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VIRTUAL EDITION

Abstract S143: Phase Ib/II study of the IDH1-mutant inhibitor ivosidenib, with the BCL2-inhibitor venetoclax +/- azacitidine in IDH1-mutated myeloid malignancies

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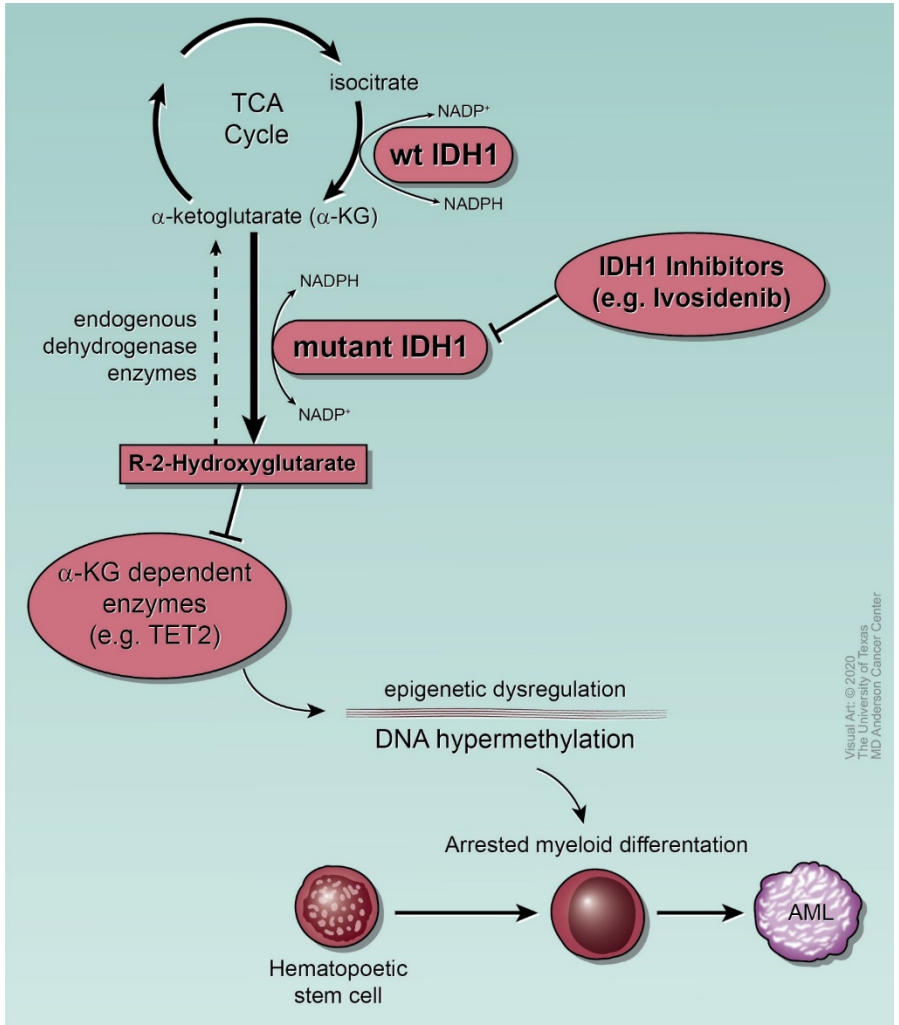
Disclosure Slide

Research Support (to institution):

- Abbvie, Agios, Calithera, Celgene, Daiichi-Sankyo

Consultant/Advisory Board:

- Abbvie, Agios, Celgene, Daiichi-Sankyo, Jazz, ImmuneOnc, Novartis, Notable Labs



IDH1 Mutations in AML

- Occur in 6-14% of AML
- Enriched older patients, often with intermediate cyto
  - ~10% of AML from MDS; ~20% of AML from MPNs
- Increased dependency on BCL-2 and lower apoptotic threshold via cytochrome C oxidase inhibition
- Ivosidenib monotherapy:
  - Treatment Naïve (TN) AML **CR/CR$_h$: 42%**
  - Relapsed/Refractory (R/R) AML **CR/CR$_h$: 30%**
- Azacitidine + ivosidenib for TN AML **CR/CR$_h$: 69%**
- Azacitidine + venetoclax for TN IDH1/2 AML **CR/CR$_h$: 71%**

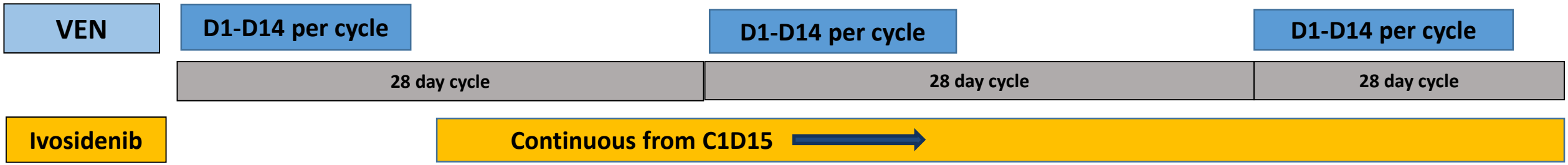
Im AP, Leukemia 2014; Molenaar et al, Leukemia 2015; DiNardo CD et al, NEJM 2018; Roboz G et al, Blood 2020; DiNardo CD SOHO 2019; DiNardo CD Blood 2019

Key Study Objectives

- Determine safety and tolerability of IVO+VEN ± AZA
- Determine MTD and RP2D
- Determine overall response rate (ORR): CR + CR_i + CR_h+ MLFS + PR
- Determine time to event endpoints
- Evaluation of MRD by flow cytometry

Study Design

Phase 1b: Dose Escalation



Phase 1 Cohorts	Venetoclax	Ivosidenib	Azacitidine
Cohort #4 (n=TBD)	800mg once daily	500mg once daily	75 mg/m2 days 1-7
Cohort #3 (n=8)*	400mg once daily	500mg once daily	75 mg/m2 days 1-7
Cohort #2 (n=6)	800mg once daily	500mg once daily	
Cohort #1 (n=7) †	400mg once daily	500mg once daily	

Complete!

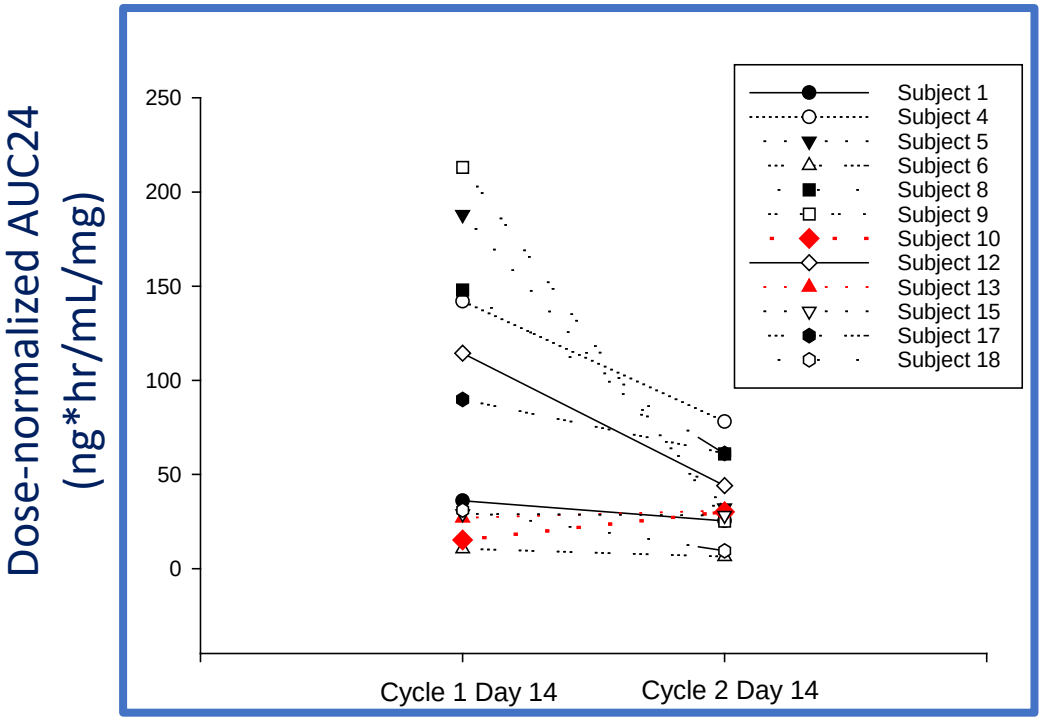
Future Phase 2: Confirm efficacy in 2 cohorts (n=20 each) of treatment-naïve and R/R IDH1-mutated patients

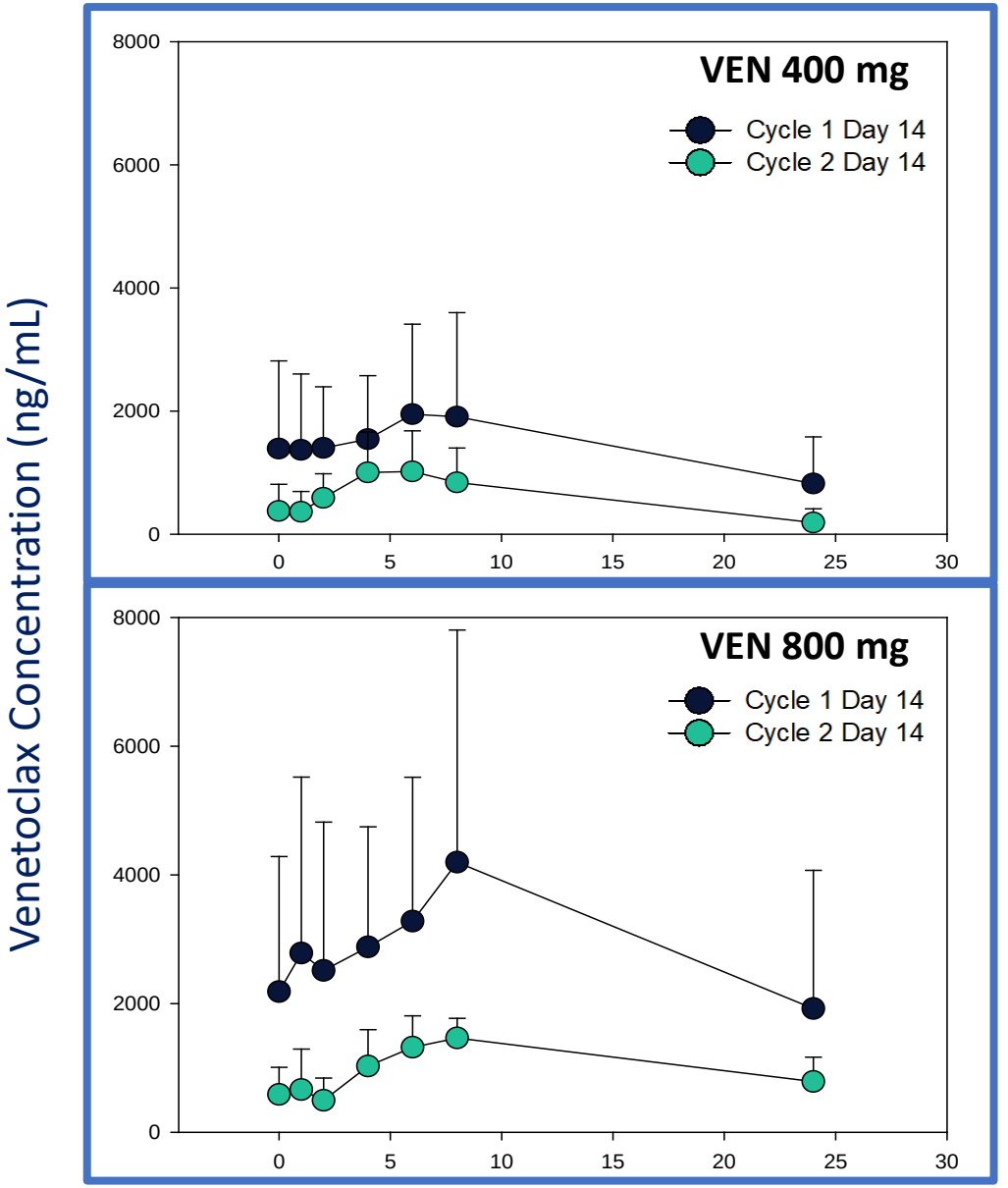
*additional 6 patients being enrolled due to 1 DLT of TLS
† One enrolled patient was invaluable and was replaced

Venetoclax PK and PD Results

VEN+IVO oral doublet combination

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





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	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				
MDS	4 (19)	1	1	2
De Novo 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 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)

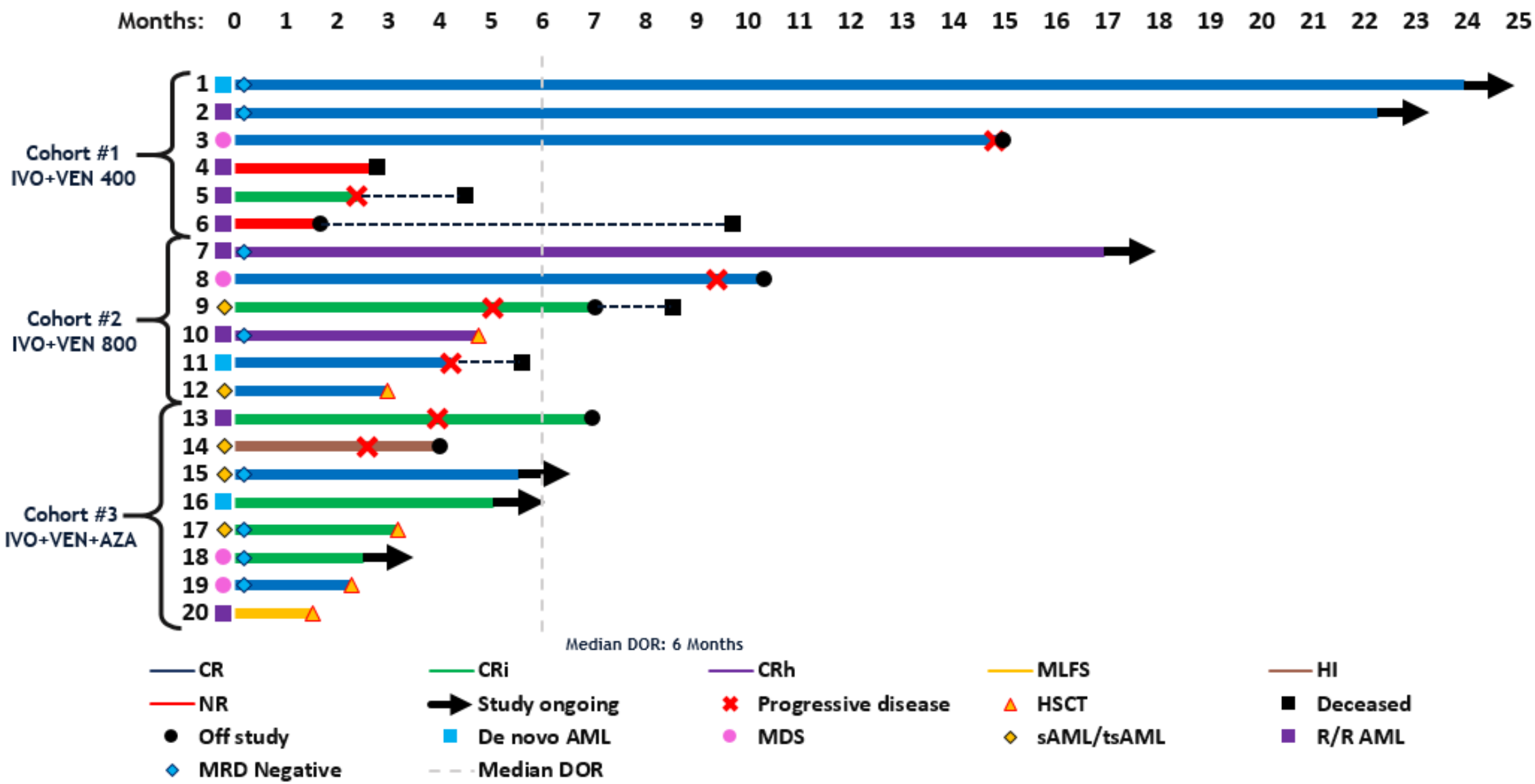
Overall Response N (%)	All Cohorts N (%)	Cohort #1 IVO+VEN 400 (N=6)‡	Cohort #2 IVO+VEN 800 (N=6)	Cohort #3 IVO+VEN+AZA (N=8)
ORR, N(%)	18 (90)	4 (67)	6 (100)	8 (100)
Composite CR*	**16 (80)**	**4 (67)**	**6 (100)**	**6 (75)**
CR	8 (40)	3 (50)	3 (50)	2 (25)
CR_h	2 (10)	-	2 (33)	-
CR_i	6 (30)	1 (17)	1 (17)	4 (50)
MLFS	1 (5)	-	-	1 (13)
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

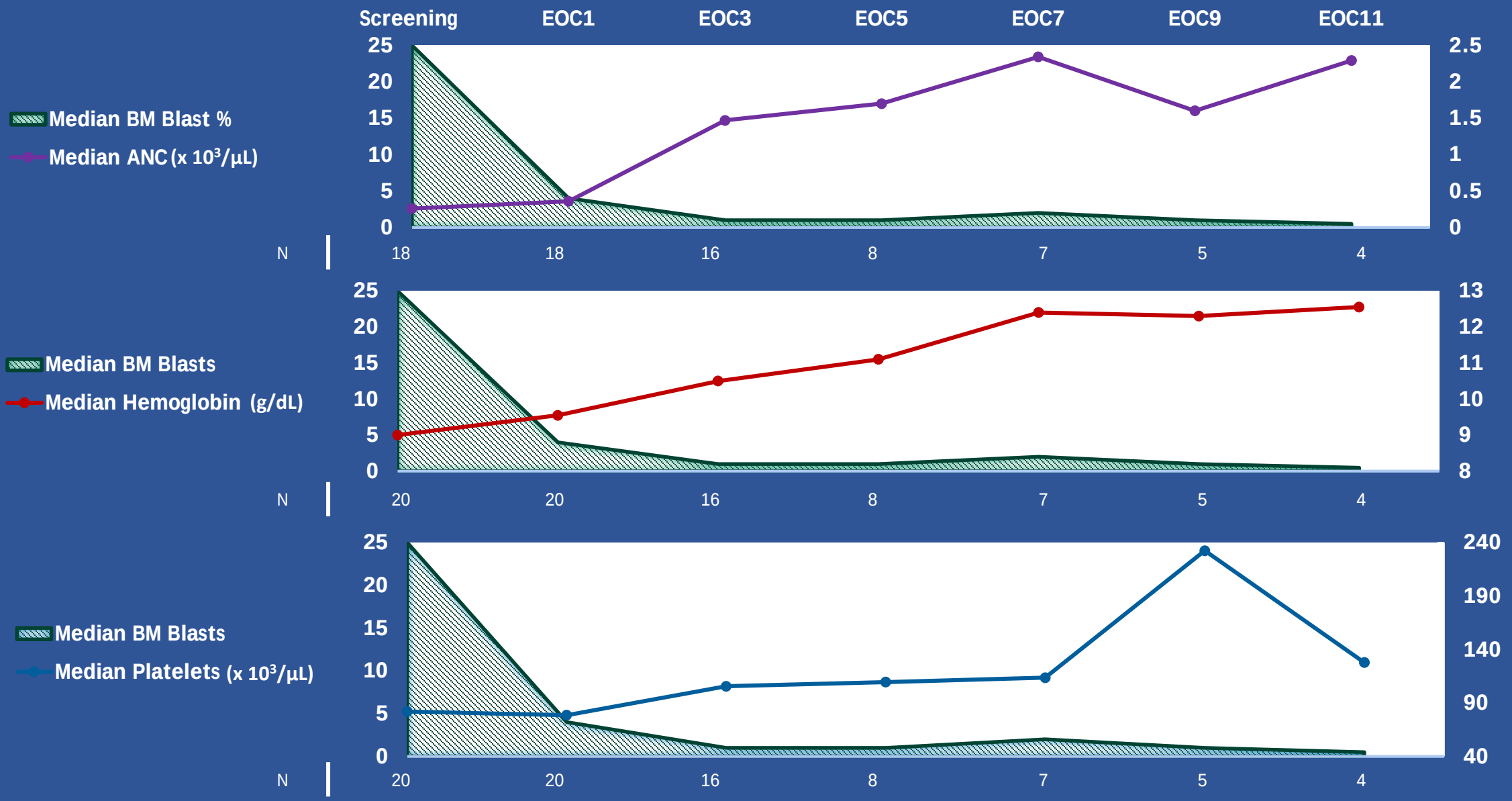
Response by Disease Subgroup

Response, N (%)	De Novo 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)
CRh	-	-	2 (25)	
CRi	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)**

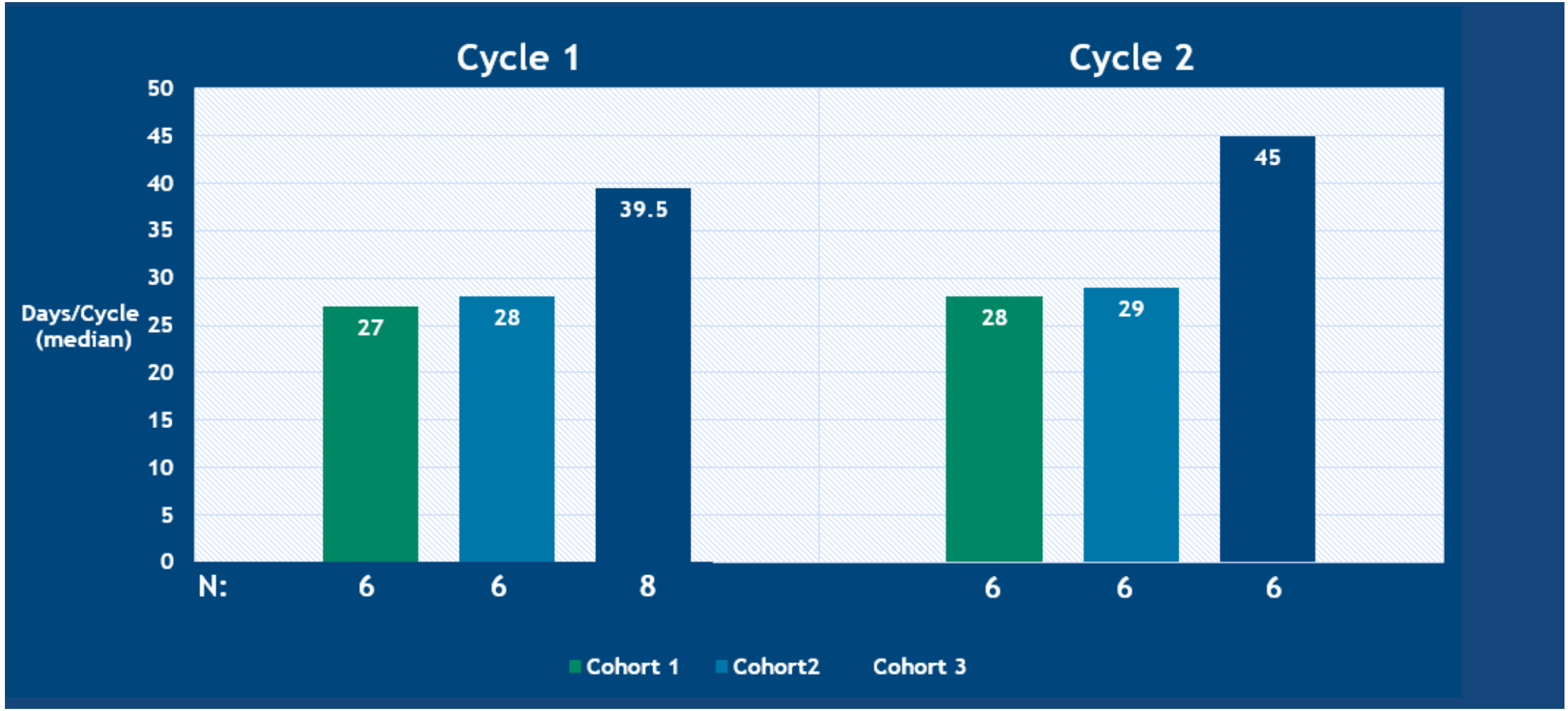
* CR_h and CR_i mutually exclusive
† Among patients achieving a Composite CR


Months: 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
Cohort #1
IVO+VEN 400
Cohort #2
IVO+VEN 800
Cohort #3
IVO+VEN+AZA
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
Median DOR: 6 Months
CR
CRi
CRh
MLFS
HI
NR
Study ongoing
Progressive disease
HSCT
Deceased
Off study
De novo AML
MDS
sAML/tsAML
R/R AML
MRD Negative
Median DOR

Hematologic Response

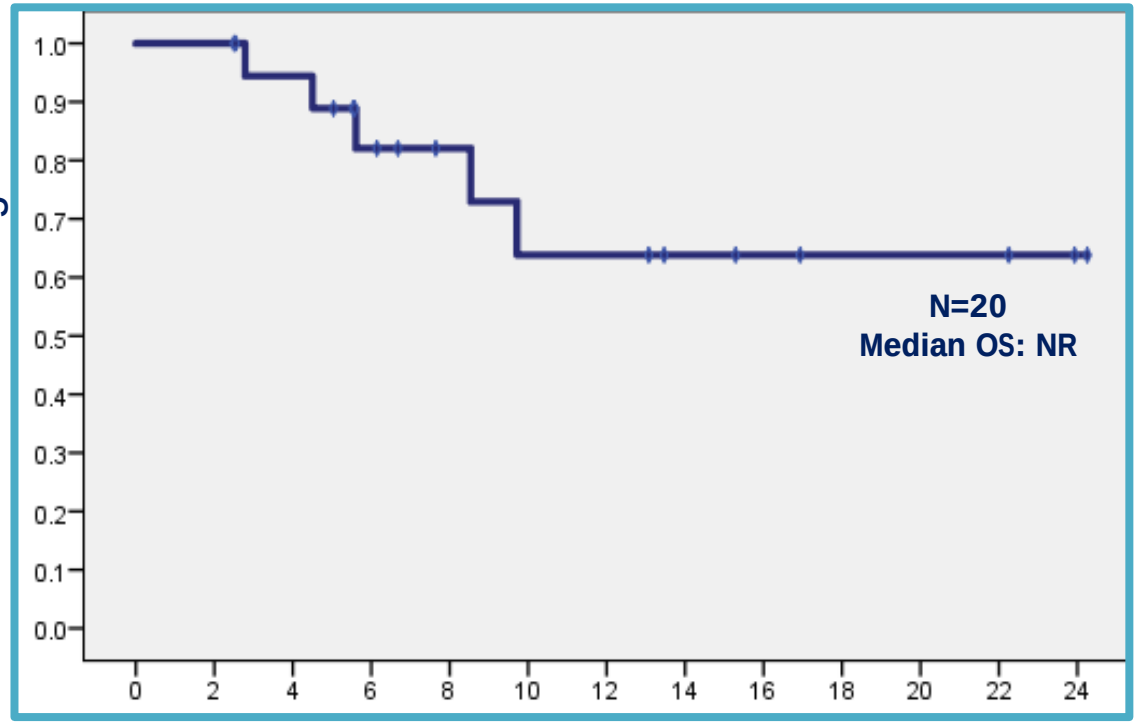


Median Cycle Lengths

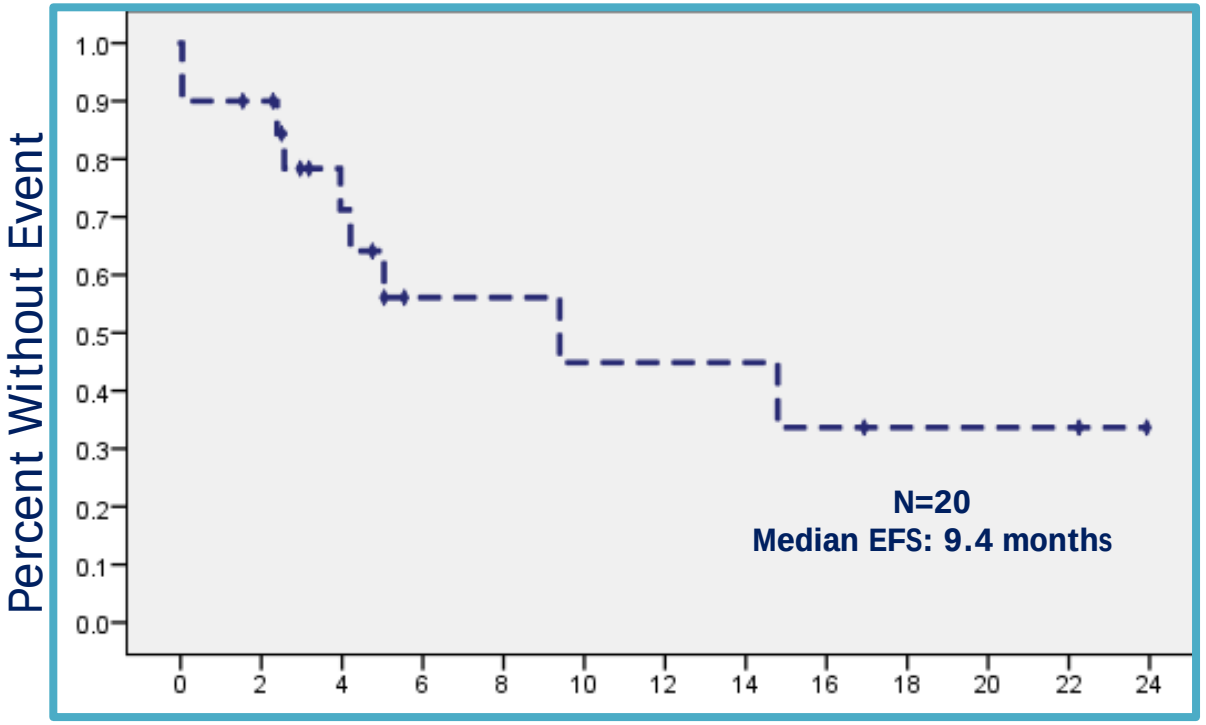


* 7 of 8 patients in **cohort 3** had received prior therapy; including 2 with relapsed MDS, and 3 with secondary AML from MDS

Overall Survival



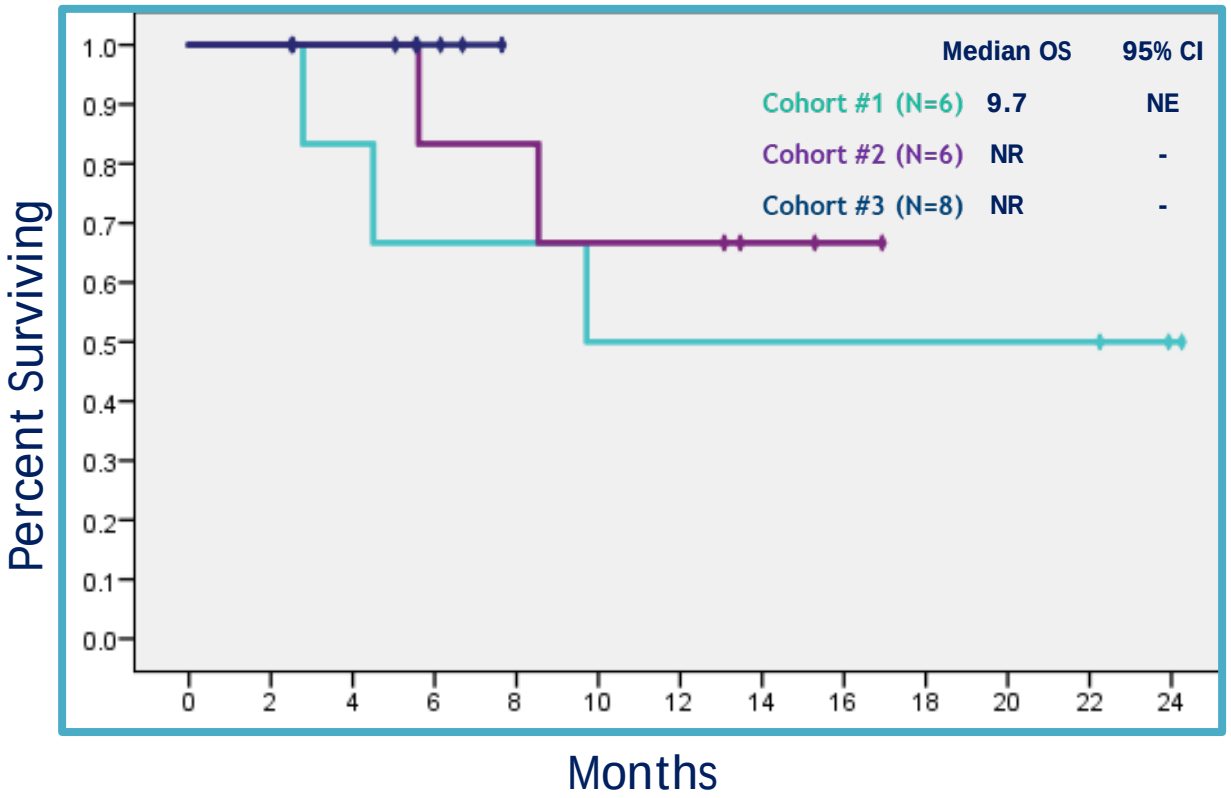
Event Free Survival



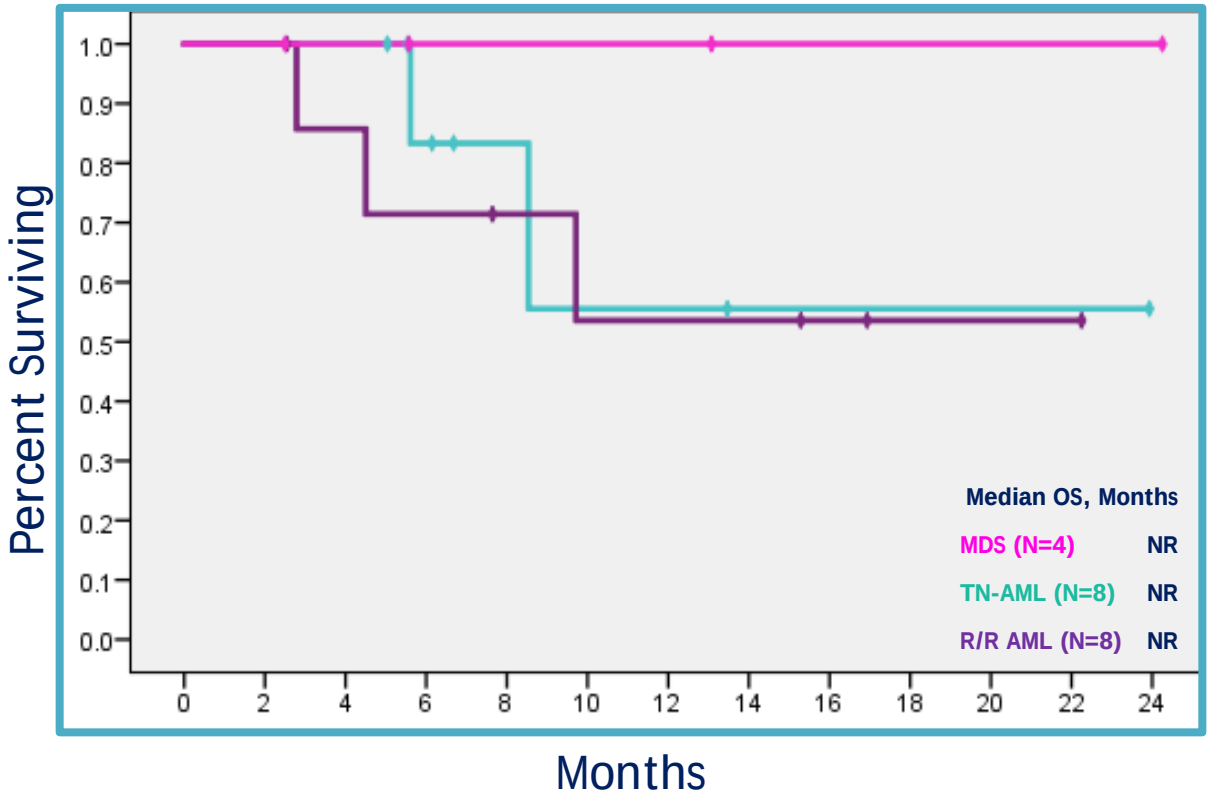
Median Follow up: 7 months

Survival Outcomes by Key Subgroups

Overall Survival by Study Cohort



Overall Survival by Disease



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)

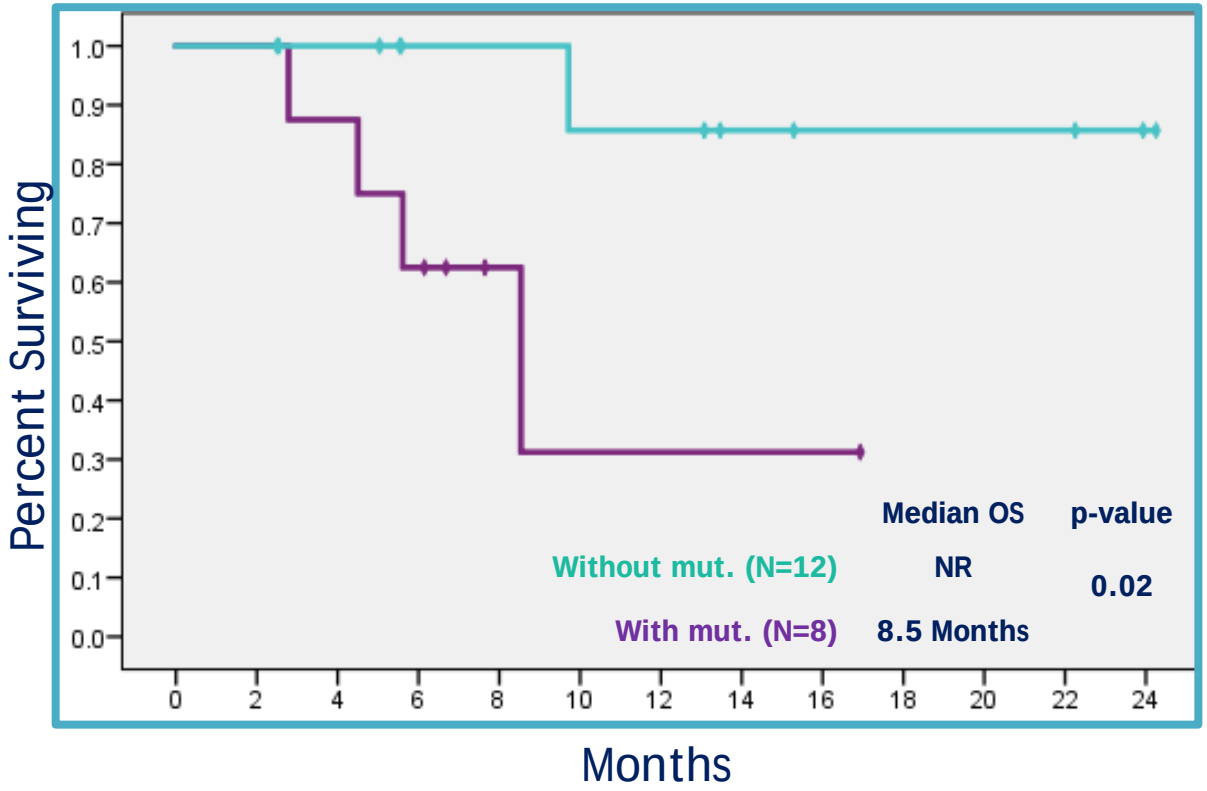
Active Signaling Mutations Associated with Treatment Resistance

Outcomes

Response, N (%)	Active Signaling (N=8)	No signaling (N=12)
Overall Response Rate, N(%)	**7 (88)**	**11 (92)**
Composite CR	**6 (75)**	**10 (83)**
CR	1 (13)	6 (50)
CR_h	1 (13)	2 (17)
CR_i	4 (50)	2 (17)
MLFS	-	1 (8)
PR	1 (13)	-
NR	1 (13)	1 (8)
MRD Negative	**2 (33)**	**6 (60)**
Median DOR, Mo. (95% CI)	1.6 (0.3-3)	11.9 (NE)*

*p-value: 0.043

Overall Survival

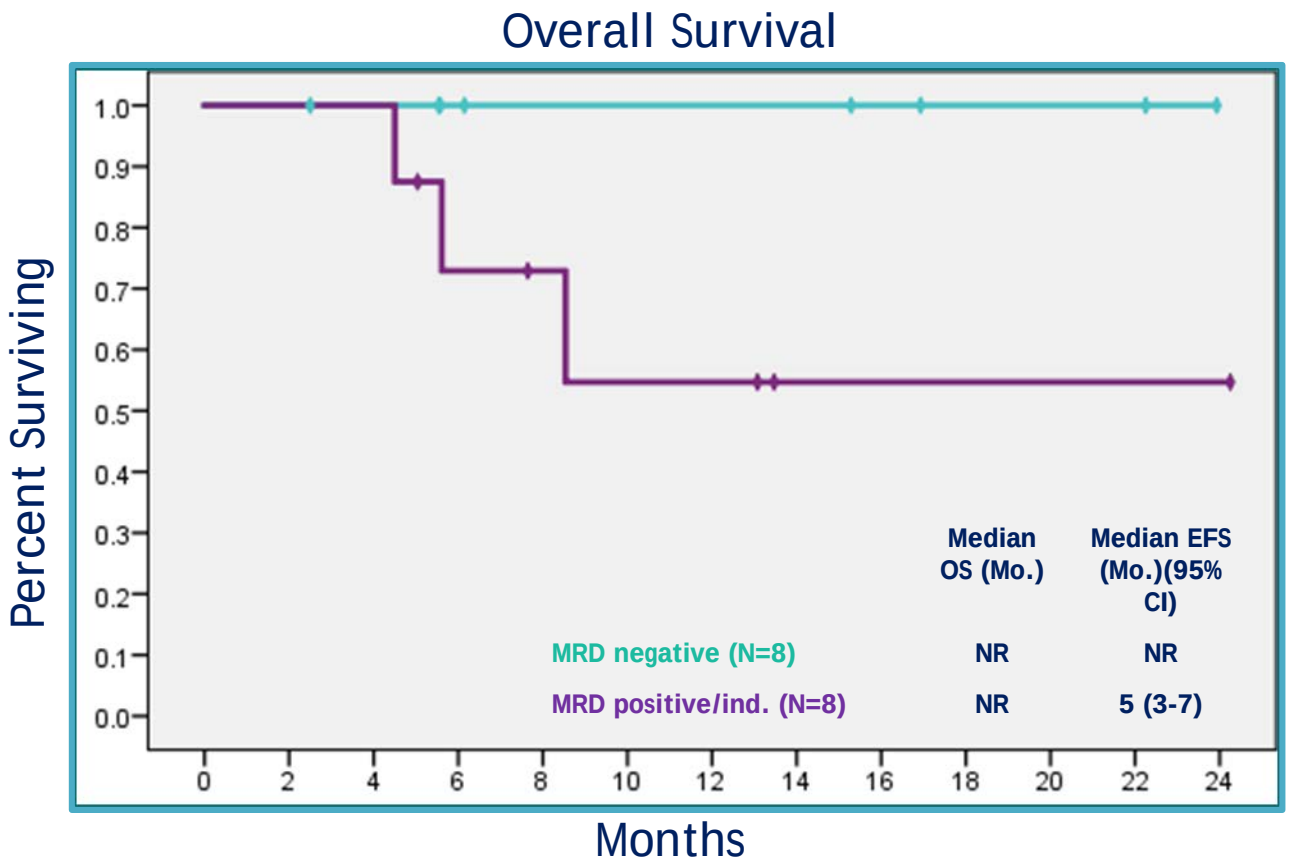


Active Signaling mutations: *NRAS, KRAS, FLT3-ITD/TKD, PTPN11, NF1*

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)
Disease subgroup			
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 grade 3/4 adverse events: pneumonia, febrile neutropenia
  - Longer treatment cycles required with the AZA + IVO + VEN triplet for cytopenias
- IVO+VEN ± AZA therapy is effective:
  - Composite complete response in 80% of patients
  - Undetectable MRD by flow in 50% of pts with CR, responses ongoing
- **Recommended phase II dose and efficacy data forthcoming**

Thank you!

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