytes or platelets Reduction in Hgb by ≥ 1.5 g/dL Transfusion dependence Increasing symptoms by ≥50% as per the MPN-SAF TSS Evidence of molecular clonal evolution
Failure	Death during treatment or disease progression characterized by worsening of cytopenia, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Additional Clinical Trial Response Criteria	
Clinical benefit	Requires 1 of the following responses in the absence of progression, CR/PR and independent of marrow response: Erythroid, Platelet, Neutrophil, Spleen or Symptom Response.

14.0 BIOSTATISTICS

14.1 Populations for Analysis

Efficacy Evaluable Population

Efficacy Evaluable Population includes all participants who have received at least one dose of study treatment. Patients that come off trial prior to the first response evaluation will be considered as failure to achieve primary response.

Exploratory Endpoint Evaluable Population: includes all participants who have received at least one dose of study treatment and have had bone marrow response evaluation.

14.2 Outcome measures

Primary Objective

- To evaluate the efficacy of E7820 in patients with relapsed/refractory myeloid malignancies with mutations in splicing factor genes as measured by the response rate within 6 cycles of therapy

AML: complete remission (CR) + complete remission with partial hematologic recovery (CRh)
MDS: CR + partial remission (PR)
CMML: CR + PR

Secondary Objectives

- To evaluate the efficacy of E7820 as measured by overall response rate within 6 cycles of therapy, which includes CR (MRD-), CR (MRD+), marrow CR, CRi, MLFS, PR and hematologic improvement.
- To assess the Event free survival (EFS). Events are defined as failure to respond within 6 cycles of therapy, relapse after achieving a response or death
- To assess the 1 year Overall Survival (OS).

Exploratory Endpoints

- Assessment of drug effects on RBM39 protein levels in patients pre- and post-treatment
- Assessment of E7820 effects on splicing of key target splicing events (as well as on splicing globally in vivo in patients).
- Effects of E7820 on variant allele frequency of splicing factor mutant clones.
- Evaluation of DCAF15 mRNA levels and response to therapy.

14.3 Trial design

It is important to note that we do not yet know whether splicing factor mutated AML, MDS, CMML will be responsive to E7820 and that we also do not know whether certain splicing factor mutations (e.g. *SF3B1* mutations) or histologic disease subtypes (e.g. AML) will be more responsive to E7820 compared to other splicing factor mutations (e.g. *SRSF2* mutations) or histologic disease subtypes (e.g. MDS or CMML). The trial will evaluate overall effect of proposed treatment on myeloid malignancies. If this trial is successful, disease specific studies will be conducted to confirm efficacy for each histologic disease subtype. Outcomes for patients with relapsed or treatment refractory AML, MDS and CMML is very poor with complete response rates with salvage therapy after prior intensive chemotherapy or lower intensity therapy with venetoclax based therapy ranging from 0-10% depending on the specific agent

and disease [7-12] Based on this information, a null unpromising ORR was set to upper limit of 10%.

An optimal Simon two-stage design will be used to differentiate between a null unpromising ORR of 10% and a promising rate of 30%.

In the first stage of the study 12 patients will enroll. If no more than one patient achieves a response, the study will close due to a lack of efficacy; otherwise, an additional 23 patients will accrue.

- If at the end of study, at least 6 of the 35 patients achieve a response, the study will be considered promising for further investigation. The type I and type II errors are both set at 0.10.
- ORR will be estimated by sample proportion and confidence intervals will be calculated based on exact binomial distribution.

Safety stopping rule: We will implement toxicity stopping rule to monitor for excess of toxicity occurring during treatment by proposed drug combination. Based on definitions in Section 10.1, toxicity event is defined as:
1. ≥ grade 4 non-hematologic toxicity or dose delays of > 14 days between cycles because of non-hematological toxicity

2. ≥ grade 3 neutropenia and thrombocytopenia of ≥ 14 days in the absence of evidence of active AML

Sequential boundaries will be used to monitor the composite rate of toxicities that are outlined above. The boundaries are based on a maximum accrual of 35 patients to the study. Accrual will be halted if the number of patients experiencing one or more of the above toxicities exceeds any threshold below:
Treatment is too toxic if above event is seen in:

- More than 1 out of 5 included patients
- More than 2 out of 15 included patients
- More than 3 out of 30 included patients
- More than 4 out of 35 included patients

With these criteria, there is a 5% of probability to stop for excessive toxicity if the actual rate is 9%, and a 90% chance of stopping if the actual rate is 20%.

14.4 Analysis plan for the secondary objectives.

Each objective will be evaluated in the efficacy evaluable population .

1. Kaplan-Meier methods will be used to estimate the overall survival. Overall survival is defined as the time from the first study dose to death. In the absence of death, patients will be censored at the last follow up.
2. Kaplan-Meier methods will be used to estimate the event free survival. Event free survival is defined as the time from the first study dose to relapse, death or primary refractory disease. If not response was achieved during course of the study, the time of the event would be day 1. In the absence of death, refractory disease, and relapse, patients will be censored at the last follow up.

14.5 Analysis plan for the exploratory objectives.

Each objective will be evaluated in the exploratory endpoint evaluable population:

1. Assessment of effects on RBM39 levels by immunoblotting will be evaluated on bone marrow biopsies collected at baseline, C2D1, every 2 months thereafter or at time of suspected response or progression. The change from baseline and the follow up time periods will be summarized using summary statistics.
2. Global splicing changes and DCAF15 mRNA levels will be evaluated by RNA-sequencing at study entry and on bone marrow biopsy samples collected at screening, C2D1, and then at time of response or progression. The change from baseline and the follow up time periods will be summarized using summary statistics.
3. Changes in the gene mutation status of leukemic cells will be explored by summarizing the changes in the variant allele frequency (VAF) of mutations from baseline to bone marrow biopsy samples collected on screening, C2D1, and at time of response or progression using next generation sequencing. The mean change in VAF will be reported along with the proportion of mutations present at screening that were not identified at the follow up time points.

14.6. Procedures for Reporting Deviations to Protocol-defined Statistical Analysis Plan

All deviations from the protocol-defined SAP will be provided in the final clinical study report.

15.0 TOXICITIES/RISKS/SIDE EFFECTS

Monitoring of Treatment-Emergent Adverse Events (AEs) will be conducted throughout the study (once subjects have received study drug); SAEs that are assessed as related to study drug that occur > 30 days post-treatment are also to be reported. All AEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es).

15.1 Adverse Event Reporting

All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the event's outcome, including lab abnormalities. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness. The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the event's outcome or lab abnormality.

Investigators will seek information on AEs at each subject contact as outlined below. All AEs, whether reported by the subject or noted by study personnel, will be recorded in the subject's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported (e.g., SAEs related to invasive study procedures such as biopsies).

After initiation of study drug, all AEs and SAEs regardless of attribution will be collected at every visit until 30 days following the last administration of study drug, until study discontinuation/termination, or until initiation of subsequent anticancer therapy, whichever

occurs first. Subjects will be assessed at the Follow-Up Visit to determine if any new AEs have occurred.

15.2 Definition of Adverse Events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values, regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. An overdose, accidental or intentional, whether or not it is associated with an AE, should be reported. Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and as an AE.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 30 days after the last dose of study drug and those SAEs made known to the investigator at any time thereafter that are suspected of being related to study drug. AEs and serious adverse events (SAEs) will be recorded in the subject's source documents. All SAEs that are unexpected and related, or otherwise determined by MSK HRPP office to require FDA submission, must be reported to Eisai Drug Safety within 1 business day of submission to the MSK IND Office by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. All other events will be submitted to Eisai in the final study report.

15.3 Expected adverse events with E7820

The most common treatment related treatment emergent adverse events (TEAE) were fatigue (45.9%), diarrhea (43.6%), nausea (36.6%), decreased appetite (33.1%), and constipation (30.2%). Overall, 102 (59.3) treated with E7820 experienced at least 1 Grade ≥3 TEAE. The most frequently reported Grade ≥3 TEAEs were neutropenia (14.0%), leukopenia (8.1%), fatigue (6.4%), aspartate aminotransferase increased (6.4%), diarrhea (5.2%), anemia (4.7%), and alanine aminotransferase increased (4.7%).

Of a total of 172 subjects exposed in clinical studies as of the cutoff date of 22 Aug 2015, 60 subjects (34.9%) experienced at least 1 serious adverse event (SAE) as of the cutoff date of 22 Aug 2015. Overall, the most frequent SAEs were pyrexia 6 (3.5%), neutropenia 6 (3.5%), abdominal pain 5 (2.9%), and nausea 5 (2.9%). Grade ≥3 SAEs were reported in 53 subjects (30.8%) who received E7820. Overall, the most frequent Grade ≥3 SAEs were neutropenia 6 (3.5%), abdominal pain 4 (2.3%), small intestinal obstruction 3 (1.7%), febrile neutropenia 2 (1.2%), thrombocytopenia 3 (1.7%), dyspnea 3 (1.7%), and pulmonary embolism 3 (1.7%).

A Summary of SAEs with a frequency ≥5% in subjects treated with E7820 is shown in Table 3.

Table 3. Summary of SAEs with Frequency ≥5% in subjects treated with E7820

System Organ Class	Study102 (N=37) n (%)		Study 110 Part A (N=15) n (%)		Study 110 Part B (N=26) n (%)		Study204 (N=41) n (%)		Study701 (N=5) n (%)		Study702 (N=48) n (%)		Combined Total (N=172) n (%)	
Preferred Term	Total	Grade ≥3	Total	Grade ≥3	Total	Grade ≥3	Total	Grade ≥3	Total	Grade ≥3	Total	Grade ≥3	Total	Grade ≥3
Musculoskeletal chest pain	1 (2.7)	0 (0)	0 (0)	0 (0)	3 (11.5)	0 (0)	1 (2.4)	0 (0)	0 (0)	0 (0)	1 (2.1)	0 (0)	6 (3.5)	0 (0)
Psychiatric disorders	9 (24.3)	0 (0)	1 (6.7)	0 (0)	7 (26.9)	0 (0)	14 (34.1)	0 (0)	0 (0)	0 (0)	5 (10.4)	0 (0)	36 (20.9)	0 (0)
Insomnia	3 (8.1)	0 (0)	0 (0)	0 (0)	7 (26.9)	0 (0)	12 (29.3)	0 (0)	0 (0)	0 (0)	2 (4.2)	0 (0)	24 (14)	0 (0)
Vascular disorders	6 (16.2)	2 (5.4)	1 (6.7)	0 (0)	8 (30.8)	2 (7.7)	7 (17.1)	0 (0)	1 (20)	0 (0)	6 (12.5)	3 (6.3)	29 (16.9)	7 (4.1)
Hypertension	1 (2.7)	0 (0)	1 (6.7)	0 (0)	4 (15.4)	1 (3.8)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4.2)	2 (4.2)	8 (4.7)	3 (1.7)
Flushing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (12.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (2.9)	0 (0)
Orthostatic hypotension	0 (0)	0 (0)	0 (0)	0 (0)	2 (7.7)	1 (3.8)	0 (0)	0 (0)	1 (20)	0 (0)	0 (0)	0 (0)	3 (1.7)	1 (0.6)
Venous occlusion	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (20)	0 (0)	0 (0)	0 (0)	1 (0.6)	0 (0)
Renal and urinary disorders	6 (16.2)	0 (0)	1 (6.7)	0 (0)	3 (11.5)	0 (0)	13 (31.7)	1 (2.4)	1 (20)	0 (0)	4 (8.3)	1 (2.1)	28 (16.3)	2 (1.2)
Dysuria	3 (8.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (20)	0 (0)	0 (0)	0 (0)	4 (2.3)	0 (0)
Injury, poisoning and procedural complications	7 (18.9)	0 (0)	0 (0)	0 (0)	4 (15.4)	0 (0)	4 (9.8)	0 (0)	0 (0)	0 (0)	2 (4.2)	0 (0)	17 (9.9)	0 (0)
Contusion	4 (10.8)	0 (0)	0 (0)	0 (0)	1 (3.8)	0 (0)	1 (2.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (3.5)	0 (0)
Cardiac disorders	3 (8.1)	0 (0)	0 (0)	0 (0)	4 (15.4)	1 (3.8)	0 (0)	0 (0)	2 (40)	1 (20)	4 (8.3)	2 (4.2)	13 (7.6)	4 (2.3)
Palpitations	3 (8.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 20)	0 (0)	1 (2.1)	0 (0)	5 (2.9)	0 (0)
Acute myocardial infarction	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (20)	1 (20)	0 (0)	0 (0)	1 (0.6)	1 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (13.5)	0 (0)	0 (0)	0 (0)	1 (3.8)	1 (3.8)	1 (2.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	7 (4.1)	1 (0.6)
Tumour pain	4 (10.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (2.3)	0 (0)

Note: Number (percentage) of subjects in each SOC represents all subjects with TEAEs in that SOC. Only those preferred terms with TEAEs occurring in ≥10% of subjects overall are included in this table. For each row category, a subject with 2 or more TEAEs in that category is counted only once. Display is in decreasing order of frequency of TEAEs in the Eisai Drug Total group, first by SOC and then by preferred term within each SOC.

SOC and PT per MedDRA Version 17.1

Data cutoff: 13 Feb 2015

AE = adverse event, MedDRA = Medical Dictionary for Drug Regulatory Activities, PT = preferred term, SOC = system organ class, TEAE = treatment-emergent adverse event.

Source: Data on File.

15.4 Assessment of safety parameters

15.4.1 Assessment of severity

CTCAE Version 5 will be utilized for toxicity evaluation.

For both AEs and SAEs, the Investigator must assess the severity / intensity of the event. The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0);
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

AEs that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term “severe” is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as “serious” which is based on subject/event outcome or action criteria associated with events that pose a threat to a subject’s life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

15.4.2 Causality

The Investigator must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:
Not suspected: A causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Suspected: There is a **reasonable possibility** that the administration of IP caused the adverse event. ‘Reasonable possibility’ means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.
If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Eisai, please provide the name of the manufacturer when reporting the event.

15.4.3 Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

15.4.4 Action Taken

The Investigator will report the action taken with the study drug as a result of an AE or SAE, as applicable (e.g., discontinuation, interruption of study drug, as appropriate) and report if concomitant and/or additional treatments were given for the event.

15.4.5 Outcome

The Investigator will report the outcome of the event for both AEs and SAEs. All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

15.4.6 Overdose

Overdose, as defined for this protocol, refers to E7820 compounds/products and dosing only (as applicable).

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of E7820 assigned to a given patient, regardless of any associated adverse events or sequelae.
PO - any amount over the protocol-specified dose.

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate.
Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported.

To date, doses of E7820 up to 100 mg QD were well tolerated in clinical trials. No information is currently available regarding overdose with E7820. In the event of overdose with toxicity, supportive clinical care should be provided.

15.4.7 Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, e.g., one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (e.g., record thrombocytopenia rather than decreased platelets).

15.4.8 Pregnancy

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study drug, or within (4 months), are considered immediately reportable events. Study drug is to be discontinued immediately. The female subject may be referred to an obstetrician-gynecologist (not

necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation. The Investigator will follow the female subject until completion of the pregnancy.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the study drug should also be reported. Any SAE that is unexpected and related, or otherwise requires reporting to the FDA, will be submitted to Eisai within 1 business day of submission to the MSK IND Office.

15.4.9 Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant while the male subject is on study treatment or within 4 months of the male subject's last study treatment, the male subject taking study drug should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

15.5 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.
The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

15.6. External SAE Reporting

The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office.

For multicenter trials where MSK is the data coordinating center, please refer to the MSK Multicenter Trial Addendum. All required SAE reporting to the funders and/or drug suppliers will be completed by MSK only

Expedited Reporting by Investigator to Eisai

Serious adverse events (SAE) are defined above. The investigator must inform Eisai in writing using the PIMS SAE report of any events that are unexpected and related to the investigational agent, or otherwise determined to require reporting to the FDA .The written report must be completed and supplied to Eisai by facsimile within 1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Eisai tracking number (for example, XX-XX-XX- PI-#####) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Eisai. A copy of the fax transmission confirmation of the SAE report to Eisai should be attached to the SAE and retained with the patient records.

In the event that Eisai should be notified of an SAE reporting, an email should be sent to the following: ESI_Safety@eisai.com

16.0 PROTECTION OF HUMAN PARTICIPANTS

16.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals/entities described in the Research Authorization form. A Research Authorization form must be approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with others at the time of study publication.

16.1.2 Good Clinical Practice

The study will be conducted in accordance with the International Council for Harmonization (ICH) for GCP and the appropriate regulatory requirement(s). The Investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

16.1.3 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The Investigator must obtain IRB/IEC approval for the investigation and must submit written documentation of the approval to the study before enrolling any subject into the study. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the subjects (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC. The IRB/IEC is to be notified of any amendment to the protocol, in accordance with local requirements. Progress reports and notifications of serious unexpected ADRs are to be provided to the IRB/IEC according to local regulations and guidelines.

16.2 Data Management

All sites involved will enter data remotely into electronic Case Report Forms (eCRFs) within the Medidata Electronic Data Capture (EDC). Data entry guidelines have been generated for this study and participating site staff will receive database training prior to enrolling the first participant. The participating site PI is responsible for ensuring these forms are completed accurately and in a timely manner. A Data and Source Documentation Submission Timeline is shown in Table 4 below.

16.2.1 Source Documentation

Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into the eCRFs. Relevant source documentation to be submitted to the MSK study coordinator throughout the study includes:

- Baseline measures to assess pre-protocol disease status (e.g. CT, PSA, bone marrow)
- Treatment records
- Toxicities/adverse events that meet study reporting requirements not previously submitted with SAE Reports
- Response designation
- Any other forms of source documentation required per protocol

Source documentation must include a minimum of two identifiers to allow for data verification. MSK will maintain the confidentiality of any subject-identifiable information it may encounter.

Data and source documentation should be entered and submitted to MSK according to the timelines in Table 4.

Table 4: Data and Source Documentation Submission Timelines

Time point	Data	Source Documentation
Baseline	Within 14 days of enrollment	Within 14 days of enrollment
Study Visits	Within 14 days of the study visit	Within 14 days of the study visit
Serious Adverse Events	Within 3 days of event; Updates to be submitted as available	Within 3 days of event

16.3 Quality Assurance

Protocol Compliance

The Investigator will conduct the study in compliance with the protocol. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The IRB/IEC may provide, if applicable, where regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the Principal Investigator, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the source documents/eCRF.

16.3.1 Data Accuracy

Source documents/eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the

subject's source document/eCRF. The source document/eCRF should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status.

The Investigator, or designated representative, should complete the source document/eCRF as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

16.4 Record Retention

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least two years after the last marketing application approval or two years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The study team must be notified in writing if a custodial change occurs.

16.5 Data and Safety Monitoring

The Data and Safety Monitoring Plan utilized for this study aligns with the MSK DSM plan. The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."

There are several different mechanisms by which clinical studies are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Deputy Physician-In-Chief, Clinical Research.

The degree of monitoring required will be determined based on level of risk and documented. The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant/or by the end of the year one if no accruals and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

17.0 REFERENCES

1. Wang E, Lu SX, Pastore A, Chen X, Imig J, Chun-Wei Lee S*, et al.* Targeting an RNA-Binding Protein Network in Acute Myeloid Leukemia. *Cancer Cell* 2019 Mar 18; **35**(3)**:** 369-384 e367.

2. Dohner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Buchner T*, et al.* Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood* 2017 Jan 26; **129**(4)**:** 424-447.

3. Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD*, et al.* Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood* 2006 Jul 15; **108**(2)**:** 419-425.

4. Savona MR, Malcovati L, Komrokji R, Tiu RV, Mughal TI, Orazi A*, et al.* An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults. *Blood* 2015 Mar 19; **125**(12)**:** 1857-1865.

5. Lancet JE, Uy GL, Cortes JE, Newell LF, Lin TL, Ritchie EK*, et al.* CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia. *J Clin Oncol* 2018 Sep 10; **36**(26)**:** 2684-2692.

6. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH*, et al.* Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. *N Engl J Med* 2020 Aug 13; **383**(7)**:** 617-629.

7. Stahl M, DeVeaux M, Montesinos P, Itzykson R, Ritchie EK, Sekeres MA*, et al.* Hypomethylating agents in relapsed and refractory AML: outcomes and their predictors in a large international patient cohort. *Blood Adv* 2018 Apr 24; **2**(8)**:** 923-932.

8. Abhishek Maiti CRR, Jorge E. Cortes et al Outcomes of Relapsed or Refractory Acute Myeloid Leukemia after Frontline Hypomethylating Agent with Venetoclax Regimens. *American Society of Hematology Meeting 2019, abstract 738* 2019.

9. Prebet T, Gore SD, Esterni B, Gardin C, Itzykson R, Thepot S*, et al.* Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. *J Clin Oncol* 2011 Aug 20; **29**(24)**:** 3322-3327.

10. Coston T, Pophali P, Vallapureddy R, Lasho TL, Finke CM, Ketterling RP*, et al.* Suboptimal response rates to hypomethylating agent therapy in chronic myelomonocytic leukemia; a single institutional study of 121 patients. *Am J Hematol* 2019 Jul; **94**(7)**:** 767-779.

11. Jabbour E, Garcia-Manero G, Batty N, Shan J, O'Brien S, Cortes J*, et al.* Outcome of patients with myelodysplastic syndrome after failure of decitabine therapy. *Cancer* 2010 Aug 15; **116**(16)**:** 3830-3834.

12. Zeidan AM, Smith BD, Carraway HE, Gojo I, DeZern A, Gore SD. A phase 2 trial of high dose lenalidomide in patients with relapsed/refractory higher-risk myelodysplastic syndromes and acute myeloid leukaemia with trilineage dysplasia. *Br J Haematol* 2017 Jan; **176**(2)**:** 241-247.

13. Obeng EA, Stewart C, Abdel-Wahab O. Altered RNA Processing in Cancer Pathogenesis and Therapy. *Cancer Discov* 2019 Nov; **9**(11)**:** 1493-1510.

14. Graubert TA, Shen D, Ding L, Okeyo-Owuor T, Lunn CL, Shao J*, et al.* Recurrent mutations in the U2AF1 splicing factor in myelodysplastic syndromes. *Nat Genet* 2011 Dec 11; **44**(1)**:** 53-57.

15. Papaemmanuil E, Cazzola M, Boultwood J, Malcovati L, Vyas P, Bowen D*, et al.* Somatic SF3B1 mutation in myelodysplasia with ring sideroblasts. *N Engl J Med* 2011 Oct 13; **365**(15)**:** 1384-1395.

16. Yoshida K, Sanada M, Shiraishi Y, Nowak D, Nagata Y, Yamamoto R*, et al.* Frequent pathway mutations of splicing machinery in myelodysplasia. *Nature* 2011 Sep 11; **478**(7367)**:** 64-69.

17. Bielski CM, Donoghue MTA, Gadiya M, Hanrahan AJ, Won HH, Chang MT*, et al.* Widespread Selection for Oncogenic Mutant Allele Imbalance in Cancer. *Cancer Cell* 2018 Nov 12; **34**(5)**:** 852-862 e854.

18. Taylor J, Mi X, North K, Binder M, Penson A, Lasho T*, et al.* Single-cell genomics reveals the genetic and molecular bases for escape from mutational epistasis in myeloid neoplasms. *Blood* 2020 Sep 24; **136**(13)**:** 1477-1486.

19. Lee SC, North K, Kim E, Jang E, Obeng E, Lu SX*, et al.* Synthetic Lethal and Convergent Biological Effects of Cancer-Associated Spliceosomal Gene Mutations. *Cancer Cell* 2018 Aug 13; **34**(2)**:** 225-241 e228.

20. Han T, Goralski M, Gaskill N, Capota E, Kim J, Ting TC*, et al.* Anticancer sulfonamides target splicing by inducing RBM39 degradation via recruitment to DCAF15. *Science* 2017 Apr 28; **356**(6336).

21. Ting TC, Goralski M, Klein K, Wang B, Kim J, Xie Y*, et al.* Aryl Sulfonamides Degrade RBM39 and RBM23 by Recruitment to CRL4-DCAF15. *Cell Rep* 2019 Nov 5; **29**(6)**:** 1499-1510 e1496.

22. Bussiere DE, Xie L, Srinivas H, Shu W, Burke A, Be C*, et al.* Structural basis of indisulam-mediated RBM39 recruitment to DCAF15 E3 ligase complex. *Nat Chem Biol* 2020 Jan; **16**(1)**:** 15-23.

23. Uehara T, Minoshima Y, Sagane K, Sugi NH, Mitsuhashi KO, Yamamoto N*, et al.* Selective degradation of splicing factor CAPERalpha by anticancer sulfonamides. *Nat Chem Biol* 2017 Jun; **13**(6)**:** 675-680.

24. Mita M, Kelly KR, Mita A, Ricart AD, Romero O, Tolcher A*, et al.* Phase I study of E7820, an oral inhibitor of integrin alpha-2 expression with antiangiogenic properties, in patients with advanced malignancies. *Clin Cancer Res* 2011 Jan 1; **17**(1)**:** 193-200.

25. Milojkovic Kerklaan B, Slater S, Flynn M, Greystoke A, Witteveen PO, Megui-Roelvink M*, et al.* A phase I, dose escalation, pharmacodynamic, pharmacokinetic, and food-effect study of alpha2 integrin inhibitor E7820 in patients with advanced solid tumors. *Invest New Drugs* 2016 Jun; **34**(3)**:** 329-337.

26. Jung SH, Lee T, Kim K, George SL. Admissible two-stage designs for phase II cancer clinical trials. *Stat Med* 2004 Feb 28; **23**(4)**:** 561-569.

18.0 APPENDICES

- Multicenter Trial addendum