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Concomitant Omacetaxine Mepesuccinate and Azacitidine for Patients with Previously Untreated High Grade Myelodysplastic Syndromes

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Concomitant Omacetaxine Mepesuccinate and Azacitidine for Patients with Previously Untreated High Grade Myelodysplastic Syndromes

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Study Location	University of Colorado Cancer Center
Protocol / COMIRB#	17-2215
Version Date	January 13, 2023
Indication to be studied	Previously untreated patients with high grade myelodysplastic syndromes (MDS) and a small expansion cohort of relapsed or refractory MDS patients
Study Agents:	1. Omacetaxine mepesuccinate (Synribo™, Teva) 2. Azacitidine (Vidaza™, Celgene)

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STATEMENT OF COMPLIANCE

This is an investigator-initiated study. The principal investigator (PI), Daniel A. Pollyea, is conducting the study and acting as the sponsor. As the sponsor-investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed.

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by applicable United States (US) laws and applications, including but not limited to United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

The PI will assure that no changes to the protocol will take place without documented approval from the Institutional Review Board (IRB). All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Daniel A. Pollyea, MD
Print/Type Name

_____
Signature

_____
Date

STUDY PERSONNEL

A complete and current listing of investigators, research personnel, research facilities and other study centers (if applicable) participating in this study will be maintained throughout the duration of this study on applicable study required forms such as an *FDA Form 1572*, the *COMIRB Research Personnel Form*, and/or a *UCCC Protocol Contact List*, incorporated herein by reference.

LIST OF ABBREVIATIONS

ACRONYM	DESCRIPTION
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CMML	Chronic myelomonocytic leukemia
CR	Complete emission
CRi	Complete remission with incomplete blood count recovery
CYP	Cytochrome P
eCRF	Electronic case report form
IIT	Investigator-Initiated Trial
INR	International normalized ratio
LDH	Lactate dehydrogenase
LSC	Leukemia stem cell
MDS	Myelodysplastic syndrome
MRD	Minimal residual disease
PI	Principal Investigator
PT	Prothrombin time
PTT	Partial thromboplastin time
RBC	Red blood cell
SAE	Serious adverse event
TLS	Tumor lysis syndrome
UAP	Unanticipated Problem
IRB	Institutional Review Board
BID	Twice Daily
ORR	Overall Response Rate
CR	Complete Response
IWG	International Working Group
CML	chronic myeloid leukemia
FAB	French-American-British
RBC	Red Blood Cells
NCI	National Cancer Institute
Hgb	Hemoglobin

ECOG	Eastern Cooperative Oncology Group
EKG	Electrocardiogram
SQ	Subcutaneous
HHT	Homoharringtonine
DNA	Deoxyribonucleic acid
TKI	tyrosine kinase inhibitor
CHR	complete hematologic response
NYHA	New York Heart Association
DMC	Data Monitoring Committee
IND	Investigational New Drug
RNA	Ribonucleic acid
WBC	White Blood Cells
BUN	Blood urea nitrogen
LDH	Lactate dehydrogenase
DSMC	Data and Safety Monitoring Committee
CTCAE	Common Terminology Criteria for Adverse Events
NADPH	nicotinamide adenine dinucleotide phosphate
WHO	World Health Organization
AST	aspartate aminotransferase
ALT	Alanine transaminase
ULN	Upper Limit of Normal
HIV	human immunodeficiency virus
HBV	hepatitis B virus
PR	Partial Response
IUD	intrauterine device
IUS	Intrauterine hormone-releasing system
eCRF	Electronic Case Report Form
SAE	Serious Adverse Event
FCBP	Female of Child Bearing Potential
HMA	Hypomethylating Agent

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1 PROTOCOL SYNOPSIS

PROTOCOL TITLE: Concomitant Omacetaxine Mepesuccinate and Azacitidine for Patients with Previously Untreated High Grade Myelodysplastic Syndromes
INDICATION: Previously untreated patients with high grade myelodysplastic syndromes (MDS)
STUDY PHASE: I/II
BACKGROUND AND RATIONALE: High grade myelodysplastic syndromes (MDS), defined as MDS with increased blasts in the bone marrow or peripheral blood, has a very poor prognosis with a median survival of 10-20 months. The two FDA approved therapies for MDS are epigenetic modifiers (azacitidine and decitabine) and response rates to these agents are low (~20% complete remission rate) and transient (remission durations <1 year). When patients either do not respond or respond and then relapse, there are no FDA-approved salvage therapies; patients in this situation have a very poor prognosis and a short life expectancy, highlighting the importance of delivering the most effective treatment possible in the up-front setting. Recent work characterizing the leukemia stem cell population in high grade MDS has shown a protein synthesis inhibitor may be effective against this population, and has additive/synergistic properties with azacitidine. Omacetaxine is an FDA approved protein synthesis inhibitor that was studied pre-clinically with azacitidine, suggesting these two therapies may be highly active in patients with high grade MDS.
STUDY OBJECTIVES: **Primary** **Phase I:** To determine the recommended omacetaxine dose in combination with azacitidine **Phase II:** To determine the response rate of omacetaxine in combination with azacitidine in the newly diagnosed setting, and to assess toxicity and early efficacy of omacetaxine in combination with azacitdine in MDS patients who have not responded to or responded and relapsed after at least one line of therapy containing a hypomethylating agent **Secondary** • To evaluate the safety of the combination of omacetaxine and azacitidine (phase I and phase II)

- To determine the hematologic improvement from this combination (phase II)
- To determine the duration of response (phase II)
- To determine the progression free survival (phase II)
- To determine the rate of transformation to acute myeloid leukemia (AML) (phase II)
- To determine the percentage of patients deemed eligible for allogeneic stem cell transplantation who are able to proceed to this intervention without a second-line therapy (phase II)
- To determine the overall survival (phase II)

STUDY DESIGN:

This is an open label, phase I/II study for previously untreated patients with high grade MDS using concomitant omacetaxine and azacitidine with a small expansion cohort for relapsed and refractory MDS patients.

During phase I dose escalation, patients will receive omacetaxine subcutaneously at one of three cohorts (0.75, 1.0 and 1.25 mg/m^2 BID) on days 1-7. Azacitidine will be given at the standard dose and schedule (75 mg/m^2) daily, days 1-7. A treatment cycle is defined as a 28-day period and will repeat indefinitely in the absence of disease progression or patient intolerance/toxicity or preference.

On cycle 1 day 8, a bone marrow biopsy will be performed. On cycle 1 day 28, a bone marrow biopsy will be performed to determine response status. This will be repeated at the conclusion of cycles 4 and 6, and every 6 cycles thereafter.

During phase II the above design will be replicated with all patients being treated at the maximum tolerated dose (MTD). An additional expansion cohort of 10 MDS patients who have failed to respond to or responded and relapsed after at least one line of therapy containing a hypomethylating agent therapy will also be accrued.

Treatments will be administered in the outpatient setting if possible, with azacitidine administered as a standard of care intervention in the infusion clinic and the omacetaxine self-administered by the patient while maintaining a diary.

STUDY ENDPOINTS:

Primary

Phase I: To determine the recommended dose for the phase II study based on the maximum tolerated dose (MTD)

Phase 2: Overall response rate (ORR), defined by the proportion of patients who achieve any category of complete remission (CR, includes CR and marrow CR) or partial remission (PR) based on the 2006 International Working Group (IWG) criteria for MDS[1].

Secondary

- Safety assessments in the form of surveillance of adverse events, laboratory test measures, physical exam findings and concomitant medication records (phase I and phase II)
- Hematologic improvement rate
- Duration of response
- Progression free survival
- Rate of transformation to AML
- Percentage of eligible patients for allogeneic stem cell transplantation who proceed to this intervention
- Overall survival

ESTIMATED DURATION FOR ACCRUAL: 3-4 years

ACCRUAL SAMPLE SIZE:

Phase I: 4-18

Phase II: 33

TOTAL: 37-51

2 SCHEDULE OF STUDY ASSESSMENTS[a]

Procedures	Screen[b]	Cycle 1									Cycles 2+	End of Study	Safety Follow-up[h]	Long-term Follow-up[i]
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 28				
Informed Consent	X													
History	X												X	
Physical Exam	X	X							X	X	X[c]	X	X	
Vital Signs	X[k]	X	X	X	X	X	X	X	X	X	X[c]	X	X	
ECOG PS	X	X								X	X[c]	X	X	
Con Meds	X	X	X	X	X	X	X	X	X	X	X[c]	X		
AEs[j]	X	X	X	X	X	X	X	X	X	X	X		X	
12-lead EKG	X													
Hematology	X	X							X	X	X[c]	X		
Chemistry	X	X							X	X	X[c]	X		
Coagulation	X													
Pregnancy	X[j]										X[j]			
Azacitidine		X	X	X	X	X	X	X			X[d]			
Omacetaxine		X	X	X	X	X	X	X			X[d]			
Bone Marrow Aspirate & Biopsy	X								X[e]	X	X[f]	X		
Dispense Calendar & Diary		X									X[c]			

Procedures	Screen[b]	Cycle 1									Cycles 2+	End of Study	Safety Follow-up[h]	Long-term Follow-up[i]
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 28				
Collect Calendar & Diary										X	X[g]	X		
Relapse & Survival Contact												X		X

[a.] For detailed description of all elements please see section 5.10

[b.] Screening assessments must occur within 14 days of cycle 1 day 1, except the bone marrow, which may be done up to 28 days prior to cycle 1 day 1.

[c.] Required on day 1 of each cycle (+/- 3 days)

[d.] Days 1-7 of each cycle

[e.] Aspirate only required

[f.] After cycle 4, cycle 6 and every 6 cycles thereafter

[g.] At the completion of each cycle

[h.] Perform for patients who discontinue for adverse events around 30 days after discontinuation and include a history, physical examination and review of systems; repeat as clinically appropriate. A separate safety visit does not need to be performed for subjects with a final visit ≥30 days after discontinuation of study drug and did not require additional AE follow up. If the safety follow-up visit occurs before 30 days, the provider must make a documented phone call or telehealth evaluation to assess AEs—this cannot be a coordinator calling.

[i.] After treatment discontinuation, all patients will be followed at least annually, in the form of a telephone call or clinic visit, for information on whether the patient has relapsed or not, and whether they are alive or deceased for up to 5 years (or death, whichever comes first).

[j.] For all woman of childbearing potential, a serum or urine pregnancy test is required at screening and prior to the initiation of each cycle.

[k.] Height will be measured at screening only.

[J] AEs will be documented through 30 days after the last dose of study drug.

3 INTRODUCTION

3.1 Background and Rationale

Myelodysplastic syndromes (MDS) comprise a heterogeneous group of stem cell malignancies characterized by morphologic dysplasia and cytopenias resulting in bone marrow failure. A significant number of patients with MDS will evolve into AML[2]. Epidemiologic data for MDS is limited, but it is believed that over 10,000 new cases of MDS occur in the United States each year, and that over 60,000 patients carry this diagnosis[3]. High risk MDS can be defined pathologically as MDS with increased (>5%) blasts (high grade disease), or clinically using the International Prognostic Scoring System[4]. High risk MDS has a very poor prognosis with a median survival of 10-20 months[4]. There are two FDA approved therapies for the most common subtypes of MDS, both in the same class of drugs called hypomethylating agents[2]. Response rates to these agents are low (~20% complete remission rate), and overall survival is between 13-16 months[5]. When patients either do not respond or respond and then relapse, there are no FDA-approved salvage therapies; patients in this situation have a very poor prognosis with a short life expectancy[6,7], highlighting the importance of delivering the highest impact treatment possible in the up-front setting.

Relatively little is known about the stem cell population in MDS. In AML, surface antigens have been used to define LSCs, including CD123 (IL3-R alpha chain)[8-10]. Expression of CD123 in the CD34+/CD38- of primary MDS cells has been reported[11], and a subsequent report noted progressive increases of CD123 expression during MDS pathogenesis[12]. We found that the expression of CD123 within the stem cell population was detectable in all high risk MDS patient samples tested, and not detected in low risk MDS (Figure 1). Upregulation of CD123 within the MDS stem cell compartment

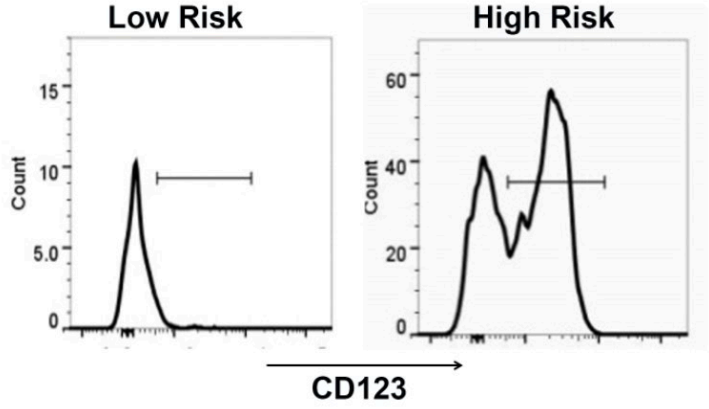

Figure 1: MDS bone marrow cells showing a high-risk specimen containing a distinct CD123+ population in comparison with a low risk specimen that does not stain for CD123

results in a change in cellular physiology, specifically with respect to upregulation of protein synthesis machinery (Figure 2, manuscript

submitted). This raised the question of whether targeting protein synthesis could result in the specific targeting of MDS stem cells.

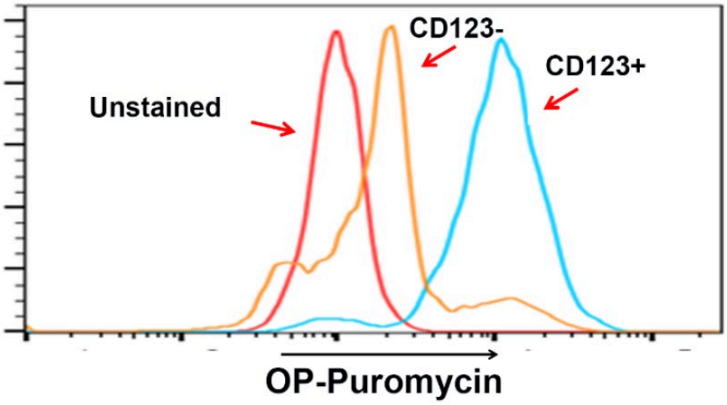

Figure 2: CD123+ cells sorted from Lin-/CD34+/CD38- high risk bone marrow specimens exhibit increased protein synthesis as measured by op-puromycin and flow cytometry of Lin-/CD34+/CD38- subpopulations.

Omacetaxine mepesuccinate (omacetaxine) is a first-in-class cephalotaxine derived from a semi-synthetic process utilizing the leaves of the evergreen plum yew *Cephalotaxus fortunei* and is chemically identical to the natural product homoharringtonine.[13] Omacetaxine acts by binding to the A-site cleft of ribosomes transiently inhibiting protein synthesis and may induce apoptosis of leukemic cells by a selective decrease in short-lived proteins, including mediators of apoptosis like Mcl-1, Bcl-2, Bax, Bcl-xl, Mapk, and Akt[14-16]. The safety and efficacy of omacetaxine has been evaluated in tyrosine kinase inhibitor resistant chronic myeloid leukemia (CML), for which this therapy has been FDA approved, and it may have activity against CML stem cells[16].

Based on its protein synthesis inhibiting properties, we explored whether omacetaxine would have specific activity in the CD123+ population, and tested this in vitro and in vivo with a primary human MDS xenograft model. The results were promising, and also showed additive properties with azacitidine, the standard of care for newly diagnosed MDS patients, when dosed concomitantly (Figure 3). Based on this data we propose a combination therapy study with omacetaxine and azacitidine for high grade, previously untreated MDS patients.

In addition, given the poor outcomes for MDS patients who fail to respond to or relapsed after responding to a hypomethylating agent (HMA) therapy, and the very limited treatment options for these patients, we propose a small

expansion cohort of these patients to receive this regimen to determine if it is tolerated and associated with preliminary signs of efficacy.

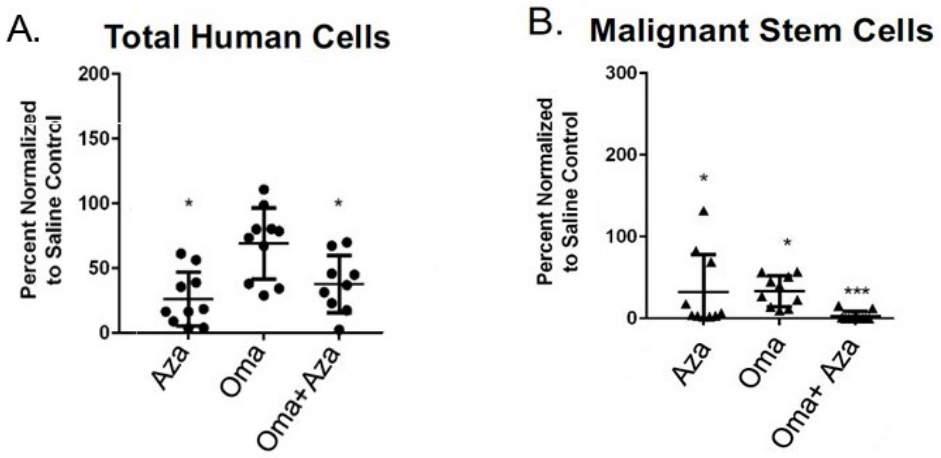

Figure 3: In vivo treatment of primary human MDS xenografts with omacetaxine and azacitidine.

Hypothesis: The combination omacetaxine and azacitidine will be well tolerated and effective in untreated high grade MDS patients.

3.2 Omacetaxine Mepesuccinate

Omacetaxine is a first-in-class cephalotaxine derived from a semi-synthetic process utilizing the leaves of the evergreen plum yew Cephalotaxus fortunei and is chemically identical to the natural product homoharringtonine.[13] Omacetaxine acts by binding to the A-site cleft of ribosomes transiently inhibiting protein synthesis and may induce apoptosis of leukemic cells by a selective decrease in short-lived proteins, including the anti-apoptotic protein Mcl-1, Bcl-2, Bax, Bcl-xl, Mapk, and Akt [14-16]. Omacetaxine has two known metabolites, 4'-DMHHT and cephalotaxine. The concentration of the primary metabolite 4'-DMHHT is approximately 10% of that of omacetaxine following subcutaneous administration and the half-life is about twice as long. Cephalotaxine, a minor metabolite, is typically not quantifiable in the plasma.

3.2.1 Pharmacokinetic Profile

The dose proportionality of omacetaxine is unknown. A 90% increase in systemic exposure to omacetaxine was observed between the first dose and steady state.

The absolute bioavailability of omacetaxine has not been determined. Omacetaxine is absorbed following subcutaneous administration, and maximum concentrations are achieved after approximately 30 minutes.

The steady-state (mean ± SD) volume of distribution of omacetaxine is approximately 141 ± 93.4 L following subcutaneous administration of 1.25 mg/m2 twice daily for 11 days. The plasma protein binding of omacetaxine mepesuccinate is less than or equal to 50%.

Omacetaxine mepesuccinate is primarily hydrolyzed to 4′-DMHHT via plasma esterases with little hepatic microsomal oxidative and/or esterase-mediated metabolism in vitro.

Based on the results of in vitro studies, there is a low probability of omacetaxine or 4′-DMHHT to inhibit metabolism via CYP enzymes or to inhibit P-gp-mediated efflux at clinically relevant concentrations. In vitro data also demonstrate a low probability of omacetaxine or 4′-DMHHT to induce the metabolism of concomitantly administered CYP1A2 substrates at clinically relevant concentrations. There is the potential for CYP3A4 activity to be induced by 4′-DMHHT at clinically relevant concentrations.

The major elimination route of omacetaxine mepesuccinate is unknown. The mean percentage of omacetaxine mepesuccinate excreted unchanged in the urine is less than 15%. The mean half-life of omacetaxine mepesuccinate following subcutaneous administration is approximately 6 hours.

3.2.2 Toxicology

No correlation between concentration and QTc was observed. Omacetaxine concentrations in patients with higher QTc intervals are within the range of omacetaxine concentrations observed in patients with QTc values less than 450 msec. There was no evidence for concentration-dependent increases in QTc for omacetaxine or 4'-DMHHT. Although the mean effect on QTc was 4.2 ms (upper 95% CI: 9.5 ms), QTc effects less than 10 ms cannot be verified due to the absence of a placebo and positive controls.

No carcinogenicity studies have been conducted with omacetaxine.

Omacetaxine was genotoxic in an in vitro chromosomal aberration test system in Chinese hamster ovary cells, but was not mutagenic when tested in an in vitro bacterial cell assay (Ames test), and it did not induce genetic damage using an in vivo mouse micronucleus assay.

Omacetaxine may impair male fertility. Studies in mice demonstrated adverse effects on male reproductive organs. Bilateral degeneration of the seminiferous tubular epithelium in testes and hypospermia/aspermia in the epididymides were reported in the highest dose group (2.33 mg/kg/day reduced to 1.67 mg/kg/day; 7 to 5 mg/m2 day) following subcutaneous injection of omacetaxine for six cycles over six months. The doses used in the mice were approximately two to three times the clinical dose (2.5mg/m2/day) based on body surface area.

Omacetaxine can cause fetal harm when administered to a pregnant woman. Omacetaxine caused embryo-fetal death in animals. Pregnant mice were administered omacetaxine SQ during the period of organogenesis at doses of 0.21 or 0.41 mg/kg/day. Drug related adverse effects included embryonic death, reduced bone ossification, and decreased fetal body weights.

3.2.3 Clinical Data

The efficacy of omacetaxine was evaluated using a combined cohort of adult patients with CML from two trials. The combined cohort consisted of patients who had received 2 or more approved TKIs and had, at a minimum, documented evidence of resistance or intolerance to dasatinib and/or nilotinib. Resistance was defined as one of the following: no complete hematologic response (CHR) by 12 weeks (whether lost or never achieved); or no cytogenetic response by 24 weeks (i.e., 100% Ph positive [Ph+]) (whether lost or never achieved); or no major cytogenetic response (MCyR) by 52 weeks (i.e., ≥35% Ph+) (whether lost or never achieved); or progressive leukocytosis. Intolerance was defined as one of the following: 1) Grade 3-4 non-hematologic toxicity that does not resolve with adequate intervention; or 2) Grade 4 hematologic toxicity lasting more than 7 days; or 3) any Grade ≥ 2 toxicity that is unacceptable to the patient. Patients with NYHA class III or IV heart disease, active ischemia or other uncontrolled cardiac conditions were excluded. Patients were treated with omacetaxine mepesuccinate at a dose of 1.25 mg/m2 administered subcutaneously twice daily for 14 consecutive days every 28 days (induction cycle). Responding patients were then treated with the same dose and twice daily schedule for 7 consecutive days every 28 days (maintenance cycle). Patients were allowed to continue to receive maintenance treatment for up to 24 months. Responses were adjudicated by an independent Data Monitoring Committee (DMC).

Harringtonine and homoharringtonine (HHT) have been used as a single agent to treat patients with high-risk MDS[17,18]. Combinations using HHT and other agents have also been reported, in largely retrospective studies.[19-21]

3.3 Azacitidine

Azacitidine, an analog of the pyrimidine nucleoside cytidine, has effects on cell differentiation, gene expression, DNA synthesis and metabolism, and causes cytotoxicity. Since the early 1970s, azacitidine has been investigated in the US for the treatment of MDS and acute leukemia.

The cytotoxic effects of azacitidine may result from multiple mechanisms, including inhibition of DNA, RNA and protein synthesis, incorporation into RNA and DNA, and activation of DNA damage pathways. The ability of azacitidine to cause differentiation is attributed to its activity as a hypomethylating agent. Therefore, an inhibitor of DNA methylation such as azacitidine would be a rational approach to revert epigenetic changes in the malignant clone and re-establish the anti-proliferative signals extinguished by hypermethylation.

3.3.1 Preclinical Pharmacokinetic Profile

Early PK studies used ^{14}C-radiolabeled azacitidine to evaluate drug disposition. Based on total radioactivity in plasma, azacitidine was absorbed when given subcutaneously (SC), with maximum concentrations found 0.5 to 2 hours after dosing. Azacitidine and/or its metabolites were then cleared by the kidneys. The plasma $t^{1/2}$ (3.4 to 6.2 hours) and amount of radioactivity recovered in urine (50-98% of administered dose) were similar after IV and SC dosing.

Drug-drug interaction studies of azacitidine have not been conducted in clinical trials. Two in vitro metabolism studies and three in vitro drug interaction studies have been completed. Some evidence of hepatic metabolism was observed when azacitidine was incubated in human liver fractions. The metabolism of azacitidine was compared using [^{14}C]5-azacitidine and hepatic S9 fractions from human and mouse origin; the formation of deaminated metabolites (formylamidinoribofuranosylbiuret and ribofuranosylbiure) was independent of nicotinamide adenine dinucleotide phosphate (NADPH), implying that metabolism was catalyzed by cytosolic enzymes. Azacitidine was not an inducer of the isozymes 1A2, 2C19, or 3A4/5. Azacitidine showed no notable inhibition of P450

isoenzymes (Cytochrome P450 [CYP450] 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4) in the concentration range of 0.1 to 100 µM. Therefore, clinically relevant inhibitory or inductive effects on the metabolism of CYP450 substrates are unlikely. Azacitidine is neither a substrate nor an inhibitor of P-glycoprotein (P-gp) and therefore unlikely to produce any clinically relevant interactions as a P-gp substrate or an inhibitor. The effect of inducers or inhibitors on the metabolism of azacitidine has not been studied.

3.3.2 Clinical Data

The safety profile of azacitidine has been well characterized and is based on an extensive amount of patient exposure across a wide range of doses and indications. Adverse events (AEs) reported most frequently were hematologic events of thrombocytopenia, neutropenia, anemia, and leukopenia, and were typically assessed as grade 3 or 4 events. Despite the increased percentages of these hematologic events, azacitidine did not appear to increase the risk of events of infection or bleeding when compared with patients treated with best supportive care only. Non-hematological AEs that were reported most often were events related to either the administration of the drug (injection site reactions, nausea, vomiting) or consequences of the antiemetic treatment (constipation). These events were generally graded 1 or 2 in intensity. The reporting frequencies for the common hematologic and non-hematological events were generally highest during cycles 1 and 2, after which time the frequencies decreased over subsequent treatment cycles. Within the cycle, the hematologic events tended to occur across the first 3 to 4 weeks of the cycle, whereas the events associated with the administration of azacitidine tended to occur in the first week. These findings suggested a lack of cumulative toxicity and that adverse effects of azacitidine attenuate over time.

4 STUDY OBJECTIVES

4.1 Primary Objectives

Phase I: To determine the recommended omacetaxine dose in combination with azacitidine

Phase II: To determine the response rate of omacetaxine in combination with azacitidine in the newly diagnosed setting, and to assess toxicity and early efficacy of omacetaxine in combination with

azacitdine in MDS patients who have failed to respond to or responded and relapsed after at least one line of therapy containing a hypomethylating agent

4.2 Secondary Objectives

- To evaluate the safety of the combination of omacetaxine and azacitidine (phase I and phase II)
- To determine the hematologic improvement from this combination (phase II)
- To determine the duration of response (phase II)
- To determine the progression free survival (phase II)
- To determine the rate of transformation to acute myeloid leukemia (AML) (phase II)
- To determine the percentage of patients deemed eligible for allogeneic stem cell transplantation who are able to proceed to this intervention without a second-line therapy (phase II)
- To determine the overall survival (phase II)

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design

This is an open label, phase I/II single institution pilot study for previously untreated high grade MDS patients to receive concomitant therapy with omacetaxine and azacitidine, with a small pilot study of relapsed or refractory MDS patients.

5.1.1 Study Schema

Phase I
After consent and screening, patients will be assigned to the appropriate omacetaxine dose cohort (Figure 4).

Cohort	Oma Dosage
0	0.5 mg/m^2
1	0.75 mg/m^2
2	1.00 mg/m^2
3	1.25 mg/m^2

Cohort 1 will receive 0.75 mg/m^2, cohort 2 1.0 mg/m^2 and cohort 3 1.25 mg/m^2 of omacetaxine subcutaneously BID. In the event that >1 dose limiting toxicity (DLT) event occurs in cohort 1, a dose de-escalation cohort (cohort 0) will enroll and patients will receive 0.5 mg/m^2 omacetaxine subcutaneous BID. Omacetaxine will be administered by the patient subcutaneously BID on days 1-7. Concomitantly, azacitidine 75 mg/m2 IV (preferred) or subcutaneous will be administered in the outpatient infusion center or the inpatient facility, depending on the needs of the patient, on days 1-7. Patients will not receive therapy for the subsequent 21 days, constituting a 28-day cycle. Cycles will continue in the absence of disease progression or patient intolerance/toxicity or preference.

On cycle 1 day 8, a bone marrow biopsy will be performed.
On cycle 1 day 28, a bone marrow biopsy will be performed to determine response status. This will be repeated at the end of cycles 4 and 6, and every 6 cycles thereafter.

Patients enrolled at dose cohorts lower than cohorts later found to be safe may dose escalate to the highest dose level deemed safe, at the discretion of the investigator.

Phase II
After the establishment of the MTD or the phase II dose if the MTD is not reached, phase II will commence. Patients enrolled at the MTD or phase II dose in phase I will roll over to phase II. The same schema for phase I will apply to phase II, except there will not be omacetaxine dose escalation. An expansion phase of 10 patients who did not respond to or responded and relapsed after at least one prior line of an HMA-containing therapy will also be accrued and treated with the same dose and schedule of omacetaxine and azacitidine as the other phase II patients.

5.1.2 Response Assessments

Response assessments will be made by evaluation of peripheral blood findings and bone marrow biopsies at end of cycle time points, using the 2006 International Working Group (IWG) criteria for MDS which will apply for response assessments as well as hematologic improvement criteria[1] (Section 5.12).

5.1.3 Continuation and Interruptions

Patients who achieve a response and are tolerating therapy can continue to receive sequential treatment cycles indefinitely. Patients who experience disease progression or significant treatment-related toxicity, as assessed by the investigator or the patient, will discontinue therapy. Patients who are deemed to be appropriate for allogeneic stem cell transplantation and have the requisite reduction in disease burden will come off study to proceed to transplant.

After cycle 1, subsequent cycle delays are not required for any grade of hematologic toxicity; however, cycles may be delayed for any grade of hematologic toxicity, particularly in the setting of a patient who achieves a marrow CR.

Subjects who require brief interruption of omacetaxine for reasons other than progression of disease will continue azacitidine therapy alone until they resume omacetaxine. When the following cycle is resumed, omacetaxine and azacitidine will resume on the same day.

Dose decreases can be considered, see Section 5.15.

Intra-patient dose escalation for patients in phase 1 is allowable if higher dose cohorts are proved to be safe, as defined by at least three patients completing a higher dose cohort without a DLT event, or if a DLT occurs, no more than 1/6 patients in a cohort experiencing a DLT. Patients may escalate to the highest safe dose after review and approval by the PI.

5.2 Study Endpoints

Primary

Phase I: To determine the recommended dose for the phase II study based on the maximum tolerated dose (MTD)

Phase 2: Overall response rate (ORR), defined by the proportion of patients who achieve any category of complete remission (CR, includes CR and marrow CR) or partial remission (PR) based on the 2006 International Working Group (IWG) criteria for MDS[1].

Secondary:

- Safety assessments in the form of surveillance of adverse events, laboratory test measures, physical exam findings and concomitant medication records (phase I and phase II)
- Hematologic improvement rate

- Duration of response
- Progression free survival
- Rate of transformation to AML
- Percentage of eligible patients for allogeneic stem cell transplantation who proceed to this intervention
- Overall survival

5.3 Selection of Study Population and Enrollment Procedures

All subjects will be screened for eligibility. The investigators will be responsible for keeping a record of all subjects who sign an informed consent form for entry into the study. After the patient has signed and dated the informed consent form, all screening procedures have been completed and clinical eligibility has been confirmed, the patient can be officially enrolled in the study. All patients must meet the qualifications as outlined below.

5.3.1 Inclusion Criteria

A subject will be eligible for study participation if he/she meets the following criteria within 14 days prior to the first day of therapy (bone marrow biopsy can be performed 28 days prior to the first day of therapy).

1. Subject must have confirmation of high grade MDS (MDS with excess blasts by WHO criteria[22]) or chronic myelomonocytic leukemia with greater than 5% bone marrow blasts[22]

2. Subjects in the newly-diagnosed Phase 2 cohort must have received no prior treatment with a hypomethylating agent for MDS. Subjects in the relapsed/refractory Phase 2 cohort must have received at least 1 prior line of an HMA-containing regimen. “Refractory” is defined as having received at least four cycles of any HMA or HMA-containing regimen with >5-19% bone marrow blasts. “Relapsed” is defined as having >5-19% bone marrow blasts after having achieved a morphologic remission (≤5% bone marrow blasts) after at least one cycle of any HMA or HMA-containing regimen.

3. Subject must be ≥ 18 years of age

4. Subject must have a projected life expectancy of at least 12 weeks

5. Subject must have an Eastern Cooperative Oncology Group (ECOG) Performance status of ≤2

6. Subject must have adequate renal function as demonstrated by a calculated creatinine clearance ≥ 30 mL/min; determined via urine collection for 24-hour creatinine clearance or by the Cockcroft Gault formula

7. Subject must have adequate liver function as demonstrated by:

   - aspartate aminotransferase (AST) ≤ 3.0 × ULN
   - alanine aminotransferase (ALT) ≤ 3.0 × ULN
   - direct bilirubin ≤ 3.0 × ULN

8. Non-sterile male subjects must use contraceptive methods with partner(s) from time of enrollment and continuing up to 90 das after the last dose of study drug. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of study drug.

9. Female subjects must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting omacetaxine; 2) throughout the entire duration of omacetaxine treatment; 3) during dose interruptions; and 4) for at least 90 days after omacetaxine discontinuation.

10. Subject must voluntarily sign and date an informed consent, approved by an Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

5.3.2 Exclusion Criteria

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Subject is known to be positive for HIV. HIV testing is not required.

2. Subject is known to be positive for hepatitis B or C infection with the exception of those with an undetectable viral load. Hepatitis B or C testing is not required and subjects with serologic evidence of prior vaccination to HBV (i.e., HBs Ag, anti-HBs+ and anti-HBc–) may participate.

3. Subject has any history of clinically significant condition(s) that in the opinion of the investigator would adversely affect his/her participating in this study including, but not limited to:

    - New York Heart Association heart failure > class 2
    - Renal, neurologic, psychiatric, endocrine, metabolic, immunologic, hepatic, cardiovascular disease, or bleeding disorder independent of leukemia

4. Subject exhibits evidence of uncontrolled systemic infection requiring therapy (viral, bacterial or fungal). Patients on antibiotics with controlled systemic symptoms will not be excluded.

5. Subject has uncontrolled diabetes

6. Subject has had a recent major hemorrhage or has a bleeding diathesis associated with a high risk of bleeding

7. Pregnant and breastfeeding females.

8. Subject has a history of other malignancies prior to study entry, except for:

    - Adequately treated in situ carcinoma of the breast or cervix uteri
    - Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin
    - Prostate cancer with no plans for therapy of any kind
    - Previous malignancy confined and surgically resected (or treated with other modalities) with curative intent.

5.4 Duration of Study

After treatment discontinuation, all patients will be followed at least annually, in the form of a telephone call or clinic visit, for information on whether the patient has relapsed or not, and whether they are alive or deceased.

5.5 Drug Administration

5.5.1 Omacetaxine Administration

Omacetaxine will be provided by Teva Pharmaceuticals. Omacetaxine will be dispensed by the investigational pharmacy and administered by the patient subcutaneously BID on days 1-7 of each

treatment cycle. Doses should be administered at the same time each day.

Omacetaxine dose decreases may be considered, see Section 5.16.5, and for adverse event management guidelines please refer to Section 6.

Patients who take more than the prescribed dose of omacetaxine should be instructed to seek emergency medical care if needed and contact study staff immediately. If a dose of omacetaxine is missed or forgotten, it should be taken as soon as possible provided it is not more than 2 hours past the planned time. If it is more than two hours it should not be given. The next dose should be given at the originally planned time. Missed doses should not be made up.

Omacetaxine will be stored and reconstituted in normal saline according to the package insert. Drug syringes will be stored at 20-25 degrees Celsius (68-77 degrees Fahrenheit); excursions permitted from 15-30 degrees Celsius (59-86 degrees Fahrenheit). Carton will be protected from light until administration.

5.5.2 Azacitidine Administration

Azacitidine will be commercially obtained. Azacitidine 75 mg/m^2 should be prepared and administered per the package insert and institutional guidelines via an intravenous route, or, if necessary, subcutaneously.

5.6 Assuring Patient Compliance

The investigator and designated and qualified representatives will dispense omacetaxine only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

Patients will receive all dosages of azacitidine in the inpatient or outpatient setting.

Patients will receive a diary to record the specific time each dose of omacetaxine was taken and to record reasons for any missed doses. Patient compliance will be assessed on day 28 of a completed cycle or day 1 of a subsequent treatment cycle. Patients will be required to bring their diary and any remaining vials, to clinic during this visit. Research personnel will record any unused drug at each visit and reconcile with the patient diary. Compliance will be monitored and

documented by the study coordinator. Poor compliance will result in counseling of the subject by study site personnel. Any unused omacetaxine will be returned to the pharmacy.

5.7 Drug Accountability

The investigator and his representatives will verify that study drug supplies are received intact and in the proper amounts. This will be documented. The investigator or his representatives will administer study drug only to subjects enrolled in the study. A current (running) and accurate inventory of study drug will be kept by the investigator and will include shipping invoices and the date on which study drug is dispensed to the subject. Upon completion or termination of the study, all original containers (containing partially used or unused study drug) will be returned to the sponsor according to their instructions. Empty containers will be destroyed at the site.

5.8 Concomitant Therapy

5.8.1 Permitted Concomitant Therapy

Transfusion of blood and blood products, antibiotics, anti-emetics and other standard supportive care medications are permitted as needed. Hydroxyurea is permitted as needed according to institutional guidelines, as needed. Filgrastrim may be used according to institutional guidelines. Antibiotics will be used for patients with infections or neutropenic fevers per institutional guidelines.

If a subject reports taking any over-the-counter or prescription medications, vitamins, and/or herbal supplements or if administration of any medication becomes necessary, beginning with the screening visit through the end of the study, the name of the medication, dosage information including dose, route and frequency, date(s) of administration including start and end dates, and reason for use must be recorded on the appropriate electronic case report form (eCRF).

5.8.2 Prohibited Concomitant Therapy

Chemotherapy, systemic or intrathecal, immunotherapy, radiotherapy and prednisone >20 mg/day are prohibited.

5.9 Contraception Recommendations

Male subjects must be surgically sterile (vasectomy with medical assessment confirming surgical success) or if the male subject has a female partner who is postmenopausal or permanently sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy), no contraception is required.

If the male subject is sexually active with female partner(s) of childbearing potential, he must agree from enrollment through 90 days after the last dose of investigational product to practice contraception with a partner who agrees to at least one of the following contraceptive measures:

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month prior to enrollment
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to enrollment
- Bilateral tubal occlusion/ligation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable)

Additionally, male subject agrees not to donate sperm from enrollment through 90 days after the last dose of investigational product.

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception (listed above) simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting omacetaxine; 2) throughout the entire duration of omacetaxine treatment; 3) during dose interruptions; and 4) for at least 90 days after omacetaxine discontinuation.

5.10 Study Procedures

Study procedures listed in section 2 are detailed in this section, with the exception of adverse event information (see Section 6). All study data will be recorded on eCRFs.

Procedures performed at screening will serve as baseline, unless repeated on cycle 1 day 1 prior to dosing, in which case this will serve as baseline.

Any abnormal laboratory or vital sign between screening and prior to administration of therapy will be recorded in the subject's medical history and will also serve as the subject's baseline.

Subjects who signed the informed consent will obtain a screening/subject number. Subjects who signed informed consent, have had at least one study procedure conducted, and who are determined to be a screen failure will not proceed to the study. The reason for the screen failure will be documented in the source document and captured in the eCRF. Screening procedures must be performed within 14 days prior to study drug administration, with the exception of the screening bone marrow biopsy, which can occur 28 days prior. Subjects who complete all screening procedures and meet the inclusion criteria (see section 5.3.1) and none of the exclusion criteria (see Section 5.3.2) will proceed to enrollment.

Informed consent
Signed informed consent will be obtained from the subject or the subject's legally acceptable representative in order to participate in the study. The IRB approved informed consent must be signed and dated by the subject or representative prior to undergoing any study procedures or before any prohibited medications are withheld from the subject in order to participate in the study.

History
Involves a complete medical history, with documentation of clinically significant medical conditions, and MDS history including the date of diagnosis of MDS and any precursor conditions. Also includes review of current medications and allergies.

Physical Exam
Symptom directed, per institutional protocol.

Vital Signs
Includes height (height at the screening only), weight, temperature, blood pressure, pulse, and respiratory rate. All methods of measurement and practices will be per institutional protocol.

ECOG PS[23]

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction

1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

AEs and Con Meds

On cycle 1 day 1, any serious adverse events observed from the signing of informed consent but prior to administration of omacetaxine and azacitidine will be reported, if considered by the investigator to be causally related to study-required procedures. At each visit, including the end of treatment visit, the subject's medical history will be reviewed and any changes from baseline will be recorded on the adverse event eCRF.

All medications, prescription and over the counter, including vitamins and/or herbal supplements, will be recorded beginning with the screening visit and through the EOS visit. No new medications will be reported after. .

12 Lead EKG

A single 12-lead resting EKG will be obtained at screening or as clinically needed. It will be recorded after the subject has been in the supine position for at least 5 minutes. Subjects will be instructed to remain stationary for the duration of the recording. An investigator will then evaluate it as clinically significant or not clinically significant, which will be entered into the CRFs.

Clinical Laboratory Tests

All laboratory tests will be performed at the time points listed in the schedule of study assessments, and will be performed at additional time points based on institutional guidelines.

Hematology

- Hematocrit
- Hemoglobin
- WBC count
- Differential (if WBC high enough, per institutional standard)
- Platelet count

Chemistry

- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Total bilirubin
- Albumin
- Alkaline phosphatase
- Sodium
- Potassium
- Chloride
- Carbon dioxide
- Glucose
- Blood urea nitrogen (BUN)
- Creatinine
- Calcium
- Magnesium
- Phosphorus
- Total Protein
- Uric acid
- Lactate dehydrogenase (LDH)

Coagulation

- Prothrombin time (PT)
- International normalized ratio (INR)
- Partial thromboplastin time (PTT)
- Fibrinogen

Azacitidine
See Section 5.5.2

Omacetaxine
See Section 5.5.1

Bone marrow aspirate and biopsy
To be performed at all time points outlined in the schedule of study assessments, in addition to at any time upon concern for relapse.
Historical bone marrow aspirates and biopsy at screening may be acceptable per Investigator discretion.

Attempts to obtain an aspirate and biopsy are required at all listed time points except day 8, when an aspirate alone is sufficient. If a patient is not aspirable after an attempt is made, additional core biopsy specimens should

be attempted per institutional protocol. On all time points except for day 8, samples should be sent for morphological assessment, flow cytometry, cytogenetic analysis and molecular testing, as is clinically appropriate. All results will be captured in the eCRF. Day 8 aspirates may not involve cytogenetic and molecular assessments, as is clinically appropriate.

Dispensing and Collecting Calendar and Diary
Subject calendars/diaries will be provided at the time of discharge from the hospital. Subjects will bring their calendars/diaries back to be reviewed at each visit.

Subjects will record the date and time of each dose of study drug taken, including whether any doses of the study drug are missed.

The calendars/diaries will be reviewed at each visit and relevant pages will be photocopied by study staff. At the end of participation, the calendars/diaries will be returned to the site and filed with the subject's source documents.

5.11 Response Assessments

Assessment of clinical responses will be made according to 2006 IWG MDS criteria[1]. The major criteria for judging responses will include physical examination and examination of blood and bone marrow. In the event that peripheral blood findings improve 14 days after a bone marrow biopsy, whether or not in the setting of a delay in treatment, the response assessment will be adjusted accordingly. Only subjects who complete cycle 1 will be evaluable for response. Patients with un-evaluable bone marrows should be reported as indeterminate and a repeat bone marrow should be completed within 1 week. Response duration is measured from the time all response criteria are first met until relapse is documented.

Complete Remission (CR)

CR requires all of the following:

- Bone marrow myeloblasts ≤5% with normal maturation of all cell lines
- Hemoglobin ≥11 g/dL
- Absolute neutrophil count ≥1.0 x 10^9/L
- Platelet count >100 x 10^9/L
- No peripheral blood blasts

Partial Remission (PR)

- All CR criteria if abnormal before treatment except:

  - Bone marrow blasts decreased by ≥50% over pretreatment but still >5%
- Cellularity and morphology not relevant

Marrow CR

- Bone marrow: ≤5% myeloblasts and decrease by ≥50% over pretreatment
- Peripheral blood: if hematological improvement responses, they will be noted in addition to marrow CR

Stable disease

- Failure to achieve at least PR, but no evidence of progression for > 8 weeks

Failure

- Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment

5.12 Hematologic Improvement (HI)[1]

The HIs are measured in patients with pretreatment abnormal values: hemoglobin <11 g/dL or RBC-transfusion dependence, platelet count <100x10^9/L or platelet-transfusion dependence, absolute neutrophil count (ANC) <1.0x10^9/L. Pretreatment baseline measures of cytopenias are averages of at least 2 measurements (not influenced by transfusions, i.e., no RBC transfusions for at least 1 week and no platelet transfusions for at least 3 days) over at least 1 week prior to therapy.

Erythroid Response

- Hgb increase by ≥1.5 g/dL
- Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 week compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation

Platelet Response

- Absolute increase of ≥30x10^9/L for patients starting with > 20x10^9/L platelets
- Increase from <20x10^9/L to >20x10^9/L and by at least 100%

Neutrophil Response

- At least 100% increase and an absolute increase > $0.5x10^9$/L

Progression or Relapse After HI

- At least 1 of the following:
- At least 50% decrement from maximum response levels in granulocytes or platelets
- Reduction in Hgb by ≥1.5 g/dL
- Transfusion dependence

5.13 Reporting of Results

At the conclusion of each bone marrow biopsy performed after C1D8, all patients will be assessed as one of the following responses:

- CR
- PR
- Marrow CR
- Stable disease
- Failure

5.14 Stopping Rules

5.14.1 Individual Patient Stopping Rules

All subjects will be included for analysis of safety data. Subjects have the right to withdraw from the study at any time. The investigator will discontinue a subject if this is felt to be necessary for any reason including:

- Non-compliance with the study protocol
- Is it believed to be in the best interests of the subject
- Disease progression
- Toxicity related to study drug that requires more than a 4-week dose interruption of therapy and in the absence of clinical benefit
- Need for other anti-neoplastic agents or radiotherapy for the development of a new primary cancer diagnosis
- Adverse event that precludes further investigational drug administration
- Development of unrelated illness which compromises further participation in the study

In the event of withdrawal or discontinuation, the reason for discontinuation will be recorded and a final visit, including a physical examination, vital signs, ECOG PS, bone marrow aspirate and biopsy, AE assessment with con meds, hematology/chemistry laboratories and collection of the calendar/diary, will be performed as soon as possible after discontinuation.

A safety follow-up visit should be performed approximately 30 days following discontinuation for adverse events, and should include a history, physical examination, and review of systems, and then should be repeated as clinically appropriate for safety assessments. Patients will be followed until a satisfactory clinical resolution of adverse events is achieved. A separate safety visit does not need to be performed for subjects with a final visit ≥30 days after discontinuation of study drug and did not require additional AE follow up. Patient refusal or inability to attend safety follow up visits will be noted in the source documentation. After treatment discontinuation, all patients will be followed at least annually, in the form of a telephone call or clinic visit, for information on whether the patient has relapsed or not, and whether they are alive or deceased for up to 5 years (or death, whichever comes first).

5.14.2 Study Stopping Rules

The study will continue until the last patient is followed one year beyond receiving the last dose of study drug. If the investigator determines that continued exposure to the study drug represents a significant risk to subjects, the study will be stopped. In addition, if the expected response rate falls below 4/18 patients in the first stage of the phase II study, the study will be stopped (see Section 8.5). All enrolled subjects will be notified of the premature discontinuation and the investigator will administer treatments with other regimens as is appropriate.

5.15 Dose Escalation for Phase I

The phase I portion is organized in a standard phase I 3+3 design. The first 3 subjects will be assigned to cohort 1. If none of the first three patients experiences DLT, escalation to the next dose cohort is permitted. If one of the first three patients experiences DLT, a total of six patients will be required in that dose cohort, and escalation will only be permitted if five of six patients do not experience DLT. If more than one DLT is observed in any cohort, this will be determined to be the maximally administered dose, and three more patients will be enrolled in the next lowest dose cohort if only three were previously treated at that dose. The MTD will

be the cohort in which ≤1/6 patients have dose limiting toxicity at the dose prior to the maximally administered dose(see Section 5.1.1. Dosing Schema). Once the MTD is established the phase II portion of the study will begin; the phase I patients treated at the MTD will roll over to the phase II portion of the study.

5.16 Dosing Delays and Modifications

5.16.1 Missed Doses

If a dose of omacetaxine is missed, it should be taken as soon as possible provided it is not more than 2 hours past the planned time. If it is more than two hours it should not be given and noted in the diary; the next dose should be given at the originally planned time. Dosing will be tracked in the patients' diaries.

5.16.2 Dose-limiting toxicity (DLT) definition

During cycle 1, the following will be considered DLT:

- Grade ≥ 3 non-hematologic toxicity, uncontrolled despite optimal medical management
    - This will exclude:
        - Grade ≥ 3 infection
        - Fever (including febrile neutropenia)
        - Grade 3 or higher electrolyte abnormalities that resolve, with or without intervention, to < Grade 2 in <72 hours; abnormalities that do not resolve, with or without intervention, to < Grade 2 in <72 hours will be considered DLT

- In subjects who achieve a CR or marrow CR, prolonged myelosuppression during the first cycle that lasts longer than 42 days after initiating cycle 1, defined as ANC < 500/μL or platelet count < 10 x 10^9/L, is defined as DLT.
- Any treatment related death will be defined as a DLT

DLTs will be assessed during the DLT assessment window of cycle 1 (up 42 days to account for treatment delays) following the first dose of study treatment.

5.16.3 Additional Doses

Patients who take more than the prescribed dose of omacetaxine should be instructed to seek emergency medical care if needed and contact study staff immediately.

5.16.4 Dose Delays

After cycle 1, the start of each subsequent cycle can proceed in the absence of possibly/related > grade 2 non-hematologic toxicity. In the presence of possibly/related > grade 2 non-hematologic toxicity, delay of the subsequent cycle for up to 14 days is allowed. If the possibly/related > grade 2 non-hematologic toxicity resolves to ≤ grade 1 within 14 days, subsequent cycles may resume.

After cycle 1, subsequent cycle delays are not required for any grade of hematologic toxicity; however, cycles may be delayed for any grade of hematologic toxicity, and myeloid growth factors may be used according to standard practices and at the discretion of the investigator, in the absence of evidence of ongoing disease.

Subjects who require brief interruption of omacetaxine for reasons other than progression of disease will continue on azacitidine therapy alone until they resume omacetaxine.

5.16.5 Dose De-Escalation

Hematologic toxicity will not be distinguishable between azacitidine and omacetaxine; therefore, when dose de-escalation for hematologic toxicity is required, it will first occur for omacetaxine. If after an additional cycle at the adjusted dose of omacetaxine the hematological toxicity persists, azacitadine will be dose adjusted.

For patients with baseline (start of treatment) WBC ≥3.0 $x10^9$ /L, ANC ≥1.5 $x10^9$ /L, and platelets ≥75 $x10^9$ /L, adjust the dose of azacitidine and omacetaxine as follows, based on nadir counts for any given cycle:

Nadir Counts		% Dose in the Next Course
ANC ($x10^9$/L)	Platelets ($x10^9$/L)	
<0.5	<25	50%
0.5-1.5	25-50	67%
>1.5	>50	100%

For patients with baseline (start of treatment) WBC <3.0 $x10^9$ /L, ANC <1.5 $x10^9$ /L, or platelets <75 $x10^9$ /L, dose adjustments should be based on nadir counts and bone marrow biopsy cellularity at the time of the nadir as noted below, unless there is clear improvement in differentiation (percentage of mature granulocytes is higher and ANC is higher than at onset of that

course) at the time of the next cycle, in which case the dose of the current treatment should be continued.

WBC or Platelet Nadir % Decrease in Counts from Baseline	Bone Marrow Cellularity at Time of Nadir (%)		
	30-60	15-30	<15
	% Dose in the Next Course		
50-75	100	50	33
>75	75	50	33

Non-hematological AEs related to omacetaxine that are >grade 3 and do not resolve to <grade 2 after a 14 day interruption of therapy will result in 5-day treatment courses of omacetaxine for all subsequent treatment cycles.

6 SAFETY PLAN

6.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a subject on the study. This can include any unfavorable or unintended sign, symptom or disease temporally associated with the use of the therapy, regardless of causality with the therapy. This may include use of the therapy as stipulated in the protocol or as labeled or from accidental or intentional overdose. Worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are AE only if they result in study discontinuation, necessitate medical intervention, meet protocol specific criteria, and/or are considered by the investigator to be clinically significant or AEs. Elective surgeries or procedures scheduled to occur during a study are not AEs if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorated unexpectedly during the study (e.g. the surgery must be performed earlier than planned) then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

A treatment-emergent AE is defined as any AE reported by a subject with onset or worsening from the time that the first dose of study drug

is administered until 30 days have elapsed following discontinuation of the therapy.

The investigators will have access to updated package inserts for omacetaxine and azacitidine as references for safety issues related to each drug.

6.2 Serious Adverse Events

If an AE meets any of the following criteria it is to be considered a serious adverse event (SAE) and must be reported to the PI and Teva within 24 hours, see Section 6.8.2.

The PI will then review and submit to the University of Colorado regulatory authorities and the FDA, if applicable, in accordance with 21 CFR 312.32.

All SAEs will be reported using the FDA 3500A Mandatory MedWatch report form. SAE form can be found at:

http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

An adverse event will be classified as an SAE if it meets one of the following criteria:

Fatal:	AE resulted in death
Life threatening:	The AEs placed the patient at immediate risk of death in the opinion of the investigator. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization or prolongation of hospitalization:	AE that required hospitalization for any length of time or prolonged inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before enrollment in the treatment plan are not SAEs by this criterion. Admissions to an outpatient facility, emergency room, palliative unit or hospice care facility are not considered to be hospitalizations and are not SAEs.

Disabling/incapacitating	AE that results in substantial and permanent disruption of the patient's ability to carry out normal life functions. Does not include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza and accidental trauma (e.g. ankle sprain)
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a patient exposed to the treatment regimen before conception or during pregnancy.
Important medical event requiring medical or surgical intervention to prevent serious outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death, life-threatening, hospitalization or prolongation of hospitalization, congenital anomaly or persistent or significant disability/incapacity). Any elective or spontaneous abortion or stillbirth is considered a SAE.

For SAEs that result in death, the date and cause of death will be recorded in the case report form.

Deaths due to disease progression will not be recorded as SAEs. Patient deaths that are later determined to be unrelated to disease progression may be reported outside the 24-hour window.

Hospitalization to allow observation and management for the purpose of TLS prophylaxis will not be considered SAEs unless there is an additional reason for hospitalization or an additional criterion for seriousness other than hospitalization (e.g., abnormal post-dose TLS laboratories that necessitate therapeutic medical intervention).

Hospitalization of a subject in post-treatment follow up or survival more than 30 days after discontinuation of the therapy will not be recorded as a SAE.

SAEs occurring after informed consent but prior to initiation of therapy will be collected only if felt by the investigator to be causally related to the study required procedures.

For hospitalizations or surgical or diagnostic procedures, the illness leading to the hospitalization or surgical or diagnostic procedure will be recorded as the SAE, not the procedure itself. The procedure will be captured in the narrative as part of the action taken in response to the illness.

6.3 Adverse Events Commonly Associated with MDS

Certain AEs are anticipated to occur in this study population at some frequency independent of drug exposure. For example, cytopenias (anemia, neutropenia, thrombocytopenia) are part of the natural history of MDS. Therefore, persistent cytopenias at the same CTCAE grade as at baseline are not be reported as AEs, unless they meet criteria for an SAE, result in permanent discontinuation of a study drug, or the investigator has an identifiable cause other than the underlying disease.

6.4 Adverse Event Severity

The investigator will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.0). If a reported AE increases in severity, the initial AE should be given final outcome date and a new AE must be reported to reflect the change in severity.

For AEs not captured by the CTCAE, the following should be used:

Grade 1	The AE is transient and easily tolerated by the subject (mild).
Grade 2	The AE causes the subject discomfort and interrupts the subject's usual activities (moderate)
Grade 3	The AE causes considerable interference with the subject's usual activities and may be incapacitating (moderate to severe)

Grade 4	The AE is life-threatening requiring urgent intervention (severe)
Grade 5	The AE resulted in death of the subject (severe)

6.5 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Reasonable Possibility of Relationship with Azacitidine	An AE where this is evidence to suggest a causal relationship between azacitidine and the AE
No Reasonable Possibility of Relationship with Azacitidine	An AE where this is no evidence to suggest a causal relationship between azacitidine and the AE
Reasonable Possibility of Relationship with Omacetaxine	An AE where this is evidence to suggest a causal relationship between omacetaxine and the AE
No Reasonable Possibility of Relationship with Omacetaxine	An AE where this is no evidence to suggest a causal relationship between omacetaxine and the AE

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered “associated.” Events assessed as having no reasonable possibility of being related to study drug will be considered “not associated.” When no reasonable possibility of an association between a study drug and a SAE exists, the investigator must provide another cause.

6.6 Deaths

Death is an outcome of an event. Deaths that occur during the AE reporting period that are attributed by the investigator to MDS progression will be recorded as such. For all deaths, the event or condition that caused or contributed to the fatal outcome will be recorded as the single medical concept on the AE CRF. If the cause of death is unknown and cannot be ascertained, “unexplained death” should be recorded. If the cause later becomes available, “unexplained death” should be replaced with the established cause of death.

6.7 Recording Adverse Events

Patient safety will be assessed by reviewing AEs during planned and unplanned visits and physical and laboratory examinations from the time the patient receives the first dose of study drug until 30 days after the patient's last study treatment. The investigator will assess and record AEs in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the AE to the study drug, and any action taken. For SAEs considered unrelated to study drug, the investigator will provide another cause for the event. AEs may be recorded as the result of a response to a query, an observation by site personnel, or due to a report from a subject. All AEs will be followed to a satisfactory conclusion.

6.8 Investigator Reporting Responsibilities

The conduct of the study will comply with all Food and Drug Administration (FDA) safety reporting requirements. If the FDA determines an IND is necessary, it is a requirement of 21 CFR 312.33 that an annual report be provided to the FDA within 60 days of the IND anniversary date. 21 CFR 312.33 provides the data elements that are to be submitted in the report. The annual report should be filed in the study's regulatory binder, and a copy provided to Teva as a supporter of this study.

6.8.1 Adverse Event Reporting

All AE reports will include the patient's number, age, sex, weight, severity of reaction (mild, moderate, severe), relationship to the study (fatal relationship, definitely related, possibly related, unrelated), date and time of administration of test medications and the investigators will notify the IRB and DSMC of a SAE according to institutional policy.

6.8.2 Reporting to Teva

Serious adverse events (SAE) are defined in Section 6.2.

In addition to compliance with all FDA reporting requirements pursuant to 21 CFR 312, the Principal Investigator shall:

a) Report to Teva all serious adverse events experienced by a study subject receiving a Teva product within 24 hours of learning of the event regardless of the relationship of the event to the Teva

product. Principal Investigator shall make available to Teva promptly such records as may be necessary and pertinent to investigate any such event, if specifically requested by Teva.

b) Copy Teva on the submission to the FDA of events meeting the definition of IND safety reports at the time of submission to the Agency; and,
c) Notify Teva upon any subjects receiving a Teva product whose pregnancy has resulted in a negative outcome or untoward event during the course of pregnancy or upon delivery.

Teva's contact for reporting serious adverse drug experiences, pregnancy experiences, non-serious adverse events of tumor lysis syndrome, and communication of FDA submissions of IND safety reports is drug.safety@tevapharm.com or fax to 215-795-4052.

Product Complaints: In addition to compliance with all FDA requirements pursuant to 21 CFR 211 and 21 CFR 820, Principal Investigator will report to Teva within 24 hours any suspected quality defect in an Teva Product or its Teva-provided packaging, labeling, or medical device component (collectively, "Product Complaint"). Principal Investigator will report Product Complaints that involve a Teva Product, whether Teva has supplied the Teva Product used in the Study or not. Teva's contact for reporting Product Complaints is 888-828-2872 or email at qas@tevapharm.com.

6.8.3 Reporting From Teva

Teva will notify the investigators via an IND Safety Report of the following information:

- Any AE associated with the use of drug in this study or in other studies that is both serious and unexpected
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity

The investigators will notify the IRB promptly of these new serious and unexpected AEs or significant risks to subjects. The investigators must keep copies of all AE information, including correspondence with Teva and the IRB, on file.

6.9 Pregnancy

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on omacetaxine, or within 28 days of the subject's last dose of omacetaxine, are considered immediately reportable events. Omacetaxine is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Teva Drug Safety immediately by facsimile or email. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Teva Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Teva Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in-utero exposure to the IP should also be reported to Teva Drug Safety immediately by facsimile 215-795-4052 or email drug.safety@tevapharm.com, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form (see Section 6.2).

Pregnancies of female partners of male study subjects are also included in the information of interest, however, will require consent of female partner with documentation if the partner refuses consent to release information on their pregnancy and outcome.

6.10 Decreased Spermatogenesis

Based on preclinical data, omacetaxine has an adverse effect on male reproductive organs. Bilateral degeneration of the seminiferous epithelium and hypospermia/aspermia in the epididymides were reported in the highest dose group (1.67 to 2.33 mg/kg/day; 5 to 7

mg/m2/day) following SQ injection of omacetaxine for 6 cycles over 6 months. The doses used in mice were approximately 2-3 times the clinical dose. The effects on omacetaxine on female and male fertility have not been studied. The effect on human fertility is unknown.

6.11 Management of Infection

Anti-infective prophylaxis will be implemented per institutional guidelines with consideration for possible drug interactions.

6.12 Management of Other Toxicities

If other events occur that are related to the study drugs, the investigator may interrupt or dose reduce the therapies has appropriate. Grade 3 or greater non-hematologic toxicity that is related to the study drugs will require interruption and possible discontinuation. Therapy may be re-introduced, potentially at a reduced dose, if the toxicity returns to baseline if grade 2 at study entry or ≤ grade 1.

7 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, good clinical practice or standard operating procedure requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6, sections:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3.
- 5.1 Quality Assurance and Quality Control, section 5.1.1.
- 5.20 Noncompliance, sections 5.20.1 and 5.20.2.

Intentional deviations are not allowed unless necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirement and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the study team will keep record of deviations and is responsible for reporting to the IRB and DSMC as required.

8 STATISTICAL METHODS

Patients who receive at least one dose of azacitidine or omacetaxine will be evaluable for safety. Patients who complete at least one cycle of therapy will be evaluable for efficacy.

8.1 Demographics

Descriptive statistics will be provided for demographic variables.

8.2 Efficacy Analysis

Efficacy will include analyses of ORR as defined as CR+PR+marrow CR, median time to achieve a response, duration of overall response, event free survival and overall survival.

8.3 Safety Analysis

Safety will be assessed by analysis of AEs, SAEs, all deaths, changes in laboratory values and vital sign parameters. Analysis of AEs will include only treatment-emergent events (events that had onset on or after the first dose of study drug). Analysis of AEs and SAEs will not include those that have an onset >30 days after the last dose of study drug. Toxicity grades using NCI CTCAE V4.0 and relationships to study drugs will be assessed. In addition, incidence of febrile neutropenia, ≥ grade 2 bleeding complications and number of transfusions received (red blood cells and platelets) will be assessed.

8.4 Deaths

The number of subject deaths will be analyzed by those that occurred within 30 days of the last dose of study drug, those that occurred more than 30 days after the last dose of study drug, those that occurred within the first 30 days of the study, those that occurred within the first 60 days of the study, those that were related to study drug and those that were unrelated to study drug.

8.5 Sample Size Determination

The total number of patients enrolled in the phase 1 study will depend on the number of dose cohorts required to identify the MTD. Design consideration were made to obtain preliminary safety information in this patient population. Escalation to the next dose cohort will depend on the identification of DLT at a given dose.

For the phase II study, it is known that hypomethylators such as azacitidine used as a single agent in newly diagnosed high-grade MDS historically are associated with about a 20% CR/marrow CR rate[5]. Our alternative hypothesis for the use of omacetaxine with azacitidine in untreated high-risk MDS patients is a 43% CR/marrow CR rate, which would be clinically significant. Using a one-sided exact test for a difference in proportion, a sample size of 23 patients is needed for this study, assuming a Type 1 error rate of 5% and a power of 80%. At least 9 of 23 patients must have a CR/marrow CR to reject the null hypothesis.

Ten MDS patients who have relapsed after or are refractory to at least one line of an HMA or HMA-containing regimen will be enrolled to determine preliminary toxicity and efficacy assessments.

A “survival” curve and its 90% confidence interval as well as the median remission duration will be computed for the data.

8.6 Statistical Analysis Plan

This study is being conducted to 1) determine the maximum tolerated dose of the treatment regimen and 2) determine efficacy of the treatment as defined by overall response rate (those who achieve any type of complete remission as well as those who achieve partial remission). A standard Phase I 3+3 design will be employed to determine MTD. All patients treated at the MTD in dose escalation will be included in analysis for the Phase II component of this study. The primary endpoint, the overall response rate proportion in patients enrolled in the Phase II portion of this study, will be assessed and formally compared—with a null hypothesis of 20% overall response rate vs. the alternative hypothesis of 43% overall response rate using a one-sided exact test. Kaplan Meier estimates of survival (overall response) at 12 months and their standard errors will be calculated. Comparisons between categorical groups will be conducted using the appropriate parametric or non-parametric statistical test (Chi-square, Student’s T, etc.)

Secondary measures of progression free survival, overall survival, and duration of response will be explored using Kaplan Meier survival analysis methods. Furthermore, other secondary endpoints such as hematologic improvement rate and rate of transformation to AML will be calculated along with their 95% confidence intervals. Laboratory test measures and physical exam findings will be described using summary measures. Exploratory analyses can

describe differences in these findings based on demographic variables.

9 ETHICS

9.1 Institutional Review Board

The protocol, informed consent form(s), and all subject materials will be submitted to the Colorado Multiple Institutional Review Board (COMIRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by COMIRB before the changes are implemented to the study. All changes to the consent form will COMIRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

9.2 Ethical Standards

Good clinical practice (GCP) requires that the protocol, amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study and any other necessary documents be reviewed by the IRB. The IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IRB approval of the protocol, informed consent and subject information will be obtained prior to the authorization of drug shipment to the study site.

Amendments to the protocol will require IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive essential documents.

During the conduct of the study the investigator will promptly provide written reports to the IRB of any changes that affect the conduct of the study and/or increase the risk to subjects.

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) GCP guidelines, applicable regulations and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki.

9.3 Informed Consent Process

Prior to the initiation of any screening or study-specific procedures, the IRB approved consent form(s) describing in detail the study agent, study procedures, and risks will be given to the subject and the investigator or her representative will explain the nature of the study to the subject and answer all questions regarding the study. Each informed consent will be reviewed, signed and dated by the subject and the person who administered the informed consent as well as the investigator. Written documentation of informed consent will be required prior to starting intervention/ administering study procedures and a copy of the informed consent will be given to the subject with the original placed in the subject's file. An entry will be made in the source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10 SOURCE DOCUMENTS AND CASE REPORT FORMS

Accurate, complete, legible and timely records and data will be kept in the source documents of all drug administration, including prescribing and dosing. Source documents are defined as original documents, data and records that pertain to the conduct of the study and distribution of the protocol therapy. These may include but are not limited to, copies of CRFs, hospital records, clinical and office charts, laboratory data/information, subject diaries or evaluation checklists, SAE reports, pharmacy dispending and other records, recorded data from automated instruments, and/or imaging studies. Data collected must be recorded on the appropriate source document.

Study documents will be retained for as long as necessary to comply with all applicable regulations and institutional requirements. By signing the protocol, the investigators agree to adhere to the document/records retention procedures.

The investigator and institution will permit study-related monitoring, audits, IRB review and regulatory inspections providing direct access to source data documents.

Case report forms (CRFs) must be completed for each subject screened/enrolled in the study.

11 STUDY OVERSIGHT – Quality Assurance and Quality Control

11.1 Data Safety and Study Oversight

The sponsor investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial including any specimens collected, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study participant safety for all clinical studies at the CU Cancer Center, which is the coordinating institution of this trial. A summary of the DSMC's activities is as follows:

• Conduct of internal audits

• Ongoing review of all serious adverse events (SAEs) and unanticipated problems (UAPs)

• May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs and UAPs are reported to the DSMC, IRB and the sponsor investigator per protocol. All SAEs and UAPs are to be reported to the DSMC within 7 (for fatal or life-threatening events) or 15 (non-life-threatening events) calendar days of the sponsor investigator receiving notification of the occurrence.

The sponsor investigator will provide a DSM progress report to the CU Cancer Center DSMC on a recurring basis (either every six or twelve months based on DSMC vote). The DSM report will include a protocol summary, current enrollment numbers, summary of toxicity data to include specific SAEs, UAPs and AEs, any dose modifications, all protocol deviations, and protocol amendments. The DSM progress report submitted

to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results and recommendations from the review of this progress report by the DSMC will then be provided to the sponsor investigator in a DSMC review letter. The sponsor investigator is then responsible for ensuring this letter is submitted to the site's IRB of record at the time of IRB continuing review.

11.2 Clinical Monitoring

Clinical site monitoring visits will be performed by the CU Cancer Center Clinical Monitor on a regular basis, pursuant to the Clinical Monitoring Plan (CMP), incorporated herein by reference. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of the monitoring reports.

Clinical site monitoring will be conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with applicable regulatory requirement(s). During these visits, information recorded on the CRFs will be verified against source documents. When necessary, requests for data clarification or correction will be sent to the appropriate site PI.

11.3 Study Auditing

Independent audits will be conducted by the CU Cancer Center DSMC to ensure monitoring practices are performed consistently across all participating sites, if applicable, and that monitors are following good clinical practices. In addition, audits may be conducted at any time by appropriate regulatory authorities and/or the IRB.

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COMIRB
APPROVED
For Use
25-May-2022
24-May-2023

Principal Investigator: **Daniel A. Pollyea, MD**
COMIRB No: **17-2215**
Version Date: **04.14.2022**

Study Title: **Concomitant Omacetaxine Mepesuccinate and Azacitidine for Patients with Previously Untreated High Grade Myelodysplastic Syndromes (MDS)**

You are being asked to participate in a research study. A member of the research team will explain what is involved in this study and how it will affect you. This consent form describes the study procedures, the risks and benefits of participation, as well as how your confidentiality will be maintained. Please take your time to ask questions and feel comfortable making a decision whether to participate or not. This process is called informed consent. If you decide to participate in this study, you will be asked to sign this form.

Why is this study being done?

The purpose of this study is to learn more about a combination of two drugs and how well it might work to treat high grade myelodysplastic syndromes (MDS). The two drugs are called omacetaxine and azacitadine. You are being asked to be in this research study because you have been newly diagnosed with MDS, have relapsed, or refractory MDS.

Omacetaxine is approved by the U.S. Food and Drug Administration (FDA) to treat a type of leukemia called chronic myeloid leukemia (CML) but is not approved to treat your specific type of cancer. Azacitadine is approved by the FDA to treat MDS.

Throughout the rest of this consent form, Omacetaxine and Azacitadine will be called the “study drugs” when referenced together.

How many people will participate?

Up to 91 people from your area will participate in the study.

What happens if I join this study?

If you join the study, you will be asked to sign this consent form. You will be given a copy to keep and the original form will be kept at the clinic. You can withdraw from the study at any time and without giving a reason. This will not affect the standard medical care you receive.

There are 3 parts to the study:

1. Screening (before beginning the study drugs)
2. Phase I (dose escalation)
3. Phase II (dose expansion) including relapsed and refractory MDS

During Phase I, the study doctors are trying to find the highest dose of omacetaxine that can be given safely with azacitadine. Certain serious or severe side effects may occur and these are likely to occur at higher doses. If certain serious or severe side effects are observed, the study will be stopped. Once this dose of omacetaxine has been determined, Phase II of the study will begin.

During Phase II, the study doctors will give the dose of omacetaxine determined during Phase I in combination with azacitadine.

The dose of omacetaxine that you will receive will depend on when you enroll in the study. The study doctor will tell you whether you will be participating in the Phase I or the Phase II portion. All those with relapsed or refractory MDS, will only be enrolled to Phase II.

The next section of this form lists what will be expected of you if you agree to join this study.

Study Procedures

While you are taking part in this study, some of the tests and procedures are the same type that would be performed as part of your regular cancer care even if you did not join the study. Some of the tests and procedures are required only for the study and are identified below as "**research**" procedures.

The screening tests and procedures will be done to see if you are eligible to join this study. You may have had some of these tests and procedures done recently as standard care for your cancer, and they may not need to be repeated.

- **Informed Consent (research)**
  This informed consent form will be discussed with you and you will be given a copy of this document. If you join the study, you will be asked to sign this consent form before you receive any study related tests or procedures.

- **Medical and Cancer History**
  Before you start the study we will record your date of birth, race, ethnicity, and complete medical history. This history will look at the background and progress of your cancer and any treatments you have received for your disease.

- **Physical Examination**
  A physical examination will be completed as part of your standard of care. We will also assess if the study drug is affecting your body functions including lungs, heart, abdomen, extremities, skin, head (eyes, ears, nose, hair, etc.) and neurologically.

- **Vital Signs**
  We will take your blood pressure, heart rate, respiratory rate, body temperature and weight. Height will be measured only during screening.

- **Performance Status**
  We will assess how well you are performing your daily activities.

- **Review of Current Medications**
  Your study doctor will let you know which medications you can and cannot take while taking part in this study. From the time you first receive the study drugs through 30 days after the last dose, we will record medications you may be taking.

- **Review of Side Effects (research)**
  Some risks have been identified because of the disease process or through use of the study drugs themselves and these will be followed very closely by the Principal Investigator and study staff. More information will be provided in the Risk area of this consent.

- **Electrocardiogram (ECG or EKG)**
  This is a simple, noninvasive procedure that records the electrical activity of the heart. Electrodes are placed on the skin of the chest and connected in a specific order to a machine. Output usually appears on a long scroll of paper that displays a printed graph.

- **Blood Tests**
  At various time points during the study, you will have blood collected for routine testing.

- **Bone Marrow Biopsy/Aspirate (research except at screening)**
  At various time points during the study, you will have bone marrow examined. This involves placing a hollow needle into your hip bone near the small of your back and taking a small sample of the bone (bone marrow biopsy) and 2-3 tablespoons of the liquid bone marrow inside the bone (bone marrow aspirate).

- **Study Drug Diary (research)**
  You will be provided with a drug diary to write down the date, time, and dose of study drug. A new diary will be provided at the beginning of each cycle and the completed diary will be collected at the end of each cycle.

- **Azacitadine administration**
  You will receive the standard dose of azacitadine (75mg/kg^2) intravenously as noted in the schedule of study visits section of this form.

- **Omacetaxine administration (research)**
  You will receive the dose of omacetaxine as an injection under the skin as noted in the schedule of study visits section of this form. You will receive instruction on how to self-administer this drug.

Study Visits

Screening Visit *(within 14 days before treatment)*

- Informed consent
- Review of medical history
- Complete physical exam
- Performance status
- Review of current medications
- Vital signs
- Blood draw for routine tests, including:
  - Hematology
  - Chemistry (including magnesium, phosphorus and LDH)
  - Coagulation tests (including PT and PTT/INR)
  - Pregnancy (for women who can get pregnant)
- Electrocardiogram (EKG)
- Bone marrow biopsy/aspirate (*may be performed up to 28 days prior to treatment*)

During the Study

Cycle 1 – Day 1 *(each cycle is 28 days)*

- Physical exam
- Performance status
- Review of side effects
- Review of current medications
- Vital signs
- Blood draw for routine tests, including:
  - Hematology
  - Chemistry (including magnesium, phosphorus and LDH)
- Receive study drug calendar and diary
- Receive azacitadine (IV)

- Receive omacetaxine

Cycle 1 – Day 2-7

- Review of side effects
- Review of current medications
- Vital signs
- Blood draw for routine tests, including:
  - Hematology
  - Chemistry (including magnesium, phosphorus and LDH)
- Receive azacitadine (IV)
- Receive omacetaxine

Cycle 1 – Day 8

- Physical exam
- Review of side effects
- Review of current medications
- Vital signs
- Blood draw for routine tests, including:
  - Hematology
  - Chemistry (including magnesium, phosphorus and LDH)
- Bone marrow aspirate

Cycle 1 – Day 28

- Physical exam
- Performance status
- Review of side effects
- Review of current medications
- Vital signs
- Blood draw for routine tests, including:
  - Hematology
  - Chemistry (including magnesium, phosphorus and LDH)
- Collect study drug calendar and diary
- Bone marrow biopsy/aspirate

Cycles 2+

- Physical exam
- Performance status
- Review of side effects
- Review of current medications

- Vital signs
- Blood draw for routine tests, including:
  - Hematology
  - Chemistry (including magnesium, phosphorus and LDH)
- Receive study drug calendar and diary
- Receive azacitadine (IV)
- Receive omacetaxine
- Bone marrow biopsy/aspirate (Day 28 only)
- Collect study drug calendar and diary (Day 28 only)

During cycles 2+, all procedures will be done on Day 1, unless otherwise indicated. Omacetaxine and Azacitadine will be given on Days 1-7.

Bone marrow aspirate and biopsy will occur after Cycle 4, Cycle 6, and every 6 cycles thereafter.

End of Study Visit

- Physical exam
- Performance status
- Review of side effects
- Review of current medications
- Vital signs
- Blood draw for routine tests, including:
  - Hematology
  - Chemistry (including magnesium, phosphorus and LDH)
- Bone marrow biopsy/aspirate
- Collect study drug calendar and diary

Safety Follow-up Visit *(30 days after end of treatment for subjects who stop the study as a result of side effects)*

- Medical history
- Physical exam
- Performance status
- Review of side effects
- Review of current medications

The study team will continue to follow up with you at least once a year, either by phone or during a routine clinic visit. Long-term follow up will continue every year up to 5 years.

How long will I be in the study?

You may continue receiving study drugs indefinitely or until your doctor determines that you should stop receiving the study drug regimen due to side effects, progression of your disease, or until you decide to stop participating in the study.

You will be followed long term for disease status and survival information for up to 5 years.

What are the possible discomforts or risks?

You may have side effects while you are in this study, but you will be carefully checked by the study doctor for any problems. There may be risks or side effects of the study treatment that are unknown at this time. You should tell the study doctor about anything that is bothering you or any side effects you have, even if you do not think they are related to the study treatment. Many side effects go away shortly after the medications are stopped, but in some cases side effects can be serious, long lasting, or permanent.

Risks of the Study Drugs

Potential Risks Associated with Omacetaxine

COMMON, SOME MAY BE SERIOUS (seen in more than 10% of patients):

- Decrease in your platelets (thrombocytopenia) which can cause bleeding
- Decrease in a type of white blood cells called neutrophils (neutropenia)
- Decrease in red blood cells (anemia)
- Diarrhea
- Muscle Pain
- Nausea
- Infusion/Injection Site Reactions
- Fatigue
- Fever
- Abdominal Pain
- Weakness
- Headache
- Joint Pain
- Nose bleeds
- Swelling in arms & legs
- Cough
- Hair Loss
- Constipation
- Vomiting
- Insomnia

- Rash
- Bone marrow failure
- Fever with low number of a type of white blood cell called neutrophils (febrile neutropenia)
- Decreased appetite
- Chills

Less Common, SOME MAY BE SERIOUS (seen in more than 1% but less than 10% of patients)

- Cardiac Disorders: rapid heart rate, palpitations, chest pain, irregular heart rate, slowed heart rate.
- Ear Disorders: ear pain, ear hemorrhage, tinnitus (ringing in ear).
- Eye Disorders: cataract, blurred vision, broken blood vessels in the eye, dry eye, excessive tearing, pink eye, double vision, eye pain, eyelid swelling.
- Gastrointestinal Disorders: inflammation to mouth & lips, mouth ulceration, abdominal distension, gas, GERD, bleeding gums, dry mouth, hemorrhoids, gastrointestinal hemorrhage, black, tarry bowel movements, mouth hemorrhage, oral pain, anal fissure, difficulty swallowing, pain in the gums.
- General Disorders: hot flashes, flu-like illness, swelling.
- Immune System Disorders: allergic reaction.
- Metabolism and Nutrition Disorders: diabetes mellitus, gout, dehydration.
- Musculoskeletal and Connective Tissue Disorders: bone pain, muscular weakness, muscle spasms, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, musculoskeletal discomfort.
- Nervous System Disorders: dizziness, bleeding in the brain, numbness & tingling, convulsion, sciatica, burning sensation, changes in taste, tremor.
- Psychiatric Disorders: anxiety, depression, agitation, confusional state.
- Urinary: painful urination, damage to the kidneys.

- Respiratory: throat pain, nasal congestion, hoarseness, productive cough, lung congestion, runny nose, coughing up blood.

- Skin Disorders: redness, itching, dry skin, red spots, excessive sweating, night sweats, bruising, purpura, skin lesion, skin ulcer, skin sloughing, skin hyperpigmentation.

- Vascular Disorders: high blood pressure, low blood pressure

Potential Risks Associated with Azacitidine

The following side effects may happen with azacitidine and are common or very common (may affect more than 1 in 100 people):

- Decrease in your platelets (thrombocytopenia)
- Decrease in red blood cells (anemia)
- Decrease in white blood cells (leukopenia)
- Decrease in a type of white blood cells called neutrophils (neutropenia)
- Fever with low number of a type of white blood cell called neutrophils (febrile neutropenia)
- Bone marrow failure
- Neutropenia with infection and the presence of bacteria in your blood stream (neutropenic sepsis)
- Bacteria or viral infections including lung infection (pneumonia), upper respiratory infection, or urinary tract infection
- Fever
- Bleeding including brain and stomach/gut bleeding
- Bruising
- Injection site pain, redness, or bruising (if receiving azacitidine as an injection under the skin)
- Damage to the kidneys or kidney failure
- Abdominal pain
- Constipation
- Diarrhea
- Feeling sick to your stomach (nausea)
- Vomiting
- Chest pain
- Shortness of breath
- Feeling tired or lethargic
- Lack of appetite or interest in food
- Weight loss
- Pain including joint, muscle pain and headache

- Dizziness
- Anxiety and difficulty sleeping
- Rash
- Itching
- Decrease in blood potassium

The following events have been reported in trials with azacitidine less frequently, but can be severe in nature. These events may or may not be related to azacitidine.

- Severe or fatal infections including severe skin infections (necrotizing fasciitis)
- Severe bleeding
- Heart problems: Cardiac arrest (heart stopped), heart attack, irregular heart beat
- Liver damage in individuals with previous liver problems Severe allergic reactions (anaphylaxis)
- Tumor lysis syndrome

With both drugs given together, additional risks, warnings, and precautions, as outlined should be discussed with your study doctor. You should contact the study doctor or study staff and get medical help if you have any of the above mentioned or any other side effects during the study. Combination of azacitidine with omacetaxine may worsen the potential side effects of azacitidine or omacetaxine, or even cause other side effects that were not known before.

Risks of the Study Procedures

Blood tests

Blood sampling and needle punctures carry some risk. Possible side effects include, but are not limited to, fainting, bleeding, bruising, discomfort, dizziness, infection and/ or pain at the puncture site.

Having an IV inserted in your vein

In this study we will insert a needle, connected to a plastic tube, into a vein in your arm. We will use the tube to take blood samples or give you fluids. You will feel some pain when we first insert the tube into your vein. You may have some redness, swelling, or bruising where the tube goes under your skin. In some cases, this type of tube can cause an infection where it goes under the skin. In rare cases, it can cause a blood clot in the vein. You will have this tube inserted for about four or five hours.

Bone marrow biopsy

In this study we will take four samples of bone marrow from your pelvic bone. Before we take each sample, we will give you some numbing medication on the skin outside your

pelvic bone (on your hip). After your skin is numb, we will push a special needle into the center of your pelvic bone. Then, we will draw the bone marrow up into the syringe. When we do this, you will have a pulling feeling as the marrow leaves the bone and goes into the syringe. The area around the bone will be sore for a few days.

There is a very small chance that you will be allergic to the numbing medicine. There is also a very small chance that you could bleed or develop an infection.

Electrocardiogram (EKG)
An electrocardiogram (EKG) is a test that records the electrical activity of the heart. Skin irritation is rare but could occur during an EKG from the electrodes or the gel that is used.

Risks Associated with Pregnancy

While participating in this research study, you should not become pregnant, nurse a baby, or father a baby. Women who are able to have children must use a highly effective means of birth control approved by your study doctor. You must continue the use of birth control during the entire time of your study participation at least 3 months after the last dose of azacitidine.

If you are a female who has stopped having menstrual periods for at least 1 year (menopause), please discuss with your study doctor the need for birth control. If you become pregnant, you must stop taking the study drugs at once and notify your doctor immediately. You will not be allowed to continue in the study. You may be asked questions about the outcome of your pregnancy and the baby.

Risk of Loss of Confidentiality

There is a risk that people outside the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

There may be other risks that could arise which are not reasonably foreseeable. If new information becomes available which could influence your willingness to continue, this new information will be discussed with you.

What are the possible benefits of the study?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other individuals with MDS in the future.

Are there alternative treatments?

There may be other ways of treating your cancer. Instead of taking part in this study:

- You may choose to receive treatment with an approved therapy or drug combination.
- You may choose to participate in a different study with another experimental drug.
- You may choose to receive comfort/ palliative care.
- You may choose to get no treatment at all.

You should talk to your doctor about your choices. Make sure you understand all of your choices before you decide to take part in this study. You may leave this study and still have these other choices available to you.

Who is paying for this study?

Teva Pharmaceuticals, Inc. is providing a grant of funding support for this study. Teva manufactures the study drug, omacetaxine, and will provide this drug for the study. This research is being conducted by Dr. Daniel Pollyea. The research study will only pay for procedures not considered standard of care.

Will I be paid for being in the study?

You will not be paid to be in the study.

Will I have to pay for anything?

The drug manufacturer, Teva, will pay for the cost of the study drug, omacetaxine. The funding for this study will also pay for any tests or procedures that are related to the research study.

The study drug, azacitadine, is considered standard treatment for your disease. This drug will be obtained through your insurance, and you will be responsible for any applicable copays required by your insurance policy.

There are some medical procedures that you would get for your condition whether you were in this study or not, such as blood draws. These are considered standard of care. You and/or your health insurance may be billed for the costs of medical care during this study, if these expenses are related to standard of care procedures. If you have health

insurance, the cost of these services will be billed to your insurance company. If your insurance does not cover these costs, or you do not have insurance, these costs will be your responsibility.

Ask your study doctor to discuss the costs that will or will not be covered by this research study. This discussion should include the costs of treating possible side effect. Otherwise, you might have unexpected expenses from being in this study.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled.

If you leave this study, you will still receive your normal medical care. The only medical care that you will lose is the medical care you are getting as part of this study. You might be able to get that same kind of medical care outside of the study. Ask your study doctor.

Can I be removed from this study?

The study doctor may decide to stop your participation without your permission if the study doctor thinks that being in the study may cause you harm, or for any other reason.

What happens if I am injured or hurt during the study?

If you have an injury while you are in this study, you should call Dr. Pollyea immediately. His phone number is 720-848-8084.

We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

Who do I call if I have questions?

The researcher carrying out this study is Daniel A. Pollyea, MD. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Dr. Pollyea at 720-848-8084. You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Dr. Pollyea with questions. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

A description of this clinical trial will be available on http://www.Clinical Trials.gov. This Web site will not include information that can identify you. You can search this Web site at any time.

Who will see my research information?

The University of Colorado Denver (UCD) and its affiliated hospital(s) have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include:

- University of Colorado Denver
- University of Colorado Hospital

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the UCD and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information but confidentiality cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Daniel A. Pollyea, MD
Anschutz Medical Campus
1665 N. Aurora Court
Mail Stop F754
Aurora, CO 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB).
- The study doctor and the rest of the study team.
- Teva Pharmaceuticals, Inc., manufacturer of omacetaxine who is also providing a grant of funding support.
- Officials at the institution where the research is conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research.

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator.

Information about you that will be seen, collected, used and disclosed in this study:

- Name and demographic information (age, sex, ethnicity, address, phone number, etc.
- Portions of your previous and current medical records that are relevant to this study, including but not limited to diagnosis(es), history and physical, laboratory or tissue studies, radiology studies, procedure results.
- Research visit and research test records.
- Blood or biopsy samples and the data with the samples.
- Billing or financial information.

What happens to Data, Tissue, Blood and Specimens that are collected in this study?

Scientists at the University of Colorado Denver and the hospitals involved in this study work to find the causes and cures of disease. The data, tissue, blood and specimens collected from you during this study are important to this study and to future research. If you join this study:

- The data, tissue, blood, or other specimens given by you to the investigators for this research no longer belong to you.
- Both the investigators and any sponsor of this research may study your data, tissue, blood, or other specimens collected from you.

- If data, tissue, blood, or other specimens are in a form that identifies you, UCD or the hospitals involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

Agreement to be in this study and use my data

The research project and the procedures associated with it have been explained to me. The experimental procedures have been identified and no guarantee has been given about the possible results. I will receive a signed copy of this consent form for my records.

I agree to participate in this study. My participation is voluntary and I do not have to sign this form if I do not want to be part of this research study.

Subject Signature: _____ Date: _____

Subject Print Name:_____

Consent form explained by: _____ Date: _____

Print Name: _____

---------- ***Use Only if Applicable*** ----------

Signature Line for witness; required for consent of non-reading subjects and consent using a short form, if you requested such consent procedures

Witness of Signature ☐
Witness of consent process ☐

Witness Signature:_____ Date:_____

Witness Print Name: _____