Supplemental Data

Pracinostat plus azacitidine in older patients with newly diagnosed acute myeloid leukemia: results of a phase 2 study

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Supplemental Table 1

Supplemental Figure 1

Supplemental Figure 2

Supplemental Table 1. List of 295 genes targeted by next generation sequencing

Gene name									
ABCC9	*CALR*	*CUL5*	*FANCD2*	*HIST1H2BF*	*LEF1*	*NBN*	*PLA2G2D*	*SF3B1*	*TINF2 (TIN2)*
ABL1	*CARD11*	*CUX1*	*FANCE*	*HIST1H3D*	*LRP1B*	*NCOR1*	*PLCG2*	*SFRS1*	*TLR2*
ACTG1	*CBL*	*CYLD*	*FANCG*	*HIST1H4D*	*LTB*	*NCOR2*	*POT1*	*SFRS7*	*TLR9*
AKT1	*CBLB*	*DAXX*	*FANCI*	*HNRNPK*	*LUC7L2*	*NF1*	*POU2AF1*	*SGK1*	*TNFAIP3*
ANKRD11	*CCND1*	*DCLRE1C*	*FANCL*	*HRAS*	*LYN*	*NFE2*	*PRDM1*	*SH2B3*	*TNFRSF14*
ARID1A	*CCND3*	*DDX3X*	*FAS*	*ICOS*	*MALT1*	*NFKB1*	*PRKCB*	*SHH*	*TNKS*
ARID1B	*CD200*	*DIS3*	*FAT1*	*ID3*	*MAP2K1*	*NFKB2*	*PTEN*	*SMAD2*	*TOX*
ARID2	*CD274*	*DKC1*	*FAT3*	*IDH1*	*MAPK1*	*NFKBIA*	*PTPN1*	*SMC1A*	*TP53*
ARID5B	*CD58*	*DLC1*	*FBXW7*	*IDH2*	*MAX*	*NFKBIE*	*PTPN11*	*SMC3*	*TRAF3*
ARPP21	*CD79A*	*DNM2*	*FGFR3*	*IKBKA*	*MDM2*	*NOTCH1*	*RAD21*	*SMC5*	*TRAF6*
ASXL1	*CD79B*	*DNMT1*	*FLI1*	*IKZF1*	*MED12*	*NOTCH2*	*RAD51C*	*SNX7*	*TYK2*
ATF7IP	*CDK4*	*DNMT3A*	*FLT3*	*IKZF2*	*MEF2B*	*NPM1*	*RAG1*	*SOCS1*	*TYK3*
ATM	*CDKN2A*	*DNMT3B*	*FNDC3A*	*IKZF3*	*MEF2C*	*NR3C2*	*RAG2*	*SOX5*	*U2AF1*
ATRX	*CDKN2B*	*EBF1*	*FOXP1*	*IL7R*	*MGA*	*NRAS*	*RASA2*	*SP140*	*U2AF2*
B2M	*CDKN2C*	*ECT2L*	*FYN*	*IRAK1*	*miR125a*	*NSD2*	*RB1*	*SPEN*	*UBR5*
BCL10	*CEBPA*	*EED*	*G6PC3*	*IRAK4*	*miR-142*	*NT5C2*	*REL*	*SPIB*	*USP29*
BCL2	*CEBPE*	*EGR1*	*GAB2*	*IRF1*	*mIR155*	*PAG1*	*RELA*	*SRSF2*	*VPREB1*
BCL6	*CHD2*	*EGR2*	*GATA1*	*IRF4*	*mIR15a*	*PALB2*	*RELB*	*STAG1*	*WHSC1*
BCL7A	*CHK2*	*ELANE*	*GATA2*	*IRF7*	*mIR16-1*	*PAX5*	*RELN*	*STAG2*	*WHSC1L1*
BCOR	*CIITA*	*EP300*	*GATA3*	*ITPKB*	*MIR17HG*	*PDCD1*	*RHOA*	*STAT1*	*WT1*
BCR	*CNOT3*	*EPHA7*	*GCET2*	*JAK1*	*mIR21*	*PDCD1LG2*	*RIPK1*	*STAT3*	*XPO1*
BIRC3	*CREBBP*	*EPOR*	*GFI1B*	*JAK2*	*mir34b*	*PDGFRB*	*ROBO1*	*SUZ12*	*ZAP70*
BLK	*CRLF2*	*ERG*	*GNA13*	*JAK3*	*mir34c*	*PEG3*	*ROR1*	*SYK*	*ZMYM2*
BMI1	*CSF2RA*	*ETV6*	*GNAS*	*JARID2*	*MLL*	*PHF6*	*RPL10*	*TBL1XR1*	*ZMYM3*
BRAF	*CSF3R*	*EZH2*	*GNB1*	*KDM4C*	*MLL2*	*PHIP*	*RPL5*	*TCF3*	*ZRSR2*
BRIP1	*CTBP1*	*FAM46C*	*GPRC5A*	*KDM6A*	*MLL3*	*PIGA*	*RUNX1*	*TERC*	
BTG1	*CTBP2*	*FAM5C*	*HAX1*	*KIT*	*MPL*	*PIK3CA*	*RUNX2*	*TERT*	
BTK	*CTCF*	*FANCA*	*HIST1H1E*	*KLHL6*	*MS4A1*	*PIK3CB*	*SAMHD1*	*TET1*	
BTLA	*CTLA4*	*FANCB*	*HIST1H2AD*	*KRAS*	*MYB*	*PIK3CG*	*SETBP1*	*TET2*	
C22orf194	*CTNNA1*	*FANCC*	*HIST1H2BE*	*LAMB4*	*MYD88*	*PIK3R1*	*SETD2*	*TGDS*	

Supplemental Figure 1. Longitudinal sequencing analysis for 10 patients who achieved CR to therapy. (A-J)

Each panel shows data for 1 patient.

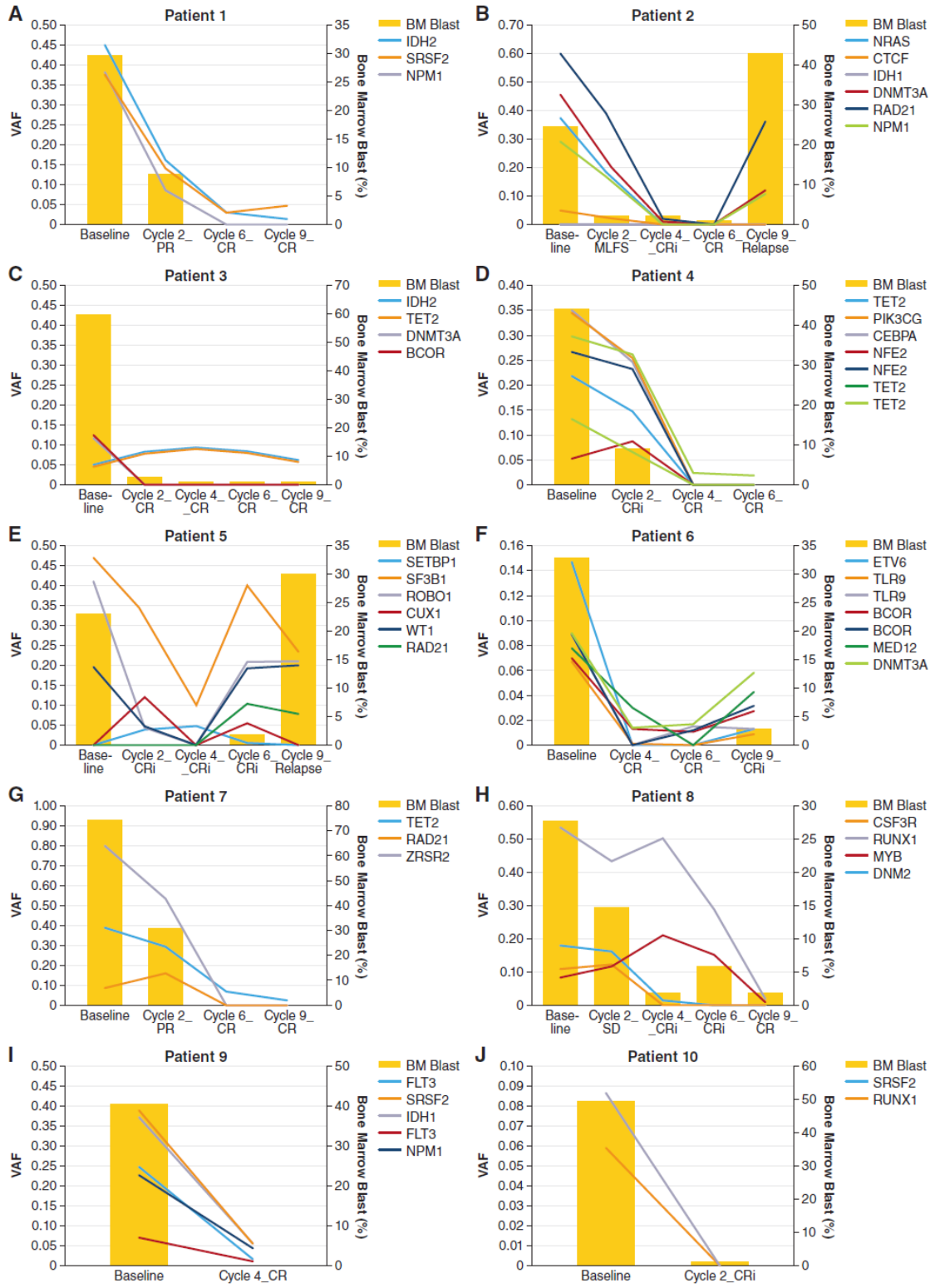
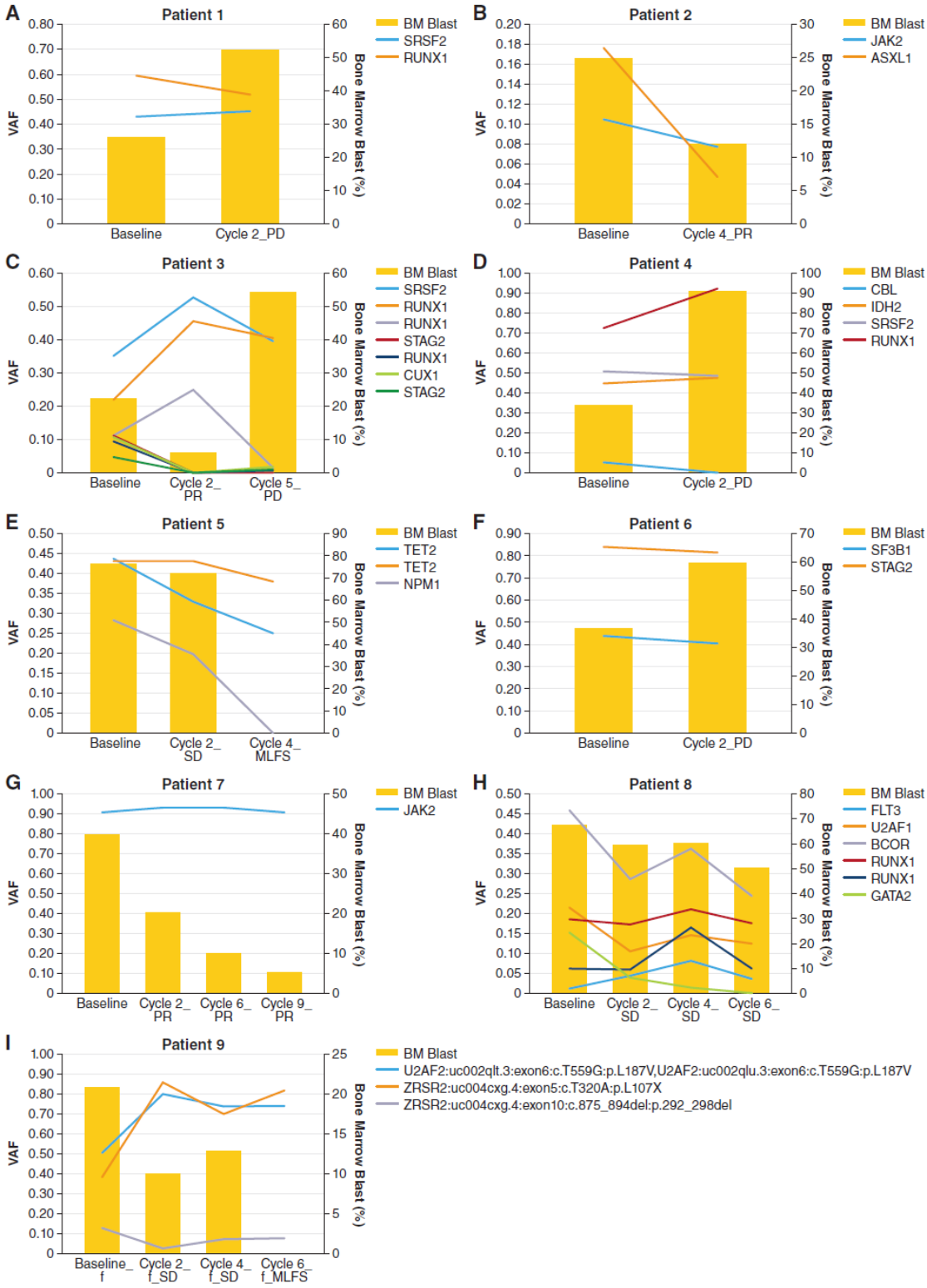


Figure S2. Longitudinal sequencing analysis for 9 patients who had no response, stable disease (SD), partial response (PR), or MLFS to therapy with pracinostat plus azacitidine. (A-I) Each panel shows data for 1 patient.



A PHASE II OPEN-LABEL, SINGLE-ARM, TWO-STAGE, MULTICENTER TRIAL OF PRACINOSTAT IN COMBINATION WITH AZACITIDINE IN ELDERLY (AGE ≥65 YEARS) PATIENTS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA (AML)

Protocol Number:	MEI-004
IND Number:	79,597
Study Drugs:	Pracinostat with azacitidine
Sponsor:	Helsinn Healthcare SA
Delegated to Conduct the Study:	MEI Pharma, Inc.
Version:	3.0
Date Amendment #3:	26 October 2016
Date Amendment #2:	30 March 2016
Date Amendment #1:	20 January 2014
Date Original:	20 June 2013

SYNOPSIS

Title of Study:	A Phase II Open-Label, Single-arm, Two-Stage, Multicenter Trial of Pracinostat in Combination with Azacitidine in Elderly (Age ≥ 65 Years) Patients with Newly Diagnosed Acute Myeloid Leukemia (AML)	
Protocol Number:	MEI-004	
Sponsor: **Delegated to Conduct the Study**	Helsinn Healthcare SA MEI Pharma, Inc.	
Study Drugs:	Pracinostat with azacitidine	
Study Duration:	The total duration of this study is planned to be approximately 21 months.	**Phase of Study:** II
Study Centers:	This is a multicenter study to be conducted in the United States.	
Number of Subjects:	Up to 50 subjects are planned to be enrolled in this study.	
Objectives:	**Primary Objective:** The primary objective of this study is to: • Estimate the rate of complete response (CR) + CR with incomplete blood count recovery (CRi) + morphologic leukemia free state (MLFS) to the combination of pracinostat and azacitidine. **Secondary Objectives:** The secondary objectives of this study are to: • Estimate the overall response rate (ORR) (CR + CRi + partial response [PR] + PR with incomplete blood count recovery [PRi] + MLFS) to pracinostat plus azacitidine • Estimate the rate of complete cytogenetic response (CRc) + molecular complete remission (CRm) to pracinostat plus azacitidine • Estimate the duration of response to pracinostat plus azacitidine • Estimate the progression-free survival (PFS) duration after pracinostat plus azacitidine • Estimate the overall survival (OS) duration after pracinostat plus azacitidine • Assess the tolerability and adverse event (AE) profile of pracinostat when combined with azacitidine.	
Study Design:	This is a Phase II nonrandomized, open-label, single-arm, uncontrolled, two-stage study of pracinostat in combination with Vidaza (azacitidine) in elderly patients with AML (referred to as subjects). In Stage 1 of the study, 27 efficacy evaluable subjects will be enrolled and assessed for response. If a CR or CRi or MLFS is reported for <3 subjects in Stage 1, the stopping criteria will be met. If a CR or CRi or MLFS is reported for 2:3 subjects in Stage 1, an additional 13 efficacy evaluable subjects will be enrolled in Stage 2 for a total of 40 subjects.	

Study Design (continued):	All subjects will receive study drug in 28-day cycles, with pracinostat administered orally (PO) 3 days a week for 3 weeks followed by 1 week of rest and azacitidine administered subcutaneously (SC) or intravenously (IV) once a day on Days 1 through 7 of each cycle or on Days 1 through 5 and Days 8 and 9 of each cycle. After providing informed consent, subjects will be assessed for eligibility and have screening safety and efficacy assessments performed, including screening bone marrow aspirate and bone marrow biopsy [BMBx] and complete blood count (CBC) with manual differential and blast counts for a screening disease assessment (efficacy) and cytogenetic classification (eligibility). Subjects must have all screening safety and eligibility assessments completed within 14 days of Cycle 1 Day 1. Subjects meeting eligibility criteria will return to the study site to receive the first doses of pracinostat and azacitidine on Cycle 1 Day 1. On Day 1 of each cycle, subjects will have pre-dose safety assessments (i.e., physical examination, vital signs, Eastern Cooperative Oncology Group [ECOG] performance status, AE and concomitant medication review, CBC with manual differential and blast counts and serum chemistry) followed by PO administration of pracinostat then SC injection or IV infusion of azacitidine. The same safety assessments will be done on Day 1 of each cycle with the exception of 12-lead electrocardiogram (ECG), which will be done before pracinostat dosing and repeated 90 minutes after initiation of pracinostat and azacitidine dosing on Day 1 of Cycles 1 and 2 and as medically needed at subsequent cycles. The full cycle of pracinostat will be dispensed to the subject on Day 1 of each 28-day cycle, to be self-administered at home. Subjects will only self-administer pracinostat at the site on Day 1 of each 28-day cycle. Depending on the selected dosing regimen, subjects will return to the study site for azacitidine administration and AE and concomitant medication review on Days 2 through 7 of each cycle or on Days 2 through 5 and Days 8 and 9 of each cycle. On Days 8, 15, and 22 of Cycle 1 only, subjects will return to the site for AE and concomitant medication review and CBC assessment at each visit, serum chemistry (Day 15 only), vital signs (Days 15 and 22 only), and drug compliance assessment (Day 22 only). At subsequent cycles, subjects will return to the site on Day 15 for CBC assessment. Bone marrow aspiration and BMBx for response assessment and cytogenetic assessment (classical cytogenetics are required at all bone marrow assessments; if abnormal, FISH and molecular studies are to be performed at all bone marrow assessments) and CBC with manual differential and blast counts (if abnormal cells are identified on the automated differential) will be done on Cycles 2, 4 and 6 (Day 28 ±4 days) and every 3 cycles thereafter (e.g., Cycles 9, 12, etc.) until CR is achieved, with evidence of normalization of peripheral blood counts, or at any time with suspicion of disease progression (PD). Treatment (pracinostat + azacitidine) should be continued until PD, intolerable toxicity, death, condition requiring prohibited therapeutic intervention, intercurrent illness, or subject/Investigator request. The median time to response was between 3 and 3.5 months in 2 small studies with single agent azacitidine; thus reasonable attempts should be made to avoid premature discontinuation. The activities under this Amendment follow the decision to close the Long-term Follow-up phase of the study, which entailed following subjects who had

Study Design (continued):	discontinued pracinostat for disease progression and survival, while allowing the subjects who benefitted from administration of pracinostat in combination with azacitidine to continue on study. These subjects will remain on study until either the Investigator deems it is in the subject's best interest to discontinue receiving pracinostat, when pracinostat is approved by the US Food and Drug Administration, or when the Sponsor or its delegate (MEI Pharma, Inc., referred to as "MEI") decides to close the study, whichever occurs first. Amendment 3 does not change study drug administration, study visits or assessments performed on active subjects, as described in Amendment 2. This phase of the study is defined as the Active Continuation Phase. Study assessments performed during the Active Continuation Phase include dispensing pracinostat, assessing for compliance and accountability, checking for SAE occurrences and response evaluation, if applicable. For the remainder of the study, paper case report forms (CRFs) will be used to collect study data. Further, overall site management activities will transition to MEI Pharma, Inc. An End of Study Visit should be done no less than 7 days and no more than 30 days after treatment ends (or prior to starting new treatment, if urgent treatment is required).
Study Drugs, Doses, and Modes of Administration:	**Pracinostat (repeated every 28 days)**: All subjects will receive pracinostat 60 mg PO once a day 3 days a week with doses approximately 48 hours apart (e.g., Monday, Wednesday, and Friday) for 3 weeks, followed by 1 week of rest. Subjects will self-administer pracinostat at the site on Day 1 of each 28-day cycle. Subjects are to be fasting for at least 2 hours on days when pracinostat is administered at the site. On all other days on which pracinostat administration is scheduled, subjects will self-administer pracinostat at home at least 2 hours after eating or 30 minutes prior to eating breakfast, at approximately the same time of each of the 3 days weekly. Pracinostat is not to be taken with food. Pracinostat is not to be taken with grapefruit or any other juice, only water. **Azacitidine (repeated every 28 days)**: All subjects will receive a standard regimen of azacitidine of 75 mg/m^2 for 7 days of each cycle. Delivery via SC injection is preferred, but IV infusion is allowed if SC injections are intolerable. Administration may be as one of two schedules: • Schedule 1: continuous therapy on Days 1 through 7 of each cycle; or • Schedule 2: a 5-2-2 schedule wherein subjects receive azacitidine for 5 consecutive weekdays (Days 1 through 5) and resume azacitidine dosing the first 2 weekdays of the next week (Days 8 and 9) of each cycle. The schedule is to be declared for each subject and used for the duration of study participation.

Inclusion Criteria:	1. Male or female subjects aged 2:65 years. 2. Voluntary written informed consent before performance of any study related procedure not part of normal medical care. 3. Newly diagnosed de novo, secondary, or treatment-related AML with intermediate or unfavorable-risk cytogenetics based on the Southwest Oncology Group (SWOG) classifications (Slovak et al, 2000). 4. One prior cycle of therapy with an approved hypomethylating agent (HMA) such as azacitidine or decitabine is allowed for either an antecedent hematologic disorder (AHD) or AML. Patients are also eligible if they have received lenolidamide, immunosuppressive therapy or low dose chemotherapy for their AHD. Prior hydroxyurea is allowed. 5. ECOG performance status of 0, 1, or 2. 6. ≥20% blasts in bone marrow. 7. Peripheral white blood cell (WBC) count <30,000/μL. 8. Adequate organ function as evidenced by: • Total bilirubin ≤2 × upper limit of normal (ULN) • Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN • Serum creatinine ≤2 × ULN 9. QT-interval corrected according to Fridericia's formula (QTcF) ≤450 milliseconds (ms) for male subjects or ≤470 ms for female subjects on ECG at Screening. 10. Male subjects who are surgically sterile or willing to use adequate contraceptive measures or abstain from heterosexual intercourse during the entire study treatment period. 11. Female subjects who are not of childbearing potential. 12. Willingness and ability to understand the nature of this study and to comply with the study and follow-up procedures.

Exclusion Criteria:	1. Acute promyelocytic leukemia (French-American-British [FAB] M3 classification). 2. Known AML-associated t(15;17), t(8;21), t(16;16), del(16q), or inv(16) karyotype abnormalities. 3. Presence of a malignant disease within the last 12 months, with the exception of adequately treated in-situ carcinomas, basal or squamous cell carcinoma, or non-melanomatous skin cancer. Other malignancies will be considered on a case-by-case basis. 4. Life-threatening illnesses other than AML, uncontrolled medical conditions or organ system dysfunction that, in the Investigator's opinion, could compromise the subject's safety, or put the study outcomes at risk. 5. Uncontrolled or symptomatic arrhythmias, unstable angina, or any Class 3 or 4 cardiac diseases as defined by the New York Heart Association (NYHA) Functional Classification. 6. Clinical evidence of central nervous system (CNS) involvement. 7. Are candidates for intensive chemotherapy (induction chemotherapy, bone marrow, or stem cell transplant) within the next 4 months. 8. Received more than one prior cycle of HMA, previous bone marrow transplant or other intensive chemotherapy regimens for either an AHD or AML. 9. Received prior radiation therapy for extramedullary disease within 2 weeks of study enrollment. 10. Received prior histone deacetylase (HDAC) inhibitor or deacetylase (DAC) inhibitor is not permitted such as Istodax (romidepsin/depsipetide) or valproic acid. 11. Received hematopoietic growth factors: erythropoietin, granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), or thrombopoietin receptor agonists within 7 days (14 days for Aranesp) prior to study enrollment. 12. Have been treated with any chemotherapeutic agent within 2 weeks or 5 half-lives of the first dose of study drug, whichever is longer. 13. Are being treated with systemic corticosteroids. Inhaled and topical steroids as well as intermittent dexamethasone for nausea or vomiting are permitted. 14. Known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV). 15. Uncontrolled active systemic infections. 16. Gastrointestinal (GI) tract disease, causing the inability to take oral medication, malabsorption syndrome, a requirement for IV alimentation, prior surgical procedures affecting absorption, or uncontrolled inflammatory GI disease (e.g., Crohn's disease, ulcerative colitis). 17. Any disease(s), psychiatric condition, metabolic dysfunction, or findings from a physical examination or clinical laboratory test result that would cause reasonable suspicion of a disease or condition, that contraindicates the use of study drugs, that may increase the risk associated with study participation, that may affect the interpretation of the results, or that would make the subject inappropriate for this study.

Criteria for Evaluation:	**Efficacy:** Efficacy will be evaluated by response assessments based on hematological and cytogenetic examination of peripheral blood and bone marrow aspirates and BMBx, using International Working Group (IWG) criteria (Cheson et al, 2003). **Safety:** Safety will be assessed by AEs (graded according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.03), laboratory safety tests including hematology (CBC) and serum chemistry, physical examination, vital signs, ECOG performance status, and 12-lead ECG.
Statistical methods:	The primary efficacy endpoint is Investigator-assessed CR + CRi + MLFS rate, defined as the proportion of subjects assessed as having a CR plus subjects with CRi plus subjects with MLFS according to the IWG criteria. The primary analysis will be based on the Efficacy Evaluable population. In previous studies of azacitidine monotherapy in subjects with AML, the CR rates ranged from 10% to 20%. This exploratory study will evaluate the CR + CRi + MLFS rate of pracinostat + azacitidine in the primary analysis. Based on the available data, a CR + CRi + MLFS rate of 10% would indicate that there is no value in further investigation of the proposed combination treatment. It is estimated that the CR + CRi + MLFS rate under the combination treatment of azacitidine and pracinostat will be 25%. To calculate sample size, Simon's two-stage design will be used. The null hypothesis with $p_0 = 0.10$ for the CR + CRi + MLFS rate will be tested against a one-sided alternative with $p_1 = 0.25$. In the first stage, 27 efficacy evaluable subjects will be enrolled. If <3 of the 27 subjects report a CR or CRi or MLFS the early stopping criteria will be met. For the second stage, an additional 13 efficacy evaluable subjects will be enrolled for a total of 40 subjects. The null hypothesis will be rejected if 7 or more responses are observed in the 40 efficacy evaluable subjects. This design yields a type I error rate of 0.10 and power of 0.90 when the true response rate is 0.25.

APPENDIX A: SCHEDULE OF ASSESSMENTS

Assessments	*Screen*[a]	*Study Treatment Cycles (28 days ±4 days)*[b]											*Response Evaluation*	*Active Continuation Phase*[d]	*End of Study Visit*[c]
Week	***-2***	***1***	***1***	***1***	***1***	***1***	***1***	***1***	***2***	***2***	***3***	***4***			
Study Day[b]	***-14***	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***15***	***22***	***[28/PD]***[e,f]		
Obtain informed consent[g]	X														
Determine eligibility[h]	X														
Medical history and prior medication[i]	X	X													
Physical examination	X	X[a]													
Vital signs[j]	X	X									[X][k]	[X][k]			
ECOG performance status	X	X													
Baseline signs and symptoms of AML	X														
AEs/toxicity assessment[l]		X	X	X	X	X	X	X	X	X	X	[X][k]		X	X
Concomitant medication review[l]		X	X	X	X	X	X	X	X	X	X	[X][k]			
12-Lead ECG[m]	X	X													
Complete blood count (CBC)[n]	X	X[a]							[X][k]		X	[X][k]			
Serum chemistry[o]	X	X[a]									[X][k]				
Bone marrow aspiration and biopsy[e,f]	X												X	X	X
Dispense/collect unused study drug[p]		X												X	X
Assess study drug compliance[p]		X										[X][k]		X	X
New treatments and survival															
Pracinostat administration[p]		X		X		X			X		X			X	
Azacitidine administration[q]															
--Azacitidine administration (1-7)[r]		X	X	X	X	X	X	X						X	
--Azacitidine administration (5-22)[s]		X	X	X	X	X			X	X				X	

AE = adverse event; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AML = acute myeloid leukemia; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CO_2 = carbon dioxide; CR = complete response; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group;
IV = intravenous; LDH = lactate dehydrogenase; PD = disease progression; QTcF = QT-interval corrected according to Fridericia's formula; SC = subcutaneous

a Screening Visit should occur ≤14 days before commencement of Cycle 1 Day 1. Day 1 physical examination does not need to be repeated if performed within 7 days of Cycle 1 Day 1, Day 1 laboratory assessments do not need to be repeated if performed within 72 hours of Cycle 1 Day 1. Subjects are to be fasting for at least 2 hours on days when pracinostat is administered at the site.

b There is ±4 day window allowable for each clinic visit.

c End-of-Study evaluations are required no less than 7 days and no more than 30 days after treatment ends (or prior to starting new treatment, if urgent treatment is required).

Active Continuation Phase: All subjects in this phase of the study should complete the End of Study visit prior to study discontinuation.

d **Active Continuation Phase: This visit should occur every 3 months (±1 month window).**

e Bone marrow [BM] aspirations and biopsies will be performed at Screening within 28 days of Cycle 1 Day 1. For response assessments, bone marrow biopsy and aspirate will be done for clinical response at Cycles 2, 4, and 6 (Day 28 ±4 days) and every 3 cycles thereafter (e.g., Cycles 9, 12 etc. [Day 28 ±4 days]) until CR is achieved, with evidence of normalization of peripheral blood counts, or at any time with suspicion of PD. Timing of response assessment is thus denoted by [28/PD]. CBC with manual differential and blasts is required for response assessment. **Active Continuation Phase: response assessment, when applicable, should be completed at each Active Continuation Phase visit and at the End of Study visit.**

f Classical cytogenetics will be required with BM aspirate and biopsies. Fluorescence in situ hybridization (FISH) and molecular studies may be conducted as per standard of care, but are not required. Subjects with abnormal cytogenetics, FISH, and/or molecular studies at Screening will have applicable follow-up assessments done with each BM biopsy. Saliva (at Screening only), bone marrow aspirate, and peripheral blood samples will be collected and stored for potential correlative molecular studies at Screening, at the initial on-study bone marrow biopsy [e.g. Cycle 2 Day 28 ±4 days] and with clinical response and/or suspicion of progression.

g Written informed consent must be obtained prior to any study-related procedure being initiated.

h Inclusion/exclusion criteria must be met prior to enrollment into the study on Cycle 1 Day 1, including results of cytogenetic testing of bone marrow aspirate and biopsies for risk classification.

i Medical history and prior medications will be collected at Screening and Cycle 1 Day 1 only.

j Vital signs are to include height (at Screening only), weight, blood pressure, heart rate, and oral temperature.

k Assessments noted with [X] are to be done during Cycle 1 only. All other assessments are to be done during all cycles including Cycle 1, unless otherwise specified.

l AEs and concomitant medications are to be monitored from the start of study treatment on Cycle 1 Day 1 until 30 days after last dose of drug taken on study or until initiation of new AML treatment, whichever occurs first. **Active Continuation Phase: During this Phase of the study, only SAEs will be followed. At the End of Study visit, SAEs should be followed until 30 calendar days of last study drug treatment, or until initiation of new therapy for AML, whichever occurs first. SAEs must be reported to MEI on the SAE form and followed until resolution (with autopsy report, if applicable).**

m ECG is to be taken in triplicate (approximately every 5 minutes) to calculate the average QTcF. On Day 1 of Cycles 1 and 2 only, triplicate ECGs will be done pre-dose, pracinostat will be taken, and azacitidine will be administered. Triplicate ECGs will be repeated 90 minutes (+/- 15 min) post-pracinostat dosing. Beyond Cycle 2, ECGs will be performed as medically necessary.

n CBC with manual differential and blast counts (if abnormal cells are identified on the automated differential) is to be performed on Day 1 and Day 15 of each 28-day cycle, on Day 8 and Day 22 of Cycle 1 only, with suspicion of PD, with evidence of normalization of peripheral blood counts, and if PD occurs during follow-up.

o Serum chemistry (glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO_2, ALP, AST, ALT, total bilirubin, total protein, albumin, and LDH) is to be performed on Day 1 of each cycle and on Day 15 of Cycle 1 only.

p Pracinostat capsules will be dispensed to the subject at the beginning of each cycle. The capsules (60 mg dose) will be self-administered by the subject orally, at least 2 hours after eating or 30 minutes before breakfast 3 days/week (e.g., Monday, Wednesday, and Friday) for 3 weeks, followed by 1 week of rest; this scheme will be repeated for every 28-day cycle. Subjects will only self-administer pracinostat at the site on Day 1 of each 28-day cycle. Subjects are to be fasting for at least 2 hours on days when pracinostat is administered at the site. Pracinostat should be taken with a full glass of water. Pracinostat is not to be taken with grapefruit or any other juice, only water. Study drug compliance will be assessed on Day 22 of Cycle 1 only. Following Cycle 1, study drug compliance will be assessed on Day 1 of each cycle and at the End of Study Visit (if applicable). **Active Continuation Phase: pracinostat administration is denoted at this visit; however, pracinostat dosing will be based on the subject's current dosing schedule**

q Azacitidine is to be administered at 75 mg/m^2 via SC injection or IV infusion 7 days of every 28-day cycle. Each subject will follow a preferred dose regimen (1-7 or 5-2-5) for the duration of study participation.

r Subjects at sites selecting a 1-7 regimen will receive azacitidine on Days 1 through 7 days of every 28-day cycle.

s Subjects at sites selecting a 5-2-2 regimen will receive azacitidine on Days 1 through 5 and Days 8 and 9 of every 28-day cycle. The weekend days (Days 6 and 7) are rest days.