

VENETOCLAX

Andre Schuh, MD

As of Saturday, June 13 at
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were created from the abstract



A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF VENETOCLAX WITH AZACITIDINE VS AZACITIDINE IN TREATMENT-NAÏVE PATIENTS WITH ACUTE MYELOID LEUKEMIA INELIGIBLE FOR INTENSIVE THERAPY – VIALE-A

Courtney DiNardo, et al.

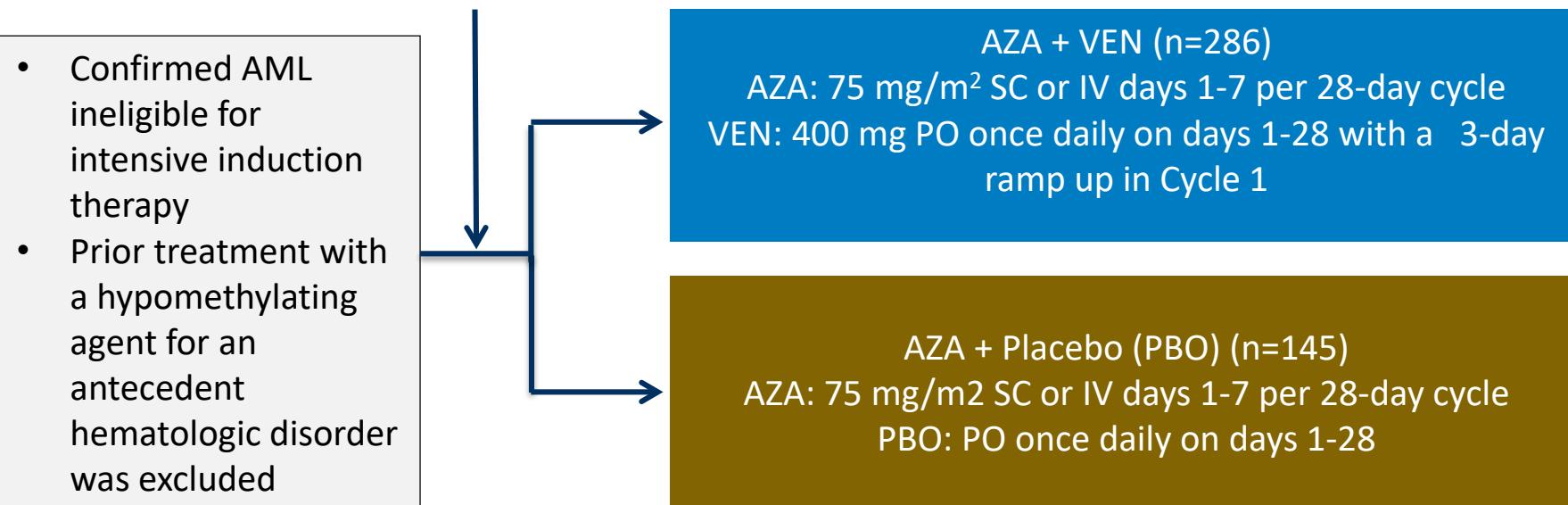
Presented at the 25th (Virtual) Congress of the European Hematology Association,
Abstract LB2601

BACKGROUND, STUDY DESIGN AND ENDPOINTS

Background

- Ventoclax (VEN) is a selective small-molecule inhibitor of BCL-2
- Data from a prior phase 1b study showed that VEN and azacitidine (AZA) combination had promising efficacy with an acceptable safety profile

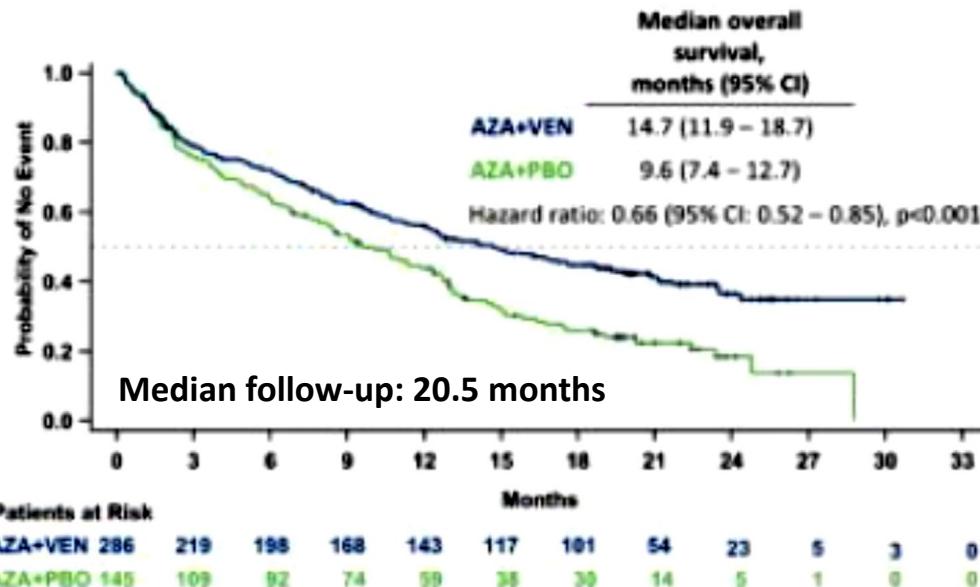
2:1 randomization



- Primary endpoint: OS
- Secondary endpoints
 - Composite complete remission (CR/CRI)
 - CR/CRI by initiation of Cycle 2
 - CR transfusion independence (TI; RBCs or platelets)
 - CR/CRI by molecular subgroups
 - EFS

VEN + AZA SHOWED SIGNIFICANTLY INCREASED RATES OF OS AND RESPONSES VERSUS AZA ALONE

Figure. Overall survival



**Median age (range) across entire study population (N=431):
76 years (49-91)**

	AZA + VEN (n=286)	AZA + PBO (n=145)	P-value
Cycles of study drug, median (range)	7 (1-30)	4.5 (1-26)	--
CR+CRi rate, % (95% CI)	66.4 (60.6-71.9)	28.3 (21.1-36.3)	<0.001
Median time to first CR/CRi response, months (95% CI)	1.3 (0.6-9.9)	2.8 (0.8, 13.2)	--
Duration of CR/CRi	17.5	13.4	--
CR + CRi by initiation of cycle 2, % (95% CI)	43.4 (37.5-49.3)	7.6 (3.8-13.2)	<0.001
Response rates: poor/int cytogenetic risk	53%/23%	74%/32%	--
Response rates de novo/secondary AML	66%/30%	67%/23%	--
CR rate, % (95% CI)	36.7 (31.1-42.6)	17.9 (12.1-25.2)	<0.001
TI: % (95% CI)			
RBCs	59.8 (53.9-65.5)	35.2 (27.4-43.5)	<0.001
Platelets	68.5 (62.8-73.9)	49.7 (42.3-58.1)	<0.001
CR+CRi rates in molecular subgroups, % (95% CI)			
IDH1/2	75.4 (62.7-85.5)	10.7 (2.3-28.2)	<0.001
FLT3	72.4 (52.8-87.3)	36.4 (17.2-59.3)	0.021
NPM1	66.7 (46.0-83.5)	23.5 (6.8-49.9)	0.012
TP53	55.3 (38.3-71.4)	0	<0.001
EFS, months (95% CI)	9.8 (8.4-11.8)	7.0 (5.6-9.5)	<0.001

SAFETY

Adverse events (AEs)	AZA+VEN (n=286)	AZA+PBO (n=145)
Grade ≥3 Hematological Adverse Events, %		
Thrombocytopenia	45	38
Neutropenia	42	29
Febrile neutropenia	42	19
Anemia	26	20
Leukopenia	21	12
All grade gastrointestinal Aes		
Nausea	44	35
Constipation	43	39
Diarrhea	41	33
Vomiting	30	23
Serious AEs Grade ≥3		
Febrile neutropenia	30	10
Pneumonia	16	22
Laboratory tumor lysis syndrome	1	--
30-day mortality rate, n (%)	21 (7)	9 (6)

DiNardo C, et al. Presented at the 25th (Virtual) Congress of the European Hematology Association, Abstract LB2601.

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CONCLUSIONS

- Among treatment-naïve, predominantly elderly patients with AML ineligible for intensive therapy, AZA+VEN led to statistically significant and clinically meaningful improvement in response rates and OS as compared to AZA alone, with a manageable safety profile

TIMING OF RESPONSE TO VENETOCLAX COMBINATION TREATMENT IN OLDER PATIENTS WITH ACUTE MYELOID LEUKEMIA

Brian A Jonas, et al.

Presented at the 2020 ASCO Virtual Scientific Program, Abstract 7531

BACKGROUND AND METHODS

Background

- Ventoclax (VEN) has synergistic activity with hypomethylating agents (azacitidine [AZA] or decitabine [DEC] or low-dose cytarabine (LDAC)
- These VEN-based combinations have demonstrated rapid median response times
- This analysis describes the rapidity and likelihood of response to VEN treatments, and its associated characteristics, on older patients with newly-diagnosed AML

Methods

- Data from two open-label trials of VEN, at label recommended doses, in combination with AZA, DEC (M14-358 study, NCT02203773; phase 1b) or LDAC (M14-387 study, NCT02287233; phase 1/2) in newly-diagnosed AML
- Patients were classified based on CR/CRI timing
 - Within 2 cycles of therapy
 - After 2 cycles
 - Never achieving CR/CRI
- Within each group, baseline and post-baseline characteristics were evaluated to determine impact on response timing
- Percentage of patients in each category and DOR in each category were also evaluated

BASELINE CHARACTERISTICS AND RESPONSE BY RESPONDER CATEGORY

	M14-358 Ven + Aza/Dec n=115	M14-387 Ven + LDAC n=82	Pooled N=197
Sex, n (%)			
Male	66 (57)	53 (65)	119 (60)
Female	49 (43)	29 (35)	78 (40)
Median age, range	74 (61–90)	74 (63–90)	74 (61–90)
Cytogenetic risk, n (%)			
Intermediate	66 (57)	49 (60)	115 (58)
Poor	48 (42)	26 (32)	74 (38)
AML type, n (%)			
<i>De novo</i>	85 (74)	42 (51)	127 (65)
<i>Secondary</i>	30 (26)	40 (49)	70 (36)
ECOG PS, n (%)			
0	21 (18)	12 (15)	33 (17)
1	64 (56)	46 (56)	110 (56)
2	28 (24)	23 (28)	51 (26)
3	2 (2)	1 (1)	3 (2)
BM blast, n (%)			
<30%	31 (27)	27 (33)	58 (30)
≥30% to <50%	43 (37)	18 (22)	61 (31)
≥50%	41 (36)	36 (44)	77 (39)
Genetic mutations, n (%)			
<i>FLT3</i>	14 (12)	16 (20)	30 (15)
<i>IDH1/2</i>	25 (22)	18 (22)	43 (22)
<i>TP53</i>	27 (24)	10 (12)	37 (19)
<i>NPM1</i>	17 (15)	9 (11)	26 (13)

*Percentages for some variables do not add up to 100% due to missing data.

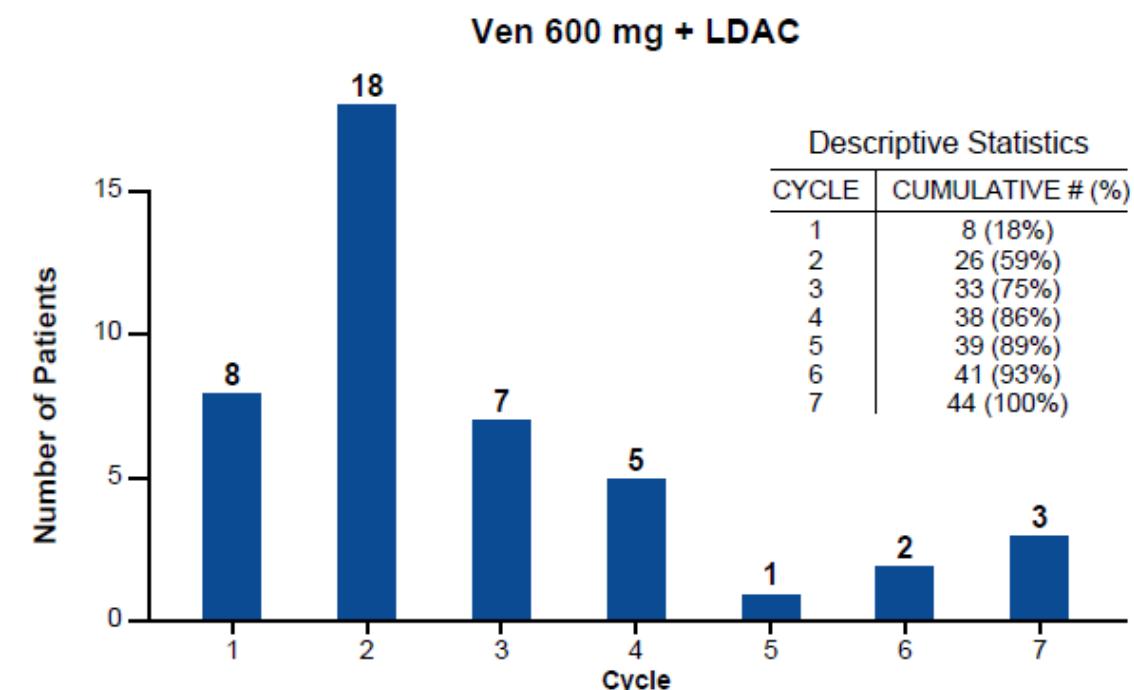
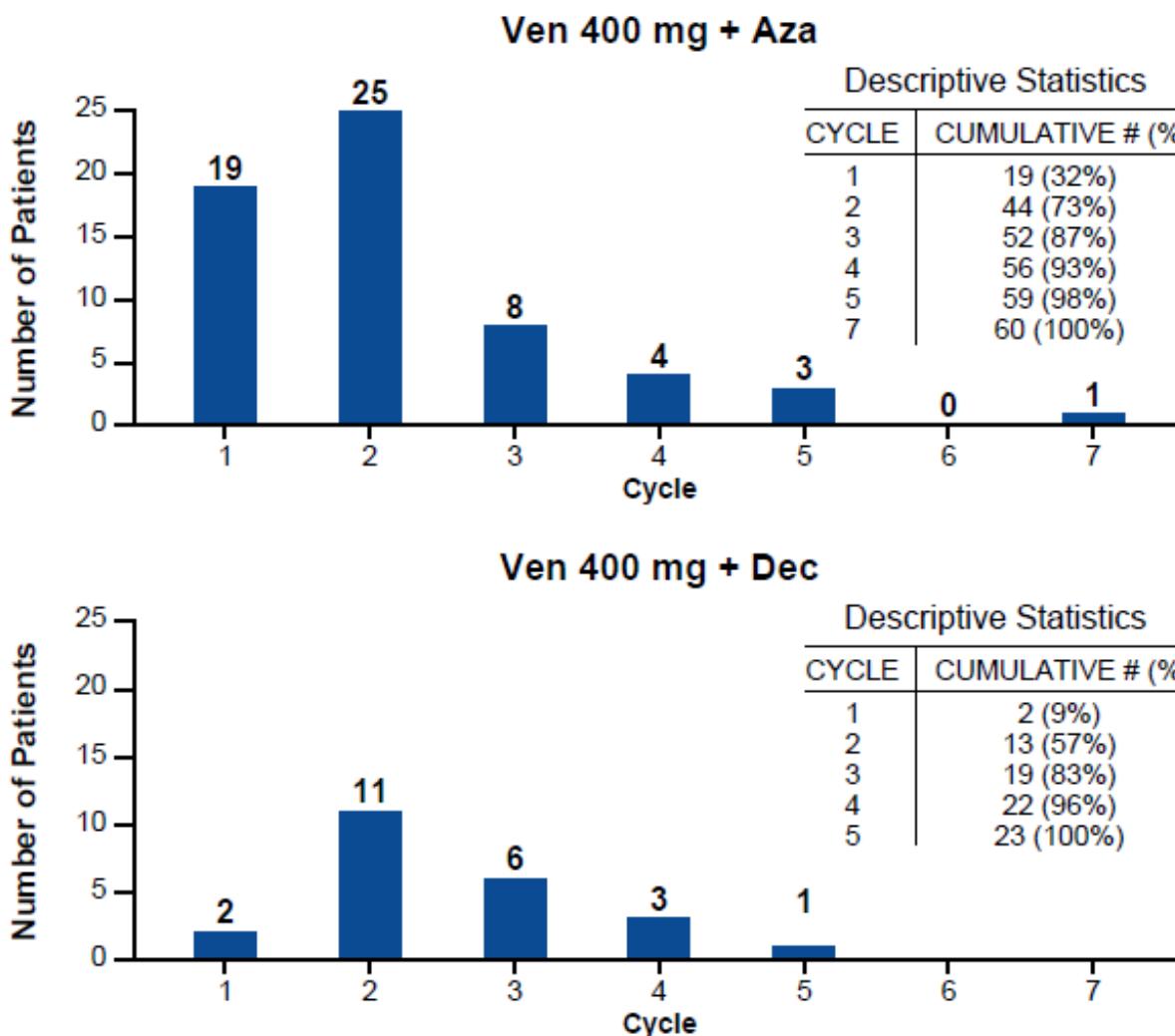
AML, acute myeloid leukemia; Aza, azacitidine; BM, bone marrow; Dec, decitabine; ECOG PS, Eastern Cooperative Oncology Group performance status; LDAC, low-dose cytarabine; Ven, venetoclax.

	Early Responder (≤2 cycles to CR/CRI) n=83	Later Responder to CR/CRI) n=44	Non- Responder n=70	Total N=197
Median time on therapy, mo	10.2 (0.3–36.2)	10.5 (3–35.8)	1.9 (0.1–16.6)	5.4 (0.1–36.2)
Achieved MLFS in cycle 1 or 2, n (%)	83 (100)	19 (43)	12 (17)	114 (58)
Median DOR (mo), (95% CI)	21.2 (14.1–NR)	8.1 (5.3–14.9)	N/A	14.9 (10.6–21.2)*
Median OS, mo	NR (16.9–NR)	18.0 (13.3–27.8)	3.7 (2.7–5.6)	--
12-mo survival estimate, % (95% CI)	71 (60–79)	75 (59–85)	13 (6–22)	--
24-mo survival estimate, % (95% CI)	53 (41–64)	42 (27–57)	N/A	--

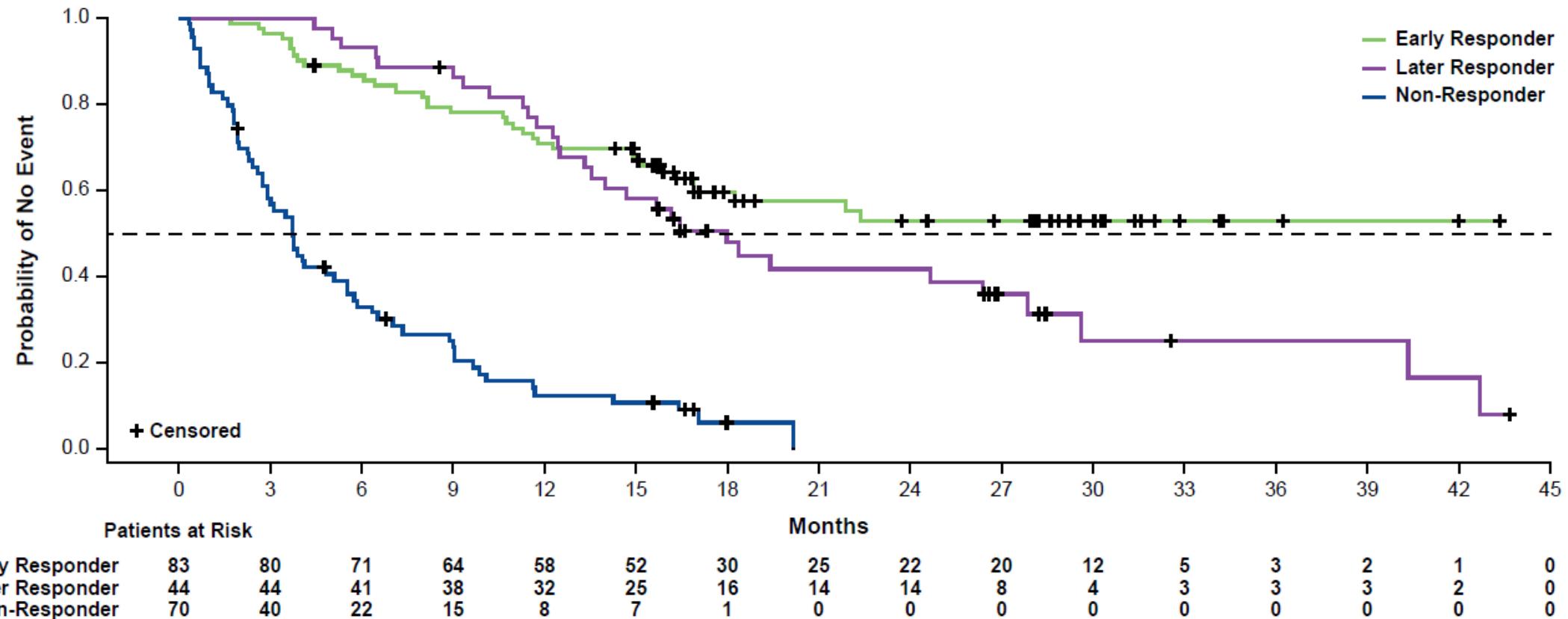
*Total n=127 (excludes non-responders).

DOR, duration of response; MLFS, morphologic leukemia-free state; mo, months; OS, overall survival.

TIME TO FIRST RESPONSE

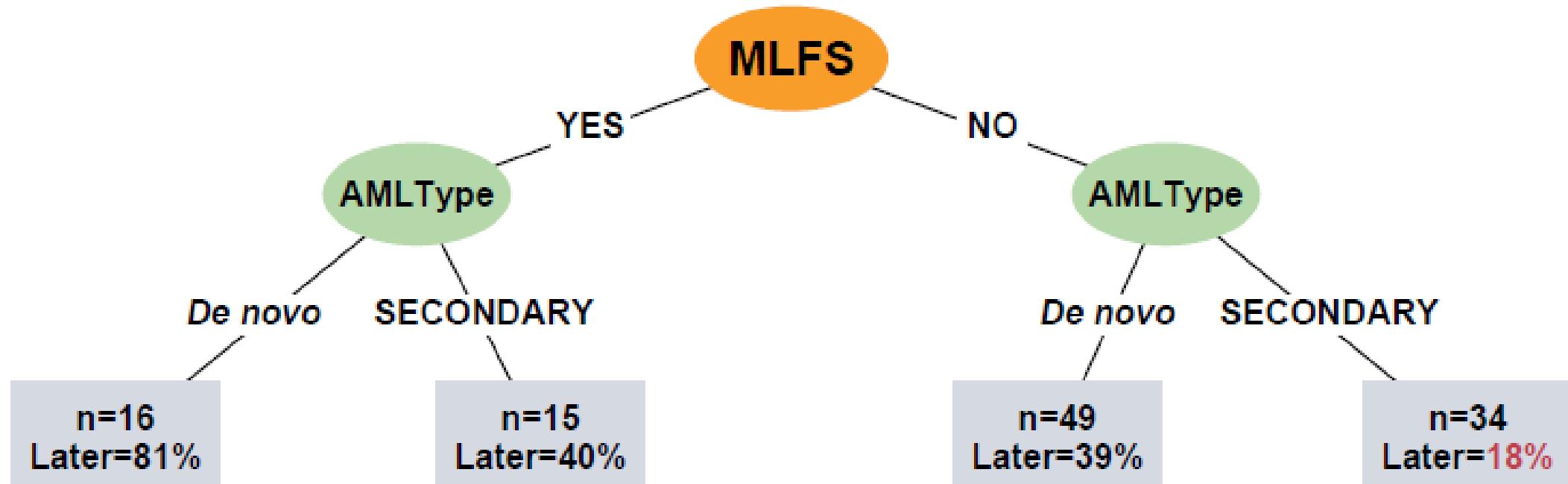


OVERALL SURVIVAL BY TIMING OF RESPONSE



CART MODEL TO PREDICT RESPONSE STATUS AMONG PATIENTS WHO HAD NOT YET ACHIEVED CR/CR_I BY END OF CYCLE 2: POOLED DATA FROM BOTH STUDIES

Later vs. Non-response (N=114)



SUMMARY OF GRADE 3/4 HEMATOLOGIC ADVERSE EVENTS

	Early Responder (≤2 cycles to CR/CRi) n=83	Later Responder (>2 cycles to CR/CRi) n=44	Non-Responder n=70	Overall N=197
Febrile neutropenia	33 (40%)	17 (39%)	38 (54%)	88 (45%)
Thrombocytopenia	25 (30%)	16 (36%)	19 (27%)	60 (31%)
Anemia	26 (31%)	18 (41%)	13 (19%)	57 (29%)
Neutropenia	17 (21%)	11 (25%)	14 (20%)	42 (21%)

CONCLUSIONS

- 35% of patients with newly-diagnosed AML ineligible for intensive chemotherapy who achieved CR/CRI with VEN + AZA, DEC, or LDAC in these two studies required up to 7 cycles of therapy to achieve response
- Patients has similar OS benefit regardless of achievement of a remission early or later
- Prior to discontinuing therapy for patients who have not achieved CR/CRI within the first two cycles, it is critical to assess key disease characteristics at baseline, such as AML type and disease improvement post-baseline (eg, whether MLFS has been achieved)

TEN-DAY DECITABINE WITH VENETOCLAX (DEC10-VEN) IN AML AND HIGH-RISK (HR) MDS

Abhishek Maiti, et al.

Presented at the 2020 ASCO Virtual Scientific Program, Abstract 7519

BACKGROUND AND METHODS

Background

- Venoclast (VEN)-based low intensity regimens have shown promise in older patients with newly diagnosed (ND) AML
 - Adding VEN to 10-day decitabine (DEC) may improve outcomes in AML and HR MDS

Eligibility

- ND AML (>60yrs), R/R AML, sAML, HR MDS
 - WBC $\leq 10 \times 10^9/L$

Excluded

- Favorable risk cytogenetics
 - APL, CBF, AML
 - Prior BCL2 inhibitor therapy



- DEC 20mg/m² x 10 days every 4-8 weeks
 - Consolidation/maintenance: DEC x days post CR/CRI
 - VEN day 1-28 for cycle 1, and day 1-21 cycle 2 onward
 - If cycle 1, day 21 bone marrow showed <5% blasts, VEN held for count recovery
 - Further reduction of VEN duration allowed for myelosuppression
 - Inpatient administration: ND patients, cycle 1 of VEN; R/R patients, 3 days of VEN dose escalation
 - VEN dose reduced by 50-75% with CYP3A4i (eg, azoles)
 - Targeted therapies allowed – FLT-3i, BCR-ABL, TKIs
 - TLS prophylaxis
 - Treatment discontinued if progression or no response after 4 or more cycles

BASELINE CHARACTERISTICS AND SAFETY

Pt Characteristics	ND AML (N=70)	Untreated sAML ¹ (N=15)	Treated sAML ² (N=28)	R/R AML (N=55)	R/R MDS (N=13)
Age, years	72 [70-78]	71 [68-76]	70 [65-76]	62 [43-73]	70 [65-76]
Age ≥ 70 yrs	53 (76)	10 (67)	15 (54)	19 (35)	7 (54)
Male sex	35 (50)	10 (67)	19 (68)	31 (56)	5 (38)
ECOG PS ≥2	24 (34)	6 (40)	8 (29)	13 (24)	3 (23)
BM blasts, %	45 [23-62]	36 [18-61]	32 [25-54]	34 [22-64]	13 [8-17]
Diagnosis					
De novo	55 (79)	0 (0)	0 (0)	51 (93)	12 (92)
Tx-related	15 (21)	1 (7)	3 (11)	4 (7)	1 (8)
ELN 2017 risk				N/A	
Favorable	18 (26)	1 (7)	4 (14)	8 (15)	
Intermediate	8 (11)	3 (20)	3 (11)	12 (22)	
Adverse	44 (63)	11 (73)	21 (75)	35 (64)	
Mutations					
<i>NPM1</i>	19 (27)	1 (7)	4 (14)	12 (22)	0 (0)
<i>FLT3</i>	14 (20)	0 (0)	2 (7)	10 (18)	0 (0)
<i>TP53</i>	21 (30)	5 (33)	8 (29)	16 (29)	2 (15)
<i>RUNX1</i>	9 (13)	1 (7)	10 (36)	9 (16)	5 (38)
<i>ASXL1</i>	9 (13)	3 (20)	9 (32)	5 (9)	5 (38)
<i>IDH1/2</i>	16 (23)	2 (13)	3 (11)	11 (20)	0 (0)
Prior therapies	0 [0]	0 [0]	2 [1-2]	2 [1-3]	1 [1-2]
HMA			25 (89)	25 (45)	12 (92)
IC			5 (18)	42 (76)	2 (15)
HMA and IC			3 (11)	12 (22)	2 (15)
HSCT			8 (29)	18 (33)	1 (8)

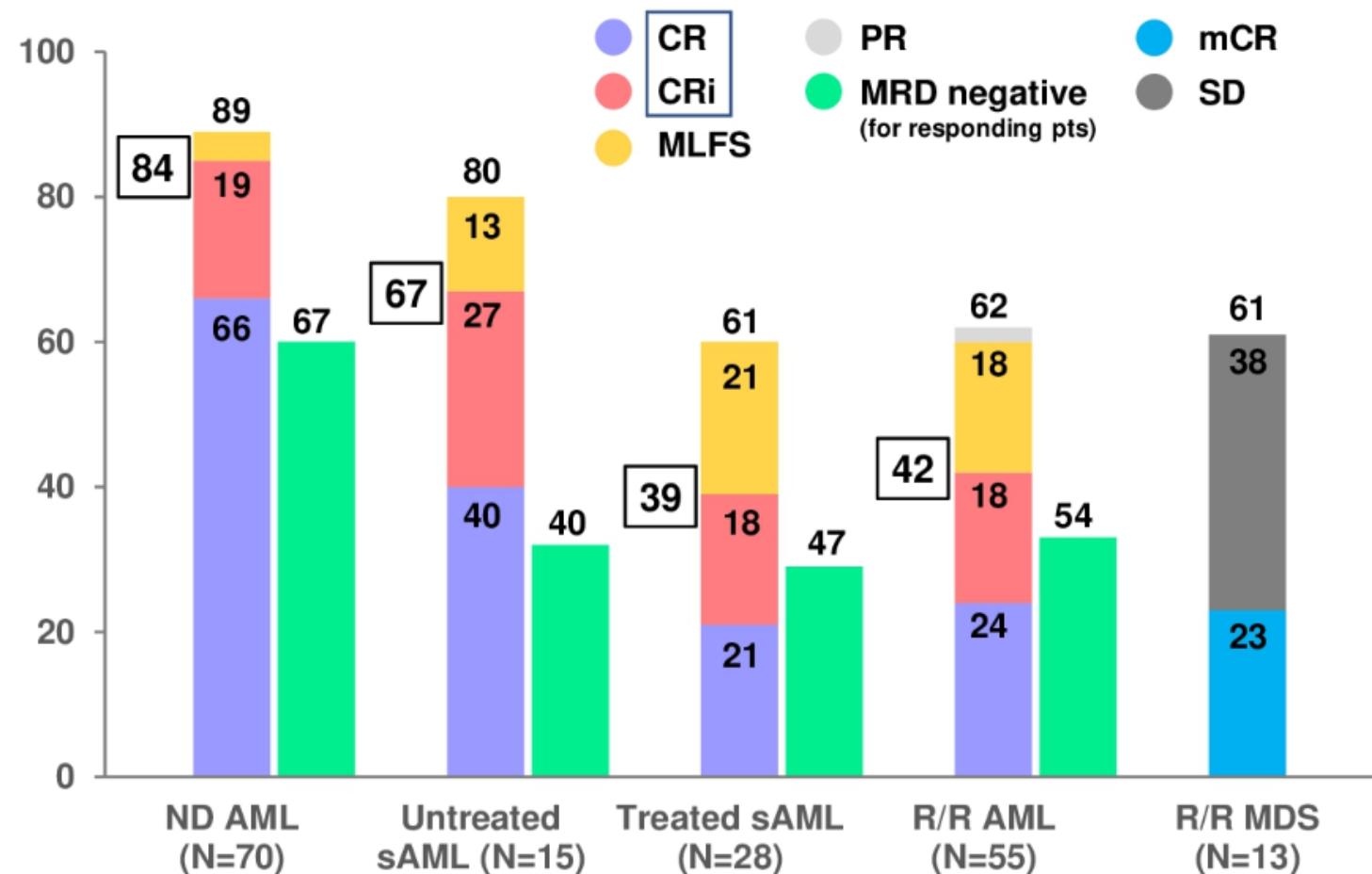
1. Prior disorder in the untreated secondary AML group included MDS (n=7) and myeloproliferative neoplasms (n=2); 2. Treated secondary AML patients had received prior therapy for preceding MDS/CMML but not for AML.

Treatment-emergent adverse events	Any grade		Grade 3/4	
	n	%	n	%
Infections with ANC <1x10 ⁹ /L	91	49	85	46
Febrile neutropenia (ANC <1x10 ⁹ /L)	52	28	51	28
Mucositis	18	10	1	1
Infections with ANC ≥1x10 ⁹ /L	16	9	14	8
Nausea	11	6	1	1
Diarrhea	10	5	2	1
Constipation	7	4	0	0
Tumor lysis syndrome	4	2	4	2
Hyperbilirubinemia	3	2	3	2
Renal Failure	3	2	2	1
ALT/AST elevation	3	2	1	1
Cardiac ischemia	1	1	1	1
Cough	1	1	1	1
Esophagitis	1	1	1	1
Fever (ANC ≥1x10 ⁹ /L)	1	1	1	1
Fracture	1	1	1	1
Intracranial hemorrhage	1	1	1	1
Muscle weakness	1	1	1	1

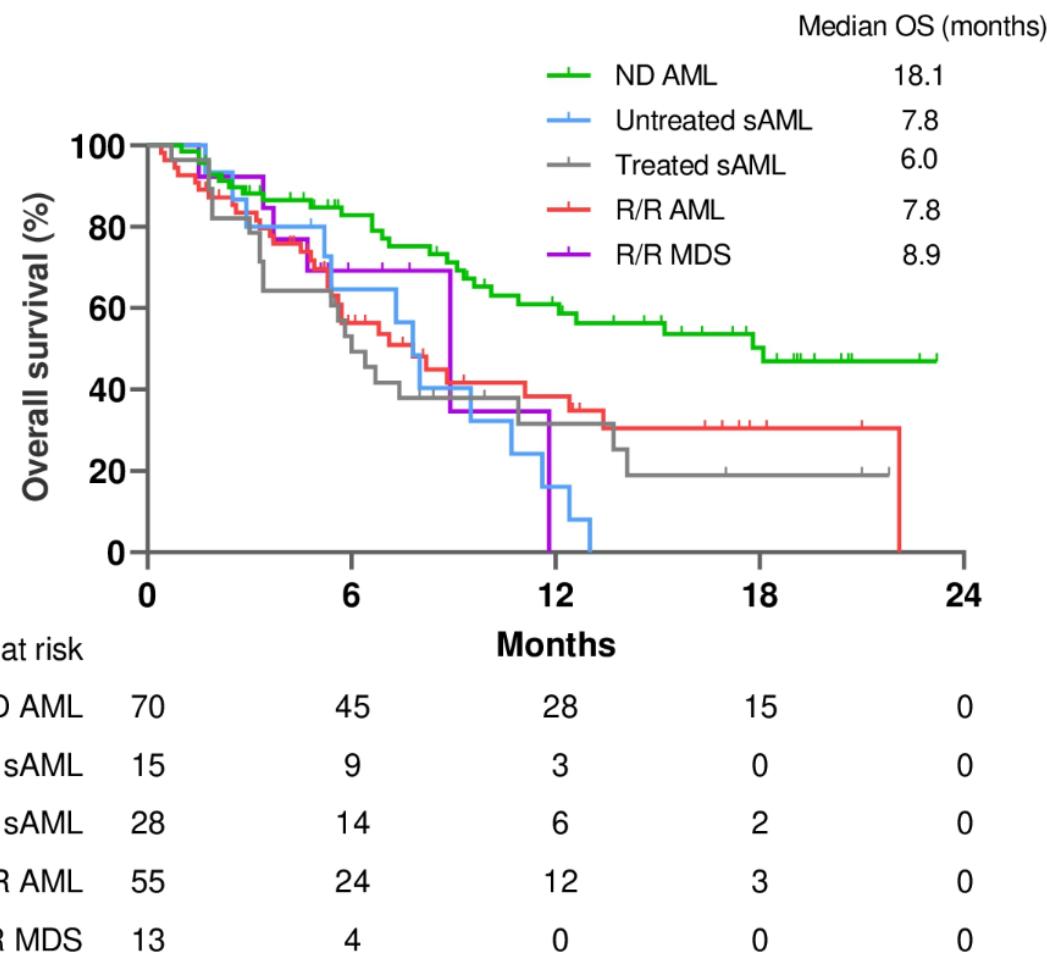
Reported are adverse events which occurred in at least 2% of the patients or with at least 1 grade 3/4 event; There were 6 grade 5 adverse events including 5 infections with grade 3/4 neutropenia and 1 grade 5 renal failure due to acute tubular necrosis.

- 30-day mortality – 3% (4 R/R, 1 sAML, 1 ND)
- 60-day mortality – 10%
- 30- and 60-day mortality for ND AML – 1.4% (n=1) and 7% (n=5)

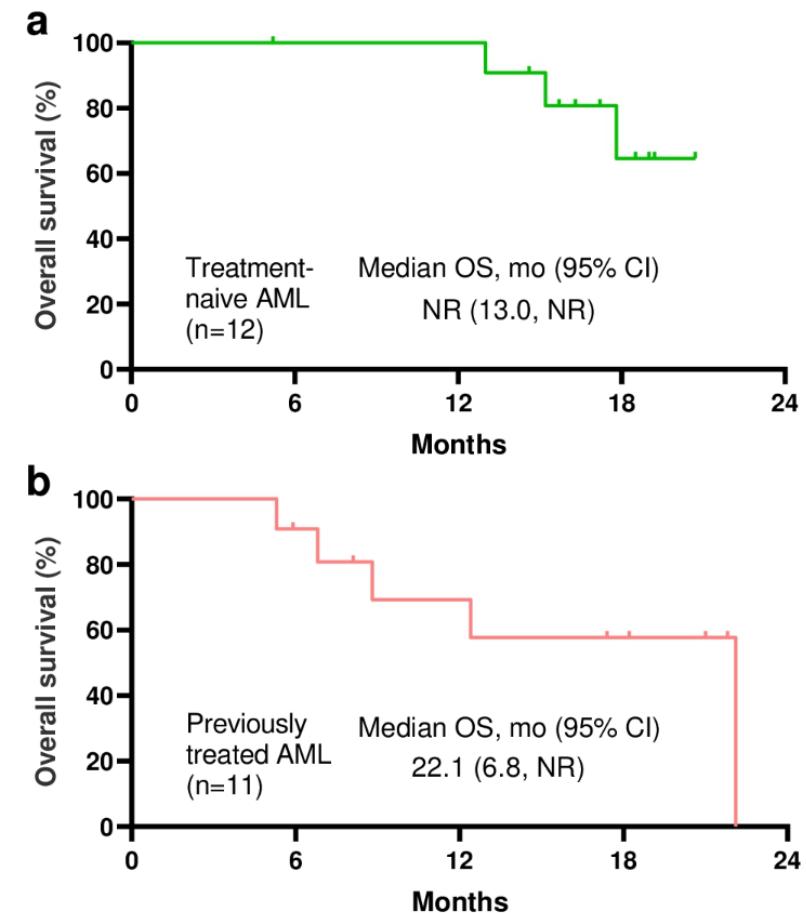
RESPONSE RATES WITH DEC10-VEN



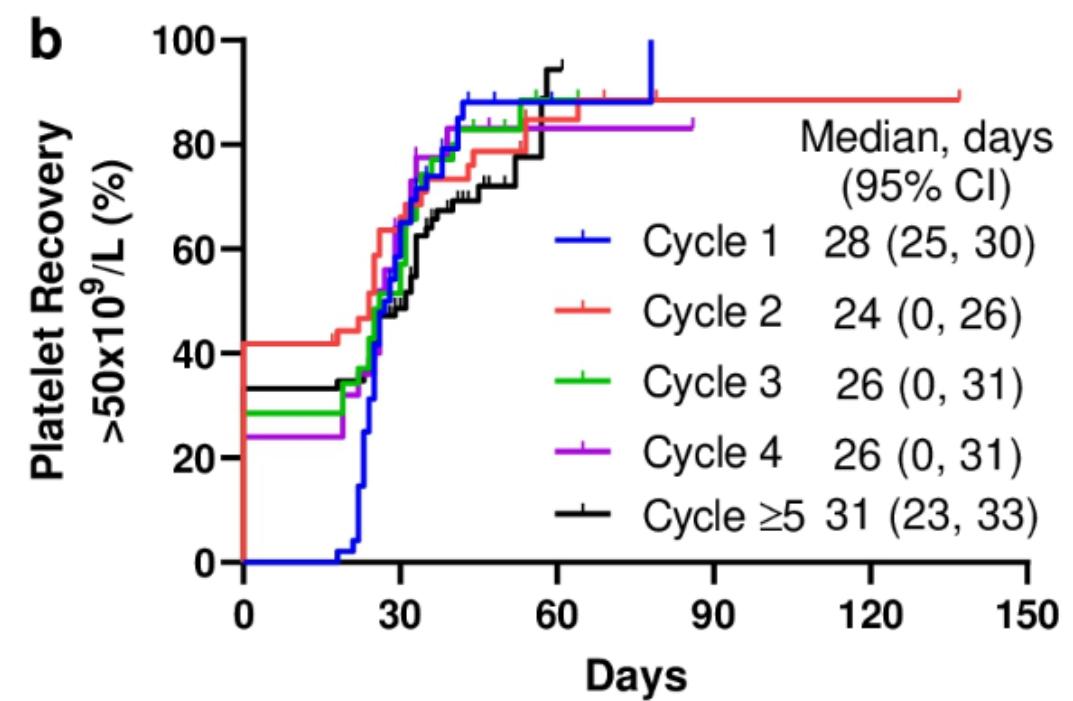
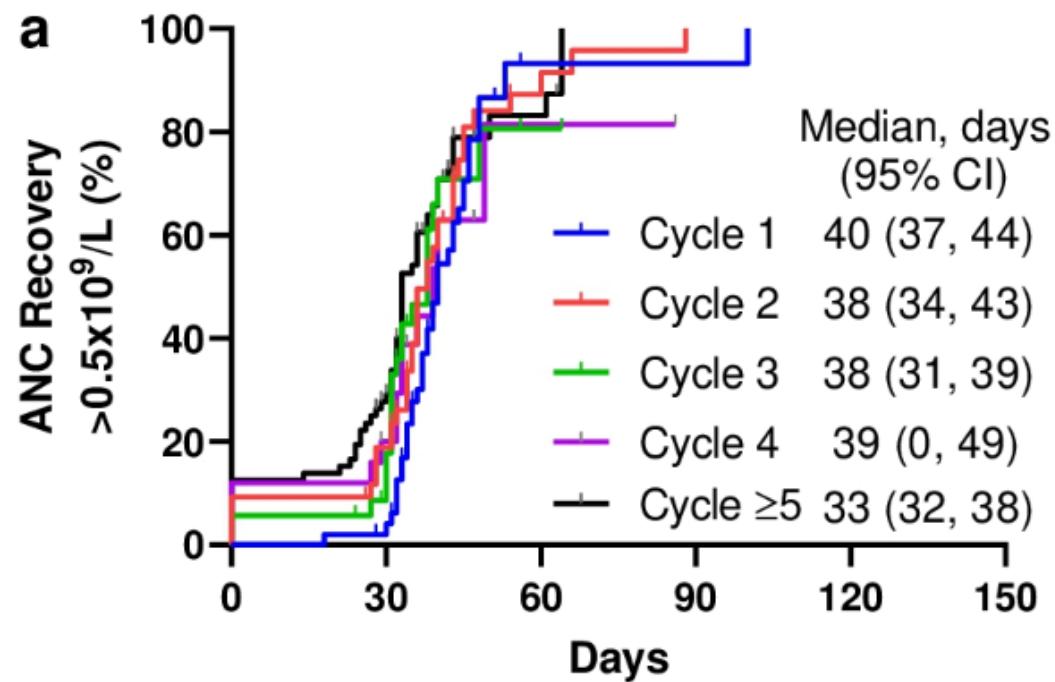
OS WITH DEC10-VEN



OS in **a.** treatment naive AML patients undergoing stem-cell transplantation (SCT), **b.** previously treated AML patients undergoing SCT



PERIPHERAL BLOOD COUNT RECOVERY IN ND-AML



CONCLUSIONS

- DEC20-VEN is safe
 - 30-day mortality 3% in all patients
 - 30-day mortality 1.4% in ND patients
- Impressive CR/CRI: 84% in ND AML
- High MRD negativity: 67% ND AML, 58% all patients
- Patients undergoing SCT had excellent outcomes
 - 100-day post-SCT mortality = 4%

A PHASE 3 STUDY OF VENETOCLAX PLUS LOW-DOSE CYTARABINE IN PREVIOUSLY UNTREATED OLDER PATIENTS WITH ACUTE MYELOID LEUKEMIA (VIALE-C): A 6-MONTH UPDATE

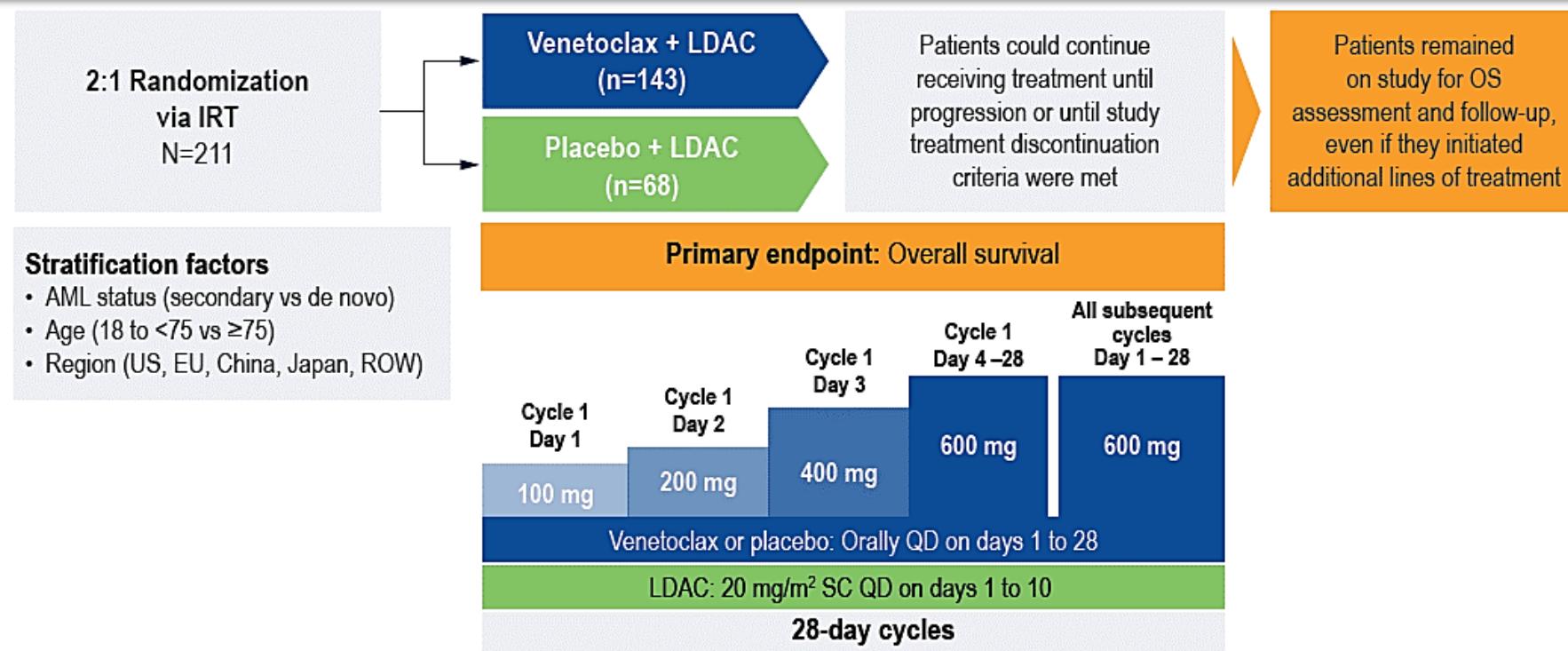
Andrew H Wei, et al.

Presented at the 2020 ASCO Virtual Scientific Program, Abstract 7511

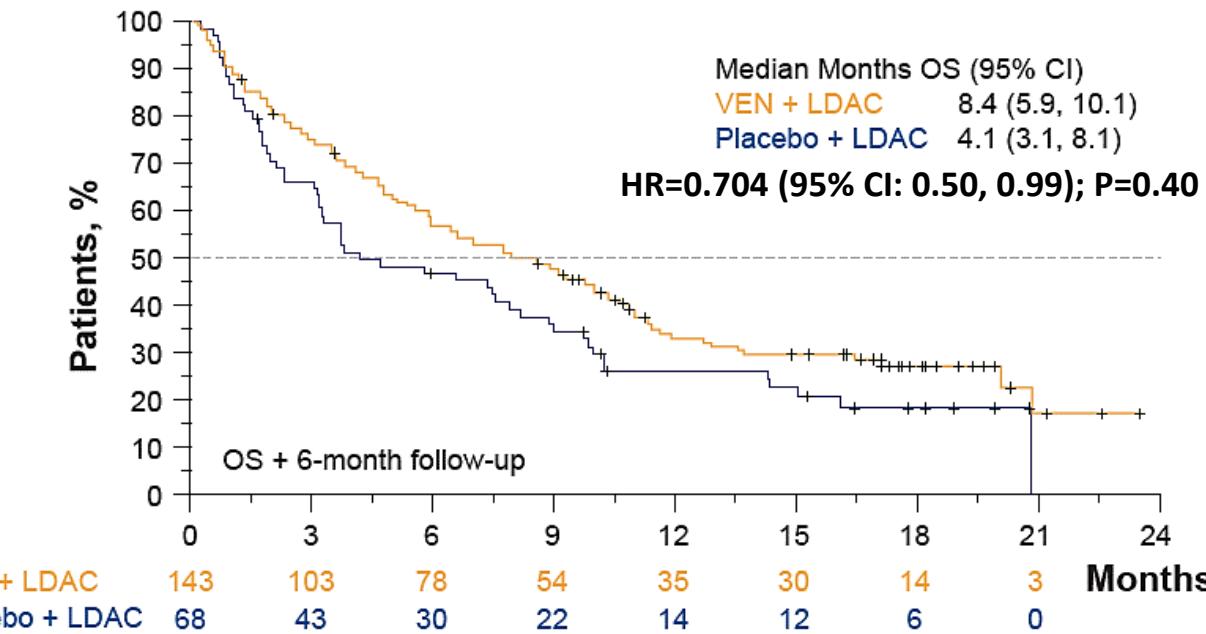
BACKGROUND AND METHODS

Background

- In the primary analysis of the phase 3 VIALE-C study, with a median time on study of 12 months, a reduction of 25% in the risk of death was observed with VEN + LDAC vs placebo + LDAC
- Median OS: 7.2 and 4.1 months; primary endpoint not met
- Results from a 6-month update are reported



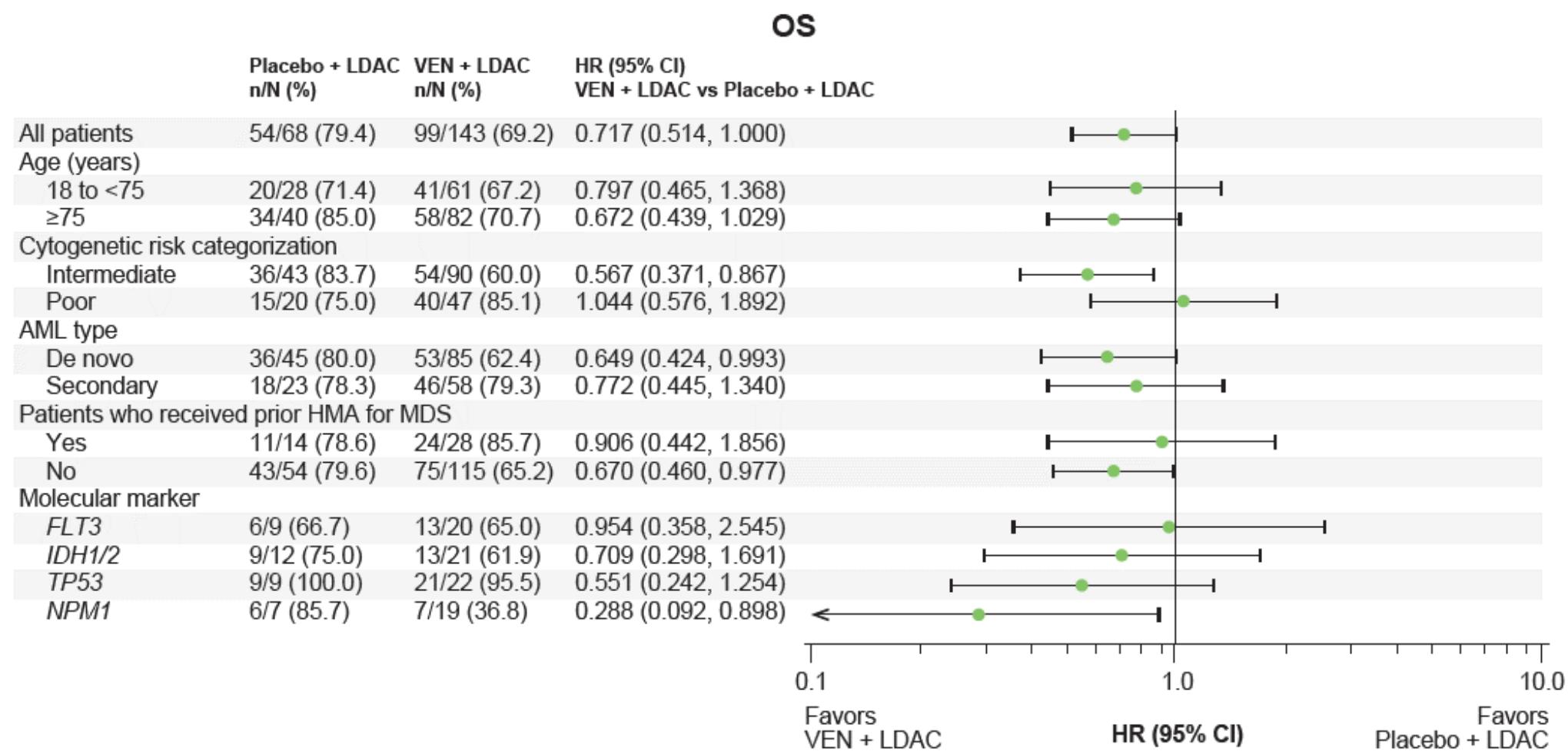
OVERALL SURVIVAL AND SUMMARY OF KEY SECONDARY ENDPOINTS



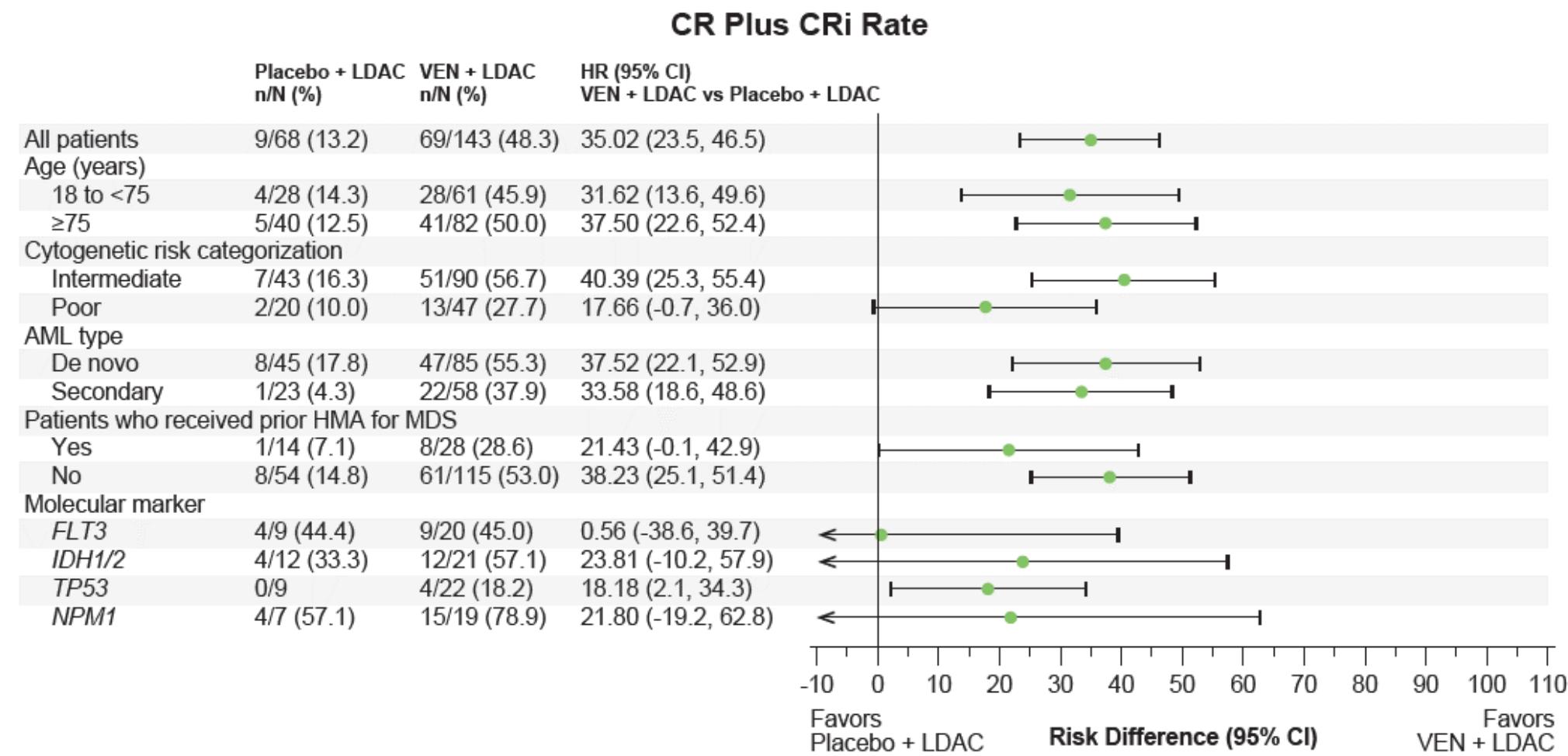
Secondary Endpoint	VEN + LDAC n=143	Placebo + LDAC n=68	P Value
Remission rates, % (95% CI)			
CR	28 (21, 36)	7 (2, 16)	<0.001
DOR, median, months	17	8	
CR/CRi			
Time to first remission, median, months (range)	1 (\leq 1-16)	4 (\leq 1-7)	
By initiation of cycle 2	34 (27, 43)	3 (0, 10)	<0.001
DOR, median, month	12	6	<0.001
CR/CRh			
Time to first remission, median, months (range)	1 (\leq 1-16)	3 (\leq 1-7)	
By initiation of cycle 2	31 (23, 39)	4 (1, 12)	<0.001
DOR, median, month	12	8	
Postbaseline transfusion independence, % (95% CI)			
Red blood cells	43 (35, 52)	19 (11, 31)	<0.001
Platelets	49 (41, 57)	32 (22, 45)	0.024
Both	39 (31, 48)	18 (10, 29)	0.002
EFS, median (95% CI), months ^a	4.9 (3.7, 6.4)	2.1 (1.5, 3.2)	0.002

EFS: HR=0.61 (95% CI: 0.44, 0.84)

ANALYSIS OF INVESTIGATOR-ASSESSED OS IN KEY SUBGROUPS

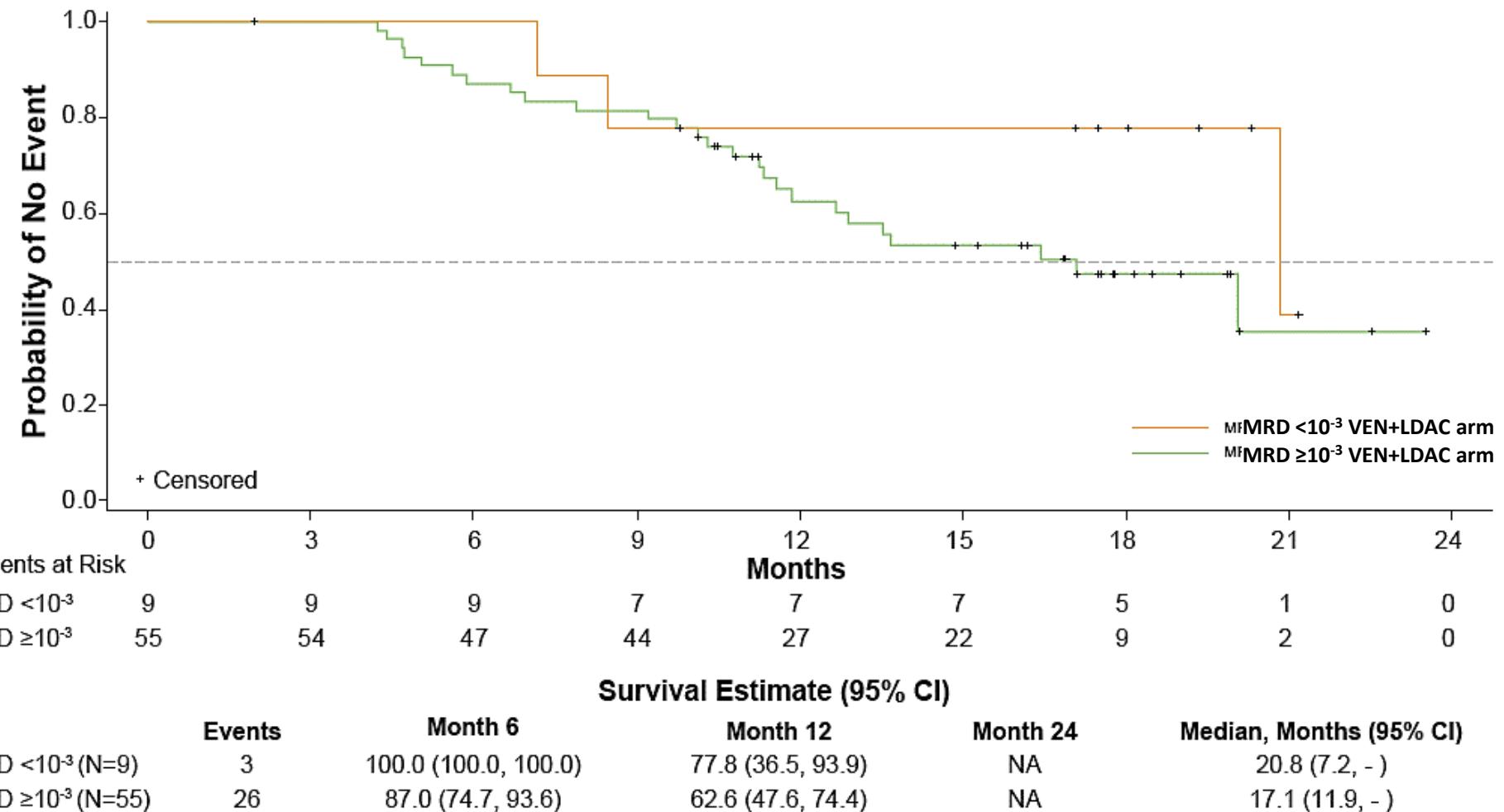


ANALYSIS OF INVESTIGATOR-ASSESSED CR PLUS CRi RATE IN KEY SUBGROUPS



OS IN PATIENTS TREATED WITH VEN+LDAC ACHIEVING CR/CRI BY BEST POSTBASELINE MRD VALUE (<10⁻³ VS ≥10⁻³)

MRD Rates in CR+CRi, n (%)	
VEN+LDAC (n=143):	69 (48%)
PBO + LDAC (n=68):	9 (13%)
P value: <0.001	



SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS

AE, n (%)	All-Grade TEAEs, ≥20% of Total Patients		Grade ≥3 TEAEs, ≥20% of Total Patients		Serious TEAEs, ≥10% of Total Patients	
	VEN + LDAC n=142	Placebo + LDAC n=68	VEN + LDAC n=142	Placebo + LDAC n=68	VEN + LDAC n=142	Placebo + LDAC n=68
Any	141 (99)	67 (99)	138 (97)	65 (96)	95 (67)	42 (62)
Hematologic	115 (81)	51 (75)	111 (78)	50 (74)	32 (23)	16 (24)
Neutropenia	69 (49)	12 (18)	69 (49)	12 (18)	4 (3)	0 (0)
Thrombocytopenia	65 (46)	27 (40)	65 (46)	26 (38)	7 (5)	2 (3)
Febrile neutropenia	46 (32)	20 (29)	46 (32)	20 (29)	24 (17)	12 (18)
Anemia	41 (29)	15 (22)	38 (27)	15 (22)	4 (3)	0 (0)
Gastrointestinal disorders	106 (75)	47 (69)	19 (13)	6 (9)	10 (7)	1 (1)
Nausea	61 (43)	21 (31)	2 (1)	0 (0)	0 (0)	0 (0)
Diarrhea	47 (33)	12 (18)	4 (3)	0 (0)	1 (1)	0 (0)
Vomiting	41 (29)	10 (15)	1 (1)	0 (0)	0 (0)	0 (0)
Constipation	29 (20)	22 (32)	1 (1)	0 (0)	0 (0)	0 (0)
Metabolism and nutrition disorder	87 (61)	40 (59)	40 (28)	22 (32)	5 (4)	0 (0)
Hypokalemia	44 (31)	17 (25)	17 (12)	11 (16)	1 (1)	0 (0)
Decreased appetite	31 (22)	13 (19)	2 (1)	0 (0)	1 (1)	0 (0)
Infections	92 (65)	41 (60)	61 (43)	34 (50)	53 (37)	25 (37)
Pneumonia	31 (22)	11 (16)	25 (18)	11 (16)	20 (14)	7 (10)

Wei WH, et al. Poster presentation at the 2020 ASCO Virtual Scientific Program, Abstract 7511.

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CONCLUSIONS

- VEN + LDAC was well tolerated in patients with AML who were not eligible for intensive chemotherapy
- VEN + LDAC demonstrated a clinically meaningful improvement in OS compared with placebo + LDAC, and has a favorable benefit-risk profile (early and sustained remission rates, longer EFS, high rates of transfusion independence)

LONG-TERM FOLLOW-UP OF A PHASE 1/2 STUDY OF VENETOCLAX PLUS LOW-DOSE CYTARABINE IN PREVIOUSLY UNTREATED OLDER ADULTS WITH ACUTE MYELOID LEUKEMIA

Andrew H Wei, et al.

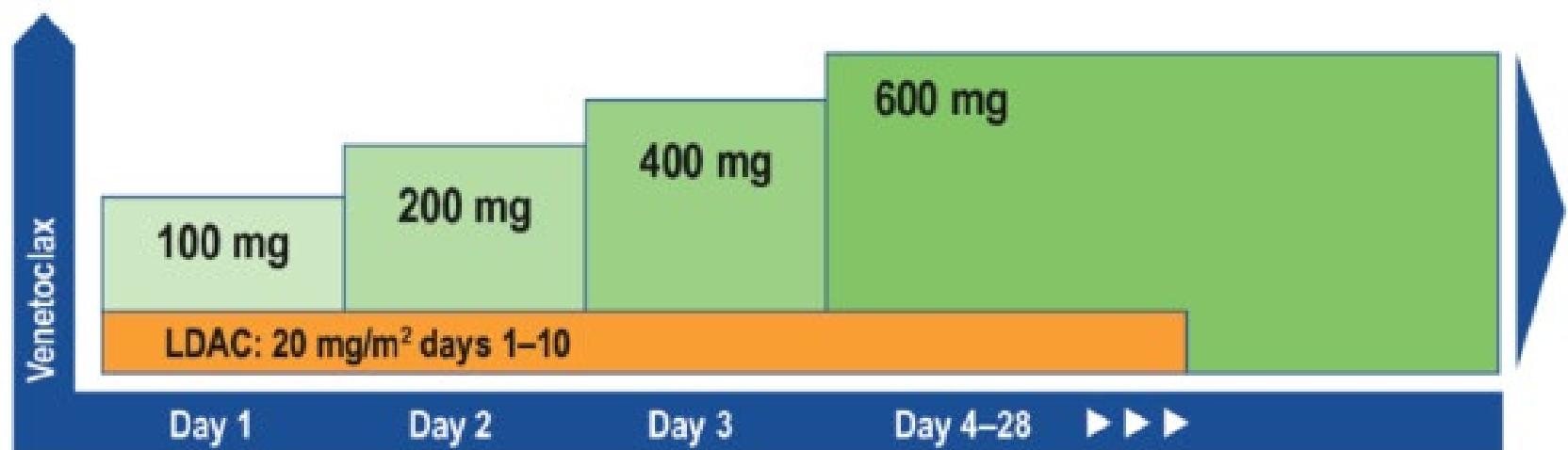
Presented at the 25th (Virtual) Congress of the European Hematology Association,
Abstract EP554

BACKGROUND, STUDY DESIGN AND ENDPOINTS

Background

- A phase 1/2 study evaluated VEN at the recommended phase 2 dose (RP2D; 600mg/day) + LDAC and demonstrated a CR/CRI rate of 54% with a median follow-up of 1.7 years in older adults with AML ineligible for intensive chemotherapy
- The long-term safety and efficacy outcomes (median follow-up 3.5 years (range .03-4.5 years) are reported here

- Patients ≥60 years with previously untreated AML ineligible for standard induction chemotherapy
 - ECOG PS 0-2 (≥ 75 yr)
 - ECOG PS 0-3 (60-74 yr)



Key objectives at RP2D

- Assess overall response rate (ORR), including CR, CRI, and partial remission, DOR, OS, and safety/tolerability

PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Characteristic, n (%)	VEN+LDAC (n=82)	Characteristic	VEN+LDAC (n=82)
Median age (range), years	74 (63-90)	Cytogenetics, n (%)	
Male, n (%)	54 (65)	Intermediate	49 (60)
ECOG PS, n (%)		Poor	26 (32)
0	12 (15)	No mitosis	7 (8)
1	46 (56)	Somatic mutations, n (%)	
2	23 (28)	<i>TP53</i>	10 (14)
3	1 (1)	<i>FLT3</i>	15 (21)
Baseline bone marrow blasts, n (%)		<i>IDH1</i>	8 (11)
<30%	27 (33)	<i>IDH2</i>	10 (14)
≥30% to <50%	18 (22)	<i>NPM1</i>	9 (13)
≥50%	36 (44)		
Secondary AML, n (%)	40 (49)		
Prior MHA treatment, n (%)	24 (29)		

SAFETY

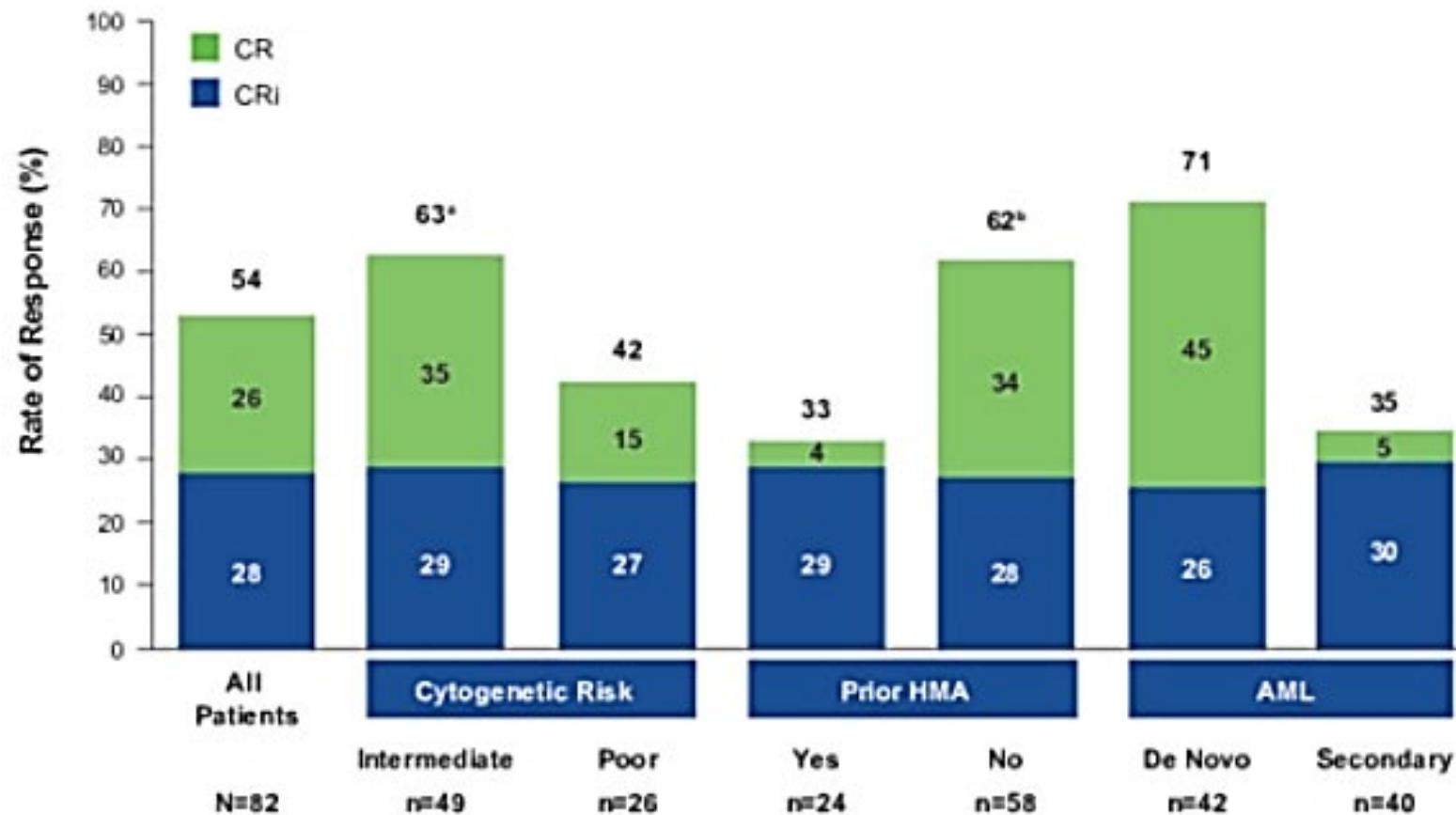
Grade 3-4 TEAEs in ≥10% of patients	VEN+LDAC (n=82)	Serious AEs in ≥5% of patients	VEN+LDAC (n=82)
Any event, n (%)	80 (98)	Any event, n (%)	75 (92)
Febrile neutropenia	35 (43)	Febrile neutropenia	23 (28)
Thrombocytopenia	32 (39)	Pneumonia	10 (12)
WBC decreased	28 (34)	Sepsis	7 (9)
Anemia	24 (29)	Device-related infection	4 (5)
Neutropenia	23 (28)		
Platelet count decreased	20 (24)		
Lymphocyte count decreased	15 (18)		
Neutrophil count decreased	14 (17)		
Hypophosphatemia	13 (16)		
Hypokalemia	12 (15)		
Pneumonia	11 (13)		
Hypertension	9 (11)		
Sepsis	9 (11)		

Wei H, et al. Poster presented at the 25th (Virtual) Congress of the European Hematology Association, Abstract EP554.

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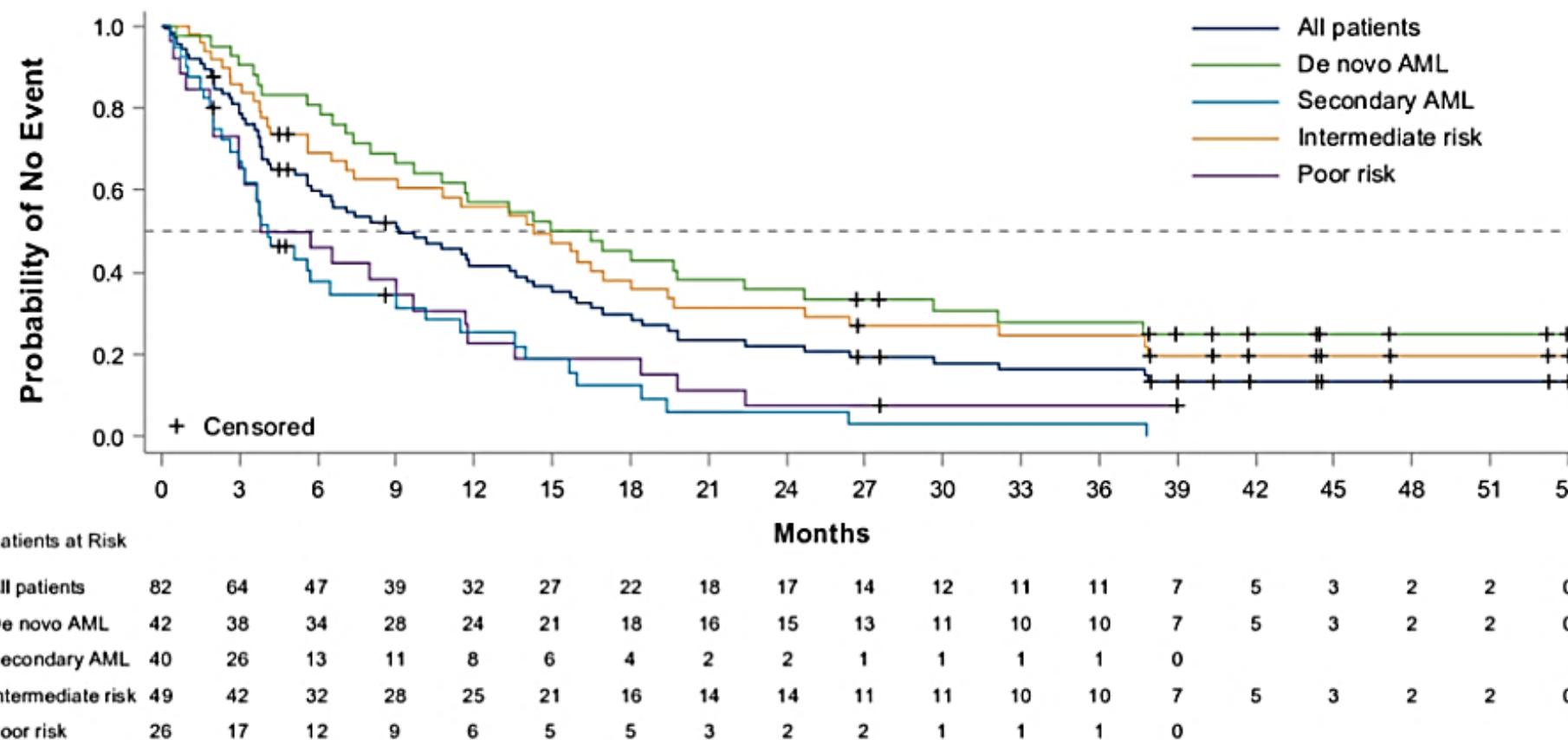
RESPONSE RATES BY KEY PATIENT SUBGROUPS



- Median treatment duration: 4.2 months (range 0.2-41.8); 26% of patients received >12 months of treatment
- Median number of cycles of therapy: 5 (range 1.0-43.0); 37 (45%) patients received >5 cycles
- CR/CRI rate was 54% (CR: 26%; CRI: 28%) with a median time to first response of 1.4 months (range 0.8-14.9); 28% of patients had achieved CR/CRI by initiation of cycle 2

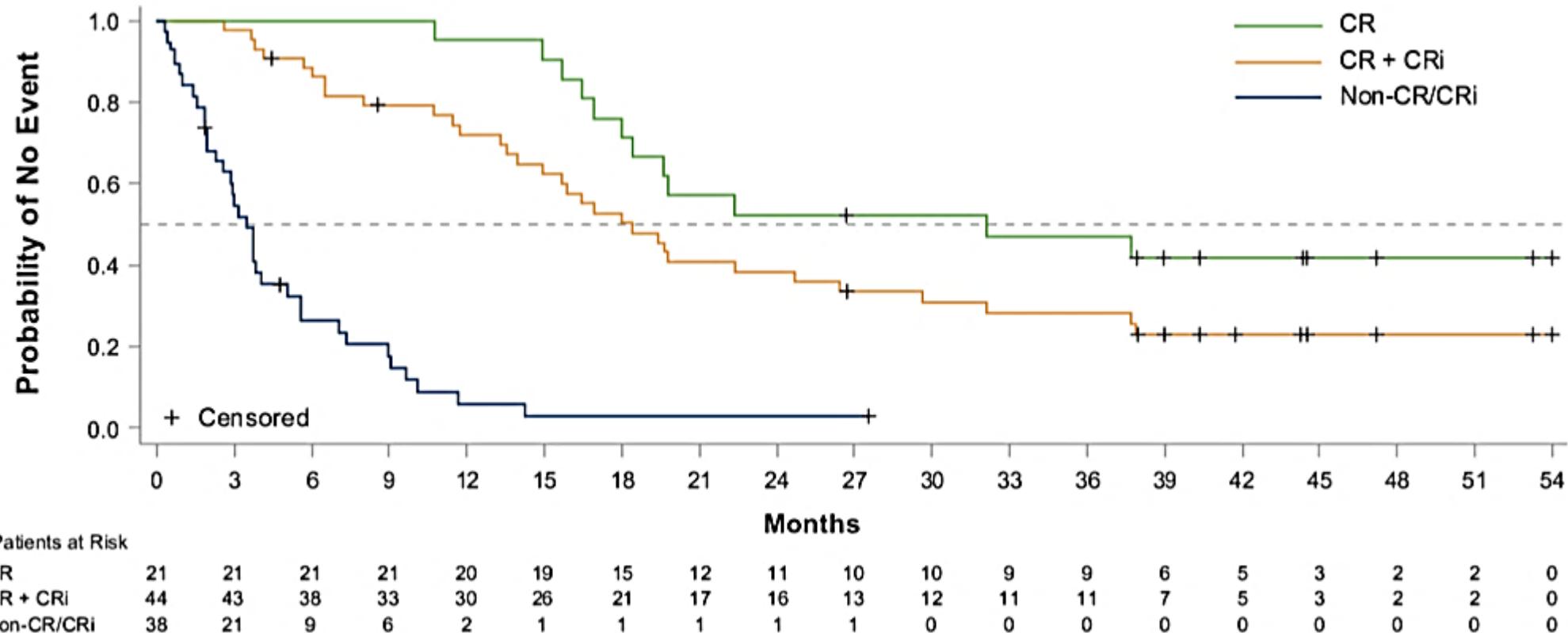
^aPercentage equal value due to rounding; CR: n=17, CRI n=14. ^bPercentage equal value due to rounding; CR: n=20, CrR: n=16
Percentage of patients with CR/CRI shown at the top of each bar.

ANALYSIS OF OS IN ALL TREATED PATIENTS



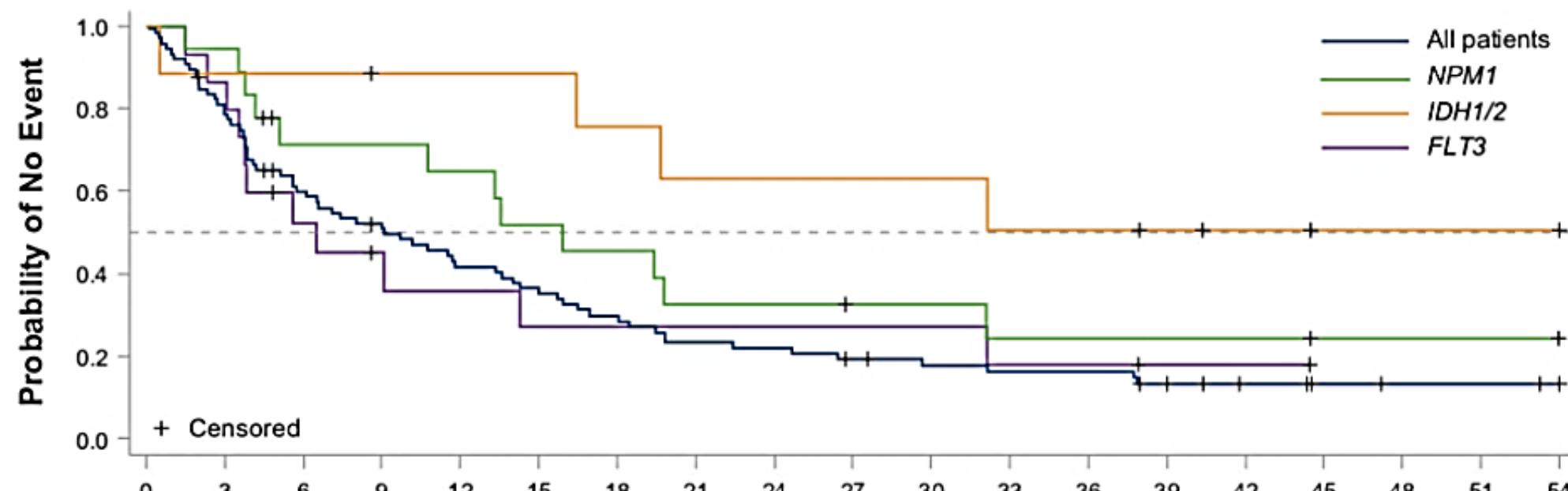
- Median follow-up of 3.5 years
- Median OS for all patients was 9.7 months (95% CI: 5.7, 14.0)
- At 2 years, 22% of the population remained alive

ANALYSIS OF OS IN PATIENTS WHO ACHIEVED CR OR CR/CRI



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ANALYSIS OF OS BY MUTATION STATUS

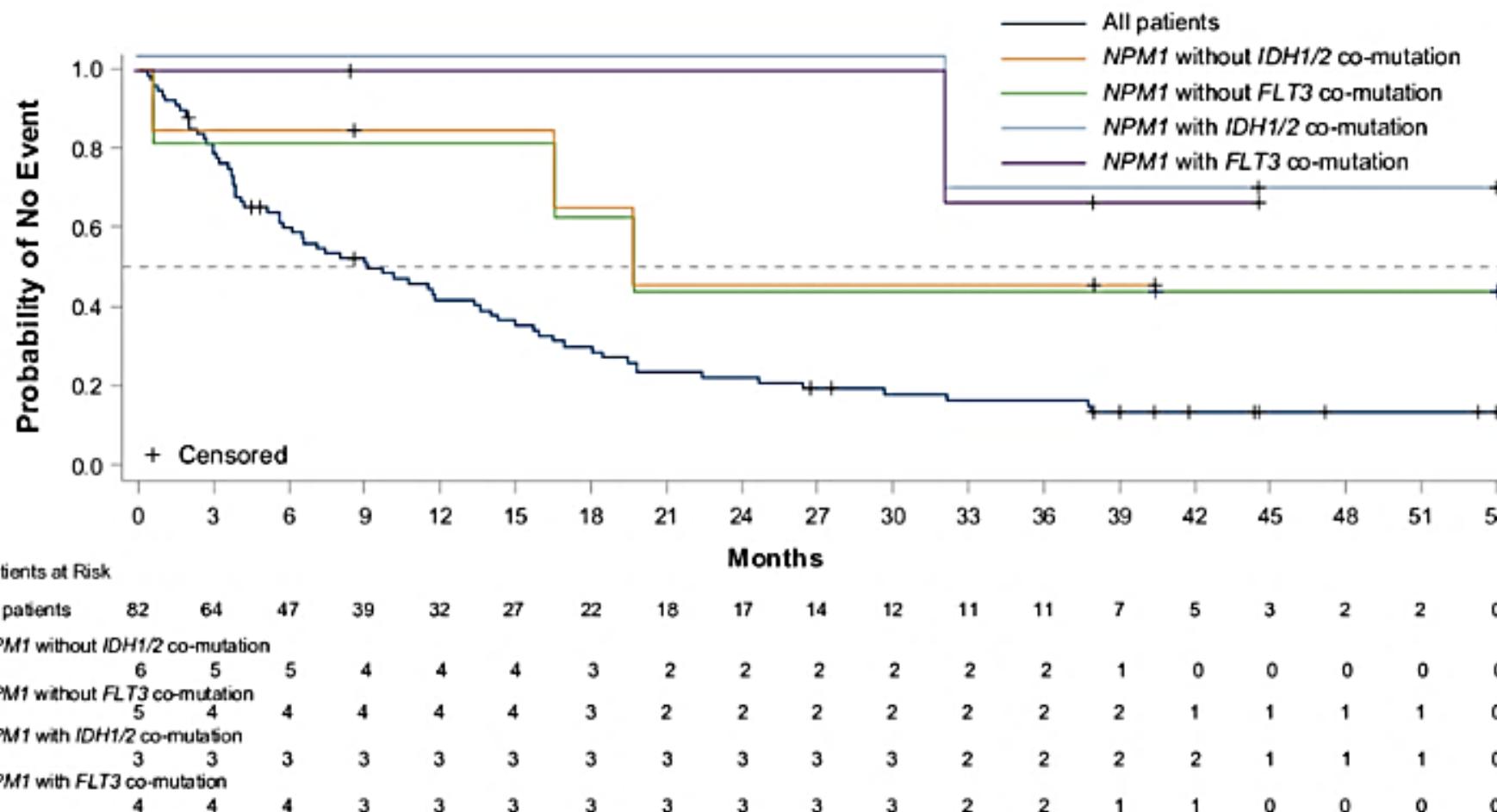


Patients at Risk

	Months																	
All patients	82	64	47	39	32	27	22	18	17	14	12	11	11	7	5	3	2	0
NPM1	9	8	8	7	7	7	6	5	5	5	5	4	4	3	2	1	1	0
IDH1/2	18	17	11	11	10	8	7	5	5	4	4	3	3	2	2	1	1	0
FLT3	15	13	7	5	4	3	3	3	3	3	3	2	2	1	1	0		

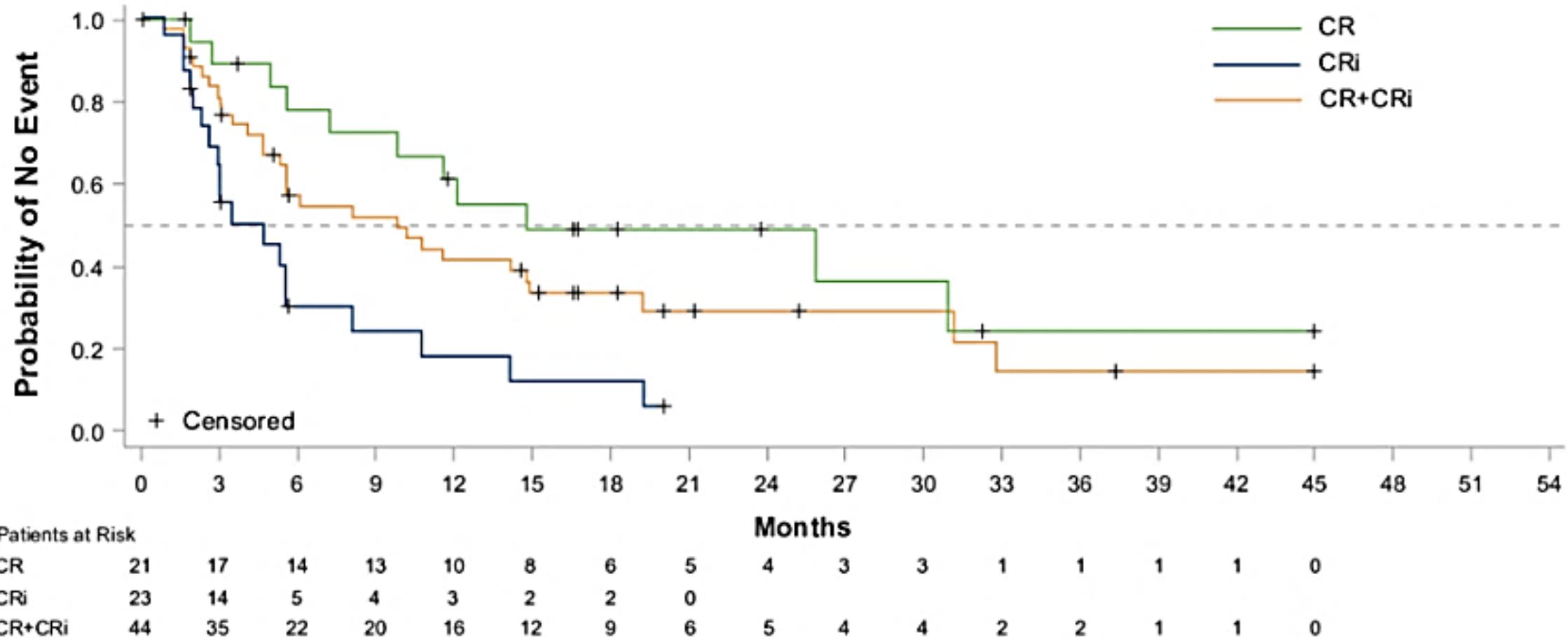
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ANALYSIS OF OS BY MUTATION STATUS (CONT'D)

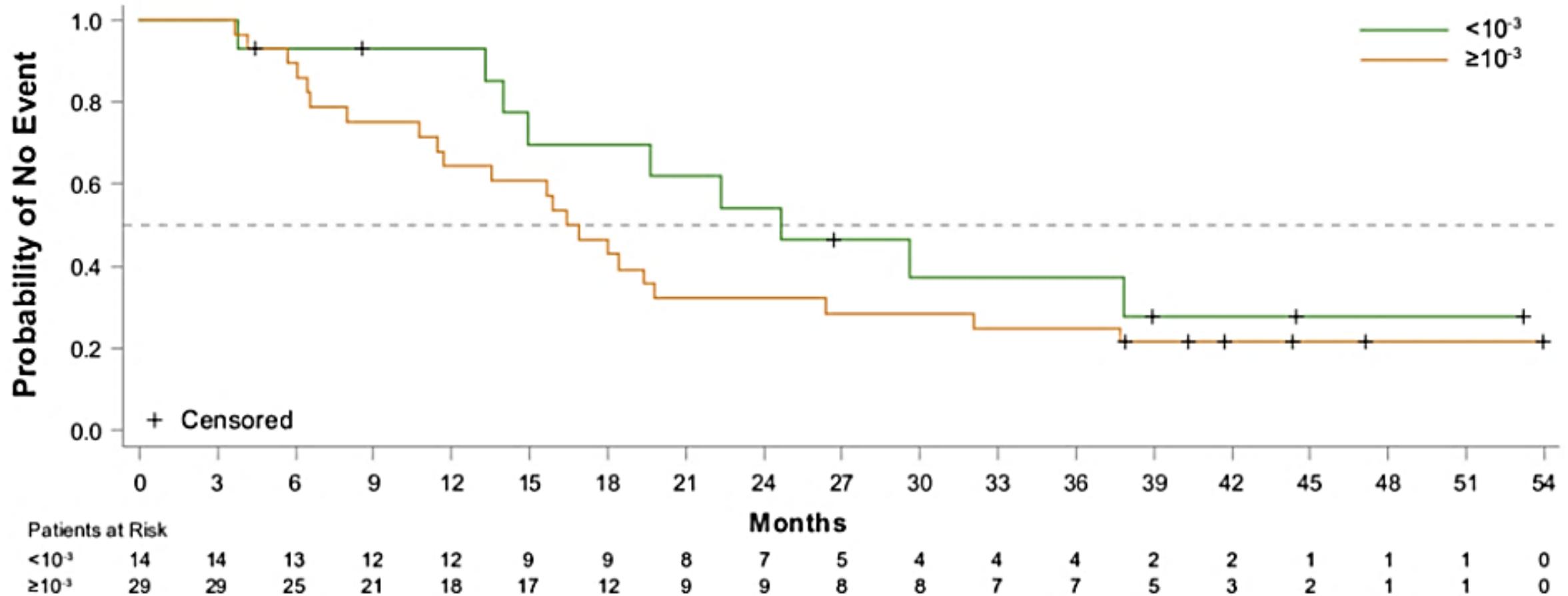


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DURATION OF REMISSION AFTER CR/CRI



OS IN PATIENTS ACHIEVING CR/CRI BY BEST POSTBASELINE MRD VALUE ($<10^{-3}$) VS $\geq 10^{-3}$



CONCLUSIONS

- Venetoclax (600 mg) in combination with LDAC has a tolerable safety profile with durable remission rates (CR/CRI) of 54% and median OS of 10 months
- At a median follow-up of 3.5 years, 22% of patients remained alive after 2 years, with the patients on study longest initiating treatment more than 4 years prior to data cut
- Patients with de novo AML or intermediate-risk cytogenetic features had a 36% and 31% chance, respectively, of remaining alive 2 years after initiating treatment
- Although the data set is small, some molecular subtypes appear to be especially responsive, and investigations into potential mechanisms are ongoing

PHASE IB/II STUDY OF THE IDH-MUTANT INHIBITOR IVOSIDENIB WITH THE BCL2 INHIBITOR VENETOCLAX ± AZACITIDINE IN IDH- 1-MUTATED HEMATOLOGIC MALIGNANCIES

Courtney Di Nardo, et al.

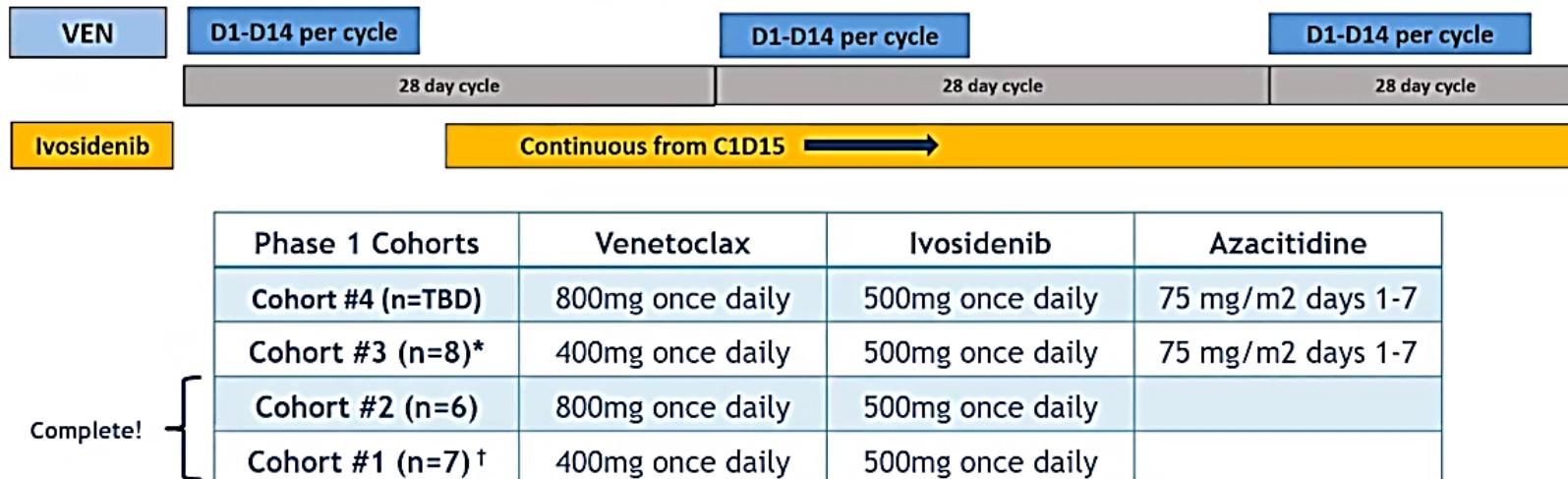
Presented at the 25th (Virtual) Congress of the European Hematology Association,
Abstract S143

BACKGROUND, STUDY DESIGN AND OBJECTIVES

Background

- Mutations in IDH1 result in myeloid differentiation arrest and accumulation of the oncometabolite 2-HG, promoting leukemogenesis
- Combination therapy of the IDH1 inhibitor ivosidenib (IVO) with venetoclax (VEN) and with or without azacitidine (AZA) was investigated in IDH1-mutated AML and related myeloid malignancies

Phase 1b: Dose Escalation



Future Phase 2: Confirm efficacy in 2 cohorts (~20 pts each) of treatment-naïve and R/R IDH1-mutated patients

*additional 6 patients being enrolled due to 1 DLT of TLS
†One enrolled patient was invaluable and was replaced

Key Study Objectives

- Determine safety and tolerability of IVO+VEN±AZA, MTD and RP2D, ORR (CR+CRi+CRh+MLFS+PR), and time to event endpoints
- Evaluation of MRD by flow cytometry

DiNardo C, et al. Oral presentation at the 25th (Virtual) Congress of the European Hematology Association, Abstract S143.

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KEY INCLUSION AND EXCLUSION CRITERIA

Key Inclusion Criteria

- Age ≥ 18
- ECOG ≤ 2
- *IDH1* R132 mutation
- Advanced Myeloid Malignancy
 - MDS (EB-1/EB-2)
 - AML (*de novo*/secondary)
 - R/R AML
- Adequate renal and liver function

Key Exclusion Criteria

- Prior ivosidenib
- Prior venetoclax
- CYP3A4 inhibitors/inducers in preceding 3 days*
- Active GVHD
- Severe GI / metabolic condition

*azoles and strong/moderate CYP3A4 inhibitors were additionally excluded during cycle 1 and 2 for accurate PK/PD assessments

PATIENT DEMOGRAPHICS

Patient Demographics	All Cohorts, N (%)	Cohort #1 IVO+VEN 400 (N=7)	Cohort #2 IVO+VEN 800 (N=6)	Cohort #3 IVO+VEN 400+AZA (N=8)
Median Age, years (range)	67	68 (37-84)	69 (44-79)	64 (57-75)
Sex, Male (N, %)	12 (57)	3 (43)	3 (50)	6 (75)
Disease Category				
High Risk MDS	4 (19)	1	1	2
De Novo Treatment Naive AML	3 (14)	1	1	1
Secondary AML	2 (10)	-	1	1
Treated Secondary AML	3 (14)	-	1	2
Relapsed/Refractory AML	9 (43)	5	2	2
ELN Risk Group				
Favorable	7 (33)	2	3	2
Intermediate	3 (14)	2	1	-
Adverse	11 (52)	3	2	6

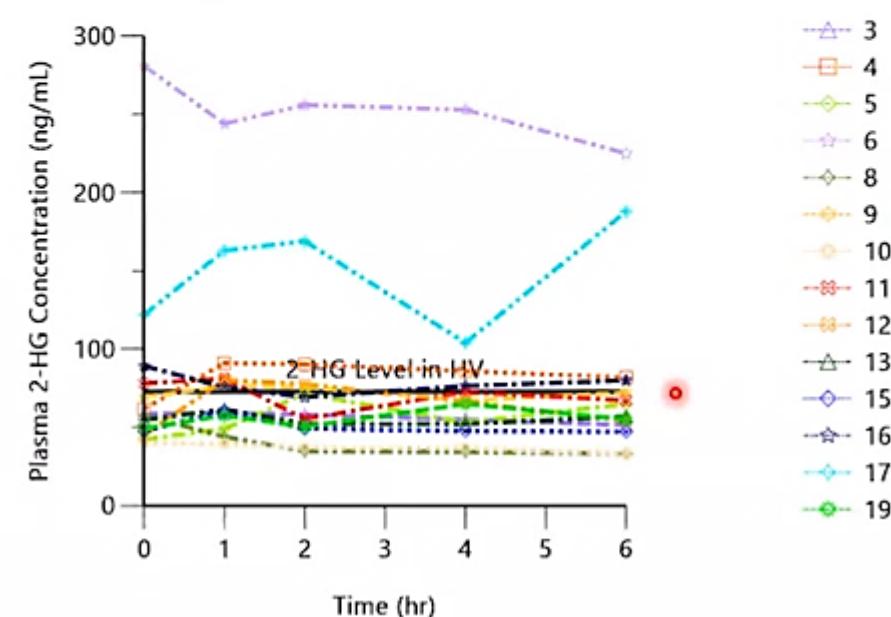
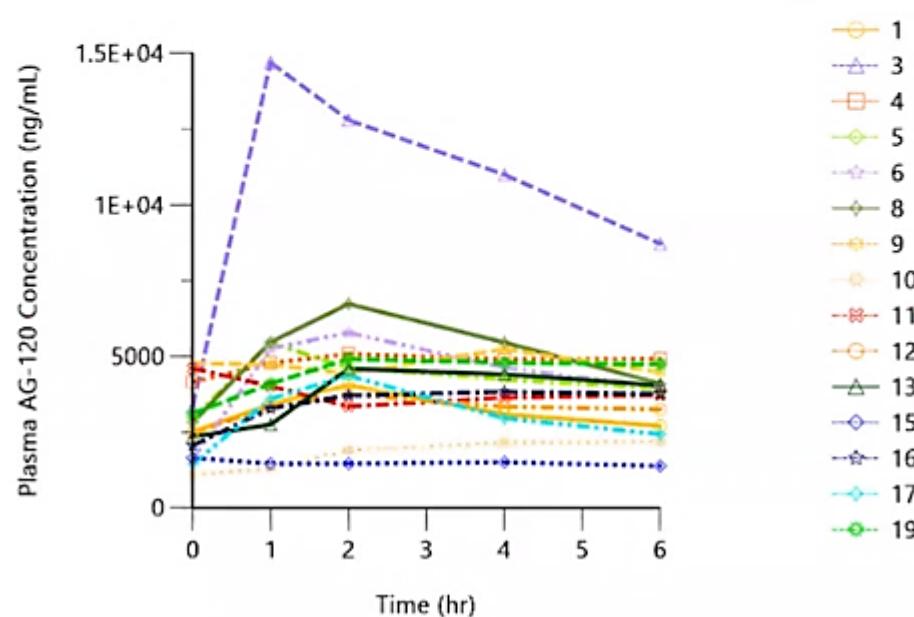
ADVERSE EVENTS

Adverse Event N(%)	Grade 1/2	Grade 3/4
Pneumonia	-	14 (70)
Febrile neutropenia*	-	10 (50)
IDH Differentiation syndrome	3 (15)	1 (5)
Abdominal pain	-	3 (15)
Tumor lysis syndrome	1 (5)	1 (5)
Acute kidney injury	-	2 (10)
Leukocytosis	-	2 (10)
Thrombocytopenia	-	2 (10)
Sepsis	-	2 (10)
Diarrhea	15 (75)	-
Nausea	6 (30)	-
Vomiting	5 (25)	-

- No 30-day or 60-day mortality
- *1 death on study due to febrile neutropenia in setting of persistent disease
- AE's of special interest: IDH differentiation syndrome (N=4), TLS (N=2)
- Dose limiting toxicities: 1 tumor lysis syndrome (occurring in patient with solitary kidney)

IVODSIDENIB PK AND PD RESULTS

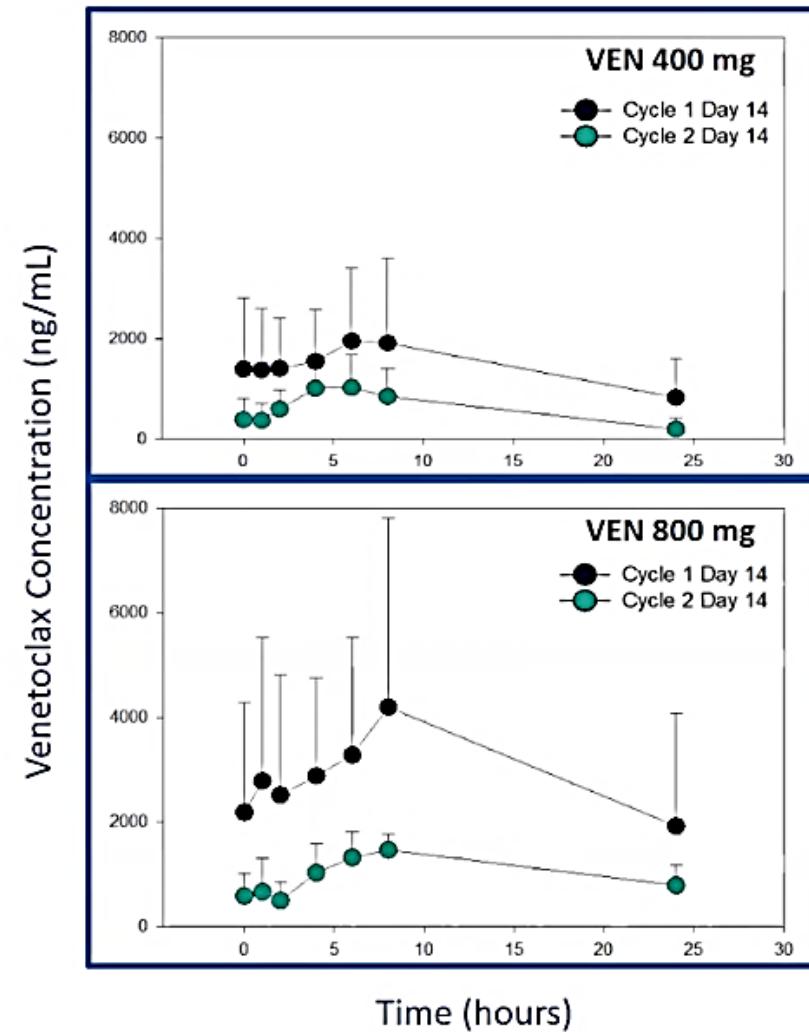
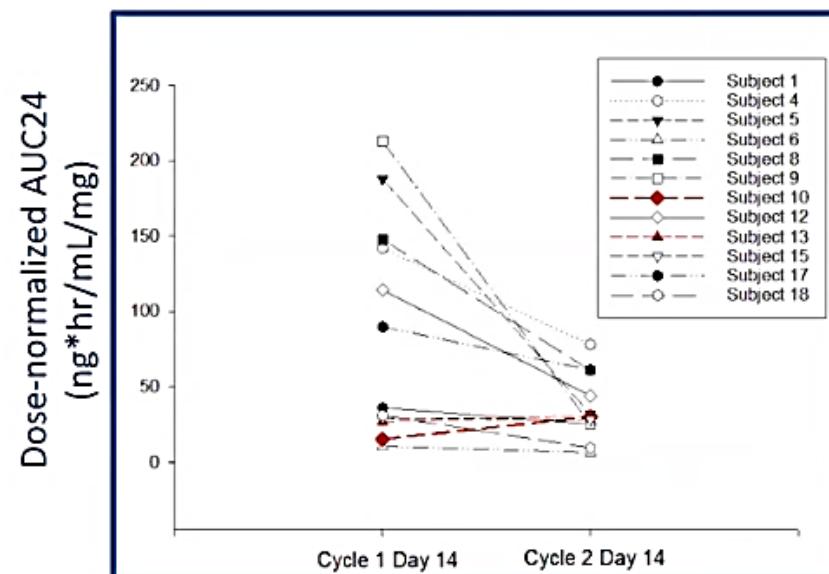
- IVO plasma concentration-time profile similar among subjects and within the variability observed following IVO monotherapy
- 2HG levels suppressed to levels of healthy volunteers (HV) after 28 days of IVO dosing in most subjects



VENETOCLAX PK AND PD RESULTS

VEN+IVO oral doublet combination

- 53% decrease in mean VEN steady state AUC
- 47% decrease in C_{max}



RESPONSE RATES

Overall Response N (%)	All Cohorts N (%)	Cohort #1 IVO+VEN 400 (N=6)‡	Cohort #2 IVO+VEN 800 (N=6)	Cohort #3 IVO+VEN+AZA (N=8)
ORR, N(%)	18 (90)	4 (67)	6 (100)	8 (100)
Composite CR*	16 (80)	4 (67)	6 (100)	6 (75)
CR	8 (40)	3 (50)	3 (50)	2 (13)
CR _h	2 (10)	-	2 (33)	-
CR _i	6 (30)	1 (17)	1 (17)	4 (38)
MLFS	1 (5)	-	-	1 (25)
HI	1 (5)	-	-	1 (13)
NR	2 (10)	2 (33)	-	-
Flow MRD Negative [†]	8 (50)	2 (50)	2 (33)	4 (67)

* CR_h and CR_i represented as mutually exclusive

† Among patients achieving a composite CR

‡ One patient in cohort 1 was inevaluable and replaced

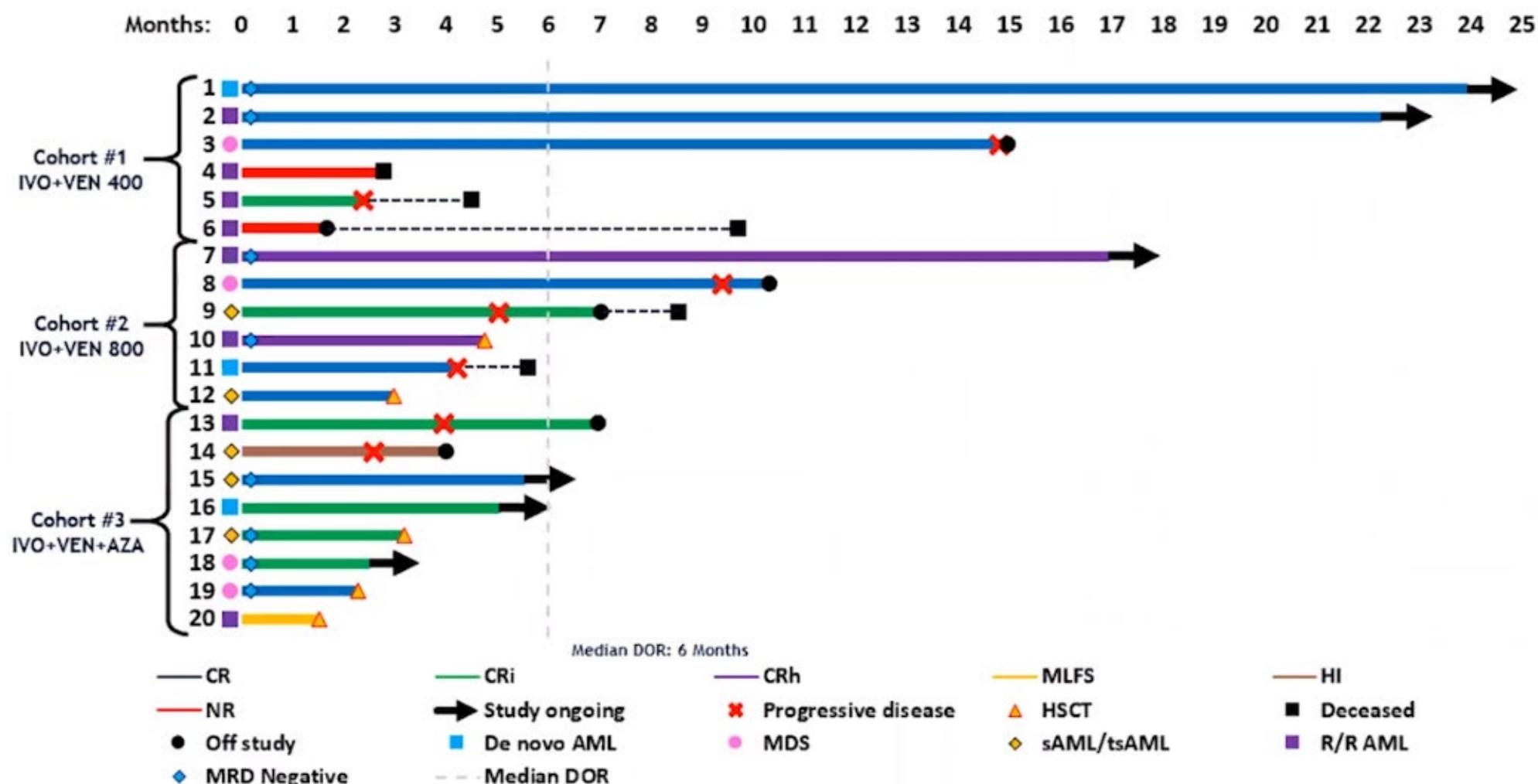
RESPONSE BY DISEASE SUBGROUP

Response, N (%)	De Novo TN AML (N=3)	sAML/ts-AML (N=5)	R/R AML (N=8)	MDS (N=4)
Overall Response Rate N(%)	3 (100)	5 (100)	6 (75)	4 (100)
Composite CR (CRc)*	3 (100)	4 (80)	5 (63)	4 (100)
CR	2 (66)	2 (40)	1 (13)	3 (75)
CR _h	-	-	2 (25)	
CR _i	1 (33)	2 (40)	2 (25)	1 (25)
MLFS	-	-	1 (13)	-
HI	-	1 (20)	-	-
NR	-	-	2 (25)	-
Flow MRD negative[†]	1 (33)	2 (50)	3 (60)	2 (50)

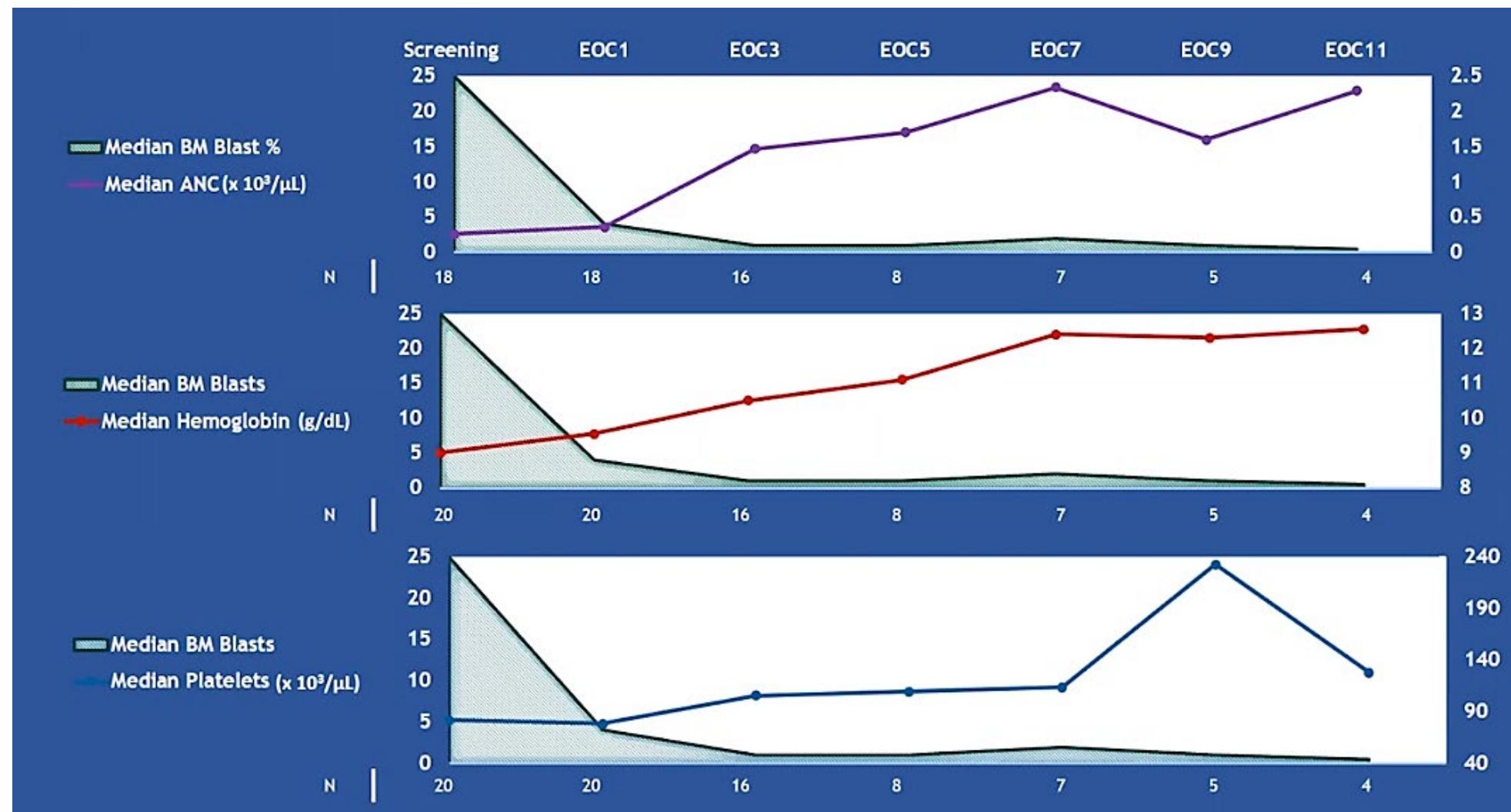
* CR_h and CR_i mutually exclusive

† Among patients achieving a Composite CR

PATIENT STATUS



HEMATOLOGIC RESPONSE

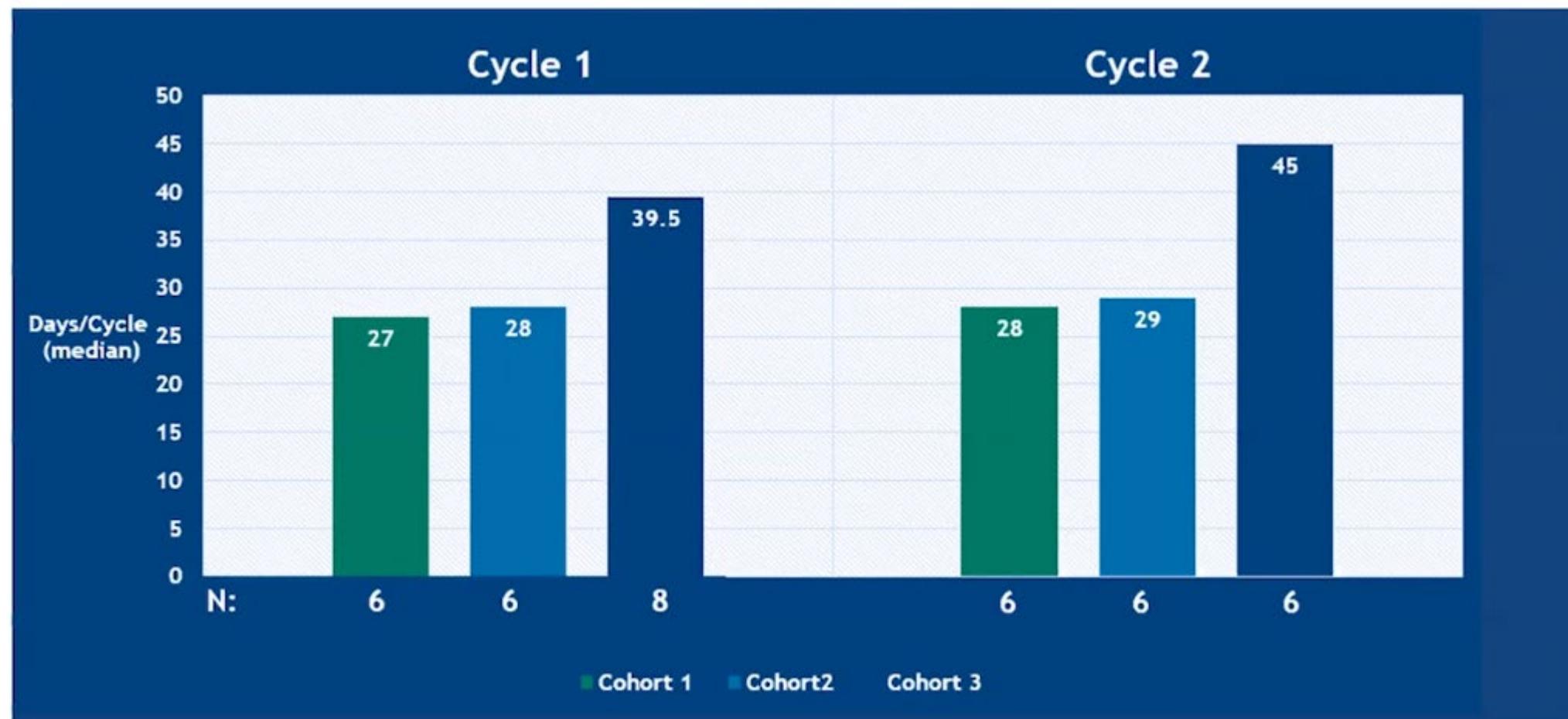


DiNardo C, et al. Oral presentation at the 25th (Virtual) Congress of the European Hematology Association, Abstract S143.

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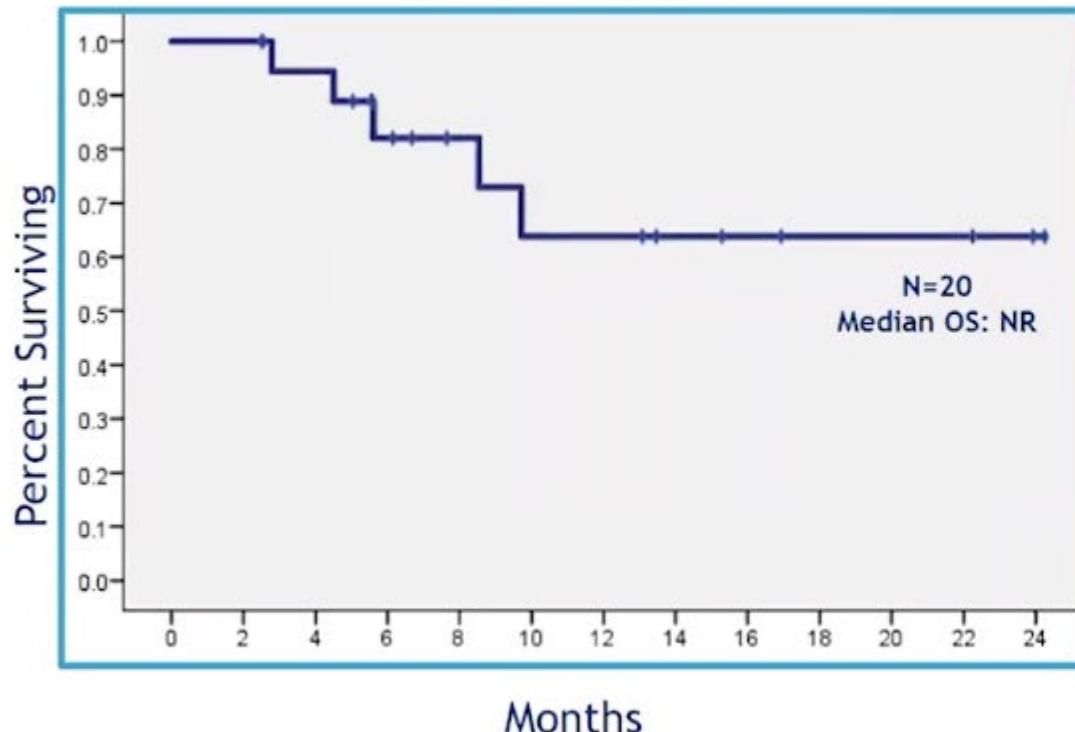
MEDIAN CYCLE LENGTHS



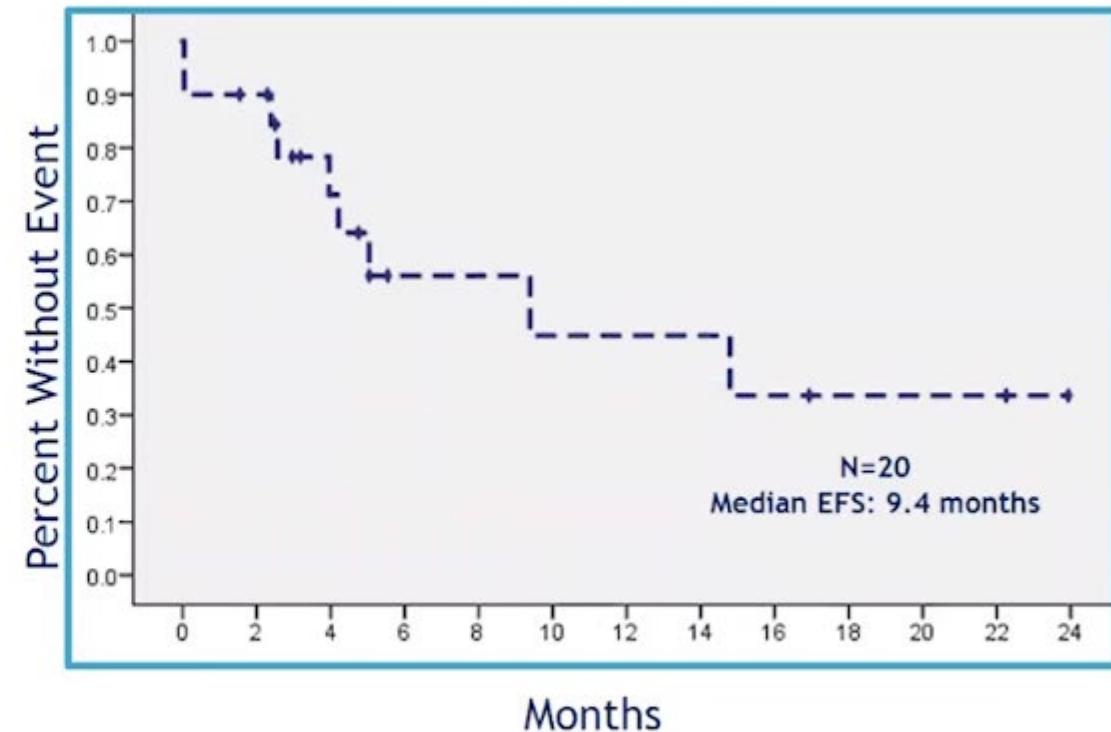
* 7 of 8 patients in cohort 3 had received prior therapy; including 2 with relapsed MDS, and 3 with secondary AML from MDS

OVERALL SURVIVAL AND EVENT FREE SURVIVAL

Overall Survival



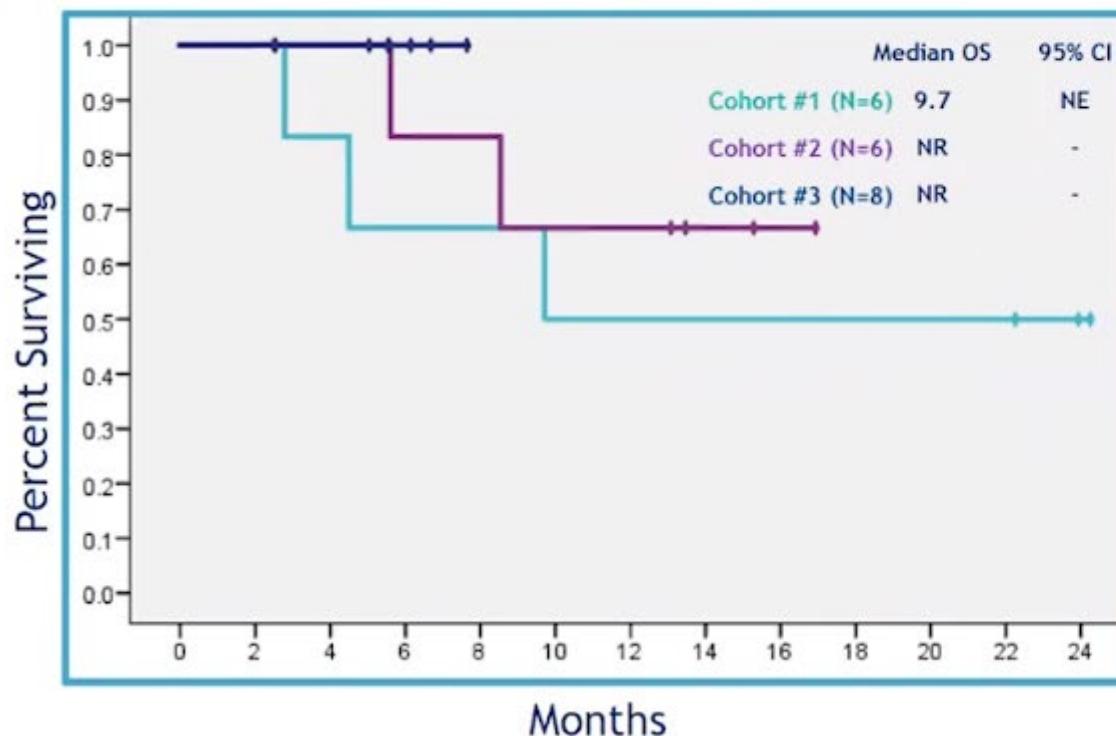
Event Free Survival



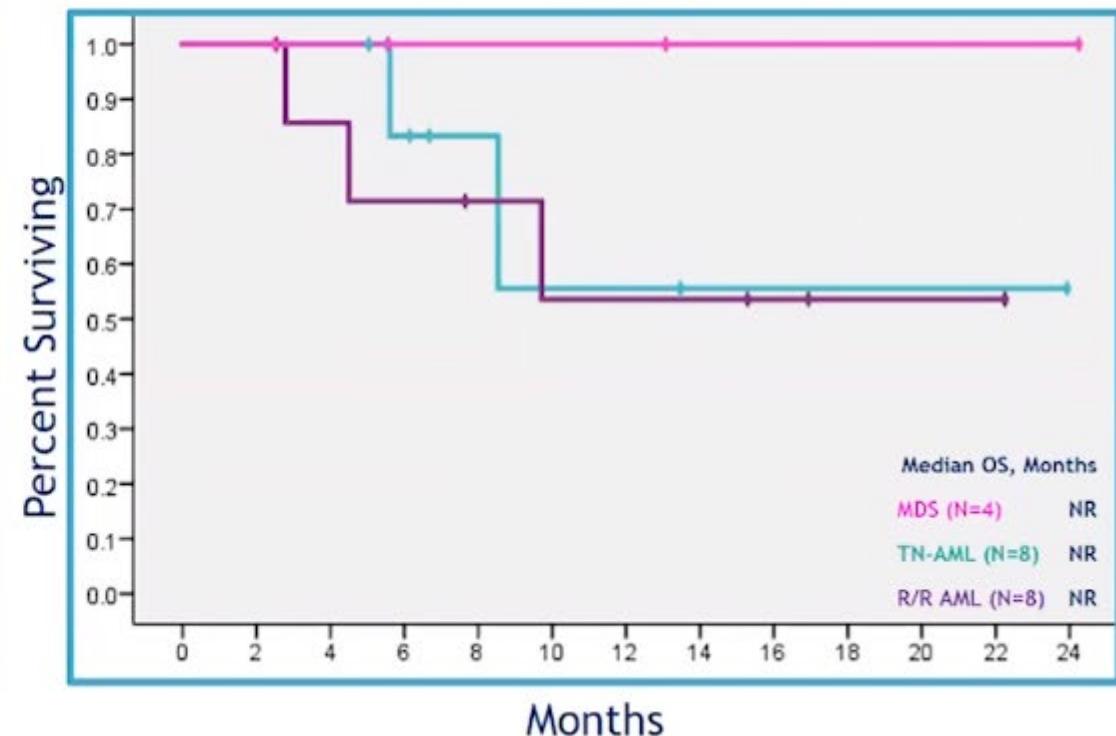
Median Follow up: 7 months

SURVIVAL OUTCOMES BY KEY SUBGROUPS

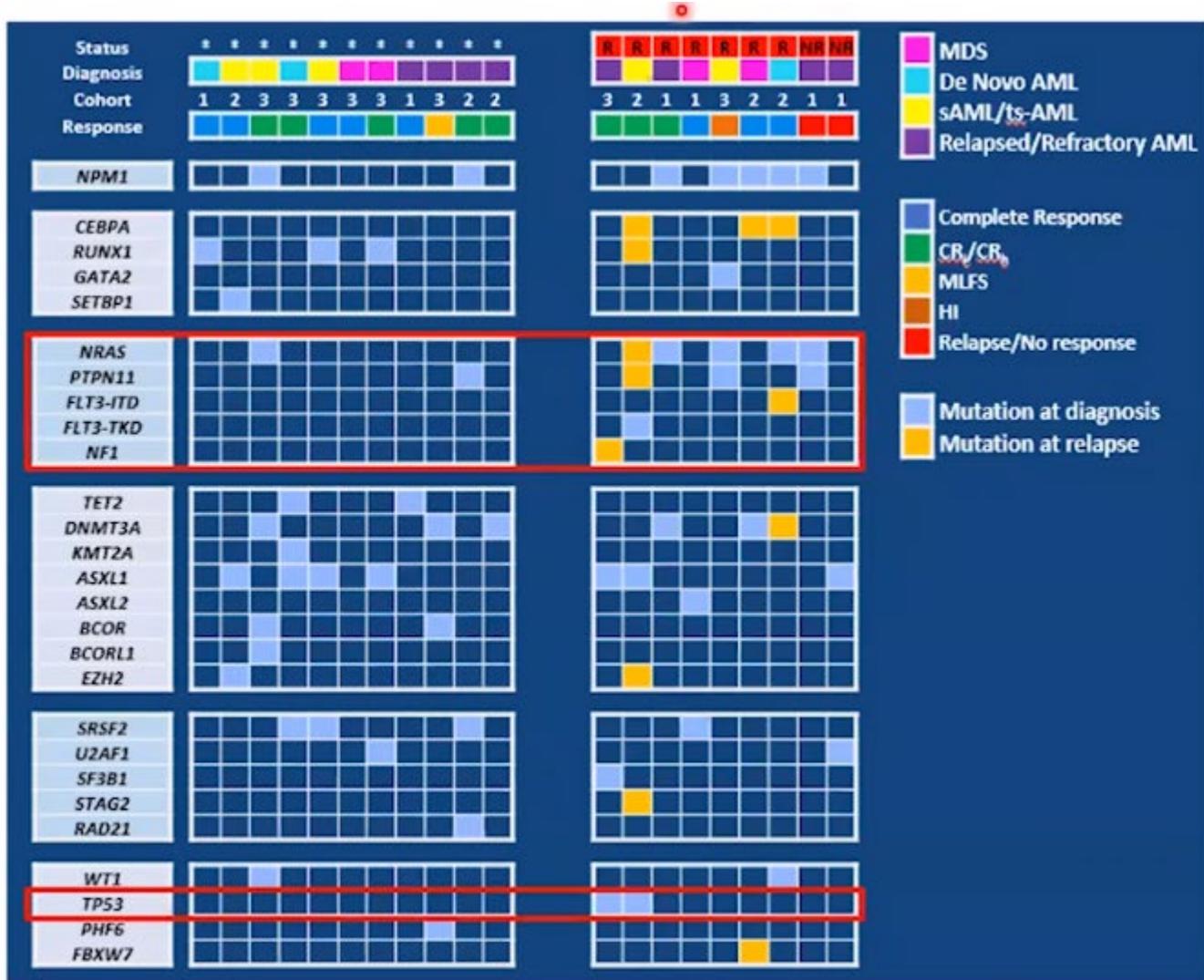
Overall Survival by Study Cohort



Overall Survival by Disease



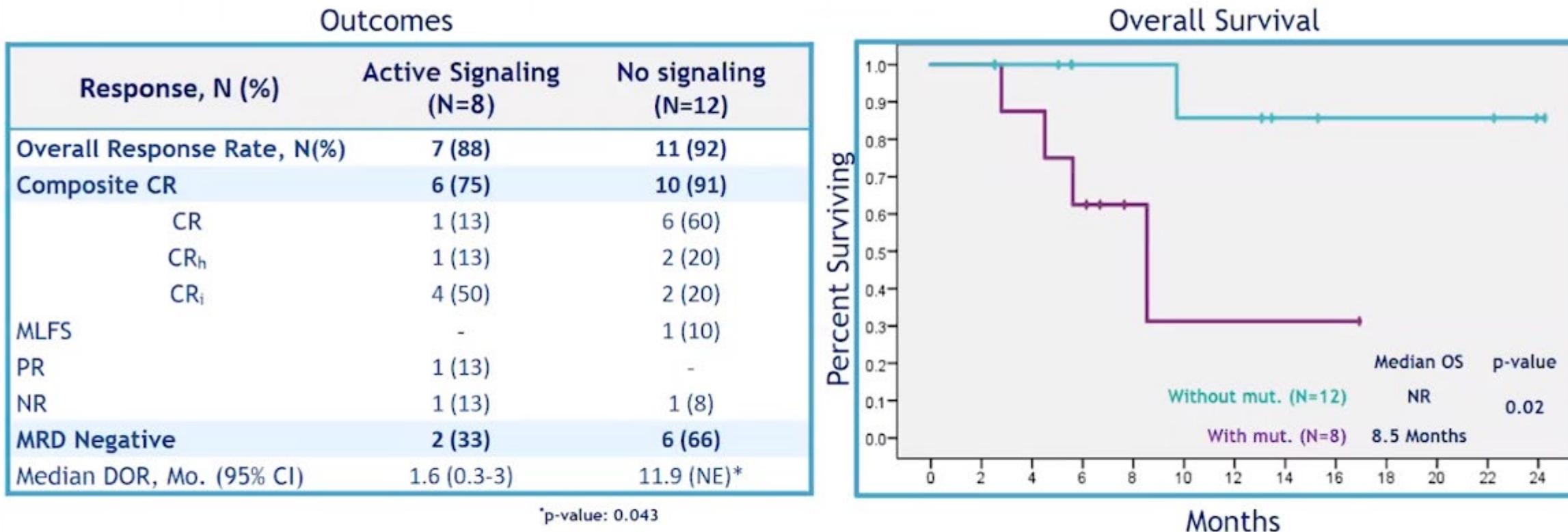
MOLECULAR PROFILING



Molecular Profiling

- Diverse molecular landscape seen across patients
 - Active signaling mutations in 66% of patients without response or with relapse
 - Molecular subgroups as defined by TCGA AML (NEJM, 2013)

ACTIVE SIGNALING MUTATIONS ASSOCIATED WITH TREATMENT RESISTANCE

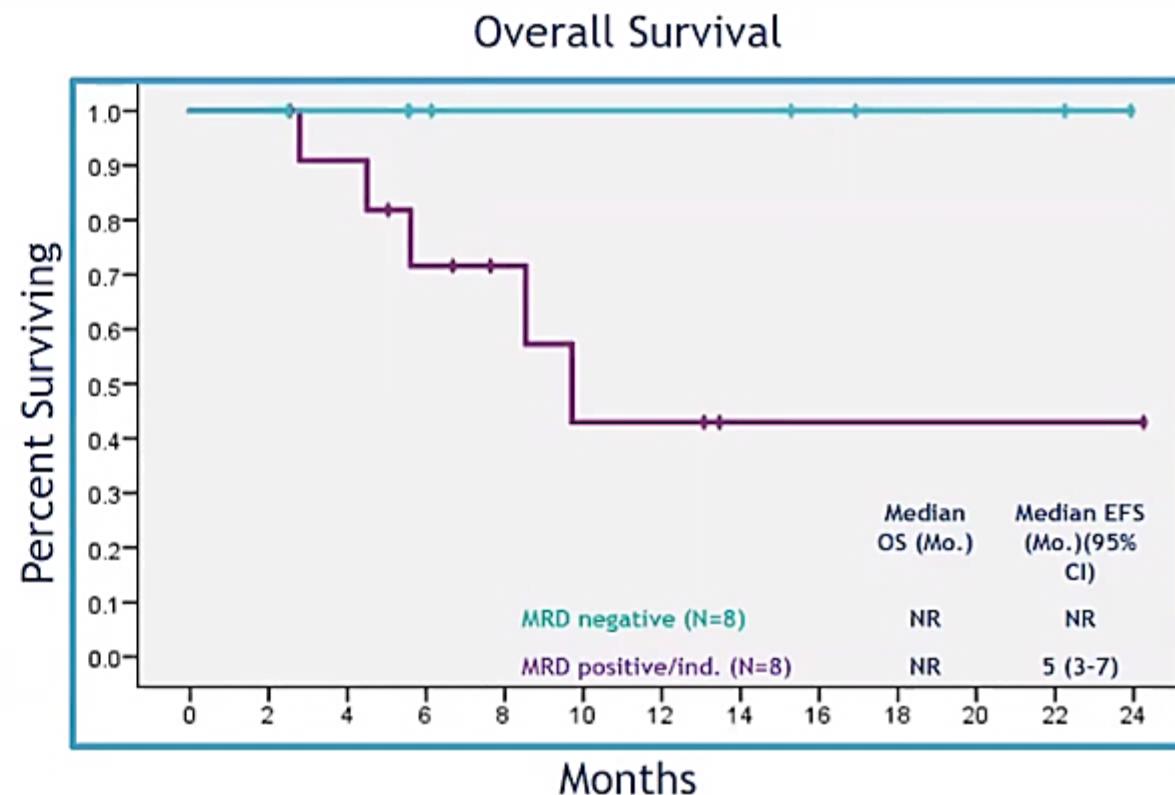


Active Signaling mutations: *NRAS*, *KRAS*, *FLT3-ITD/TKD*, *PTPN11*, *NF1*

UNDETECTABLE FLOW MRD AT CR ASSOCIATED WITH SUPERIOR SURVIVAL

Demographics	All CR	MRD neg. (N=8)	MRD Pos/Indeter (N=8)
Cohort #1, N (%)	4	2 (50)	2 (50)
Cohort #2, N (%)	6	2 (33)	4 (67)
Cohort #3, N (%)	6	4 (67)	2 (33)
<i>Disease subgroup</i>			
MDS	4	2 (50)	2 (50)
De Novo AML	3	1 (33)	2 (67)
sAML/ts-AML	4	2 (50)	2 (50)
R/R (AML/MDS)	5	3 (60)	2 (40)
Progressive disease	6	-	6 (100)
Median DOR, Mo. (95% CI)	5.7 (1-23)	NR*	3.0 (1.5-4.6)

*Median follow up: 2.5 Months



CONCLUSIONS

- IVO+VEN ± AZA is an effective and molecularly targeted regimen for advanced *IDH1* mutated myeloid malignancies
- IVO+VEN ± AZA is well tolerated
 - Common expected grade 3/4 adverse events: pneumonia, febrile neutropenia
 - Longer treatment cycles required with the AZA + IVO + VEN triplet
- IVO+VEN ± AZA therapy is effective:
 - Composite complete response in 80% of patients
 - Undetectable MRD by flow in 50% of pts with CR, leading to durable remissions
- **Recommended phase II dose and efficacy data forthcoming**

PHASE 1B STUDY OF CPX-351 LOWER-INTENSITY THERAPY (LIT) PLUS VENETOCLAX AS FIRST-LINE TREATMENT FOR PATIENTS WITH AML WHO ARE UNFIT FOR INTENSIVE CHEMOTHERAPY

Tara L Lin, et al.

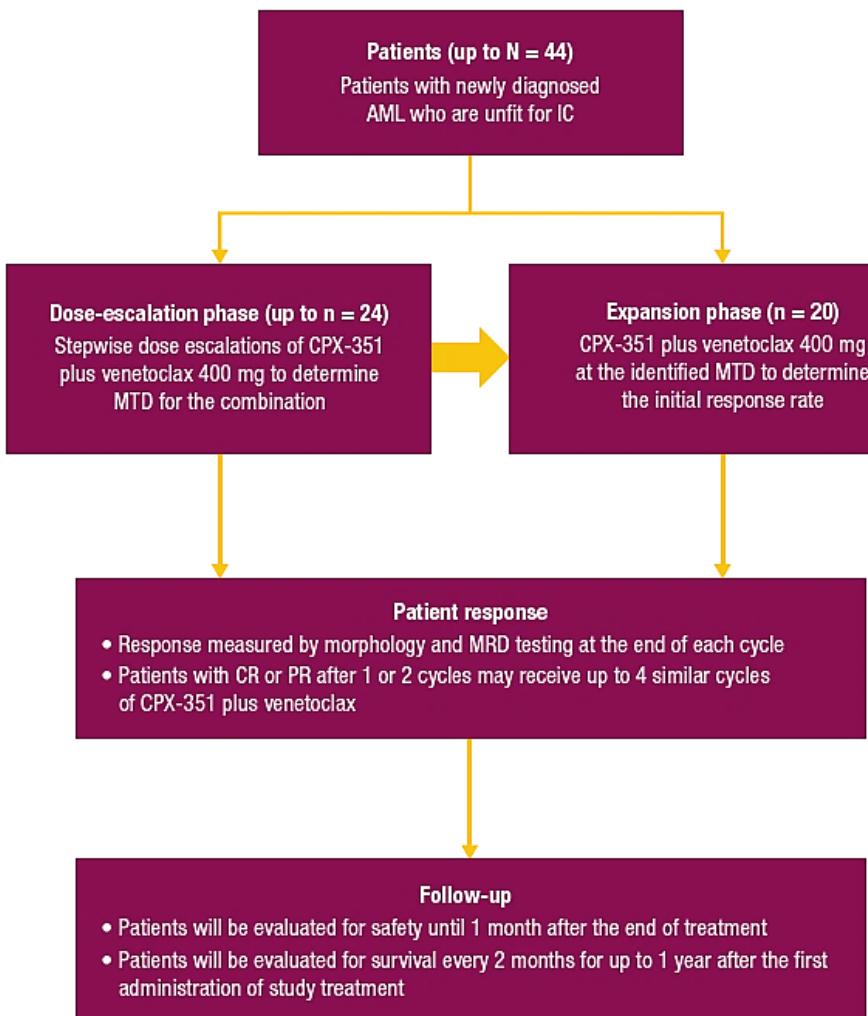
Presented at the 2020 ASCO Virtual Scientific Program, Abstract TPS7567

BACKGROUND

Background

- CPX-351 (Vyxeos; daunorubicin and cytarabine liposome for injection) is approved by the FDA and EMA for the treatment of adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes.
- It may not be appropriate to administer CPX-351 at the label dosage in patients unfit for IC
- Venetoclax (VEN), a BCL-2 inhibitor, has clinical efficacy in combination with low-dose cytarabine in AML patient unfit for IC, and preclinical data suggest a rationale for combining CPX-351 with VEN
- This study evaluates CPX-351 lower-intensity therapy (LIT) in combination with VEN in AML patients unfit for IC

STUDY DESIGN AND DOSE ESCALATION



Dose-escalation Levels^a

Dose level	CPX-351 dosing (per 28-day cycle ^{b,c})	Venetoclax dosing (per 28-day cycle ^b)
1	20 units/m ² on Days 1 and 3	400 mg/day on Days 2 to 21
2	40 units/m ² on Days 1 and 3	400 mg/day on Days 2 to 21
3	60 units/m ² on Days 1 and 3	400 mg/day on Days 2 to 21
4	75 units/m ² on Days 1 and 3	400 mg/day on Days 2 to 21

^aEach dose escalation will be confirmed by a safety assessment committee.

^bPatients may receive up to 4 cycles of therapy.

^c1 unit = 1 mg cytarabine + 0.44 mg daunorubicin.

- 3+3 dose-escalation scheme (up to 24 patients unfit for IC)
- Dose-limiting toxicity (DLT) observation period of 28 to 49 days (Cycle 1)
- Patients who achieve hematologic count recovery may proceed to Cycle 2 once they complete the minimum DLT observation period

ELIGIBILITY CRITERIA

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none">Histologically confirmed (per WHO criteria) newly diagnosed AML and unfit for IC<ul style="list-style-type: none">Age ≥ 75 years ORAge 18 to 74 years and ≥ 1 of the following criteria:<ul style="list-style-type: none">ECOG PS 2 to 3History of CHF requiring treatment or LVEF $\leq 50\%$DLCO $\leq 65\%$ or FEV1 $\leq 65\%$CrCl ≥ 30 to <45 mL/minModerate hepatic impairment with total bilirubin >1.5 to $\leq 3.0 \times$ ULNOther comorbidity incompatible with conventional ICECOG PS 0 to 2 if aged ≥ 75 yearsAdequate renal function: CrCl ≥ 30 mL/minAdequate liver function (unless considered to be due to leukemic organ involvement): AST $\leq 3.0 \times$ ULN; ALT $\leq 3.0 \times$ ULN; bilirubin $\leq 1.5 \times$ ULN (patients aged <75 years may have bilirubin $\leq 3.0 \times$ ULN)WBC count $\leq 25 \times 10^9/L$	<ul style="list-style-type: none">ECOG PS >3 regardless of agePrior AML treatment, with the exception of hydroxyureaFavorable-risk cytogenetics per NCCN guidelines: t(8;21), inv(16), t(16;16), or t(15;17) karyotype abnormalitiesAntecedent MPN including myelofibrosis, essential thrombocythosis, polycythemia vera, or CML with or without <i>BCR-ABL1</i> translocation and AML with <i>BCR-ABL1</i> translocationAcute promyelocytic leukemiaCNS involvementHIV infectionHepatitis B virus or hepatitis C virus infection

ENDPOINTS AND STUDY UPDATE

Primary endpoints

- MTD as determined by the specified dose escalation and MTD algorithm
- Safety and tolerability based on the incidence of AEs and DLTs

Secondary endpoints

- Proportion of patients who achieved CR, CRi, PR, and CRc (CR+CRi) by completion of treatment (up to 4 cycles of therapy)
- Proportion of patients who achieved ORR, defined as best response (CR+CRi+PR) by completion of treatment (up to 4 cycles of therapy)
- Proportion of patients who achieved CR or CRi with MRD status (negative/positive) by completion of treatment (up to 4 cycles of therapy)
- Pharmacokinetics

Exploratory endpoints

- Duration of remission
- OS 1 year after first administration of treatment
- EFS 1 year after first administration of treatment

Study Update

- This study is ongoing and actively enrolling patients at multiple sites in the United States