Phase Ib/II Study of the IDH1-mutant inhibitor ivosidenib with the BCL2 inhibitor venetoclax +/- azacitidine in IDH1-mutated hematologic malignancies

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DISCLOSURES

- **Research Support**
  - Abbvie, Agios, Calithera, Celgene, Daiichi-Sankyo
- **Consultant/Advisory Board**
  - Abbvie, Agios, Celgene, Daiichi-Sankyo, Jazz, ImmuneOnc, Novartis, Notable Labs

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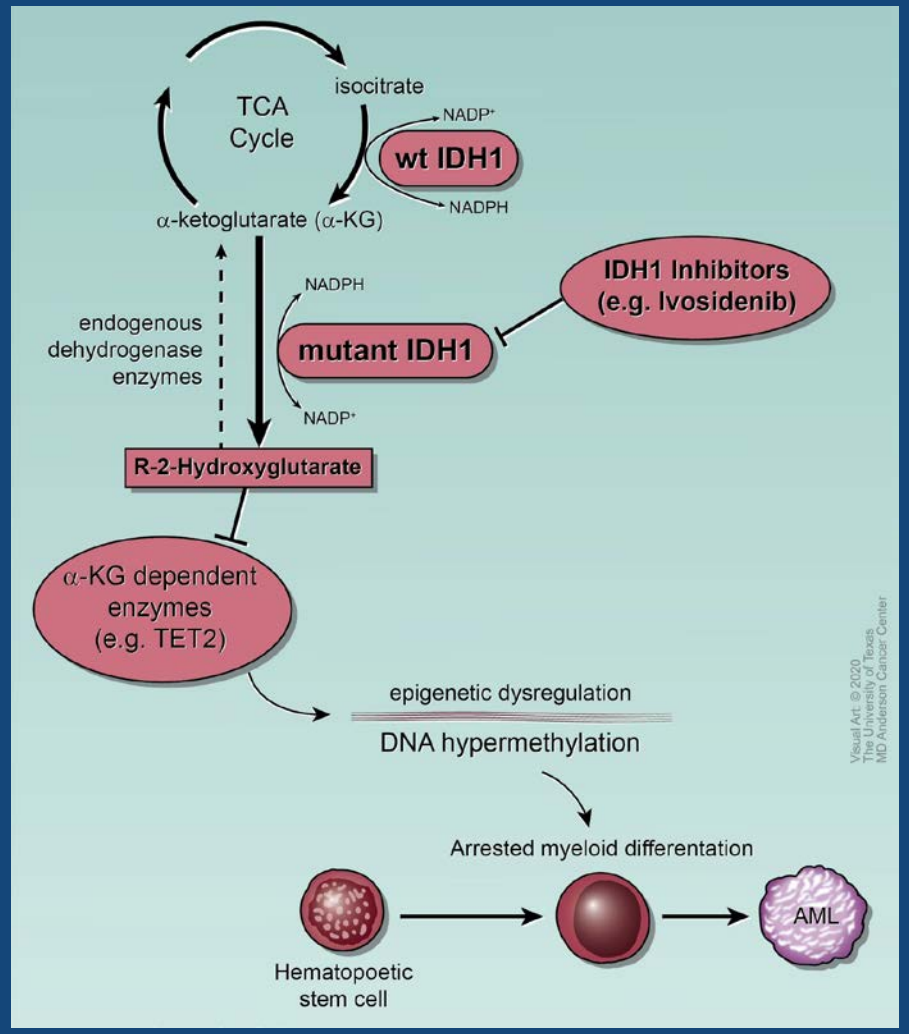
Isocitrate Dehydrogenase-1 (IDH1) in AML



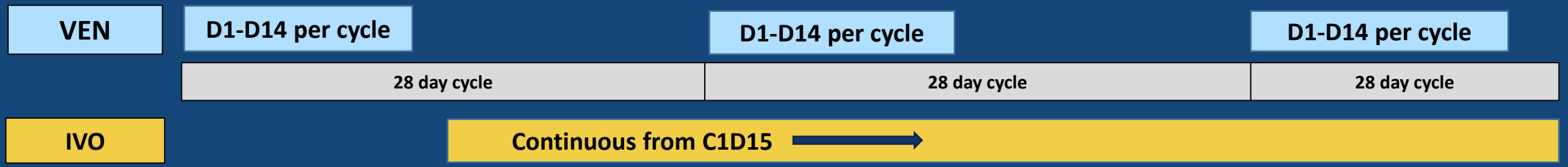
- Present in 7-14% of cases of AML
- Enriched in CN-AML, older patients, *NPM1* mutated AML
- Variable impact on OS
- Increased dependency on BCL-2 and lower apoptotic threshold via cytochrome C oxidase inhibition
- Single agent ivosidenib:
  - Treatment Naïve (TN) AML CR/CR_h : 42%
  - Relapsed/Refractory (R/R) AML CR/CR_h : 30%

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 (N=30)



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

Phase II : Confirm efficacy in 2 cohorts (N=20 each) of TN and R/R patients including phase Ib participants at RP2D.

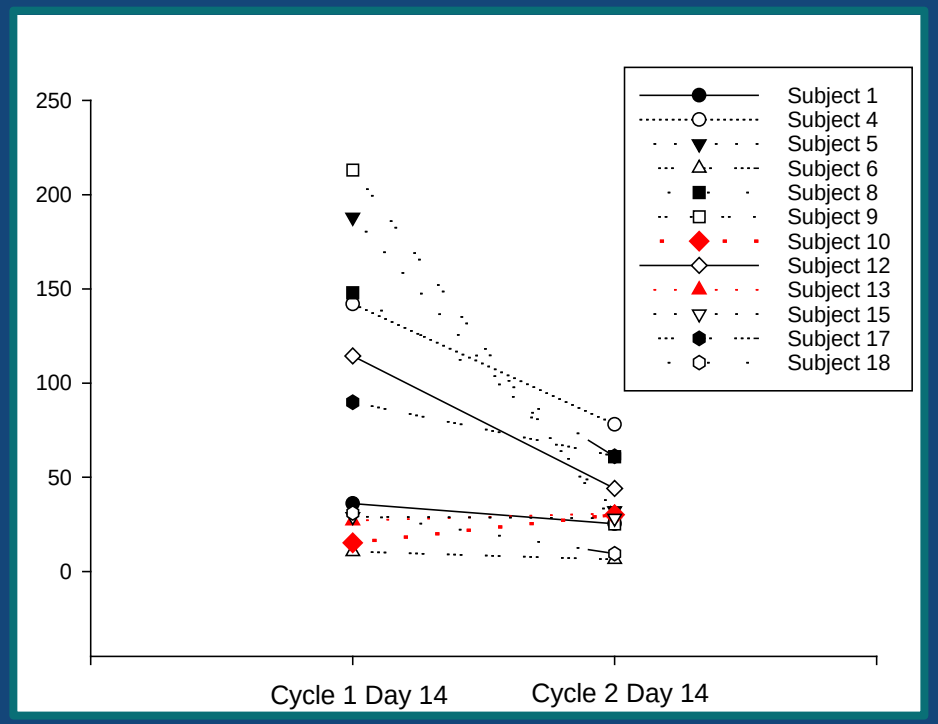
*additional 6 patients being enrolled due to 1 DLT
† One enrolled patient was invaluable and was replaced

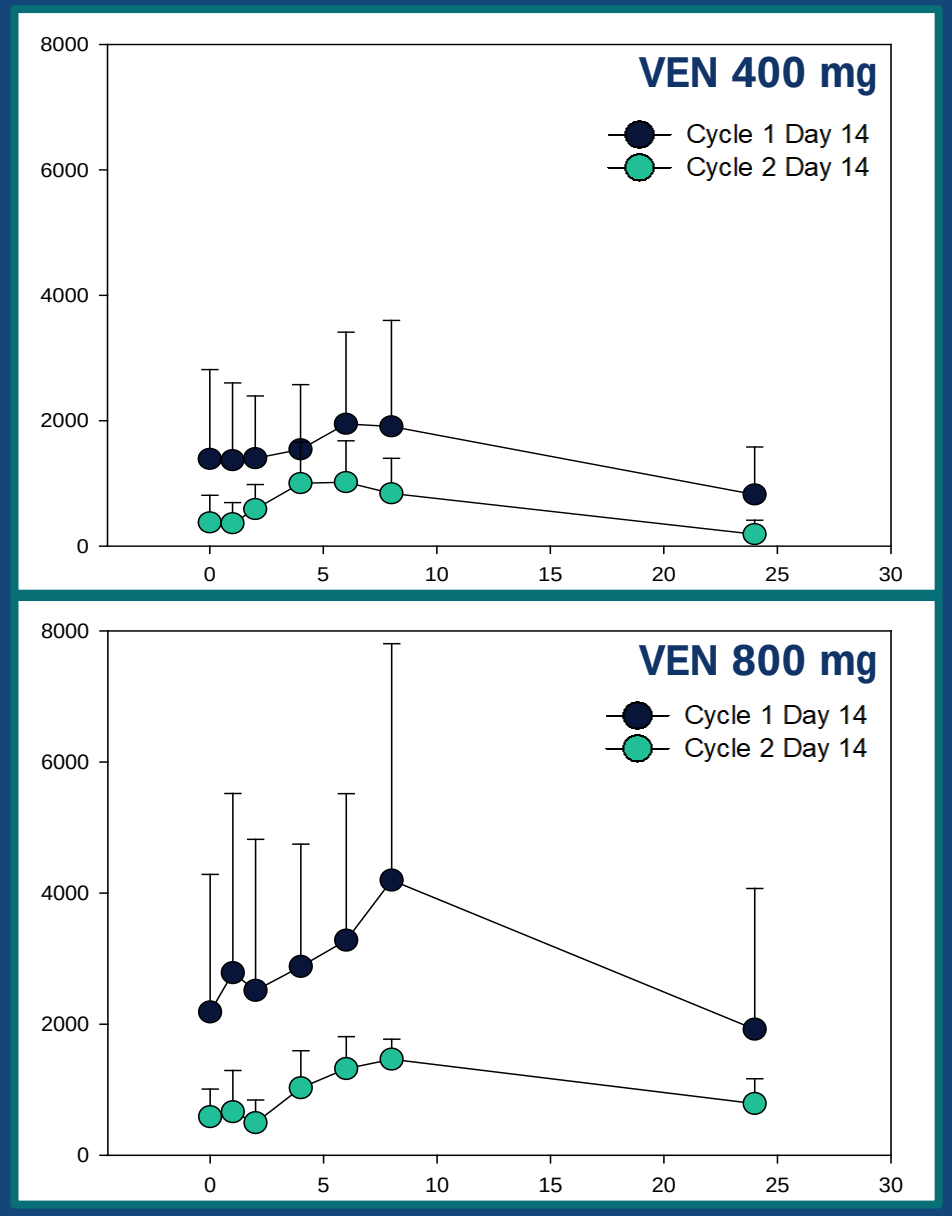
PK and PD Results

VEN+IVO combination

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

Comparison of dose-adjusted AUC_{0-24}





Study Design

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
- Direct bilirubin < 2 x ULN
- ALT and/or AST < 3x ULN
- eGFR > 30 mL/min

Key Exclusion Criteria

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

Patient Demographics

Demographic	All Cohorts, N (%)	Cohort #1 IVO+VEN 400 (N=6)	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 (60)**	3 (50)	3 (50)	6 (75)
Disease Category				
MDS	**4 (20)**	1	1	2
De Novo AML	**3 (15)**	1	1	1
Secondary AML	**2 (10)**	-	1	1
Treated Secondary AML	**3 (15)**	-	1	2
Relapsed/Refractory AML	**8 (40)**	4	2	2
ELN Risk Group				
Favorable	**7 (35)**	2	3	2
Intermediate	**3 (15)**	2	1	-
Adverse	**10 (50)**	2	2	6

Grade 3/4 Serious Adverse Events ≥ 10%

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
- AE's of special interest: IDH differentiation syndrome (N=4), TLS (N=2)
- Dose limiting toxicities: 1 (TLS)
- *1 death occurred on study or within 30-days of study discontinuation due to febrile neutropenia

Overall Response

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)	-	-
MRD Negative†	**8 (50)**	**2 (50)**	**2 (33)**	**4 (67)**

* CR_h and CR_i mutually exclusive

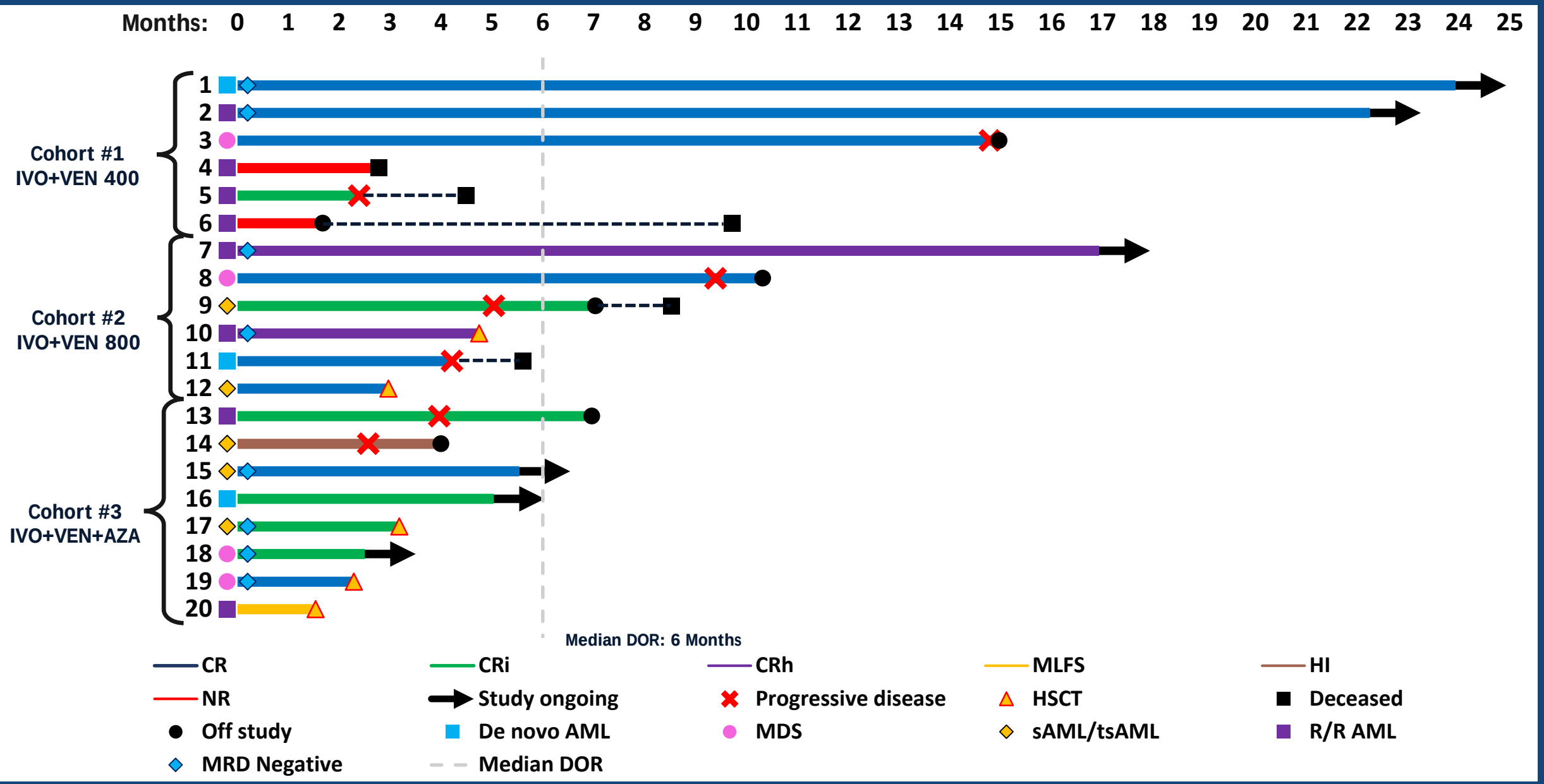
† Among patients achieving a composite CR

Response by Disease Subgroup

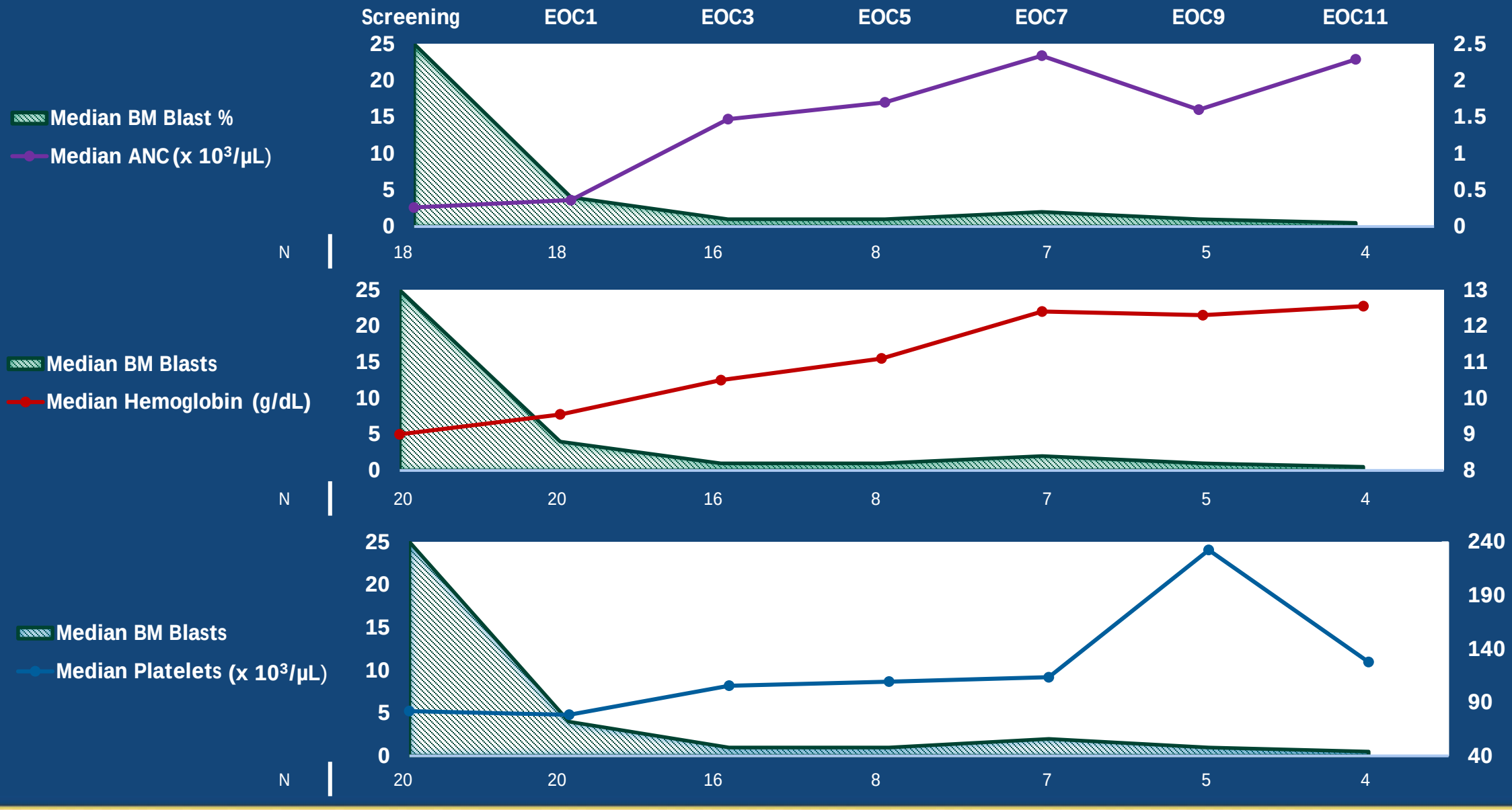
Response, N (%)	De Novo AML (N=3)	sAML/ts-AML (N=5)	R/R AML (N=8)	MDS (N=4)
Overall Response Rate N(%)	3 (100)	5 (100)	6 (75)	4 (100)
Composite CR (CRc)*	**3 (100)**	**4 (80)**	**5 (63)**	**4 (100)**
CR	2 (66)	2 (40)	1 (13)	3 (75)
CRh	-	-	2 (25)	
CRi	1 (33)	2 (40)	2 (25)	1 (25)
MLFS	-	-	1 (13)	-
HI	-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

* CR_h and CR_i mutually exclusive

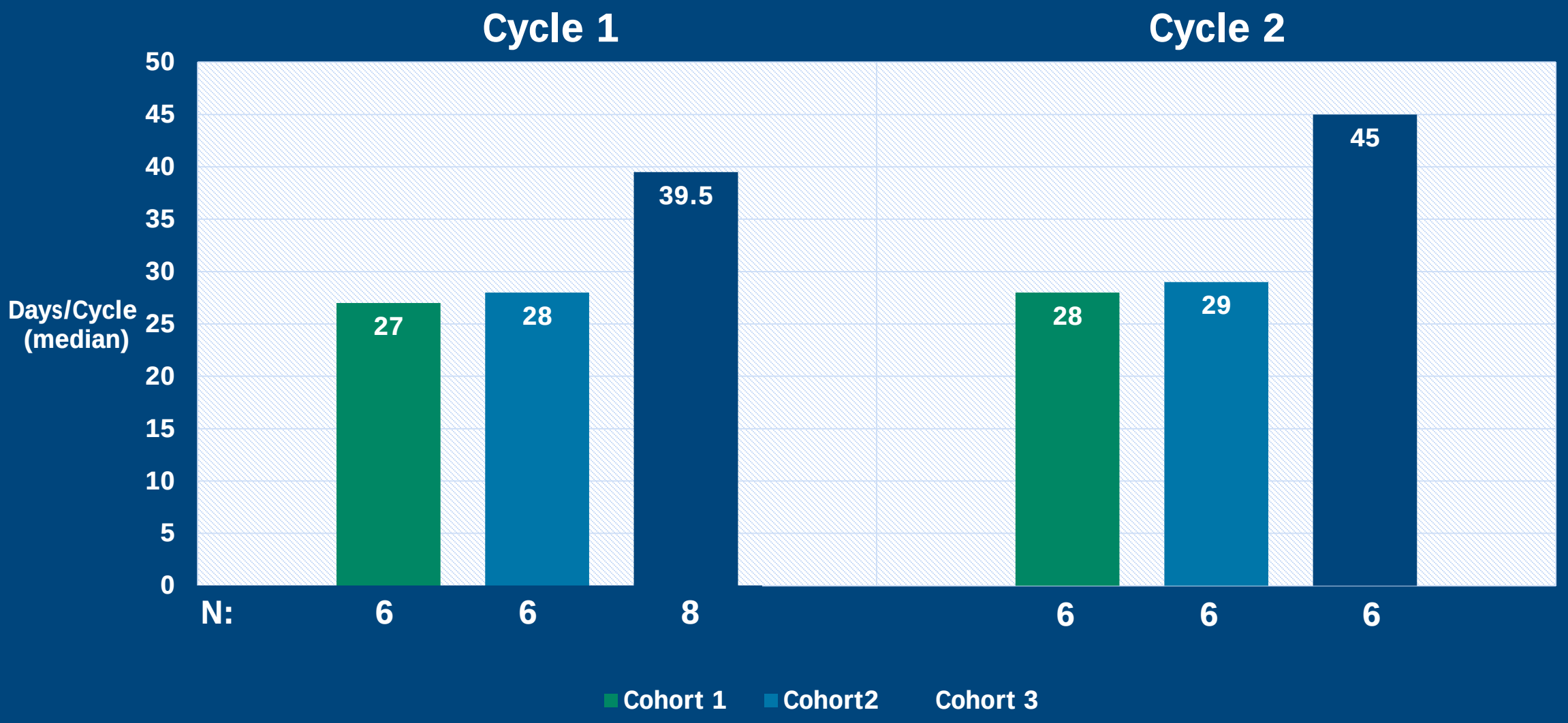
† Among patients achieving a Composite CR



Hematologic Response

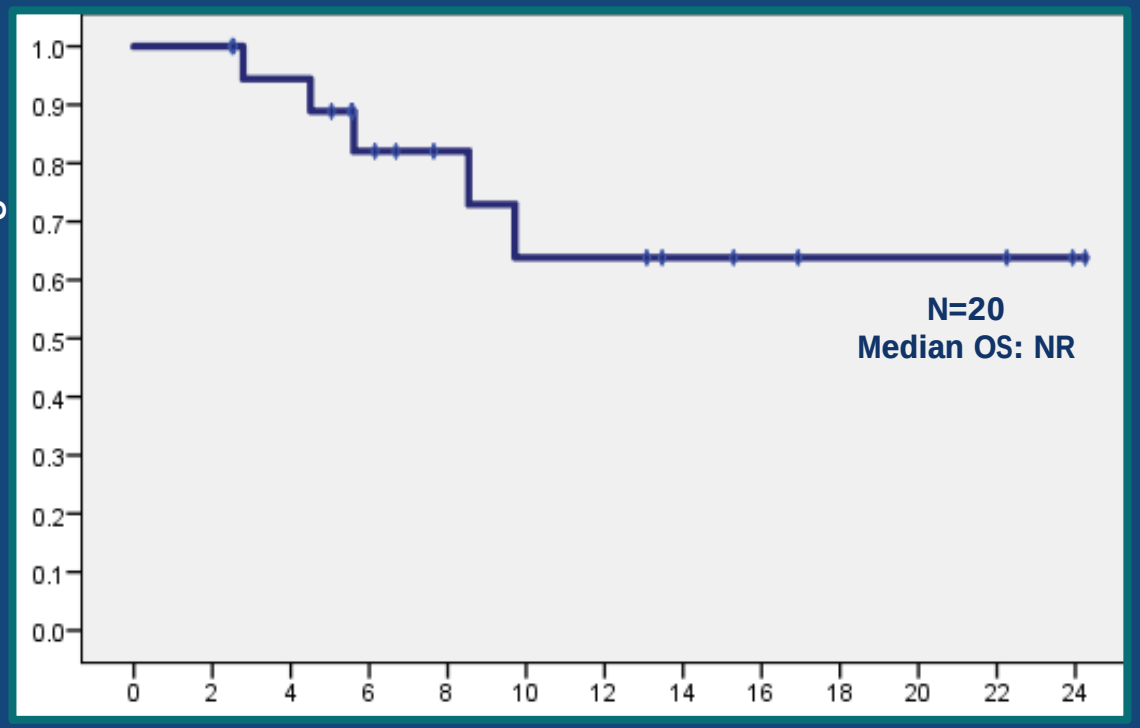


Median Cycle Length

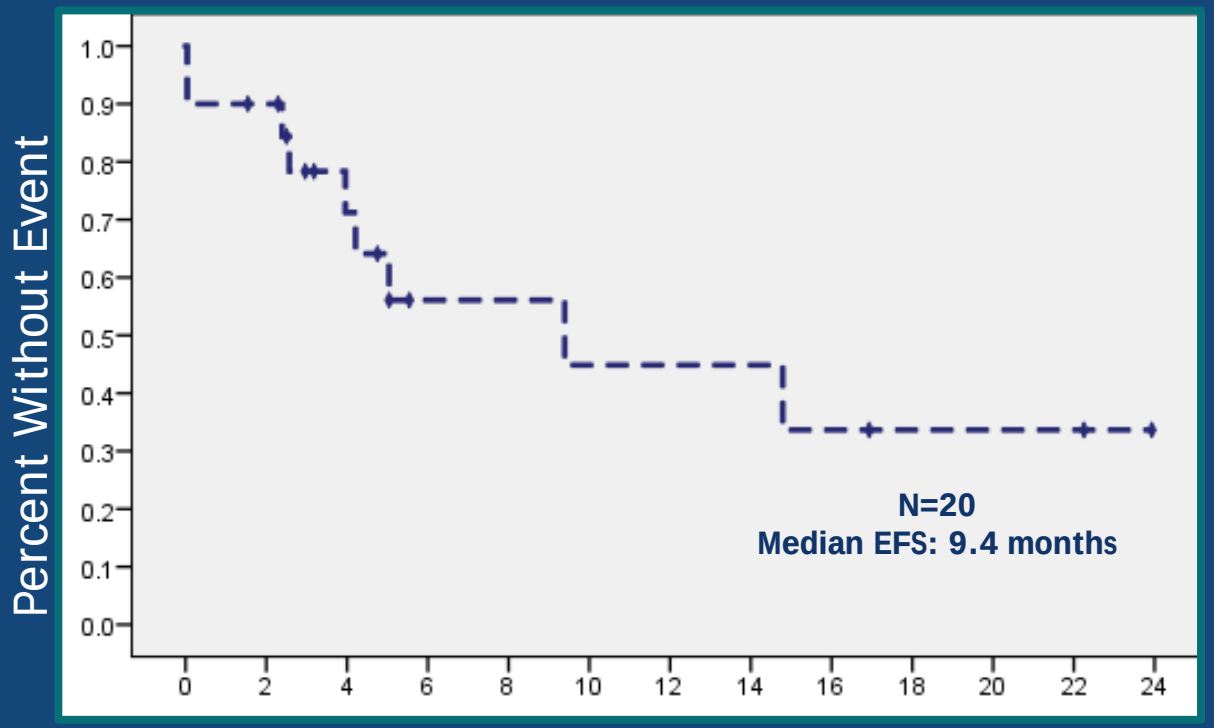


Survival Outcomes

Overall Survival



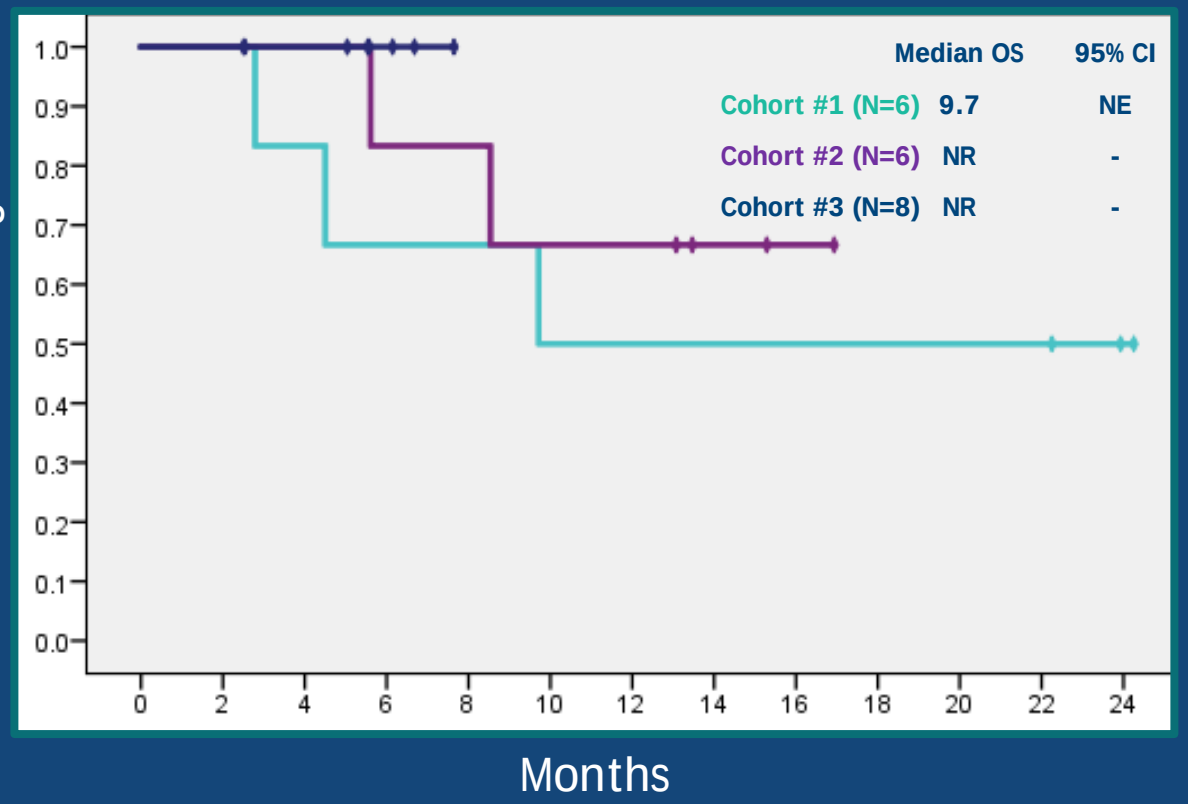
Event Free Survival



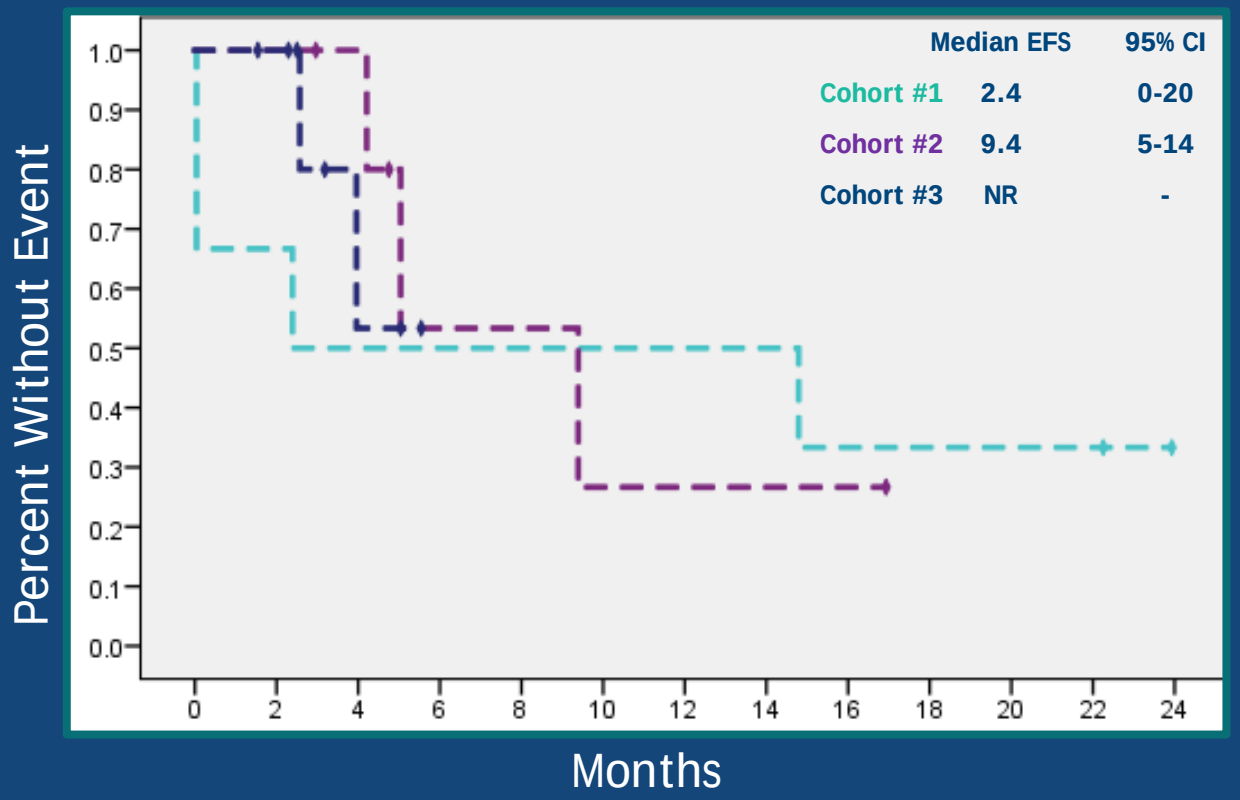
Median Follow up: 7 months

Survival Outcomes by Cohort

Overall Survival

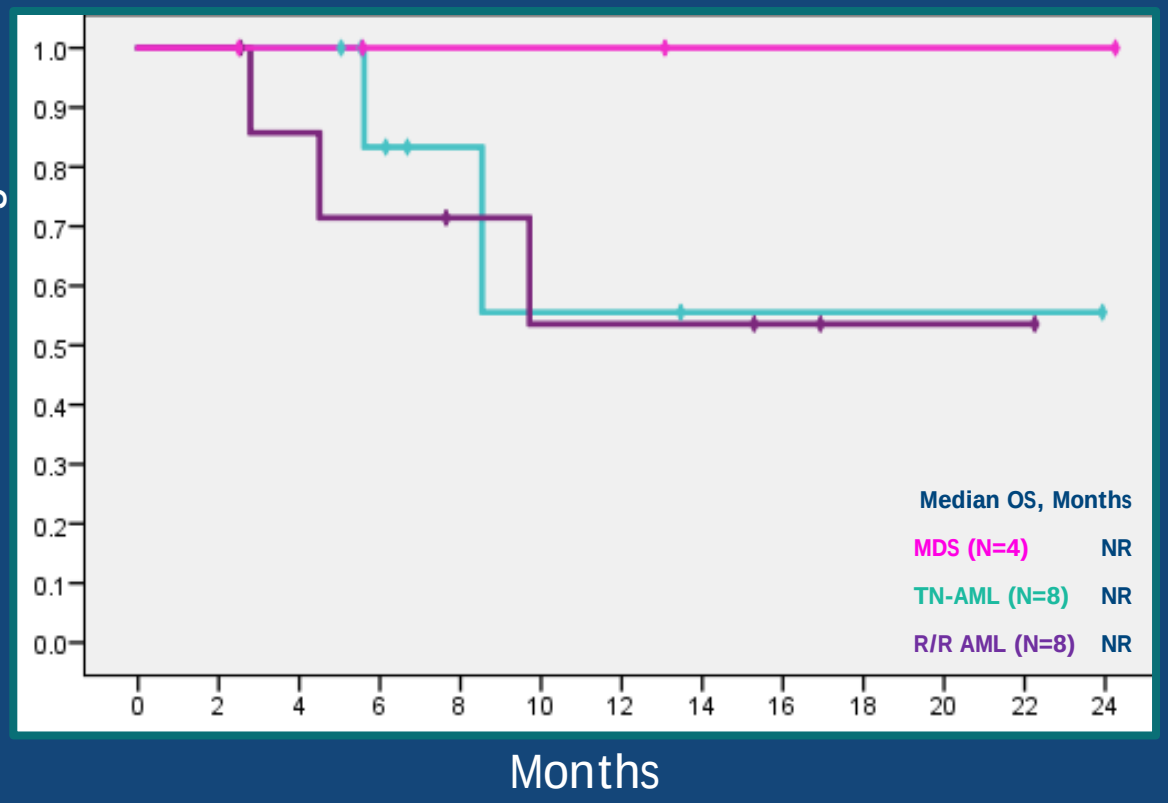


Event-Free Survival

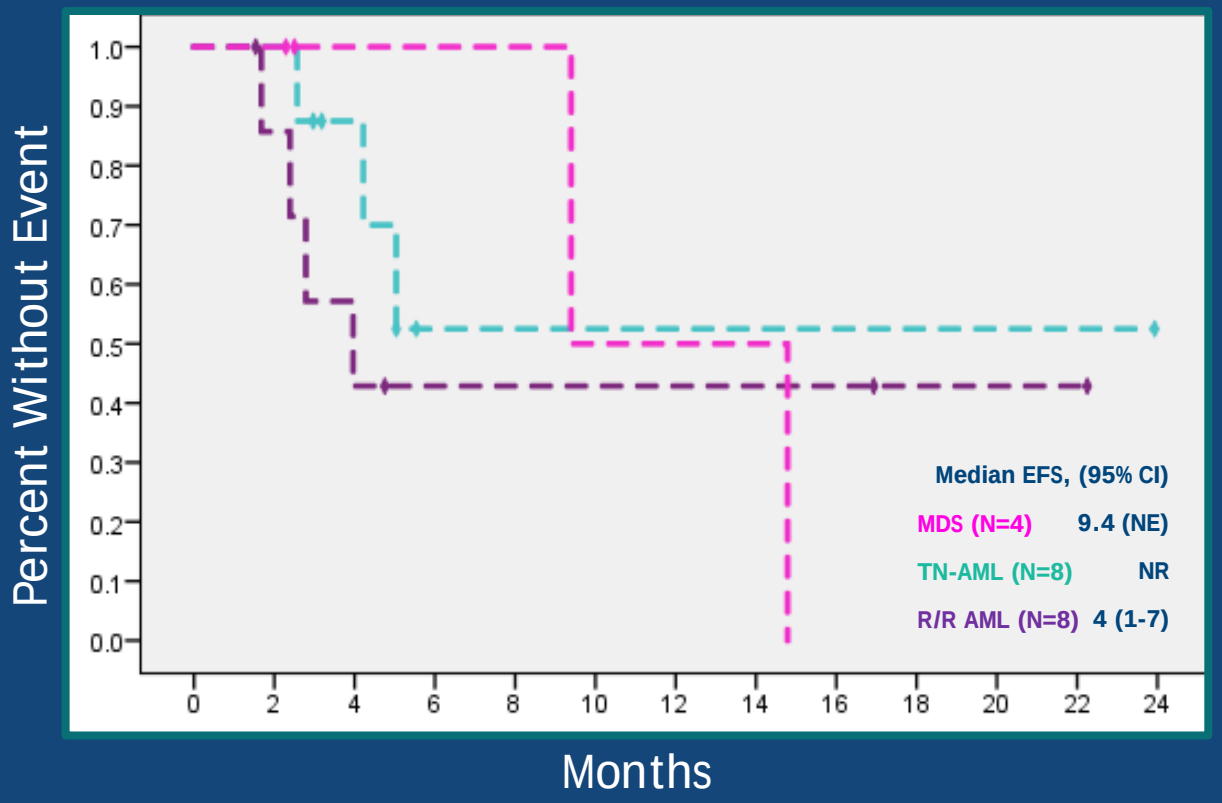


Survival Outcomes by Disease

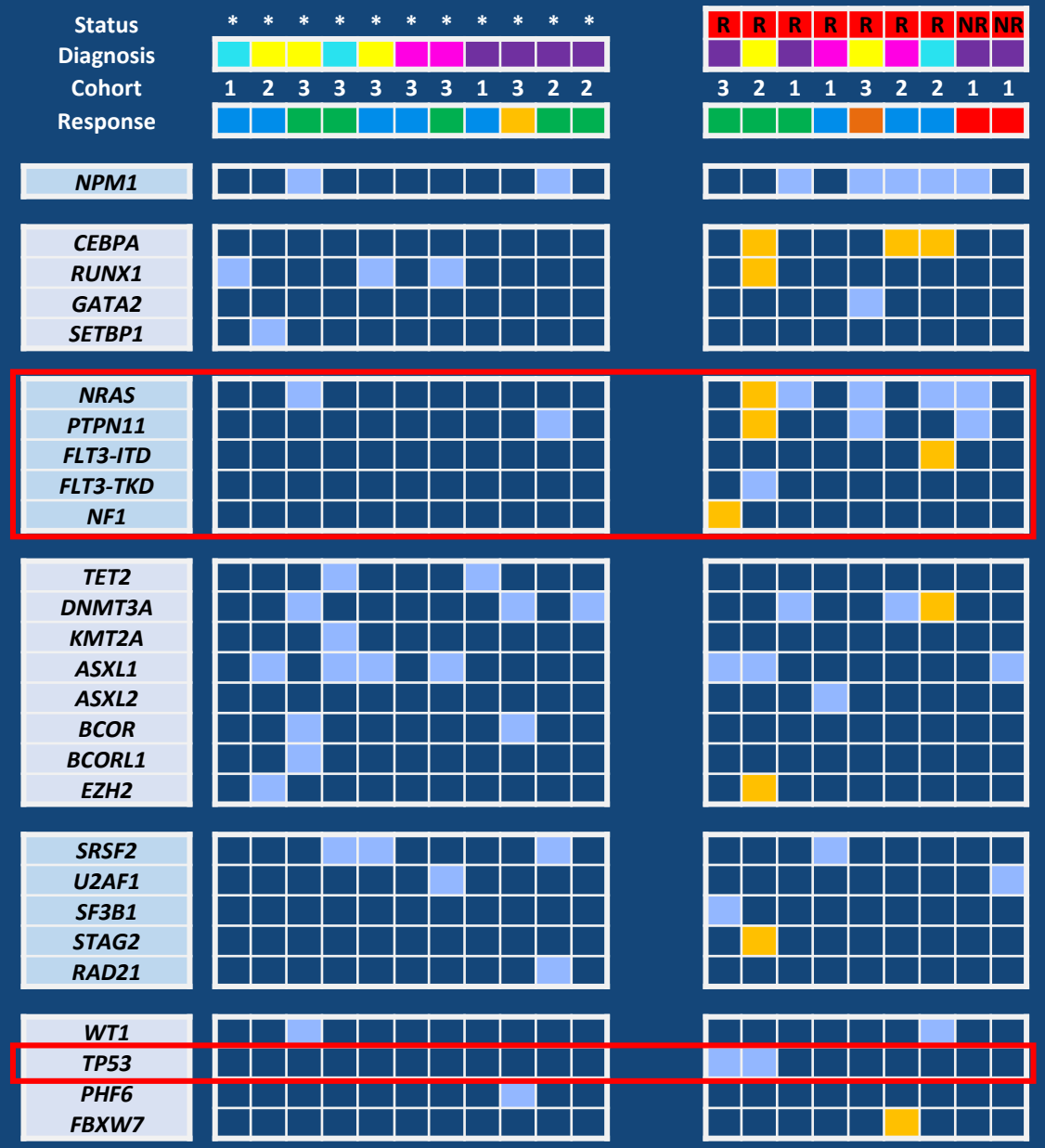
OS: MDS vs. TN-AML vs. R/R AML

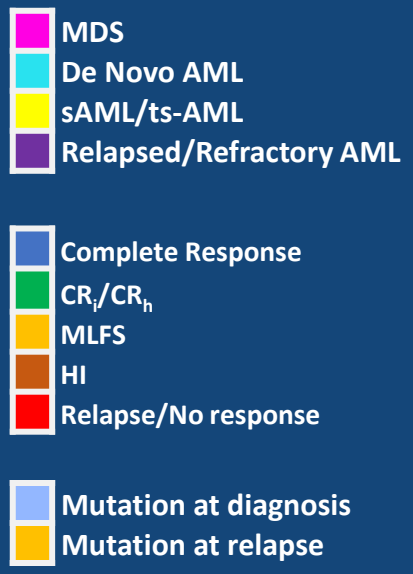


EFS: MDS vs. TN-AML vs. R/R AML



TN-AML: De novo + sAML+ ts-AML





Molecular Profile

- Diverse molecular landscape across all groups
- Active signaling mutations in 66% of patients with no response or relapse
- *TP53* mutations in 2 patients with relapse

* Molecular subgroups as defined by TCGA AML analysis (*NEJM, 2013*)

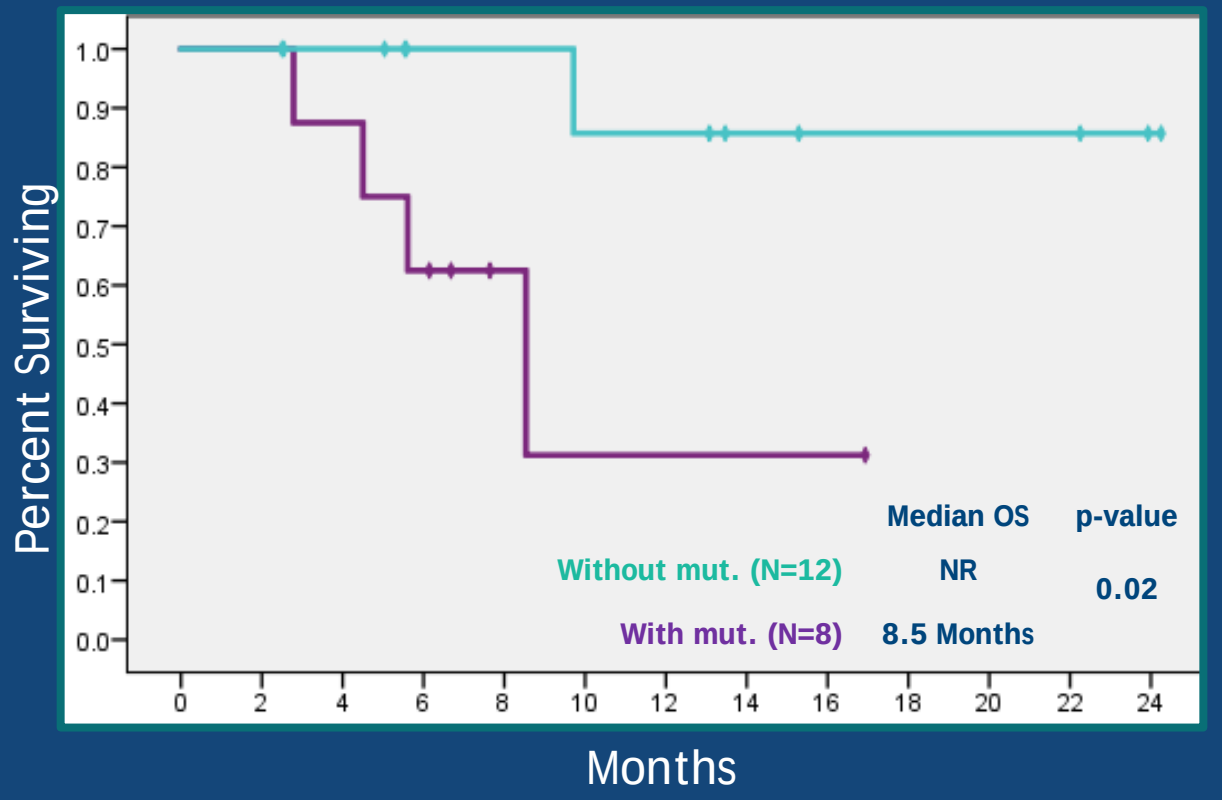
Active Signaling Mutations Portend Poor Prognosis

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: RAS, RTK, or phosphatase pathway mutations (*NRAS, FLT3-ITD/TKD, PTPN11, NF1)*

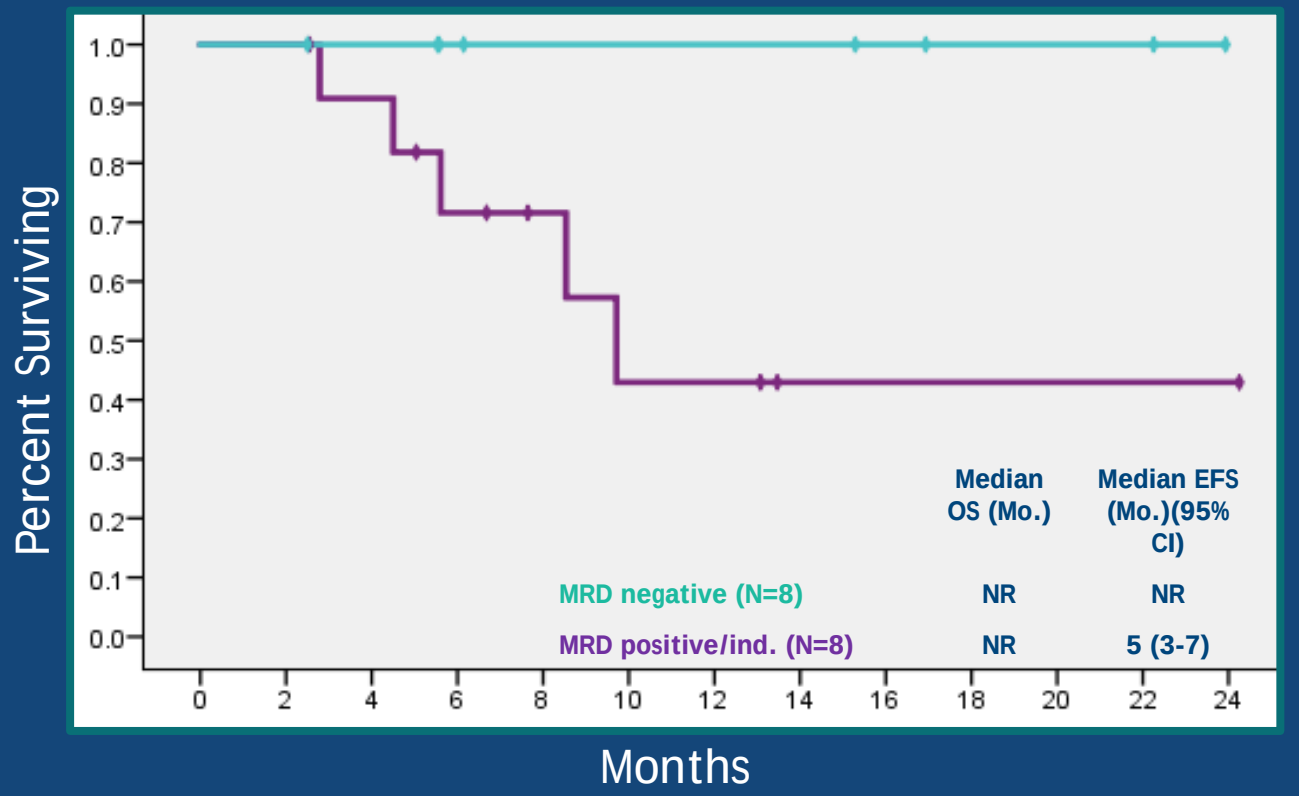
MRD Negative CR Associated with Superior Survival

Outcomes

Demographic	All CR	MRD neg. (N=8)	MRD pos. / ind. (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**

Overall Survival



Conclusions

- **IVO+VEN ± AZA is an effective, molecularly targeted, regimen for advanced *IDH1* mutated myeloid malignancies**
- **IVO+VEN ± AZA is well tolerated**
  - Common grade 1/2 adverse events: nausea, vomiting, diarrhea
  - Common grade 3/4 adverse events: pneumonia, febrile neutropenia
- **IVO+VEN ± AZA therapy associated with:**
  - Composite complete response in 80% of patients
  - MRD negative CR achieved in 50% of patients, responses ongoing
- **Recommended phase II dose and efficacy data forthcoming**

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