SUPPLEMENTARY APPENDIX

METHODS

Eligibility criteria

Inclusion criteria

1. Patients with AML, biphenotypic or bilineage leukemia (including a myeloid component) or mixed phenotype acute leukemia (MPAL) who have failed prior therapy. Patients with AML should have failed prior therapy or have relapsed after prior therapy. Patients with isolated extramedullary AML are eligible.
2. Elderly (>60 year old) patients with newly diagnosed AML or mixed phenotype acute leukemia (MPAL) not eligible for intensive chemotherapy.
3. AML patients with prior history of MDS or CMML who received any therapy or no therapy for the MDS or CMML and progressed to AML, are eligible at the time of diagnosis of AML regardless of any prior therapy for MDS. The WHO classification will be used for AML.
4. Patients with high-risk MDS, and chronic myelomonocytic leukemia (CMML) with bone marrow blasts between 10% and 20%, relapsed or refractory to prior hypomethylating agent (HMA) therapy, defined as prior receipt of 4 cycles of HMA therapy with failure to attain a response, or relapse after prior response to HMA therapy.
5. Age ≥18 years
6. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤3
7. White blood cell count≤10,000.
8. Adequate renal function including creatinine < 2 unless related to the disease.
9. Adequate hepatic function including total bilirubin < 2x upper limit of normal (ULN) unless increase is due to Gilbert's disease or leukemic involvement, and ALT < 3x ULN unless considered due to leukemic involvement
10. Provision of written informed consent
11. Oral hydroxyurea and/or one dose of cytarabine (up to 2 g/m^2) for patients with rapidly

proliferative disease is allowed before the start of study therapy and while the patient is on active study treatment through cycle 1, as needed, for clinical benefit and after discussion with the PI. Concurrent therapy for central nervous system (CNS) prophylaxis or continuation of therapy for controlled CNS disease is permitted.

12. Females must be surgically or biologically sterile or postmenopausal (amenorrheic for at least 12 months) or if of childbearing potential, must have a negative serum or urine pregnancy test within 72 hours before the start of the treatment
13. Women of childbearing potential must agree to use an adequate method of contraception during the study and until 3 months after the last treatment. Males must be surgically or biologically sterile or agree to use an adequate method of contraception during the study until 3 months after the last treatment.

Exclusion criteria:

1. Patients having received any prior BCL2 inhibitor therapy.
2. Patients with t(15;17) karyotypic abnormality or acute promyelocytic leukemia (French-American-British [FAB] class M3-AML).
3. Patients with symptomatic CNS leukemia or patients with poorly controlled CNS leukemia.
4. Active and uncontrolled comorbidities including active uncontrolled infection, uncontrolled hypertension despite adequate medical therapy, active and uncontrolled congestive heart failure NYHA class III/IV, clinically significant and uncontrolled arrhythmia as judged by the treating physician.
5. Patients with known infection with human immunodeficiency virus (HIV) or active Hepatitis B or C.
6. Any other medical, psychological, or social condition that may interfere with study participation or compliance, or compromise patient safety in the opinion of the investigator.
7. Pregnant or breastfeeding.

Tumor lysis syndrome prophylaxis

The venetoclax dose titration scheme utilized in the AML studies performed to date to mitigate the risk of tumor lysis syndrome (TLS) will be employed. All patients will be hospitalized for the entirety of the venetoclax dose escalation starting at least on day -1 of treatment initiation and until 24 hours after the completion of venetoclax dose escalation. Venetoclax will be administered at a dose of 100 mg on day 1, 200 mg on day 2, and 400 mg on day 3-28 of the first cycle. See Section

To mitigate the risk for TLS, subjects must be receiving tumor lysis prophylaxis, including hydration (oral, intravenous) and treatment with a uric acid reducing agent (allopurinol, rasburicase) prior to and during the venetoclax ramp up period of Cycle 1.

TLS chemistry tests (potassium, uric acid, creatinine, calcium and phosphorus) will be obtained prior to dosing and 6-8 hours after each day of a new venetoclax dose. TLS chemistry test results will be reviewed by the investigator in real time and prior to the subject's next dose to ensure appropriate management. If a subject meets criteria for clinically significant laboratory or clinical TLS, no additional venetoclax should be administered until resolution.

Venetoclax interruption for up to 72 hours following transient (< 48 hours) chemical changes and laboratory TLS will be allowed and will not require a dose reduction.

Intrathecal chemoprophylaxis

Intrathecal prophylaxis with cytarabine and/or methotrexate is standard in the therapy of acute lymphoblastic leukemia, but not currently a part of standard AML protocols. Patients with high-risk disease, including WBC higher than $100x10^9$/L at presentation, those with LDH higher than 700 units/L, and those with *FLT3*^{mut} disease may be at higher risk of central nervous system (CNS) disease.[1] Enrolled patients were eligible to receive intrathecal cytarabine administered via lumbar puncture (LP) or through Ommaya reservoir on cycle 1 day 21 (+/- 7 days) or Cycle 2 Day 14 +/- 7 days. Peripheral WBC at the time of LP should be ≤1 $x10^9$/L and peripheral blasts should be ≤1%. Patients with controlled CNS leukemia will be allowed to continue on clinical trial.

Response Criteria

Modified International Working Group Response Criteria for AML (1). Responders are patients who obtain a CR, CRp, CRi, PR or marrow clearance of blasts ("morphologic leukemia-free state") within 3 months of treatment initiation. Briefly, criteria are as follows:

Response	**Response criteria**
Complete remission (CR)	Peripheral blood counts: • No circulating blasts • Neutrophil count ≥1·0 x10^9/L • Platelet count ≥100 x10^9/L Bone marrow aspirate and biopsy: • ≤5% blasts • No Auer rods • No extramedullary leukemia Peripheral blood counts: • No circulating blasts • Neutrophil count ≥1·0 x10^9/L • Platelet count ≥100 x10^9/L
Complete remission with incomplete blood count recovery (CRi)	Peripheral blood counts: • No circulating blasts • Neutrophil count <1·0 x10^9/L, or • Platelet count <100 x10^9/L Bone marrow aspirate and biopsy: • ≤5% blasts • No Auer rods • No extramedullary leukemia
Partial remission	All CR criteria if abnormal before treatment except: • ≥50 % reduction in bone marrow blast but still >5%
Morphologic leukemia-free state (MLFS)	Bone marrow: ≤5% myeloblasts

PCR-based 81-gene Next Generation Sequencing (NGS) panel

Genomic DNA was extracted from bone-marrow aspirates. Amplicon-based NGS targeting the entire coding regions of a panel of 81 genes associated with myeloid neoplasms was done with a MiSeq platform (Illumina, San Diego, CA, USA). Analyzed genes included *ANKRD26, ASXL1, ASXL2, BCOR, BCORL1, BRAF, BRINP3, CALR, CBL, CBLB, CBLC, CEBPA, CREBBP, CRLF2, CSF3R, CUX1, DDX41, DNMT3A, EED, ELANE, ETNK1, ETV6, EZH2, FBXW7, FLT3, GATA1, GATA2, GF11, GNAS, HNRNPK, HRAS, IDH1, IDH2, IKZF1, IL2RG, IL7R, JAK1, JAK2, JAK3, KDM6A, KIT, KMT2A, KRAS, MAP2K1, MPL, NF1, NOTCH1, NPM1, NRAS, PAX5, PHF6, PIGA, PML, PRPF40B, PTEN, PTPN11, RAD21, RARA, RUNX1, SETBP1, SF1, SF3A1, SF3B1, SH2B3, SMC1A, SMC3, SRSF2, STAG2, STAG1, STAT3, STAT5A, STAT5B, SUZ12, TERC, TERT, TET2, TP53, U2AF2, U2AF1, WT1, ZRSR2*.

A sequencing library was prepared using 250 ng DNA template. Equal quantities of DNA from purified sequencing libraries were used for TruSeq paired-end sequencing on the MiSeq sequencer, using the MiSeq Reagent Kit v2 (500 cycles). Variant calling was performed with Illumina MiSeq Reporter Software, using human genome build 19 (hg 19) as a reference. For clinical reporting, a minimum of 250 times sequencing coverage (bi-directional true paired-end sequencing) was required. The analytical sensitivity was established at 5% mutant reads in a background of wild-type reads. Previously described somatic mutations registered at the Catalogue of Somatic Mutations in Cancer (COSMIC: http://cancer.sanger.ac.uk/cosmic) were considered as potential driver mutations.

BCL2 expression by flow cytometry

BCL2 expression in neoplastic cells was assessed by multiparameter flow cytometry (MFC) analysis, which was performed on FACS Canto II analyzers (BD Biosciences, Mountain View, CA) using bone marrow aspirate material collected in EDTA. Details of the MFC panel and gating strategies used at MD Anderson Cancer Center were described by our group previously.[2] The blast gate was defined on the basis of CD45dim expression and side-scatter characteristics and quantified as a percentage of total gated events. BCL2 expression was measured using a FITC-conjugated anti-BCL2 antibody from Dako (clone 124, Glostrup, Denmark) according to the manufacturer's recommendation. A control tube including all antibodies (CD45, CD34, CD117) except for BCL2, was served as florescence minus one (FMO) control. BCL2 expression on T-cells was used as an internal positive control. For BCL2 expression, the measurements included the percent of expression over FMO, mean fluorescence intensity (MFI) and relative mean fluorescence intensity (RFI) ratio over FMO controls. At least 200,000 events per sample were acquired. Data were analyzed using FCS Express software (De Novo Software, Los Angeles, CA).

Statistical Methods

Interim Monitoring Rules: For any particular disease arm, if at any time during the study we determine that there was less chance (i.e., <2.5%) that the response rate improves, the corresponding disease arm would be stopped due to futility. Similarly, if it was likely (i.e., >95%) that the unacceptable toxicity rate was higher than 30%, the patient enrollment would be suspended.

Assumptions for determining sample sizes of respective cohorts: If the study is not stopped early and continues through to full enrollment and all patients are treated and evaluated, then assuming 72 responders out of 120 older patients with ND AML, the 95% CI for ORR will be (0.51, 0.69); assuming 20 responders out of 80 patients with sAML with history of AHD, the 95% CI for ORR will be (0.16, 0.35); assuming 20 responders out of 80 patients with R/R AML, the 95% CI for ORR will be (0.16 ,0.35); assuming 8 responders out of 40 patients with high-risk MDS/CMML, R/R to prior HMA, the 95% CI for ORR will be (0.09, 0.33) and assuming 20 responders out of 40 younger patients with ND adverse risk AML with complex cytogenetics or *TP53*^{mut}, the 95% CI for ORR will be (0.35, 0.65).

Prespecified population as per protocol and post-hoc assessments: All patients receiving at least one dose of decitabine and venetoclax were eligible for safety and response assessments regardless of duration of treatment. Patients who experienced adverse events during the screening period but who did not start on study treatment due to reason that include, but not limited to ineligibility, screen failure, death or withdrawal of consent, were not included in the safety or response evaluable population. The prespecified population for ORR included all patients per protocol, for OS included all patients per protocol, for CR/CRi DOR included all patients achieving CR/CRi, for MRD assessment included all patients per protocol, for adverse events included all patients per protocol. For post-hoc assessment, patients were categorized as those who were treatment-naïve and those who had received prior treatment for AHD or AML.

The treatment-naïve AML group included ND AML and untreated sAML with AHD. The previously treated AML group included sAML with prior therapy for MDS/CMML, and R/R AML.[3] A separate post-hoc assessment was conducted for patients proceeding to stem-cell transplantation after response with study treatment.

SUPPLEMENTAL RESULTS

Table S1. Response rates by subgroups of treatment-naïve AML, including newly diagnosed AML and untreated secondary AML

Subgroups	ORR	CR	CRi	MLFS	MRD-	CR/CRi DOR	OS	1-year OS
	n (%) or n/N (%)					months, median		%
De novo AML (n=55)	49 (89)	38 (69)	8 (15)	3 (5)	29/41 (71)	NR	NR	74
Therapy-related AML (n=16)	14 (88)	8 (50)	5 (31)	1 (6)	6/12 (50)	7·0	6·9	10
ELN Risk Groups								
Favorable (n=19)	19 (100)	15 (79)	2 (11)	2 (11)	12/15 (80)	NR	NR	75
Intermediate (n=11)	11 (100)	10 (91)	1 (9)	0 (0)	6/10 (60)	NR	17·8	86
Adverse (n=55)	44 (80)	27 (49)	14 (25)	3 (5)	21/37 (57)	7·0	9·3	38
Mutational Subgroups								
NPM1 (n=21)	21 (100)	17 (81)	3 (14)	1 (5)	15/17 (88)	NR	NR	82
FLT3-ITD/TKD (n=14)[1]	12 (86)	10 (71)	2 (14)	0 (0)	8/10 (80)	NR	NR	78
TP53 (n=26)	20 (77)	13 (50)	5 (19)	2 (8)	8/16 (50)	5·7	6·9	12
RUNX1 (n=10)	9 (90)	5 (50)	4 (40)	0 (0)	3/9 (33)	NR	8·3	44
ASXL1 (n=12)	8 (67)	2 (17)	4 (33)	2 (17)	4/7 (57)	NR	12·1	63
IDH1/2 (n=18)[2]	17 (94)	14 (78)	1 (6)	2 (12)	9/13 (69)	NR	NR	92
N/KRAS (n=19)	16 (84)	7 (37)	7 (37)	2 (11)	8/14 (57)	6·7	15·2	56
ELN Cytogenetic Risk Group								
Intermediate risk (n=44)	41 (93)	32 (73)	8 (18)	1 (2)	27/36 (75)	NR	NR	72
Adverse risk (n=40)	32 (80)	19 (48)	9 (23)	4 (10)	12/26 (46)	5·7	8·0	27

ORR = overall response rate, CR = complete remission, CRi = CR with incomplete hematologic recovery, MRD- = minimal residual disease negative by flow cytometry at the time of response, DOR = CR/CRi duration of response, OS = overall survival, NR = not reached, 1. Including low ITD (n=10), high ITD (N=1) and TKD (n=3); 10 patients received FLT3 inhibitors and 9 patients achieved CR/CRi. 2. 1 patient received enasidenib

Table S2. Response rates by subgroups of previously treated AML patients, including treated secondary AML and relapsed or refractory AML

Subgroups	ORR	CR	CRi	MLFS	MRD-	CR/CRi DOR	OS	1-year OS
	n (%) or n/N (%)					months, median		%
Relapsed or refractory *de novo* AML (n=51)	30 (59)	12 (24)	10 (20)	8 (16)	14/25 (56)	16·8	7·8	38
Therapy-related AML (n=7)	3 (43)	1 (14)	0 (0)	2 (29)	0/1 (0)	NA	5·3	21
Diploid cytogenetics (n=28)	26 (93)[1]	11 (39)	10 (36)	4 (14)	14/20 (70)	NR	13·7	64
Mutational subgroups								
NPM1 (n=16)	13 (81)	6 (38)	5 (31)	2 (13)	7/9 (78)	NR	12·4	57
FLT3-ITD/TKD (n=12)[2]	8 (67)	3 (25)	2 (17)	3 (25)	3/6 (50)	6·6	12·4	56
TP53 (n=24)	11 (46)	4 (17)	3 (13)	4 (17)	4/8 (50)	16·8	4·9	13
RUNX1 (n=19)	14 (74)	5 (26)	4 (21)	5 (26)	5/11 (45)	15·3	14·1	56
ASXL1 (n=14)	7 (50)	1 (7)	5 (36)	1 (7)	3/6 (50)	NR	14·1	62
IDH1/2 (n=14)[3]	10 (71)	4 (29)	3 (21)	3 (21)	6/10 (60)	17·5	7·8	44
N/KRAS (n=20)	9 (45)	2 (10)	4 (20)	3 (15)	4/8 (50)	NR	8·8	44
Prior therapies								
Hypomethylator (HMA) (n=50)	30 (60)	8 (16)	12 (24)	10 (20)	12/25 (48)	NR	6·0	27
≥ 4 cycles (n=30)	19 (63)	5 (17)	6 (20)	8 (27)	7/17 (41)	9·8	6·6	23
Intensive chemotherapy (IC) (n=47)	28 (60)	11 (23)	6 (13)	11 (23)	11/21 (52)	12·9	6·8	28
HMA and IC (n=16)	10 (63)	2 (13)	3 (19)	5 (31)	3/7 (43)	NR	5·7	0
Stem-cell transplantation (n=26)	12 (46)	4 (15)	3 (12)	5 (19)	5/10 (50)	16·8	5·4	32
First salvage therapy for AML (n=25)	15 (60)	7 (28)	5 (20)	3 (12)	7/13 (54)	NR	NR	57
Second salvage therapy for AML (n=15)	9 (60)	4 (27)	2 (13)	3 (20)	2/7 (29)	12·9	8·8	31

ORR = overall response rate, CR = complete remission, CRi = CR with incomplete hematologic recovery, MRD- = minimal residual disease negative by flow cytometry at time of response, CR/CRi DOR = CR/CRi duration of response, OS = overall survival, NR = not reached, NA = not applicable. 1. One patient achieved partial response of extramedullary disease on PET/CT, 2. FLT3 inhibitor used in all patients, 3. 1 patient received enasidenib

Table S3. Causes of death in all patients regardless of attribution

Cause of death	ND AML (N=70)	Untreated sAML (N=15)	Treated sAML (N=28)	R/R AML (N=55)	All patients (N=168)
Pneumonia (unknown pathogen)	8 (11)	4 (27)	3 (11)	9 (16)	24 (14)
Unknown reason	6 (9)	2 (13)	9 (32)	7 (13)	24 (14)
Death in hospice	6 (9)	5 (33)	5 (18)	7 (13)	23 (14)
Bacteremia	3 (4)	0 (0)	0 (0)	3 (5)	6 (4)
Pneumonia (bacterial, viral or fungal)	2 (3)	1 (7)	1 (4)	2 (4)	6 (4)
Intracranial hemorrhage	0 (0)	1 (7)	0 (0)	2 (4)	3 (2)
Cardiac arrest	0 (0)	0 (0)	1 (4)	0 (0)	1 (1)
Liver failure	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)
Malignant pleural effusion	0 (0)	0 (0)	1 (4)	0 (0)	1 (1)
Pericardial effusion	0 (0)	0 (0)	0 (0)	1 (2)	1 (1)
Renal failure	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)
Total	27 (39)	13 (57)	20 (71)	31 (56)	91 (54)

Results reported as n (%)

Table S4. Multivariable Cox model for overall survival

Parameter		Hazard Ratio	95% Confidence Interval	p-value
CR[1]	Yes vs no	0·24	0·14, 0·41	<0·0001
t-AML	Yes vs no	1·81	0·99, 3·28	0·053
Prior HMA	Yes vs no	2·40	1·14· 5·03	0·021
Prior IC	Yes vs no	2·84	1·37, 5·91	0·005
ELN CG risk	Adverse vs Intermediate	2·12	1·24· 3·60	0·006
TP53	Mutated vs wild type	2·55	1·50, 4·34	0·001
Cohorts	ND AML vs untreated sAML	0·27	0·14, 0·55	<0·001
	R/R AML vs untreated sAML	0·21	0·07, 0·62	0·005
	Treated sAML vs untreated sAML	0·41	0·15, 1·15	0·09

1. CR included as a time-dependent covariate, CR = complete remission, HMA = hypomethylating agent, IC = intensive chemotherapy, ND = newly diagnosed, sAML = secondary AML, R/R = relapsed/refractory

Table S5. Multivariable Cox model for duration of response

Parameter		Hazard Ratio	95% Confidence Interval	p-value
Cohorts	ND AML vs. untreated sAML	0·17	0·06, 0·46	0·001
	R/R AML vs untreated sAML	0·14	0·04, 0·49	0·002
	Treated sAML vs untreated sAML	0·24	0·06, 1·02	0·053
TP53	Mutated vs wild type	6·18	2·82, 13·55	<0·001

ND = newly diagnosed, sAML = secondary AML, R/R = relapsed/refractory

Table S6: Univariate Cox model for overall survival in all patients (n=168)

Parameter		Hazard ratio (95%CI)	p-value	Overall p-value
Gender	Male vs female	1·24(0·81,1·88)	0·32	
ECOG PS	0 vs. 2,3	0·50(0·34,1·05)	0·07	
	1 vs. 2,3	0·85(0·55,1·33)	0·47	
Diagnosis	ND AML vs. Untreated sAML	0·32(0·16,0·63)	<0·01	0·002
	R/R AML vs. Untreated sAML	0·67(0·35,1·29)	0·24	
	Treated sAML vs. Untreated sAML	0·82(0·41,1·66)	0·58	
t-AML	yes vs. no	2·04(1·18,3·52)	0·01	
ELN CG risk	Intermediate vs adverse	0·3(0·2,0·47)	<0·01	
ELN Risk Group	Adverse vs intermediate	1·85 (1·02, 3·36)	0·05	0·008
	Favorable vs intermediate	0·49 (0·20,1·19)	0·12	
Prior therapies	0 vs. >1	0·49 (0·31,0·78)	<0·01	0·01
	1 vs. >1	0·66(0·37,1·19)	0·17	
Prior HMA	yes vs. no	2·00(1·3,3·06)	<0·01	
Prior IC	yes vs. no	1·61(1·04,2·51)	0·03	
Prior SCT	yes vs. no	1·59(0·95,2·67)	0·08	
WBC count, $x10^9/L^1$	≥10 vs. <10	1·05(0·38,2·91)	0·92	
CR	Yes vs no	0.28()0.17,0.48)	<0·01	
Mutations	**Mutated vs wild type**			
ASXL1		0·92(0·5,1·69)	0·79	
ASXL2		14·63(1·89,113·3)	0·01	
BCOR		0·43(0·14,1·37)	0·15	
CALR		5·76(0·78,42·5)	0·09	
CBL		0·23(0·03,1·66)	0·15	
CEBPA		1·81(0·79,4·15)	0·16	
CREBBP		5·12(1·24,21·07)	0·02	
DDX41		0·59(0·14,2·39)	0·46	
DNMT3A		0·64(0·38,1·06)	0·08	
EED		5·3(0·72,38·95)	0·10	
ETNK1		1·88(0·46,7·69)	0·38	
ETV6		0·52(0·07,3·72)	0·51	
EZH2		1·57(0·57,4·28)	0·38	
FBXW7		5·3(0·72,38·95)	0·10	
FLT3		0·64(0·33,1·24)	0·19	
GATA2		2·13(0·77,5·86)	0·14	
HNRNPK		1·25(0·17,8·99)	0·83	
IDH1/2		0·25(0·12,0·54)	<0·01	
IKZF1		1·74(0·43,7·09)	0·44	
JAK2		0·82(0·2,3·32)	0·78	
KDM6A		1·89(0·26,13·64)	0·53	
KIT		2·25(0·55,9·17)	0·26	
KMT2A		1·03(0·14,7·41)	0·98	
MPL		6·32(0·85,46·69)	0·07	
NF1		1·14(0·36,3·6)	0·83	
NPM1		0·38(0·21,0·7)	0·00	

N/KRAS	1·2(0·75,1·92)	0·44
PHF6	0·52(0·13,2·13)	0·37
PTPN11	1·54(0·62,3·86)	0·35
RUNX1	0·68(0·38,1·23)	0·21
SETBP1	2·98(0·92,9·62)	0·07
SF3B1	1·19(0·57,2·46)	0·64
SH2B3	10·56(1·4,79·91)	0·02
SMC1A	0·98(0·24,3·99)	0·98
SRSF2	0·39(0·19,0·8)	0·01
STAG2	1·05(0·38,2·85)	0·93
TET2	0·88(0·51,1·52)	0·65
TP53	3·77(2·46,5·77)	<0·01
U2AF1	0·91(0·46,1·82)	0·80
WT1	0·83(0·36,1·91)	0·67

1· Indicator variable to account for change in inclusion criteria to WBC count <10x10^9/L; ECOG PS = Eastern Cooperative Oncology Group Performance Status, ND = newly diagnosed, sAML = secondary AML, R/R = relapsed/refractory, t-AML = therapy-related AML, ELN = European LeukemiaNet 2017, CG = cytogenetic, HMA = hypomethylating agent, IC = intensive chemotherapy, SCT = allogeneic stem cell transplantation·

Table S7: Univariate Cox model for duration of response in patients achieving CR/CRi (n=103)

Parameter		Hazard Ratio (95% CI)	p-value	Overall p-value
Gender	Male vs· female	1·49(0·74,3)	0·27	
ECOG PS	0 vs· 2,3	0·64(0·22,1·89)	0·64	0·72
	1 vs· 2,3	0·88(0·40,1·92)	0·88	
Diagnosis	ND AML vs· Untreated sAML	0·25(0·10,0·67)	0·006	0·04
	R/R AML vs· Untreated sAML	0·29(0·09,0·91)	0·03	
	Treated sAML vs· Untreated sAML	0·22(0·06,0·92)	0·04	
t-AML	yes vs· no	2·3(0·93,5·69)	0·07	
ELN CG risk	Intermediate vs adverse	0·29(0·14,0·58)	<0·01	
ELN Risk Group	Adverse vs intermediate	1·32 (0·57,3·08)	0·52	0·02
	Favorable vs intermediate	0·18(0·04,0·86)	0·03	
Prior therapies	0 vs. >1	0·84(0·36,1·97)	0·69	0·40
	1 vs. >1	0·34(0·07,1·64)	0·18	
Prior HMA	yes vs. no	0·7(0·27,1·81)	0·46	
Prior IC	yes vs. no	1·45(0·59,3·53)	0·42	
Prior SCT	yes vs. no	1·29(0·39,4·25)	0·68	
WBC count, $x10^9/L$[1]	≥10 vs. <10	1·46(0·35,6·00)	0·60	
Mutations	**Mutated vs wild type**			
ASXL1		0·21(0·03,1·57)	0·13	
BCOR		0·31(0·04,2·26)	0·25	
CBL		2·84(0·86,9·41)	0·09	
DNMT3A		1·06(0·5,2·25)	0·87	
FLT3		0·58(0·18,1·9)	0·37	
GATA2		1·9(0·25,14·34)	0·53	
IDH1/2		0·32(0·11,0·91)	0·03	
JAK2		1·73(0·23,12·74)	0·59	
KIT		2·32(0·31,17·18)	0·41	
KMT2A		3·32(0·45,24·74)	0·24	
NF1		3·08(0·41,23·35)	0·28	
NPM1		0·36(0·14,0·94)	0·04	
N/KRAS		1·42(0·64,3·17)	0·39	
PHF6		0·98(0·13,7·23)	0·99	
PRPF40B		5·32(0·7,40·32)	0·11	
PTPN11		1·91(0·45,8·04)	0·38	
RUNX1		0·86(0·33,2·24)	0·76	
SF3B1		1·39(0·33,5·85)	0·65	
SRSF2		0·33(0·1,1·09)	0·07	
STAG2		0·65(0·09,4·78)	0·67	
TET2		0·58(0·22,1·5)	0·26	
TP53		4·63(2·27,9·45)	<0·01	
U2AF1		1·06(0·37,3·02)	0·91	
WT1		0·91(0·22,3·86)	0·90	

1· Indicator variable to account for change in inclusion criteria to WBC count $<10x10^9/L$; ECOG PS = Eastern Cooperative Oncology Group Performance Status, ND = newly diagnosed, sAML = secondary AML, R/R = relapsed/refractory,

t-AML = therapy-related AML, ELN = European LeukemiaNet 2017, CG = cytogenetic, HMA = hypomethylating agent, IC = intensive chemotherapy, SCT = allogeneic stem cell transplantation·

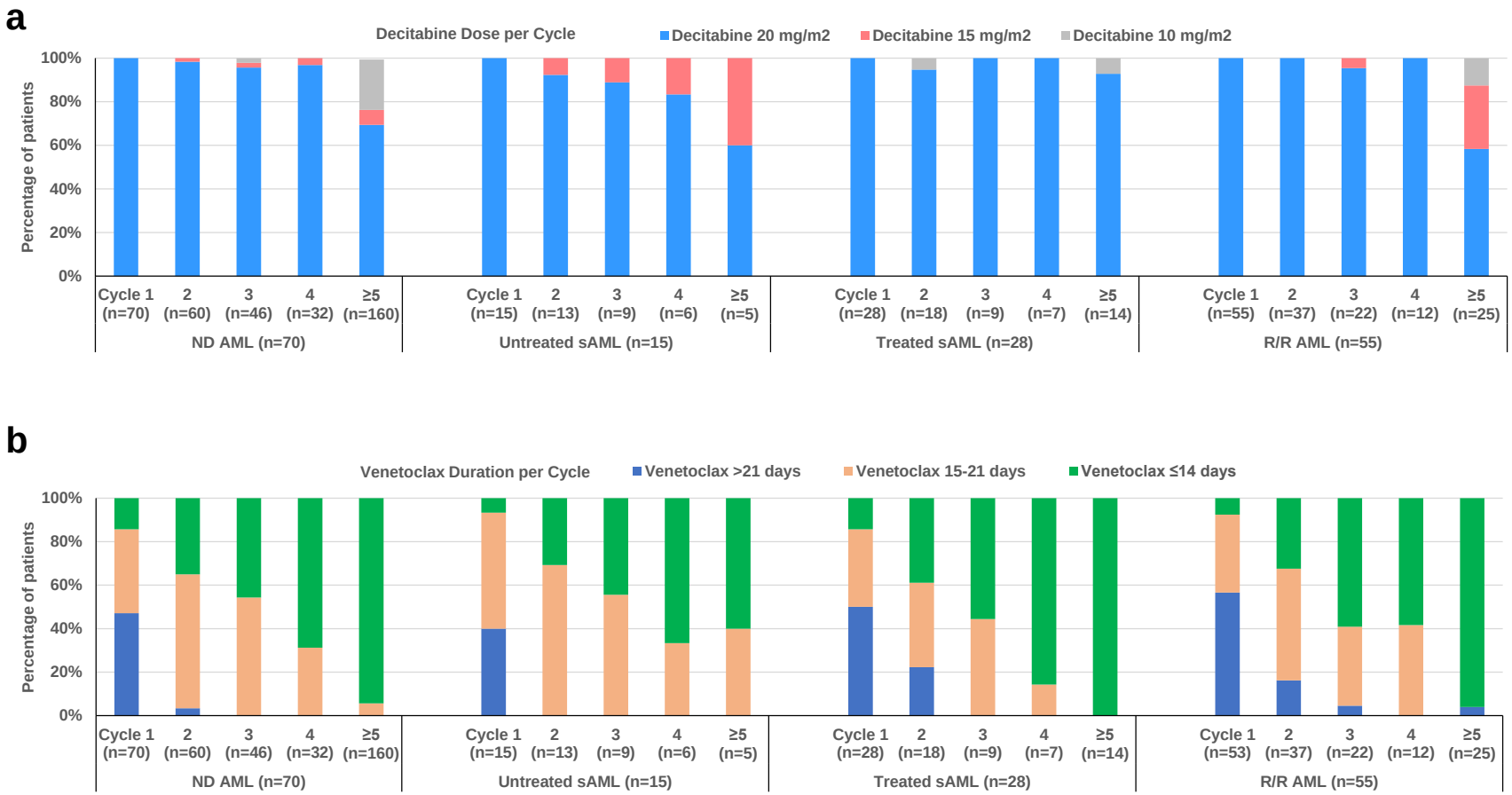

Fig. S1a. Decitabine dose distribution across subgroups, **b.** venetoclax duration distribution across subgroups

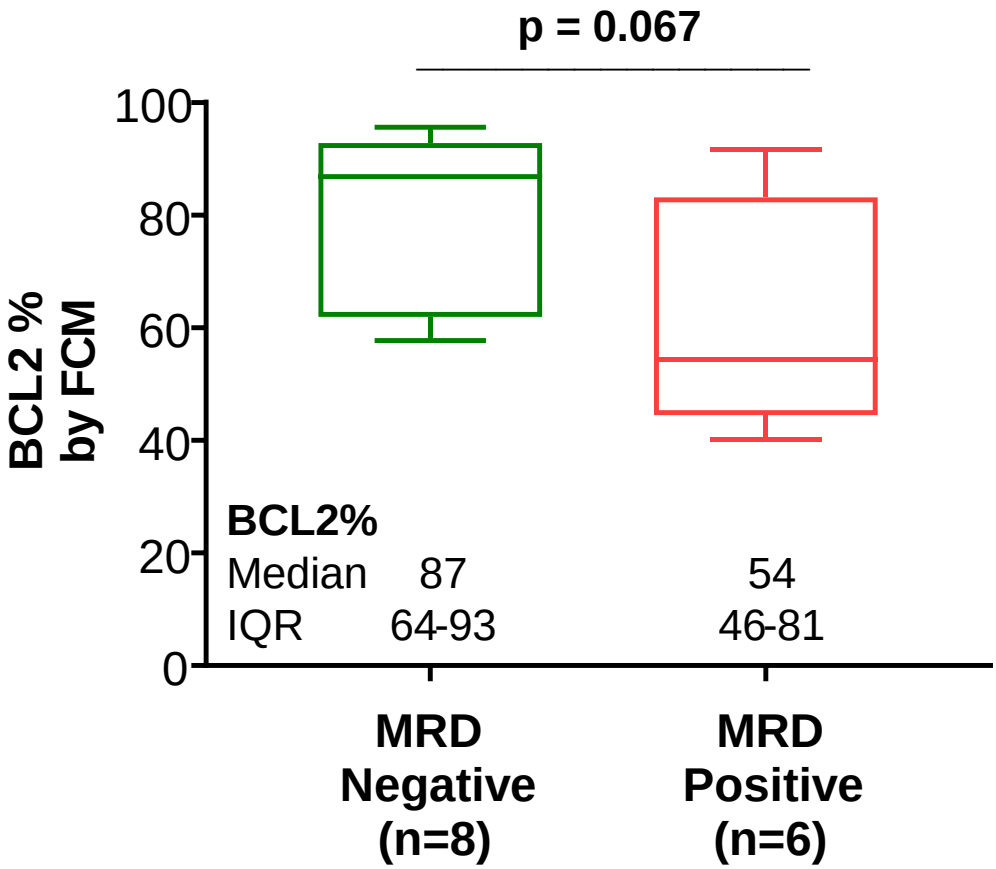

Fig. S2. Baseline BCL2 expression in CD34+ blasts (%) by flow cytometry (FCM) in patients achieving negative minimal residual disease (MRD) vs. detectable MRD by FCM.

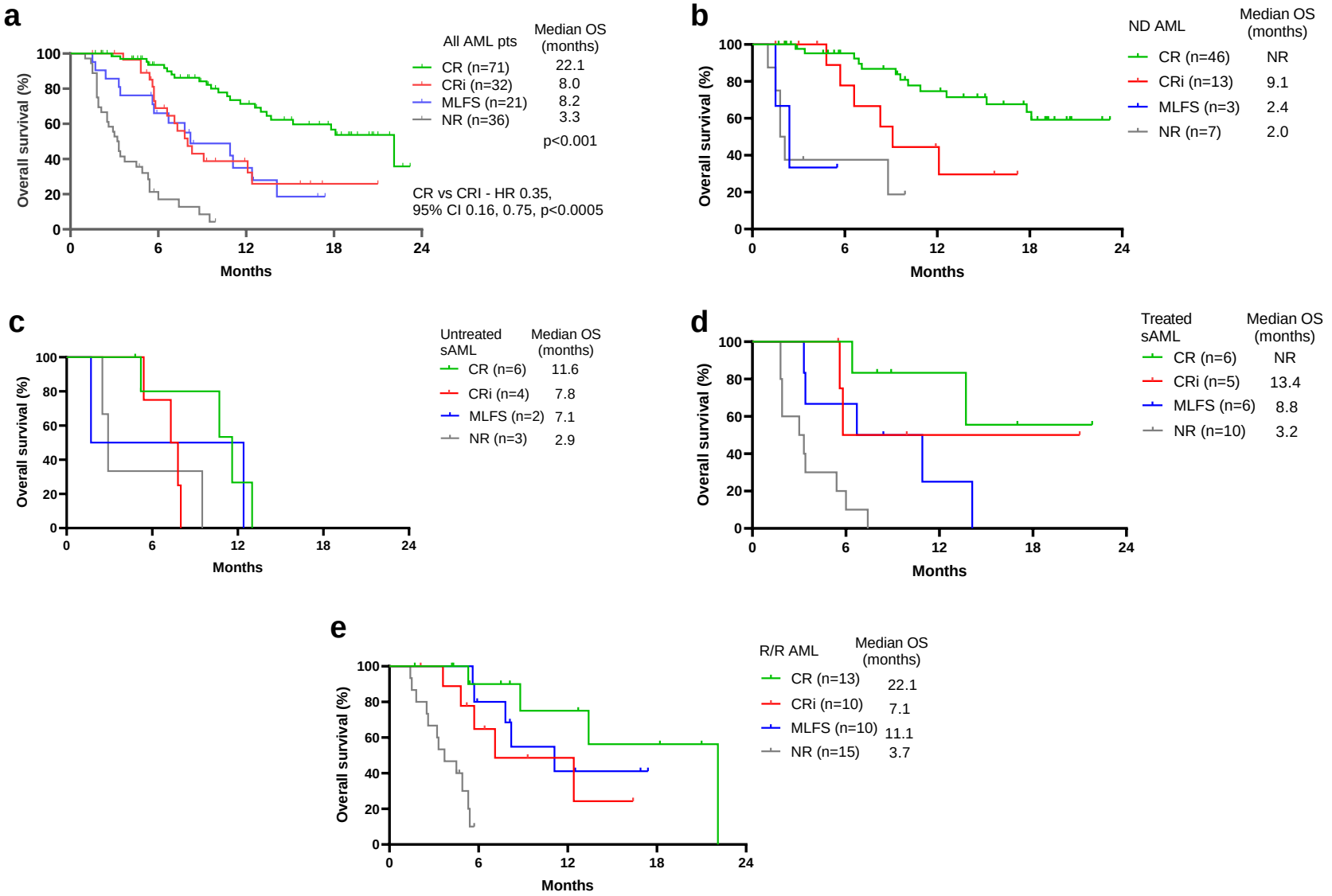

Figure S3. Overall survival (OS) with ten-day decitabine and venetoclax in **a.** in all patients with AML, **b.** in patients with newly diagnosed (ND) AML, **c.** untreated secondary AML (sAML), **c.** treated sAML, **d.** relapsed or refractory (R/R) AML, CR = complete remission, CRi = CR with incomplete hematologic recovery, MLFS = morphologic leukemia free state, NR = no response.

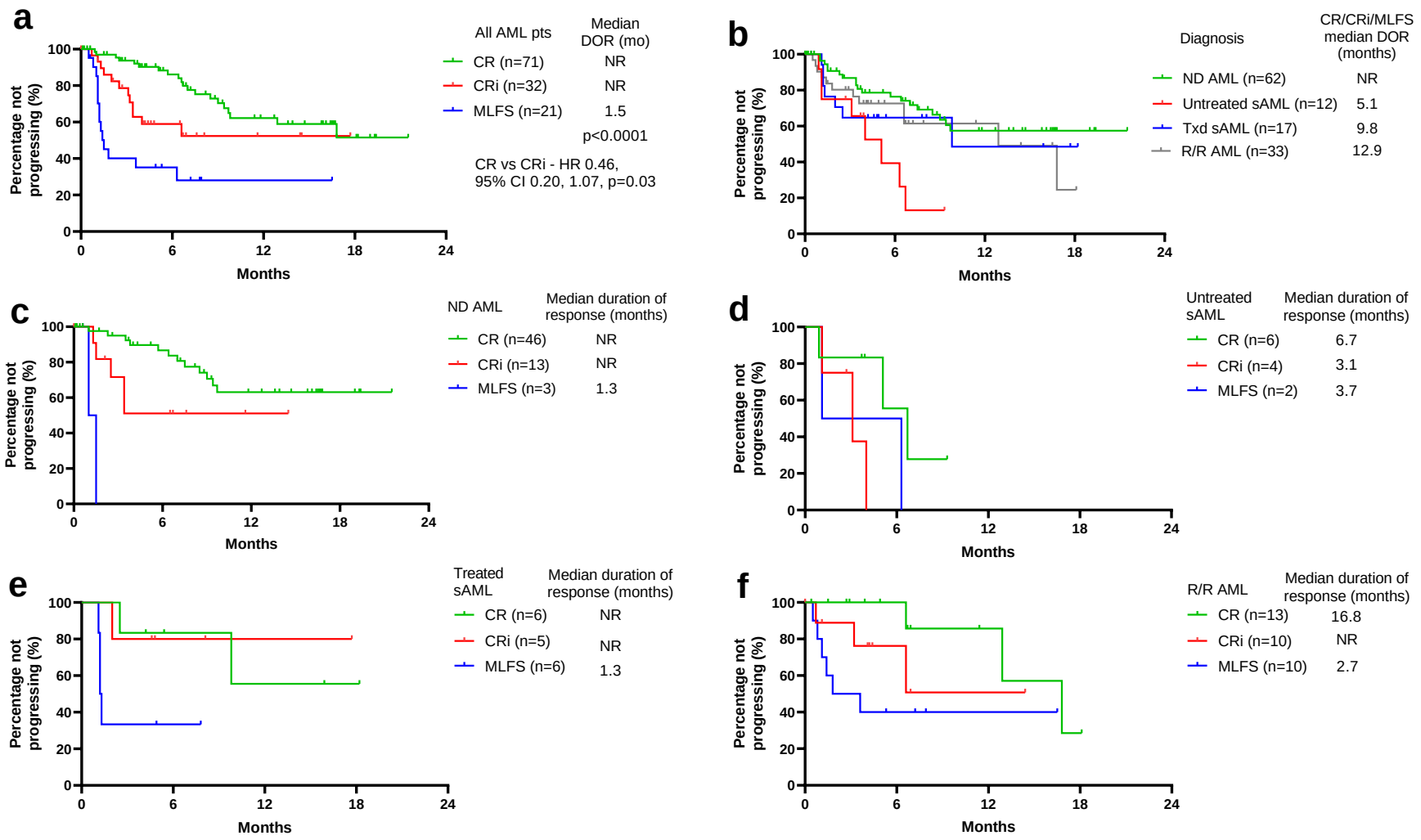

Figure S4. Duration of response with 10-day decitabine and venetoclax in **a.** all patients with AML, by response, **b.** all patents achieving CR/CRi/MLFS, **c.** in patients with newly diagnosed (ND) AML, **d.** untreated secondary AML (sAML), **e.** treated sAML, **f.** relapsed or refractory (R/R) AML, CRi = CR with incomplete hematologic recovery, MLFS = morphologic leukemia free state.

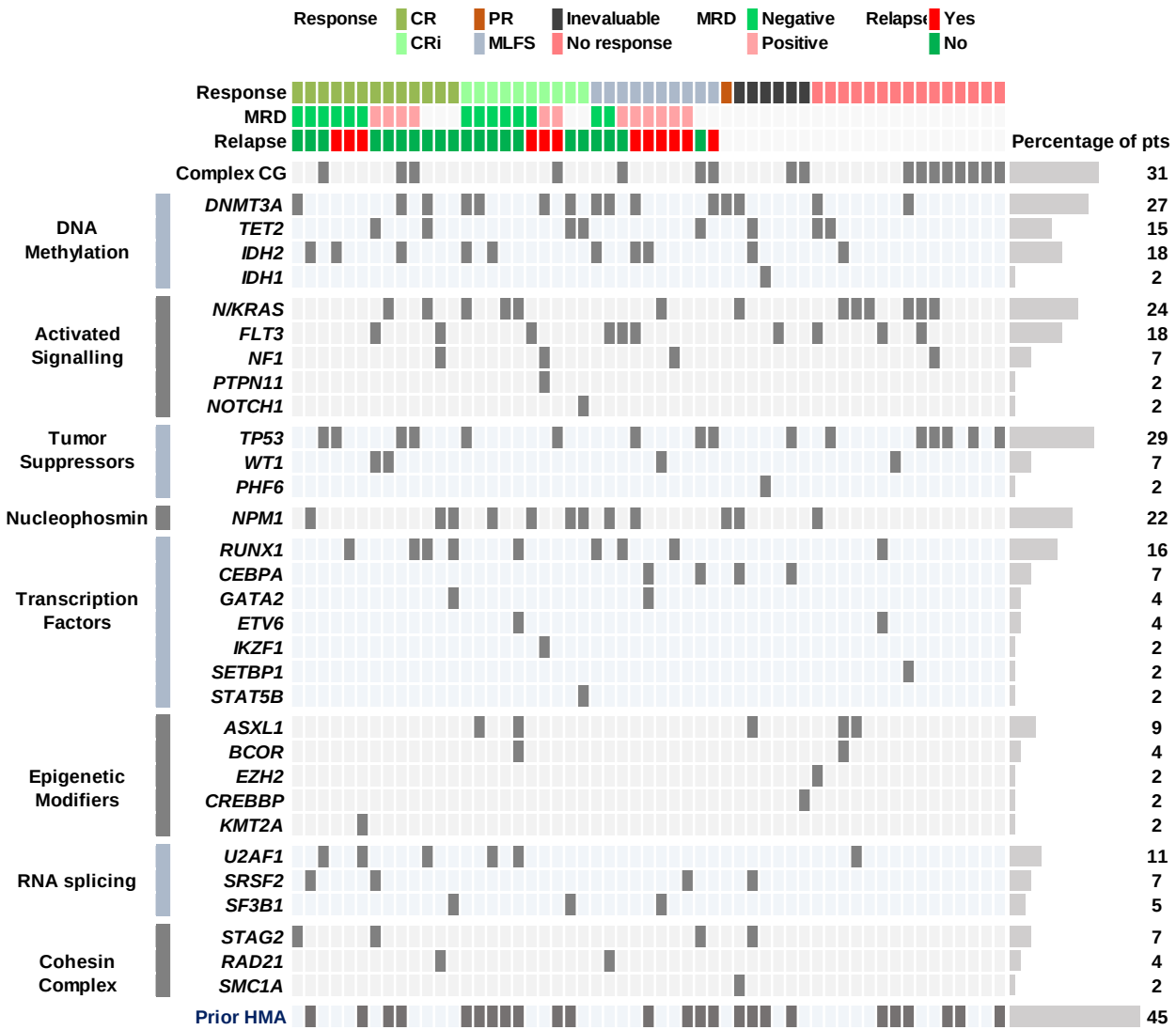

Fig. S5 Mutational landscape of 55 patients with relapsed/refractory AML. CR = complete remission, CRi = CR with incomplete hematologic recovery, MLFS = morphologic leukemia-free state, IE = inevaluable, NR = no response, pts = patients

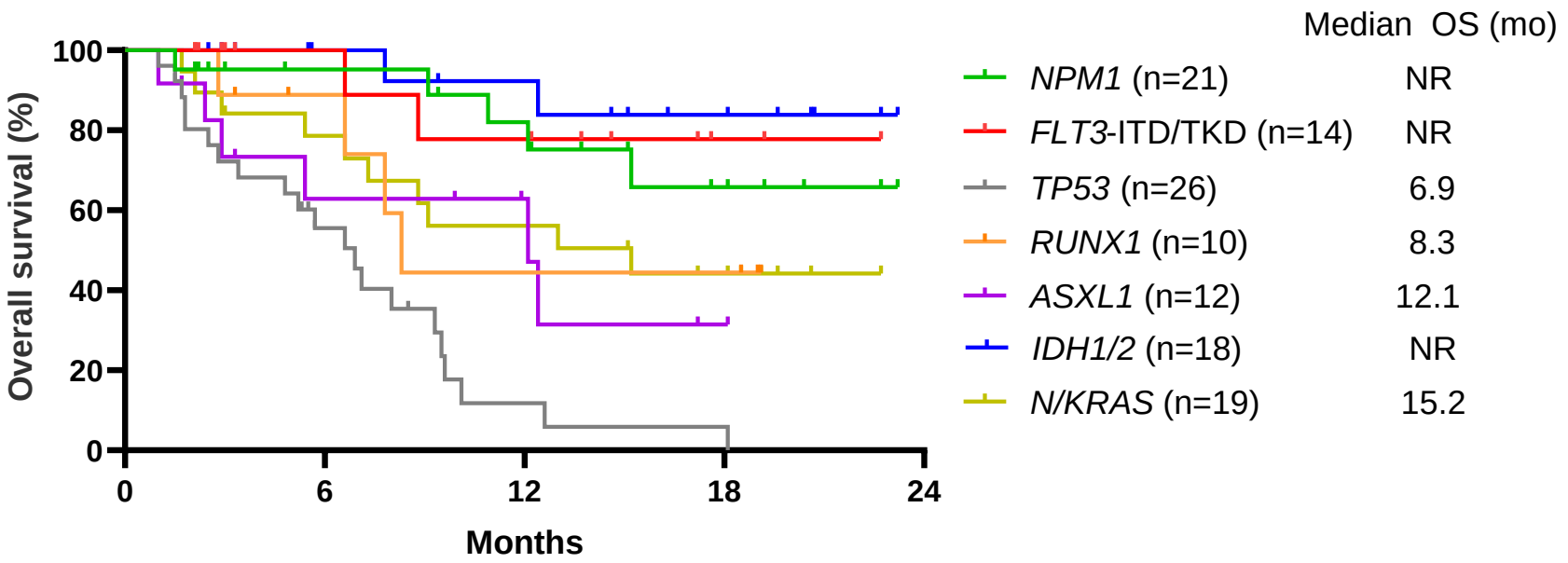

Figure S6. Overall survival of mutational subgroups of treatment-naïve AML patients (includes newly diagnosed AML and untreated secondary AML). NR = not reached

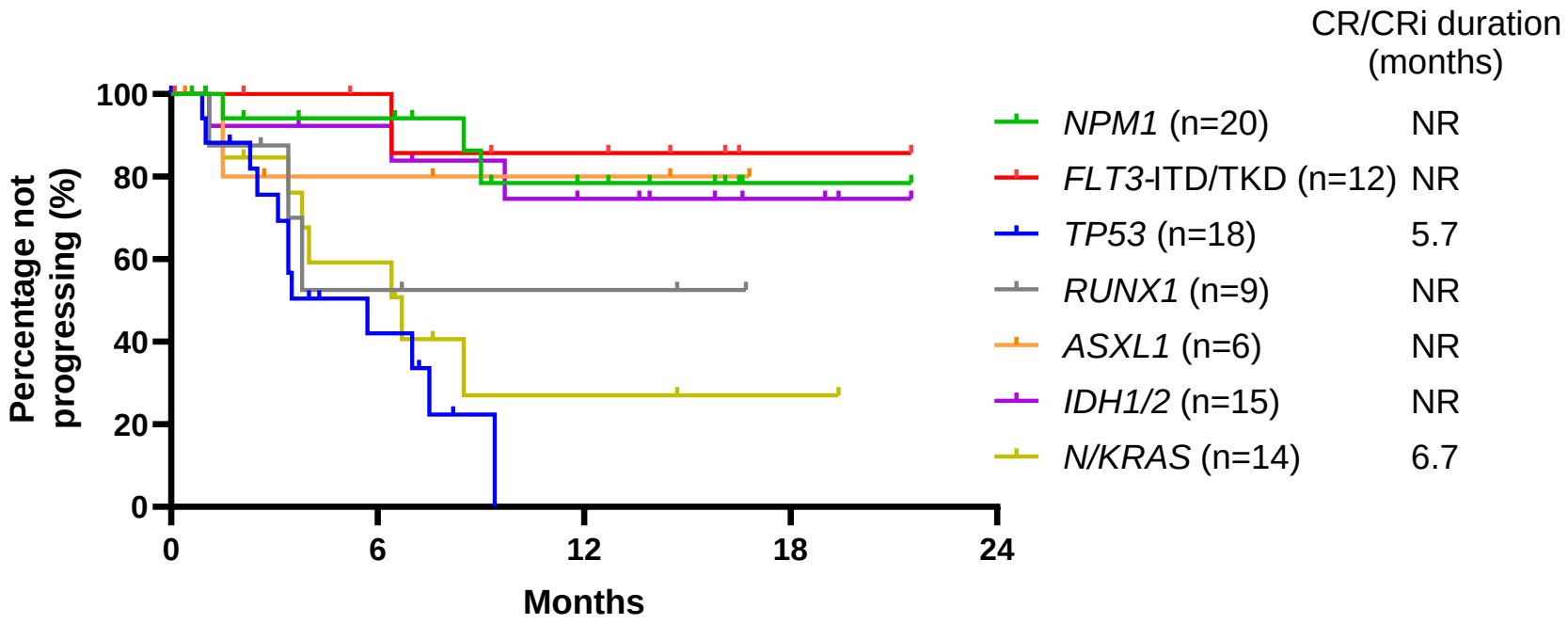

Figure S7. Duration of response of mutational subgroups of treatment-naïve AML patients including newly diagnosed AML and untreated secondary AML. NR = not reached

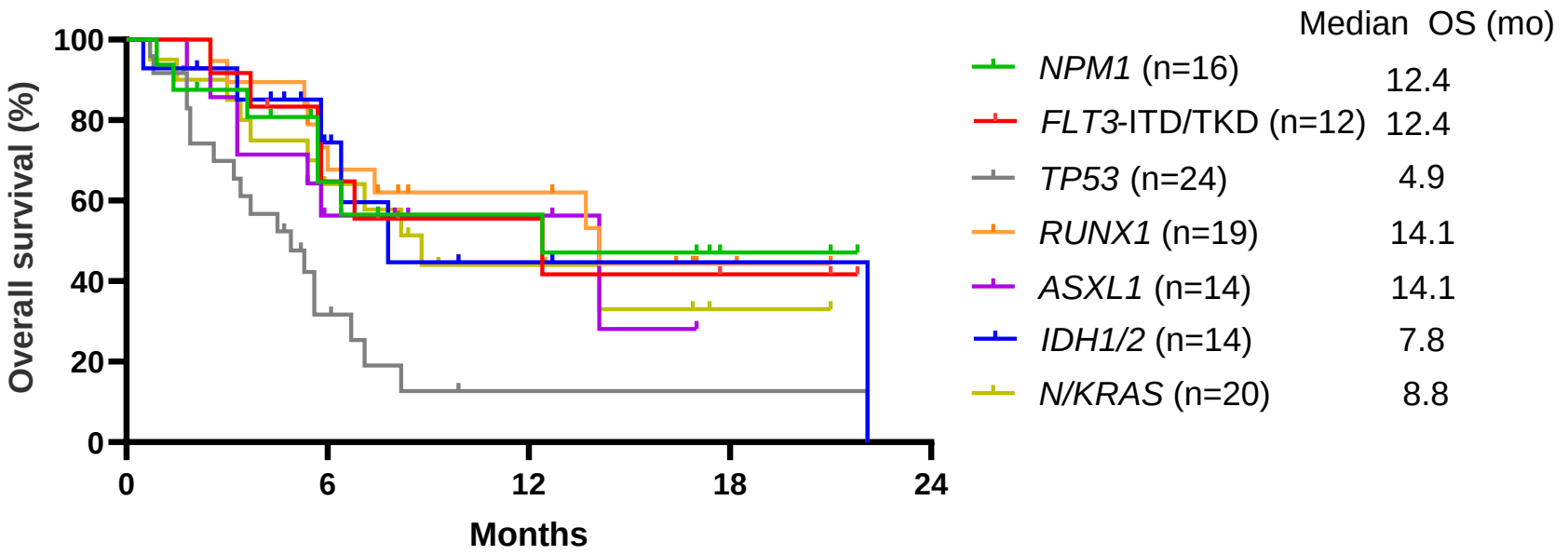

Figure S8. Overall survival of mutational subgroups of previously treated AML patients, including treated secondary AML patients and relapsed or refractory AML patients. NR = not reached.

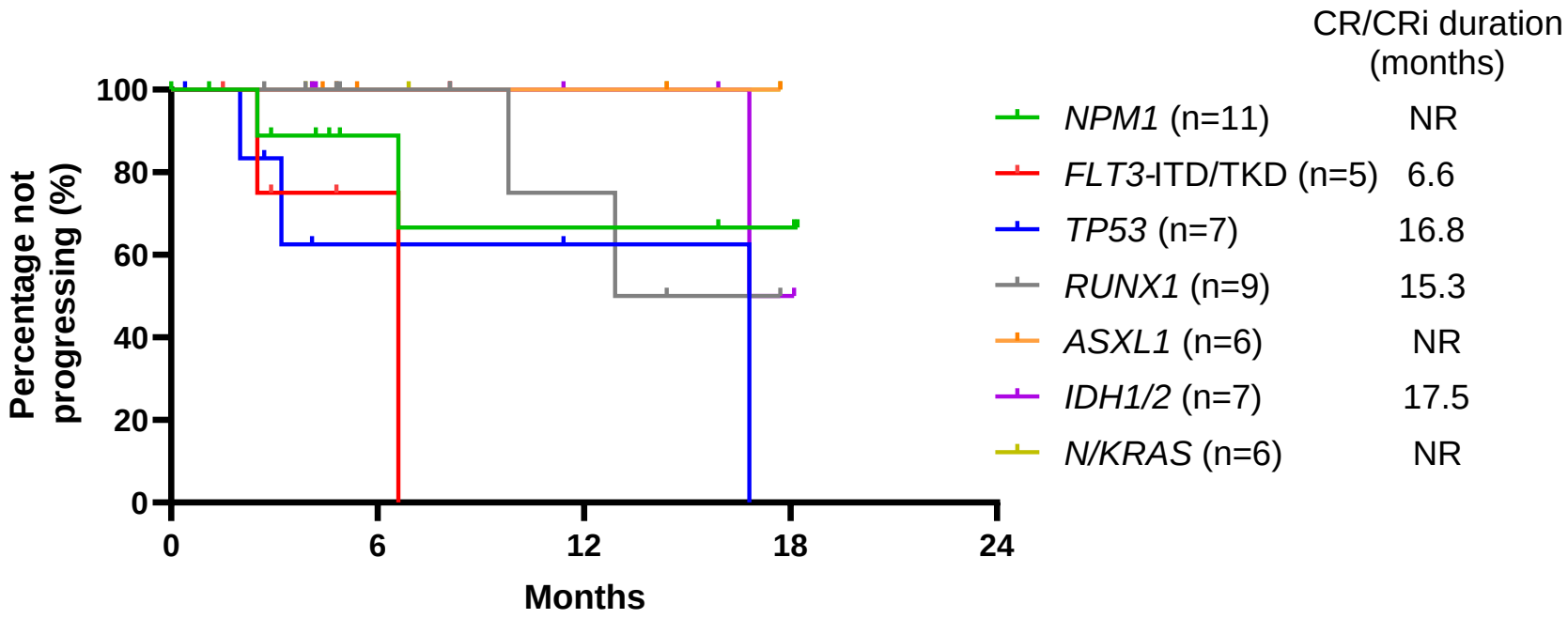

Figure S9. Duration of response of mutational subgroups of previously treated AML patients, including treated secondary AML patients and relapsed or refractory AML patients. NR = not reached

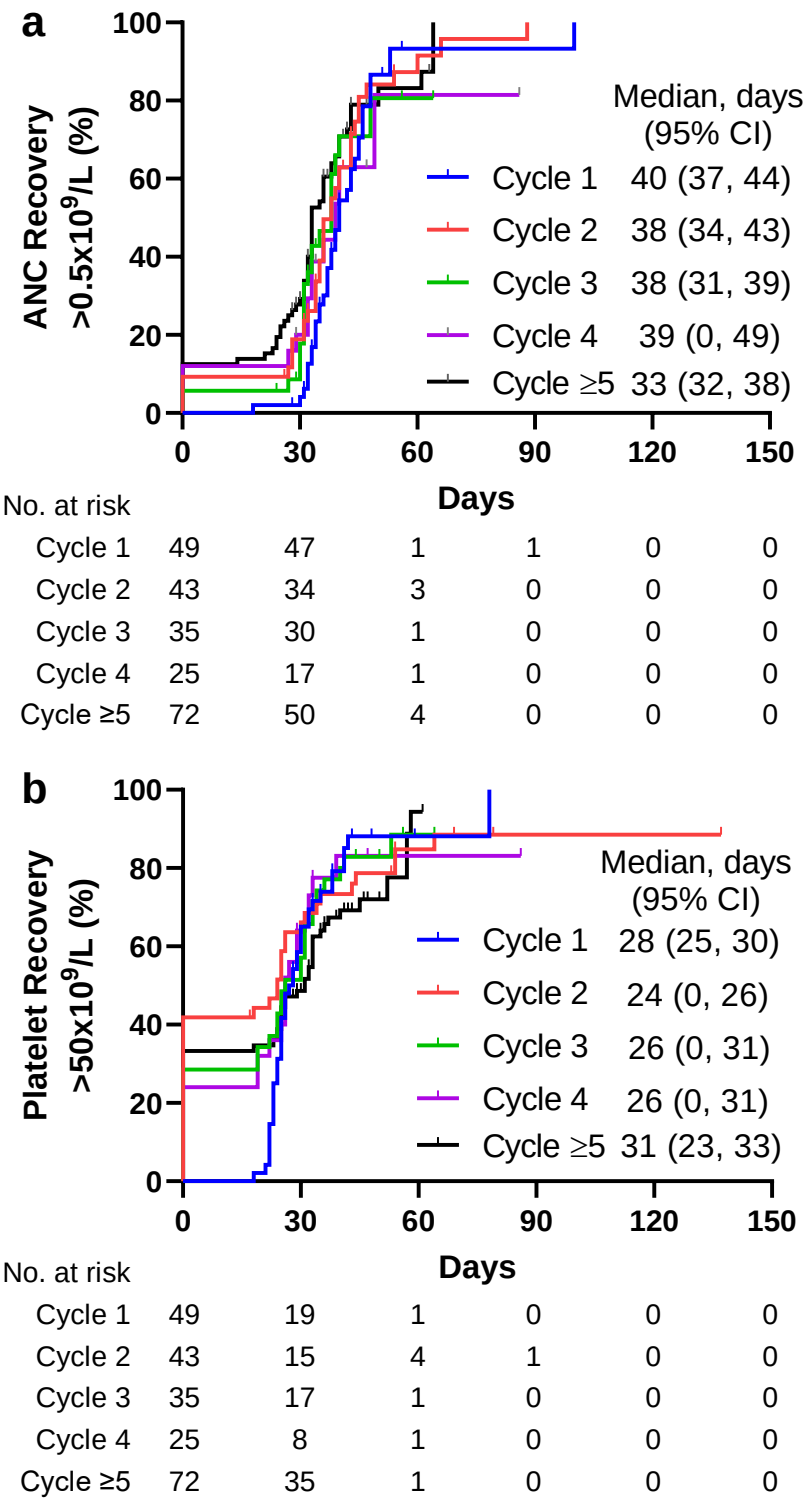

Figure S10. Peripheral blood count recovery in patients with newly diagnosed AML achieving CR/CRi/MLFS, **a.** absolute neutrophil count (ANC) recovery to more than 0·5 x10^9/L, **b.** platelet recovery to 50 x10^9/L.

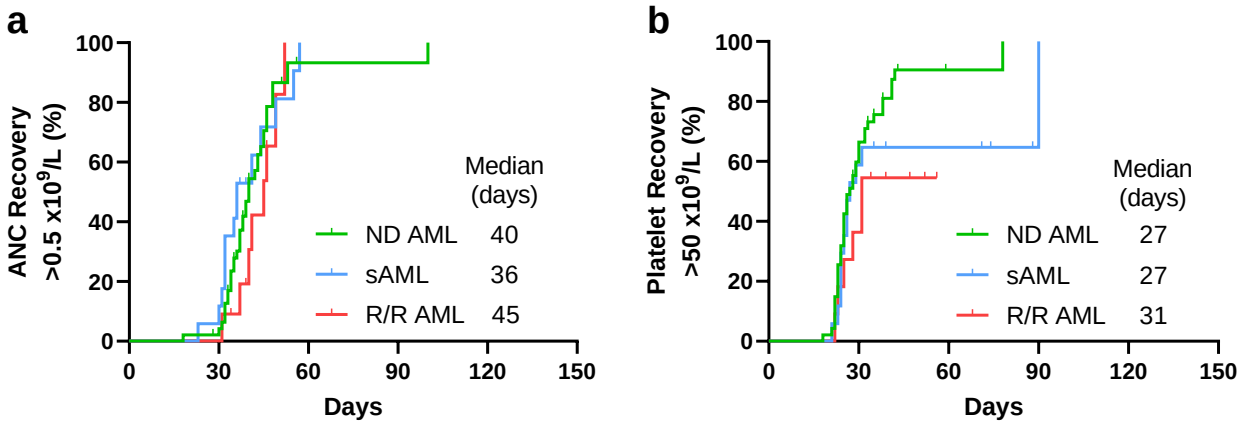

Figure S11. Peripheral blood count recovery after cycle 1 in all AML patients achieving CR/CRi **a.** absolute neutrophil count (ANC) recovery to more than 0·5 x10^9/L, **b.** platelet recovery to 50 x10^9/L, and in all patients achieving CR/CRi. NR = not reached, ND = newly diagnosed, sAML = secondary AML, R/R = relapsed/refractory.

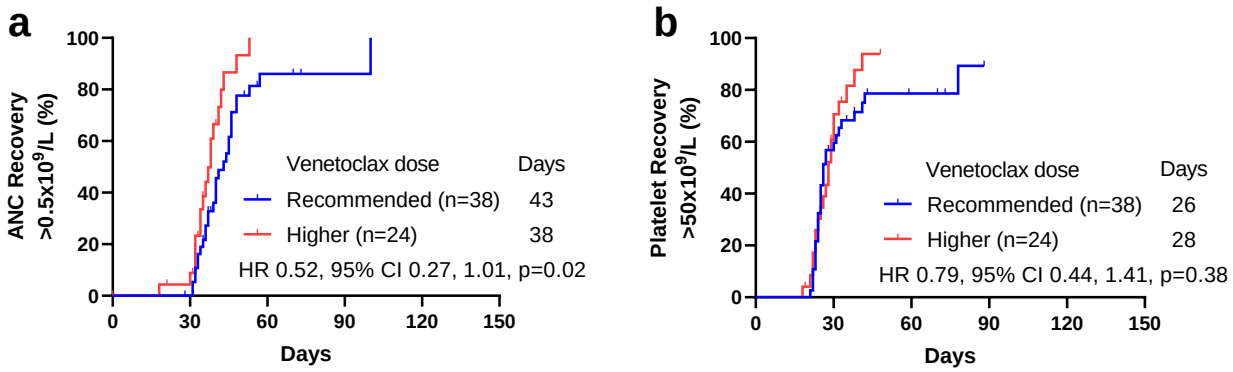

Fig S12. Cycle 1 peripheral blood count recovery in treatment-naïve **AML** patients achieving CR/CRi, by venetoclax dose of 400 mg daily or equivalent, compared to more than 400 mg daily or equivalent

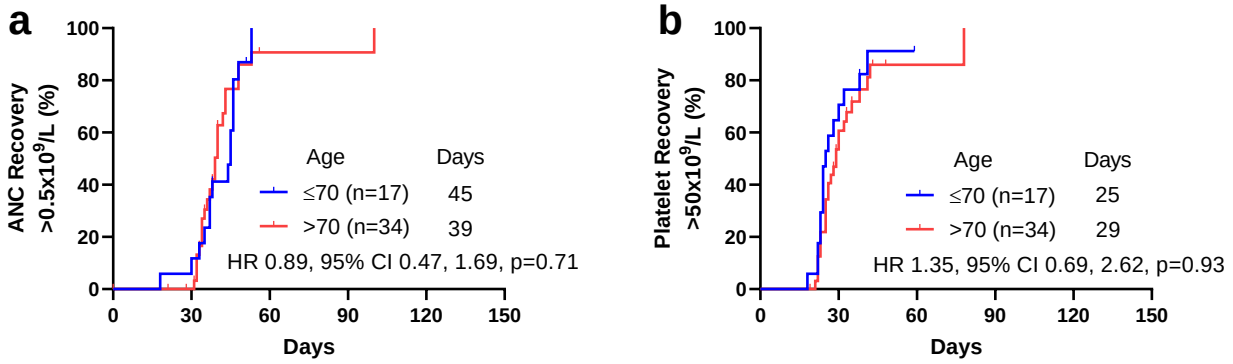

Fig S13. Cycle 1 peripheral blood count recovery in newly diagnosed AML patients achieving CR/CRi, by age.

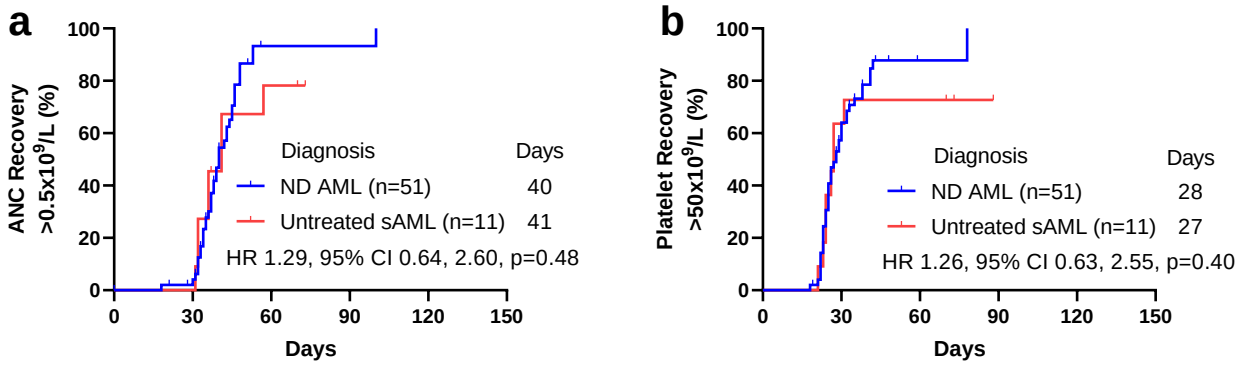

Fig S14. Cycle 1 peripheral blood count recovery in newly diagnosed (ND) AML patients and untreated secondary AML patients achieving CR/CRi.

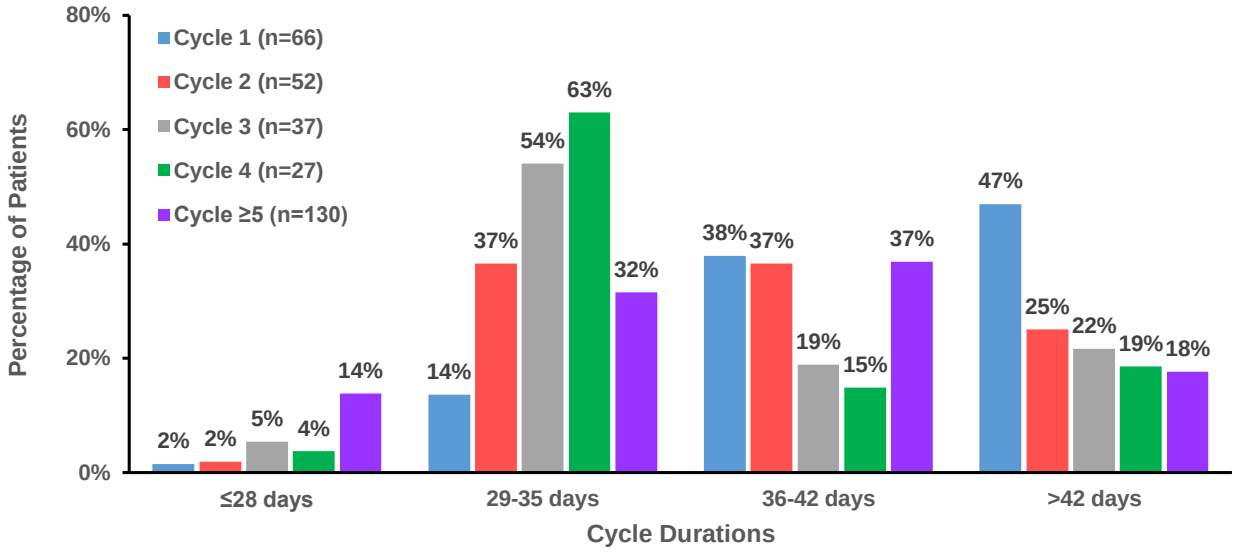

Fig. S15 Cycle durations in patients with treatment-naïve AML who achieved a response (CR/CRi). Last ongoing cycles of treatment on trial or cycles during which a patient relapsed were excluded.

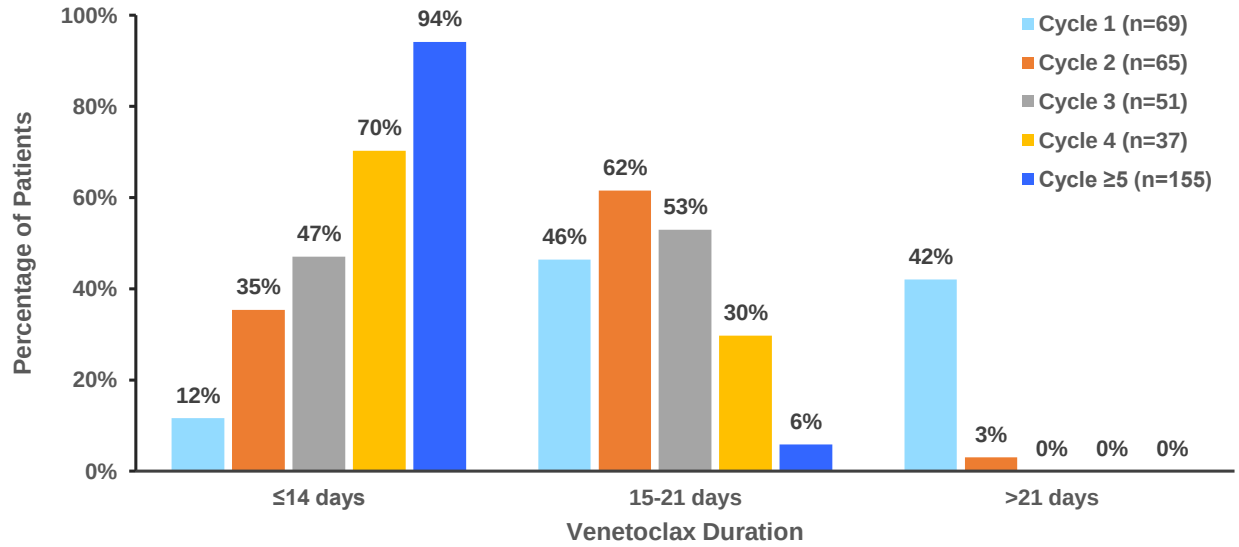

Fig. S16 Venetoclax durations in patients with treatment-naïve AML who achieved a response (CR/CRi).

All patients who completed greater than 7 days of each cycle were included for both venetoclax and course duration analyses. Only those whose last cycle completed prior to data cutoff date were included for course duration analysis

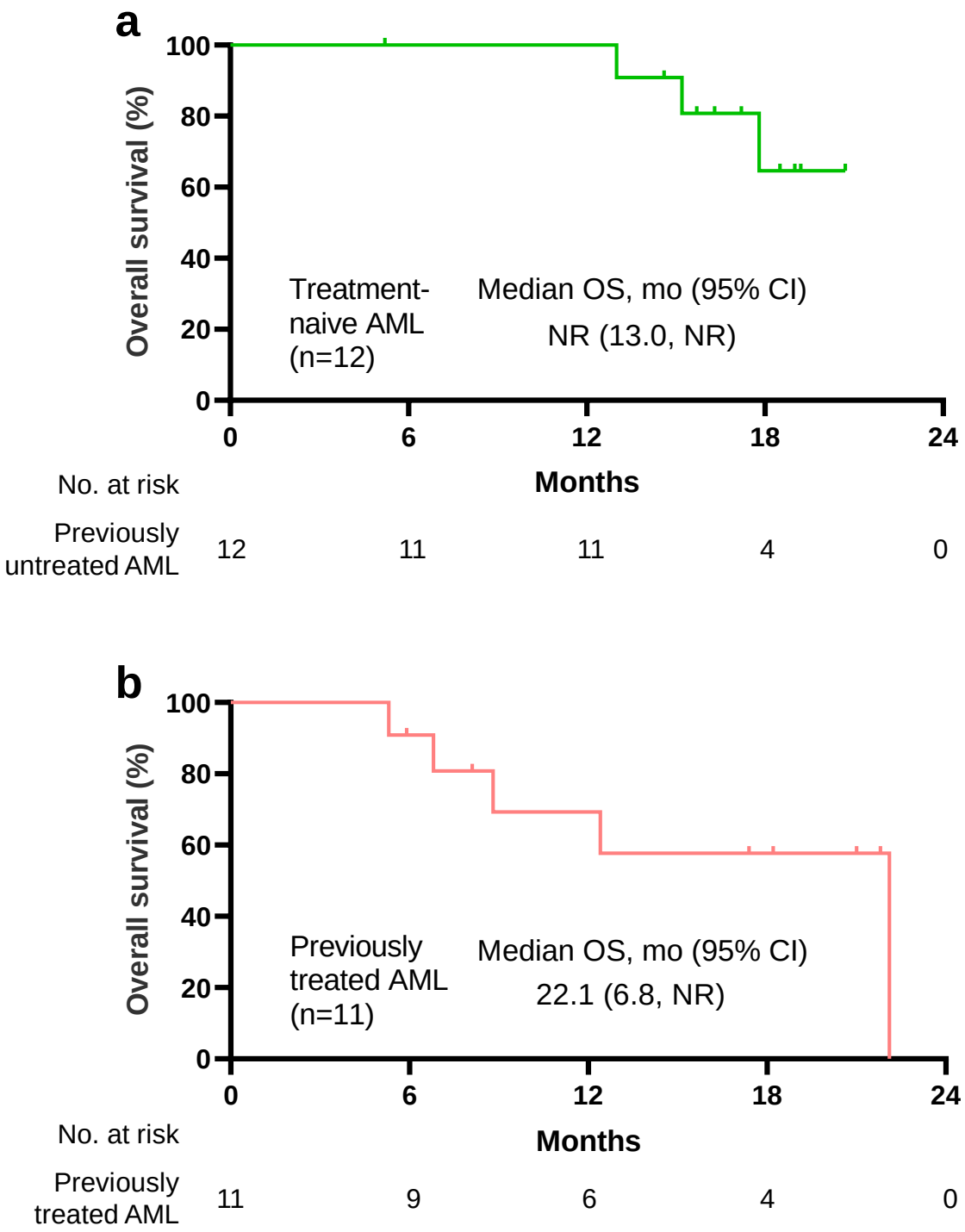

Fig S17. Overall survival (OS) in **a.** untreated AML patients undergoing stem-cell transplantation (SCT) (n=12, including newly diagnosed AML [n=10] and untreated secondary AML [n=2]), **b.** previously treated AML patients undergoing SCT (n=11, relapsed or refractory AML [n=10] and treated secondary AML [n=1]).

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Title: 2017-0912

A Phase II Study of Venetoclax in Combination with 10-day Decitabine in Newly Diagnosed Elderly or Relapsed/Refractory Acute Myeloid Leukemia and Relapsed High-risk Myelodysplastic Syndrome

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Wei Qiao, Ph.D.

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Amendment 10:	February 18, 2019
Amendment 11:	June 24, 2019
Amendment 12:	September 11, 2019
Amendment 13:	October 29, 2019

Contents

Appendices

1. OBJECTIVES

1.1 Primary Objective

- To determine the overall response rate (ORR) of venetoclax in combination with 10-day decitabine in patients with refractory/relapsed acute myeloid leukemia (AML); elderly (>60 year old) patients with newly diagnosed AML not eligible for intensive chemotherapy; patients with high-risk MDS with bone marrow blasts between 10% and 20%, relapsed or refractory to prior hypomethylating agent (HMA) therapy, or chronic myelomonocytic leukemia (CMML) with bone marrow blasts ≥ 10% regardless of prior therapy; AML patients with prior history of MDS or CMML who received therapy for the MDS or CMML and progressed to AML, and younger patients with newly diagnosed AML with poor risk complex karyotype and/or TP53 deletions/mutations.

1.2 Secondary Objectives

- To determine the duration of response, disease-free survival (DFS), and overall survival (OS) of patients with refractory/relapsed AML treated with this combination.
- To determine the number of patients who achieve a hematologic improvement (HI) in platelets, hemoglobin, or ANC and the number of patients who achieve > 50% reduction in blasts on therapy with venetoclax/10-day decitabine.
- To determine the safety of venetoclax in combination with 10-day decitabine in patients with refractory/ relapsed AML.
- To determine the number of patients who transition towards stem cell transplantation upon achieving response with the combination venetoclax/10-day decitabine regimen.
- To determine the incidence of infectious complications per cycle with venetoclax in combination with 10-day decitabine.

1.3 Exploratory Objective:

- To investigate possible relationships between baseline protein and gene expression signatures/mutation profile and BH3 profiling in predicting clinical response to the combination.
- To characterize the pharmacokinetic (PK) profiles of venetoclax in combination with decitabine and antifungals in plasma samples

2.0 BACKGROUND

2.1 Acute myeloid leukemia

AML is a malignancy of immature granulocytes or monocytes. The malignancy is characterized by accumulation of leukemic blasts and blockade of normal bone marrow production resulting in thrombocytopenia, anemia, and neutropenia. There are approximately 13,000 new cases of AML per year in the United States, with an estimated 10,000 deaths occurring in the same time period[1]. Almost all newly diagnosed cases, as well as deaths, will be in adults[2]. Standard treatment for AML includes systemic combination chemotherapy to control bone marrow and systemic disease. Treatment is generally divided into an induction phase, to attain remission, and a maintenance phase[2]. Approximately 60% to 70% of adults with AML can be expected to attain complete remission status following appropriate induction therapy. Remission rates in adult AML are

inversely related to age, with an expected remission rate of >65% for those younger than 60 years. Increased morbidity and mortality during induction appear to be directly related to age[3-5].

2.2 Relapsed/ Refractory AML

Approximately, 30-40% of adults with AML fail to achieve CR with 1 or 2 cycles of induction chemotherapy, and are deemed primary refractory. The outcome of patients with acute myeloid leukemia (AML) who are refractory to induction therapy are dismal, with low response rates to salvage chemotherapy and poor long-term survival [6-8]. We have previously reported a dismal median OS of 3.8 months for patients with AML who are refractory to HiDAC-containing induction therapy (defined as ≥ 1gm/m^2 cytarabine per dose)[7]. Salvage therapy in such patient populations yielded a response rate of 18% and median response duration of 9 months.

These results emphasize the need to explore alternate salvage regimens for patients with relapsed/refractory AML. The development of novel and effective anti-AML agents and/or combinations is crucial to improving the outcome of AML.

2.3 Myelodysplastic syndromes (MDS)

Myelodysplastic syndromes (MDS) are malignant clonal disorders characterized by ineffective hematopoiesis, bone marrow dysplasia, peripheral cytopenias including thrombocytopenia, and a propensity to transform into acute myeloid leukemia (AML).[9, 10] Classically, MDS is associated with apoptosis and excessive proliferation, resulting in a paradoxical combination of a hyper-cellular marrow and peripheral cytopenias.[11] The incidence of MDS in the United States is rising, with approximately 20,000 to 30,000 new cases of MDS diagnosed annually, and a median age at diagnosis of 70 years.[12-14]

The therapeutic options for MDS remain limited. A small percentage of patients are candidates for curative therapies such as allogeneic stem cell transplant. For the vast majority of patients the lack of acceptable donors, advanced age, and/or serious co-morbid medical conditions and organ dysfunction prevent access to this option. For similar reasons, AML-like intensive chemotherapy regimens represent an unacceptable benefit/risk ratio for many patients. In fact, the standard of care in MDS has generally been accepted as supportive in nature.

Over the past decade, clinical use of the hypomethylating agents (HMA) including azacitidine (Vidaza) have been shown to improve patient quality of life, decrease transfusion requirements, and improve outcome parameters in MDS patients, and now represent the standard of care for MDS patients requiring therapy. However, not all patients respond to HMAs, and unfortunately patients initially responding to HMAs will ultimately progress on therapy. Current evidence demonstrates ORRs to HMAs of 28-48% and CR rates of 6-34% in all patients treated with HMAs, with a median length of response in HMA-responders of only 8 to 10 months.[14, 15]

Prognosis in HMA-failure patients is extremely poor. Jabbour et al report a median survival of merely 4 months in MDS patients with progressive disease after decitabine, and Prebet et al identified a median survival of 5.6 months in MDS patients with progressive disease after azacitidine. There are no currently approved agents in the setting of HMA-failure MDS patients, and there are limited therapeutic options, particularly given the increased age and frequent comorbidities of this population.

2.4 The Treatment - Decitabine (5 aza-2'deoxycytidine, Decitabine)

Decitabine is a deoxycytidine analog which is phosphorylated to its nucleotide and incorporated into DNA. Once incorporated, it covalently binds to DNA-methyltransferases and traps the enzyme thus acting as an irreversible inhibitor of DNA-methyltransferase. Decitabine produces marked DNA hypomethylation (superior to azacytidine in this effect) via inhibition of DNA methyltransferase.[16-18] At high doses, decitabine appears to cause DNA synthesis arrest due to the formation of a DNA/DNA-methyltransferase adducts, which results in cytotoxicity and apoptosis. At low doses, minimal cytotoxicity is observed, and treated cells exhibit marked reduction in DNA-methyltransferases activity, reduced overall and gene-specific DNA methylation and reactivation of silenced genes. This is associated with tumor suppressor gene activation, induction of cellular differentiation, and inhibition of clonogenic growth of leukemic progenitors.

2.4.1 Clinical Experience with Decitabine at standard doses at MD Anderson

A phase 2 trial of Decitabine in accelerated phase (CML-AP) and blastic phase CML (CML-BP) was completed at MD Anderson. Initially, patients were treated at 100 mg/m^2 q12h for 5 days (1,000 mg/m^2 per course) but the dose had to be reduced initially by 25% and eventually by 50% because of prolonged myelosuppression. In CML-BP, a total of 42 patients were treated, with a complete hematologic response seen in 5%, partial hematologic response in 5% and hematologic improvement in 19%, for a total response rate of 29%. In CML-AP, a total of 39 patients were treated. CHR was seen in 18%, PHR in 38% and HI in 8%, for a response rate of 62%. Unique features of decitabine in this setting were:(1) a slow pattern of reduction of blasts, (2) a rapid rise in platelets following therapy, and (3) occasional responses late into therapy (after 2 cycles). These suggested that responses to decitabine might involve a differentiation component, similar to what was observed with other differentiating agents in leukemia. A subset analysis of older (>50 years) patients in CML-BP showed that decitabine therapy resulted in better survival than historical controls treated with combination chemotherapy.[19, 20]

2.4.2 Clinical Experience with low-dose Decitabine at MD Anderson

Based on in-vitro data suggesting greater hypomethylating activity at lower doses, a phase I biological study of decitabine was initiated at MD Anderson. To maximize the hypomethylating effects of decitabine, multiple low dose schedules in patients with relapsed/refractory myeloid malignancies were tried. Initially, patients were treated at 5 mg/m^2 IV over 1 hour daily for 10 days (dose 30 fold lower than the reported MTD). The dose was then escalated to 10, 15 and 20 mg/m^2 daily for 10 days. Finally, a group of patients received 15 mg/m^2 daily for 15 days then 20 days. A total of 48 patients were enrolled on the study. Responses were seen at all dose levels, but 15 mg/m^2 appeared to induce the most responses, with no further benefit for increasing the dose or duration of administration. There were 9 complete remissions (CR 18%) and 7 partial remissions (14%), for a response rate of 32%. Responses were seen in refractory/relapsed AML (8/37=22%), myelodysplastic syndrome (MDS) (4/7=57%), and CML (4/5=80%). In some patients who responded, there was a gradual diminution of blasts over 2-4 weeks, and eventual recovery of normal hematopoiesis at 5-6 weeks, suggesting a non-cytotoxic mode of action for this regimen. Response duration ranged from 2 months to 10+ months. DNA methylation studies suggested that hypomethylation of Alu repeats was associated with response. Therefore low-dose decitabine is an effective agent in myeloid malignancies, and appears to induce remissions in part through demethylation rather than cytotoxicity. The effective low dose administration schedule derived from this phase I study is 15 mg/m^2 IV over 1 hour daily for 10 days.[21]

2.4.3 Studies of Decitabine in AML

We have previously investigated whether treatment with hypomethylating agents (5-azacytidine /decitabine) leads to an improved outcome in patients with AML who are older and/or have adverse

cytogenetics.[22] Between January 2004 and December 2007, 81 patients (37 [46%] with AML [>or=20% blasts]; 44 [54%] with high-risk MDS) with chromosome 5 and 7 abnormalities were treated with hypomethylating agents as their initial therapy. These included 68 patients with complex (>or=3) abnormalities and 13 with <3 aberrations. During the same period, 151 patients (126 with AML, 25 with MDS) with chromosome 5 and 7 abnormalities (128 complex, 23 noncomplex) were treated with intensive chemotherapy (including cytarabine-based regimens in 72% and other regimes in 28%). The median ages for the 2 groups were 66 years and 61 years, respectively (ranges, 37-85 years and 19-89 years). Thirty-three (41%) patients in the hypomethylating group achieved complete remission (CR) versus 53 (35%) in the chemotherapy group (P=.395). With a median follow-up of 51 weeks (range, 12-101 weeks) and 40 weeks (range, 5-128 weeks), 22 of 33 patients in the hypomethylating group and 33 of 53 patients in the chemotherapy group had developed disease recurrence. The median CR duration was 45 weeks and 23 weeks, respectively (P=.153). The overall survival was superior for the hypomethylating group compared with the chemotherapy group (P=.019). The investigators concluded that treatment with hypomethylating agents may be superior to chemotherapy in patients with chromosome 5 and 7 abnormalities.[22]

In a multicenter, phase II study, patients older than 60 years who had AML (ie, > 20% bone marrow blasts) and no prior therapy for AML were treated with decitabine 20 mg/m^2 intravenously for 5 consecutive days of a 4-week cycle. Response was assessed by weekly CBC and bone marrow biopsy after cycle 2 and after each subsequent cycle.[23] Patients continued to receive decitabine until disease progression or an unacceptable adverse event occurred. Fifty-five patients (mean age, 74 years) were enrolled and were treated with a median of three cycles (range, one to 25 cycles) of decitabine. The expert-reviewed overall response rate was 25% (complete response rate, 24%). The response rate was consistent across subgroups, including in patients with poor-risk cytogenetics and in those with a history of myelodysplastic syndrome. The overall median survival was 7.7 months, and the 30-day mortality rate was 7%. The most common toxicities were myelosuppression, febrile neutropenia, and fatigue. The investigators concluded that decitabine given in a low-dose, 5-day regimen has activity as upfront therapy in older patients with AML, and it has acceptable toxicity and a low 30-day mortality.[23]

In another phase II clinical trial with decitabine in older patients (>or=60 years) with previously untreated AML who were not candidates for or who refused intensive chemotherapy, subjects received low-dose **decitabine at 20 mg/m^2 IV over 1 hour on days 1 to 10.** Fifty-three patients were enrolled with a median age of 74 years (range, 60-85).[24] Nineteen (36%) had antecedent hematologic disorder or therapy-related AML; 16 had complex karyotypes (>or=3 abnormalities). The complete remission rate was 47% (n = 25), achieved after a median of three cycles of therapy. Nine additional subjects had no morphologic evidence of disease with incomplete count recovery, for an overall response rate of 64% (n = 34). Complete remission was achieved in 52% of subjects presenting with normal karyotype and in 50% of those with complex karyotypes. Median overall and disease-free survival durations were 55 and 46 weeks, respectively. Death within 30 days of initiation of treatment occurred in one subject (2%), death within 8 weeks in 15% of subjects. They also examined the relationship of clinical response and pretreatment level of miR-29b, previously shown to target DNA methyltransferases. Higher levels of miR-29b were associated with clinical response (P = 0.02). They concluded that this schedule of decitabine was highly active and well tolerated in this poor-risk cohort of older AML patients.[24]

Most recently a multicenter, randomized, open-label, phase III trial compared the efficacy and safety of decitabine with treatment choice (TC) in older patients with newly diagnosed acute myeloid leukemia (AML) and poor- or intermediate-risk cytogenetics.[25] Patients (N = 485) age ≥ 65 years were randomly assigned 1:1 to receive decitabine 20 mg/m^2 per day as a 1-hour intravenous infusion for five consecutive days every 4 weeks or TC (supportive care or cytarabine 20 mg/m^2

per day as a subcutaneous injection for 10 consecutive days every 4 weeks). The primary end point was overall survival (OS); the secondary end point was the complete remission (CR) rate plus the CR rate without platelet recovery (CRp). Adverse events (AEs) were recorded. The primary analysis with 396 deaths (81.6%) showed a non-significant increase in median OS with decitabine (7.7 months; 95% CI, 6.2 to 9.2) versus TC (5.0 months; 95% CI, 4.3 to 6.3; P = .108; hazard ratio [HR], 0.85; 95% CI, 0.69 to 1.04). An unplanned analysis with 446 deaths (92%) indicated the same median OS (HR, 0.82; 95% CI, 0.68 to 0.99; nominal P = .037). The CR rate plus CRp was 17.8% with decitabine versus 7.8% with TC (odds ratio, 2.5; 95% CI, 1.4 to 4.8; P = .001). Adverse events were similar for decitabine and cytarabine, although patients received a median of four cycles of decitabine versus two cycles of TC. The most common drug-related AEs with decitabine were thrombocytopenia (27%) and neutropenia (24%). Therefore, in older patients with AML, decitabine improved response rates compared with standard therapies without major differences in safety. An unplanned survival analysis showed a benefit for decitabine, which was not observed at the time of the primary analysis.[25]

Recent report of a single institution study in AML and MDS patients with unfavorable risk cytogenetic abnormalities and/or TP53 mutations showed favorable clinical responses and robust mutation clearance after receiving serial 10-day courses of decitabine. These responses translated in rates of overall survival that were similar to those among patients with AML who had an intermediate-risk cytogenetic profile and who also received serial 10-day courses of decitabine.[26]

2.5 Overview of investigational treatment - venetoclax

2.5.1 Venetoclax

See the Venetoclax Investigator's Brochure (IB) (Attached) for additional details on nonclinical and clinical studies.

Bcl-2 overexpression has been implicated in maintaining the survival of AML cells and has been associated with resistance to chemotherapy and inferior overall survival [27]. Venetoclax (VEN) is a potent and selective small-molecule inhibitor of Bcl-2 that has demonstrated cell-killing activity against a variety of leukemia cell lines, primary patient samples and leukemia stem/progenitor cells [28, 29]. VEN also has been found to synergize with agents known to down-regulate Mcl-1, including azacytidine[30].

Based on the mechanism of action and nonclinical and clinical data available to date, the safety profile of venetoclax is well described. The most common adverse drug reactions across all indications are nausea, diarrhea, hematological effects, and serious and/or opportunistic infections. Hematologic effects include neutropenia/febrile neutropenia, thrombocytopenia, anemia, and lymphopenia. Upper respiratory tract infections are among the most common infections. TLS is an important identified risk and is predominantly seen in the CLL population with high tumor burden. Based on pre-clinical data, decreased spermatogenesis has been identified as a potential risk for venetoclax.

2.5.2 Summary of Venetoclax Nonclinical Pharmacology

Venetoclax is a potent, selective and orally bioavailable small molecule inhibitor of Bcl-2 that binds with > 1,000-fold higher affinity for Bcl-2 (dissociation constant [K_i] < 0.010 nM) than for Bcl-X_L (K_i - 48 nM or Mcl-1 (K_i > 444 nM).[28] In vitro, venetoclax has demonstrated cell killing activity against patient-derived chronic lymphocytic leukemia (CLL) cells and a variety of lymphoma and leukemia cell lines[28]. Venetoclax has demonstrated potent killing of AML cell lines, primary patient samples, and leukemic stem/progenitor cells ex vivo, and has also exhibited anti-tumor efficacy in vivo, inhibiting the growth of AML cells systemically engrafted into immunocompromised mice.

2.5.3 Summary of Venetoclax Nonclinical Pharmacokinetics

The pharmacokinetics of venetoclax was evaluated in mice, rats, monkeys, and dogs. Venetoclax pharmacokinetic (PK) profile was characterized by low plasma clearance and low to moderate volumes of distribution. Half-lives ranged from 2.2 hours in monkeys to 12 hours in dogs.

Venetoclax demonstrated high protein binding to human, rat, dog, and monkey plasma proteins (> 99.9%). Blood to plasma ratios showed that venetoclax does not partition preferentially into the red blood cells. Following oral administration of venetoclax to nonclinical species and humans, parent compound and metabolites were mainly cleared via biliary excretion and fecal elimination, with minimal renal clearance.

Venetoclax is predominantly metabolized by cytochrome P450 (CYP) 3A4 (CYP3A4) in vitro; UDP-glucuronosyltransferases (UGTs) are not involved in the metabolism of venetoclax. In addition, venetoclax is also a substrate for P-gp and BCRP. Active uptake of venetoclax was not observed in cells overexpressing OATP1B1, OATP1B3 or OCT1. In vitro studies indicated that venetoclax is not an inhibitor or inducer of CYP1A2, CYP2B6, CYP2C19, CYP2D6, or CYP3A4 at clinically relevant concentrations. Venetoclax is a weak inhibitor of CYP2C8, CYP2C9, and UGT1A1 in vitro, but it is not predicted to cause clinically relevant inhibition due to high plasma protein binding. Venetoclax is a P-gp and BCRP inhibitor and weak OATP1B1 inhibitor in vitro. In vitro, venetoclax is metabolized by CYP3A4 and is a moderate inhibitor of CYP2C8. Definitive in vitro experiments showed that venetoclax is not predicted to be an inducer or inhibitor of the metabolism of CYP2C9 substrate compounds. Venetoclax is not a reversible inhibitor of CYP1A2, CYP2B6, CYP2D6, CYP2C19 or CYP3A4 (IC_{50} > 30 μM) in vitro and does not induce CYP3A4 or CYP1A2 at concentrations up to 10 μM.

2.5.4 Summary of Nonclinical Toxicology

Venetoclax has been assessed in repeated-dose general toxicology studies and in genetic, developmental/reproductive, and safety pharmacology studies. The primary toxicities associated with venetoclax administration included effects on the hematologic system (decreased lymphocytes and erythrocytes) in mice and dogs, the male dog reproductive system (testicular germ cell depletion), and embryo-fetal toxicity in mice.

2.5.5 Summary of Venetoclax Clinical Data

Clinical Efficacy Data for Venetoclax: Preliminary efficacy results are available for subjects with a variety of hematological neoplasms; the drug is approved for the treatment of CLL patients whose cells have a 17p chromosomal deletion. Preliminary data indicate that venetoclax shows promising efficacy in AML.

- In study M14-212 the ORR for subjects treated with ventoclax monotherapy was 19%.[31]
- In Study M14-358 the ORR for AML subjects (given venetoclax plus azacitidine or decitabine) was 68%.[32]
- In Study M14-387 the ORR for AML subjects (given venetoclax plus low dose ara-C) was 75%.[33]

Venetoclax Clinical Pharmacology and Pharmacokinetics: Venetoclax clinical pharmacology is being evaluated in several Phase I to III clinical trials, and preliminary data are available from 3 Phase I studies (M12-175, M13-367, M12-630), 4 Phase IB studies (M13-365, M12-901, GO29440, GP28331), 1 Phase II study (M14-212) and 5 dedicated clinical pharmacology studies (Study M13-364, M14-497, M13-363, M14-253 and M15-101).

In the Phase 1 Study M14-358, preliminary pharmacokinetic results in 31 treatment-naïve AML subjects were available for venetoclax doses ranging from 400 mg to 800 mg when given in combination with decitabine (Arm A) or azacitidine (Arm B) and with or without posaconazole (Arm C). For Arm A and Arm B, venetoclax steady-state mean Cmax and AUC24 (Cycle 2 Day 5) ranged from 1.77 – 3.36 µg/mL and 24.7 – 59.5 µg/mL, respectively. Based on the limited preliminary pharmacokinetic data, there was no evidence to suggest a marked effect of the co-administration of decitabine and azacitidine on the pharmacokinetics of venetoclax. In Arm C of this study, preliminary pharmacokinetic results from 6 subjects were available on Cycle 1 Day 20 (venetoclax 400 mg alone QD until Day 20) and Cycle 1 Day 28 (venetoclax 100 mg QD with posaconazole given from Day 21 to Day 28). Venetoclax Cmax and AUC following co-administration of venetoclax 100 mg with posaconazole were 2.1- and 2.7-fold higher respectively, compared to venetoclax 400 mg dosing alone.

Moderate and strong CYP3A inhibitors alter venetoclax pharmacokinetics and require dose adjustments. In many instances, neutropenic patients (AML) require antifungal prophylaxis with azole therapy. Azole antifungals are moderate (isavuconazole) to strong (voriconazole, and posaconazole) CYP3A inhibitors and require a 50% dose reduction (200 mg). These dose adjustments are recommended based on clinical judgement. However, there is no pharmacokinetics data to guide the accurate dose adjustments needed for the moderate and strong CYP3A inhibiting antifungals.

Preliminary pharmacokinetic results of venetoclax are available from 12 treatment-naïve subjects with AML in Cohorts 1 (600 mg) and 2 (800 mg) from the ongoing Phase 1 combination study of venetoclax and low dose cytarabine (Study M14-387). On Cycle 1 Day 10 (with cytarabine), venetoclax mean Cmax and AUC24 values ranged from 2.25 – 2.56 µg/mL and 34.7 – 44.6 µg•hr/mL, respectively. On Cycle 1 Day 18 (venetoclax alone), mean Cmax and AUC values of venetoclax ranged from 2.38 – 2.89 µg/mL and 37.9 – 45.3 µg•hr /mL. Dose-normalized Cmax and AUC24 of venetoclax on Cycle 1 Day 10 (with cytarabine) were comparable to dose normalized Cmax and AUC24 on Cycle 1 Day 18 (venetoclax alone), suggesting that co administration of cytarabine did not markedly affect venetoclax exposures.

Clinical Safety Data for Venetoclax: As of 05 June 2017, three Phase 1/2 studies have been conducted in the AML indication as described below.

Overview of Phase 2 Study M14-212: Venetoclax Monotherapy in AML

This is a completed study with single agent venetoclax in subjects with R/R AML and those unfit for intensive therapy. A total of 32 subjects were dosed. Exposure, safety, and efficacy data are available for this study.[31] The most common adverse events observed in ≥ 30% of the subjects in Study M14-212 were nausea (59.4%); diarrhea (56.3%); hypokalemia, vomiting (40.6% each); fatigue, headache (34.4% each); hypomagnesemia (37.5%); febrile neutropenia (31.3%); abdominal pain, cough, hypophosphatemia (28.1% each); epistaxis, hyperphosphatemia, hypocalcemia, malignant neoplasm progression (25.0% each); dyspnea, hypotension, peripheral edema, pyrexia, and pneumonia (21.9% each). Serious adverse events were reported in 27 subjects (84.4%), the most common being febrile neutropenia (28.1%), malignant neoplasm progression (25.0%), and pneumonia (15.6%). Three serious adverse events were considered to have a reasonable possibility of being related to venetoclax (i.e., 1 event each of diarrhea, febrile neutropenia, and pseudomonal bacteremia). No cases of TLS occurred during venetoclax treatment.

In this phase II multicenter trial single agent VEN produced an overall response in 5/32 relapsed/refractory AML patients (CR in 1 patient, CRi in 4 patients) [34]. Of the 5 patients with

CR/CRi, 3 had *IDH* mutations suggesting that patients with *IDH* mutations may be particularly sensitive to VEN.

Two ongoing trials are evaluating VEN combination regimens in treatment naïve patients with AML who are ≥65 years of age and who are not eligible for standard induction: (a) to evaluate the efficacy and tolerability of the combination of VEN with a methyltransferase inhibitor (azacytidine or decitabine) (ClinicalTrials.gov Identifier: NCT02203773); (b) to evaluate VEN with low-dose cytarabine (ClinicalTrials.gov Identifier: NCT02287233).

Overview of Ongoing Phase 1b Study (M14-358): Venetoclax in Combination with HMA in Treatment Naïve AML

As of 09 March 2016, a total of 45 subjects ≥ 65 years of age with treatment naïve AML ineligible to receive standard induction therapy were enrolled into the escalation stage at 3 dose levels of venetoclax at 400 mg, 800 mg, and 1200 mg. Venetoclax was administered daily during the 28-day cycles in combination with decitabine (20 mg/m^2 intravenously on Days 1 – 5 once every 28 days) or azacitidine (75 mg/m^2 intravenously or subcutaneously on Days 1 – 7 once every 28 days). Preliminary safety and efficacy data are available from the ongoing dose escalation stage of this trial.[33, 35]

The most common adverse events for all subjects in Study M14-358 were nausea (53.3%), diarrhea (44.4%), febrile neutropenia (40.0%), neutrophil count decreased (31.1%), platelet count decreased, cough, and fatigue (28.9% each), edema peripheral and hypokalemia (26.7% each). Events grade 3 and above were reported for the majority (91.1%) of subjects; the most common event was febrile neutropenia (40.0%). Serious adverse events were reported for 27 (60.0%) subjects, including febrile neutropenia (11 subjects), malignant neoplasm progression (3 subjects) atrial fibrillation, abdominal pain, non-cardiac chest pain, pyrexia, pneumonia, sepsis, bone pain (2 subjects each). All other events occurred in 1 subject each. The combination of venetoclax with decitabine and azacitidine demonstrates a tolerable safety profile.

As of 09 March 2016, the ORR, as assessed by the investigators for the subjects enrolled into the 3 dose levels, was 62.2% (28 of 45), with CR in 12 (26.7%), CRi in 15 (33.3%), and PR in 1 (2.2%). Four subjects (8.9%) were reported to have morphologic leukemia-free state (less than 5% blasts in bone marrow aspirate sample with at least 200 nucleated cells) after completion of Cycle 1. Eight patients (17.8%) had resistant disease. However, all of the patients with resistant disease had evidence of blast reduction at completion of Cycle 1. The patients enrolled into the 1200 mg dose level had a shorter follow-up at the time of this analysis.

The maximum tolerated dose has not been reached in either arm and dose escalation stage has completed enrollment. Enrollment into safety expansion at 400 mg and 800 mg dose of venetoclax in combination with both HMAs is ongoing.

Study M14-387: Study M14-387 titled, "A Phase 1/2 study of venetoclax in combination with low-dose cytarabine in treatment naïve subjects with acute myeloid leukemia who are ≥ 65 years of age and who are not eligible for standard anthracycline-based induction therapy," is an ongoing, open-label, multicenter safety and pharmacokinetics study. The primary objectives of the Phase 1 portion are to assess the safety profile, characterize pharmacokinetics, and determine the dose schedule, the MTD, and the RPTD of venetoclax in combination with low-dose cytarabine (LCD) in treatment-naïve AML subjects. The primary objectives of the Phase 2 portion of the study are to evaluate preliminary estimates of efficacy (including ORR and TTP) and to characterize the toxicities of the combination at RPTD. Secondary objectives of the Phase 2 portion include evaluating leukemia response (rates of CR, CRi, PR, RD, and HR including transfusion support

needs) and DOR. An additional exploratory objective includes the evaluation of biomarkers that may serve as surrogate or predictors for clinical outcomes for future studies.
Of the 25 subjects in Study M14-387, 24 (96.0%) experienced at least 1 treatment-emergent adverse event. The most common adverse events for all subjects in Study M14-387 were: nausea (54%), febrile neutropenia (41%), diarrhea (44%), decreased appetite (33%), and peripheral edema (31%). Adverse events leading to study drug discontinuation occurred in 4 (16.0%) subjects, including 1 event each of disease progression, acute hepatic failure, Candida pneumonia, and subdural hemorrhage. Fatal adverse events occurred in 5 (20.0%) subjects: 2 events of malignant neoplasm progression and 1 event each of acute hepatic failure, Candida pneumonia, and lung infection.[32]

For further details of venetoclax preclinical studies, clinical studies, toxicities, pharmacokinetics, and adverse events please see the venetoclax Investigator Brochure (attached).

Experience with Venetoclax in combination therapy in relapsed and refractory myeloid malignancies
Efficacy of venetoclax combinations in the salvage setting will be presented at ASH 2017. Twenty-seven patients treated at our institution with relapsed/refractory AML (n=24), MDS (n=2) or BPDCN (n=1) received combinations including with decitabine (n=16) or azacitidine (n=5). Objective responses were achieved in 22% (n=6) of patients after a median of 1 cycle (range 1-4), including 11% with CRi and 11% with MFLS. 4 of the 6 responding patients received decitabine + venetoclax combinations, including 2 patients treated on the 5-day schedule and 2 patients treated on the 10-day schedule.

Interim Analysis of current study (Abstract submitted to ASH 2019, under review)
Between January and November 2018 we enrolled 101 pts with newly diagnosed (ND) AML (n=40), untreated sAML (n=9), treated sAML (n=19) and R/R AML (n=33). The data cut-off date was 03.08.19.

This high-risk cohort included 52% of pts ≥70 yrs (interquartile range [IQR], 61-74), 28% pts with ECOG PS ≥2, and 67% pts with adverse-risk AML. 30 and 60-day mortality were both 2.5% for ND pts, and 5% and 9%, respectively, for all pts. Treatment-emergent adverse events were infections with grade 3/4 neutropenia (61%), febrile neutropenia (35%), and TLS (4%).

The CR/CRi rate in ND AML was 95%, in untreated sAML was 67%, in treated sAML was 37%, and in R/R AML was 27%. In previously untreated AML (defined as ND AML + untreated sAML), CR/CRi rate in ELN favorable, intermediate and adverse risk pts were 100% (n=11), 100% (n=6), and 84% (n=32). CR/CRi rate in t-AML was 100% (n=7). In previously treated AML (treated sAML + R/R AML), CR/CRi rate in HMA refractory pts was 39% (n=18), in pts with prior intensive chemotherapy (IC) was 21% (n=33), in pts with prior HMA and IC was 17% (n=12), in pts with prior stem cell transplantation (SCT) was 22% (n=18).

At median follow-up of 8.1 months (mo), the 6-mo OS in ND AML was 90%, in untreated sAML was 56%, in treated sAML was 62%, and R/R AML was 53%. Among all pts, achievement of CR conferred better DOR and OS compared to CRi/MLFS (median DOR not reached [NR] vs 4.0 mo, censored at SCT, HR 0.21 95% CI 0.09-0.49, p=0.002, and median OS NR vs 7.8 mo, censored at SCT, HR 0.31, 95% CI 0.13-0.74). 70% of all responding pts were minimal residual disease negative (MRD-) by flow cytometry and MRD- status was associated with longer OS (NR vs 7.8 mo, censored at SCT, HR 0.35, p=0.01). Median DOR in pts achieving CR/CRi in ND AML was 8.5 mo, in the untreated sAML was 6.3 mo, in treated sAML was 4.8 mo, and in R/R AML was 6.6 mo.

Among ND AML pts achieving CR/CRi, median time to count recovery after 1st, 2nd and 3rd cycles for ANC >0.5x10^9/L was 42 days (95% CI 37-46), 40 days (95% CI 35-44), and 38 days (95% CI 32-NR), respectively; and for platelet ≥50 x10^9/L was 28 days (95% CI 25-32), 25 days (95% CI 0-34), and 26 days (95% CI 19-33), respectively.

78 pts (77%) discontinued treatment, and 59 pts (58%) are alive. Common reasons for discontinuation were non-response in 24 pts (24%), SCT in 20 pts (20%), and relapse in 18 pts (18%). Pts receiving SCT (n= 20) had excellent outcomes with 100-day post-SCT mortality of 0%.

In conclusion, the Decitabine x 10 day/Venetoclax regimen is an effective therapy for ND elderly pts, as well as in R/R AML as an effective bridge to SCT, with an acceptable safety profile. Given its high efficacy exceeding what was reported for approved 5-day Decitabine/Venetoclax regimen in newly diagnosed elderly AML and AML from MDS, and rapid accrual with few remaining slots (Cohort 2 Elderly new AML maximum accrual: 80, accrual to date (9/4/2019): 65 with 15 slots available; Cohort 3 AML from MDS maximum accrual: 40 patients, accrual to date: 32 with 8 slots available), the protocol is being amended to add additional 40 slots/each in these two cohorts.

3.0 STUDY RATIONALE

The current standard dose for decitabine in MDS and AML is 20 mg/m^2 daily x 5 days. A study conducted by the Ohio State University has produced significantly higher response rate when an extended schedule of decitabine 20 mg/m^2 daily x 10 days was used. Study from Washington University showed favorable responses in poor-risk patients with inverse risk cytogenetics and TP53 mutations, using 10-day decitabine regimen. Combination of venetoclax with 5-day Decitabine regimen in frontline elderly AML demonstrated tolerability and encouraging efficacy. The objective of this Phase 2 study is to determine the overall response rates and safety of a combination of venetoclax with 10-day decitabine, in AML or high-risk MDS patients with generally poor outcomes.

RATIONALE FOR TREATMENT OF PATIENTS WITH COMPLEX KARYOTYPE AND/OR TP53 DELETIONS/MUTATIONS REGARDELSS OF AGE

Historically, patients harboring TP53 mutations have inferior outcomes with standard chemotherapy, with reported CR rats of only 28%. [36] In Washington University decitabine x10 day study, 53% of TP53-mutated AML achieved objective responses. In a completed multi-center Phase II study, the CR/CRi rates for patients with poor risk cytogenetics (n=30) in decitabine x 5 day/venetoclax arm reached 70%, and in TP53-mutant cohort (n=16) it was 56.3% (manuscript submitted). In our preliminary analysis of the ongoing study, the response rates of all TP53-mutant AML patients is 67%; 4/7 in relapsed/refractory cohort and 4/4 in newly diagnosed cohort achieved CR/CRi. These findings indicate superior response rates in this poor risk category of patients with decitabine/venetoclax combination regimens.

4.0 ELIGIBILITY CRITERIA

4.1 Inclusion criteria

1. Patients with AML,biphenotypic or bilineage leukemia (including a myeloid component) or mixed phenotype acute leukemia (MPAL) who have failed prior therapy. Patients with AML should have failed prior therapy or have relapsed after prior therapy. Patients with isolated extramedullary AML are eligible.
2. Elderly (>60 year old) patients with newly diagnosed AML or mixed phenotype acute leukemia (MPAL) not eligible for intensive chemotherapy.
3. Patients with newly diagnosed AML with poor risk complex karyotype and/or TP53 deletions/mutations equal or younger than 60 year old

4. AML patients with prior history of MDS or CMML who received any therapy or no therapy for the MDS or CMML and progressed to AML, are eligible at the time of diagnosis of AML regardless of any prior therapy for MDS. The WHO classification will be used for AML.
5. Patients with high-risk MDS with bone marrow blasts between 10% and 20%, relapsed or refractory to prior hypomethylating agent (HMA) therapy, defined as prior receipt of 4 cycles of HMA therapy with failure to attain a response, or relapse after prior response to HMA therapy. Patients with high risk chronic myelomonocytic leukemia (CMML) with bone marrow blasts ≥ 10% regardless of prior therapy.
6. Age >/=18 years
7. Eastern Cooperative Oncology Group (ECOG) Performance Status </=3
8. White blood cell count≤10,000.
9. Adequate renal function including creatinine < 2 unless related to the disease.
10. Adequate hepatic function including total bilirubin < 2x upper limit of normal (ULN) unless increase is due to Gilbert's disease or leukemic involvement, and ALT < 3x ULN unless considered due to leukemic involvement
11. Provision of written informed consent
12. Oral hydroxyurea and/or one dose of cytarabine (up to 2 g/m^2) for patients with rapidly proliferative disease is allowed before the start of study therapy and while the patient is on active study treatment through cycle 1, as needed, for clinical benefit and after discussion with the PI. Concurrent therapy for central nervous system (CNS) prophylaxis or continuation of therapy for controlled CNS disease is permitted.
13. Females must be surgically or biologically sterile or postmenopausal (amenorrheic for at least 12 months) or if of childbearing potential, must have a negative serum or urine pregnancy test within 72 hours before the start of the treatment
14. Women of childbearing potential must agree to use an adequate method of contraception during the study and until 3 months after the last treatment. Males must be surgically or biologically sterile or agree to use an adequate method of contraception during the study until 3 months after the last treatment.

4.2 Exclusion criteria:

1. Patients having received any prior BCL2 inhibitor therapy.
2. Patients with t(15;17) karyotypic abnormality or acute promyelocytic leukemia (French-American-British [FAB] class M3-AML).
3. Patients with symptomatic CNS leukemia or patients with poorly controlled CNS leukemia.
4. Active and uncontrolled comorbidities including active uncontrolled infection, uncontrolled hypertension despite adequate medical therapy, active and uncontrolled congestive heart failure NYHA class III/IV, clinically significant and uncontrolled arrhythmia as judged by the treating physician.
5. Patients with known infection with human immunodeficiency virus (HIV) or active Hepatitis B or C.
6. Any other medical, psychological, or social condition that may interfere with study participation or compliance, or compromise patient safety in the opinion of the investigator.
7. Pregnant or breastfeeding.

5.0 TREATMENT PLAN

This study is a Phase II single center clinical trial designed to assess the efficacy, safety and tolerability of venetoclax in combination with the 10-day regimen of decitabine for the treatment of relapsed/refractory AML. Patients will be treated with IV decitabine and venetoclax daily oral.

5.1 Decitabine

Decitabine will be administered at 20 mg/m^2 IV over approximately 1 hour daily x 10 days on days 1-10 of each treatment cycle. Treatment cycles will begin on day 1 of each new decitabine cycle.

Decitabine will be dosed based on actual body weight. However, at the treating physician's discretion an adjusted body weight may be used, if actual body weight is >40% over ideal body weight. Adjusted body weight = ((Actual body weight – Ideal body weight) 0.4) + Ideal body weight.

Decitabine may be subsequently administered at any of the Houston Area Locations (HAL) or at the patients' local oncologist offices.

Patients will receive one course every 4-8 weeks; however delays of more than 8 weeks may be allowed if determined by the investigator to be in the best interest of the patient after discussion with the PI and the discussion documented in the patient's medical record.

Patients may receive 5 day Decitabine dosing after achieving CR/CRi during consolidation/ maintenance. The 5 day dosing may also be initiated in patients not achieving CR/CRi after the first course if it is thought to be in the best interest of the patient after discussion with the PI and the discussion documented in the patient's medical record.

5.2 Venetoclax.

Venetoclax will be administered orally daily on days 1-28 of the first cycle; and days 1-21 for subsequent cycles. If bone marrow performed on day 21 (+/- 3 days) of the 1st cycle shows clearance of the blasts (<5%), venetoclax should be held to allow count recovery. Ventoclax may be also held in patients with persistent disease in Day 21 bone marrow, if determined by the investigator to be in the best interest of the patient after discussion with the PI (for example in the setting of infection).
The patient will be admitted to the hospital for the 1st cycle of concomitant decitabine-venetoclax therapy (e.g., Days 1 through Day 10) of cycle 1. To mitigate the risk for TLS, patients must be receiving tumor lysis prophylaxis, including hydration (oral, intravenous) and treatment with a uric acid reducing agent (allopurinol, rasburicase) during Cycle 1. If no evidence of TLS for the first 3 days of combination therapy, patients can be discharged upon discussion with the Principal Investigator.

If venetoclax is not available at the start of therapy due to different reasons (insurance, financial, transportation, others), decitabine can start and venetoclax is added when it becomes available.

If decitabine cycles are delayed, venetoclax therapy may continue on Days 1 -21 of a 4 week cycle after discussion with the PI or Co-PI and documentation in the medical record.

5.3 Duration of Therapy

In the absence of treatment delays due to clinically significant study drug related adverse events, treatment may continue until one of the following criteria applies:

- Clinically significant progressive disease; no response after ≥ 4 courses. Patients may continue therapy as long as they have stable disease, as long as it is determined to be in the best interest of the patient.
- Intercurrent illness that prevents further administration of treatment,

- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Up to a total of 24 courses of therapy; estimated 2 to 3 years.

a. Patients may receive further courses of therapy not earlier than 4 weeks from the previous course, provided the patient has recovered from myelosuppression considered to be related to chemotherapy. Patients with rapid increase in blasts may start additional therapy before 28 days from start of the previous course.

b. A minimum of 1 full course (or 4 weeks from the start of therapy) will be required for a patient to be considered as having received an adequate trial to evaluate efficacy. All patients receiving at least one dose of any of the two drugs will be considered evaluable for toxicity. Patients achieving a partial response or with stable disease may continue on therapy until definite evidence of disease progression.

c. In instances where one drug is not available or transiently interrupted because of safety or other reasons, the administration of the other drug may continue as scheduled. If the drug that is held can resume at a later time, no doses will be made up and the administration will follow the originally defined schedule calendar according to the drug that was continued.

5.4 Dose Adjustments

5.4.1 Decitabine and Venetoclax dose adjustments for hematological drug-related adverse events (AE):

Dose reduction/interruption/discontinuation decisions should be based on the CTCAE version 4.0 of the toxicity and the guidelines provided below. Dose modifications outside of those provided in Table 1 are allowable after discussion with the PI and documentation in the medical record, if in the best interest of the patient.

- Patients with acute leukemia's usually present with abnormal peripheral blood counts at the time therapy is started and myelosuppression is an expected event during the course of therapy for acute leukemia's. Thus, no dose adjustments or treatment interruptions for myelosuppression will be planned in the presence of residual leukemia. Dose-interruptions of Decitabine and Venetoclax in these patients should be considered on an individual case and discussed with the PI.
- Patients with a response (no marrow evidence of leukemia) who have prolonged (>42 days) count recovery, may have the treatment with Decitabine and Venetoclax interrupted at the discretion of the treating physician after discussing with the PI until neutrophils recover to ANC is ≥ 500/μL and platelets to >50 $x10^9$/L. After interruption, dose adjustment for venetoclax, decitabine or both can be made as follows:

Table 1. Dose de-escalation for venetoclax and Decitabine

Dose Level	Decitabine mg/m^2 daily	Venetoclax dose mg	Venetoclax duration
0 **(starting dose)**	20	400	21 days
-1	15	200	21 days
-2	10	200	14 days

- A reduction of 2 dose levels may be considered if the myelosuppression was deemed severe and life threatening by the treating physician, and if it is in the patient's best interest.
- If additional dose reductions are thought to be necessary by the investigator a discussion with the PI is required on an individual case.

5.4.2 Decitabine and Venetoclax dose adjustments for non-hematologic drug-related AEs

Investigators should, whenever possible, determine which medication is causing the toxicity and interrupt or dose reduce Decitabine and/or Venetoclax, as applicable. Dose reductions will be as per Table 1 and 2 recommendations. Dose reductions different than Table 1 or Table 2 are allowed if determined to be in the patient's best interest and rationale documented in patient record.

The investigators will use their clinical judgment to determine whether toxicity is caused by Decitabine, venetoclax or both. Dose reductions of one of the agents, or both are allowed after discussion with the PI or Co-PI and documentation in the medical record.

Table 2. Dose adjustments for non-hematologic drug-related AEs, clinically significant in the opinion of the investigator

Grade	Occurrence	Dose modification
1 or 2	Any time	No dose reduction
3 or 4 (Persistent grade 2: Consider similar dose adjustments if persistent and not responding to optimal management in the opinion of PI and treating physician)	1st and 2nd time	Hold Decitabine and Venetoclax. Resume Decitabine and Venetoclax at prior dose if recovery to ≤ Grade 1 occurs within 14 days. If toxicity persists for 15-28 days, hold therapy and resume Decitabine and Venetoclax at prior dose if recovery to ≤ Grade 1 OR resume Venetoclax and/or Decitabine at ONE dose level below current dose if recovery to ≤ Grade 2. Dose re-escalation to prior doses is permitted in accordance with the dose-escalation guidelines in Section 5.4.3.
	3rd and 4th time	Hold Decitabine and Venetoclax. Follow until toxicity ≤ Grade 2. Resume Venetoclax and/or Decitabine at ONE dose level below current dose. Dose re-escalation to prior dose is permitted in accordance with the dose-escalation guidelines in Section 5.4.3.
	5th time	Hold Decitabine and Venetoclax. Follow until toxicity ≤ Grade 2. Resume Venetoclax and/or Decitabine at TWO dose levels below current dose. Dose re-escalation by ONE dose level every 4 weeks is permitted in accordance with the dose-escalation guidelines in Section 5.4.3.

5.4.3 Modifications of dose schedules other than the above will be allowed within the following guidelines:

- Further dose reductions can be made to keep clinically significant toxicities grade ≤ 2.
- Dose adjustments by more than 1 dose level at a time can be considered when judged in the best interest of the patient (e.g. severe myelosuppression) when toxicity has resolved. The reason for this reduction will be discussed with the PI or Co-PI and documented in the medical record.

- A patient who has had a dose reduction because of any of the reasons mentioned above may have their dose escalated provided the patient has remained free of toxicity requiring dose adjustments as defined above for at least 1 month. Escalation will be made by 1 dose-level increment only, and not more frequent than every month.
- Treatment interruptions and dose modifications other than the ones mentioned above can be considered after discussion with the PI and proper documentation of the rationale. Dose adjustment/delay of only one of the agents is permissible if the toxicity is most likely judged to be related to one of the agents by the investigator.

5.5 TARGETED THERAPY:

Approximately a third of patients with AML may harbor activating FLT3 mutations; and 10-15% of AML harbor IDH1 or IDH2 mutations. It has been previously shown that combining sorafenib or midostaurin with chemotherapy in patients with activating FLT3 mutations is both safe and efficacious[37 38]; and combining IDH1/IDH2 inhibitors with chemotherapy or hypomethylating agents is safe and efficacious.[39, 40] Therefore, patients with known activating FLT3mutations will be allowed to receive targeted FLT3 inhibitor therapy on Days 1-14 during induction and then continuously for 28 days per cycle starting with Cycle 2, at the discretion of the treating physician. Patients with known IDH1 mutations will be allowed to receive FDA approved IDH1 inhibitor ivosidenib, and patients with IDH2 mutations IDH2 inhibitor enasidenib at the approved doses. Similarly, in the setting of PH+ AML, tyrosine kinase inhibitor therapy (i.e. imatinib, dasatinib, ponatinib, etc.) can be utilized as per standard of care. Dose adjustments and interruptions should be initiated are per standard.

Concurrent administration of ivosidenib with venetoclax may decrease venetoclax exposure, as previous data has indicated moderate CYP3A inducers decreased venetoclax AUC by 50-60%.[41] Based on the potential anticipated clinical drug-drug interaction of venetoclax exposure in the presence of ivosidenib, the dosage of venetoclax may be increased to compensate the loss of venetoclax exposure.

5.6 INTRATHECAL PROPHYLAXIS

Intrathecal prophylaxis with araC and/or methotrexate is standard in the therapy of acute lymphoblastic leukemia, but not currently a part of standard AML protocols. Patients with high-risk disease, including those with WBC > 100 at presentation, those with LDH > 700, and those with FLT3(+) disease may be at higher risk of central nervous system (CNS) disease.[42] Enrolled patients will be eligible to receive intrathecal Cytarabine administered via lumbar puncture (LP) or through Ommaya reservoir on Cycle 1 Day 21 (+/- 7 days) or Cycle 2 Day 14 (+/- 7 days. Peripheral WBC at the time of LP should be ≤ 1 and peripheral blasts should be ≤ 1%.

5.7 Supportive Care:

Supportive care measures including blood products, infection prophylaxis and growth factors will be administered according to institutional and Leukemia Department guidelines. Concomitant intrathecal chemotherapy and/or radiation therapy is permitted where indicated in patients with extramedullary disease.

5.8 Concomitant medications

Recommendations with regard to specific types of concomitant therapies, supportive care; diet and other interventions are as follows:

Concomitant medications are recommended as prophylaxis for nausea, vomiting, and infections, and are recommended according to institutional standards. Myelosuppression is expected in patients with AML due to underlying disease, as well as due to chemotherapy (such as decitabine), or both. Most patients have neutropenia, thrombocytopenia, or both at study entry. Significant or life-threatening myelosuppression may be managed with growth factor support and blood transfusion according to institutional standard of care, American Society of Clinical Oncology (ASCO) Practice Guidelines, and/or NCCN Practice Guidelines.

Infections secondary to myelosuppression are common in patients with AML, and may be related to underlying disease, chemotherapy, or both. Therefore, the use of prophylactic antibiotics, antifungal agents, and antiviral agents is recommended according to institutional standards.

Since the effect of both decitabine and venetoclax may be delayed for up to 4 weeks, patients with high WBC counts may receive hydroxyurea and up to 1 dose of cytarabine (up to 2 g/m^2) prior to study entry, and through the first cycle on therapy. Hydroxyurea and cytarabine use would be recorded in the CRF. Concurrent therapy for CNS prophylaxis or continuation of therapy for controlled CNS disease is permitted. With the exception of these agents, concomitant systemic chemotherapy or radiation therapy is not permitted. Subjects are not allowed to participate concurrently in any other therapeutic clinical study.

All ongoing medications and therapies (including herbal products, nutritional supplements, and nontraditional medications) at screening will be considered prior medications. If a prohibited medication is considered essential for the patient well-being, continuation on study with concomitant administration of such medication(s) will need to be discussed with and approved by the principal investigator. Prohibited or restricted medications are shown in Table 3.

Table 3. Excluded, Cautionary and Allowed Medications

Drug or Therapy	Comments
Warfarin (due to expected inhibition of the metabolism of CYP2C9 substrates)	**Allowed**
Weak/moderate CYP3A inducers e.g., rufinamide, pioglitazone, modafinil	**Cautionary;** potential induction of the metabolism of venetoclax
CYP2C8 substrates e.g. glitazones, select statins	**Cautionary;** potential adverse reaction, expected inhibition of the metabolism of CYP2C8 substrates
CYP2C9 substrates e.g., losartan, phenytoin, tolbutamide	**Cautionary;** potential adverse reaction, expected inhibition of the metabolism of CYP2C9 substrates
Best supportive care and treatment e.g., antiemetics, antibiotics, transfusions, nutritional support, pain control, etc.	**Allowed**
Anti-herpes and anti-Pneumocystis prophylaxis	**Allowed**
Bactrim (trimethoprim sulfamethoxazole) for anti-Pneumocystis prophylaxis	**Allowed;** with close clinical monitoring due to potential drug-drug interaction

A sample list of moderate and strong CYP3A inducers and inhibitors can be found in Appendix A.

5.8.1 CYP3A Inducers and Inhibitors:

Moderate and strong CYP3A inducers and inhibitors (Appendix A) are discouraged during venetoclax administration. If a patient requires use of CYP3A inducers, use with caution. In many

instances, such as antifungal prophylaxis with “azole” therapy in neutropenic patients, CYP3A inhibitors are required in AML patients. Venetoclax should be administered at 200 mg (50% dose reduction) in the setting of moderate CYP3A inhibitors (i.e. isavuconazole, ciprofloxacin, diltiazem) and at 100 mg (75% dose reduction) in the setting of strong CYP3A inhibitors (i.e. posaconazole, voriconazole). The venetoclax dose reduction should continue for the duration of co-administration. In the event the co-administered CYP3A inhibitor is discontinued, the assigned venetoclax dose should be resumed 2-3 days after discontinuation.

Note: If any of the cautionary or allowed medications is also a CYP3A inhibitor or potent inducer, the medication should be used with caution.

Note: Every effort will be made to adhere to the venetoclax dose reduction. Variations in schedule of events such as late/missed interventions that do not affect the rights and safety of the patient will not be considered as deviations.

5.8.2 Tumor Lysis Prophylaxis:

The venetoclax dose titration scheme utilized in the AML studies performed to date to mitigate the risk of tumor lysis syndrome (TLS) will be employed. All patients will be hospitalized for the entirety of the venetoclax dose escalation starting at least on day -1 of treatment initiation and until 24 hours after the completion of venetoclax dose escalation. Venetoclax will be administered at a dose of 100 mg on day 1, 200 mg on day 2, and 400 mg on day 3-28 of the first cycle. Venetoclax will be administered at a dose of 100 mg on day 1, and 200 mg on day 2-28 of the first cycle, if concomitant moderate CYP3A inhibitor administration; or at the dose of 100 mg daily if concomitant use of strong CYP3A inhibitor.

To mitigate the risk for TLS, subjects must be receiving tumor lysis prophylaxis, including hydration (oral, intravenous) and treatment with a uric acid reducing agent (allopurinol, rasburicase) prior to and during the venetoclax ramp up period of Cycle 1.

TLS chemistry tests (potassium, uric acid, creatinine, calcium and phosphorus) will be obtained prior to dosing and 6-8 hours after each day of a new venetoclax dose. TLS chemistry test results will be reviewed by the investigator in real time and prior to the subject’s next dose to ensure appropriate management. If a subject meets criteria for clinically significant laboratory or clinical TLS, no additional venetoclax should be administered until resolution.

Venetoclax interruption for up to 72 hours following transient (< 48 hours) chemical changes and laboratory TLS will be allowed and will not require a dose reduction.

5.8.3. Meals and Dietary Requirements:

Each dose of venetoclax should be taken with approximately 240 mL of water within 30 minutes after the completion of a meal, preferably breakfast.

Subjects should not consume grapefruit or grapefruit products, Seville oranges, or Star fruit within the 3-day period prior to the first venetoclax administration and until the last day of venetoclax is completed due to possible CYP3A mediated metabolic interaction.

5.9 Study Medications

5.9.1 Decitabine

Chemical Name

- 4-amino-1-(2-deoxy-ß-D-erythro-pentofuranosyl)-1,3,5-triazin-2(1H)-one
- Other Names: deoxyazacytidine, 5-aza-2'-deoxycytidine, 1-(2'-deoxy-D-ribofuranosyl)-5-azacytosine, DAC, 5-Aza-CdR, dezocitidine
- Classification: Antimetabolite, DNA hypomethylating agent
- Molecular Formula: C8H12N4O4 M.W.: 228.21
- Approximate Solubility: Slightly soluble in water (25mg/mL), ethanol and virtually insoluble in chloroform

Mode of Action:

Hypomethylation of DNA followed by stimulation of gene expression and cell differentiation. Inhibits DNA methyltransferase. Targets for latter mechanism are selected genes silenced by DNA methylation. Inhibits DNA synthesis

How Supplied:

Decitabine is supplied as a lyophilized white to almost white, finely crystalline, odorless powder for injection in 20mL vial glass vials, containing 50 mg of decitabine, monobasic potassium phosphate, and sodium hydroxide.

Preparation:

When reconstituted with 10 mL of sterile water for injection each mL will contain 5 mg of decitabine, 6.8 mg of KH_2PO_4, and approximately 1.1 mg NaOH. The pH of the resulting solution is 6.5 - 7.5.

The reconstituted solution can be further diluted to a concentration of 1 mg/mL or 0.1 mg/mL in cold infusion fluids (0.9% Sodium Chloride Injection USP, 5% Dextrose in Water Injection, USP, or Lactated Ringer's Injection USP).

Storage and Stability:

Vials should be stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). After reconstitution, use decitabine within 15 minutes. If diluted with cold (2°C to 8°C) fluids, the diluted solution is stable for up to 7 hours if stored between 2°C and 8°C (36°F to 46°F).

Reconstitution and dilution of the powder for injection (with 10mL of sterile water for injection) results in a rapidly decomposing solution. The concentration of decitabine in the reconstituted and diluted solution decreases about 10 % after 4 hours at 25°C or about 10% after 24 hours at 4°C. Since 10% is the maximum allowable decomposition, and the solution will also decompose during administration (infusion), the solution should be prepared just prior to administration. If this is not possible the solution should be prepared at least twice a day and kept in a refrigerator (2-8°C) until administration. Furthermore, the solution should be prepared only with cold infusion fluids at a temperature of 2-8°C; (36-46°F). This solution can be infused over a maximum period of 3 hours.

Route of Administration:

Intravenous

Precautions:
Drug handling precautions will be strictly followed. Skin contact with the solution should be avoided and protective gloves should be worn. Drug spilling can be inactivated by 2 M sodium hydroxide solution. The skin should be treated with a borax buffer solution pH 10 and after that thoroughly washed with water and soap.

Drug supply and distribution:
Decitabine will be obtained from commercial source. For further details, please refer to the prescribing information (Appendix B).

5.9.2 Venetoclax:

International Non-proprietary name	venetoclax (formerly ABT-199)
Manufacturer	Abbvie/Genentech
Dose	100 - 400 mg daily
Route of Administration	oral
Formulation	Capsule formulation (10 mg, 50 mg and 100 mg)

Venetoclax will be obtained from commercial source. For further details, please refer to the prescribing information (Appendix C).

5.10 PATIENT EVALUATION

Every effort will be made to adhere to the schedule of events and all protocol requirements. Variations in schedule of events and other protocol requirements that do not affect the rights and safety of the patient will not be considered as deviations. Such variations may include laboratory assessments completed outside of schedule, occasional missed required research samples such correlative assays.

5.10.1 Pre-Treatment Evaluation

- All pretreatment studies should be obtained within 14 days of entry into the trial, unless otherwise stated.
- A complete history and physical, documentation of all measurable disease, concomitant medications and performance status.
- CBC, platelet count, differential (differential can be omitted if WBC is ≤0.5 $x10^9$/L).
- Creatinine, total bilirubin, ALT.
- Pregnancy test (urine or plasma) in females of childbearing potential should be performed within 72 hours before initiation of study.
- Bone marrow biopsy and aspirate during the last 28 days preceding study initiation. Cytogenetics and the Leukemia mutation panel will be obtained prior to therapy (results from prior analysis can be used for this purpose).
- Pretreatment correlative studies (see below)

5.10.2 Evaluation During Treatment

- Physical exam at the start of each cycle (± 4 days) and documentation of all concomitant medications.
- CBC, platelet count, differential once weekly (±4 days) for the first 4 cycles, then every 2-4 weeks (differential can be omitted if WBC is ≤0.5 $x10^9$/L)
- Creatinine, total bilirubin, ALT once weekly (±4 days) for the first 4 cycles, then every 2-4 weeks.

- TLS chemistry tests (potassium, uric acid, creatinine, calcium and phosphorus) will be obtained prior to dosing and 6-8 hours after each day of a new venetoclax dose, during the ramp up portion of the study.
- Post-treatment correlative studies (see below)
- Bone marrow biopsy and aspiration on day 21 (+/- 3 days); if aparticlulate, bone marrow can be repeated on day 28 (+/- 7 days). Bone marrow biopsy and aspiration after cycle 2 and cycle 4; subsequently bone marrow aspirate, or biopsy and aspirate, every 3-4 cycles. Bone marrow tests can be ordered more frequently if mandated by development of peripheral blood counts. No repeat bone marrow is necessary if nonresponse or progressive disease can be unequivocally diagnosed from peripheral blood tests or, in patients with a WBC < 0.3 if the bone marrow test is considered noncontributory by the investigator at any time point.
- Cytogenetics at remission if abnormal pre-therapy any time a bone marrow exam is performed. Omissions will not be considered as deviations.
- Molecular testing depending on the positive tests pre-study (specific mutations, whole genome sequencing) any time a bone marrow exam is performed. Omissions will not be considered as deviations.
- Multi-parameter flow cytometry for the presence of leukemia associated immunophenotype (minimal residual disease) any time a bone marrow exam is performed. Omissions will not be considered as deviations.
- Concomitant medication data will not be collected or entered into the case report form except for concomitant hydroxyurea and cytarabine if these are administered during the first cycle; however, the subject's medication record will contain a list of concomitant medications.
- Correlative Studies (mandatory)**:**
  - Peripheral blood up to 30 mL (within 24 hours) will be collected for testing of biomarkers at the following time points
  - Baseline (prior to decitabine dose), Day 3 of therapy, between days 21 to 28 on cycle 1, at the end of cycle 2 and cycle 4. Subsequently, peripheral blood will be obtained at progression if possible.
  - Samples will be collected at progression whenever possible.
  - Bone Marrow:
  - Bone marrow samples will be collected for testing of biomarkers at baseline, at day 21 (+/- 3 days) or day 28 (+/- 7days); , after cycle 2 and cycle 4; then every 3-4 cycles, and at progression if feasible. Buccal smear will be collected once at the end of Cycle 1.
  - All these samples can be obtained +/- 3 days. Missed samples for correlative studies will not constitute protocol deviations.
  - If needed, additional samples to be studied will come from those collected under sample collection and banking protocols LAB01-473, LAB03-0320, PA14-0241. Patients will be consented separately on these IRB approved consents for collection of additional material. Correlative laboratory studies will be conducted under this clinical trial protocol as described below. Additionally, left over samples from clinical laboratory could be included for analyses.

- For patients that remain on study with no significant toxicity for more than 6 months, subsequent evaluations during study may be modified after discussion with the principal investigator. These include a decrease in frequency of bone marrow aspirations to every 6-12 months (or as clinically indicated), other laboratory tests to once every cycle.
- The first cycle of decitabine must be administered at the MDACC. Subsequently, patients will have the option of receiving decitabine infusions at the MDACC outpatient clinic or local ambulatory treatment center. During the first cycle all the laboratory evaluations will be

done at MDACC. Subsequently, the patient may have the laboratory work done at a local clinic and the results reported to the research nurse for the study. The laboratory work done at the local clinic will be forwarded to the patient's attending physician at MDACC or PI of the study, who will sign off on the labs to verify that the results have been reviewed.

5.10.3 Outside Physician Participation During Treatment

1. MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician.
2. This will be documented in the patient record.
3. A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care (Appendix D).
4. Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.
5. A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.
6. Documentation to be provided by the local physician will include progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.
7. The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.
8. Stable patients with evidence of response can have follow-up visits locally, upon discussion with the patient's attending physician at MDACC and PI of the study. Patients must present to MDACC at least every 3 cycles.
9. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.

5.10.4 Follow-up

Patients with an objective response at completion of active study treatment will be followed for survival at MD Anderson Cancer Center (MDACC) every 3 to 6 months for up to 5 years after completion of active treatment and while still on study. If the patient is unable to return to MDACC the follow-up visits may be conducted via telephone.

5.10.5 Schedule of Study Assessments:

Study Period/ Cycle	Screen-ing			Treatment																		End of Study (EOS)[h]
				Cycle 1					Cycle 2				Cycle 3				Cycle 4				Sub-sequent Cycles	
Cycle Day		**1**	**2**	**3**	**5**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	
Study Day	**-14 to 0**	**1**	**2**	**3**	**5**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**-**	
Complete history	X	X							X				X				X				X	
Physical examination[a]	X	X							X				X				X				X	X
Performance status	X																					
Document all measurable disease (if present)	X																					
Concomitant medications[a]	X	X							X				X				X				X	
CBC with differential[b]	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Creatinine, total bilirubin, ALT[b]	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[c]	X																					
Bone marrow biopsy and aspirate[d]	X							Day 21 (or 28)				End of cycle 2								End of cycle 4	X[i]	X
correlatives on blood[e]		Day 1		Day 3				Day 21 (or 28)				End of cycle 2								End of cycle 4		X

Study Period/ Cycle	Screen-ing			Treatment																	End of Study (EOS)[h]
				Cycle 1					Cycle 2				Cycle 3				Cycle 4				Sub-sequent Cycles	
Cycle Day		**1**	**2**	**3**	**5**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	
Study Day	**-14 to 0**	**1**	**2**	**3**	**5**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**-**	
correlatives on bone marrow[f]	X							Day 21				End of cycle 2								End of cycle 4		X
correlatives buccal smear								Day 28														
Optional Peripheral blood PK[g]					X		X															

a) A complete physical examination and documentation of concomitant medications will be done on day 1 of each cycle (+/- 4 days).
b) CBC with differential, creatinine, total bilirubin, ALT will be done at least once weekly (+/- 4 days) for the first 4 cycles, then every 2-4 weeks on subsequent cycles.
c) Pregnancy test either urine or plasma should be done in women of childbearing potential 72 hours before initiation of protocol therapy.
d) Bone marrow biopsy and aspiration must be done within 28-days of initiation of therapy; then after cycle 2 and cycle 4. Cytogenetics may be used from prior bone marrow analysis if these were not reported on the screening bone marrow.
e) Correlative studies will be collected on peripheral blood at Day 1 (prior to Decitabine/Ven dose), Day 3 Cycle 1, between days 21 to 28 on cycle 1 and at the end of cycle 2 and cycle 4. Subsequently, peripheral blood will be obtained at progression if possible. All these tests can be +/- 3 days
f) Correlative studies will be collected on bone marrow at baseline (prior to Decitabine/Ven dose), on day 28 (+/-7 days), at the end of cycle 2 and cycle 4, then every 3-4 cycles, and at progression.
g) Plasma PK draws on cycle 1 Day 5 and cycle 1 Day 15.
h) EOS visits include a physical examination, CBC with differential and platelets and a limited chemistry profile (total bilirubin, serum creatinine, SGPT or SGOT). A bone marrow aspiration may be done if non-response or progressive disease cannot be unequivocally diagnosed from peripheral blood.
i) At subsequent cycles bone marrow (aspiration or biopsy/aspiration) will be performed every 3-4 cycles at the discretion of the treating physician

5.10.6 PK schedule (Optional)

For the evaluation of plasma concentrations of venetoclax (and any possible metabolites), the blood samples will be collected from consenting subjects on different azoles according to the Schema below, at the following time points: 0 h (pre-dose), 2 h, 4h, 8 h and 24 h. We will study a cohort of 10 patients/each, and collect samples at two time-points (day 5 and day 15).

Schema:
Arm A : Decitabine + Venetoclax + Voriconazole (C1D5); Venetoclax + Voriconazole (C1D15)
Arm B : Decitabine + Venetoclax + Posaconazole (C1D5); Venetoclax + Posaconazole (C1D15)
Arm C : Decitabine + Venetoclax + Isavuconazole (C1D5); Venetoclax + Isavuconazole (C1D15)

Five ml of blood sample will be collected at each time point in potassium-EDTA containing tubes, and processed to separate the plasma and stored in -80^{o}C to analyze the samples in a batch to determine venetoclax plasma levels via previously described HPLC-MS/MS method.[43]

Briefly, venetoclax will be extracted from the plasma via liquid-liquid extraction. The analytes from extracted samples will be chromatographically separated with a reverse-phase analytic column (Waters Atlantis dC18, 2.1 × 50 mm, 3 μm) running under isocratic condition (55/45 [v/v] acetonitrile/water with 0.1% formic acid). The high resolution MS/MS acquisitions will be performed using Agilent mass spectrometer fitted with an electrospray ionization source to determine venetoclax concentration in the plasma. Venetoclax pharmacokinetics analysis will be performed via non-compartmental analysis method using Phoenix WinNonlin-Certara. We will estimate venetocalx Cmax, Tmax, half-life, clearance and $AUC_{0\text{-}24}$ (area under the curve in 24 hours). We will then compare the venetoclax pharmacokinetics parameters in presence and absence of concomitant drugs to determine if there was significant change in pharmacokinetics, which would warrant dose adjustments.

6.0 RESPONSE DEFINITIONS

6.1 Study Endpoints:

The primary endpoint is the overall response rate (ORR), defined as the proportion of patients who had CR (complete remission), CRp (complete remission with incomplete platelet recovery), CRi (complete remission with incomplete count recovery), PR (partial response) or marrow clearance of blasts within 3 months of treatment initiation among adult patients with AML; and complete remission (CR), partial remission (PR) or marrow CR† (mCR) lasting at least 4 weeks for patients with MDS.

6.1.1 AML - Primary Efficacy Analysis:

Response criteria will be modified from the International Working Group for AML[44]. Responders are patients who obtain a CR, CRp, CRi, PR or marrow clearance of blasts ("morphologic leukemia-free state") within 3 months of treatment initiation. Briefly, criteria are as follows:

Complete remission (CR):

- Peripheral blood counts:
  - No circulating blasts
  - Neutrophil count >/=1.0 x10^9/L
  - Platelet count >/=100 x10^9/L
- Bone marrow aspirate and biopsy:
  - ≤5% blasts
  - No Auer rods
  - No extramedullary leukemia

Complete Remission with Incomplete Platelet Recovery (CRp):
For patients to be classified as being in CRp, they must achieve CR except for incomplete platelet recovery (<100 × 10^9/L).

Complete remission with incomplete blood count recovery (CRi):

- **Peripheral blood counts:**
  - No circulating blasts
  - Neutrophil count <1.0 x10^9/L, or
  - Platelet count <100 x10^9/L
- **Bone marrow aspirate and biopsy:**
  - </= 5% blasts
  - No Auer rods
  - No extramedullary leukemia

Partial remission:

- All CR criteria if abnormal before treatment except:
- >/=50 % reduction in bone marrow blast but still >5%

Morphologic leukemia-free state:

- Bone marrow: </=5% myeloblasts

6.2.1 MDS - Primary Efficacy Analysis:

Clinical activity for MDS patients will be assessed based on Modified IWG Response Criteria for MDS (Cheson et al, 2006).

Proposed Modified International Working Group Response Criteria for Altering Natural History of MDS Category	**Response criteria (Responses must last at least 4 weeks)**
Complete remission	Bone marrow: ≤5% myeloblasts with normal maturation of all cell lines* Persistent dysplasia will be noted*† Peripheral blood‡ Hgb ≥11 g/dL Platelets ≥100 × 10^9/L Neutrophils ≥1.0 × 10^9/L† Blasts = 0%
Partial remission	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by ≥50% over pretreatment but still >5% Cellularity and morphology not relevant
Marrow CR†	Bone marrow: ≤5% myeloblasts and decrease by ≥50% over pretreatment† Peripheral blood: if HI responses, they will be noted in addition to marrow CR†
Stable disease	Failure to achieve at least PR, but no evidence of progression for >8 wks
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
Relapse after CR or PR	At least 1 of the following: Return to pretreatment bone marrow blast percentage Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets Reduction in Hgb concentration by ≥1.5 g/dL or transfusion dependence
Cytogenetic response	Complete: Disappearance of the chromosomal abnormality without appearance of new ones Partial: At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with: Less than 5% blasts: ≥50% increase in blasts to >5% blasts 5%-10% blasts: ≥50% increase to >10% blasts 10%-20% blasts: ≥50% increase to >20% blasts 20%-30% blasts: ≥50% increase to >30% blasts Any of the following: At least 50% decrement from maximum remission/response in granulocytes or platelets Reduction in Hgb by ≥2 g/dL Transfusion dependence
Survival	Endpoints: Overall: death from any cause Event free: failure or death from any cause PFS: disease progression or death from MDS DFS: time to relapse Cause-specific death: death related to MDS

Source: (Cheson, et al. 2006) Abbreviations: MDS = myelodysplastic syndromes; CR = complete remission; Hgb = hemoglobin; HI = hematologic improvement; PR = partial remission; FAB = French-American-British; AML = acute myeloid leukemia; PFS = progression-free survival; DFS = disease-free survival. Note: Deletions to IWG response criteria are not shown. Note: To convert hemoglobin from g/L to g/dL, divide g/L by 10. *Dysplastic changes should consider the normal range of dysplastic changes (modification). †Modification to IWG response criteria (Cheson, et al. 2003) ‡In some circumstances, protocol therapy may require the initiation of further treatment (e.g., consolidation, maintenance) before the 4-week period. Such subjects can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

Hematologic Improvement Response Criteria:

*Responses must last at least 8 weeks

Proposed Modified International Working Group Response Criteria for Hematologic Improvement Hematologic improvement*	**Response criteria (Responses must last at least 8 weeks)†**
Erythroid response (pretreatment, < 11 g/dL)	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 wk compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hgb of ≤9.0 g/dL pretreatment will count in the RBC transfusion response evaluation†
Platelet response (pretreatment, < 100 × 10^9/L)	Absolute increase of ≥30 × 10^9/L for patients starting with >20 × 10^9/L platelets Increase from <20 × 10^9/L to >20 × 10^9/L and by at least 100%†
Neutrophil response (pretreatment, < 1.0 × 10^9/L)	At least 100% increase and an absolute increase >0.5 × 10^9/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

Source: (Cheson, et al. 2006) Abbreviations: Hgb indicates hemoglobin; RBC: red blood cell; HI: hematologic improvement. Note: Deletions to the IWG response criteria are not shown. Note: To convert hemoglobin from g/L to g/dL, divide g/L by 10. *Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) ≥1 week apart (modification).

†Modification to IWG response criteria (Cheson, et al. 2003) ‡In the absence of another explanation, such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth.

6.3 Primary Safety Endpoint:

The overall incidence and severity of all adverse events using Common Toxicity Criteria v 4.0.

Primary safety endpoint: The overall incidence and severity of all reported adverse events using Common Toxicity Criteria v 4.0.

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices".

6.4 Exploratory Biomarker Analysis:

Peripheral blood and bone marrow aspirate samples will be obtained at study specified time points. Biomarker assays may include, but are not limited to, BH3 profiling and characterization of BCL-2 and related proteins, and assessment of the depth of response and monitoring of disease recurrence by assessment of MRD in the bone marrow.

6.4.1 Leukemia mutation panel

As a standard of care all AML patients at MDACC are evaluated for karyotype and molecular mutation profile using a CLIA-certified next-generation gene sequencing platform. The effects of the combination will be compared not only to historical outcomes in matched groups of patients, but also at the molecular and cellular level by correlating with karyotype and molecular mutation profile. The Leukemia mutation panel will be performed on the screening BM aspirate and the progression/relapse BM aspirate. An aliquot of DNA will be stored for additional analysis of DNA mutations in responding patients, if these are not identified by the Leukemia mutation panel.

6.4.2 Minimal Residual Disease assessment by flow-cytometry

As a standard of care all BM aspirates including but not limited to the screening BM, end of cycle 1 BM, end of cycle 2 and end of cycle 4 BM, will be evaluated for MRD by validated 17-color multiplanar flow-cytometry.

6.4.3 Gene expression signatures by RNA sequencing and/or RT-PCR, and methylation signatures using post-bisulfite adaptor tagging (PBAT).[45]

We will assess transcriptomic signatures using RNAseq assay established in a laboratory of our collaborator Dr. Yoko Tabe (Juntendo Tokyo), in bone marrow or peripheral blood samples collected at screening and at the time of progression. We will assess changes in methylation profiling using PBAT assay established in a laboratory of our collaborator Dr. Yoko Tabe (Juntendo Tokyo), in bone marrow or peripheral blood samples collected at screening, at the end of cycle 1 and at the time of progression.

6.4.4 CyTOF analysis (MDACC)

We will analyze BCL-2 family expression, stem cell surface markers and intracellular signaling markers in AML cells by CyTOF (mass cytometry) assay established in Dr Konopleva's laboratory, on the screening BM, end of cycle 1 BM, end of cycle 2 and end of cycle 4 BM and at the time of progression.

6.4.5. Analysis of mutation clearance

We will assess tumor burden by allele frequency of patient-specific mutations assay established in a laboratory of our collaborator Dr. John Welch (Wash U ST Louis), in bone marrow or peripheral blood samples collected at screening, end of cycle 1 BM, end of Cycle 2 and end of cycle 4 bone marrow and at the time of progression. As a germline control, buccal smear will be collected at the end of Cycle 1.

6.4.6 BH3 profiling of BCL-2 family member dependency

BH3 profiling will be performed peripheral blood or bone marrow at screening and at the time of progression.

6.4.7. Metabolomics signature associated with acute cellular response to therapy.

Metabolomics analysis will be collected on peripheral blood samples collected pre-treatment and on Day 3 of therapy. Patient samples will be processed in Konopleva's lab, snap frozen in liquid nitrogen and maintained at -80C until analysis. Samples will be picked up and transferred to the core facility by our collaborator Dr. Vlad Sandulache (Assistant Professor, Bobby R. Alford Department of Otolaryngology - Head and Neck Surgery, Baylor College of Medicine, Houston, TX). Analysis will be conducted in a batched fashion through the Baylor College of Medicine Metabolomics Core. All specimens will be de-identified prior to metabolomics analysis and no identifiable patient information will be made available to collaborators or investigators outside of the primary institution.

6.4.8. Ex vivo testing of tumor cells before after initial few days of therapy to a panel of FDA-approved chemotherapy and targeted agents (Notable Labs).

Ex vivo sensitivity testing will be conducted on peripheral blood samples collected pre-treatment; on Day 3 of therapy; and at the time of relapse/progression. PB sample (5-10mL) will be collected into green top tube (Sodium Heparin) and shipped overnight to Notable Labs, 900 Gateway Blvd, South San Francisco, CA 94080. Notable Labs uses a flow cytometric-based assay to test a panel of FDA-approved chemotherapy and targeted agents, singly and in combinations using a custom robotic platform, to determine anti-cancer effect against individual patient's tumor cells.[46, 47] All specimens will be de-identified prior to shipment and no identifiable patient information will be made available to collaborators or investigators outside of the primary institution.

6.4.9. Analysis of immune profiling using single cell genomic/transcriptomic platforms like CITE-Seq and TCR-Seq in a laboratory of our collaborator Dr. Ioannis Iafantis (NYU), in bone marrow or peripheral blood samples collected at screening, in remission and at the time of progression.

Additional material will be stored in Dr. Konopleva's laboratory for potential studies of interest.

7.0 REGULATORY AND REPORTING REQUIREMENTS

7.1 Informed Consent:

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

The acquisition of informed consent should be documented in the subject's medical records, and the informed consent form should be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legally acceptable representative.

7.2 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IEC/IRB for written approval.

The investigator must submit and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent form.
The investigator should notify the IEC/IRB of deviations from the protocol or serious adverse events occurring at the site.

The investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study.

7.3 Subject Confidentiality

In compliance with ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the regulatory agency(s), and the IEC/IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

7.4 Study Documentation and Archival

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on case report forms will be included on the Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Case report form entries may be considered source data if the CRF is the site of the original recording (ie, there is no other written or electronic record of data). In this study, case report forms calculating IPSS may be used as source documents for IPSS risk category assignment**.**

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by applicable regulatory authorities. Elements should include:

- Subject files containing completed case report forms, and subject identification list

- Study files containing the protocol with all amendments, investigator's brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB

8.0 DISCONTINUATION OF TREATMENT:

Discontinuation Criteria for Individual Patients

8.1 Patient Withdrawal

Patients may voluntarily withdraw consent to participate in the clinical study at any time and without giving any reason. Their withdrawal will not jeopardize their relationship with their healthcare providers or affect their future care. Patients may also choose to withdraw from study treatment, but agree to remain in the study for follow-up procedures.

8.2 Investigator Discontinuation of Patient

The investigator may exercise medical judgment to discontinue study treatment if clinically significant changes in clinical status or laboratory values are noted.

8.3 Criteria for Protocol-Defined Required Discontinuation of Treatment

The protocol requires discontinuation of study treatment for the following reasons:

1. Patient requests discontinuation.
2. Unacceptable toxicity that in the opinion of the investigator makes it unsafe to continue therapy.
3. Clinically significant progressive disease.
4. Investigator discretion.

8.4 Follow-Up at Treatment Discontinuation or Early Withdrawal

Patients who discontinue treatment for any reason should complete end-of-treatment procedures when possible. End of treatment procedures will include a physical examination, CBC with differential and platelets and a limited chemistry profile (total bilirubin, serum creatinine, SGPT or SGOT). A bone marrow aspiration may be recommended only if non-response or progressive disease cannot be unequivocally diagnosed from peripheral blood. Although treatment will be discontinued at that time, all patients who do not withdraw consent for follow-up, die, or become lost to follow-up, will remain on study for follow-up evaluations. Subject will be followed for toxicity for at least 30 days after the last protocol treatment. The 30-day follow-up visit will be scheduled as a clinic visits for clinical evaluation and physical examinations. If the patient cannot make it to the MDACC clinic for this visit, the required follow up treatment procedures may be done with a local physician and the records forwarded to MDACC. The research nurse will contact the patient by telephone and get a verbal assessment

of the patient's condition. The phone conversation will then be documented in the patient's charts.

8.5 Study Stopping Rules

The principal investigator has the right to terminate this clinical study at any time. The principal investigator, as appropriate, will be involved in any decisions regarding terminating the study, temporarily suspending enrollment, or stopping ongoing treatment with study treatment.

Reasons for terminating the clinical study or a study site's participation include, but are not limited to, the following:

- The incidence or severity of an adverse reaction related to treatment in this study or other studies indicates a potential health hazard to patients
- Data recording is significantly inaccurate or incomplete
- Study site personnel are noncompliant with study procedures
- Pattern of noncompliance is observed

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design

This is a phase II study of venetoclax in combination with 10-day decitabine. The primary objective of the phase II study is to determine the efficacy of venetoclax in combination with 10-day decitabine in patients with refractory/relapsed acute myeloid leukemia (AML); elderly (>60 year old) patients with newly diagnosed AML not eligible for intensive chemotherapy; patients with high-risk MDS or chronic myelomonocytic leukemia (CMML) with bone marrow blasts between 10% and 20%, relapsed or refractory to prior hypomethylating agent (HMA) therapy; AML patients with prior history of MDS or CMML who received therapy for the MDS or CMML and progressed to AML, and patients with newly diagnosed AML with poor risk complex karyotype or TP53 deletions/mutations equal or younger than 60 year old. The primary endpoint is the overall response rate (ORR), defined as the proportion of patients who had CR (complete remission), CRp (complete remission with incomplete platelet recovery), CRi (complete remission with incomplete count recovery), PR (partial response) or marrow clearance of blasts within 3 months of treatment initiation among adult patients with AML. For the futility monitoring purpose, the response will be evaluated during the first 4 cycles. Up to 360 patients will be enrolled in 5 cohorts of the study: 80 patients of refractory/relapsed acute myeloid leukemia (AML); 120 elderly (>60 year old) patients with newly diagnosed AML not eligible for intensive chemotherapy; 40 patients with high-risk MDS or chronic myelomonocytic leukemia (CMML) with bone marrow blasts between 10% and 20%, relapsed or refractory to prior hypomethylating agent (HMA) therapy; 80 AML patients with prior history of MDS or CMML who received therapy for the MDS or CMML and progressed to AML; and 40 younger patients with newly diagnosed AML with poor risk complex karyotype and/or TP53 deletions/mutations. The method of Thall, Simon and Estey[48] will be used for futility and toxicity monitoring in this study. The design software Multc Lean Desktop (version 2.1) developed by the Department of Biostatistics at M D Anderson Cancer Center (MDACC) was used to generate the stopping boundaries for futility and the operating characteristics table for futility and toxicity monitoring.

9.2 Toxicity monitoring

9.2.1 Toxicity monitoring regarding 1)AML patients with prior history of MDS or CMML who received therapy for the MDS or CMML and progressed to AML or 2) patients with refractory or relapsed AML :

For AML patients with prior history of MDS or CMML who received therapy for the MDS or CMML and progressed to AML or patients with refractory or relapsed AML, toxicity monitoring will be performed in these cohorts (N=80 per cohort) throughout the study. Unacceptable toxicities are defined as any Grade 3 or higher clinically significant non-hematologic, or Grade 3 or higher clinically significant hematologic treatment-related toxicities by CTCAE criteria within the first treatment cycle. Denote the probability of toxicity by P_T. We assume as a priori, P_T ~ beta (0.6, 1.4). Our stopping rule is given by the following probability statement:

$$Pr(P_T > 0.30 \mid data) > 0.95.$$

That is, we will stop the trial for new patient enrollment if at any time during the study, we determine that there is more than 95% chance that the unacceptable toxicity rate is more than 30%. This toxicity monitoring rule will be applied after the first 5 patients have been enrolled and evaluated, and then will be monitored when there are 15, 25, 35, 45, 55, 65,75, and 80 patients enrolled. Stopping boundaries corresponding to this stopping rule are listed in Table 4a.

Table 4a. Early stopping boundaries for toxicity monitoring (n=80 patients)

# of patients (in cohort size of 10, starting from the 5th patient)	Stop this cohort if there are this many patients with toxicities:
5	4-5
15	8-15
25	12-25
35	16-35
45	19-45
55	23-55
65	26-65
75	30-75
80	32-80

9.2.2 Toxicity monitoring regarding cohorts :

1) patients with high-risk MDS or chronic myelomonocytic leukemia (CMML) with bone marrow blasts between 10% and 20%, relapsed or refractory to prior hypomethylating agent (HMA) therapy; or chronic myelomonocytic leukemia (CMML) with bone marrow blasts ≥ 10% regardless of prior therapy; 2) younger patients with newly diagnosed AML with poor risk complex karyotype and/or TP53 deletions/mutations

Toxicity monitoring will be performed in each patient cohort (N=40 per cohort) throughout the study. Unacceptable toxicities are defined as any Grade 3 or higher clinically significant non-hematologic, or Grade 3 or higher clinically significant hematologic treatment-related toxicities

by CTCAE criteria within the first treatment cycle. Denote the probability of toxicity by P_T. We assume as a priori, P_T ~ beta (0.6, 1.4). Our stopping rule is given by the following probability statement:

$$Pr(P_T > 0.30 \mid data) > 0.95.$$

That is, we will stop the trial for new patient enrollment if at any time during the study, we determine that there is more than 95% chance that the unacceptable toxicity rate is more than 30%. This toxicity monitoring rule will be applied after the first 5 patients have been enrolled and evaluated, and then will be monitored when there are 15, 25, 35, and 40 patients enrolled. Stopping boundaries corresponding to this stopping rule are listed in Table 4a.

Table 4b. Early stopping boundaries for toxicity monitoring (n=40 patients)

# of patients (in cohort size of 10, starting from the 5th patient)	Stop this cohort if there are this many patients with toxicities:
5	4-5
15	8-15
25	12-25
35	16-35
40	18-40

9.2.3 Toxicity monitoring for elderly (>60 year old) patients with newly diagnosed AML not eligible for intensive chemotherapy (n=120);

For elderly (>60 year old) patients with newly diagnosed AML not eligible for intensive chemotherapy (n=120), toxicity monitoring will be performed in this cohort throughout the study. Unacceptable toxicities are defined as any Grade 3 or higher clinically significant non-hematologic, or Grade 3 or higher clinically significant hematologic treatment-related toxicities by CTCAE criteria within the first treatment cycle. Denote the probability of toxicity by P_T. We assume as a priori, P_T ~ beta (0.6, 1.4). Our stopping rule is given by the following probability statement:

$$Pr(P_T > 0.30 \mid data) > 0.95.$$

That is, we will stop the trial for new patient enrollment if at any time during the study, we determine that there is more than 95% chance that the unacceptable toxicity rate is more than 30%. This toxicity monitoring rule will be applied after the first 5 patients have been enrolled and evaluated, and then will be monitored when there are 15, 25, 35, 45, 55, 65, 75, 85, 95,105,115,and 120 patients enrolled. Stopping boundaries corresponding to this stopping rule are listed in Table 4c.

Table 4c. Early stopping boundaries for toxicity monitoring (n=120 patients)

# of patients (in cohort size of 10, starting from the 5th patient)	Stop this cohort if there are this many patients with toxicities:
5	4-5
15	8-15
25	12-25
35	16-35
45	19-45
55	23-55
65	26-65
75	30-75
85	33-85
95	37-95
105	40-105
115	43-115
120	45-120

9.3.1 Futility monitoring for 1) AML patients with prior history of MDS or CMML who received therapy for the MDS or CMML and progressed to AML or 2) Futility monitoring for patients with refractory or relapsed AML (n=80);

For the cohorts of patients (n=80 patients per cohort) with refractory or relapsed AML or AML patients with prior history of MDS or CMML who received therapy for the MDS or CMML and progressed to AML or patients with refractory or relapsed AML, we assume a target response rate of 25% and a response rate of 15% or lower will be considered not desirable. The study will be stopped early if the data suggest that:

$$Pr(P_E > P_H + 0.10 \mid data)<0.025$$

where P_E and P_H are the response rates for this combination and historical treatment, respectively. That is, if at any time during the study we determine that there is less than 2.5% chance that the response rate improves over historical rate by more than 10%, the trial will be stopped due to futility. P_E and P_H are assumed to follow a prior of Beta (0.3, 1.7). The stopping boundaries for futility based on these assumptions and monitoring conditions are provided in Table 5. We will apply these stopping boundaries after the first 5 patients, and then will be monitored when there are 15, 25, 35, and 45, 55, 65, 75, and 80 patients enrolled. The operating characteristics for futility and toxicity monitoring are summarized in Table 6.

Table 5. Stopping boundaries for futility monitoring(n=80 patients)

# of patients evaluated for response	Stop this cohort if # of patients with response is less than or equal to:
5	Never stop with this many patients
15	0-1
25	0-2
35	0-4
45	0-6
55	0-8
65	0-10
75	0-12
80	0-13

If the study is not stopped early and 80 patients have been treated and evaluated in the study, assuming 20 of the 80 patients achieve response, then the 95% credible interval for response rate will be (0.16 ,0.35).

Table 6. Operating characteristics for futility and toxicity monitoring (n=80 patients)

True response rate	True toxicity rate	Prob(stop the trial early)	Average number of patients treated
0.15	0.20	0.78	44.20
	0.30	0.80	41.25
	0.40	0.93	31.30
0.25	0.20	0.16	71.80
	0.30	0.27	66.15
	0.40	0.73	44.28
0.35	0.20	0.03	78.25
	0.30	0.16	71.63
	0.40	0.68	47.88

9.3.2 Futility monitoring for elderly (>60 year old) patients with newly diagnosed AML not eligible for intensive chemotherapy

For the cohort of elderly (>60 year old) patients with newly diagnosed AML not eligible for intensive chemotherapy (n=120), we assume a target response rate of 60%. The study will be stopped early if the data suggest that:

$$Pr(P_E > 0.6| \text{ data})<0.025$$

where P_E is the response rates for this combination treatment. That is, the trial will be stopped early due to futility, if during the study we determine that there is less than 2.5% chance that the response rate is at least 60%. Assuming that the prior distribution of $p(P_E)$ is beta (1.2, 0.8), the stopping boundaries for futility based on the assumption and monitoring conditions are provided in Table 7. We will apply these stopping boundaries after the first 5 patients, and will be monitored when there are 15, 25, 35, 45, 55, 65, 75, 85, 95, 105, 115 and 120 patients enrolled. The operating characteristics for futility and toxicity monitoring are summarized in Table 8.

Table 7. Stopping boundaries for futility monitoring (n=120 patients)

# of patients evaluated for response	Stop this cohort if # of patients with response is less than or equal to:
5	0
15	0-5
25	0-9
35	0-15
45	0-20
55	0-25
65	0-31
75	0-36
85	0-41
95	0-47
105	0-52
115	0-58
120	0-61

Table 8. Operating characteristics for futility and toxicity monitoring (n=120 patients)

True response rate	True toxicity rate	Prob(stop the trial early)	Average number of patients treated

0.5	0.20	0.70	71.85
	0.30	0.75	65.6
	0.40	0.95	41.0
0.6	0.20	0.11	111.1
	0.30	0.25	99.6
	0.40	0.85	54.3
0.75	0.20	0.01	118.5
	0.30	0.17	106.4
	0.40	0.84	57.1

If the study is not stopped early and 120 patients have been treated and evaluated in the study, assuming 72 of the 120 patients achieve response, then the 95% credible interval for response rate will be (0.51,0.69).

9.3.3 Futility monitoring for patients with high-risk MDS with bone marrow blasts between 10% and 20%, relapsed or refractory to prior hypomethylating agent (HMA) therapy; or high-risk CMML with bone marrow blasts ≥ 10% regardless of prior therapy

For the cohort of patients with high-risk MDS with bone marrow blasts between 10% and 20%, relapsed or refractory to prior hypomethylating agent (HMA) therapy (n=40); or chronic myelomonocytic leukemia (CMML) with bone marrow blasts ≥ 10% regardless of prior therapy, we assume a target response rate of 20% and a response rate of 10% or lower will be considered not desirable. The study will be stopped early if the data suggest that:

$$Pr(P_E > P_H + 0.10 \mid data) < 0.025$$

where P_E and P_H are the response rates for this combination and historical treatment, respectively. That is, if at any time during the study we determine that there is less than 2.5% chance that the response rate improves over historical rate by more than 10%, the trial will be stopped due to futility. P_E and P_H are assumed to follow a prior of Beta (0.2, 1.8). The stopping boundaries for futility based on these assumptions and monitoring conditions are provided in Table 9. We will apply these stopping boundaries after the first 5 patients, and will be monitored when there are 15, 25, 35, and 40 patients enrolled. The operating characteristics for futility and toxicity monitoring are summarized in Table 10.

Table 9. Stopping boundaries for futility monitoring (n=40 patients)

# of patients evaluated for response	Stop this cohort if # of patients with response is less than or equal to:
5	Never stop with this many patients
15	0

25	0-1
35	0-3
40	0-3

Table 10. Operating characteristics for futility and toxicity monitoring (n=40 patients)

True response rate	True toxicity rate	Prob(stop the trial early)	Average number of patients treated
0.10	0.20	0.5776	31.6
	0.30	0.6077	30.2
	0.40	0.7685	25.5
0.20	0.20	0.0924	38.5
	0.30	0.1840	36.4
	0.40	0.4897	30.6
0.30	0.20	0.0195	39.5
	0.30	0.1177	37.4
	0.40	0.4523	31.0

If the study is not stopped early and 40 patients have been treated and evaluated in the study, assuming 8 of the 40 patients achieve response, then the 95% credible interval for response rate will be (0.09,0.33).

9.3.4 Futility monitoring for younger patients with complex karyotype and/or TP53 deletions/mutations

For the cohort of younger patients with complex karyotype and/or TP53 deletions/ mutations patients (n=40), we assume a target response rate of 50%. The study will be stopped early if the data suggest that:

$$Pr(P_E > 0.5| \text{ data})<0.025$$

where P_E is the response rates for this combination treatment. That is, the trial will be stopped early due to futility, if during the study we determine that there is less than 2.5% chance that the response rate is at least 50%. Assuming that the prior distribution of $p(P_E)$ is beta (1, 1), the stopping boundaries for futility based on the assumption and monitoring conditions are provided in Table 11. We will apply these stopping boundaries after the first 5 patients, and will be monitored when there are 15, 25, 35, 40 patients enrolled. The operating characteristics for futility and toxicity monitoring are summarized in Table 12.

Table 11. Stopping boundaries for futility monitoring(n=40 patients)

# of patients evaluated for response	Stop this cohort if # of patients with response is less than or equal to:
5	0
15	0-3
25	0-7
35	0-11
40	0-13

Table 12. Operating characteristics for futility and toxicity monitoring (n=40 patients)

True response rate	True toxicity rate	Prob(stop the trial early)	Average number of patients treated
0.3	0.20	0.77	27.83
	0.30	0.78	26.79
	0.40	0.87	23.45
0.5	0.20	0.06	38.92
	0.30	0.15	36.88
	0.40	0.48	30.63
0.6	0.20	0.02	39.59
	0.30	0.11	37.40
	0.40	0.45	31.08

If the study is not stopped early and 40 patients have been treated and evaluated in the study, assuming 20 of the 40 patients achieve response, then the 95% credible interval for response rate will be (0.35,0.65).

9.4 Statistical Analysis Plan:

All patients who receive at least 1 dose of venetoclax will be included in the analysis of safety and efficacy regardless of the duration of treatment. Patients who experience adverse events during the screening period but who do not start on study treatment due to reasons that include, but are not limited to ineligibility/screen failure, death or withdrawal of consent, will not be included in the safety or efficacy evaluable population.

Descriptive statistics including plots, mean, median and standard deviations will be used to summarize data. For the primary efficacy analysis, we will estimate the ORR for the combination treatment, along with the 95% confidence interval. Patients who drop out of the study before completing all the cycles will be treated as “failures” for the primary analysis. The association between ORR and patient’s clinical characteristics will be examined by Wilcoxon’s rank sum test

or Fisher's exact test, as appropriate. Toxicity type, severity and attribution will be summarized for each patient using frequency tables. The distribution of time-to-event endpoints including duration of response, DFS and OS will be estimated using the method of Kaplan-Meier. Comparisons of time-to-event endpoints by important subgroups will be made using the log-rank tests. Baseline protein, gene expression signatures/mutation profile and BH3 profiling will be summarized with descriptive statistics. The correlation with endpoints of anti-tumor activity will be explored when possible. Exact logistic regression analysis will be used to evaluate the association of PD/PK parameters with response.

10.0 PROTOCOL ADMINISTRATION

10.1 Protocol Amendments

Changes to the protocol will be made only when protocol amendments have been signed by the principal investigator and approved by the sponsor and the IRB of the study center.

10.2 Archival of Data

All patient data (including source data) generated in connection with this study will be kept in the archives of the MDACC for at least 15 years after the study has been completed. All data will be available for inspection by company representatives of the Medical Department and by regulatory authorities.

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