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A Phase II Study of Pevonedistat (MLN4924, TAK924) and Azacitidine as Maintenance Therapy after Allogeneic Stem Cell Transplantation for Non-Remission Acute Myelogenous Leukemia

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Common abbreviations used in oncology protocols are provided below. Program-specific or protocol-specific abbreviations must be added to this list, and unnecessary abbreviations removed, as applicable. Abbreviations that are retained should not be changed.

Abbreviation	Term
5-HT ₃	5-hydroxytryptamine 3 serotonin receptor
AE	adverse event
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
Ara-C	Cytarabine
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
AUC _{24 hr}	area under the plasma concentration versus time curve from zero to 24 hours
AUC _{inf}	area under the plasma concentration versus time curve from zero to infinity
AUC _τ	area under the plasma concentration versus time curve from zero to next dose
BCRP	breast cancer resistance protein
βhCG	beta-human chorionic gonadotropin
BCRP	breast cancer-resistance protein
BID	bis in die; twice a day
BM	bone marrow
BSA	body surface area
BUN	blood urea nitrogen
BZD	Benzodiazepines
CBC	complete blood count
CFR	Code of Federal Regulations
CL	clearance, IV dosing
CL _p	plasma clearance
CL _{Total}	total clearance
C _{max}	single-dose maximum (peak) concentration
CNS	central nervous system
CO ₂	carbon dioxide
CR	complete remission
CRi	complete remission with incomplete blood count recovery
CRM	continual reassessment method

Abbreviation	Term
CRP	C-reactive protein
CSF-1R	colony-stimulating factor 1 receptor
CT	computed tomography
C _{trough}	single-dose end of dosing interval (trough) concentration
CV	coefficient of variation
CYP	cytochrome P ₄₅₀
DLT	dose-limiting toxicity
DME	drug metabolizing enzymes
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EOS	End of Study (visit)
EOT	End of Treatment (visit)
EU	European Union
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GM-CSF	granulocyte macrophage colony-stimulating factor.
GGT	gamma glutamyl transferase
GI	Gastrointestinal
GLP	Good Laboratory Practices
GM-CSF	granulocyte macrophage-colony stimulating factor
GMP	Good Manufacturing Practice
Hb	Hemoglobin
Hct	Hematocrit
HDPE	high-density polyethylene
hERG	human ether-à-go-go related gene
HIV	human immunodeficiency virus
HNSTD	highest nonseverely toxic dose
IB	Investigator's Brochure
IC ₅₀	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
ITT	intent-to-treat

Abbreviation	Term
IV	intravenous; intravenously
IVRS	interactive voice response system
K _i	inhibition constant
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
LFT	liver function test(s)
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MRI	magnetic resonance imaging
MRU	medical resource utilization
MTD	maximum tolerated dose
MUGA	multiple gated acquisition (scan)
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NPO	nothing by mouth
NYHA	New York Heart Association
OATPs	organic anion-transporting proteins
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease (disease progression)
Pgp	P-glycoprotein
PK	pharmacokinetic(s)
PO	<i>per os</i> ; by mouth (orally)
PR	partial remission
PRO	patient-reported outcome
PSA	prostate-specific antigen
QD	<i>quaque die</i> ; each day; once daily
QID	<i>quater in die</i> ; 4 times a day
QOD	<i>quaque altera die</i> ; every other day
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SC	Subcutaneous
SD	stable disease
SmPC	Summary of Product Characteristics

Abbreviation	Term
$t_{1/2}$	terminal disposition half-life
TGI	tumor growth inhibition
T_{\max}	single-dose time to reach maximum (peak) concentration
UK	United Kingdom
ULN	upper limit of the normal range
US	United States
V_z	volume of distribution in the terminal phase
WBC	white blood cell
WHO	World Health Organization

1.0 Objectives

1.1. Primary Objective

To assess the toxicity and efficacy of a combination of Pevonedistat and Azacitidine as post allogeneic hematopoietic stem cell transplant maintenance therapy for non-remission AML.

1.2. Secondary Objectives

To assess the overall disease free survival, relapse, and GVHD after the above noted treatment.

1.3. Primary Endpoint

- One year overall survival

1.4. Secondary Endpoints

- One-year disease-free survival
- Cumulative incidence of relapse at 2 years
- Two-year and five-year disease-free and overall survival
- Treatment related mortality/morbidity
- Toxicity related to Pevonedistat
- Incidence and severity of acute and chronic GVHD

2.0 Background

2.1. Background

2.1.1. High-risk AML particularly Non-remission AML

Although hematopoietic stem cell transplantation (HSCT) is curative for many patients with AML, AML in relapse at the time of transplant is still a major challenge with low rates of leukemia-free survival even with an intensive myeloablative conditioning. In 1997 Seattle data suggested that long term survival rate is quite low in AML with peripheral circulating blasts at the time of transplant¹. Similar data have been reported from EBMT. Also, in our own historical data, these patients are very difficult to achieve long term remission.

Recently, reduced intensity transplant have shown that even elderly patients can undergo allogeneic stem cell transplantation²⁻⁵. It is associated much less complications compared to myeloablative conditioning therapy, but anti-tumor effect may also be weaker. More recently, it has been shown that reduced intensity transplant may be associated with more relapse, particularly in non-remission malignancies^{6, 7}.

FluBu4 conditioning regimen was developed as a full intensity, reduced toxicity conditioning regimen^{8, 9}. It has been associated with much less toxicity compared to conventional myeloablative regimens, and may be stronger compared to reduce intensity

regimens in terms of anti-leukemic effect, but still may be associated with relatively high rate of relapse in non-remission malignancies.

There are a large number of elderly patients with non-remission AML because of the complete remission rate with induction chemotherapy decreases with age¹⁰, and such older patients do not tolerate conventional myeloablative conditioning regimens. Thus, an effective and tolerable way of conducting stem cell transplantation for non-remission AML patient is a great unmet need for current transplant practice.

2.1.2. Intensification of conditioning – experience with CloBu4 conditioning trials for Non-remission AML

Clofarabine is a second generation nucleoside analogue, similar to fludarabine and cladribine, with promising activity in refractory AML. Clofarabine has been shown to be well-tolerated with manageable side effects, particularly in elderly patients¹¹. The drug's main toxicity is bone marrow suppression, and non-hematologic toxicities are relatively mild.

The University of Michigan BMT program has conducted a phase I/II study using Clofarabine/Busulfan 4 (CloBu4) for non-remission hematologic malignancies (PI, Shin Mineishi, M.D.)¹². All patients had a hematologic malignancy that was not in remission at the time of transplant. Busulfan was administered once daily at 3.2 mg/kg IV x 4days (days -5 to -2) and Clofarabine once daily at 20, 30 or 40 mg/m² IV x 5days (days -6 to -2) with the specific dose determined by the Time to Event-Continuous Reassessment Method (TITE-CRM). Of 46 patients enrolled, 31 patients had AML. Among AML patients, the median age was 53 years (range 1-68). A quarter of patients had previous allogeneic HSCT, 45% had high risk cytogenetics, and 71% had circulating blasts at the time of transplant. In this very high-risk population, overall survival at 12 months was 48%. As seen in the figure, the relapse rate in this population was much lower than historical control.

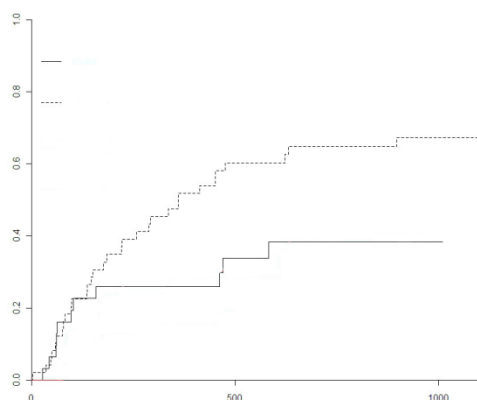


Figure: Cumulative Incidence of relapse in AML patients, compared to historical control. Solid line: CloBu4, Broken line: Other myeloablative regimens. P=0.04

Using CloBu4 conditioning, we were successful in suppressing the relapse rate in this population, but some of these patients still relapse. To decrease the relapse rate furthermore, another approach to overcome aggressive leukemia should be sought.

2.1.3. Relapsed AML after allogeneic HSCT, another population with Poor Prognosis

Relapsed AML after allogeneic HSCT would conform another population of the patients with very poor prognosis, to median survival of only 3-4 months without active treatment. Particularly patients who relapsed within 6 months have <5% 1 year survival¹³⁻¹⁵. Various treatment strategies such as decreasing immunosuppression, DLI, Azacitidine or second transplant can be employed in such patients. Second transplant could potentially provide with an opportunity for cure but the results in this highly selected group of patient who are eligible for second transplant are still disappointing with <20% 6 month survival with especially poor survival in patient with residual disease at transplant. A recent study suggested superiority of second HSCT over chemotherapy (58 vs 14%, 1 year survival) but the advantage was lost at 2 years due to relapse of disease¹⁶. Another study showed that remission could be achieved in all patients with second HSCT but was lead to failure again by disease relapse¹⁷. These patients can possibly achieve a remission with a second transplant more difficulty is in maintaining remission. A maintenance treatment strategy would theoretically of benefit in such population to achieve longer remission.

2.1.4. Maintenance therapy after allogeneic stem cell transplantation

Although maintenance therapies are commonly used in the treatment of hematologic malignancies, such as acute lymphoblastic leukemia or multiple myeloma, the concept of maintenance therapy in AML after allogeneic HSCT is relatively new. One reason is that allogeneic HSCT has been considered as the “final” therapy, and physicians doing transplant have not been interested in giving any therapy after transplant. This tendency was also supported by the idea of “graft-versus-leukemia (GVL) effect”¹⁸. GVL effect itself is a sort of “maintenance therapy”, thus it was assumed that no other therapy is necessary. The other reason is that, because allogeneic HSCT itself has been associated with many complications, such as toxicity from high-dose chemotherapy, or graft-versus-host disease (GVHD), physicians have been hesitating to give any treatment after allogeneic HSCT.

This has been changing recently. As maintenance therapy has become a standard after autologous stem cell transplantation for multiple myeloma, there have been studies giving salvage/maintenance therapy for myeloma, even after allogeneic stem cell transplantation¹⁹. As stated above, allogeneic stem cell transplantation itself has many complications, so maintenance therapy agents should be less toxic. This has been impossible when mainstay of the leukemia/lymphoma/myeloma therapy has been cytotoxic chemotherapy. More recently, there have been many new agents, such as bortezomib (Velcade) or lenalidomide (Revlimid), introduced in the treatment of hematologic malignancies, most of them are targeted agents or agents with different mechanisms of action, and may not be very toxic.

Azacitidine is one agent used for maintenance therapy for AML after allogeneic stem cell transplantation, study recently conducted at M. D. Anderson Cancer Center²⁰. Azacitidine is a good agent for this purpose, but it is somewhat myelosuppressive, thus the dose being used for maintenance therapy is much lower (25 mg/m²/day as opposed to 75 mg/m²/day) than the usual dose. The study showed that in some relapsed AML cases Azacitidine was able to induce remissions. There is a concern if single agent Azacitidine is potent enough for very high risk AML remission maintenance.

2.1.5. Use of Azacitidine post-transplant

Azacitidine has been used post-transplant for maintenance as well as treatment of patients with relapsed AML. A study recently reported by the MD Anderson group showed some efficacy of use of Azacitidine in post-transplant population for AML and MDS patients. Forty-five high-risk patients were treated. Median age was 60 years; median number of comorbidities was 3; 67% were not in remission. By using a Bayesian adaptive method to determine the best dose/schedule combination based on time to toxicity, the authors investigated combinations of 5 daily Azacitidine doses, 8, 16, 24, 32, and 40 mg/m², and 4 schedules: 1, 2, 3, or 4 cycles, each with 5 days of drug and 25 days of rest. Cycle 1 started on Day +40. Reversible thrombocytopenia was the dose-limiting toxicity. The optimal combination was 32 mg/m² given for 4 cycles. Median follow-up was 20.5 months. One-year event-free and overall survivals were 58% and 77%²¹. In another recent publication, a combination of Azacitidine with gemtuzumab-ozogamicin was tested in ten patients with high-risk AML, eight males and two females, at a median age of 49.5 years (range: 17–65 years) as maintenance therapy after allogeneic stem cell transplant. AZA at 30 mg/m² was administered intravenously on days 1–7, followed by GO at 3 mg/m² on day 8. AZA-GO was repeated every 4 weeks or as soon as possible after hematological recovery. All patients developed grade IV hematological toxicities and received platelet transfusions. The overall survival was 70% at 1 year with disease free survival at 60%²².

Studies are also published showing activity of Azacitidine in relapsed AML after allogeneic SCT. It has been shown to re induce complete remissions in this high pretreated and resistant population²³. This shows the likely activity of Azacitidine alone and in combination post-transplant but the common toxicity in all these studies is hematologic toxicity which likely could be improved by reducing the dose of Azacitidine but that in turn would limit the leukemicidal ability of Azacitidine necessary to overcome the relapsing disease and to allow enough time for the GVL effect to take place to induce long term remission. Multiple studies have also published result in evaluating the effects of Azacitidine on GVHD. There is convincing evidence that Azacitidine infusion in post-transplant population can lead to in vivo expansion of regulatory T cell (CD4+ CD25+ FOXP3+ T cells) which can reduce GVHD while having no significant effect on GVL effect^{24, 25}. This dual purpose of Azacitidine can make it an ideal drug for post-transplant treatment and maintenance therapy however again as mentioned above the therapeutic potential in anti-leukemia activity is limited by dose limitation due to hematologic toxicity.

2.2. Scientific Background of Pevonedistat

The ubiquitin-proteasome system (UPS) is responsible for much of the regulated protein turnover in the cell. The UPS maintains cellular homeostasis and impacts signaling pathways that regulate cell cycle progression and regulation of transcription. It is a complex, multi-protein system that utilizes distinct enzyme classes that coordinate ubiquitination and mediate ubiquitin-dependent degradation through the proteasome²⁶. A proteasome inhibitor, bortezomib, was shown to be very effective in the treatment of various hematologic malignancies including multiple myeloma and mantle cell lymphoma, suggesting that compounds targeting other components of the UPS could prove useful in the treatment of malignancies.

The polyubiquitination reaction involves the coordination of 3 classes of enzymes, E1 (ubiquitin activating), E2 (ubiquitin conjugating), and E3 (ligases). The E3 ligases are multiprotein

complexes whose specificity is established by the members of the protein complex. A subset of E3 ligases, cullin-dependent ubiquitin E3 ligases (CDLs) also undergoes neddylation and this modification is necessary for their activity. Activation of the Nedd8 pathway that leads to conjugation of the E3 ligases with Nedd8 shares similarities to the ubiquitin conjugating system. Nedd8-activating enzyme (NAE) is the first step in activation of the neddylation pathway and through transfer to the conjugating enzyme, Ubc12, leads to neddylation of the cullin family of proteins²⁷. The cullin-specific ligases control the timely ubiquitination and subsequent degradation of many proteins with important roles in cell cycle progression (such as p27, cyclin E), DNA damage (chromatin licensing and DNA replication factor-1 [Cdt-1]), stress response (nuclear factor (erythroid derived 2)-related factor 2 [NRF-2], hypoxia-inducible factor 1alpha [HIF-1 α]), and signal transduction (phosphorylated I kappa B alpha [pIkB α]).

Pevonedistat (also known as TAK 924 and MLN4924; hereinafter referred to as Pevonedistat) is a first-in-class, small molecule inhibitor of neural precursor cell expressed, developmentally down-regulated 8 (NEDD8)-activating enzyme (NAE) under development for the treatment of malignancies. The NEDD8 conjugation (neddylation) pathway is responsible for much of the regulated protein turnover in the cell^{26, 27}, which is similar to the ubiquitin-proteasome system (UPS). However, UPS is known to regulate a myriad of processes in eukaryotic cells, whereas only a limited number of neddylation substrates have been described to date. VELCADE® (bortezomib) for Injection, a drug that acts by inhibiting the 26S proteasome, has proven utility in the treatment of multiple myeloma and mantle cell lymphoma²⁸. Therefore, it is anticipated that other compounds directed against different components of the UPS and/or the NEDD8 conjugation pathway may prove useful in the treatment of malignancies.

NAE, E1 ligase, is an essential component of the NEDD8 conjugation pathway, which initiates the neddylation to protein substrates. Specifically, NEDD8 conjugation to cullin dependent ubiquitin E3 ligases (CDLs) is necessary for their activity. The ligases in the NEDD8 conjugation pathway control the timely neddylation of many substrate proteins with important roles in cell cycle progression and signal transduction. The ubiquitination/neddylation of proteins targets them for proteasomal degradation. These cellular processes are relevant to tumor cell growth, proliferation, and survival; as such, inhibitors of NAE activity may be of therapeutic value in the treatment of various cancers by inhibiting the degradation of a subset of proteins that are regulated by the proteasome. In nonclinical studies, treatment of cells with Pevonedistat results in the accumulation of CDL substrates, followed by a deoxyribonucleic acid (DNA) damage response and cell death. Pevonedistat treatment results in tumor growth inhibition (TGI) in mouse tumor xenograft models of solid tumors, lymphoma, and acute myeloid leukemia (AML).

2.3. Preclinical Experience with Pevonedistat

Pevonedistat is a potent and selective inhibitor of NAE activity (Pevonedistat was at least 300- and 1800- fold more selective for NAE than for the closely related ubiquitin activating enzyme and sumo activating enzyme, respectively). Pevonedistat treatment of cultured tumor cells resulted in growth inhibition of a wide variety of cell lines derived from acute leukemia's, lymphomas, multiple myeloma, and a range of solid tumor types. Changes in protein levels observed in cultured cells treated with Pevonedistat were consistent with the inhibition of NAE, in particular a decrease in NEDD8-cullin levels and a reciprocal increase in the levels of known CDL substrates, including NFE2-related factor 2 (Nrf2) and chromatin-licensing and DNA-replication factor-1 (Cdt-1). In most cell lines evaluated, NAE inhibition by Pevonedistat led to DNA re-replication and accumulation of cells in the S phase of the cell cycle; this resulted in DNA damage and subsequent cell death through apoptosis²⁹⁻³¹. When administered in

combination with hypo ethylating agents Azacitidine and Decitabine demonstrated synergistic activity in AML cell lines.

Pevonedistat demonstrated pharmacodynamic and antitumor activity in solid tumor, lymphoma, and AML xenograft models when administered to immunocompromised mice by the subcutaneous (SC) route. Antitumor activity of Pevonedistat in mice bearing HL-60 and THP-1 tumor xenografts was enhanced by combination treatment with Azacitidine. Combination treatment with Pevonedistat and docetaxel significantly inhibited tumor growth in the PHTX-02B primary human breast cancer model and the LU1143 primary human squamous non-small cell lung cancer (sqNSCLC) xenograft model. Combination treatment with Pevonedistat and carboplatin in both NCI-H69 human small cell lung cancer (SCLC) xenografts and LU1143 primary sqNSCLC xenografts resulted in significant antitumor activity.

In vitro assay results indicated a low risk for human ether-à-go-go related gene (hERG) channel inhibition by Pevonedistat or its 3 major circulating metabolites. In a Good Laboratory Practices (GLP)-compliant cardiovascular safety pharmacology assessment in male beagle dogs dosed via intravenous (IV) infusion at 15, 30, or 40 mg/kg (300, 600, or 800mg/m², respectively), Pevonedistat was not well tolerated at doses ≥ 30 mg/kg (≥ 600 mg/m²). Mortality and/or moribundity were observed within 24 hours post dose as a result of gastrointestinal injury at 40 mg/kg. Increased heart rate was observed at all doses. In a separate GLP-compliant, 2-cycle, repeat-dose toxicology study in dogs, no test article-related effects were noted in the electrocardiogram (ECG) data.

The dose-limiting toxicities (DLTs) in the 2-cycle studies for rats and dogs were gastrointestinal toxicity and bone marrow and lymphoid tissue depletion. Most adverse effects were resolving or had resolved after a 2-week recovery period. Pevonedistat did not result in lethality in either of the 5-cycle studies. The primary adverse test article-related effects in IV-dosed dogs included an acute phase response (increased body temperature, decreased albumin, increased globulin, increased monocytes and neutrophils, and increased fibrinogen levels); neutrophilic infiltrates in multiple sites tissues; and in males, vacuolation and degeneration of the seminiferous epithelium of the testes. Most adverse effects were reversing or had reversed after a 2-week recovery period in both rats and dogs. Given that there were prominent effects on testes and ovaries noted at all doses tested in the GLP-compliant repeat-dose toxicology studies in both dogs and rats, Pevonedistat likely represents a substantial reproductive and developmental hazard. Pevonedistat was not mutagenic in the bacterial reverse mutation assay (Ames assay).

Pevonedistat was highly bound in whole blood and plasma of mice, rats, dogs, monkeys and humans. No metabolite unique to humans was observed in vitro. In vitro, Pevonedistat is predominantly metabolized by the cytochrome P450 (CYP) isozyme 3A4. There is potential for drug drug interactions (DDIs) if Pevonedistat is co-administered with drugs that are CYP3A inhibitors or inducers. Pevonedistat is neither an inhibitor of CYP1A2, 2C9, 2C19, 2D6, or 3A4/5 ($IC_{50} > 100$ μ M and $K_i > 50$ μ M) nor an inducer of CYP1A2, 2B6, or 3A4/5 (at concentrations up to 30 μ M), but is a weak inhibitor of CYP2B6 and 2C8 ($IC_{50} = 97.6$ and 23.1 μ M, respectively). The major elimination pathway of Pevonedistat in animals is through the hepatic route. Pevonedistat is a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance protein 2 (MRP2) in Caco 2 cells. Pevonedistat is also a weak inhibitor of P-gp ($IC_{50} = 41.2$ to 56.0 μ M) and BCRP ($IC_{50} = 6.3$ μ M), but not of MRP2 ($IC_{50} > 200$ μ M). Additionally, Pevonedistat is not a substrate for organic anion-transporting proteins (OATPs).

Detailed information regarding the nonclinical pharmacology and toxicology of Pevonedistat is provided in the Investigator's Brochure (IB).

2.4. Clinical Experience with Pevonedistat

The clinical development program of Pevonedistat began with 4 phase 1 studies of single agent Pevonedistat at doses ranging from 25 to 278 mg/m²:

- Study C15001 in patients with solid tumors³².
- Study C15002 in patients with lymphoma or multiple myeloma³³.
- Study C15003 in patients with AML, high-grade myelodysplastic syndrome (MDS), or acute lymphoblastic leukemia (ALL)³⁴.
- Study C15005 in patients with melanoma³⁵.

In these studies, toxicity involving multi organ failure on C1D1, including serious adverse events (SAEs) of renal, hepatic, and cardiac failure, some with a fatal outcome, was identified at doses equal to or above 110 mg/m². On the basis of a comprehensive review of the available phase 1 clinical safety data at the time, a revised risk mitigation strategy, including limiting the dose to no higher than 100 mg/m² for single agent administration, was implemented across the Pevonedistat program in October 2012. The current understanding of the renal toxicity observed with Pevonedistat suggests that it is not a primary event but is likely secondary to hemodynamic changes occurring in the setting of a type of acute phase response.

As of January 2017, a total of 227 patients were treated in single agent phase I and a total of 451 patients received at least one dose of Pevonedistat including combination studies, and no C1D1 SAEs of multi-organ failure as described above have been observed. These patients received Pevonedistat at a dose of 50 to 100 mg/m² as a single agent (after October 2012), a dose of 15 to 30 mg/m² in combination with different standard of care therapies, or a dose of 8 mg/m² to 20 mg/m² in combination with a CYP3A inhibitor.

Current development is focused on Pevonedistat in combination with standard clinically available therapies in hematologic malignancies and solid tumors. Two phase 1b clinical studies are closed to enrollment but are still ongoing with active patients:

- Study C15009 (phase 1b) evaluated the maximum tolerated dose (MTD) of Pevonedistat on Days 1, 3, and 5 in combination with 75 mg/m² Azacitidine (administered on a 5-on/2-off [weekend]/2-on schedule) in a 28 day treatment cycle in elderly patients with treatment-naïve AML³⁶.
- Study C15010 (phase 1b) evaluated the MTD of Pevonedistat plus docetaxel, gemcitabine, or the combination of carboplatin and paclitaxel, in patients with solid tumors^{37, 38}.

Additionally, Study C15011 (phase 1) is evaluating the effects of CYP3A mediated inhibition of Pevonedistat in patients with solid tumors (DDI assessment; Part A). After completion of the DDI assessment portion of the study, patients have the opportunity to continue in the study by participating in Part B (Pevonedistat plus docetaxel or the combination of carboplatin and paclitaxel).

The cumulative enrollment in all clinical studies through 22 January 2017 is approximately 451 patients (defined as having received at least 1 dose of study drug).

Two studies are currently enrolling:

- Study 2001: A Phase 2, randomized, controlled Open-Label Clinical study of the efficacy and safety of Pevonedistat plus Azacitidine versus single-agent Azacitidine in patients with higher-risk myelodysplastic syndromes, chronic myelomonocytic leukemia and low-blast acute myelogenous leukemia.
- Study 1012: A phase 1/1b, Open-label Study of Pevonedistat (MLN4924, TAK-924) as Single Agent and in Combination with Azacitidine in adult East Asian patients with acute myeloid leukemia or myelodysplastic syndromes

2.4.1. Pharmacokinetics

The clinical pharmacokinetics (PK) of Pevonedistat have been evaluated in 4 monotherapy phase 1 studies in 96 patients with solid tumors (C15001 and C15005) and 109 patients with hematologic malignancies (C15002 and C15003). These studies have evaluated the single- and multiple-dose PK of Pevonedistat administered via IV infusion across the 25 to 278 mg/m² dose range and at various daily or intermittent dosing schedules within 21 day treatment cycles.

Plasma concentrations of Pevonedistat declined in a bi-exponential manner at the end of IV infusion, with little or no drug accumulation following intermittent dosing or once-daily dosing for 5 consecutive days of a 21 day cycle. Mean terminal disposition t_{1/2z} was estimated to be approximately 10 hours (range 7.7-15.2) across doses and schedules. Consistent with in vitro data, Pevonedistat is extensively partitioned in human blood (mean blood-to-plasma concentration ratio of approximately 65) with whole blood and plasma kinetics declining in parallel over time. Pevonedistat generally exhibited linear PK over the dose range studied. Observed inter individual variability (IIV) was generally moderate with 18% to 41% coefficient of variation (CV) for maximum concentration (C_{max}), 12% to 56% CV for area under the plasma concentration-time curve from time zero to 24 hours post dose (AUC₂₄), and 15% to 33% CV for the area under the plasma concentration-time curve from time zero to the end of the dosing interval when Pevonedistat was administered on Days 1, 3, and 5. Body size influences Pevonedistat systemic clearance and volume of distribution, thus supporting body surface area (BSA)-normalized dosing to reduce variation in systemic exposure of Pevonedistat in cancer patients. Pevonedistat clearance tended to gradually decrease in elderly patients (by approximately 25% over the 30-90 age range). There was also no apparent effect of renal function status (as assessed by estimated creatinine clearance > 30 mL/min) on Pevonedistat PK.

Additionally, evaluation of Pevonedistat PK is ongoing for 2 studies of Pevonedistat in combination with different standard-of-care therapies, and for a DDI study evaluating the effects of CYP3A mediated inhibition on Pevonedistat. Pevonedistat PK was not altered in the presence of Azacitidine when compared to historical single agent data. Also, no obvious changes in the PK behavior of Pevonedistat in the presence of docetaxel or gemcitabine have been observed whereas a trend towards increasing plasma concentrations of Pevonedistat in the presence of carboplatin + paclitaxel was evident [12-13]. This apparent drug interaction effect, which cannot be explained at this time, warrants further understanding of the disposition properties of Pevonedistat in humans. Lastly, multiple doses of fluconazole, a moderate CYP3A inhibitor, had minimal effect (13% increase in mean area under the plasma concentration time curve from zero to

infinity [AUC_{inf}]) on the single-dose IV PK of Pevonedistat, while Pevonedistat systemic exposure increased by 23% on average in the presence of the strong CYP3A inhibitor, itraconazole.

For detailed information please consult the current IB.

2.4.2. Pharmacodynamics

Preliminary data provide evidence of pathway inhibition downstream of NAE and biological activity of Pevonedistat in skin and tumor tissue (solid tumor or AML bone marrow derived blasts) at all doses tested in pharmacodynamic assays. These doses range from 25 to 261 mg/m² across the various single-agent, phase 1 Pevonedistat trials.

For detailed information please consult the current IB.

Summary of Safety and Efficacy Data Findings Available on Takeda Sponsored Trials

For detailed information please consult the current IB.

2.4.3. Phase 1 Monotherapy Studies

Overall, 99 patients with advanced solid tumors or melanoma in Study C15001 and Study C15005 were treated with single-agent Pevonedistat at doses ranging from 25 to 278 mg/m². Common AEs (reported by $\geq 25\%$ of patients in either study) were fatigue, nausea, anemia, decreased appetite, vomiting, diarrhea, myalgia, constipation, arthralgia, dizziness, and peripheral neuropathy. DLTs included increased LFTs, increased creatinine, acute renal failure and acute hepatic failure, hypophosphatemia, and myocarditis. Acute renal failure occurred in 3 patients: 2 patients on Study C15001 at 196 mg/m² (1 patient also reported acute hepatic failure); and 1 patient on Study C15005 at 157 mg/m², who also reported myocarditis and hyperbilirubinemia. Deaths on study that were considered related to study treatment included multi-organ failure (at 61 mg/m² QD \times 5 consecutive days and 196 mg/m² in Study C15001), disease progression (at 83 mg/m² in Study C15001), and renal failure acute (at 209 mg/m² in Study C15005).

A total of 128 patients with hematologic malignancies (lymphoma, multiple myeloma, AML, MDS, or ALL) in Study C15002 and Study C15003 were treated with single-agent Pevonedistat at doses ranging from 25 to 261 mg/m². Common AEs (reported by $\geq 25\%$ of patients in either study) were ALT increased, anemia, AST increased, chills, constipation, decreased appetite, diarrhea, dizziness, dyspnea, fatigue, febrile neutropenia, headache, muscle spasms, myalgia, nausea, peripheral edema, pyrexia, and vomiting. DLTs included increased LFTs, febrile neutropenia, muscle spasms, thrombocytopenia, acute renal failure, orthostatic hypotension, cardiac failure, rash morbilliform, GI necrosis, hypotension, lactic acidosis, and myocardial ischemia. Deaths on study that were considered related to study treatment (all in Study C15003) included 2 deaths from multi organ failure (at 110 and 147 mg/m²), 1 from sepsis (at 78 mg/m²), and 1 from cardiopulmonary failure (at 45 mg/m²).

The primary aims of the phase 1 monotherapy studies were to establish the safety profile and to determine the MTDs of Pevonedistat administered by several different dose

schedules in both hematologic and solid tumor settings. While safety, PK, and pharmacodynamic objectives were the primary focus of these studies, disease response was also assessed. A total of 12 patients experienced PRs or better in the phase 1 monotherapy studies.

2.4.4. Phase 1 Combination Studies

C15009

Study C15009 is an ongoing phase 1b study evaluating the MTD of Pevonedistat on Days 1, 3, and 5 in combination with 75 mg/m² Azacitidine (administered on a 5-on/2-off [weekend]/2-on schedule) in a 28-day treatment cycle in patients 60 years of age or older with treatment naïve AML who are unlikely to benefit from standard induction therapy. As of 22 June 2016, enrollment had completed and 15 patients remained on study. As of 22 January 2017, preliminary data are available for 64 patients enrolled in the study who received at least 1 dose of Pevonedistat in combination with Azacitidine; these patients had completed a total of approximately 360 cycles, with a median of 4 cycles of treatment. In the dose escalation cohorts, 6 patients received 20 mg/m² Pevonedistat, and 3 patients received 30 mg/m². The most common events (reported by ≥ 25% of patients) were constipation (45%), nausea (42%), fatigue (39%), anemia (34%), febrile neutropenia (30%), decreased appetite (28%), and thrombocytopenia (27%). The MTD in this study was determined to be 20 mg/m² Pevonedistat given on Days 1, 3, and 5, in combination with 75 mg/m² Azacitidine given on Days 1 through 5, 8, and 9, in 28 day treatment cycles. A total of 45 (70%) patients experienced at least 1 SAE. A total of 14 SAEs were reported for more than 1 patient, including: febrile neutropenia (16 patients); pneumonia (8 patients); pyrexia (4 patients); AML and sepsis (3 patients); and acute myocardial infarction, cellulitis, diverticulitis, dyspnea, embolism, hypoxia, mental status changes, multi-organ failure, and transaminase increased (2 patients each). A total of 19 patients treated with Pevonedistat (either 20 mg/m² or 30 mg/m²), discontinued from Study participation because of a TEAE. No other events leading to discontinuation were assessed by study investigators as at least possibly related to study drug treatment. 11 on-study deaths had been reported; none assessed as related to study treatment. A total of 31 patients experienced PR or better. Eighteen patients had a best response of CR, 4 patients had a best response of CRi, and 9 patients had a best response of PR. One patient in the 30 mg/m² dose level group achieved a CR; all other responses occurred in patients treated with 20 mg/m².

C15010

Study C15010 is an ongoing phase 1b study evaluating the MTD of Pevonedistat plus docetaxel, gemcitabine, or a combination of carboplatin and paclitaxel, in patients with solid tumors. As of 22 January 2017, enrollment has completed; 2 patients remain on study. The treatment arms are:

- Arm 1: Pevonedistat dosing on Days 1, 3, and 5 with 75 mg/m² docetaxel dosing on Day 1 in a 21-day cycle.
- Arm 2 Lead-in: Pevonedistat dosing on Days 1, 3, and 5 with AUC6 carboplatin dosing on Day 1 in a 21-day cycle.
- Arm 2: Pevonedistat dosing on Days 1, 3, and 5 with paclitaxel dosing on Day 1 and carboplatin dosing on Day 1 in a 21-day cycle. Per protocol, the dose levels

for paclitaxel and carboplatin were to be based on the DLTs in the Arm 2 Lead-in cohort; because there were 2 DLTs in the Arm 2 Lead-in cohort doses were set at 175 mg/m² paclitaxel and AUC5 for carboplatin.

- Arm 3: Pevonedistat dosing on Days 1, 8, and 15 with 1000 mg/m² gemcitabine dosing on Day 1, 8, and 15 in a 28-day cycle.

As of 22 January 2017, preliminary data are available for 64 patients enrolled who received at least 1 dose of Pevonedistat in combination with standard of care; these patients had completed a total of approximately 330 cycles, with medians ranging from 2 to 6 cycles of treatment across the 4 treatment groups. The starting dose levels for dose escalation and determination of Pevonedistat MTD were 15 mg/m² for Arm 1 and Arm 2, and 25 mg/m² for Arm 3. Overall, the most common AEs (occurring in $\geq 25\%$ of patients were fatigue (56%), nausea (48%), anemia (41%), diarrhea (34%), constipation and AST increased (31% each), ALT increased (30%), and vomiting (28%).

Per the data cut off, 15 patients experienced Cycle 1 DLTs in Study C15010. Increased ALT or AST (or both) accounted for DLTs in 11 patients, febrile neutropenia was reported for 3 patients, and 1 patient experienced thrombocytopenia.

The MTD for Arm 1 was determined to be 25 mg/m² Pevonedistat (dosing on Days 1, 3, and 5 with 75 mg/m² docetaxel dosing on Day 1 in a 21 day cycle). No MTD was determined for the Arm 2 Lead-in per protocol, but these DLTs informed the dose selection for paclitaxel and carboplatin in Arm 2: paclitaxel dose 175 mg/m² and a reduced dose for carboplatin of AUC5. The MTD for Arm 2 was determined to be 20 mg/m² Pevonedistat (dosing on Days 1, 3, and 5 with 175 mg/m² paclitaxel and AUC5 carboplatin dosing on Day 1 in a 21 day cycle). The gemcitabine combination arm (Arm 3) was closed to enrollment due to lack of tolerability (MTD was not determined). A total of 26 (41%) patients experienced at least 1 SAE. Febrile neutropenia was the only event reported for at least 1 patient in each of the 4 treatment arms (reported for 2 of 26 patients in Arm 2 and 2 of 10 patients in Arm 3). Dyspnea was reported for 3 of the 22 patients in Arm 1 and for 1 patient in Arm 3. Abdominal pain was reported for 1 patient each in Arm 1 and Arm 3 and pneumonia was reported for 2 patients in Arm 1; all other events were reported for only 1 patient across the treatment arms. Fifteen patients discontinued the Study because of TEAEs. Events that resulted in study discontinuation that were assessed at least possibly related to study drug treatment included ALT and AST increased, blood bilirubin increased, and blood creatinine increased (1 patient each in Arm 1); platelet count decreased, peripheral neuropathy, and neutropenia (1 patient each in Arm 2); leukopenia, lymphopenia, and pneumonitis (1 patient each in Arm 3), and febrile neutropenia (2 patients in Arm 3). Six on study deaths (within 30 days of the last dose of study drug) were reported with one death (Arm 3; due to febrile neutropenia) assessed as related to study treatment (Pevonedistat and gemcitabine). Twelve patients on Study C15010 had achieved PR or better. Two patients in Arm 2 achieved a CR; 3 patients in Arm 1, 1 patient in the Arm 2 Lead in, and 6 patients in Arm 2 achieved a PR.

C15011

Study C15011 is an ongoing phase 1 study evaluating the PK drug interaction between pevonedistat and CYP3A inhibitors (fluconazole or itraconazole) in patients with advanced solid tumors (Part A). As of 22 January 2017, enrollment has completed. In Part A of Study C15011, patients receive a single dose of Pevonedistat given as an IV infusion on Day 1 and Day 8, and either concomitant oral fluconazole or itraconazole on

Day 4 through Day 10. Patients are assessed for eligibility to continue in Part B (optional) after completion of Part A during a 2- to 8 week washout period. Thirty-six of the 51 patients enrolled in Study C15011 continued into Part B of the study, with 4 patients ongoing as of 22 January 2017. The 36 patients in Part B have received a total of approximately 203 cycles of pevonedistat in combination with either docetaxel (n=23; median, 4 cycles; range, 2-10) or the combination of carboplatin and paclitaxel (n=13; median, 5 cycles; range, 2-27). Data are available for 51 patients in Study C15011 as of 22 January 2017; 36 patients continued into Part B of the study, with 4 patients ongoing as of this date. Overall, the most common AEs (occurring in $\geq 30\%$ of patients in Part A or Part B) were fatigue, vomiting, nausea, decreased appetite, dehydration, constipation, anemia, stomatitis, diarrhea, headache, and hypokalaemia. Most SAEs (inclusive of Part A and Part B) were reported for 1 patient only; events reported for 3 or more patients included dyspnea (6 patients); pneumonia (5 patients); abdominal pain, abdominal pain upper, nausea, vomiting, failure to thrive, aspiration pneumonia, hypotension (4 patients each); and small intestinal obstruction, hyperkalemia (3 patients each). Thirty (59%) patients who participated in Part A experienced an SAE; in Part B, 16 (70%) patients in the pevonedistat+docetaxel group and 6 (46%) patients in the carboplatin+paclitaxel group also experienced an SAE. All but 2 of these SAEs (esophageal hemorrhage and dyspnoea) occurred during the washout period. Esophageal bleeding started before the second dose of itraconazole; dyspnoea was reported after the last dose of fluconazole and within the same month as the last dose of fluconazole, so it is within 2 weeks of the washout period, but the exact date is unknown. Six patients experienced a total of 10 SAEs during Part B that were assessed as related to study treatment; these events included pneumonia (reported for 2 patients), nausea and vomiting, chest discomfort and dyspnea, septic shock, failure to thrive and hypovolemic shock, and respiratory failure. As of 22 January 2017, 4 patients in Study C15011 achieved a PR in Part B of the study.

2.5. Potential risks of Pevonedistat

There are potential risks in the Pevonedistat program that require monitoring. While these toxicities may be severe or life threatening, it is anticipated that they can be managed by clinical monitoring and intervention. Patients will be monitored for these potential toxicities and for unanticipated toxicities when they receive Pevonedistat for at least 30 days after their last dose.

2.5.1. Potential Risks from Phase 1 Studies

Events have been reported in completed phase 1 studies primarily at doses and schedules substantially higher than doses administered in current clinical studies. These events are being considered potential risks for the doses and schedules in the current studies, as follows:

- Multi-organ failure that could result in death.
- Renal failure.
 - The events of multi organ failure (hepatic, renal, and cardiac) with a fatal outcome, and renal failure alone, have been reported at doses of Pevonedistat ranging from 110 to 278 mg/m².
- Cardiac arrhythmias.
 - All events were supraventricular arrhythmias; all except 1 were unrelated. The events of supraventricular arrhythmias were all considered as

unrelated to Pevonedistat except for 1 event of atrial fibrillation that occurred in a patient with a history of risk factors for cardiac disease.

- Myelosuppression with increased susceptibility to infection, bleeding, and anemia.
- Acute phase response.
- GI toxicity including or resulting in dehydration and/or electrolyte imbalance.
- Hypophosphatemia.

2.5.2. Potential Risks Confounded by Underlying Disease or Malignancy

Events have been reported from clinical trials that are confounded by the patient's underlying medical condition, including malignancy. These events are noted in the absence of randomized, controlled data:

- Fatigue.
- Chills.
- Decreased appetite.
- Neutropenia.
- Febrile neutropenia.
- GI bleeding.
 - All events were assessed by the investigator as unrelated; the majority occurred in the setting of thrombocytopenia.

2.5.3. Potential Risks Primarily Based on Findings from Animal Studies

Potential risks that are derived from findings in animal studies in rats and dogs include:

- Myocardial degeneration and thrombosis.
- Pulmonary hypertension.
- Cardiovascular changes that could result in tachycardia, decreased or increased systolic blood pressure, and increased diastolic blood pressure.
- Enteropathy (including dehydration and electrolyte loss) with secondary sepsis.
- Effects on the testes and ovaries that represent a reproductive hazard including sterility.
- Increased developmental risk to the fetus or embryo.
- Decreased trabecular bone (graded minimal to moderate) was noted in the femur and in the sternum in rats at all dose groups (low, medium, high). This finding was considered adverse in the high-dose group; however, no bone fractures were noted at any of the doses.
- Prolongation of the aPTT.
- Local tissue injury when administered SC.
-

It is possible that Pevonedistat will have toxicities that were not observed in or predicted from the studies completed in rats and dogs, or have not yet been identified in patients, which may be severe or fatal.

For detailed information please consult the current IB.

2.5.4. Additional Safety Considerations

Cycle 1, Day 1 Toxicity/Multi Organ Failure

A comprehensive review of the clinical trial safety data has shown that C1D1 toxicity involving multi-organ failure, including SAEs of renal, hepatic, and cardiac failure, some with a fatal outcome, has been observed in phase 1, single agent Pevonedistat studies at doses equal to or above 110 mg/m². Based on the observation that these events are associated with higher Pevonedistat doses, Millennium Pharmaceuticals, Inc. determined that all newly enrolling patients would receive Pevonedistat at doses equal to or below 100 mg/m².

The current understanding of the renal toxicity observed with Pevonedistat suggests that it is not a primary event but is likely secondary to hemodynamic changes occurring in the setting of a type of acute phase response.

Nonclinical investigative activities were undertaken to better understand the potential physiology behind the C1D1 events observed with Pevonedistat dosing. As summarized in the latest IB, a model in which a minimally toxic, single dose of Pevonedistat was administered with TNF α had several hallmarks associated with septic and/or cytokine-induced shock. The overall time course and target organs affected in this nonclinical model also appeared to closely mimic those observed in clinical C1D1 events at single agent doses ranging from 110 to 278 mg/m².

In October 2012, a revised risk mitigation strategy including limiting the dose to no higher than 100 mg/m² for single agent administration was implemented across the Pevonedistat program. As of January 2016, approximately 180 additional patients have been treated in single agent and combination studies, and no C1D1 SAEs as described above have been observed. These patients received Pevonedistat at a dose of 50 to 100 mg/m² as a single agent, a dose of 15 to 30 mg/m² in combination with different standard of care therapies, or a dose of 8 mg/m² in combination with a CYP3A inhibitor.

Guidance for Clinical Assessment and Management of Hemodynamic Compromise

Due to the underlying conditions of patients with advanced malignancies, patients must be carefully evaluated at screening and before each Pevonedistat dose for early symptoms and signs of hemodynamic compromise and active infection. Particular attention should be paid to unexplained fever, tachycardia, hypotension, orthostasis, tachypnea, recent nausea and vomiting, and clinical evidence of dehydration. For those patients for whom there is a concern of dehydration, the following guidance for rehydration before Pevonedistat dosing may be considered: 500 mL/hour of 0.5 N saline given over 2 to 4 hours for a total of 1 to 2 L of fluid as clinically appropriate. For all patients with anemia, and especially for patients with hemoglobin values \leq 8 g/dL at screening or during the conduct of the study, RBC transfusions should be considered before Pevonedistat dosing based on the patient's risk of inadequate oxygenation, underlying cardiopulmonary status, clinical judgment, and/or hospital guidelines. Patients who experience signs and symptoms of hemodynamic compromise after Pevonedistat dosing (e.g., tachycardia, hypotension, orthostasis, and changes in mental status, syncope, and dizziness) should be followed closely and managed with supportive care, including hospitalization as clinically indicated.

Guidance for Management of Patients with Blood Cell Counts Greater than 50,000/ μ L

One patient died of AML complicated by leukostasis within hours after receiving the first dose of Pevonedistat. This patient experienced rapidly increasing blast counts (to levels greater than 100,000/ μ L) before receiving the first dose of Pevonedistat on C1D1. This patient was not treated with hydroxyurea before receiving treatment with Pevonedistat. Patients with AML who experience extremely high leukemic blast cell count are at high risk of leukostasis, an AML complication characterized by an extremely elevated blast cell count causing symptoms of decreased tissue perfusion. To mitigate the risk of leukostasis, Study C15003 was amended to require that patients have a WBC count \leq 50,000/ μ L at screening and before Pevonedistat dosing during the first cycle of treatment.

In response to this event, AML clinical study protocols were updated to include a monitoring and treatment plan for leukocytosis and an exclusion criterion requiring a WBC count below 50,000/ μ L at screening and on Pevonedistat dosing days in Cycle 1. For patients who develop symptoms of leukostasis while on the study, Pevonedistat treatment should be withheld until the leukostasis symptoms are controlled. Treatment of leukostasis symptoms may include leukapheresis and hydroxyurea administration per study site institutional guidelines. When the WBC count of the patient is $<$ 50,000/ μ L and symptoms are improved, Pevonedistat treatment may be restarted after consulting with the project clinician.

Increases in Serum Creatinine

At current doses equal to or below 100 mg/m² on a Day 1, 3, and 5 or a Day 1, 4, 8, and 11 schedules, there have been reports of changes in serum creatinine from baseline levels of Grade 0 to Grade 1, and from baseline levels of Grade 1 to Grade 2.

Increases in Liver Enzymes and Biochemical Tests

Grade 1 to Grade 4 increases in adverse events related to liver function analyses (such as for liver transaminases [up to Grade 4], bilirubin [up to Grade 3], and alkaline phosphatase [up to Grade 3]), have been noted following administration of Pevonedistat in patients with advanced malignancies receiving Pevonedistat as a single agent and in combination with standard of care cytotoxic therapies. Among the single-agent studies, one patient in Study C15001 with metastatic colon cancer experienced a Grade 4 adverse event related to liver function analyses (alanine aminotransferase increased). In Study C15009, in patients with AML treated with Pevonedistat in combination with Azacitidine, Grade 4 increases for adverse events related to liver function analyses occurred in 2 patients as DLTs (alanine aminotransferase increased, aspartate aminotransferase increased). A third patient in Study C15009 experienced a Grade 4 adverse event (aspartate aminotransferase increased) that was not assessed as a DLT. In Study C15010 in patients with solid tumors treated with Pevonedistat in combination with docetaxel, gemcitabine, or carboplatin plus paclitaxel, and also in Study C15011, a drug-drug interaction study, adverse events related to liver function analyses up to Grade 3 were observed.

All patients experiencing these increases in laboratory values have been asymptomatic. The elevations in laboratory values have been reversible with dose modification including dose delay and reduction.

Drug Drug Interactions (DDIs)

Because the metabolic and excretion pathways of Pevonedistat remain to be characterized in humans, the risk of DDIs between Pevonedistat and concomitantly administered drugs is currently informed by available nonclinical and clinical data. On the basis of preliminary

findings, administration of Pevonedistat with moderate CYP3A inhibitors is permitted, while use of strong CYP3A inhibitors or inducers should be avoided. On the basis of in vitro transport studies, and until further investigation is performed, co administration with BCRP inhibitors should not be allowed in clinical studies of Pevonedistat.

As a general precaution, patients receiving concomitant medications, particularly those with narrow therapeutic indices, should be carefully monitored as the DDI potential between Pevonedistat and other drugs has not been formally studied in humans. Patients should also be instructed to consult with the investigator before taking any new medications, including over-the-counter products and herbal supplements.

Experience with Pevonedistat in AML induction and post-transplant treatment

It has been reported that there were 15 patients placed in phase I relapse or refractory AML protocol (Study C15003). Among them, 3 complete remissions have been recorded. Toxicities were not much, only reversible liver enzyme abnormalities. It is of note that no myelosuppression was reported. One patient who relapsed early after CloBu4 transplant (who was treated with Pevonedistat after relapse) and brought back into remission with 100% donor cells in bone marrow, without much toxicity. She was treated with 25 mg dose level. Afterwards she remained in CR for more than 8 months. Another patient who also relapsed early after stem cell transplant, and placed on this agent, went into CRi (without platelet recovery). In addition, other post-transplant patients had either hematologic improvement or partial response in granulocytic sarcoma. Although only a few cases, this experience may suggest us that Pevonedistat may work very well after allogeneic HSCT, with only little toxicity. An agent which is not myelosuppressive, and not too toxic after allogeneic HSCT, is ideal for maintenance therapy after HSCT.

2.6. Azacitidine and Pevonedistat as combination therapy for AML

In preclinical studies Pevonedistat has shown significant single agent activity against mouse xenograft models of AML cell Line HL-60. Also this effect seemed to be synergistically enhanced by combining it with Azacitidine. In clinical arena, Pevonedistat has shown single agent activity in heavily pretreated patients with AML. In Study C15003, responses (complete responses [CRs] and partial responses [PRs]) were observed in a variety of patient settings, including post allogeneic transplant, therapy-related AML, and primary refractory AML, although some of the responses were of relatively short duration. Study C15009 is an ongoing phase 1b study evaluating the MTD of Pevonedistat on Days 1, 3, and 5 in combination with 75 mg/m² Azacitidine (administered on a 5-on/2-off [weekend]/2-on schedule) in a 28-day treatment cycle in patients 60 years of age or older with treatment naïve AML who are unlikely to benefit from standard induction therapy. As of 22 June 2017, enrollment had completed and 15 patients remained on study. As of 22 January 2017, preliminary data are available for 64 patients enrolled in the study who received at least 1 dose of Pevonedistat in combination with Azacitidine; these patients had completed a total of approximately 360 cycles, with a median of 4 cycles of treatment. In the dose escalation cohorts, 6 patients received 20 mg/m² Pevonedistat, and 3 patients received 30 mg/m². The most common events (reported by $\geq 25\%$ of patients) were constipation (45%), nausea (42%), fatigue (39%), anemia (34%), febrile neutropenia (30%), decreased appetite (28%), and thrombocytopenia (27%). The MTD in this study was determined to be 20 mg/m² Pevonedistat given on Days 1, 3, and 5, in combination with 75 mg/m² Azacitidine given on Days 1 through 5, 8, and 9, in 28 day treatment cycles. A total of 45 (70%) patients experienced at least 1 SAE. A total of 14 SAEs were reported for more than 1 patient, including: febrile neutropenia (16 patients); pneumonia (8 patients); pyrexia (4 patients); AML and sepsis (3 patients); and acute myocardial infarction, cellulitis, diverticulitis, dyspnea, embolism, hypoxia, mental status changes,

multi-organ failure, and transaminase increased (2 patients each). A total of 19 patients treated with Pevonedistat (either 20 mg/m² or 30 mg/m²), discontinued from Study participation because of a TEAE. No other events leading to discontinuation were assessed by study investigators as at least possibly related to study drug treatment. 11 on-study deaths had been reported; none assessed as related to study treatment. A total of 31 patients experienced PR or better. Eighteen patients had a best response of CR, 4 patients had a best response of CRi, and 9 patients had a best response of PR. One patient in the 30 mg/m² dose level group achieved a CR; all other responses occurred in patients treated with 20 mg/m².

The following studies are currently enrolling.

- Study 2001: A Phase 2, randomized, controlled Open-Label Clinical study of the efficacy and safety of Pevonedistat plus Azacitidine versus single-agent Azacitidine in patients with higher-risk myelodysplastic syndromes, chronic myelomonocytic leukemia and low-blast acute myelogenous leukemia.
- Study 1012: A phase 1/1b, Open-label Study of Pevonedistat (MLN4924, TAK-924) as Single Agent and in Combination with Azacitidine in adult East Asian patients with acute myeloid leukemia or myelodysplastic syndromes

Hence owing to the current knowledge of clinical and preclinical experience with Azacitidine and Pevonedistat alone and in combination, this combination appears feasible for testing in patients post-transplant with at very high risk of relapse.

2.7. Proposed Study

We propose a study using a combination of Pevonedistat and Azacitidine for maintenance therapy after allogeneic HSCT for non-remission. Patients will receive up to five 28 day cycles of the investigational maintenance therapy. Maintenance therapy will begin between days +30 to +45 post-transplant.

3.0 Inclusion and Exclusion Criteria

3.1. Inclusion Criteria for Study Registration

1. Age \geq 18 years (or age of majority at participating site, whichever is greater) and \leq 75 years.
2. Non-remission AML at the time of transplant proven via bone marrow aspiration and/or biopsy.
 - “Not in remission” is defined as “greater than 5.0% bone marrow blasts by aspirate morphology,” as determined by a bone marrow aspirate obtained within 2 weeks of study registration.
 - For primary induction failure patients: Patients must have failed at least 2 induction regimens.
 - For patients with relapsed disease: Patients who relapse more than 1 year after preceding remission must fail at least one reinduction regimen to be eligible. For patients in whom the preceding remission is equal to or shorter than 1 year duration, no re-induction regimen is required to qualify for this protocol.
 - If the pre-transplant bone marrow aspirate and biopsy are hypo plastic (less than 10% cellularity), and blast percentages cannot be determined, the patient is eligible if the preceding bone marrow met the above criteria.
 - Patients with peripheral circulating blasts or patients with extramedullary leukemia are eligible if bone marrow aspirate and biopsy meets the above criteria.

3. Karnofsky Performance Scale (KPS) above or equal to 70%
4. Clinical laboratory values within the following parameters:
 - a) Creatinine clearance ≥ 50 mL/min
 - b) Hemoglobin > 8 g/dL. Patients may be transfused to achieve this value.
 - c) LFTs (ALT, AST) equal or less than 2.5 times upper limit of normal value.
 - d) Bilirubin $\leq x 1.5$ ULN
5. Female patients who:
 - Are postmenopausal for at least 1 year before the screening visit, OR
 - Are surgically sterile, OR

If they are of childbearing potential:

- Agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception, at the same time, from the time of signing the informed consent through 4 months after the last dose of study drug (female and male condoms should not be used together), or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post ovulation methods] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (i.e., status post vasectomy), who:

- Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug (female and male condoms should not be used together), or
 - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post ovulation methods for the female partner] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)
6. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
 7. Patient has consented to be in the IBMTR registry study.

3.2. Exclusion Criteria for Study Registration

1. Treatment with any investigational products within 21 days of study registration.
2. Known hypersensitivity to Azacitidine.
3. Active uncontrolled infections or severe infectious disease, such as severe pneumonia, meningitis, or septicemia.
4. Known central nervous system (CNS) involvement.
5. Known human immunodeficiency virus (HIV) positivity.
6. Known hepatitis B surface antigen-positive, or known active hepatitis C infection.
 - Note: Patients who have isolated positive hepatitis B core antibody (ie, in the setting of negative hepatitis B surface antigen and negative hepatitis B surface antibody) must have an undetectable hepatitis B viral load. Patients who have positive hepatitis C antibody may be included if they have an undetectable hepatitis C viral load.

7. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of study procedures
8. Major surgery within 14 days before the first dose of any study drug or a scheduled surgery during study period.
9. Diagnosed or treated for another malignancy within 2 years before randomization or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone resection.
10. Life-threatening illness unrelated to cancer.
11. Patients with uncontrolled coagulopathy or bleeding disorder.
12. Known hepatic cirrhosis or severe pre-existing hepatic impairment
13. Known cardiopulmonary disease defined as:
 - Unstable angina;
 - Congestive heart failure (New York Heart Association [NYHA] Class III or IV);
 - Myocardial infarction (MI) within 6 months prior to first dose (patients who had ischemic heart disease such as a (ACS), MI, and/or revascularization greater than 6 months before screening and who are without cardiac symptoms may enroll);
 - Cardiomyopathy;
 - Clinically significant arrhythmia:
 - a) History of polymorphic ventricular fibrillation or torsade de pointes,
 - b) Permanent atrial fibrillation [a fib], defined as continuous a fib for ≥ 6 months,
 - c) Persistent a fib, defined as sustained a fib lasting > 7 days and/or requiring cardioversion in the 4 weeks before screening,
 - d) Grade 3 a fib defined as symptomatic and incompletely controlled medically, or controlled with device (e.g. pacemaker), or ablation and
 - e) Patients with paroxysmal a fib or $< \text{Gr } 3$ a fib for period of at least 6 months are permitted to enroll provided that their rate is controlled on a stable regimen.
 - Implantable cardioverter defibrillator;
 - Moderate to severe aortic and/or mitral stenosis or other valvulopathy (ongoing);
 - Pulmonary hypertension
14. Uncontrolled high blood pressure (i.e., systolic blood pressure > 180 mm Hg, diastolic blood pressure > 95 mm Hg).
15. Prolonged rate corrected QT (QTc) interval ≥ 500 msec, calculated according to institutional guidelines.
16. Left ventricular ejection fraction (LVEF) $< 50\%$ as assessed by echocardiogram or radionuclide angiography.
17. Known moderate to severe chronic obstructive pulmonary disease, interstitial lung disease, and pulmonary fibrosis. FVC, FEV1, or DLCO (corrected with hemoglobin) less than 40% of expected value.
18. Systemic antineoplastic therapy or radiotherapy for other malignant conditions within 14 days before the first dose of any study drug, except for hydroxyurea.
19. Female patients who are both lactating and breastfeeding or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before first dose of study drug.
20. Female patients who intend to donate eggs (ova) during the course of this study or 4 months after receiving their last dose of study drug(s).
21. Male patients who intend to donate sperm during the course of this study or 4 months after receiving their last dose of study drug(s).

22. Patients who need to use clinically significant CYP3A enzyme inducers (listed on Appendix A)

3.3. Additional Eligibility Criteria for Initiating Study Treatment

The following criteria are to be met to initiate each 28 day cycle of study treatment. The assessment will take place on Day 1 of each cycle (except item 5, 6).

1. No treatment with clinically significant metabolic enzyme inducers (Appendix A) within 14 days of first dose. Use of these drugs is not permitted on study.
2. Performance Status 60% KPS or above.
3. LFTs (ALT, AST) equal or less than 2.5 times upper limit of normal value.
4. Bilirubin \leq x 1.5 ULN limit
5. Must have results of a day +30 (\pm 7) post-transplant bone marrow aspirate / biopsy. The results will be recorded. Does not require CR to initiate study treatment. This item is only to initiate cycle #1.
6. White blood cell (WBC) count $< 50,000/\mu\text{L}$ before administration of Pevonedistat on cycle 1 day 1. Note: Hydroxyurea may be used to control the level of circulating leukemic blast cell counts.

The following additional criteria need to be met to initiate each cycle of Azacitidine treatment.

7. ANC equal to or more than 1,000/mm³
8. Platelets equal to or more than 20,000/mm³
9. Albumin >2.7 mg/dl
10. Creatinine Clearance should be ≥ 30 ml/min

3.4. Inclusion of Women and Minorities:

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

3.5. Vulnerable Populations

The following populations of patients are not enrolled into the study.

Adults who cannot sign on consents
Pregnant Women
Prisoners

3.6. Registration and Early Withdrawal/Discontinuation of the Study

3.6.1. REGISTRATION PROCEDURES

Eligible patients will be registered on study by the Penn State Hershey Cancer Institute, Clinical Trials Office (PSHCI-CTO) by the Study Coordinator. The subject's Eligibility Worksheet will be completed electronically in its entirety prior to registration, and source documentation verifying each eligibility criterion must be available. Following registration, patients should begin protocol treatment within 2 weeks. Issues that would cause treatment delays should be discussed with the Principal Investigator and documented in the chart.

3.6.2. Discontinuation of the Study/Withdrawal

The study may be discontinued for following reasons.

The patient can withdraw the consent and withdraw from the study any time.

If the patient is noncompliant or for other reasons if the treating physician determine it may be inappropriate to continue the study.

3.6.3. Follow-up for withdrawn subjects

The patients withdrawn from study treatment will be followed as a study patient as far as the patient allows data collection. Please see section 7.12.

4.0 Recruitment Methods

4.1. Identification of subjects

Patients undergoing hematopoietic stem cell transplantation at Penn State Hershey Medical Center will be identified as the possibly eligible patients.

4.2. Recruitment process

Treating physicians, investigators, or coordinators will introduce the study to the patient and will discuss with them. If patients agree to participate, they will sign on the study consent and proceed.

4.3. Recruitment materials

Consent form will be given to the patients to read beforehand and they will be given time to read and ask questions.

4.4. Eligibility/screening of subjects

Screening tests, including blood tests, Pulmonary Functions Tests, Echocardiogram/MUGA scan will be ordered by transplant coordinators and results will be reviewed by them with physicians. Eligibility checklist will be filled to confirm that all the eligibility criteria are met before the registration.

5.0 Consent Process and Documentation

Consenting process will follow “SOP: Informed Consent Process for Research (HRP-090)”. HRP-090 can be accessed by clicking the Library link in CATS IRB (<http://irb.psu.edu>).

5.1. Consent Process

5.1.1. Obtaining Informed Consent

5.1.1.1. Timing and Location of Consent

Consenting will take place mainly at the Hematology/Bone Marrow Transplant Clinic in the Cancer Institute in average a few weeks before the transplant admission. Exceptions will be allowed (For example, inpatient room if the patient is in the hospital at the time of consenting.).

5.1.1.2. Coercion or Undue Influence during Consent

The treating physicians and/or Investigators, transplant coordinators will explain about the protocol in detail and the patients will be given time to think, discuss with someone else, and ask questions. Patients will be informed that participation is voluntary and that a decision not to participate will not be held against them.

5.1.2 Waiver or alteration of the informed consent requirement

N/A

5.2. Consent Documentation

5.2.1. Written Documentation of Consent

The consenting process will follow “SOP: Written Documentation of Consent (HRP-091)” for information about the process to document the informed consent process in writing. HRP-091 can be accessed by clicking the Library link in CATS IRB (<http://irb.psu.edu>).

5.2.2. Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)

N/A

5.2.3. Consent – Other Considerations

5.2.3.1. Non-English Speaking Subjects

N/A Non-English Speaking subjects will not be enrolled on the study.

5.2.3.2. Cognitively Impaired Adults

N/A Cognitively impaired adults who cannot sign the consent will not be enrolled on the study.

5.2.3.3. Subjects who are not yet adults (infants, children, teenagers)

N/A One of the eligibility criteria is 18 years or older.

6.0. HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1. Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

- ☐ Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study. *[Mark all parts of sections 6.2 and 6.3 as not applicable]*
- ☒ Authorization will be obtained and documented as part of the consent process. *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*
- ☐ Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained). *[Complete all parts of sections 6.2 and 6.3]*
- ☐ Full waiver is requested for entire research study (e.g., medical record review studies). *[Complete all parts of sections 6.2 and 6.3]*

- ☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2. Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

N/A

6.3. Waiver or alteration of authorization statements of agreement

N/A

7.0. Study Design and Procedures

7.1. Study Treatment

The study treatment will be started after transplant. The definition of transplant here is “the infusion of donor stem cells”. It includes donor lymphocyte infusion used as the 2nd transplant if the graft includes mobilized donor stem cells.

Cycle 1 Day 1 of study treatment will be between day +30 and day +45 post-transplant (but can be delayed up day 73 as described in Section 7.3). Each 28-day cycle is comprised of Pevonedistat at 20 mg/m² IV infusion over 1 hour on days 1, 3 and 5 and Azacitidine at 25 mg/m² IV infusion over 10 minutes on days 1, 2, 3, 4, 5, 8 and 9. The drugs can be administered either through a central catheter or a peripheral line.

Premedication for Azacitidine will be given according to the institutional standard.

Pevonedistat is known to have associated with nausea, vomiting and diarrhea and has also been associated with episodes of hypotension, thus patient will be pre-medicated with anti-emetics. It is recommended to administer Zofran at 16mg IV 30 minutes prior to the each dose of Pevonedistat. Patients will also have other anti-emetic and antidiarrheal medications available to be used PRN.

For those patients for whom there is a concern of dehydration, the following guidance for rehydration before Pevonedistat dosing may be considered: 500 mL/hour of 0.5 normal saline given over 2 to 4 hours for a total of 1 to 2 L of fluid as clinically appropriate, or at the treating physician’s discretion.

For patients with hemoglobin values < 8 g/dL at the beginning of a cycle RBC transfusions should be considered before Pevonedistat dosing based on the patient’s risk of inadequate oxygenation, underlying cardiopulmonary status, treating physician judgment, and/or institutional guidelines.

Bilirubin and LFTs need to be checked before each dose of Pevonedistat. If bilirubin is > 1 and ≤ 1.5 of UNL, the dose of Pevonedistat will be reduced from 20 mg/m² to 15 mg/m². If total bilirubin is again > 1 and ≤ 1.5 of UNL in the next cycle the dose of Pevonedistat will be further reduced to 10 mg/m².

Table 7-1 Study Treatment / Post Transplant Maintenance Therapy

28 day cycles. 1 st cycle beginning between day +30 and day +45 post-transplant and continued up to 5 cycles.					
Agent	Pre-medications; Precautions	Dose*	Route	Schedule	Cycle Length
Pevonedistat	Zofran 16 mg IV 30 minutes prior to Pevonedistat. Consider: Hydration; RBC transfusions if indicated.	20 mg/m ² 15 mg/m ² 10 mg/m ²	Intravenous infusion given over 1 hour.	Days 1, 3, and 5 of each cycle.	28 days (4 weeks)
Azacitidine	Pre-meds per institutional guidelines.	25 mg/m ²	Intravenous infusion given over 10 minutes.	Days 1, 2, 3, 4, 5, 8, and 9 of each cycle.	

*Please see the section 7.1 and 7.3.

7.2. Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented prior to drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified sub investigator(s).

If Pevonedistat dosing is delayed, a minimum of 1 full calendar day between any 2 doses should be maintained. In each cycle, a maximum of 3 doses of Pevonedistat should not be exceeded.

The amount of study drug to be administered will be based on body surface area (BSA). BSA will be calculated using Mostellar's formula on Cycle 1 Day 1, and on Day 1 of subsequent cycles if the patient experiences a >5% change in body weight from the weight used for the most recent BSA calculation.

7.3. Delay of Medications/Dose Modifications at each cycle:

Cycle 1:

If the criteria # 1, 2, 3, 4, 5, 6 noted in section 3.3 are not met within the target range of days +30 to +45 post-transplant, the treatment may be delayed for up to 4 weeks to allow for resolution. Cycle 1 may begin up to day +73 post-transplant at the latest. The delay should be minimal, thus the patient should be assessed for eligibility to start treatment weekly.

If the patient does not meet the criteria #1, 2, 3, 4, 5, and 6 by day 73, then the cycle 1 will be skipped and the patient will be assessed to start next cycle 2 two weeks later.

If the criteria # 7, 8, 9, and 10 noted in section 3.3 are not met but the other criteria (#1, 2, 3, 4, 5, 6) are met, the cycle will be started with Pevonedistat only.

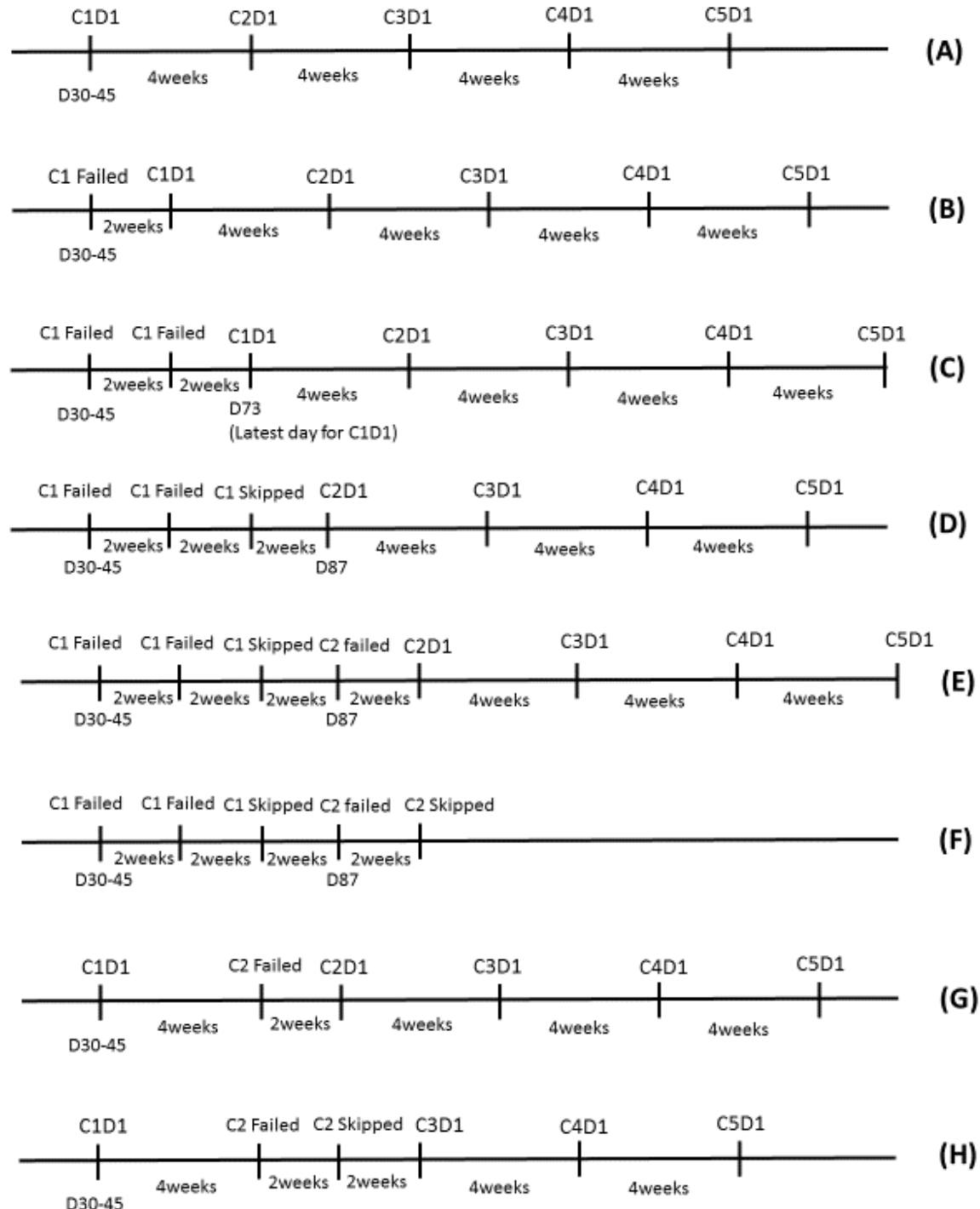
Cycles 2 – 5:

If the criteria, # 1, 2, 3, 4 noted in section 3.3 are not met beginning of each subsequent cycle, then 2 weeks of delay between cycles will be allowed. If still not eligible after 2 week delay then that cycle will be skipped. The next scheduled cycle may resume if eligible at the original scheduled time, which

will be 2 weeks from the last skipped cycle. If 2 straight cycles are skipped before the patient receives 2 cycles, the patient is off study and not considered evaluable for efficacy. (Patient is still evaluable for toxicity if the patient received at least one dose of Pevonedistat.)

Once the cycle is initiated, the dosage of the drugs will not be modified provided that bilirubin and LFTs are inside the acceptable range per the inclusion criteria (please refer to Section 3.3. However, the dose can be held if the treating physician thinks that the patient has unacceptable side effects due to the drugs. In this case PI or coordinating MD should be contacted.

Please refer to the following diagram for delaying the cycles.



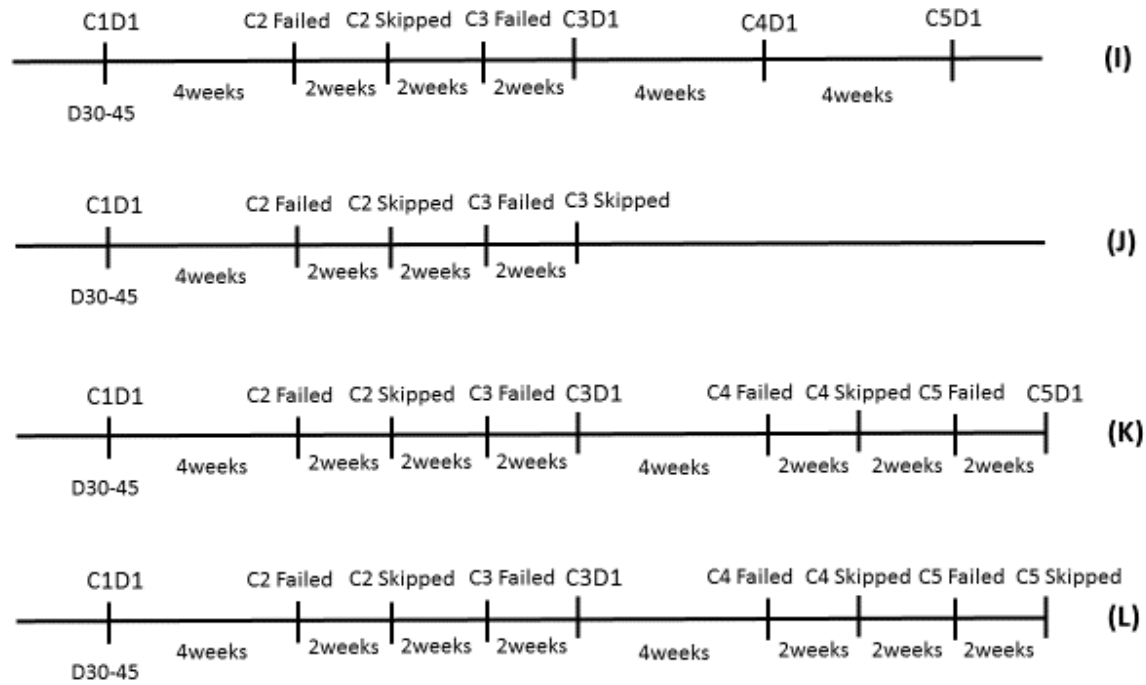


Figure: Schematic diagram of delays. (A) Each cycle every 28 days (standard). (B) Cycle 1 (C1) failed and then resumed 2 weeks later. (C) C1 failed initially and again 2 weeks later, then another 2 weeks later C1 was successfully started before or on day 73. (D) C1 failed initially then 2 weeks and 4 weeks later, thus C1 was skipped and C2 was started another 2 weeks later. C1 can be delayed up to 4 weeks but in subsequent cycles (C2-C5) delays are allowed only up to 2 weeks. (E) C1 was skipped and C2D1 was delayed by 2 weeks. (F) C1 was skipped and C2 was also skipped, at that point the patient comes off study. (G) C1 was given on schedule; C2 was delayed by 2 weeks. (H) C1 was given on schedule, but C2 was delayed but 2 weeks later eligibility criteria were not met again, thus C2 was skipped. (I) C1 was given, C2 was skipped, and C3 was delayed by 2 weeks but then C3 was started with 2 weeks delay. (J) C1 was given on schedule, but C2 and C3 were skipped, then this patient comes off study. (K, L) The patient already received C1 and C3 thus can stay on study until completion.

7.4. Other Dose-Modification Guidelines

7.4.1. General Guideline for dose modification

If the section 7.1 determines the dose modification, that will be prioritized above the rule in this section.

If patient bilirubin values before dosing are >1 and ≤ 1.5 of UNL, the dose of Pevonedistat will be reduced from 20 mg/m^2 to 15 mg/m^2 . If total bilirubin is again >1 and ≤ 1.5 of UNL in the next cycle the dose of Pevonedistat will be further reduced to 10 mg/m^2 .

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

7.4.2. Criteria for Retreatment and Dose Delays

Retreatment within a Cycle

If dosing of either drug is delayed for safety reasons, retreatment may be resumed upon resolution of the safety condition. For Pevonedistat, a minimum of 1 full calendar day between

any 2 doses should be maintained. A maximum of 3 doses of Pevonedistat should not be exceeded.

If dosing is interrupted within a cycle because of drug-related toxicity, and if the sponsor investigator (or designee) agrees that it is in the patient's interest to continue therapy with the study drug(s), then after recovery of the toxicity or toxicities in question to \leq Grade 1 or to the patient's baseline values, the dose of study drug may be reduced in the next cycle. For toxicity not related to drug (eg, disease-related toxicity), although a similar dose reduction is permitted, in general it is discouraged. If the reduced dose is well tolerated and the toxicity leading to dose reduction was \leq Grade 3, has resolved, and does not reoccur, the dose may resume at the original dose level in the next cycle after endorsement by the sponsor investigator (or designee).

Initiation of a New Cycle

Treatment with study drugs will be repeated every cycle. For therapy to resume, toxicity considered related to treatment with study drugs must have resolved to Grade 1, to the patient's baseline values, or to a level considered acceptable by the sponsor investigator.

If a patient fails to meet the criteria for retreatment, initiation of the next cycle of treatment may be delayed for up to 2 weeks. At the end of that time, the patient should be reevaluated to determine whether the criteria for retreatment have been met. A dose reduction would be triggered if treatment is delayed for >2 weeks because of incomplete recovery from treatment related toxicity. If the reduced dose is well tolerated and the toxicity leading to dose reduction was \leq Grade 3, has resolved, and does not reoccur, the dose may resume at the original dose level in the next cycle after endorsement by the sponsor investigator (or designee). For toxicity not related to drug (eg, disease-related toxicity), although a similar dose reduction is permitted, in general it is discouraged. If the dose is well tolerated and the toxicity leading to dose reduction was \leq Grade 3, has resolved, and does not reoccur, the dose may resume at the original dose level in the next cycle.

For hematologic toxicity a delay in the initiation of a cycle by 4 weeks or greater because of lack of recovery from treatment-related hematologic toxicity (resolved to Grade 1, to patient's baseline values, or to a level considered acceptable by the sponsor investigator) that is not related to leukemic infiltration will trigger a dose reduction if treatment resumes. If indicated, bone marrow evaluation will be performed to establish whether continued myelosuppression is related to persistent or progressing leukemic infiltration. The Pevonedistat dose should be reduced by at least 1 dose level. *(if applicable)*

7.4.3. Dose Modifications for Hematologic Toxicities

It is not anticipated that Pevonedistat dose modifications would be necessary due to myelosuppression. However, if clinically indicated in the opinion of the investigator, the Pevonedistat dose may be reduced one dose level. The Pevonedistat dose may be re-escalated at the next cycle, if the toxicity has recovered to \leq Grade 1 or the patient's baseline.

Pevonedistat should be held for symptoms of leukostasis until the leukostasis is treated per institutional guidelines. Pevonedistat may be restarted when WBC count is $<50,000/\mu\text{L}$ and following agreement by the sponsor investigator. *(if applicable)*

7.4.4. Dose Modifications for Non-hematologic Toxicities

7.4.4.1. Pevonedistat Dose Adjustment Based on Serum Transaminases and Total Bilirubin

It is anticipated that LFTs (AST, ALT, and occasionally bilirubin) may be elevated for approximately 48 hours following the end of Pevonedistat infusion on Cycle 1 Day 1.

For elevated LFTs of Grade 2 or 3 that occur on or after Cycle 1 Day 3, Pevonedistat should be held; once the elevated AST or ALT returns to \leq Grade 1, and/or elevated bilirubin returns to $\leq 1.5 \times \text{ULN}$ or the patient's baseline level, Pevonedistat dose may be resumed. For Pevonedistat, a minimum of 1 full calendar day between any 2 doses should be maintained, and a maximum of 3 doses of Pevonedistat within the cycle must not be exceeded.

For elevated LFTs of Grade 4 that occur on or after Cycle 1 Day 3, the Pevonedistat dose should be held for the remainder of the cycle; if the elevated AST or ALT returns to \leq Grade 1, and/or elevated bilirubin returns to $\leq 1.5 \times \text{ULN}$ or the patient's baseline level, then Pevonedistat may be restarted at the next cycle at a reduced dose. If the toxicity returns to \leq Grade 1 or the patient's baseline status, Pevonedistat may be re-escalated.

7.4.4.2. Pevonedistat Dose Adjustment Based on Hypophosphatemia

If hypophosphatemia is \geq Grade 3, study drug treatment should not be resumed until the hypophosphatemia is \leq Grade 2. Hypophosphatemia should be evaluated (including severity and etiology), monitored, and treated according to institutional guidelines.

7.4.4.3. Pevonedistat Dose Adjustment for Other Toxicities

For other \geq Grade 2 non-hematologic toxicities potentially related to Pevonedistat, the Pevonedistat dose may be reduced at the discretion of the sponsor investigator as clinically indicated. If the toxicity returns to \leq Grade 1 or the patient's baseline status, Pevonedistat may be re-escalated at the next cycle.

7.5. GVHD and Immunosuppression

At any point during the study treatment, if patient experiences acute GVHD grade III to IV, study treatment will be held until the GVHD improves to grade II or lower, then the study treatment can be resumed.

If the patient has any liver or gut GVHD, Pevonedistat should not be given.

7.6. Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

Table 7-6 Concomitant Medications Excluded During the Study

Therapy	Comment/Exceptions
Acetaminophen and acetaminophen-containing products	May be used judiciously but should not exceed a dose of 2 g in 24 hours.
Systemic antineoplastic therapy, except for hydroxyurea	Hydroxyurea dosing during the study treatment phase may be adjusted to control the level of circulating blast counts to no lower than 10,000/ μ L while on study treatment. The dosing of hydroxyurea and changes to dosing of hydroxyurea must be recorded.
Clinically significant metabolic enzyme inducers	Excluded.
Known BCRP inhibitors (ie, cyclosporine)	Excluded but limited use is permitted only if clinically necessary and no suitable alternative exists . The patient may receive the BCRP inhibitor from 24 hours after the last Pevonedistat dose until 72 hours before the next Pevonedistat dose. For example, if a patient receives Pevonedistat on a Monday (Day 1), Wednesday (Day 3), Friday (Day 5) schedule, then the BCRP inhibitor may be administered from the Saturday after the Day 5 dose (Day 6) up to the Friday (Day 26) before the Monday dose of the next cycle. <u>Tacrolimus is permitted</u> .
Any investigational agent other than Pevonedistat, including but not limited to androgens, supraphysiologic doses of corticosteroids, erythropoietin, eltrombopag [Promacta], or romiplostim [Nplate]	
BCRP=breast cancer resistance protein, CYP=cytochrome P450,	

7.7. Permitted Concomitant Medications and Procedures**Table 7-7 Concomitant Medications and Procedures Permitted During the Study**

Therapy	Comment
Anti-platelet agents (eg, aspirin, clopidogrel) and anticoagulants	May be used in patients who have controlled coagulopathy at baseline, as well as those who develop a coagulopathy on study. Note that patients with active uncontrolled coagulopathy are excluded from enrollment.
Myeloid growth factors (eg, G-CSF, GM-CSF)	In general, the use of myeloid growth factors is discouraged and should be restricted. For patients in CR, CRi, or marrow CR, growth factors may be used in specific circumstances after discussion with the project clinician or designee. Use of growth factors may also be used in patients with Grade 3 or Grade 4 febrile neutropenia after discussion and agreement with the project clinician or designee. Additionally to avoid dose delays, patients who experience Grade 4 neutropenia (ANC <500/ μ L) with or without fever may receive granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF) between days 28-42 days of Azacitidine monotherapy or combination after discussion and agreement with the sponsor investigator (or designee). Patients who receive myeloid growth factors will not be included in assessment of neutrophil response.
Platelet transfusion	Permitted as medically necessary per institutional guidelines (e.g., for platelets <10,000/ μ L in the absence of clinical bleeding)

Table 7-7 Concomitant Medications and Procedures Permitted During the Study

Therapy	Comment
Red blood cell transfusion	To be considered for all patients with anemia, especially those with hemoglobin values ≤ 8 g/dL.

G-CSF=granulocyte colony-stimulating factor, GM-CSF=granulocyte macrophage colony-stimulating factor.

7.8. Study Treatment Period

The “Study Treatment Period” is from the start of study treatment, cycle 1 day 1 until the study treatment completion visit. Last treatment dose of azacitidine is being given on day 9 of the last cycle, and study treatment completion visit will be scheduled between 42 days and 56 days after the day 1 of the last treatment cycle.

AEs and SAEs will be reported during the Study Treatment Period. AEs and SAEs initiated during this period will be followed until they resolve.

7.9. Treatment Cycles

Treatment will be continued until cycle 5 is completed or the study is terminated for the patient. The cycles will be repeated every 28 days.

7.10. Evaluable patients

Patients who received at least one dose of Pevonedistat will be considered evaluable for toxicity assessment. Patients who received at least 2 cycles of Pevonedistat treatment will be considered as evaluable for efficacy.

The patients who were registered and/or underwent transplant but did not receive study drug will be considered unevaluable and replaced.

7.11. Removal from the study

Patients will be removed from the study in the following cases. If the patient receives at least one dose of Pevonedistat the patient is evaluable for toxicity assessment.

- Unequivocal progression of AML after the initiation of the study drug. One of the following criteria should be met: (a) if the patient was in CR when the study drug was started, overt relapse would be considered “unequivocal” progression. (b) if the patient was not in CR when the drug was started, more than double the blast percentage would be defined as “unequivocal”.
- The occurrence of unacceptable toxicity indicating the need for cessation of treatment.
- Non-compliance by the patient with protocol requirements.
- Patient is lost to follow-up. If a patient does not return for scheduled visits, every effort should be made to re-establish contact. If patient cannot be contacted and removed from the study, every effort should be made to document patient outcome.
- Patient becomes pregnant.

- Termination of the study by investigator or sponsor agency.

7.12. Withdrawal from the study

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Adverse event
- Protocol violation
- Lost to follow-up
- Progressive disease
- Note: patients with PD may remain on the study, after discussion with Millennium Inc., if it is judged that they are deriving a clinical benefit from doing so.
- Initiation of hematopoietic stem cell transplant
- Subsequent anti-cancer therapy
- Withdrawal by subject
- Study terminated
- Other

Patients will be offered alternative options at that time. Even if the patient withdraws, patient may be evaluable based on criteria 7.10. If a subject withdraws consent completely, we will stop collecting their health information for this study; however, we may continue to use and share the subject's health information that was already obtained as necessary for safety and scientific soundness of the research study. We will not be able to take back information that has already been used or shared with others.

7.13. Precautions and Restrictions

Pregnancy

It is not known what effects Pevonedistat has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use highly effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the Screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception, at the same time, from the time of signing the informed consent through 4 months after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post ovulation methods] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

- Female patients must agree to not donate eggs (ova) during the course of this study or 4 months after receiving their last dose of study drug(s).

Male patients, even if surgically sterilized (i.e., status post vasectomy), must agree to 1 of the following:

- Practice highly effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, or
- Practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post ovulation methods for the female partner] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Male patients must agree to not donate sperm during the course of this study or 4 months after receiving their last dose of study drug(s).

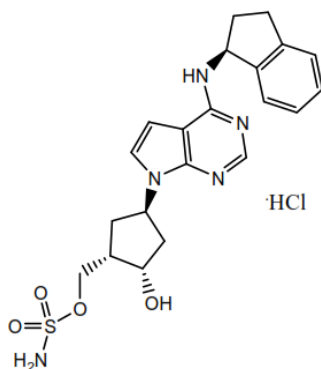
7.14. Test Article(s) (Study Drug(s) and/or Study Device(s))

7.14.1. Pevonedistat (MLN4924, TAK924)

Chemical Characteristics

The chemical name of the drug substance, Pevonedistat, is ((1*S*, 2*S*, 4*R*)-4-{4-[(1*S*)-2, 3-dihydro-1*H*-inden-1-ylamino]-7*H*-pyrrolo [2, 3-*d*] pyrimidin-7-yl}-hydroxycyclopentyl) methyl sulfamate hydrochloride.

Structure of Pevonedistat



Available Forms

The drug product is labeled Pevonedistat (TAK-924/MLN4924) Concentrate for Solution for Infusion. The MLN4924-003 Injection Drug Product formulation consists of 10 mg/mL (as free base) of MLN4924-003 in an aqueous solution of 7.45 mg/mL citric acid (anhydrous), 3.29 mg/mL trisodium citrate dihydrate and 100 mg/mL β-Cyclodextrin sulfobutyl ether (Captisol®) at pH 3.3. Each USP Type I glass vial nominally contains 5 mL of compounded sterile solution, sealed with a Teflon®-coated butyl rubber stopper and over sealed with an aluminum seal and a plastic cap.

Each MLN4924-003 Injection Drug Product vial contains nominally 5 mL (50 mg

MLN4924-003 as free base). Pevonedistat (TAK-924/MLN4924) will be provided in 10-mL glass vials at a concentration of 10 mg/mL.
Full details are available in the IB.

Storage and Handling

The study agent Pevonedistat (MLN4924) is provided by the manufacturer. MLN4924-003 Injection Drug Product is a cytotoxic anticancer drug. As with other potentially toxic compounds, caution should be exercised when handling MLN4924. All investigational supplies are to be kept in a secure area with controlled access.

Refer to institutional guidelines regarding the proper handling and disposal of cytotoxic agents.

MLN4924-003 Injection Drug Product vials should be stored refrigerated at 2°C to 8°C. Before use, MLN4924-003 Injection Drug Product vials should be brought to ambient conditions (15°C-30°C) by removing the vials from the refrigerator and placing them at room temperature. Accelerated warming methods such as a water bath must not be used.
The vial must not be shaken at any time during dose preparation.

Using sterile technique, the appropriate volume of drug should be withdrawn from vial(s) and injected into a 250-mL IV bag containing a 5% dextrose solution. The bag must be gently inverted repeatedly to mix the contents. Discard bag, needle, and syringe in a proper biohazard container according to institutional guidelines.

MLN4924-003 Injection Drug Product is stable at ambient temperature for 8 hours before dilution. Once it is diluted in 5% dextrose, the prepared MLN4924-003 IV bag must be used within 6 hours (time to the end of an injection) if stored at ambient temperature. Alternatively, the prepared IV bag is chemically stable and may be stored for up to 18 hours at 2°C to 8°C. After 18 hours of storage at 2°C to 8°C, the prepared IV bag must be used within 3 hours (time to the end of an injection) upon coming to ambient temperature.

Study drug will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The amount of drug to be administered will be based on body surface area (BSA). BSA will be calculated using a standard nomogram on Cycle 1, Day 1, and at subsequent visits if the patient experiences a > 5% change in body weight from the weight used for the most recent BSA calculation.

The pharmacist will maintain records of drug receipt (if applicable), drug preparation, and dispensing, including the applicable lot numbers, and total drug administered in milliliters and milligrams.

All patients will receive Pevonedistat diluted with 5% dextrose in a 250-mL IV bag via IV infusion via a 60-minute IV infusion. Pevonedistat should be administered through central or peripheral venous access. The infusion may be slowed or stopped and restarted for any associated infusion-related reactions. All infusion times must be recorded. The total time from drug reconstitution to end of infusion must not exceed 6 hours. Doses of Pevonedistat must be separated by at least 1 full calendar day.

Toxicity

Safety information gained from clinical studies and toxicology studies has been used to guide the safety evaluation of Pevonedistat.

Potential risks of Pevonedistat from phase 1 studies conducted at higher doses than currently investigated in the clinical development program are multi-organ failure that could result in death, renal failure, cardiac arrhythmias, acute phase response, GI toxicity including or resulting in dehydration and/or electrolyte imbalance, hypophosphatemia, and myelosuppression with increased susceptibility to infection, bleeding, and anemia.

Potential risks of Pevonedistat confounded by underlying disease or malignancy are fatigue, chills, decreased appetite, neutropenia, febrile neutropenia, and GI bleeding.

Potential risks of Pevonedistat primarily based on findings from animal studies are myocardial degeneration and thrombosis, pulmonary hypertension, effects on the testes and ovaries that represent a reproductive hazard including sterility, increased developmental risk to the fetus or embryo, decreased trabecular bone without fractures, prolongation of the activated partial thromboplastin time, local tissue injury (when administered SC), and cardiovascular changes that could result in tachycardia, decreased or increased systolic blood pressure, and increased diastolic blood pressure.

Tumor lysis may occur if the patient with active leukemia is given pevonedistat. Tumor lysis syndrome is caused by the acute lysis of leukemia cells and is characterized by high potassium, high phosphorus, low calcium, high uric acid, high BUN, and may be associated with coagulopathy. It can be prevented/appropriately treated with awareness of this condition. It should be treated with hydration, correction of electrolytes, allopurinol, and may require rasburicase in severe cases.

Drug-drug interaction

Pevonedistat is metabolized by the liver predominantly through the CYP isozyme CYP3A4, with a small contribution from CYP2D6 (approximately 3%). There is a potential risk for a drug-drug interaction when Pevonedistat is co-administered with drugs that are CYP3A inhibitors or inducers (Appendix A). Consequently, co-administration of strong CYP3A inhibitors or inducers is not permitted in clinical studies of Pevonedistat. Per protocol, treatment with strong CYP3A inhibitors or inducers must be discontinued 14 days before initiation of Pevonedistat therapy. Patients must have no history of amiodarone use in the 6 months before the first dose of Pevonedistat.

Adverse Drug Reactions

All the events included in this section are considered expected for the purpose of regulatory reporting and must remain unchanged throughout the DSUR reporting period.

Cardiac disorders:

- Increased heart rate

Gastrointestinal disorders:

- Diarrhea
- Nausea
- Vomiting

General disorders and administration site conditions:

- Pyrexia

Investigations:

- Liver function test abnormal

Musculoskeletal and connective tissue disorders:

- Musculoskeletal pain/myalgia

Warnings and Precautions

Acetaminophen:

For patients in the dose-escalation phase of a clinical study, agents such as acetaminophen and acetaminophen-containing products should not be administered 24 hours before, on the day of, and 24 hours after dosing with Pevonedistat. For patients not in dose escalation, agents such as acetaminophen and acetaminophen-containing compounds may be used judiciously and should not exceed a dose of 2 g of acetaminophen in a 24-hour period.

Statins:

Use of statins had been restricted to hold dosing on the day before, day of, and day after administration of Pevonedistat. Because this restriction on statins was instituted, further analyses have been performed supporting the lifting of this restriction.

Hepatotoxicity:

Hepatotoxicity has been noted following administration of Pevonedistat in patients with advanced malignancy, including elevations of liver transaminases, ALP, and bilirubin.

Grade 1, 2, and 3 increases in ALT and AST have been observed in patients receiving the 50-mg/ m² dose on Days 1, 3, and 5 in Schedule E of Study C15003. The patients experiencing these changes in laboratory values have been asymptomatic. This type of elevation in transaminases had been observed previously in patients treated with Pevonedistat. The elevations in laboratory values have been reversible with dose modification including dose delay and reduction. Patients with elevated transaminases have been successfully re-challenged at lower doses.

Guidance for Clinical Assessment and Management of Hemodynamic Compromise

Patients must be carefully evaluated at screening and before each Pevonedistat dose for early symptoms and signs of hemodynamic compromise and active infection. Particular attention should be paid to unexplained fever, tachycardia, hypotension, orthostasis, tachypnea, recent nausea and vomiting, and clinical evidence of dehydration. For those patients for whom there is a concern of dehydration, the following guidance for rehydration before Pevonedistat dosing may be considered: 500 mL/hour of 0.5 N saline given over 2 to 4 hours for a total of 1 to 2 L of fluid as clinically appropriate. For all patients with anemia, and especially for patients with hemoglobin values < 8 g/dL at screening or during the conduct of the study, RBC transfusions should be considered before Pevonedistat dosing based on the patient's risk of inadequate oxygenation, underlying cardiopulmonary status, clinical judgment, and/or hospital guidelines. Patients who experience signs and symptoms of hemodynamic compromise after Pevonedistat dosing (e.g., tachycardia, hypotension, orthostasis, and changes in mental status, syncope, and dizziness) should be followed closely and managed with supportive care, including hospitalization as clinically indicated.

Guidance for Management of Leukostasis

Pevonedistat treatment should be withheld for patients who develop symptoms of leukostasis. Treatment may include leukapheresis and hydroxyurea administration, per institutional guidelines. When the WBC of the patient is <50,000/ μ L and symptoms are improved, Pevonedistat treatment may be restarted after consulting with the sponsor investigator (or designee).

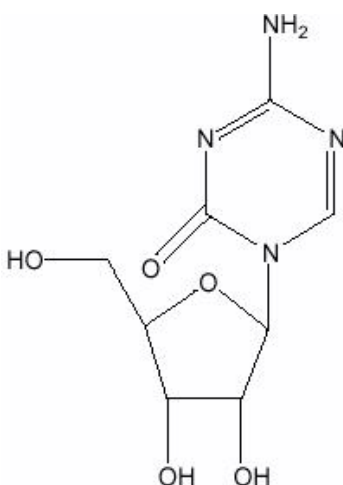
Guidance for Management of Extravasation

Based on nonclinical findings as detailed in the IB, Pevonedistat is considered a non-vesicant drug. Although no published guidelines are available for extravasation of non-vesicants, the investigator is encouraged to follow institutional guidelines. Some general advice in case of extravasation includes immediately stopping drug infusion and elevating the affected limb to minimize swelling.

7.14.2. Azacitidine (Vidaza)

Chemical Characteristics

Azacitidine for injectable suspension contains Azacitidine, which is a pyrimidine nucleoside analog of cytidine. Azacitidine is 4-amino-1- β -D-ribofuranosyl-s-triazin-2(1*H*)-one. The structural formula is as follows:



The empirical formula is C₈ H₁₂ N₄ O₅. The molecular weight is 244. Azacitidine is a white to off-white solid. Azacitidine was found to be insoluble in acetone, ethanol, and methyl ethyl ketone; slightly soluble in ethanol/water (50/50), propylene glycol, and polyethylene glycol; sparingly soluble in water, water saturated octanol, 5% dextrose in water, N-methyl-2-pyrrolidone, normal saline and 5% Tween 80 in water; and soluble in dimethyl sulfoxide (DMSO).

Available Forms

Azacitidine for injection is commercially available as Vidaza and is supplied as Lyophilized powder in 100 mg single-use vials.

The product is supplied in a sterile form for reconstitution as a suspension for subcutaneous injection or reconstitution as a solution with further dilution for intravenous infusion. Vials of contain 100 mg of Azacitidine and 100 mg mannitol as a sterile lyophilized powder.

Storage and Handling

Azacitidine for injection is commercially available and will be prescribed for this trial. Store un-reconstituted vials at 25° C (77° F); excursions permitted to 15°-30° C.

Procedures for proper handling and disposal of anticancer drugs should be applied. Several guidelines on this subject have been published³⁰⁻³². There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Reconstitute the appropriate number of vials to achieve the desired dose. Reconstitute each vial with 10 mL sterile water for injection. Vigorously shake or roll the vial until all solids are dissolved. The resulting solution will contain Azacitidine 10 mg/mL. The solution should be clear. Parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Withdraw the required amount of Vidaza solution to deliver the desired dose and inject into a 50 -100 mL infusion bag of either 0.9% Sodium Chloride Injection or Lactated Ringer's Injection.

Toxicity

Anemia, Neutropenia and Thrombocytopenia

Vidaza causes anemia, neutropenia and thrombocytopenia. Monitor complete blood counts frequently for response and/or toxicity, at a minimum, prior to each dosing cycle. After administration of the recommended dosage for the first cycle, adjust dosage for subsequent cycles based on nadir counts and hematologic response

Vidaza Toxicity in Patients with Severe Pre-existing Hepatic Impairment

Because Azacitidine is potentially hepatotoxic in patients with severe pre-existing hepatic impairment, caution is needed in patients with liver disease. Patients with extensive tumor burden due to metastatic disease have been reported to experience progressive hepatic coma and death during Azacitidine treatment, especially in such patients with baseline albumin <30 g/L. Azacitidine is contraindicated in patients with advanced malignant hepatic tumors.

Renal Toxicity

Patients with renal impairment may be at increased risk for renal toxicity. Also, Azacitidine and its metabolites are primarily excreted by the kidney. Therefore, these patients should be closely monitored for toxicity.

Renal toxicity ranging from elevated serum creatinine to renal failure and death have been reported in patients treated with intravenous Azacitidine in combination with other chemotherapeutic agents for non-MDS conditions. In addition, renal tubular acidosis, defined as a fall in serum bicarbonate to <20 mEq/L in association with an alkaline urine and hypokalemia (serum potassium <3 mEq/L) developed in 5 patients with CML treated with Azacitidine and etoposide. If unexplained reductions in serum bicarbonate <20 mEq/L or elevations of BUN or serum creatinine occur, the dosage should be reduced or held.

Most Commonly Occurring Adverse Reactions (SC or IV Route): nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, injection site erythema, constipation, neutropenia, ecchymosis. The most common adverse reactions by IV route also included petechiae, rigors, weakness and hypokalemia.

Administration

Azacitidine solution is administered intravenously. Administer the total dose over a period of 10 minutes. The administration must be completed within 1 hour of reconstitution of the Azacitidine vial. Azacitidine reconstituted for intravenous administration may be stored at 25°C (77°F), but administration must be completed within 1 hour of reconstitution.

Incompatibilities

Azacitidine is incompatible with 5% Dextrose solutions, Hespan, or solutions that contain bicarbonate. These solutions have the potential to increase the rate of degradation of Azacitidine and should therefore be avoided.

Drug-Drug Interactions

No formal clinical drug interaction studies with Azacitidine have been conducted.

An *in vitro* study of Azacitidine incubation in human liver fractions indicated that Azacitidine may be metabolized by the liver. Whether Azacitidine metabolism may be affected by known microsomal enzyme inhibitors or inducers has not been studied. An *in vitro* study with cultured human hepatocytes indicated that Azacitidine at concentrations up to 100 µM (IV C_{max} = 10.6 µM) does not cause any inhibition of CYP2B6 and CYP2C8. The potential of Azacitidine to inhibit other cytochrome P450 (CYP) enzymes is not known. *In vitro* studies with human cultured hepatocytes indicate that Azacitidine at concentrations of 1.0 µM to 100 µM does not induce CYP 1A2, 2C19, or 3A4/5.

7.15. Method for Assigning Subject to Treatment Groups

N/A

7.16. Subject Compliance Monitoring

Subjects will be followed at BMT clinic regularly and compliance will be monitored as a standard procedure after allogeneic stem cell transplant.

7.17. Blinding of the Test Article

N/A

7.18. Receiving, Storage, Dispensing and Return

7.18.1. Receipt of Test Article

Pevonedistat will be distributed by Takeda to Investigational Drug Pharmacy Service. (IDS) of PSCI.

Commercial supply will be used for azacitidine.

7.18.2. Storage

MLN4924-003 Injection Drug Product vials should be stored refrigerated at 2°C to 8°C.

Before use, MLN4924-003 Injection Drug Product vials should be brought to ambient conditions (15°C-30°C) by removing the vials from the refrigerator and placing them at room temperature. Accelerated warming methods such as a water bath must not be used.

7.18.3. Preparation and Dispensing

Pevonedistat is a cytotoxic anticancer drug, and as with the other potentially toxic compounds, caution should be exercised when handling Pevonedistat.

The specified number of Injection Drug Product vials should be removed and allowed to equilibrate to room temperature prior to dilution. The vial must not be shaken at any time during dose preparation.

Using aseptic technique, the appropriate volume of drug should be withdrawn from vials(s), then injected into a 250-mL IV bag containing 5% dextrose solution, and then gently inverted repeatedly to mix. The Pevonedistat prepared IV bag must be used within 6 hours (time to the end of an injection) if stored at ambient temperature. Alternatively, the prepared IV bag is chemically stable and may be stored for up to 18 hours at 2°C to 8°C. After 18 hours of storage at 2°C to 8°C, the prepared IV bag must be used within 3 hours (time to the end of an injection) upon coming to ambient temperature. Discard bag, needle and syringe in a proper biohazard container according to institutional guidelines.

7.18.4. Return or Destruction of the Test Article

Pevonedistat will be returned to Takeda after the study, or appropriately destroyed according to the manufacturer's direction.

7.19. Required Observations

Required observations will be monitored as follows:

7.19.1. Pre-Transplant / Study Registration:

Pre-Transplant required observations (performed within 35 days prior to study registration and/or day of final evaluation before transplant).

1. History and physical exam (including Vital Signs (VS) and Karnofsky Performance Status (KPS) score).
2. CBC with differential (diff), Complete Metabolic Panel (CMP) with LDH, Magnesium, Phosphate, Uric Acid and Direct Bilirubin.
3. Echocardiogram or MUGA.
4. 12 lead ECG.
5. Unilateral bone marrow aspirate and biopsy (morphology, and cytogenetics) performed within 2 weeks before study registration to confirm non-remission AML.
6. Urinalysis with microscopic analysis
7. Coagulation including PT, PTT, INR
8. Serum pregnancy test for women with childbearing potential.

CMP includes: Na, K, Bicarbonate (HCO₃), BUN, Creatinine, Glucose, Calcium, ALT, AST, Alkaline Phosphatase, Total Bilirubin, Albumin, and Total Protein.

7.19.2. Post-Transplant / Day +30:

1. History and physical exam (including VS and KPS score).
2. CBC with diff, CMP with LDH, Magnesium, Phosphate, Uric Acid, and Direct Bilirubin.
3. Unilateral bone marrow aspirate and biopsy (morphology, and cytogenetics) at day 30 (± 7) post-transplant.

7.19.3. Study Treatment Initiation:

Study treatment will be initiated between day +30 and day +45 post-transplant, after bone marrow aspiration/biopsy morphology result is obtained.

7.19.4 During Study Treatment:

1. History and physical exam (including VS and KPS score) on each day when Pevonedistat is given
2. CBC with diff, CMP with LDH, Magnesium, Phosphate, Uric Acid, and Direct Bilirubin., on each day when Pevonedistat is given and weekly during the Treatment Cycles (days 1, 3, 5, 8, 15 and 22.). The bilirubin assessment must be performed and read prior to dosing Pevonedistat.
3. On each cycle, the results of assessment on Day 1 will be used to meet the criteria 3.3.
4. Tumor Lysis Labs (CMP, LDH, Phosphate, Uric Acid) will be drawn every 8 hours during the first cycle of Pevonedistat treatment if the disease is not in remission at the time of initiation of Pevonedistat. In this case the patient will be admitted to the hospital and allopurinol will be given. Tumor Lysis Labs will be stopped when the risk of tumor lysis is determined minimal.
5. Urinalysis with microscopic analysis and Coagulation (including PT and aPTT) on day 1 of each cycle.
6. 12-lead ECG on day 1 of each cycle
7. Serum Pregnancy Test at day 1 of each cycle for women with childbearing potential.

7.19.5. At Study Treatment Completion Visit (Day 42-56 after day 1 of the last cycle)

1. History and physical exam (including VS and KPS score).
2. CBC with diff, CMP with LDH, Magnesium, Phosphate.
3. Unilateral bone marrow aspirate and biopsy (morphology, and cytogenetics) ± 15 days of the study completion visit.
4. Urinalysis with microscopic analysis and Coagulation (including PT and aPTT)
5. 12-lead ECG

7.19.6. Yearly visits after stem cell transplant (± 1 month of 1 to 5 years after transplant)

Yearly visits are based on transplant date, not study initiation date.

1. History and physical exam (including VS and KPS score).
2. CBC with diff, CMP with LDH, Magnesium, Phosphate.
3. Unilateral bone marrow aspirate and biopsy (morphology, and cytogenetics) 1 month of the 1-year post transplant yearly visit.

7.19.7. Post study-treatment required observations and follow-up plans

Recommended follow-up is once a week until day 100, once in 2 weeks to once a month until day 365, then once a month to once in 2-6 months until year 3, then at least once a year until year 5. The patient who progressed on this protocol will be followed only for survival.

Regimen-related toxicity (RRT) will be recorded using the definition of CTCAE version 5. Acute and chronic GVHD will be recorded using the standard criteria (Appendix C, D)³⁹. Overall and disease-free survival will be analyzed using the method of Kaplan and Meier. One-year, two-year and five-year overall and disease-free survival will be examined. Cumulative incidence of relapse will be calculated.

8.0. Subject Numbers and Statistical Plan

8.1. Simon's two stage design

The primary endpoint is one year overall survival rate. The one-year survival rate for the historic control of in this population is 10% and is assumed to be 34% for this treatment. We shall use Simon's (Simon 1989) two-stage design so that a quick termination can be made if the new treatment does not outperform historical control. The main outcome of one year survival, however, requires to wait potentially for one full year for a patient. To speed up the trial, for the conduct of this trial, we shall use the half-year survival rate as the primary outcome (Note, however, all patients will be followed for at least one year when the trial is complete so that the one year-survival probability can be estimated). For this purpose, we assume that the half-year survival rate is 33% for the historic control and 60% for the new treatment. The Simon's two stage design based on $H_0: P_0=0.33$ and $H_1: P_1=0.60$ is then

Stopping Rules:

Stage 1:

Enroll 20 subjects. Stop and accept the null hypothesis if the survival rate is less than or equal to 7/20. Otherwise, continue to stage 2.

Stage 2:

Enroll 10 additional subjects. Accept the null hypothesis if the survival rate is less than or equal to 14/30. Otherwise, reject the null hypothesis.

8.2. Statistical Analysis plan:

The primary decision rules for the effectiveness of the new treatment are the two-stage rule described above.

For time-to-event variables such as overall survival and progression free survival, the Kaplan-Meier plots will be provided to describe the complete survival process. One year survival rate and cumulative incidence at 2 years will be estimated with 95% confidence intervals. Summaries of the number and percentage of patients survived at different time points along with median OS will be presented. These survival curves will be compared to that of the historic controls.

All patients who receive treatment in this study will be included in the ongoing safety analysis. Descriptive statistics will be used to summarize the safety and efficacy variables collected and the baseline demographic data. Continuous variables will be summarized using mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized using frequency counts and percentages and corresponding exact 95% confidence intervals will be estimated for the secondary endpoints. The detailed tabulation of adverse events will be provided and reported for safety monitoring.

10.0. Confidentiality, Privacy and Data Management

See the Research Data Plan Review Form

10.0. DATA REPORTING / REGULATORY REQUIREMENTS

10.1. Confidentiality of Records:

The original data collection forms will be stored in secured cabinets at the originating institution. Institutional policy and guidance on requirements for managing clinical research data will be followed, including the appropriate levels of safeguard to ensure the confidentiality, integrity and availability of clinical research data.

10.2. Patient Consent Form:

Prior to commencement of any screening activities, written, signed and dated patient consent must be obtained. A copy of the signed and dated consent form must be provided to the patient. The original signed consent form and additional copies must be maintained per institutional standards (i.e., with research records, medical chart).

10.3. Registration Eligibility Worksheet:

At the time of registration, the information requested on the On-Study/Eligibility Form will be completed. Confirmation of eligibility will be confirmed by the investigator's signature on the completed worksheet. The investigator is responsible for enrolling only those patients who have met protocol eligibility criteria.

10.4. Data Collection Forms and Submission Schedule:

Direct data entry into to the Penn State Cancer Institute OnCore CTMS will be utilized for this study. Electronic data capture will occur via electronic case report forms in OnCore®. OnCore® (On-line Clinical Oncology Research Environment) is the primary data management system for clinical trials activity at PSCI.

OnCore® was developed by Forte, Inc., and is a highly secure, web-based, customizable system that provides fully integrated clinical data management and protocol management capabilities. OnCore® houses regulatory tracking information, study management activity and clinical data. Data entry requirements are as follows:

Event	Data Entry Timeline
Subject registration	48 hours
On-study form completion	Within 2 weeks of subject on study
Each course of treatment, all required forms completion (includes response evaluation, where applicable)	Within 2 weeks of course completion
Follow-up per protocol	Within 2 weeks of follow-up time point

The data to be transcribed and entered into the study database will include but is not limited to demographics, medical history, concomitant medications, safety data, and those data needed to answer the study objectives. Eligibility assessment will be coded as met or not met with reasons rather than including each criterion related data. The assessments and interventions noted in the Table of Interventions and Assessments (Appendix C) e.g. data related to dates and results of physical examinations, vital signs, performance status, laboratory results (CBC, Chemistry, etc.), etc will not be entered into the database. However, any abnormal results of the assessments will be captured as an AE according to the criteria noted in Section 18.0. For those who consent but are not eligible (screen failure) only data related to failure reason and demography will be captured.

10.5. Site Monitoring:

To ensure compliance with current federal regulations and the ICH guidelines, data generated by this study must be available for inspection upon request by representatives of the FDA, national and local health authorities, the Sponsor-Investigator and duly authorized representative of any entity providing support for this trial. Routine monitoring or audit activities for this study will be conducted by representatives of the PSCI Clinical Trials Office. The general scope of such visits would be to inspect study data (regulatory requirements), source documentation and CRF completion in accordance with current FDA Good Clinical Practices (GCP), the ICH guidelines and the respective local and national government regulations and guidelines.

10.6. Institutional Review Board Approval:

This protocol, the informed consent document, relevant supporting information and all types of patient recruitment and advertisement information must be submitted to the local IRB for review and must be approved before the study is initiated. An amendment to remove a life-threatening situation can be implemented by the Investigator prior to obtaining IRB approval by the site. In such situations, the IRB must be notified immediately and the amendment forwarded to the IRB for their consideration.

The investigator is responsible for keeping their local IRB informed of the progress with study renewal at least once a year. The investigator must also keep the local IRB informed of any significant adverse events, per local institutional guidelines. Adverse event reporting guidelines can be found in Section 18.0, Reporting Adverse Events.

10.7. Records Retention:

FDA regulations (21 CFR 312.62) require clinical investigators to retain all study-related documentation, including source document and CRFs, long enough to allow the sponsor to use the data to support marketing applications. If this study is conducted under an IND, all records must be maintained for:

- Two years after the FDA approved the marketing application, or
- Two years after the FDA disapproves the application for the indicating being studied, or
- Two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

For all studies, including studies with FDA-IND exemption, the Investigator/Institution/Sponsor will take measures to prevent accidental or premature destruction of study documents. For such studies conducted under IND exemption, records will be retained for a minimum of seven (7) years past official study termination.

10.8. Data Safety Monitoring Plan

The Penn State Hershey Cancer Institute Data and Safety Monitoring Committee (PSCI DSMC) will serve as the internal DSMC for data and safety review for this protocol. The principal investigator (PI) will continuously monitor study progress for safety and will hold routine meetings with the study team and disease center personnel to review overall conduct and progress of this study. The frequency of such meetings will be dependent upon accrual to the trial and issues that arise. Study team and disease team meetings will include discussion of accrual, adverse events/safety issues, response and overall progress of the trial.

On an annual basis, the PI will provide the PSCI DSMC with reports showing the number of subjects enrolled, SAE assessments, information on any protocol deviations or breaches of confidentiality, response if appropriate, and overall status of the trial. The PSCI DSMC meets quarterly as well as on an ad hoc basis. The investigator will be asked for a report for the DSMC sufficiently in advance of annual IRB renewal in order to include DSMC findings with annual IRB submission. Adverse event reporting to the IRB will occur in compliance with IRB guidelines. A summary of all adverse events will be reported to the IRB annually; unexpected adverse events will be reported as they arise as well as any significant literature reporting developments that may affect the safety of participants in this study. Serious and unexpected adverse events will be reported to PSCI DMSC simultaneously with the IRB reporting.

11.0 Risks

There are additional risks related to study treatment Pevonedistat and Azacitidine, in addition to the risks associated with standard allogeneic stem cell transplantation.

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

There may not be any direct benefits to the subjects.

12.2 Potential Benefits to Others

Future patients may benefit from the knowledge obtained through this study.

13.0 Sharing Results with Subjects

The results will not be shared with subjects or others.

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

N/A

15.0 Economic Burden to Subjects

15.1 Costs

There will be no additional costs for this research.

15.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

16.0 Resources Available

16.1 Facilities and locations

The research will be conducted in the inpatient and outpatient unit of Penn State Cancer Institute.

16.2 Feasibility of recruiting the required number of subjects

We have about 2 cases/months of patients who may qualify for this protocol, including the relapse/2nd transplant cases. Most of these patients will be enrolled into this study.

16.3 PI Time devoted to conducting the research

Five % of PI time will be devoted to this protocol.

16.4 Availability of medical or psychological resources

All medical and psychological consulting services are available. PSU Blood and Marrow Transplant Program is accredited with FACT (Foundation for the Accreditation of Cell Therapy) which requires all the consultation resources are available.

16.5 Process for informing Study Team

We will have a Site Initiation Meeting and also will have repeated lectures in Science Meetings of hematology/BMT Program.

17.0. Other Approvals

17.1. Other Approvals from External Entities

N/A

17.2. Internal PSU Committee Approvals**Check all that apply:**

☐ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of HRP-902 - Human Tissue For Research Form on the “Supporting Documents” page in CATS IRB. This form is available in the CATS IRB Library.

☐ Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – Hershey only – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes, but are no longer needed for clinical use. Upload a copy of HRP-901 - Human Body Fluids for Research Form on the “Supporting Documents” page in CATS IRB. This form is available in the CATS IRB Library.

☐ Clinical Research Center (CRC) Advisory Committee– All campuses – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of HRP-903 - Radiation Review Form on the “Supporting Documents” page in CATS IRB. This form is available in the CATS IRB Library.

X IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

X Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at:

<http://www.pennstatehershey.org/web/irb/home/resources/investigator>

18.0. Adverse Event Reporting

Adverse events occurring following study registration, but prior to beginning study agent therapy will not be reported. Protocol related therapy does not begin until patients receive their first dose of study agent.

18.1. Definition of Adverse events

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a medicinal product; the untoward medical occurrence does not necessarily have a causal relationship

with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

Reporting requirements may include the following considerations:

1. The characteristics of the adverse event including the grade (severity);
2. The relationship to the study therapy (attribution); and
3. The prior experience (expectedness) of the adverse event.

Expected events are those that have been previously identified as resulting from administration of the agent. For commercially available agents, an adverse event is considered unexpected, for reporting purposes only, when either the type of event or the severity of the event is not listed in the current NCI Agent-Specific Adverse Event List located in the drug package insert. Except where otherwise specified, Common Terminology Criteria for Adverse Events (CTCAE) v.5 will be used to grade adverse events in this study.

18.2. Required Adverse Events Reporting

Therapy for hematological malignancies, with or without stem cell transplantation, is associated with significant toxicity. These toxicities are generally viewed as an anticipated consequence of therapy rather than an adverse event. To summarize, adverse events with severity grades 1, 2 will not be reported to the IRB, as they are expected in patients undergoing stem cell transplantation for hematological malignancies. Only grade 3, 4 toxicity events with a possible, probable or definite relation to the study drug and all grade 5 events will be reported to IRB.

18.3. Serious Adverse Event Reporting Procedures

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death**.
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see [clarification](#) in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein

transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described above, and are usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm³ to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

All serious adverse events (SAE) which require reporting must be reported immediately (i.e. within 24 hours of awareness) to the Principal Investigator of the Coordinating Center or designee, followed by written documentation to each IRB from the Principal Investigator (including the PI's or designee's medical summary of the SAE) within 4 days of the Investigator's knowledge of occurrence to the Penn State Cancer Institute CTO. The staff of the PSCI CTO will coordinate the reporting process between the investigators, PIs and each IRB as well as other applicable reporting agencies (such as FDA), including the reporting of SAEs on a MEDWATCH 3500A form to FDA. Copies of all correspondence and reporting documents will be maintained in a regulatory file held by the PSCI CTO. Institution and Investigator understand and agree that Investigator and Institution are obligated under applicable law and regulations to report any serious and related adverse event, if any, which occurs during treatment with Pevonedistat and Azacitidine to the Institution's IRB/Ethics Committee and to the governing regulatory authority in accordance with applicable filing timelines promptly after any such event occurs.

18.4. Procedures for Reporting Serious Adverse Events to Supporting Company (Millennium/Takeda)

Adverse Events may be spontaneously identified by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Adverse Events which are **serious** must be reported to Millennium Pharmacovigilance (or designee) from the first dose of Pevonedistat up to and including 30 days after administration of the last dose of Pevonedistat. Any SAE that occurs at any time after completion of Pevonedistat treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Millennium Pharmacovigilance (or designee). Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness (es).

Since this is an investigator-initiated study, the principal investigator Dr. Shin Mineishi also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's EC or IRB.

Regardless of expectedness or causality, all SAEs must also be reported in English to Millennium Pharmacovigilance or designee:

Fatal and Life Threatening SAEs within 24 hours of the sponsor-investigator's observation or awareness of the event

All other serious (non-fatal/non life threatening) events within 4 calendar days of the sponsor-investigator's observation or awareness of the event

The SAE report must include at minimum:

- Event term(s)
- Serious criteria
- Intensity of the event(s): Sponsor-investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version specified in the protocol, as a guideline, whenever possible. The criteria are available online at <http://ctep.cancer.gov/reporting/ctc.html>.
- Causality of the event(s): Sponsor-investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration.

Follow-up information on the SAE may be requested by Millennium Pharmacovigilance (or designee).

In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Millennium Pharmacovigilance (or designee) from all sites participating in the study. Sub-investigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to the required regulatory agencies and to Millennium Pharmacovigilance, unless otherwise agreed between the sponsor-investigator and sub-investigator(s).

Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

US and Canada

Toll-Free Fax #: 1-800-963-6290

E-mail: takedaoncocases@cognizant.com

All other countries (Rest of World)

Fax #: 1 202 315 3560

E-mail: takedaoncocases@cognizant.com

Suggested Reporting Form:

- US FDA MedWatch 3500A:
<http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm>
- Any other form deemed appropriate by the sponsor-investigator

Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must fax a completed Pregnancy Form to the Millennium Pharmacovigilance or designee immediately.

The pregnancy must be followed for the final pregnancy outcome (i.e., delivery, still birth, miscarriage) and Millennium Pharmacovigilance or designee will request this information from the sponsor-investigator.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to the Millennium Pharmacovigilance or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

18.5. ADMINISTRATIVE REQUIREMENTS

18.5.1. Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact Millennium (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

For Product Complaints, call

Phone 1-844-ONC-TKDA (1-844-662-8532)

Email: GlobalOncologyMedinfo@takeda.com

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Millennium Pharmacovigilance.

18.6 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

18.6.1 Written IND/IDE Safety Reports

Initial reporting: IND application sponsor must report any suspected adverse reaction or adverse reaction to study treatment that is both serious and unexpected.

Unexpected serious suspected adverse reactions and observations from animal studies suggesting significant risk to human subjects must be reported to FDA as soon as possible but no later than within 15 calendar days following the sponsor's initial receipt of the information.

Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported to FDA as soon as possible but no later than 7 calendar days following the sponsor's initial receipt of the information.

•Follow-up reporting: Any relevant additional information obtained by the sponsor that pertains to a previously submitted IND safety report must be submitted as a Follow-up IND Safety Report. Such report should be submitted without delay, as soon as the information is available but no later than 15 calendar days after the sponsor receives the information.

All IND safety reports must be submitted on Form 3500A and be accompanied by Form 1571. The type of report (initial or follow-up) should be checked in the respective boxes on Forms 3500A and 1571.

The submission must be identified as:

- “IND safety report” for 15-day reports, or
- “7-day IND safety report” for unexpected fatal or life-threatening suspected adverse reaction reports, or
- “Follow-up IND safety report” for follow-up information.

18.6.2 Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions

In addition to the subsequent submission of a written IND Safety Report, the sponsor shall notify the FDA by telephone or by facsimile transmission of any human adverse event that is (i) Associated with the use of the drug; (ii) Unexpected; and (iii) Fatal or Life-threatening.

18.7 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

18.8 Unblinding Procedures

N/A

18.9 Stopping Rules

Stopping rule is incorporated in the Simon’s two-step design (Section 8.1).

19.0 Study Monitoring, Auditing and Inspecting

Quality Assurance and Quality Control

The study will be monitored by the Clinical Trial Monitoring Team from the Department of Public Health Sciences at Penn State Hershey College of Medicine. The monitors will provide an independent review of the regulatory and subject records and the data collected to assure compliance with the protocol, GCP, and applicable federal regulations. The monitoring will occur at regular intervals after the enrollment of the first subject and the times will be predetermined by the monitoring plan developed by the Clinical Trial Monitoring Team.

Research Quality Assurance (RQA) office will conduct post-approval monitoring after the first and 3rd subjects are enrolled. PI will notify RQA at that time.

20.0. Future Undetermined Research: Data and Specimen Banking

N/A

21.0. References

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APPENDIX A

Prohibited Medications

Inducers of CYP3A

Strong Inducers
(≥80% decrease in AUC)

Carbamazepine
Phenytoin
Phenobarbital
Primidone
Rifabutin
Rifampin
Rifapentine
St. John's wort

Abbreviations: AUC=area under the plasma concentration versus time curve; CYP=cytochrome P450.

Please refer to the following sources for additional information: <http://medicine.iupui.edu/clinpharm/ddis/main-table/> and <http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/%20druginteractionslabeling/ucm093664.htm>

1. Corticosteroids may be administered as required for the treatment of GVHD or for other clinical concerns

APPENDIX B**Karnofsky performance status scale****KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA**

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Appendix C Acute GVHD

GVHD Staging			
Stage	Skin	Liver (total bilirubin)	GI tract (diarrhea output/day)
0	No GVHD rash	<2 mg/dl	Adult: <500 ml/d *Child: <10 ml/kg/d
1	Maculopapular rash <25% body surface area	2-3 mg/dl	Adult: 500-999 ml/d Child: 10-19.9 ml/kg/d -or- persistent nausea, vomiting, or anorexia with a positive upper GI biopsy
2	Maculopapular rash 25-50% BSA	3.1-6 mg/d	Adult: 1000-1500ml/d Child: 20-30 ml/kg/d
3	Maculopapular rash >50% BSA	6.1-15 mg/dl	Adult: >1500ml/d Child: >30 ml/kg/d
4	Generalized erythroderma (>50% BSA) plus bullous formation or desquamation >5% BSA	>15 mg/dl	Severe abdominal pain with or without ileus, or grossly bloody diarrhea
*Use adult values for patients ≥ 50 kg			
Overall Clinical Grade:			
Grade 0: No GVHD of any organ			
Grade 1: Stage 1-2 skin and no liver OR GI tract involvement			
Grade2: Stage 3 skin and/or stage 1 liver and/or stage 1 GI tract			
Grade 3: Stage 0-3 skin with stage 2-3 liver and/or stage 2-3 GI tract			
Grade 4: Stage 4 skin, liver, and/or GI tract			

Acute GVHD will be described as follows:

“Skin 2, Liver 0, Gut 1, Overall Grade 2”

Appendix D Chronic GVHD (From Reference 39)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: <div style="border: 1px solid black; width: 50px; height: 20px; margin: 5px 0;"></div> KPS ECOG LPS	<input type="checkbox"/> Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	<input type="checkbox"/> Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	<input type="checkbox"/> Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	<input type="checkbox"/> Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† <div style="border: 1px solid black; width: 50px; height: 20px; margin: 5px 0;"></div>				
SCORE % BSA <u>GVHD features to be scored by BSA:</u> Check all that apply:	<input type="checkbox"/> No BSA involved	<input type="checkbox"/> 1-18% BSA	<input type="checkbox"/> 19-50% BSA	<input type="checkbox"/> >50% BSA
<input type="checkbox"/> Maculopapular rash/erythema <input type="checkbox"/> Lichen planus-like features <input type="checkbox"/> Sclerotic features <input type="checkbox"/> Papulosquamous lesions or ichthyosis <input type="checkbox"/> Keratosis pilaris-like GVHD				
SKIN FEATURES SCORE:	<input type="checkbox"/> No sclerotic features	<input type="checkbox"/> Superficial sclerotic features "not hidebound" (able to pinch)		Check all that apply: <input type="checkbox"/> Deep sclerotic features <input type="checkbox"/> "Hidebound" (unable to pinch) <input type="checkbox"/> Impaired mobility <input type="checkbox"/> Ulceration
<u>Other skin GVHD features (NOT scored by BSA)</u> Check all that apply:				
<input type="checkbox"/> Hyperpigmentation <input type="checkbox"/> Hypopigmentation <input type="checkbox"/> Poikiloderma <input type="checkbox"/> Severe or generalized pruritus <input type="checkbox"/> Hair involvement <input type="checkbox"/> Nail involvement <input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				
MOUTH <u>Lichen planus-like features present:</u>	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Mild symptoms with disease signs but not limiting oral intake significantly	<input type="checkbox"/> Moderate symptoms with disease signs with partial limitation of oral intake	<input type="checkbox"/> Severe symptoms with disease signs on examination with major limitation of oral intake
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	<input type="checkbox"/> Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), WITHOUT new vision impairment due to KCS	<input type="checkbox"/> Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) OR unable to work because of ocular symptoms OR loss of vision due to KCS
<i>Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:</i>				
<input type="checkbox"/> Yes				
<input type="checkbox"/> No				
<input type="checkbox"/> Not examined				

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):

GI Tract	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Symptoms without significant weight loss* ($<5\%$)	<input type="checkbox"/> Symptoms associated with mild to moderate weight loss* (5-15%) OR moderate diarrhea without significant interference with daily living	<input type="checkbox"/> Symptoms associated with significant weight loss* $>15\%$, requires nutritional supplement for most calorie needs OR esophageal dilation OR severe diarrhea with significant interference with daily living
Check all that apply:				
<input type="checkbox"/> Esophageal web/proximal stricture or ring				
<input type="checkbox"/> Dysphagia				
<input type="checkbox"/> Anorexia				
<input type="checkbox"/> Nausea				
<input type="checkbox"/> Vomiting				
<input type="checkbox"/> Diarrhea				
<input type="checkbox"/> Weight loss $\geq 5\%*$				
<input type="checkbox"/> Failure to thrive				
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify):				

LIVER	<input type="checkbox"/> Normal total bilirubin and ALT or AP < 3 x ULN	<input type="checkbox"/> Normal total bilirubin with ALT ≥ 3 to 5 x ULN or AP ≥ 3 x ULN	<input type="checkbox"/> Elevated total bilirubin but ≤ 3 mg/dL or ALT > 5 ULN	<input type="checkbox"/> Elevated total bilirubin > 3 mg/dL
--------------	---	---	---	---

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):

LUNGS**				
Symptom score:	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Mild symptoms (shortness of breath after climbing one flight of steps)	<input type="checkbox"/> Moderate symptoms (shortness of breath after walking on flat ground)	<input type="checkbox"/> Severe symptoms (shortness of breath at rest; requiring O_2)

Lung score:	<input type="checkbox"/> FEV1 $\geq 80\%$	<input type="checkbox"/> FEV1 60-79%	<input type="checkbox"/> FEV1 40-59%	<input type="checkbox"/> FEV1 $\leq 39\%$
% FEV1 <input type="text"/>				

Pulmonary function tests

☐ Not performed

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score <i>(see below)</i> Shoulder (1-7): ____ Elbow (1-7): ____ Wrist/finger (1-7): ____ Ankle (1-4): ____	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	<input type="checkbox"/> Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL	<input type="checkbox"/> Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				
GENITAL TRACT <i>(See Supplemental figure[†])</i> <input type="checkbox"/> Not examined Currently sexually active <input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> No signs	<input type="checkbox"/> Mild signs [†] and females with or without discomfort on exam	<input type="checkbox"/> Moderate signs [†] and may have symptoms with discomfort on exam	<input type="checkbox"/> Severe signs [†] with or without symptoms
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				
Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0, mild -1, moderate -2, severe – 3)				
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 50%;"> <input type="checkbox"/> Ascites (serositis) ____ </div> <div style="width: 50%;"> <input type="checkbox"/> Myasthenia Gravis ____ </div> <div style="width: 50%;"> <input type="checkbox"/> Pericardial Effusion ____ </div> <div style="width: 50%;"> <input type="checkbox"/> Peripheral Neuropathy ____ </div> <div style="width: 50%;"> <input type="checkbox"/> Eosinophilia > 500/μl ____ </div> <div style="width: 50%;"> <input type="checkbox"/> Pleural Effusion(s) ____ </div> <div style="width: 50%;"> <input type="checkbox"/> Polymyositis ____ </div> <div style="width: 50%;"> <input type="checkbox"/> Platelets <100,000/μl ____ </div> <div style="width: 50%;"> <input type="checkbox"/> Nephrotic syndrome </div> <div style="width: 50%;"> <input type="checkbox"/> Weight loss>5%* without GI symptoms </div> <div style="width: 50%;"> <input type="checkbox"/> Others (specify): _____ </div> </div>				
Overall GVHD Severity <i>(Opinion of the evaluator)</i> <div style="display: flex; justify-content: space-around; margin-top: 5px;"> <input type="checkbox"/> No GVHD <input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe </div>				
Photographic Range of Motion (P-ROM) <div style="display: flex; align-items: flex-start; margin-top: 10px;"> <div style="margin-right: 10px;"> Shoulder Elbow Wrist/finger Ankle </div> <div> </div> </div>				

Table 2

NIH Global Severity of chronic GVHD

Mild chronic GVHD

1 or 2 Organs involved with no more than score 1 *plus*

Lung score 0

Moderate chronic GVHD

3 or More organs involved with no more than score 1

OR

At least 1 organ (not lung) with a score of 2

OR

Lung score 1

Severe chronic GVHD

At least 1 organ with a score of 3

OR

Lung score of 2 or 3

Key points:

In skin: higher of the 2 scores to be used for calculating global severity.

In lung: FEV1 is used instead of clinical score for calculating global severity.

If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.

If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

APPENDIX E

STUDY CALENDAR

	Pre-Transplant Registration (#1)	Post-Transplant Day 30	Treatment Cycle (#6)											At Study Treatment Completion	Yearly Visits after Transplant
			Day 1 (#5)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 15	Day 22		
History	X	X	X		X		X							X	X
Physical Exam (#2)	X	X	X		X		X							X	X
CBC with diff	X	X	X		X		X							X	X
CMP with LDH, Magnesium, Phosphate, Uric Acid and Direct Bilirubin (#3)	X	X	X		X		X			X		X	X	X	X
Tumor Lysis Lab (#7)			First cycle of Pevonedistat (if not CR) every 8 hours until risk of tumor lysis is minimal												
Echo or MUGA	X														
12 lead ECG	X		X											X	
Pulmonary Function Test	X														
Bone Marrow Aspiration and Biopsy	X (#4)	X												X	X(#8)
Urinalysis with microscopic analysis	X		X											X	
Coagulation Labs including PT, PTT, INR	X														
Serum Pregnancy Test for Women in childbearing age	X		X												
Study Treatment	Pevonedistat		X		X		X								
	Azacitidine		X	X	X	X	X			X	X				
AE, Concurrent Meds			X											X	

- #1. Performed within 35 days prior to study registration and/or day of final evaluation before transplant.
- #2. Includes Vital Signs and Karnofsky Performance Status score.
- #3. CMP = Comprehensive Metabolic Panel (please see section 7.19.4)
- #4. Performed within 2 weeks before study registration to confirm non-remission AML.
- #5. Pre-treatment assessments are performed on Day 1 of each cycle (Section 3.3 and 7.19.4).
- #6. Follow Section 7.1.
- #7. Please see section 7.19.4
- #8. Performed \pm 1 month of 1-year post transplant visit only.

Note: Serum pregnancy test will be done for females of childbearing potential prior to first infusion of each cycle.

APPENDIX F. REQUIRED DATA COLLECTION

For the purpose of this study, the following data will be collected and entered in the Oncore study database. Other data needed to answer the study objectives may be added as needed. Information from the standard evaluations noted in the above Appendix E e.g. physical examinations, performance status, vital signs, general (CBC, Chemistry) laboratory results, etc. will not be entered into the database. Any abnormal results of the assessments will be captured as an AE according to the criteria noted in Section 18.

Unique Identification Number

Date of Consent

Eligibility met? Yes or No with reason (identify as screen failure if not met)

General demographics (e.g. age, gender, race, etc.)

Modifications made to prescribed conditioning or GVHD med regimen? No or Yes, specify

Safety data/AEs/SAEs as defined in Section 18.0.

Survival status – cause of death if applicable; date of last known alive (mm/dd/yy),

Study status – on study date, off evaluation, withdrawal/off study with reason, etc.

The following data is collected and entered into CIBMTR by a BMT Primary Data Collection and Analysis Coordinator at Penn State Cancer Institute. Therefore, the patients in this study will be required to participate in this research database trial maintained by CIBMTR, entitled “Protocol for a research database for hematopoietic cell transplantation, other cellular therapies and marrow toxic injuries” IRB #2002-198EP). The CIBMTR is a voluntary organization of basic and clinical scientists who share information on results of blood and marrow transplants and cellular therapies. The following data entered in CIBMTR will be extracted and utilized for the purpose of this study.

Significant Past medical history

Medications taken within past 30 days

Concomitant medications as described in Section 7.6 and 7.7

Donor Type/relationship (unrelated, sibling, mother, father, aunt, uncle, cousin, other, specify)

Donor demographics (as identified in recipients chart only e.g. gender, age if known)

Donor product cell counts (e.g. CD3, CD34, MNC)

Date of initiation of conditioning regimen (mm/dd/yy)

Date of HSCT infusion Date(s) (mm/dd/yy)

Cyclophosphamide infusion dates

Cyclophosphamide doses (mg/kg)

Any interruption or modification in the cyclophosphamide? No or Yes with reason.

Number of days to ANC engraftment

Graft failure prior to Day 100? Yes or No

Acute GVHD by Day 100 Yes or No. If yes, start date (mm/dd/yy), site, max grade, duration

Chronic GVHD - Yes or No. If yes, start date (mm/dd/yy), site, max grade, duration

Stem cell boost administered? If yes, date (mm/dd/yy)

Donor Lymphocyte Infusions? if yes, doses, date(s), and indication for administration

Routine immune reconstitution results (CD34, CD3, etc.)

Chimerism results (donor/host)

Ongoing disease status evaluation with dates

Research specific immune results will be maintained in the laboratory investigators database.