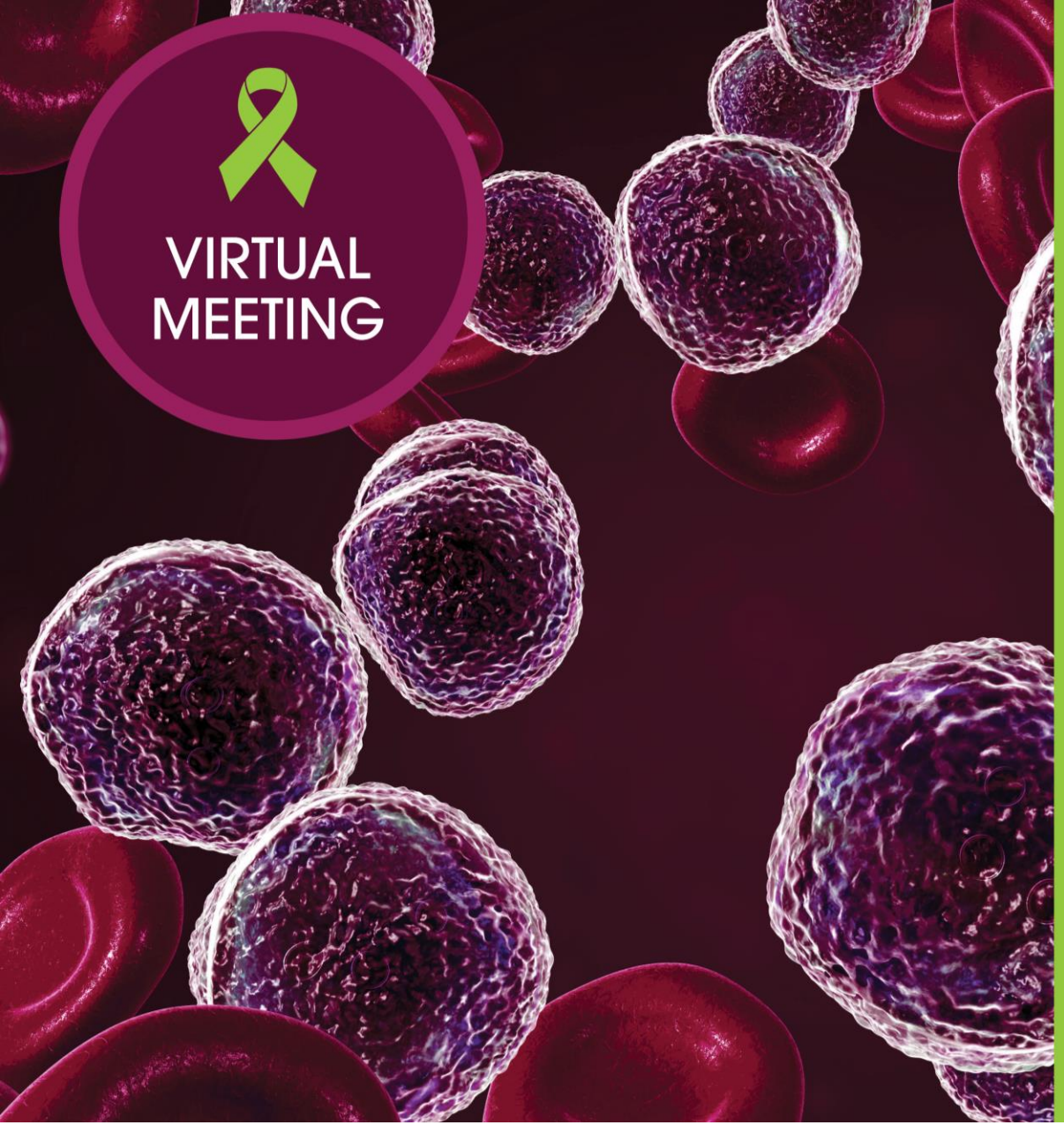
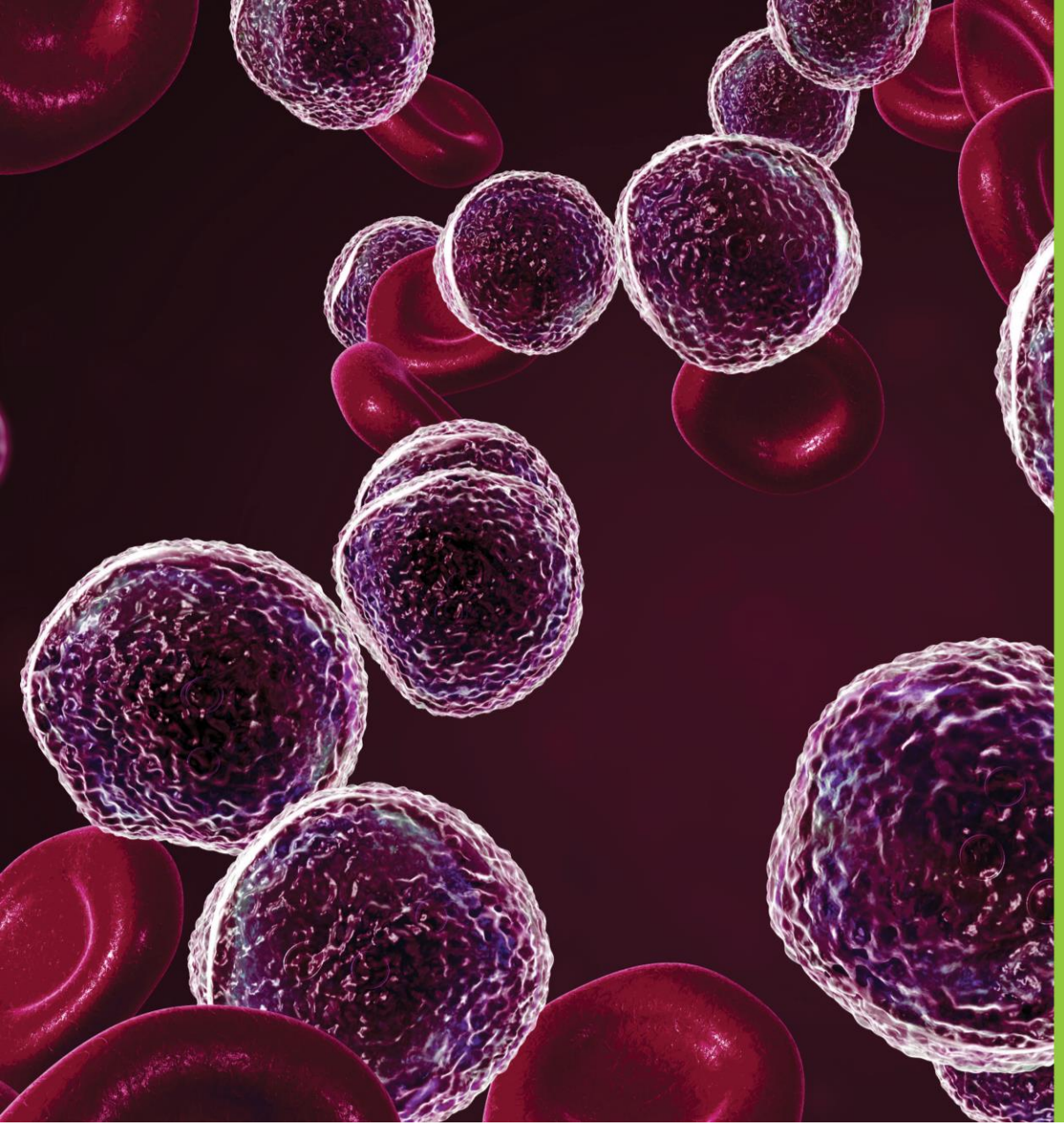


BEYOND THE CONGRESS

Key Conversations from the 2021 Hematology Annual Meeting™

FRIDAY, FEBRUARY 4, 2022

This activity is jointly provided by PIM Postgraduate Institute for Medicine and Bio Ascend™



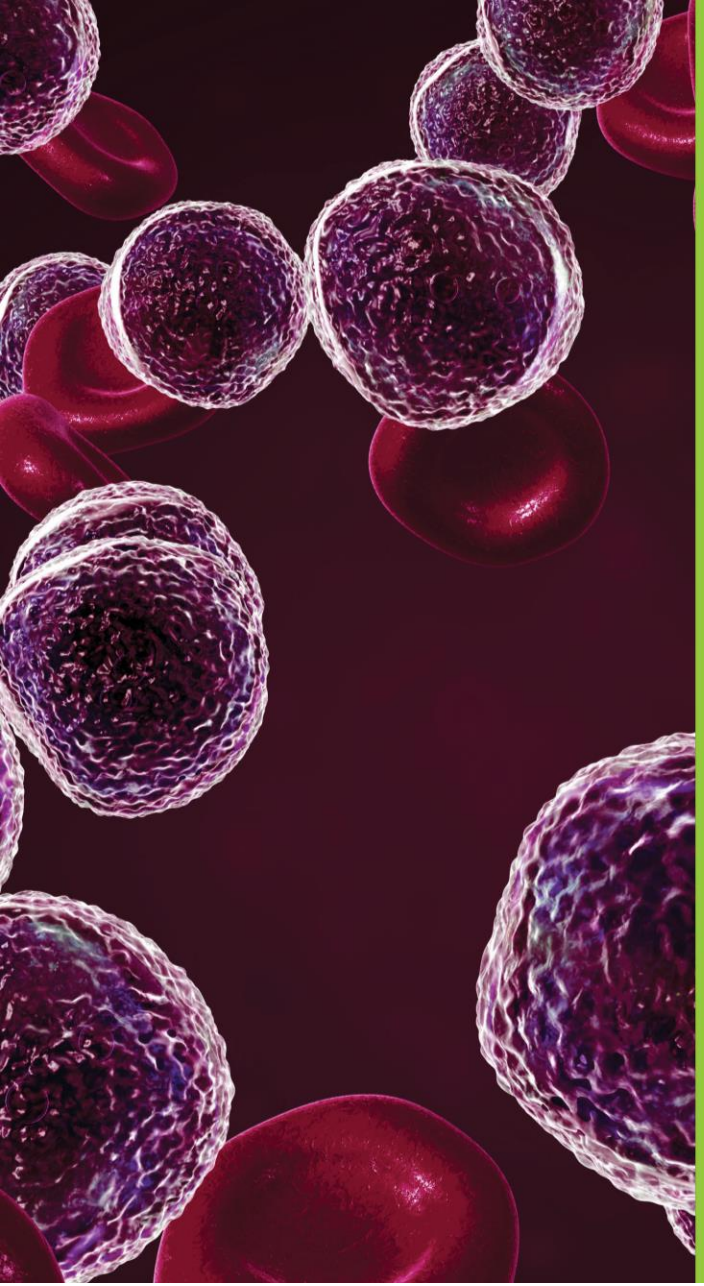
BEYOND THE CONGRESS

Key Conversations from the 2021 Hematology Annual Meeting™

FRIDAY, FEBRUARY 4, 2022

Courtney DiNardo, MD
MD Anderson Cancer Center

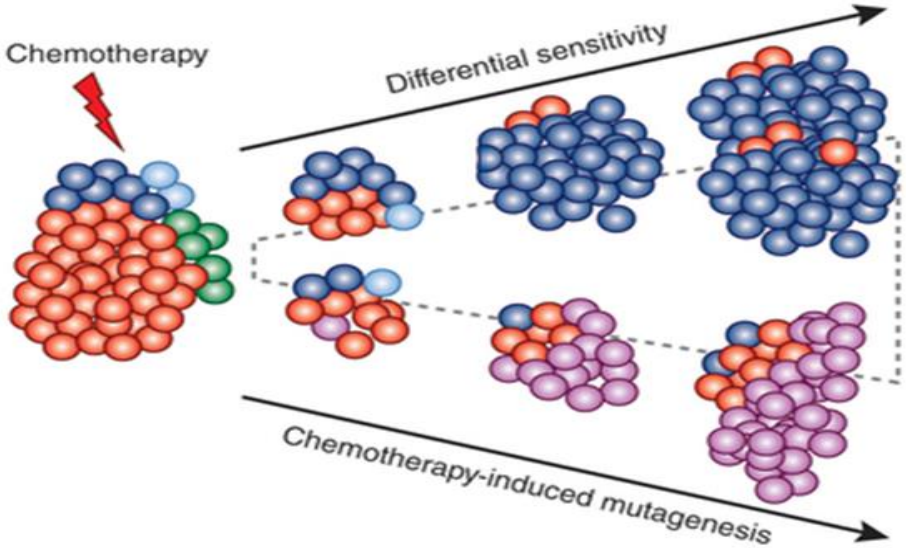
This activity is jointly provided by PIM Postgraduate Institute for Medicine Bio Ascend™



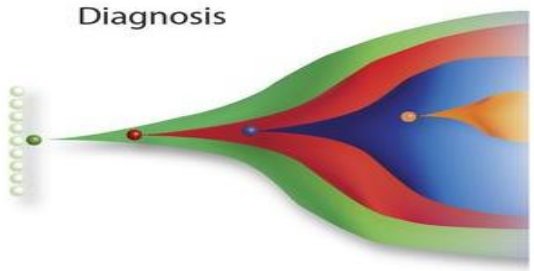
New Directions in Relapsed/Refractory AML

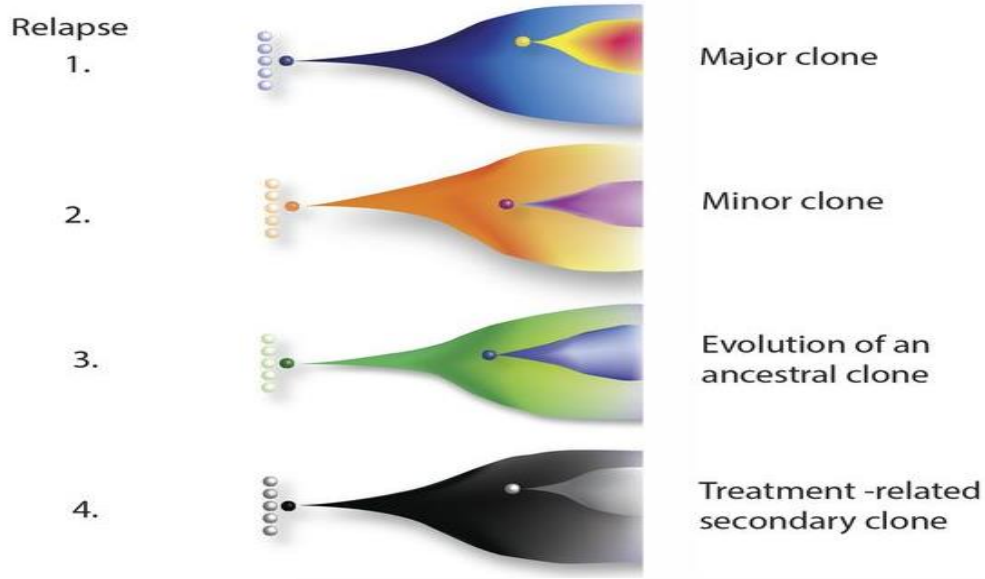
This activity is jointly provided by PIM Postgraduate Institute for Medicine Bio Ascend™

Individualizing Therapy at Relapse is Essential



Leukemia is not a static condition or diagnosis;
Repeat genomic analysis at relapse is necessary

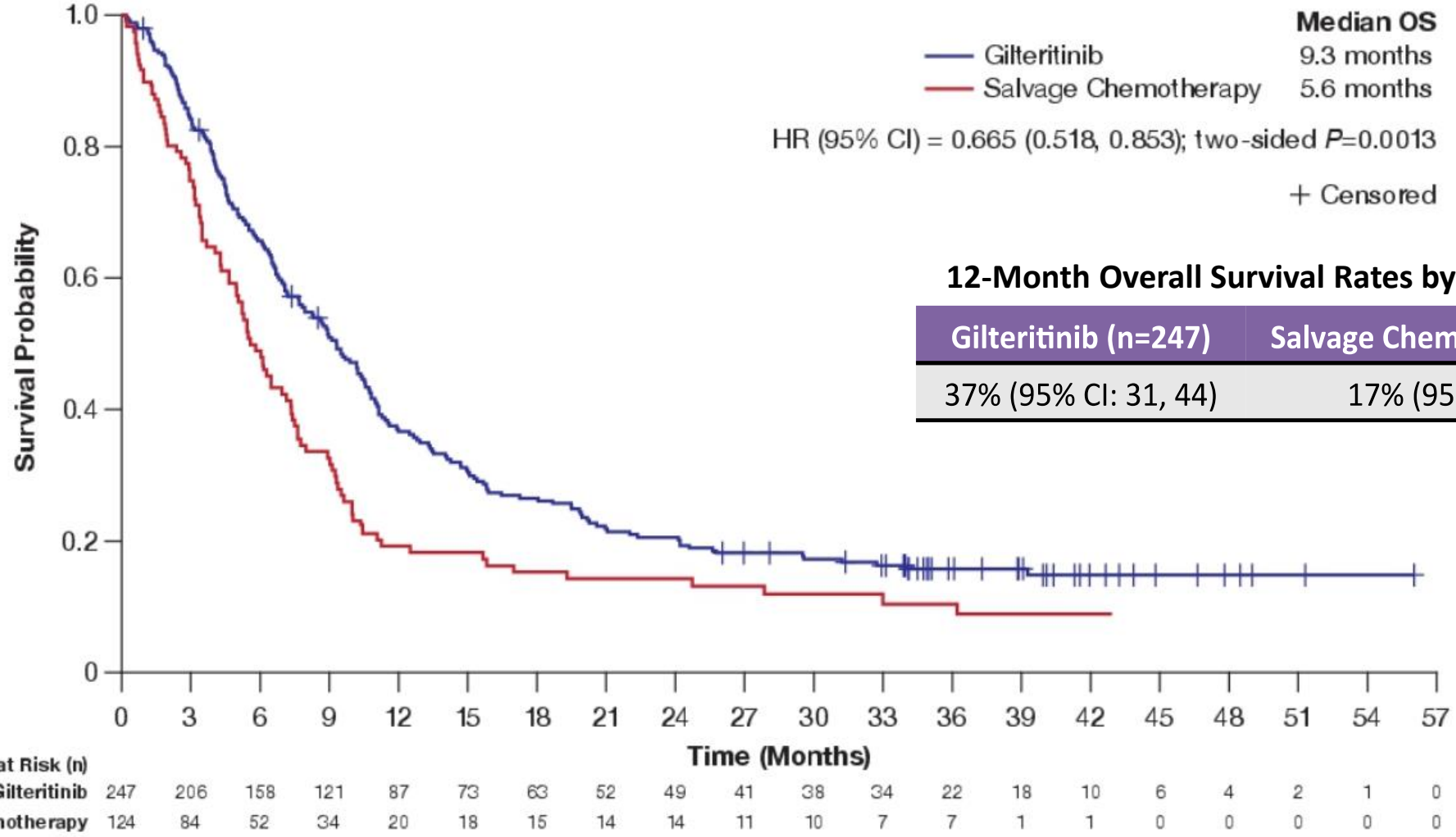




Kleppe M & Levine RL, Nat Med 2014

Grimwade D et al, Blood 2016

ADMIRAL: Longer Follow-Up Confirms OS Benefit With Gilteritinib in R/R *FLT3* Mutant AML[1]



12-Month Overall Survival Rates by Treatment Arm

Gilteritinib (n=247)	Salvage Chemotherapy (n=124)
37% (95% CI: 31, 44)	17% (95% CI: 10, 25)

1. Perl A et al. ASCO 2021. Abstract 7013.

VEN + GILT in *FLT3*-Mutated R/R AML

Phase 1b Study Design

Key Eligibility Criteria

- R/R AML
- *FLT3*mut or wt (escalation); *FLT3mut* (expansion)
- ≥ 1 prior line of therapy*
- WBC count ≤ 25 x 10^9/L at start of study drug
- ECOG PS 0 to 2

Dose escalation phase *FLT3*mut and wt
N=7: VEN 400 mg + GILT 80 mg
N=8: VEN 400 mg + GILT 120 mg

Dose expansion *FLT3*mut only
N= 46: VEN 400 mg + GILT 120 mg **(RP2D)**

Primary endpoint: mCRc
Secondary endpoints: CR+CRh, DOR for mCRc
Exploratory endpoints: OS in *FLT3*mut

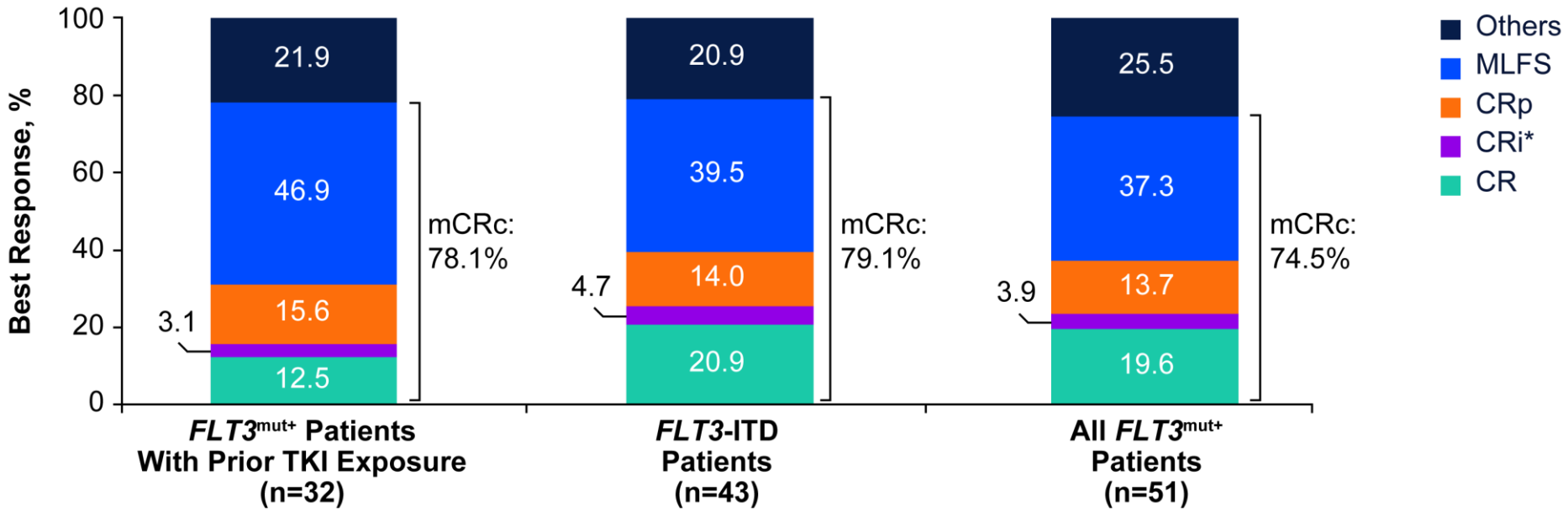
Patient Characteristics		VEN/GILT at RP2D (N=54)
Median age (range), years		64 (21 to 85)
FLT3 mutation, n (%)	**ITD only**	**41 (76)**
	TKD only	8 (15)
	ITD + TKD	3 (6)
NCCN cytogenetic risk, n (%)	Favorable	2 (4)
	Intermediate	28 (54)
	Poor	18 (35)
	No mitoses	4 (8)
De novo AML, n (%)		42 (78)
Median prior therapies (range), n		2 (1 to 5)
≥3, n (%)		18 (33)
Prior treatment, n (%)	**≥1 FLT3i**	**32 (59)**
	Gilt	**0**
	Ven	**10 (19)**
	AlloSCT	**17 (31)**

•*Prior VEN exposure was permitted in a protocol amendment (unless received as part of a RCT); FLT3i (including GILT) were allowed during dose escalation; FLT3i except GILT were permitted during dose expansion; prior HSCT was permitted.

Daver N et al, ASH 2021 #691; NCT03625505

This activity is jointly provided by PIM Postgraduate Institute for Medicine Bio Ascend™

Venetoclax + Gilteritinib for R/R *FLT3*-Mutated AML: Efficacy



	FLT3^{mut+} Patients With Prior TKI Exposure (n=32)	*FLT3*-ITD Patients (n=43)	All *FLT3*$^{mut+}$ Patients (n=51)
mCRc[a], n (%)	25 (78.1)	34 (79.1)	38 (74.5)
CR+CRp+CRi[b]*	10 (31.3)	17 (39.5)	19 (37.3)
MLFS	15 (46.9)	17 (39.5)	19 (37.3)

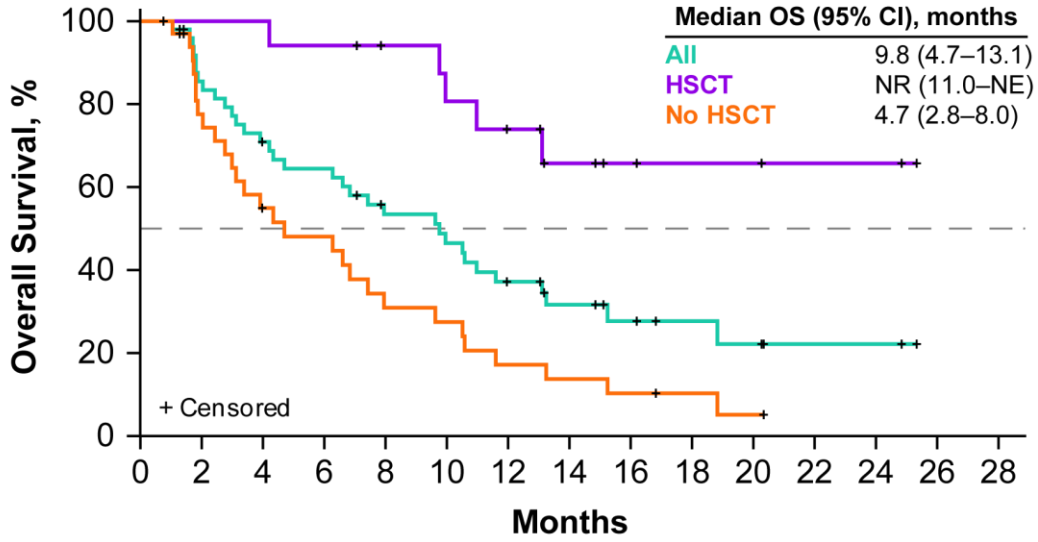
The mCRc rate in this study was **74.5%**. The CRc rate in the ADMIRAL Phase 3 study for single agent Gilt was 54.3% (using the same response parameters).[1]

- [a]mCRc defined as CR+CRp+CRi*+MLFS, per modified IWG response criteria. [b]Hematology criteria for CRi* is ANC ≤1×10^9/L and platelet >100×10^9/L, which is mutually exclusive with IWG response CRp.
- 1. Perl AE, et al. *N Engl J Med.* 2019;381(18):1728–1740.

Daver N et al, ASH 2021 #691

Venetoclax + Gilteritinib for R/R *FLT3*-Mutated AML: OS

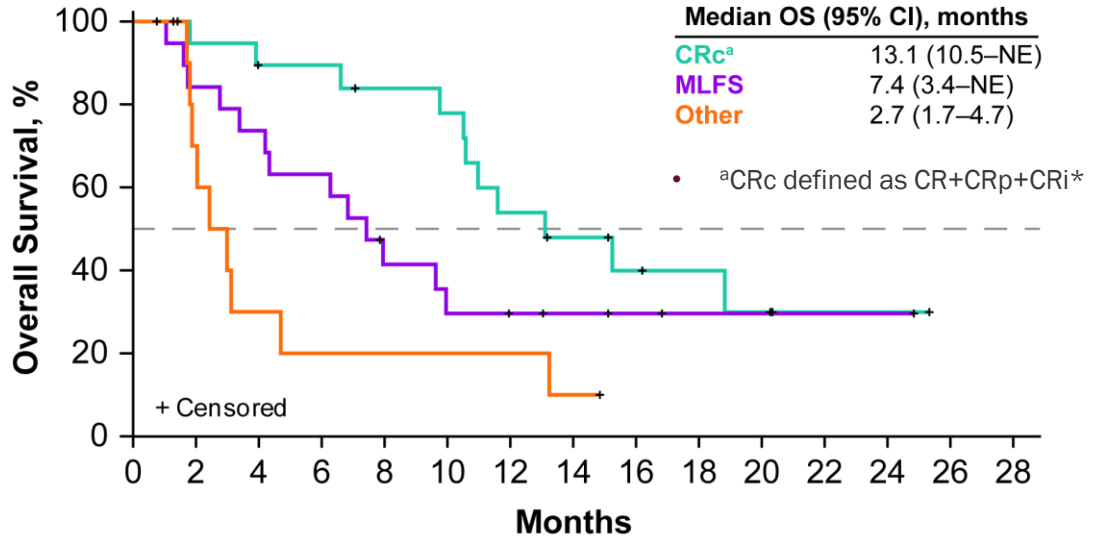
OS by Transplant Status (*FLT3*$^{mut+}$ Patients)



Patients at Risk

All	51	41	33	30	23	20	15	11	7	5	4	2	2	0
HSCT	17	17	17	16	14	12	10	7	4	3	3	2	2	0
No HSCT	34	24	16	14	9	8	5	4	3	2	1	0		

OS by Best Response Status (*FLT3*$^{mut+}$ Patients)



Patients at Risk

CRc	19	18	16	16	14	13	9	7	5	4	3	1	1	0
MLFS	19	16	14	12	7	5	4	3	2	1	1	1	1	0
Other	13	7	3	2	2	2	2	1	0					

- Median duration of follow-up was 15.1 months (range, 0.8–25.3)
- Median OS for *FLT3*-ITD patients was 10.0 months (95% CI, 6.6–13.2)
- FLT3 molecular clearance (<10^{-2}): 60% of CRc patients

Daver N et al, ASH 2021 #691

IDHentify Phase 3 Study of Enasidenib vs Other Lower-Intensity Therapies in Patients With *IDH2*-Mutated R/R AML

Key Eligibility Criteria
- Age ≥60 years
- de novo or secondary AML with m*IDH2*
- 2-3 prior lines of AML therapy
- ECOG PS 0-2

CCR Preselection
- **AZA:** 75 mg/m^2 SUBQ x 7d
- **LDAC:** 20 mg SUBQ BID x 10d
- **BSC-Only**
- **IDAC:** 0.5-1.5 g/m^2 IV x 3-6d

1:1 Randomization[a]

- ENA (n=139) 100 mg QD (continuous) → *Repeated 28d cycles*
- Preselected CCR (n=128) [AZA (n=69), LDAC (n=37), BSC-only (n=22)]

→ Followed for survival until death, loss to follow-up, withdraw of consent, or study termination

Data cutoff: March 17, 2020
69 pts (ENA 17, CCR 52) received only 1 cycle of study drug

Primary endpoint: OS
Secondary endpoints: ORR, EFS, TTF, ORR, HI & TI, safety

Patient Characteristics		ENA (n=139)	CCR (n=128)
Median age (range), years		72 (60-85)	72 (60-86)
Prior therapies, n (%)	≤2	114 (82)	100 (78)
	≥3	25 (18)	28 (22)
Prior IC, n (%)		102 (73)	92 (72)
Prior HSCT, n (%)		11 (8)	14 (11)
Primary refractory AML,[c] n(%)		62 (45)	47 (37)
ELN risk category, n (%)	Favorable	11 (8)	5 (4)
	Intermediate	25 (18)	22 (17)
	Adverse	83 (60)	81 (63)
	NE	20 (14)	20 (16)
Median BM blasts (range), %		44 (5-99)	42 (6-100)
Median ANC (range), 10^9/L		0.39 (0.0-15.4)	0.58 (0.0-11.4)
Median Hgb (range), g/L		92.5 (57-137)	91 (54-132)
Median Plt (range), 10^9/L		37 (4-655)	35.5 (6-382)
Median WBC (range), 10^9/L		2.5 (0.2-107)	2.5 (0.3-191)

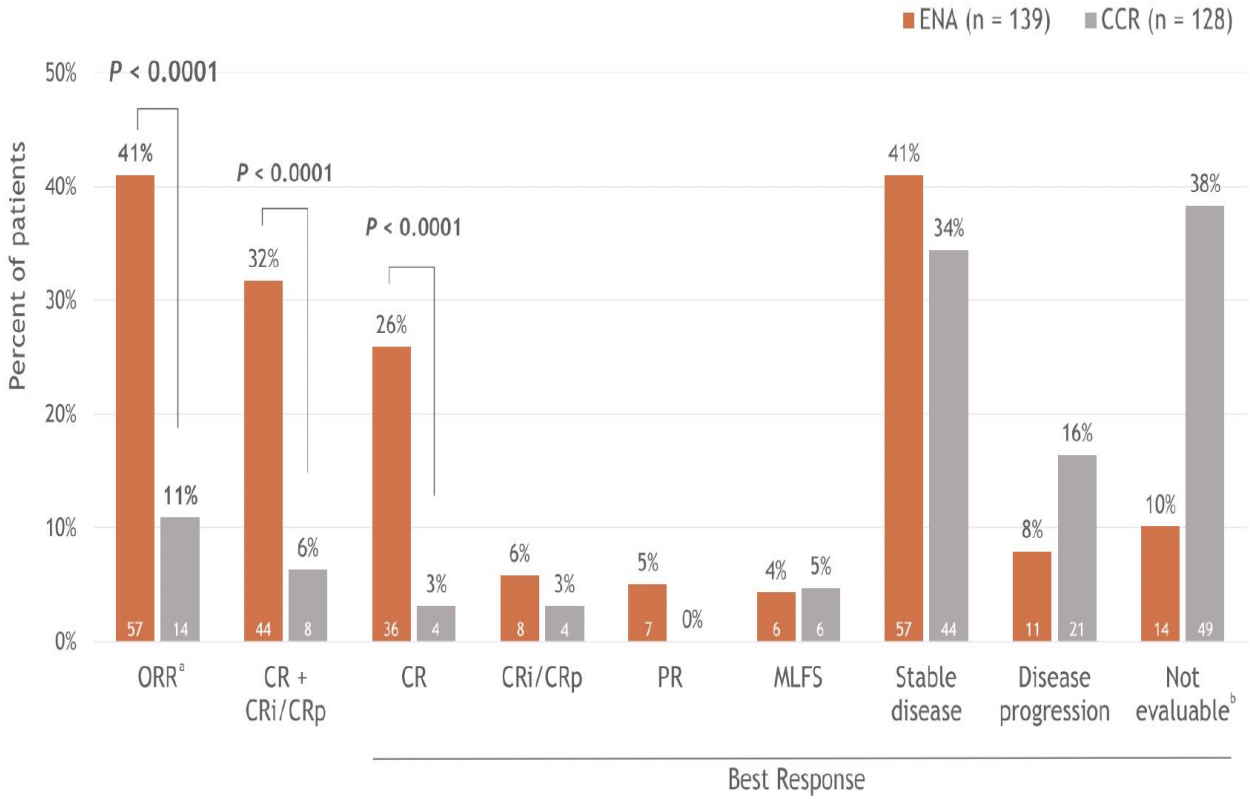
[a]Randomization was stratified by prior intensive AML therapy, primary refractory AML, and prior HSCT

DiNardo CD, et al. ASH 2021. Abstract 1243.

This activity is jointly provided by PIM Postgraduate Institute for Medicine Bio Ascend™

IDHentify Phase 3 of Enasidenib vs Other Lower-Intensity Therapies in *IDH2*-Mutated R/R AML

Clinical Response Rates



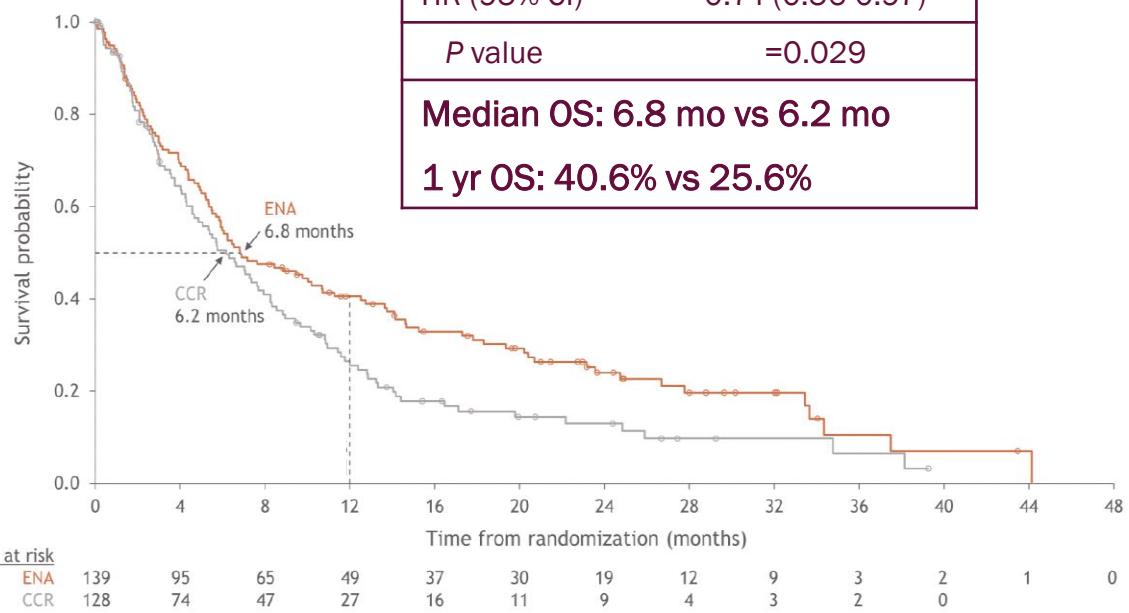
Hematologic Response		ENA (n=139)	CCR (n=128)
RBC TI, n/N (%)	RBC TD at BL, achieved TI on-study	29/93 (31.2)	8/76 (10.5)
	RBC TI at BL, retained TI on-study	28/45 (62.2)	7/37 (18.9)
Platelet TI, n/N (%)	Platelet TD at BL, achieved TI on-study	24/80 (30.0)	6/57 (10.5)
	Platelet TI at BL, retained TI on-study	42/58 (72.4)	19/56 (33.9)
Any HI, n (%)		57 (41.0)	16 (12.5)
HI-Erythroid		18 (12.9)	8 (6.3)
HI-Neutrophil		50 (36.0)	11 (8.6)
HI-Platelet		27 (19.4)	5 (3.9)

DiNardo CD, et al. ASH 2021. Abstract 1243.

IDHentify Phase 3 of Enasidenib vs Other Lower-Intensity Therapies in *IDH2*-Mutated R/R AML

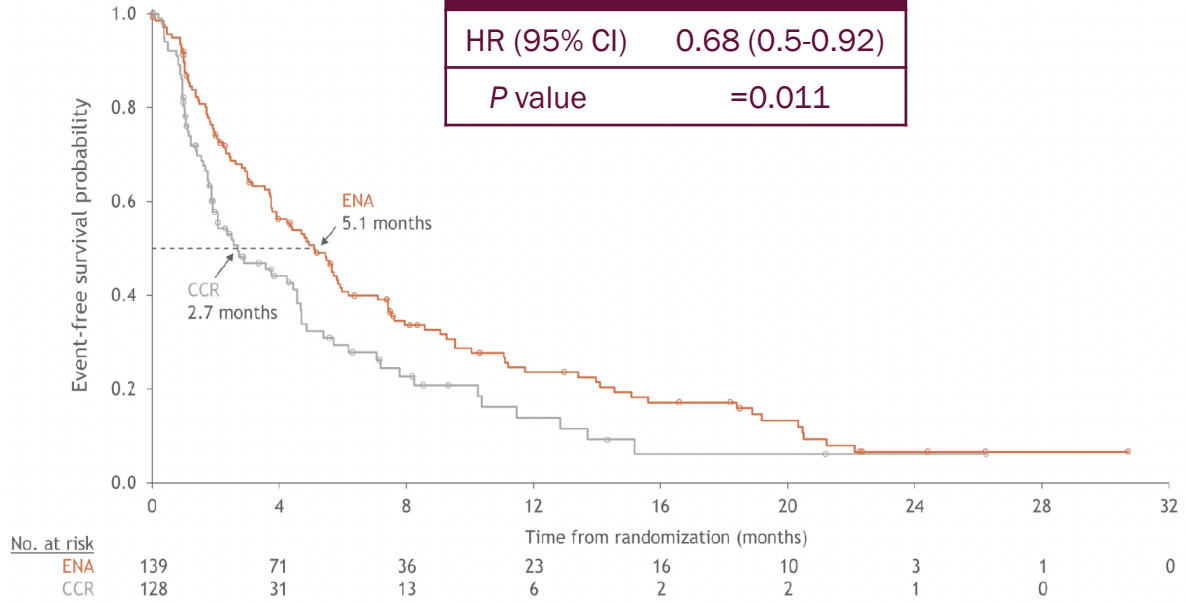
OS

OS: ENA vs CCR	
HR (95% CI)	0.74 (0.56-0.97)
P value	=0.029
Median OS: 6.8 mo vs 6.2 mo	
1 yr OS: 40.6% vs 25.6%	



EFS

EFS: ENA vs CCR	
HR (95% CI)	0.68 (0.5-0.92)
P value	=0.011



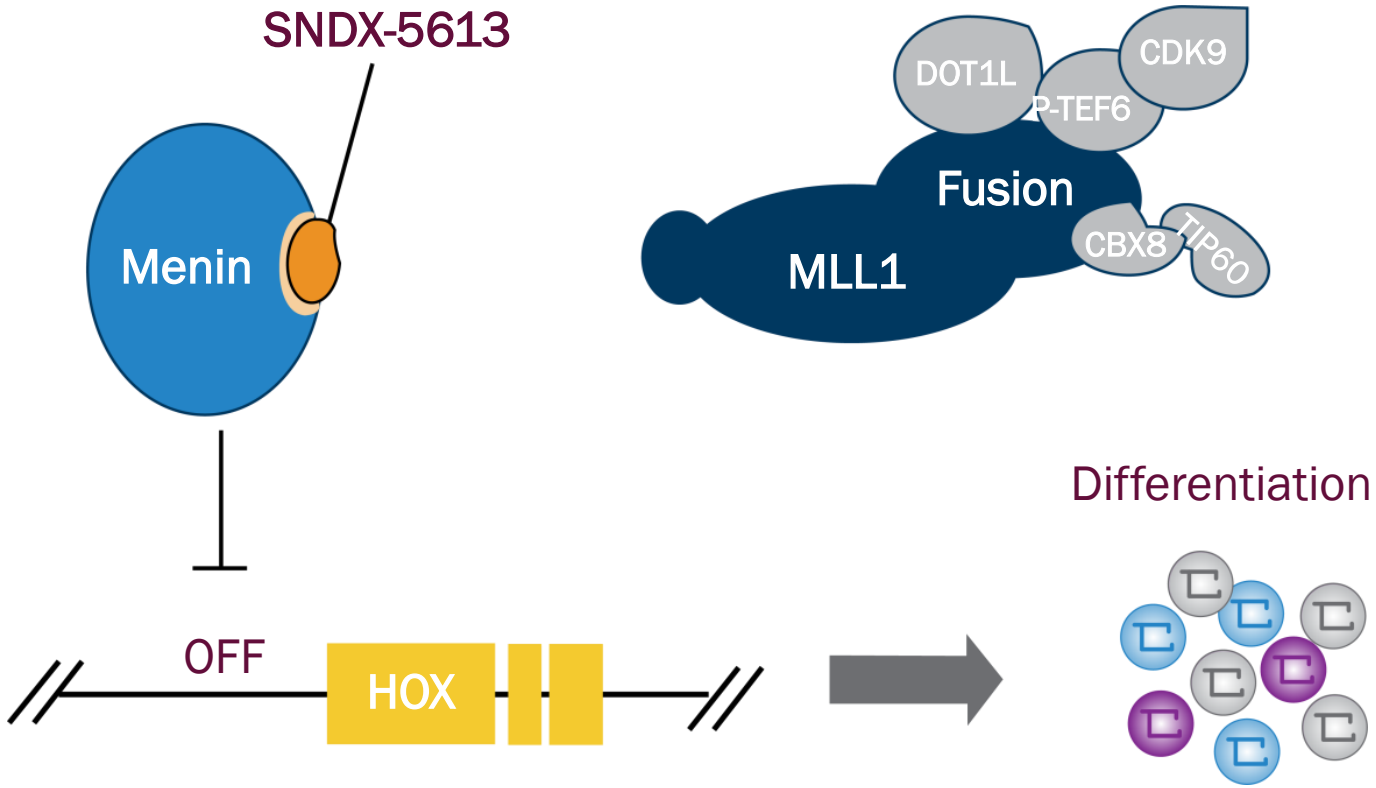
Efficacy-evaluable population; ENA (n=133), CCR (n=110)		
OS	HR (95% CI)	0.70 (0.53-0.93)
	P value	=0.013

- Patients who received additional AML treatment after discontinuing study treatment
  - 43 ENA (31%)
  - 52 CCR (41%); 12 (9%) received commercially available ENA

- DiNardo CD, et al. ASH 2021. Abstract 1243.

Menin Inhibition Is a Potentially Potent Strategy for Targeting MLLr and NPM1mut Leukemias

Mixed lineage leukemia-rearranged (MLLr) occurs in ~15% of pediatric and 5-10% of adult leukemias, and is associated with poor prognosis[1,2]



1. MLLr fusion proteins bind with high affinity to the nuclear protein menin[2]
2. The menin–MLL interaction enables leukemic transformation by driving a specific transcription program[2]
3. In preclinical studies, inhibition of the menin–*MLL1* interaction led to tumor cell differentiation and death[2]

1. Uckelmann HJ et al. ASH 2018. Abstract 546.
2. Kuhn MW, Armstrong SA. *Cancer Cell*. 2015;27:431-433.

This activity is jointly provided by PIM Postgraduate Institute for Medicine Bio Ascend™

SNDX-5613 Is a Potent, Selective Protein–Protein Interaction Menin Inhibitor

Currently being evaluated in the phase 1/2 AUGMENT-101 study (N = 54)[1]

Median age was 47 years

- 83% (n = 49) of patients had AML
- 64% (n = 38) had MLLr leukemia
- 22% (n = 13) had mutated *NPM1* leukemia

Two parallel dose-escalation cohorts

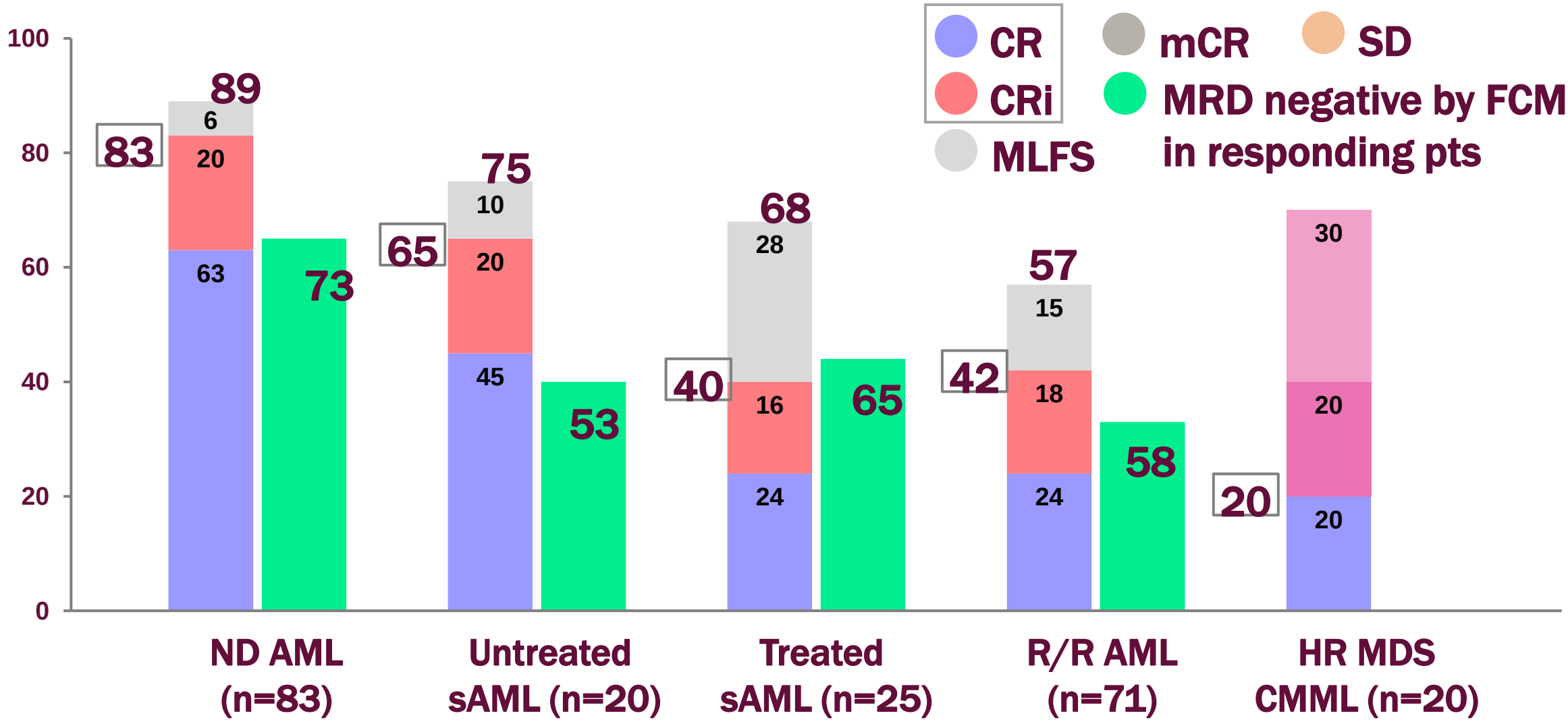
- Arm A: not taking strong CYP3A4 inhibitors
- Arm B: strong CYP3A4 inhibitors
- SYNDX-5613 dosing: orally Q12h in continuous 28-day cycles

MTD was 276 mg Q12h in arm A and 163 mg Q12h in arm B

Best Response, n (%)		Efficacy Population (n=51)
Response	ORR	28 (55)
	CR	8 (16)
	CRh	4 (8)
	CRp	7 (14)
	MLFS	9 (18)
MRD neg	CRc MRD neg rate	16/51 (31)
	within CR/CRh MRD neg	11/12 (92)
	within CR/CRh/CRp MRD neg	16/19 (84)
MLLr	**ORR**	**23/38 (61)**
	CR/CRh	**9/38 (24)**
NPM1 mut	ORR	5/13 (38)
	CR/CRh	3/13 (23)

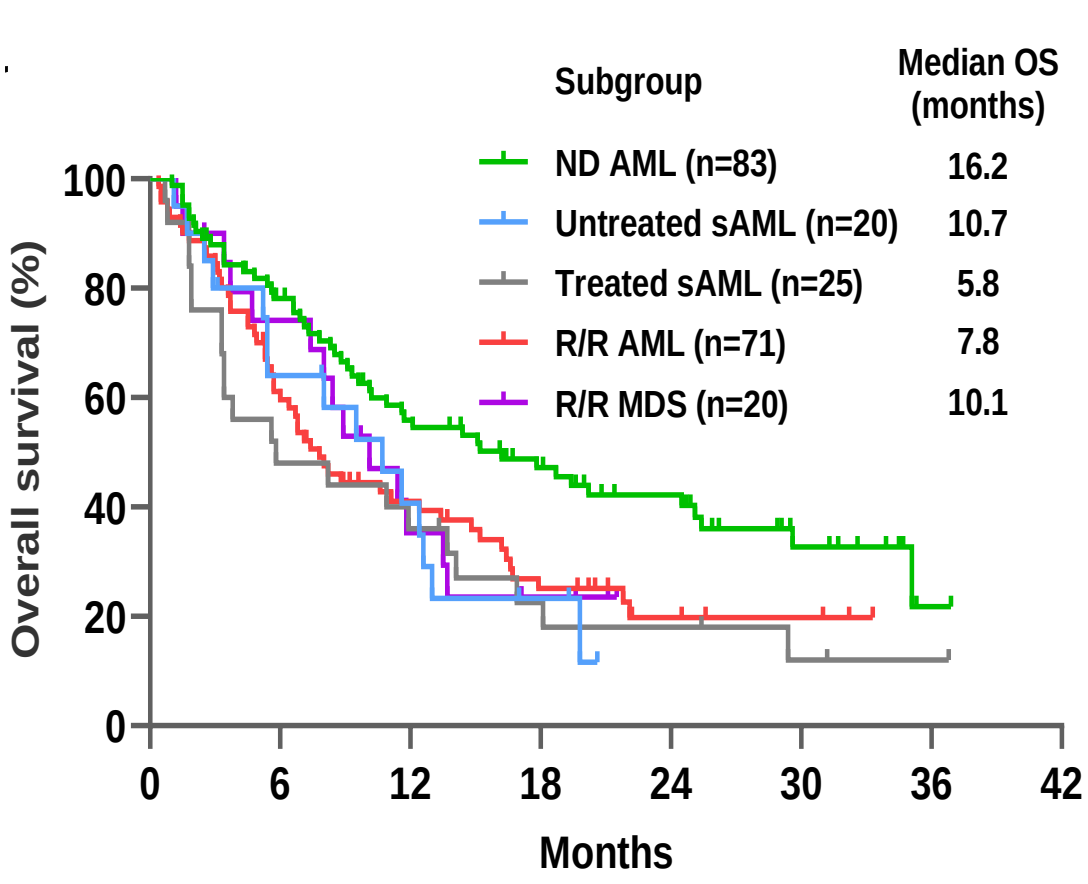
Stein E et al. ASH 2021. Abstract 699.

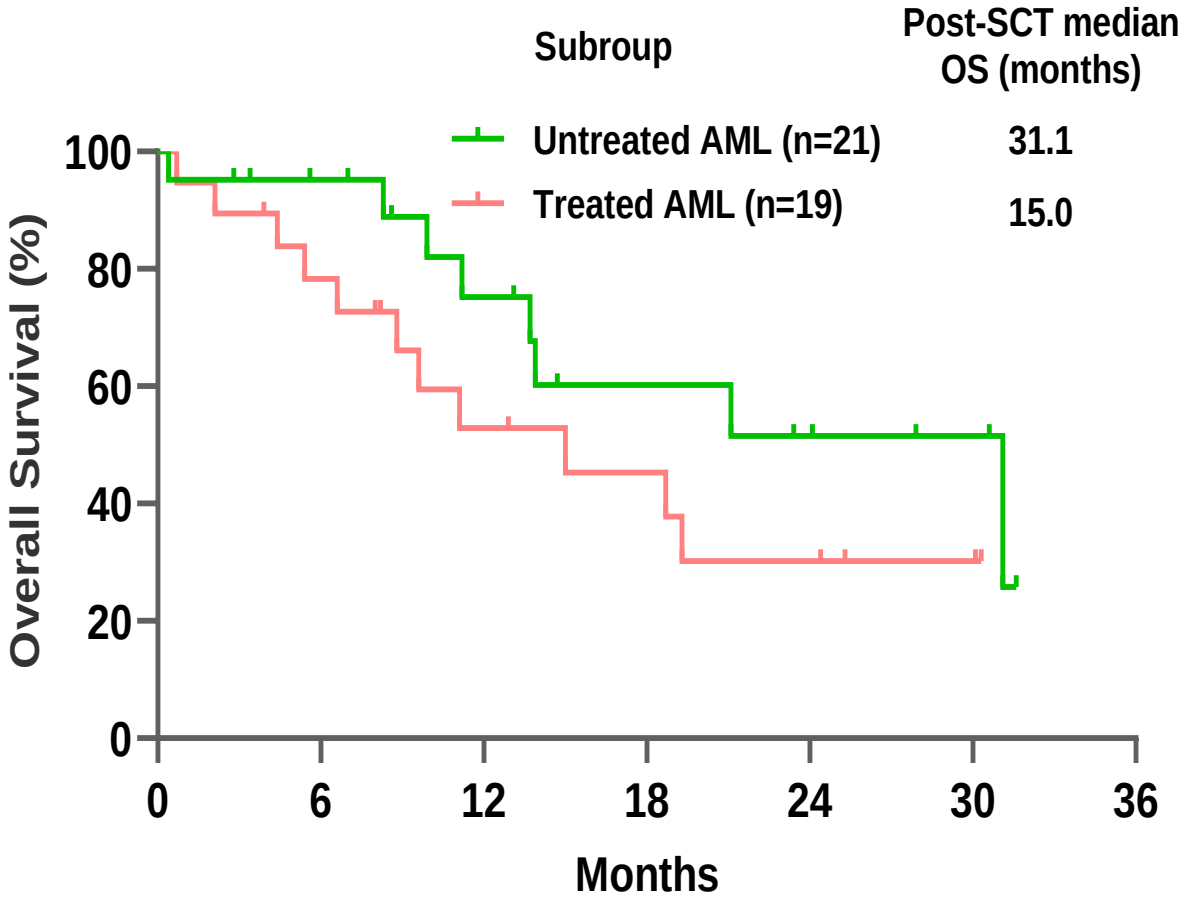
DAC10 + VEN for Newly Dx and R/R AML and MDS



Maiti A et al. ASH 2021. # 1270

DAC10 + VEN for Newly Dx and R/R AML and MDS





Maiti A et al. ASH 2021. # 1270

THANK YOU!

cdinardo@mdanderson.org

This activity is jointly provided by PIM Postgraduate Institute for Medicine Bio Ascend™