Acute Leukemia Review January 2024

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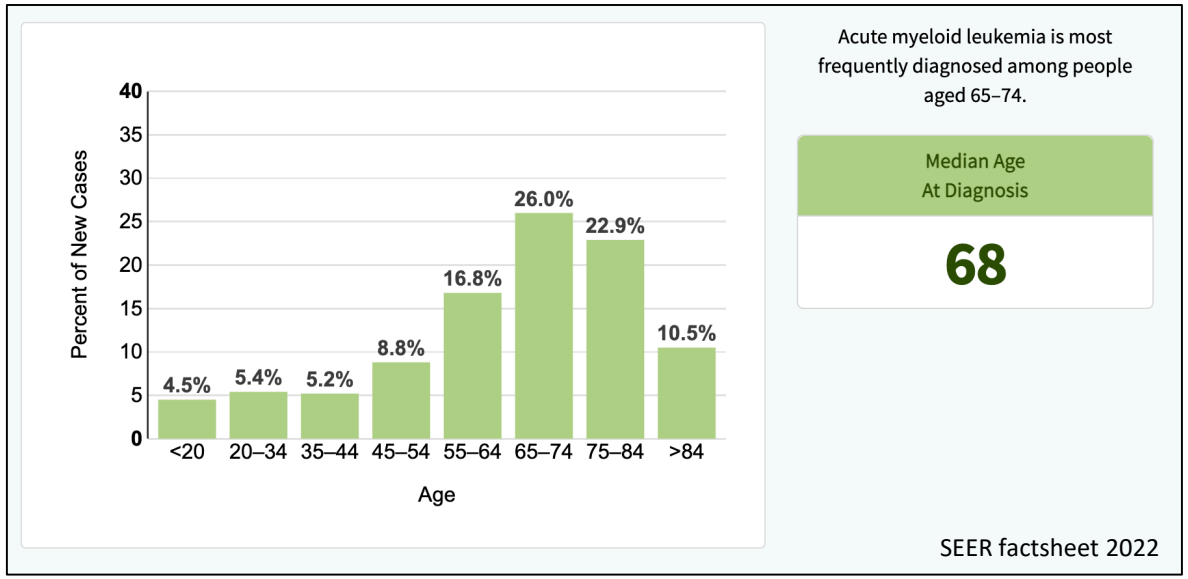
Conflict of interest

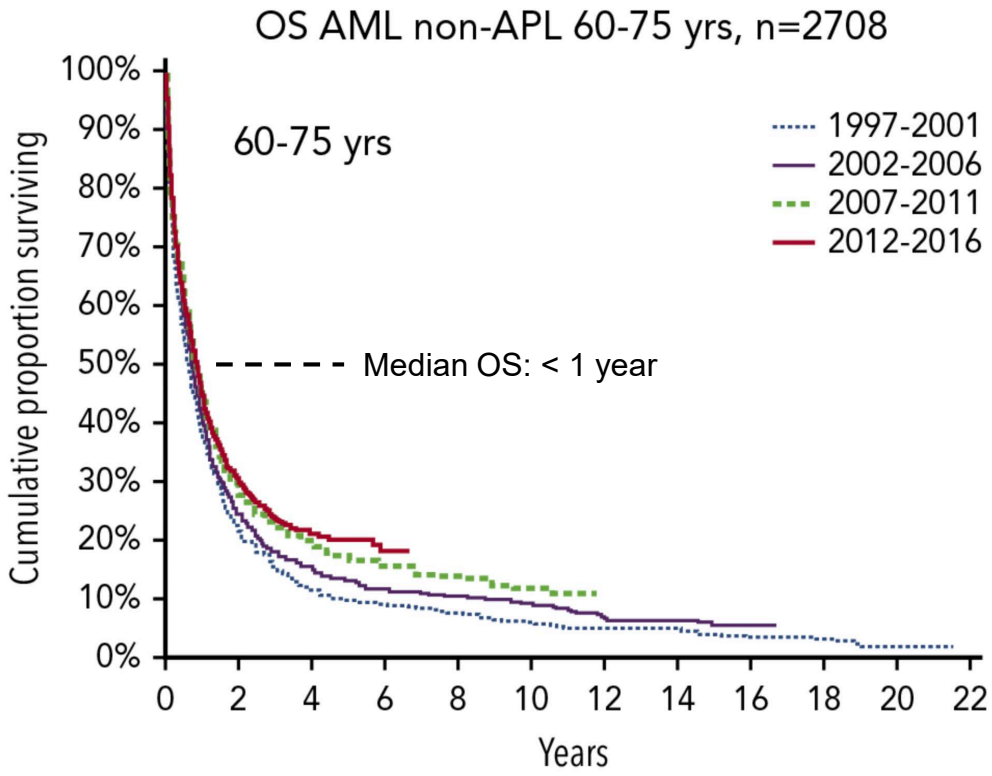
Consultancy: COTA Healthcare
Advisory board: AbbVie, Rigel, Servier

Epidemiology

Acute myeloid leukemia is an aggressive hematologic malignancy in older adults

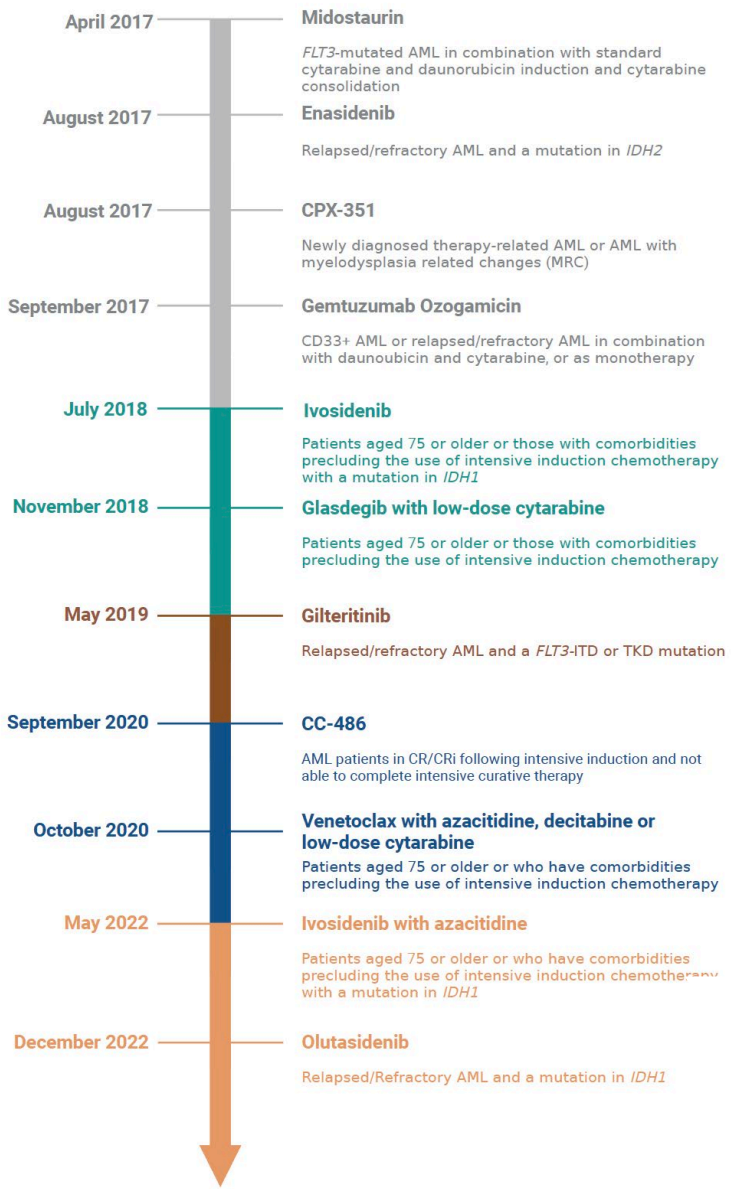


Overall survival in older (i.e., most) patients treated with intensive chemotherapy remains poor



Juliusson et. al. *Blood* 2019

Standard of care targeted options



← Midostaurin

← CPX-351 (Vyxeos)

← Gemtuzumab

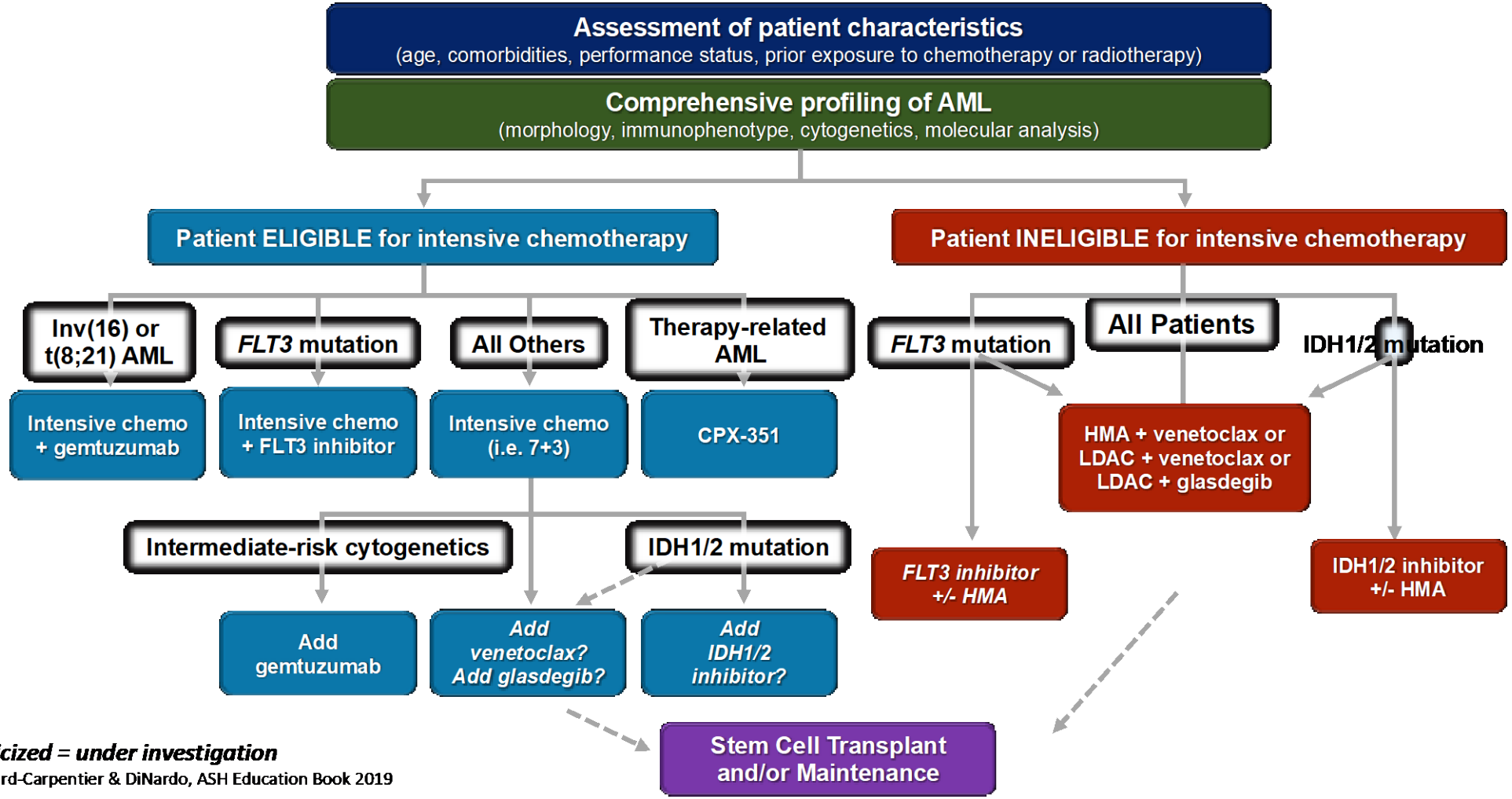
← Ivosidenib

← HMA/LDAC+venetoclax

← Ivosidenib + azacitidine

Frontline options (recent addition: quizartinib in *FLT3*-ITD mutated AML)

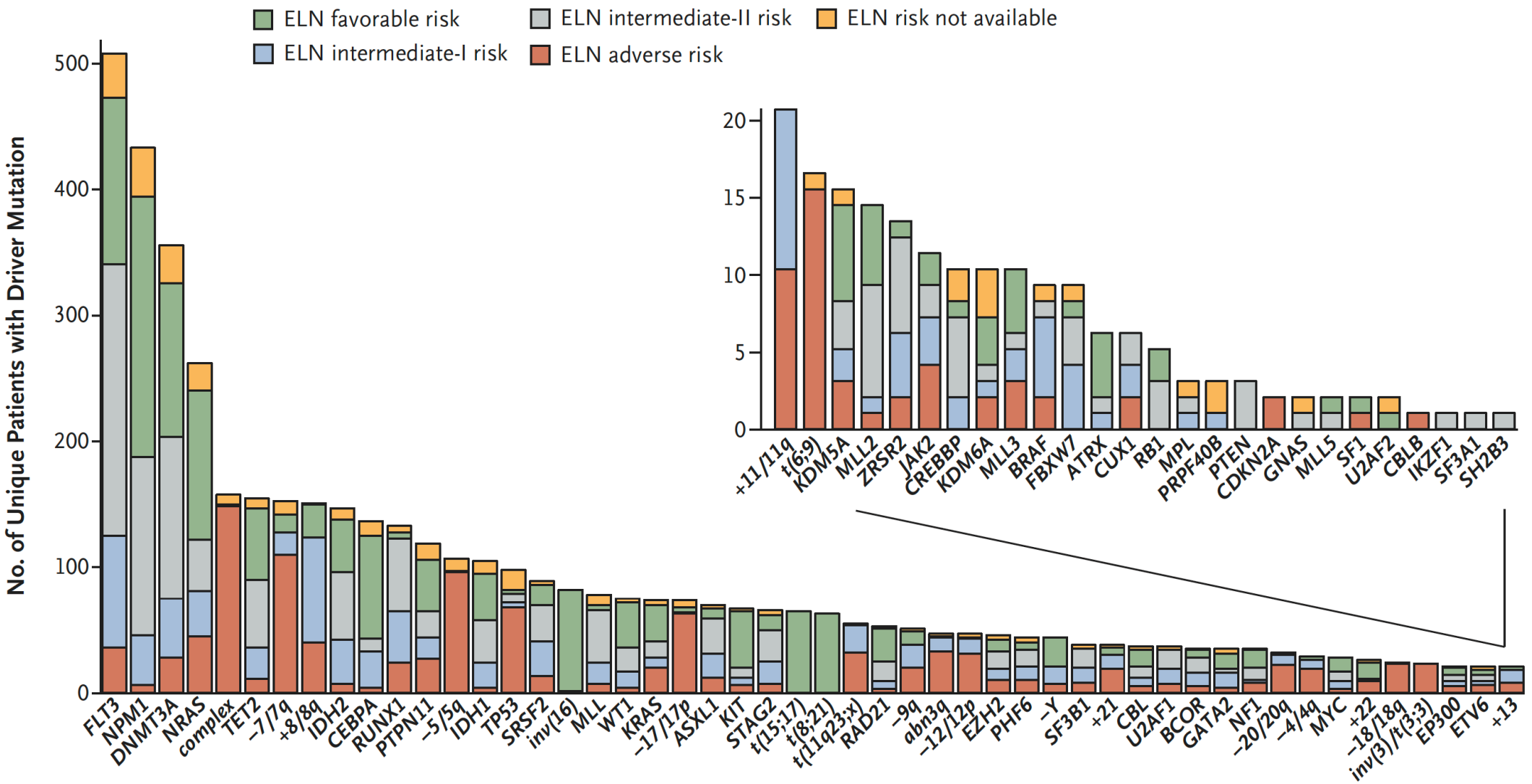
AML Treatment approach



Italicized = under investigation

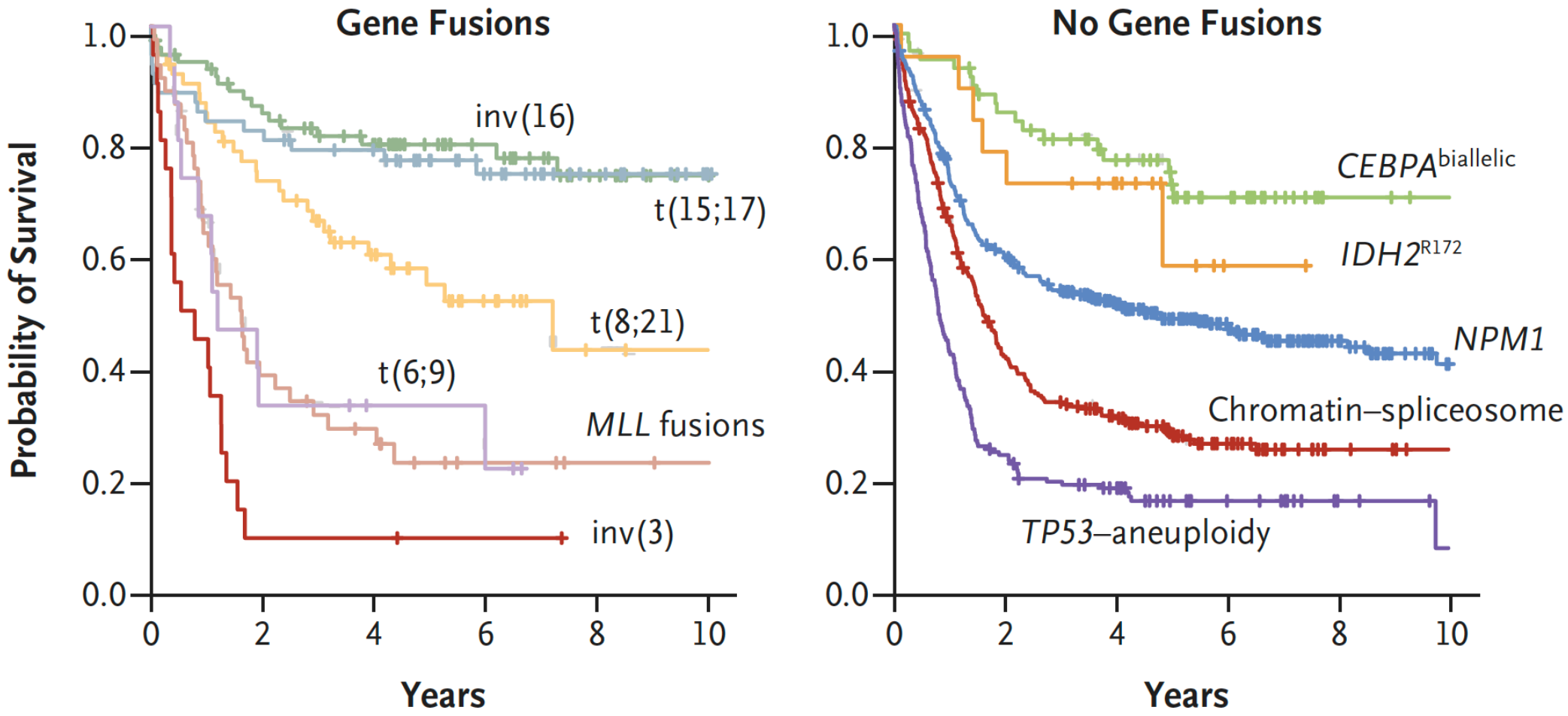
Richard-Carpentier & DiNardo, ASH Education Book 2019

Prognostication: Genomic landscape



Pappaemanuil et. al. *NEJM* 2016

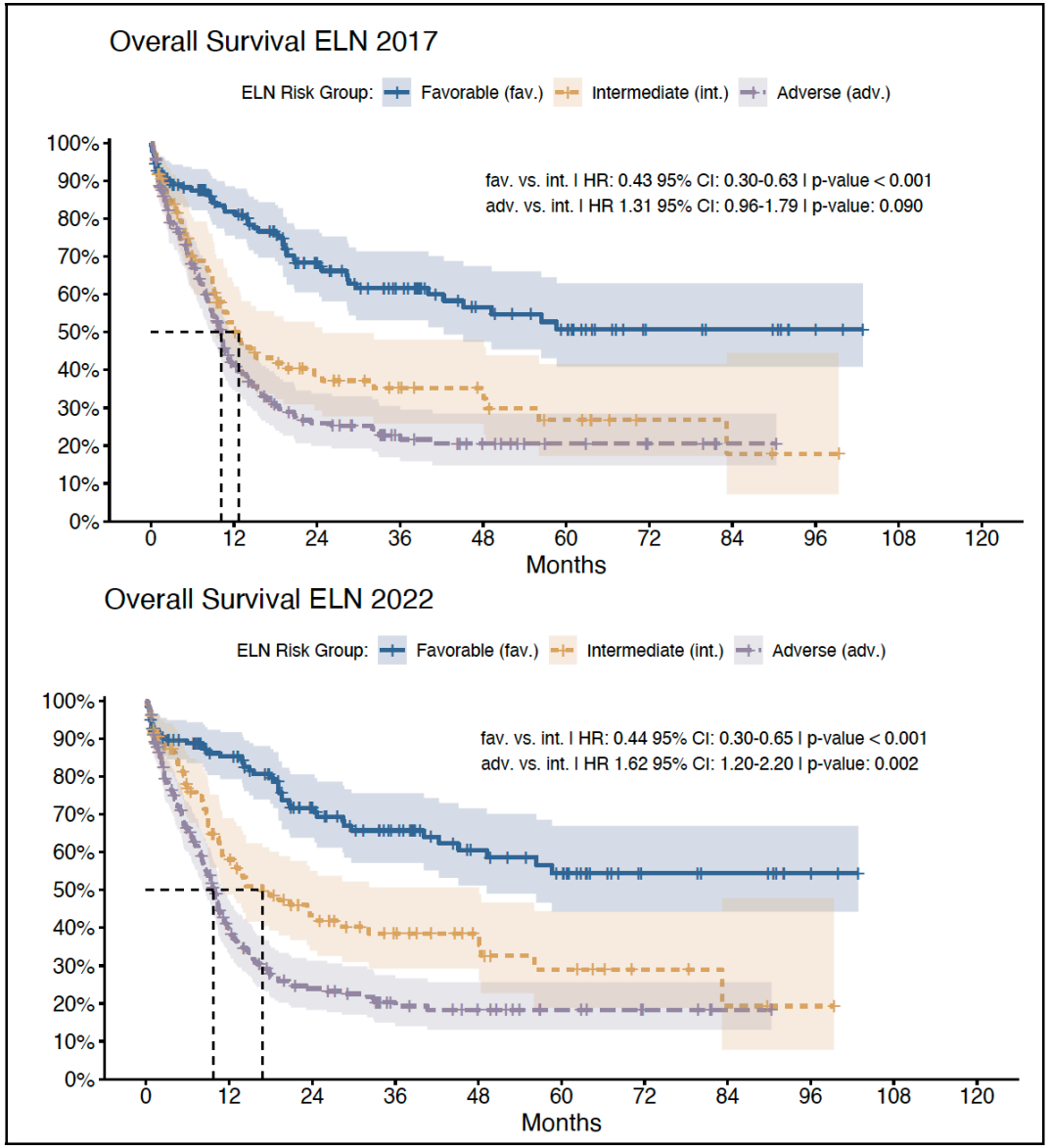
Prognostication: Genomic landscape



Pappaemanuil et. al. *NEJM* 2016

ELN 2022: A step forward…

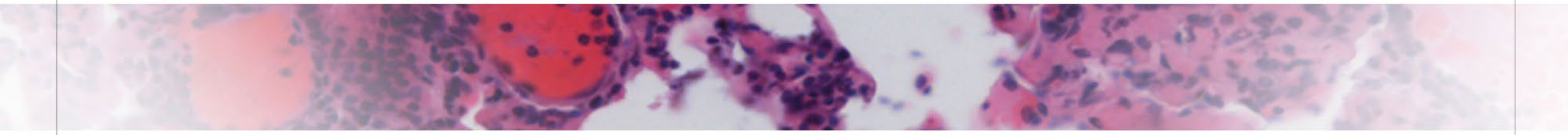
Risk category†	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*†,‡ • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*†,‡ • Mutated *NPM1*†,§ without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged# • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*, *MECOM(EVI1)* • t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype,** monosomal karyotype†† • Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and/or *ZRSR2*‡‡ • Mutated *TP53*[a]



Döhner et. al. *Blood* 2022; Lachowiez C, Long N et. al. *Blood Advances* 2022

AML Prognosis: Intensive chemotherapy

American Society of Hematology
Helping hematologists conquer blood diseases worldwide



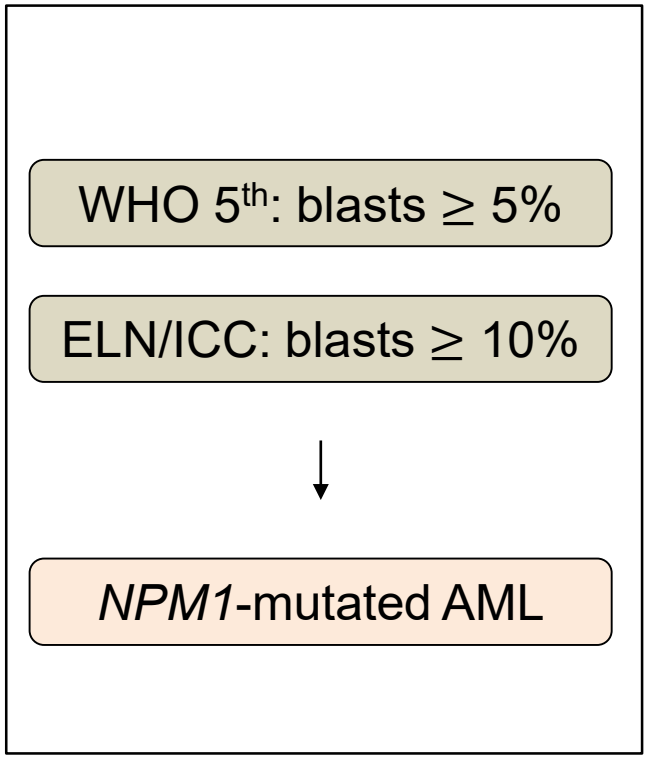
Influence of Bone Marrow Blast Enumeration and Co-Occurring Myelodysplasia Related Gene Mutations in *NPM1*-Mutated Myeloid Malignancies

Curtis A Lachowiez, MD[1], Georgios Asimomitis[2,3], Elsa Bernard, PhD[2], Ivory Tang[4], Yanis Tazi, MSc, BSc[4], Amanda Gilkes[5], Ian Thomas[6], Lars Bullinger[8], Konstanze Döhner[9], Hartmut Dohner, MD[9], Brian Huntly, PhD[10,11], Nigel H. Russell, MD[12], Sanam Loghavi, MD[13*], and Elli Papaemmanuil[15*]

[1]Knight Cancer Institute, Oregon Health & Science University, Portland, OR, [2]Computational Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY, [3]Biomedical Systems Laboratory, Department of Mechanical Engineering, National Technical University of Athens, Athens, Greece, [4]Memorial Sloan Kettering Cancer Center, New York, NY, [5]Cardiff University, Cardiff, GBR, [6]Cardiff University, Cardiff, United Kingdom, [8]Charité Universitätsmedizin Berlin, Berlin, Germany, [9]Department of Internal Medicine III, University Hospital of Ulm, Ulm, Germany, [10]Wellcome - MRC Cambridge Stem Cell Institute, Cambridge, United Kingdom, [11]Cambridge Institute For Medical Research, University of Cambridge, Cambridge, GBR, [12]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom, [13]Department of hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX, [15]Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, NY. *Indicates dual senior authors

Background: Unanswered questions in *NPM1*-mutated MN

WHO 5th edition and ICC/ELN guidelines differ for definition of *NPM1*-mutated AML[5,6]



Does blast enumeration impact LFS and OS in *NPM1*-mutated myeloid neoplasms?

Myelodysplasia (MR) associated gene mutations currently considered adverse-risk prognostic markers unless occurring with *NPM1*[6]

Risk category†	Genetic abnormality
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Do MR-gene mutations impact outcomes when associated with a co-occurring *NPM1* mutation?

[5]Khoury et. al. Leukemia 2022, [6]Döhner et. al. Blood 2022

Study design: Blast enumeration and MR mutations in *NPM1*-mutated MN

NPM1-mutated MN cohort

International Working Group for Prognosis in MDS cohort[7] (N=3,323)

↓

Pathogenic/likely-pathogenic *NPM1* mutation (N=38)

- Blasts < 10% (N=20)
- Blasts 10-19% (N=18)

Clinical demographics

Molecular landscape

Leukemia-free and overall survival

NPM1-mutated AML cohorts

UK National Cancer Research Institute & AML Study Group Cohorts[8] (N=3,653)

↓

Pathogenic/likely-pathogenic *NPM1* mutation (N=1,093)

- MR wild-type (N=935)
- MR mutated (N=158)

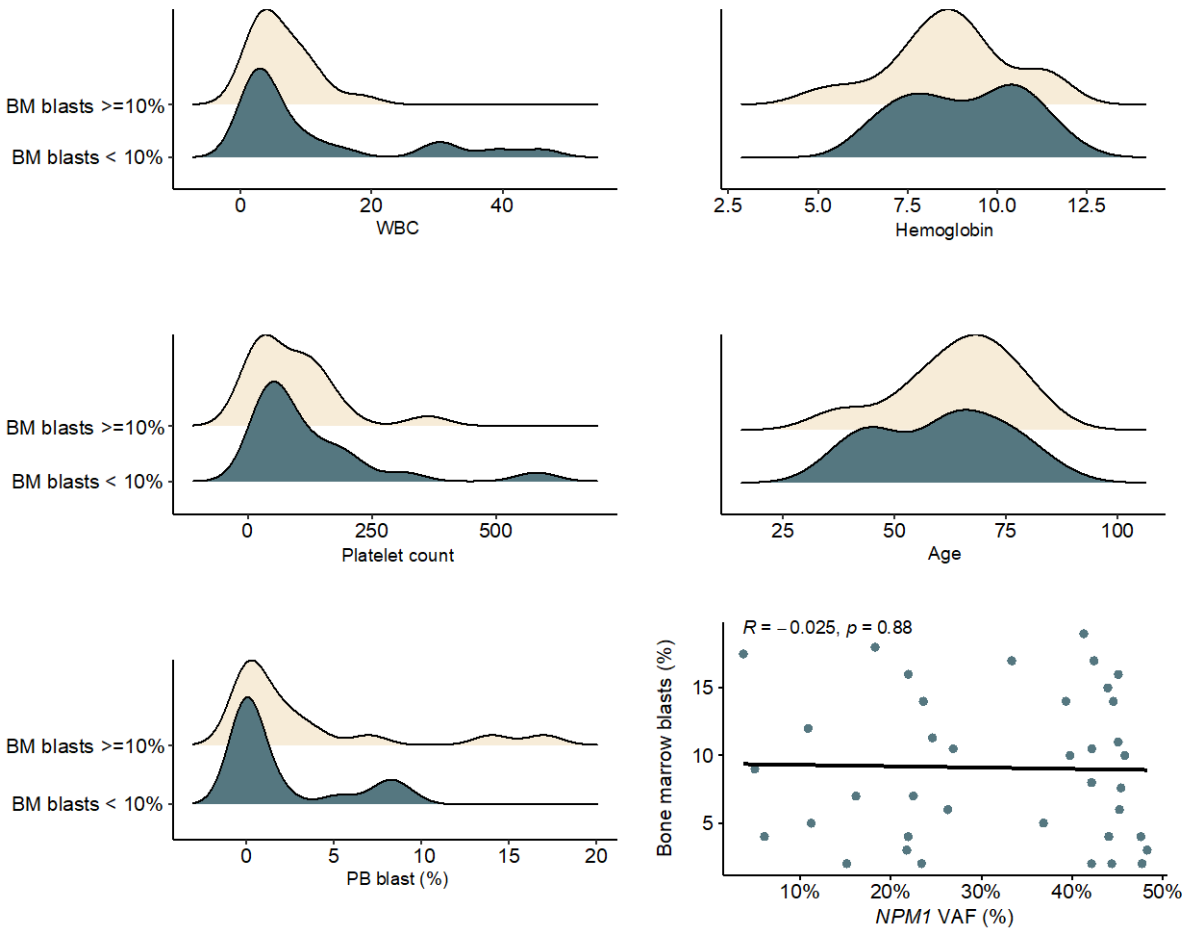
Clinical demographics

Clonal hierarchy of co-mutations

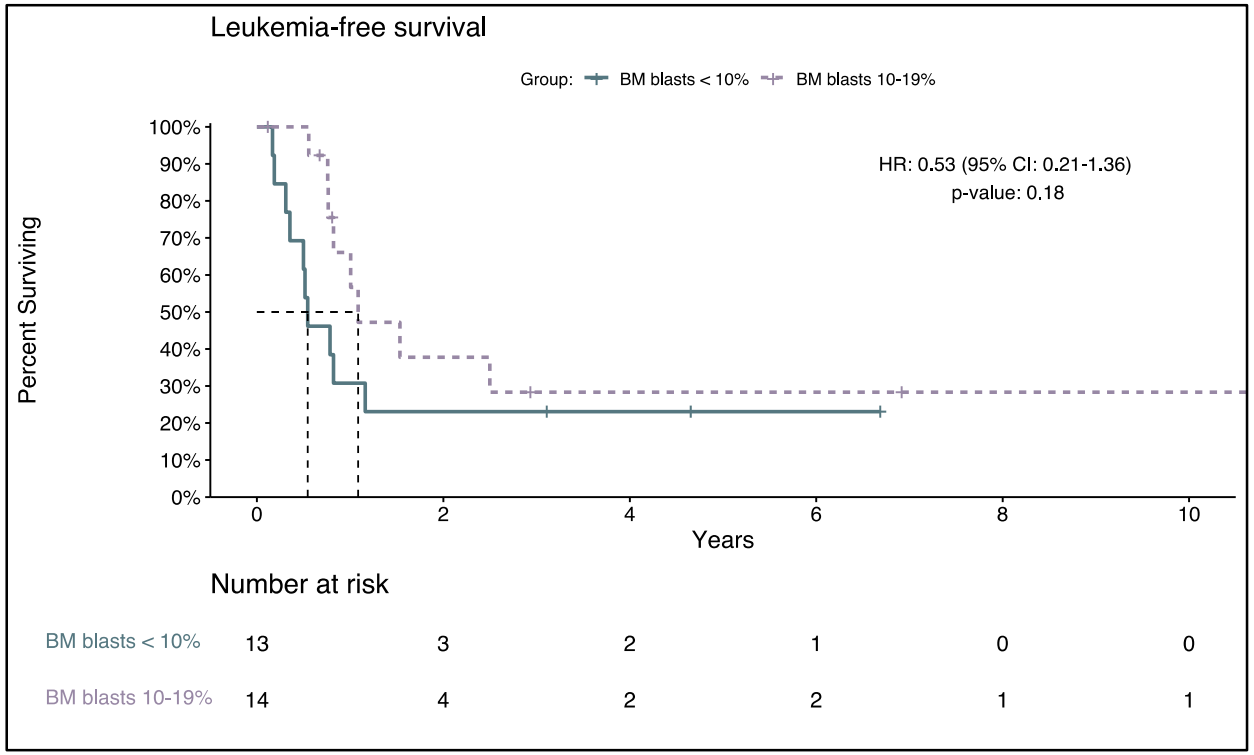
Overall survival

[7]Bernard et. al. NEJM Evidence 2022

Results: Blast enumeration and MR mutations in *NPM1*-mutated MN



In patients with MN and blasts < 20%, no significant difference was observed with respect to clinical or hematologic parameters between patients with blasts < 10% vs. 10-19%.



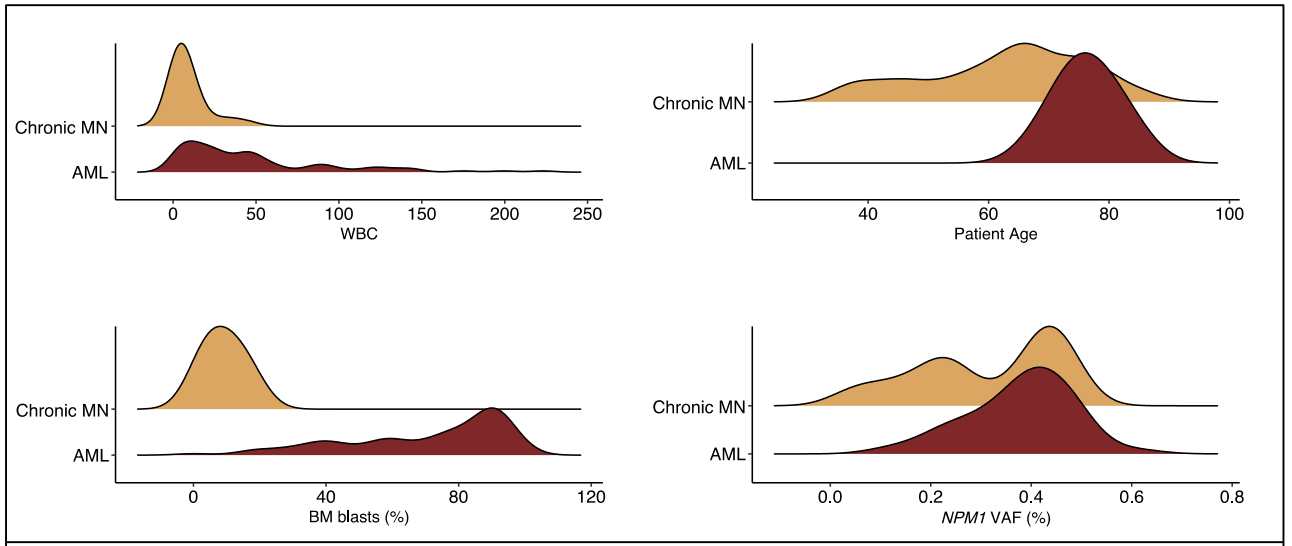
Results: Similar survival in *NPM1*-mutated MN and AML treated with HMAs

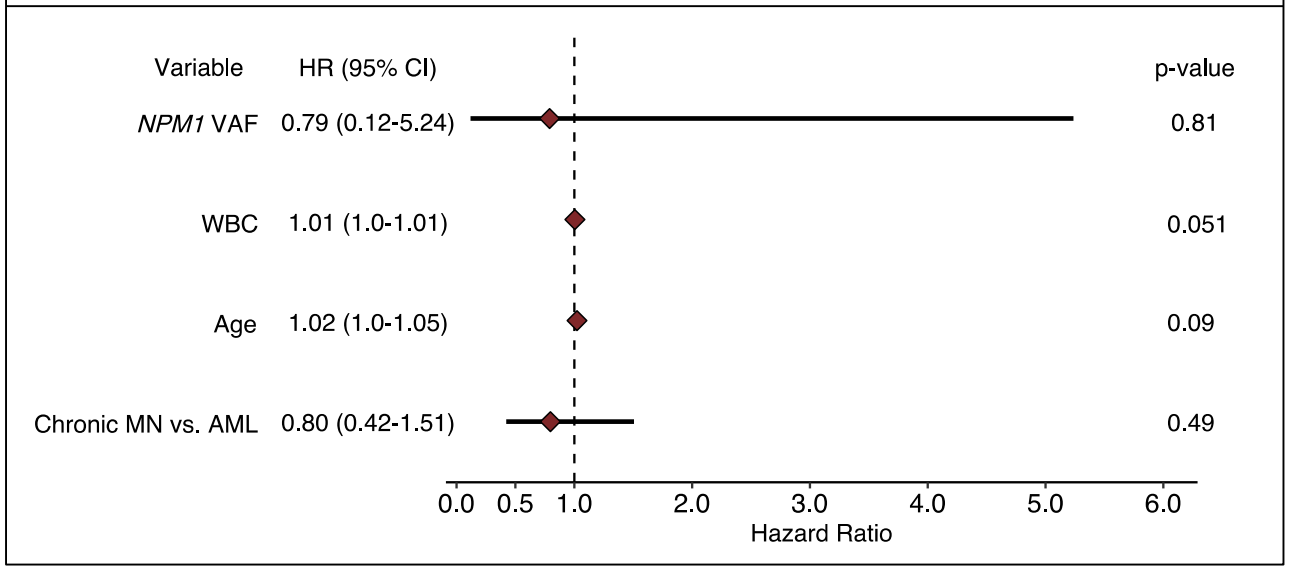
Comparative cohort of *NPM1*-mutated MN vs. *NPM1*-mutated AML treated with lower intensity therapy

NPM1-mutated Chronic MN (N=37)

NPM1-mutated AML (N=87)

→ *NPM1*-mutated Chronic MN/ AML (N=124)



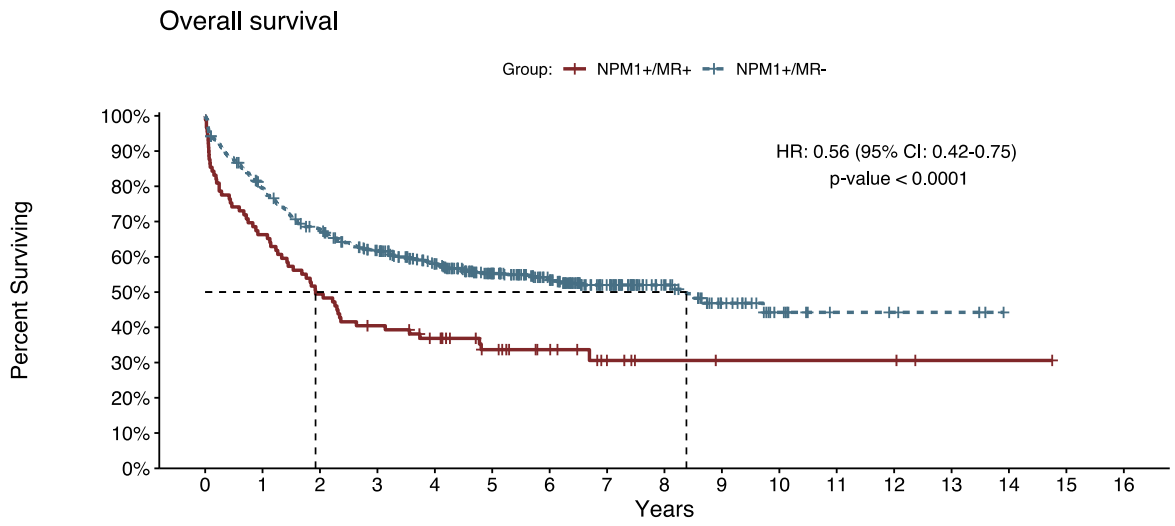


After adjustment for baseline variables, OS did not significantly differ between patients with *NPM1*-mutated MN vs. AML

Median OS: 0.3 vs. 1.1 years, p-value: 0.49

Results: Inferior survival observed with MR mutations in ELN favorable-risk AML

In patients with ELN 2022 favorable-risk AML, co-mutations in MR mutations were associated with inferior survival

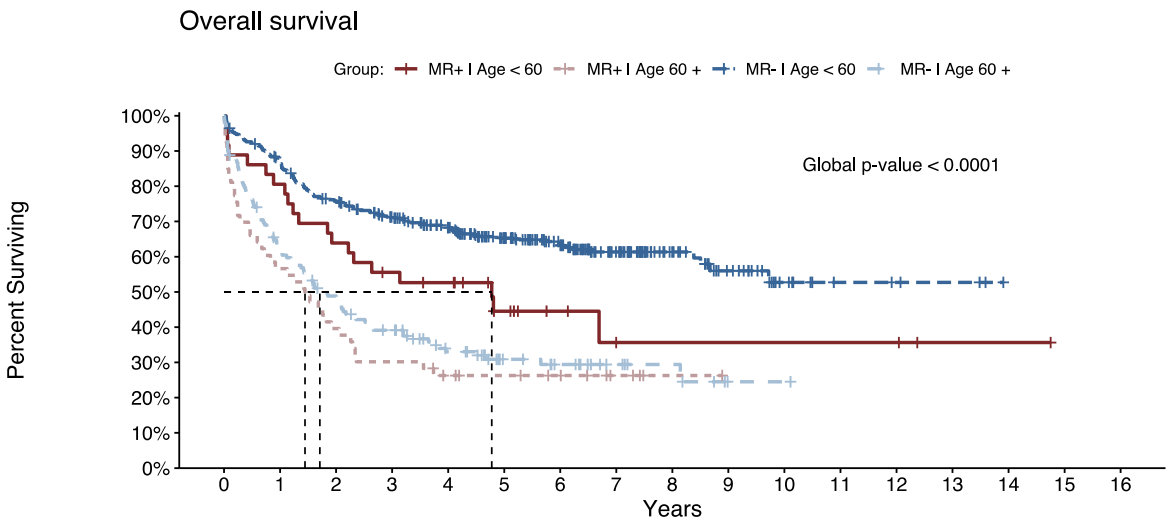


Number at risk

NPM1+/MR+	89	59	44	35	29	20	14	7	4	3	3	3	3	1	1	0	0
NPM1+/MR-	482	377	317	274	228	174	134	85	47	26	12	5	4	3	0	0	0

Median OS: 1.9 vs. 8.8 years, p-value < 0.0001

Inferior survival largely appeared driven by MR mutations in younger (age < 60) patients with AML



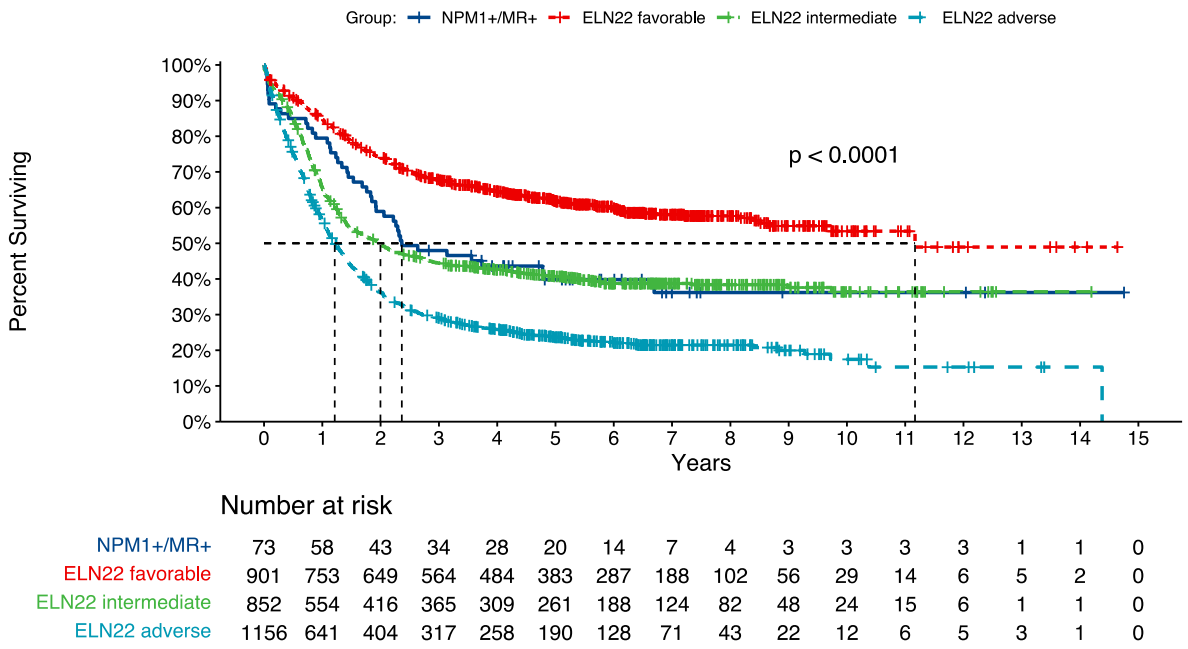
Number at risk

MR+ | Age < 60	36	29	23	19	17	10	6	3	3	3	3	3	3	1	1	0	0
MR+ | Age 60 +	53	30	21	16	12	10	8	4	1	0	0	0	0	0	0	0	0
MR- | Age < 60	339	290	251	223	193	152	117	76	41	25	11	5	4	3	0	0	0
MR- | Age 60 +	143	87	66	51	35	22	17	9	6	1	1	0	0	0	0	0	0

Median OS: 4.8 vs. NR, global p-value < 0.0001

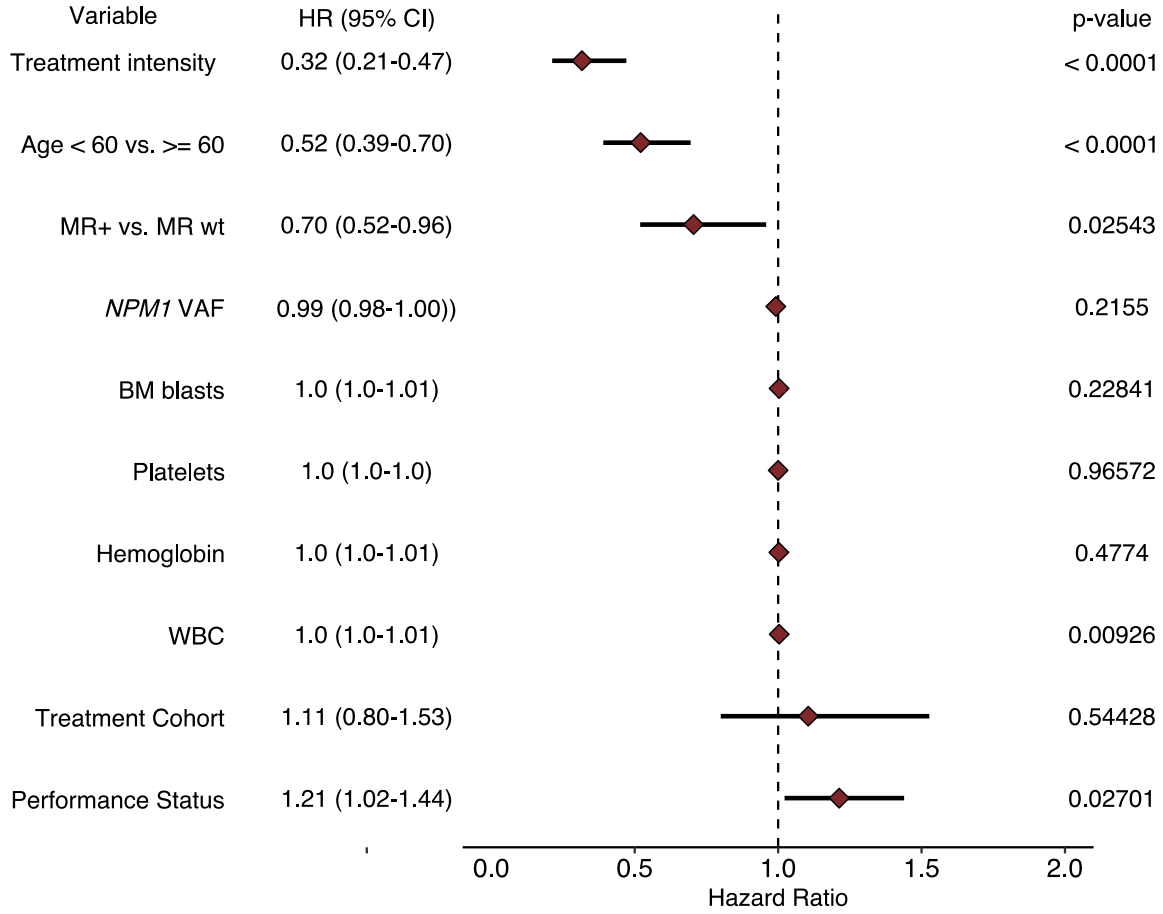
Results: Inferior survival observed with MR mutations in ELN favorable-risk AML

Patients with mutations in MR genes and *NPM1* have survival similar to ELN 2022 intermediate risk AML when treated with intensive chemotherapy without venetoclax



Median OS: 2.4 vs. 2.0 years

Co-occurring MR mutations independently associated with inferior OS in ELN favorable-risk *NPM1*-mutated AML



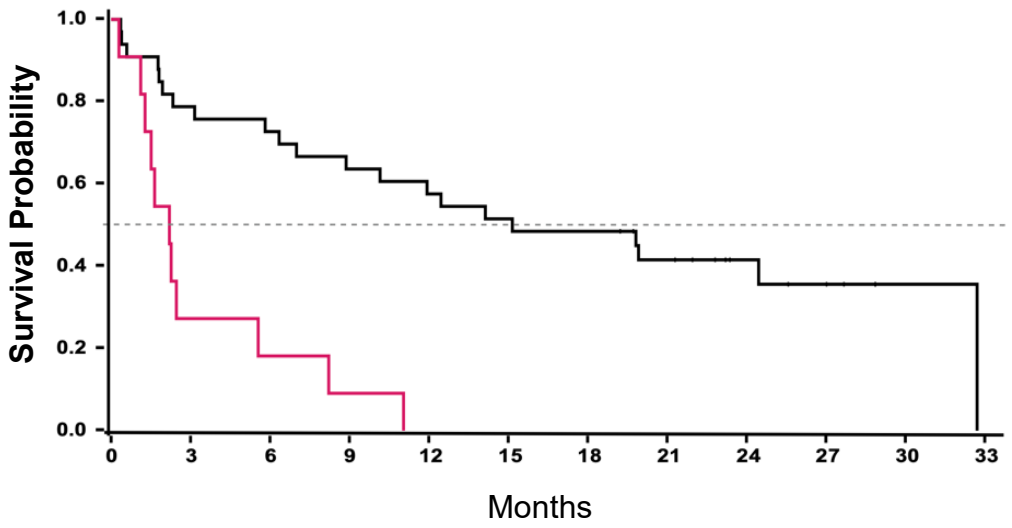
AML Treatment: Lower intensity therapy

Doublet combinations

IDH1-mutated AML: AZA+VEN & IVO+AZA

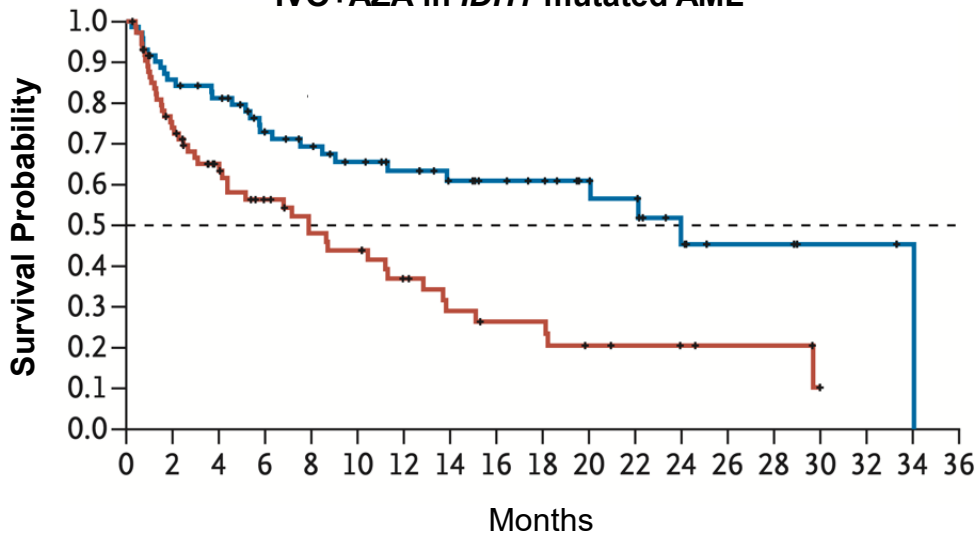
AZA+VEN and IVO+AZA both active in *IDH1*-mutated AML

AZA+VEN in *IDH1*-mutated AML



Median OS: 15.2 months (95% CI: 7.0-NE)
24-month OS: 41.6%
N= 33 patients

IVO+AZA in *IDH1*-mutated AML



Median OS: 24 months (95% CI, 11.3 to 34.1)
24-month OS: 50%
N= 72 patients

Key questions:

1. Improved outcomes with sequencing or combined therapy?
2. AE profile of combinations?
3. Durability of response?

Pollyea et. al. Clinical Cancer Research 2022; Montesinos et. al. NEJM 2022

A Comparison of Acute Myeloid Leukemia Regimens: Hypomethylating Agents Combined with Ivosidenib or Venetoclax in Newly Diagnosed Patients with *IDH1* Mutations – A Real-World Evidence Study

B. Douglas Smith[1], Curtis A. Lachowiez[2], Alexander Joseph Ambinder[1], Gary Binder[3], Anne Angiolillo[3], Assaf Vestin[3], Robert Paglia[3], Ravi Potluri[4], Eros Papademetriou[4], Thomas W. LeBlanc[5]

[1]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; [2]Knight Cancer Institute, Oregon Health & Science University, Portland, OR; [3]Servier Pharmaceuticals LLC, Boston, MA; [4]Putnam Associates, Boston, MA; [5]Duke Cancer Center, Durham, NC

Presented at the 65th Congress of the American Society of Hematology (ASH), December 9–12, 2023, San Diego, CA

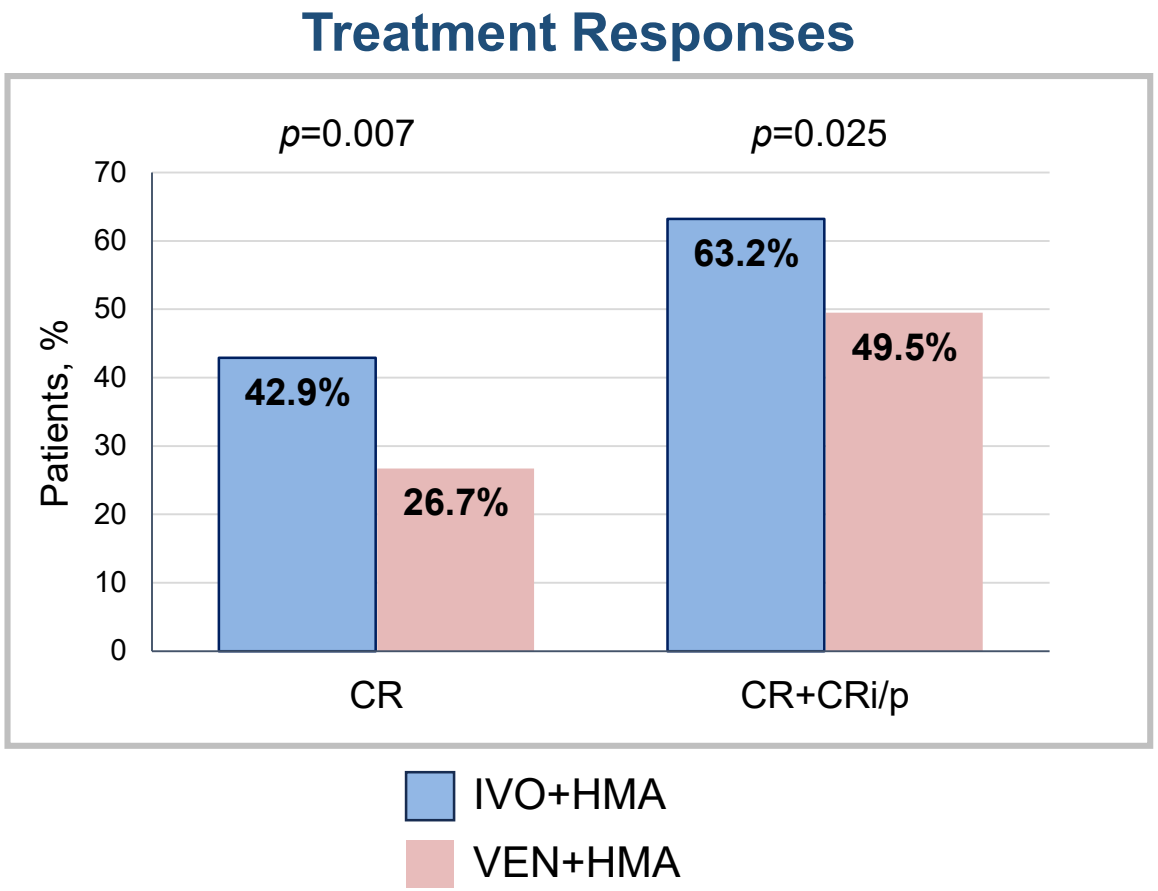
Results – Baseline Characteristics

	Overall		Ivosidenib with HMA		Venetoclax with HMA		P value
	n	%	n	%	n	%	
Total	**283**	100.0%	**182**	100.0%	**101**	100.0%	
ECOG Performance score							
0 - 1	215	76.0%	143	78.6%	72	71.3%	0.169
2 - 4	68	24.0%	39	21.4%	29	28.7%	
ELN cytogenetic risk status							
Favorable	58	20.5%	45	24.7%	13	12.9%	0.026‡
Intermediate	169	59.7%	103	56.6%	66	65.3%	
Poor	43	15.2%	29	15.9%	14	13.9%	
Not assessed	13	4.6%	5	2.7%	8	7.9%	
Disease history							
MDS	66	23.3%	41	22.5%	25	24.8%	0.530
Myeloproliferative neoplasms (MPN)	25	8.8%	19	10.4%	6	5.9%	
Secondary AML	9	3.2%	7	3.8%	2	2.0%	
Secondary AML-like mutations	5	1.8%	4	2.2%	1	1.0%	

†P-value from a Chi-Squared test for categorical variables, Kruskal-Wallis for continuous variables. ‡Indicates statistical significance.

AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; ELN, European LeukemiaNet; MDS, myelodysplastic syndromes; MPN, myeloproliferative neoplasms; HMA, hypomethylating agent.

Results – Treatment Response



- Median time to best response:
  - IVO+HMA = 3.3 mos
  - VEN+HMA = 4.1 mos (p=0.02)
- Median time to first bone marrow biopsy on treatment across cohorts was 56 days

CR, complete response; CRi/p, CR with incomplete count recovery or incomplete platelet recovery; IVO+HMA, ivosidenib+hypomethylating agent; VEN+HMA, venetoclax+hypomethylating agent.

Results – Bridge to Transplant and Event-free Survival

	IVO+HMA	VEN+HMA	P Value
Bridge to Allogenic Transplant	11.5%	5.0%	0.066
Event-Free Survival* (6 mos EFS)	56.0%	39.6%	0.044
Hazard Ratio = 0.773			

* Defined as CR within 24 weeks, and no relapse or death
* Bridge to Transplant was considered a competing risk

CR, complete response; EFS, event-free survival; IVO+HMA, ivosidenib+hypomethylating agent; VEN+HMA, venetoclax+hypomethylating agent.

Results – Safety

Adverse Events	Ivosidenib with HMA		Venetoclax with HMA		P value
	n	%	n	%	
n	182	100.0%	101	100.0%	
Adverse Event					
Febrile neutropenia (Grade 3+)	20	11.0%	13	12.9%	0.636
Sepsis	8	4.4%	3	3.0%	0.552
Infection (Grade 3+)	15	8.2%	11	10.9%	0.460
Pneumonia (Grade 3+)	6	3.3%	5	5.0%	0.490
Neutropenia (Grade 3+)	21	11.5%	10	9.9%	0.673
Thrombocytopenia (Grade 3+)	24	13.2%	10	9.9%	0.415
Leukocytosis (Grade 3+)	7	3.8%	3	3.0%	0.702
Differentiation syndrome	2	1.1%	0	0.0%	0.290
None of above	122	67.0%	69	68.3%	0.825
Adverse Event within 30 days of start of treatment					
Febrile neutropenia (Grade 3+)	3	1.6%	8	7.9%	0.009*

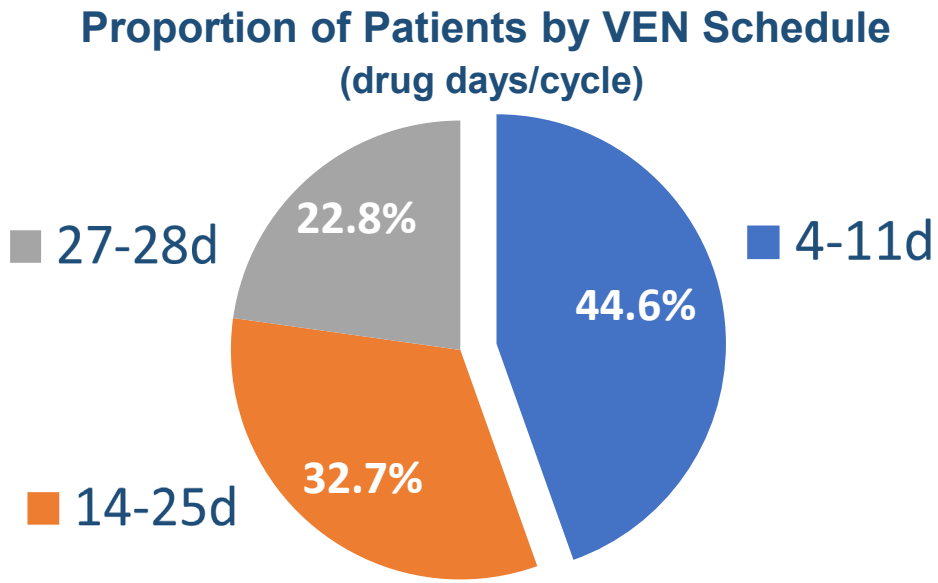
- Incidence of prespecified selected expected Grade 3+ toxicity was similar except for higher febrile neutropenia rates for VEN+HMA vs IVO+HMA within 30 days of initiation (7.9% vs 1.6%; *p*=0.009)
- Unscheduled acute care was needed for 42.9% of patients receiving IVO+HMA in the first 12 weeks vs 70.3% for VEN+HMA, resulting in a 64% higher relative risk (*p*<0.001)

*Indicates statistical significance.
HMA, hypomethylating agent; IVO+HMA, ivosidenib+hypomethylating agent; VEN+HMA, venetoclax+hypomethylating agent.

Results – Treatment Patterns: Schedule per Cycle

Dose and Schedule Intensity

- Few patients in either cohort changed dose or schedule (apart from planned VEN initial ramp-up)
- Treatment discontinuation was 37% for both regimens
- Due to prior reports of varied treatment schedules for VEN, VEN schedule length per cycle was captured
  - Only 22.8% received the full FDA-approved 28 days of VEN during the 28-day cycles
  - 41.6% received ≤ 7 days of VEN per cycle raising questions about the impact on response



FDA, US Food and Drug Administration; VEN, venetoclax.

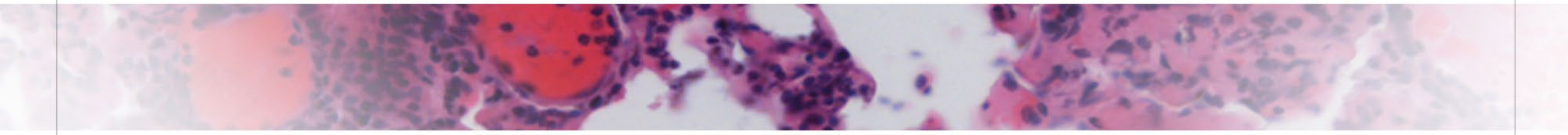
Conclusions

- In a large, balanced cohort of nearly 300 patients with ND ICi m*IDH1* AML, patients treated with IVO+HMA had higher rates of CR and CR+CRi/p, achieved CR faster, and had longer EFS compared to those treated with VEN+HMA
- ~ 41% of patients receiving VEN did not receive >7-day schedules, potentially impacting the regimen's efficacy
- Despite the modified schedule of VEN, patients receiving VEN+HMA had higher early incidence of febrile neutropenia and greater need for unscheduled acute care than those receiving IVO+HMA

AML, acute myeloid leukemia; CR, complete response; CRi/p, CR with incomplete count recovery or incomplete platelet recovery; EFS, event-free survival; ICi, induction chemotherapy ineligible; IVO+HMA, ivosidenib+hypomethylating agent; m*IDH1*, mutant isocitrate dehydrogenase 1; ND, newly diagnosed; VEN+HMA, venetoclax+hypomethylating agent; VEN, venetoclax.

Triplet combinations

American Society of Hematology
Helping hematologists conquer blood diseases worldwide



Phase Ib/2 Study of Oral Decitabine/Cedazuridine (ASTX727) and Venetoclax in Combination with the Targeted Mutant *IDH1* Inhibitor Ivosidenib or the Targeted Mutant *IDH2* Inhibitor Enasidenib: 2023 Update

Himachandana Atluri, MD[1], Jillian Mullin, MS[2], Koichi Takahashi, MD, PhD[3], Sanam Loghavi, MD[4] Abhishek Maiti, MD[3], Koji Sasaki, MD[3], Naval G. Daver, MD[3], Yesid Alvarado,MD[3], Naveen Pemmaraju, MD[3], Gautam Borthakur, MD[3], Danielle Hammond,MD[3], Kelly Chien,MD[3], Alessandra Ferrajoli, MD[3], Nicholas J. Short, MD[3], Hussein A. Abbas, MD, PhD[3], Elias Jabbour,MD[3], Michael Andreeff, MD, PhD[3], Farhad Ravandi, MD[3], Rebecca S. S. Tidwell, MS[5], Xuemei Wang, MS[5], Marina Konopleva, MD[6] , Guillermo Garcia-Manero, MD[3], Hagop M. Kantarjian[3], Courtney D. DiNardo, MD[3]

Selection Criteria & Objectives

Selection Criteria

Inclusion Criteria

- *IDH 1* or *2* mutation
- ND AML not eligible for intensive chemotherapy or R/R AML
- Adequate hepatic (dbili ≤ 2x ULN or ALT/AST < 3x ULN) and renal (Cr < 1.5) function

Exclusion Criteria

- Active GvHD or concomitant gastrointestinal disorder preventing medication absorption
- Active Hepatitis B/C or HIV

Objectives

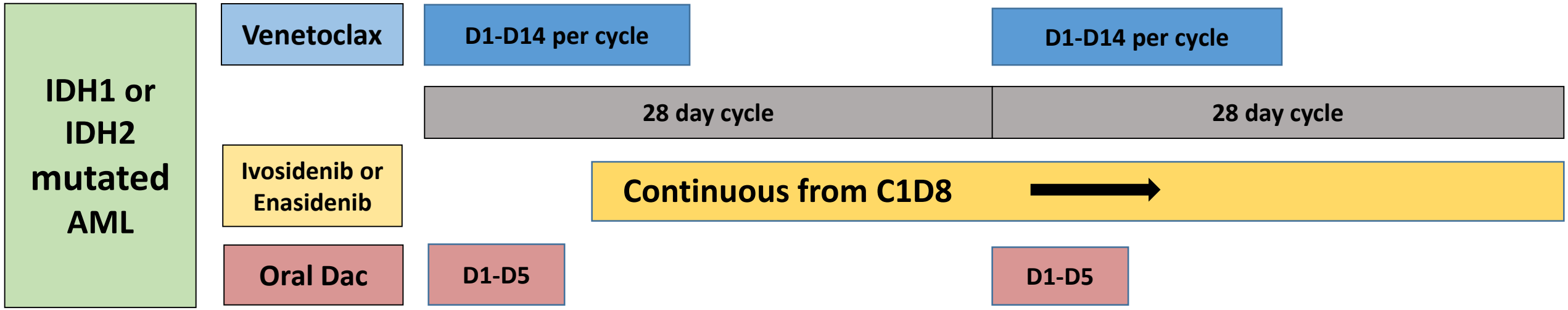
Primary Objectives

- **Phase I:** Safety and tolerability and RP2D of ASTX727 and VEN in combination with either IVO (Arm A) or ENA (Arm B) for patients with AML
- **Phase II:** Composite remission rate (CR, CRh and CRi)

Secondary Objectives

- DOR, EFS, OS, ORR (CR, CRh, CRi, MLFS, PR)
- MRD negativity by flow

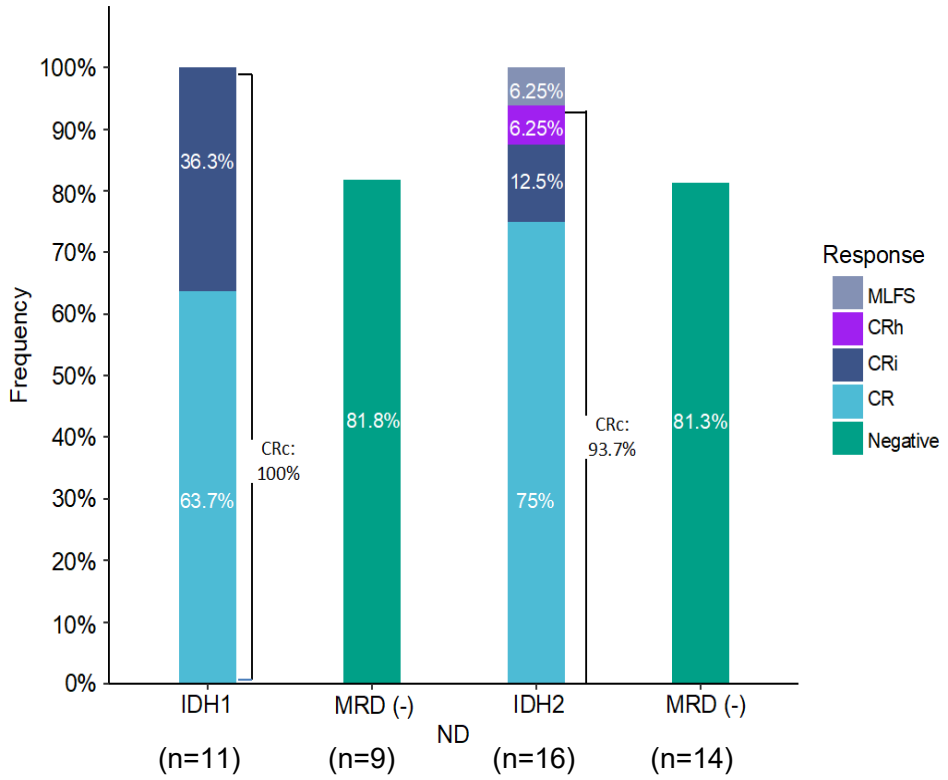
Treatment Schema

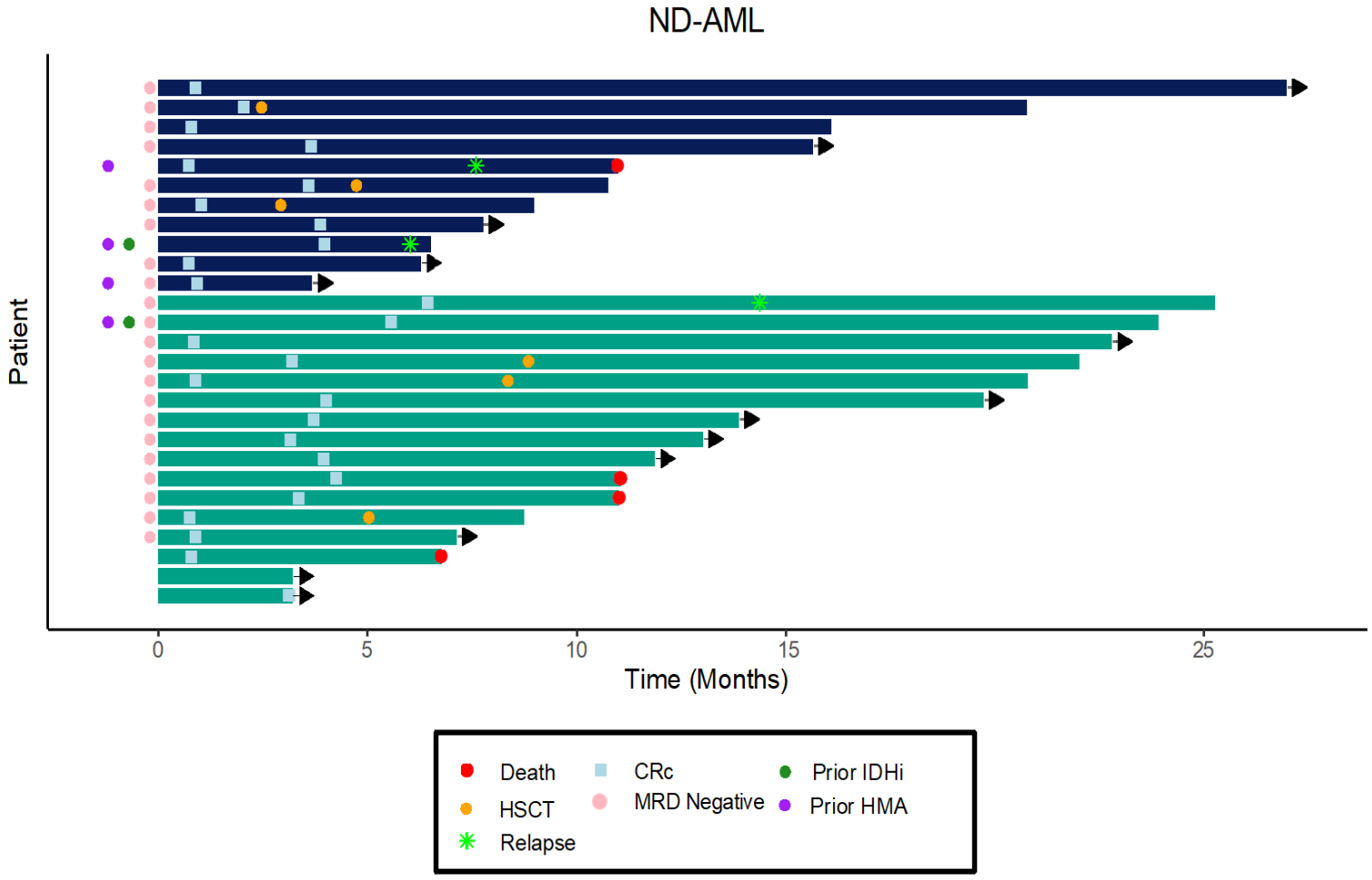


Selected RP2D Combination Doses
Arm A (IDH1): ASTX727 (D1-5) + VEN 600 mg (D1-14) + Ivosidenib 500 mg daily (D8 onwards)
Arm B (IDH2): ASTX727 (D1-5) + VEN 400 mg (D1-14) + Enasidenib 100 mg daily (D8 onwards)

Friese et al. J Clin Pharmacology. 2017
Lachowiez et al. Blood Advances. 2022

CRc Rates in ND-AML

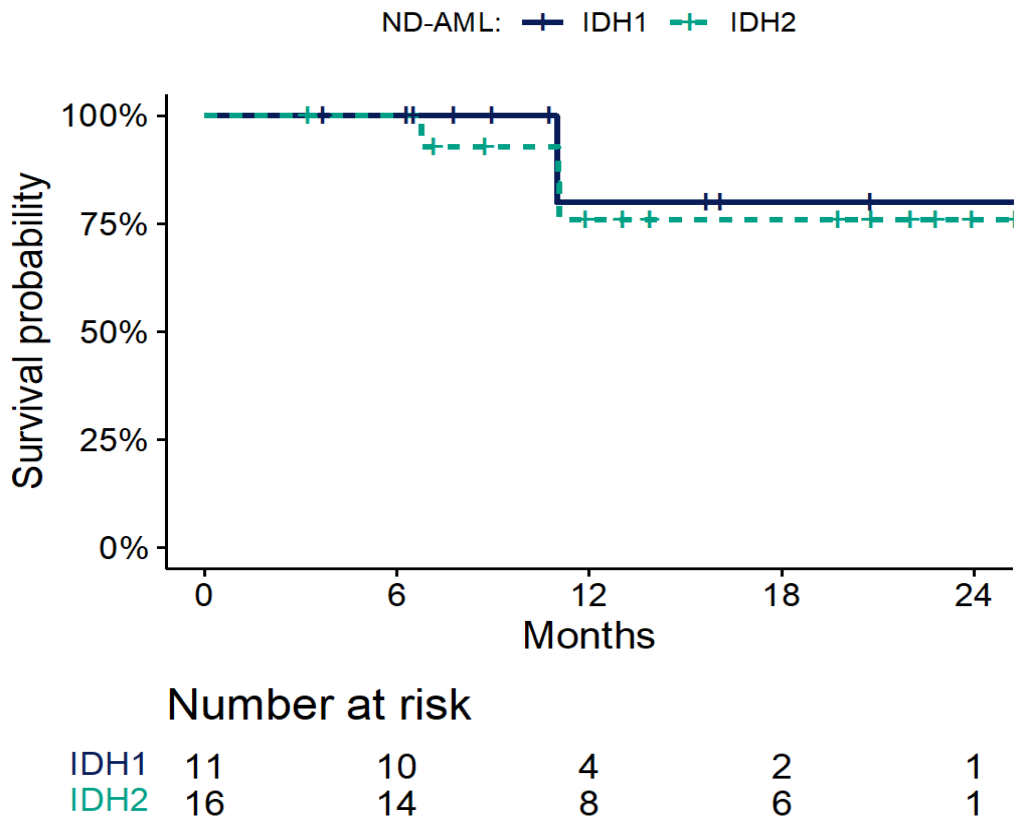




Overall CRc 96.2% with 85% MRD negative by multiparameter flow cytometry

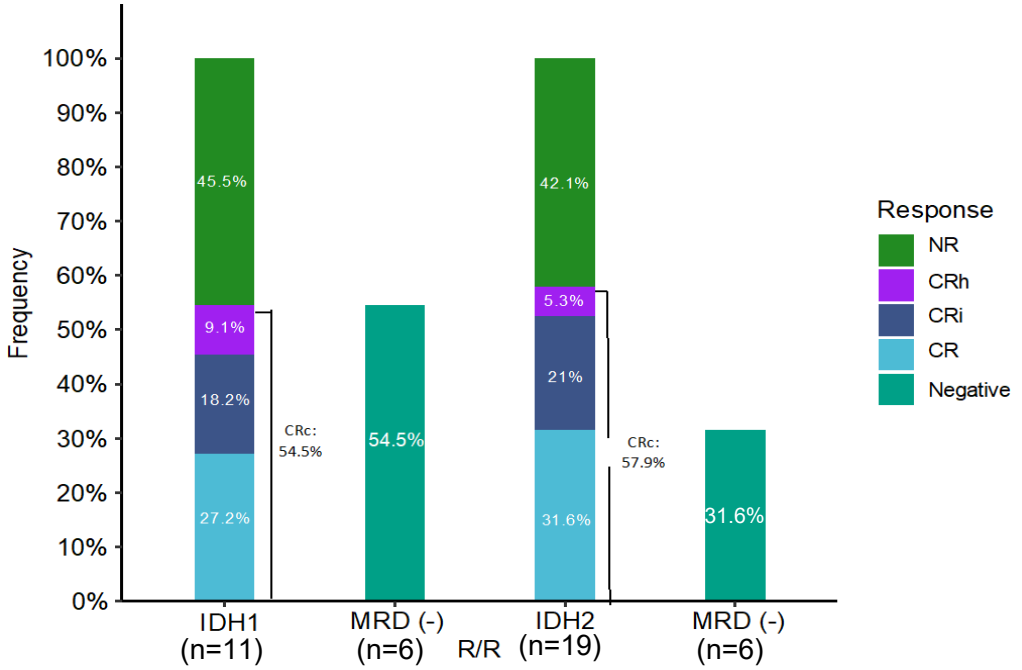
OS and DOR in ND-AML

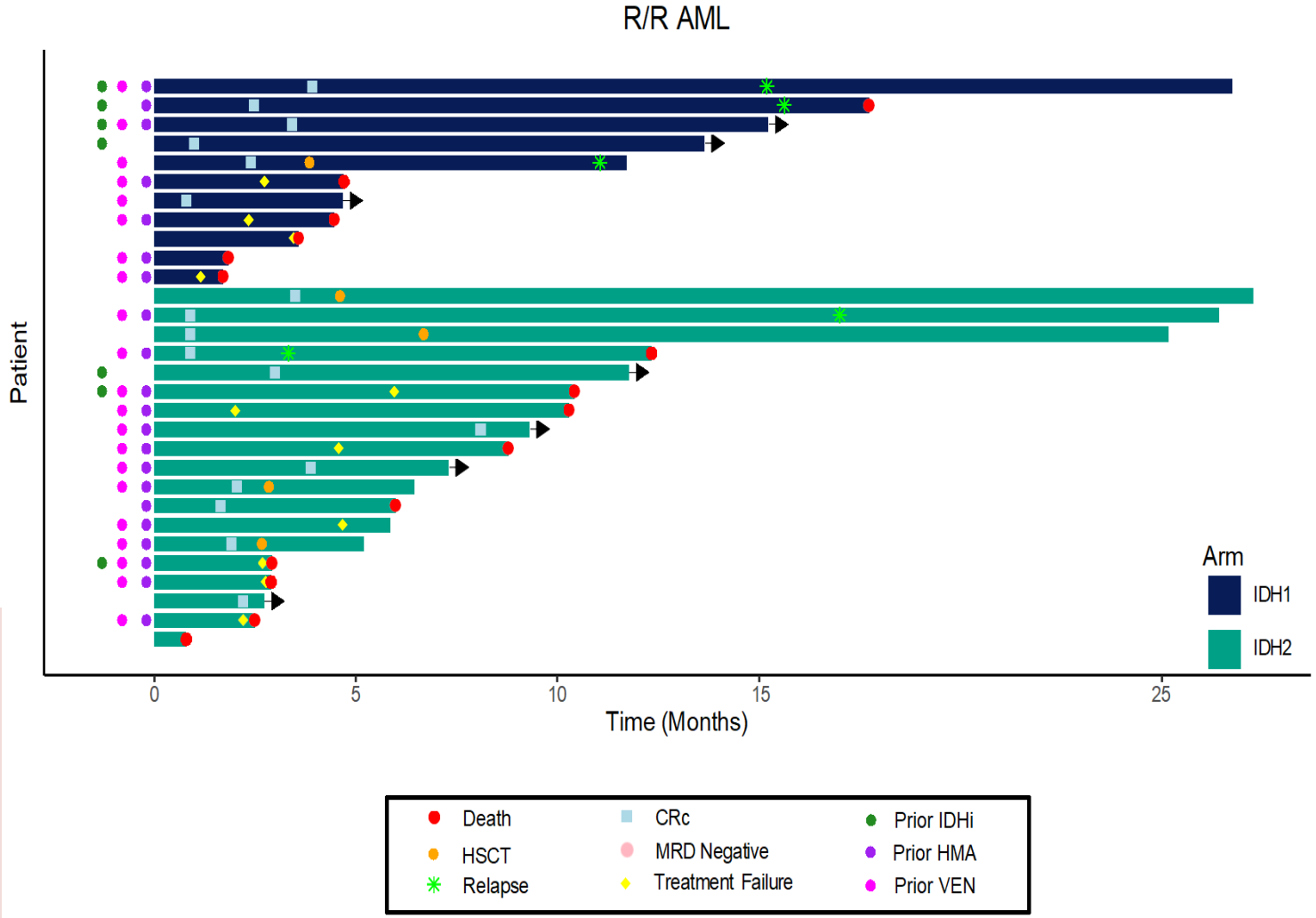
Overall Survival



ND-AML		
Outcome (months)	**IDH1 (n=11)**	**IDH2 (n=16)**
Median DOR	NR (6.88-NR)	NR (10.1-NR)
Median OS	NR	NR

CRc Rates in R/R AML





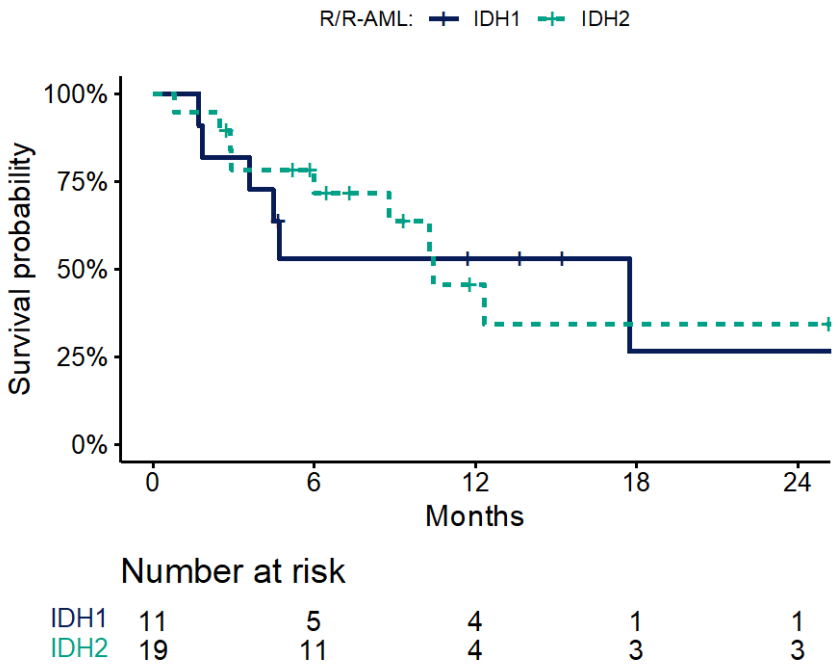
***Overall CRc 56.6% with 70.5% MRD negative by multiparameter flow cytometry.**

***CRc of 47.6% in those who received prior VEN (n=21), 77.7% in those VEN naïve (n=9) and 71% in those with prior IDHi (n=7)**

***MRD (-) CRc of 78% in those who were VEN naive**

OS and DOR in RR-AML

Overall Survival



R/R-AML		
Outcome (months)	**IDH1 (n=11)**	**IDH2 (n=19)**
Median DOR	**13.8 (13.2-NR)**	**16.1 (NR-NR)**
Median OS	**17.7 (4.47-NR)**	**10.4 (8.78 – NR)**

Outcomes by Prior therapy				
	Prior VEN (n=21)	**VEN Naïve (n=9)**	**Prior IDHi (n=7)**	**TP53 Mut (n=10)**
Median DOR	**14.5 (14.5 –NA)**	**13.2 (NR-NR)**	**13.8 (13.16 – NR)**	**13.2 (NR-NR)**
Median OS	**10.4 (4.7 – NR)**	**17.7 (5.99-NR)**	**17.7 (10.4-NR)**	**4.59 (2.93 -NR)**

Adverse Events

Adverse Events		
	Grade 1/2	Grade 3/4
Febrile Neutropenia	-	27 (47)
Hyperbilirubinemia*	7 (12)	3 (5)
Mucositis**	5 (9)	2 (3)
GI Toxicity	12 (21)	1 (2)
ALT/AST Elevation	17 (29)	1 (2)
Creatinine Elevation	16 (28)	-
Electrolyte abnormalities	12 (21)	-

*Related to known inhibition of UGT1A1 by enasidenib
**1 case attributed to hydroxyurea use

Adverse Events of Special Interest		
Adverse Event	IDH1 (n=22)	IDH2 (n=35)
Tumor Lysis	1 (5)	1 (3)
DS	3 (14)	2 (6)

Mortality		
Mortality	ND-AML	RR-AML
30 Day Mortality	0%	3.3%
60 Day Mortality	0%	6.6%

Cycle Lengths		
	ND-AML	R/R AML
Cycle 1	36 (23-72)	36 (23-92)
Cycle 2	35 (28-76)	48(28-88)
Cycle 3	40 (28-75)	36 (28 – 68)

*Medians reported in days (range)

Conclusions

- Safety profile and tolerability of triplet combination of ASTX727 + VEN + IDHi in both ND and R/R AML is acceptable
- CRc rates of 96.2% (ND-AML) and 56.6% (RR-AML) with high rates of MRD-negativity
- Median OS NR for ND-AML; mOS 17.7 and 10.4 months for *IDH1* and *IDH2* RR-AML respectively
- Future randomized trials are being planned

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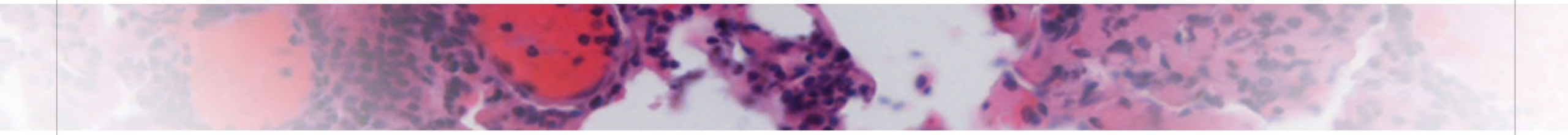


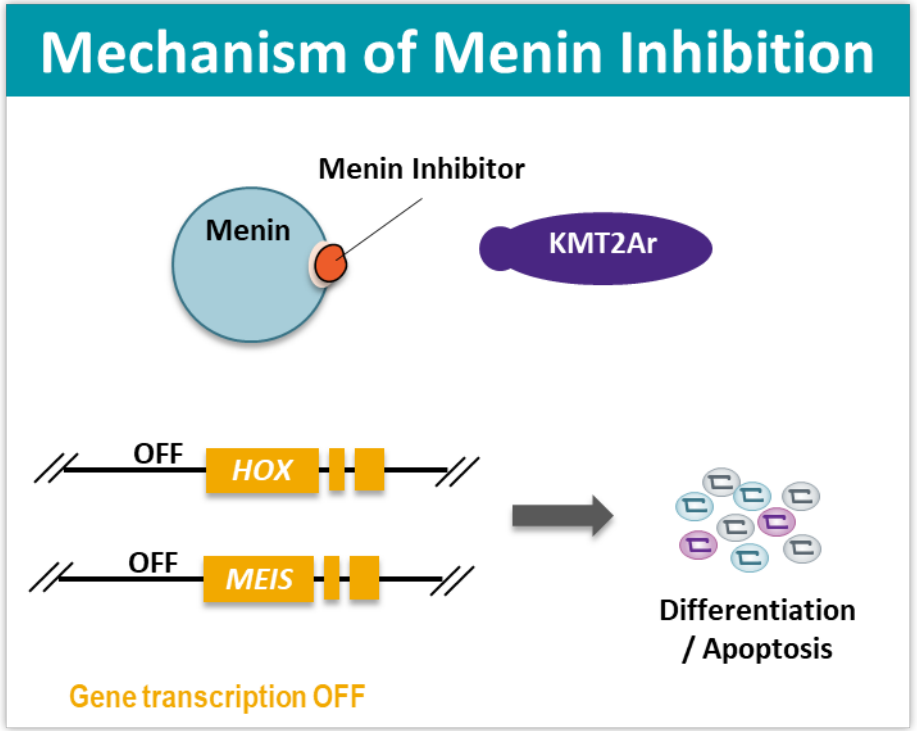
Early Results of the Phase I/II Study Investigating the All-Oral Combination of the Menin Inhibitor Revumenib (SNDX-5613) with Decitabine/Cedazuridine (ASTX727) and Venetoclax in Acute Myeloid Leukemia (SAVE)

Ghayas C. Issa[1], Branko Cuglievan[2], Courtney D. DiNardo[1], Nicholas J. Short[1], David McCall[2], Amber Gibson[2], Cesar Nunez[2], Miriam B. Garcia[2], Michael Roth[2], Aram Bidikian[1], Allison Pike[1], Sheila Tan[1], Brianna Kammerer[1], Musa Yilmaz[1], Tapan M. Kadia[1], Naveen Pemmaraju[1], Maro Ohanian[1], Naval Daver[1], Elias Jabbour[1], Gautam Borthakur[1], Farhad Ravandi[1], Guillermo Garcia-Maner[1], Michael Andreeff[1] and Hagop M. Kantarjian[1]

[1]Department of Leukemia, [2]Division of Pediatrics, The University of Texas MD Anderson Cancer Center, Houston, TX

Introduction – Menin Inhibition

- Menin-KMT2A interaction is a dependency in *KMT2Ar* or *NUP98r* or *NPM1mt* leukemias[1,2,3]
- Revumenib (previously SNDX-5613), is a potent, oral, selective inhibitor of the menin–KMT2A interaction
  - **R/R *KMT2Ar* or *NPM1mt:* ORR 53%, CR/CRh 30% → MRD-neg 78%[4]**
- Need to improve chances of responses and decrease risk of relapse



1. Grembecka J et al. Nat Chem Biol 2012;8:277-84. 2. Uckelmann HJ et al. Science 2020;367:586-90. 3. Heikamp EB et al. Blood 2022;139:894-906. 4. Issa GC et al. Nature. 2023;615:920-924.

SAVE Phase 1/2 Study Design

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Abstract #58 SAVE

- Age ≥12 years
- R/R AML or Myeloid MPAL
- *KMT2Ar* or *NPM1mt* or *NUP98r*
- ECOG ≤2
- Adequate organ function

Revumenib (SNDX-5613)
DL-0: 113 mg
DL-1: 163 mg (**RP2D of monotherapy**)

PO Q12h D1-D28 + a strong CYP3A4i

ASTX727
1 tablet (35 mg decitabine and 100 mg cedazuridine) PO daily for D1-D5

Venetoclax
400 mg target dose* with ramp up PO D1-D14
*adjusted with azoles

D14 bone marrow for early response

Primary objectives:
- **Phase 1 (3+3 design)**
  Safety, MTD and RP2D
- **Phase 2**
  Efficacy

Secondary objectives:
- Phase 2
  OS, RFS, CRD, MRD

Maintenance revumenib post-HSCT for 1 year

Baseline Characteristics - Ph1 SAVE

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Characteristic	N = 9
Median age, years [range]	30 [12-63]
12-18 years, n (%)	3 (33%)
Female, n (%)	7 (78%)
BM Blasts, % [range]	24 [4-45]
AML, n (%)	8 (89%)
MPAL, n (%)	1 (11%)
Medullary and extramedullary	1 (11%)
Therapy-related AML	2 (22%)
Genotype, n (%)	
KMT2Ar	5 (56%)
NUP98r	3 (33%)
NPM1mt	1 (11%)

Co-occurring mutations, n (%)	
WT1	4 (44%)
RAS	3 (33%)
IDH2	2 (22%)
FLT3	1 (11%)
Previous therapies	
Median no. [range]	3 [1-5]
Venetoclax, n (%)	5 (55%)
Menin inhibitor, n (%)	1 (11%)
HSCT, n (%)	6 (67%)

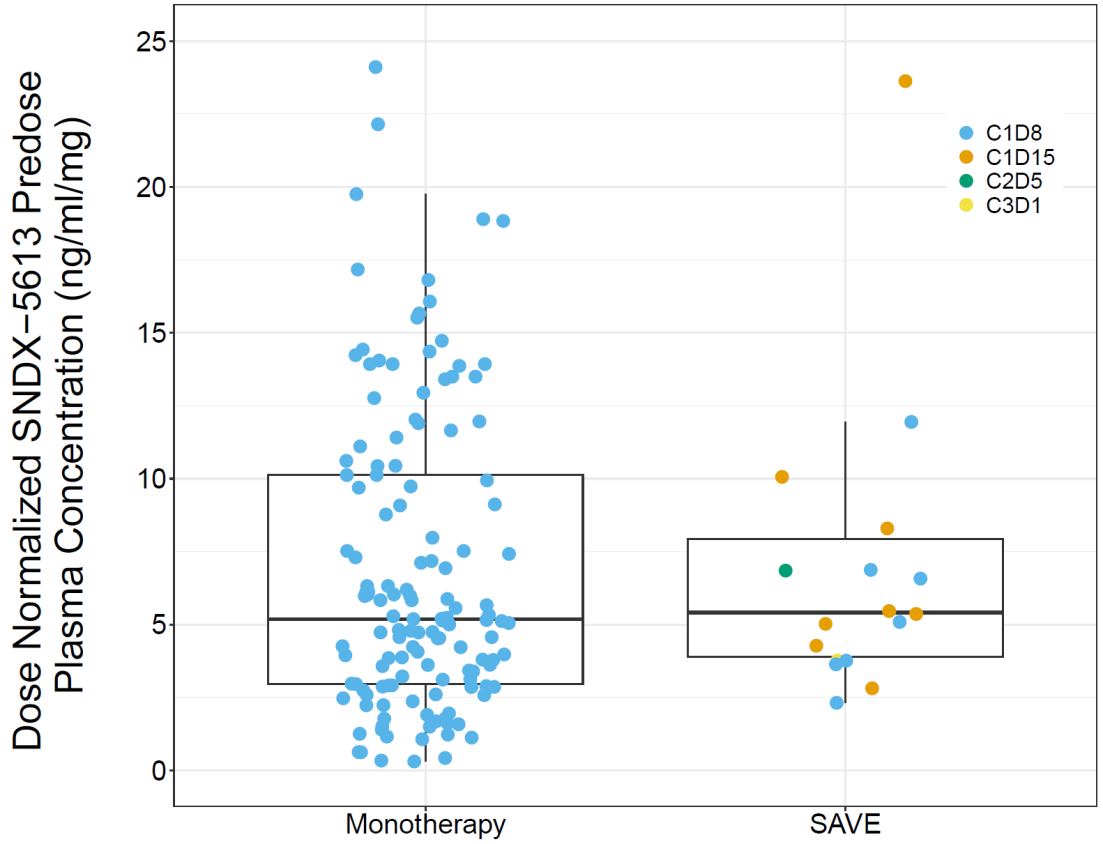
Data Cutoff 11/01/2023

PK Analysis – Ph1 SAVE

The dose-normalized, steady-state plasma concentrations of revumenib (SNDX-5613) in SAVE are comparable to monotherapy (both with strong CYP3A4i)

	Monotherapy	SAVE
N	137	18
Mean (SD)	7.11 (6.09)	8.05 (7.19)
Median (min, max)	5.18 (0.30, 45.89)	5.41 (2.31, 29.26)
Geomean (%CV)	5.05 (85.7%)	6.28 (89.3%)

The geomean of SAVE samples is higher, but exposures were overlapping and within the patient variability.
All patients included in this analysis received strong CYP3A4 inhibitors (azoles).



Patient Disposition– Ph1 SAVE

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No discontinuations for treatment-related AEs, 5 received HSCT consolidation

Patient Disposition, n (%)	N = 9	
Ongoing patients	5 (56%)	
Ongoing response without HSCT	1 (11%)	
Off treatment during HSCT	2 (18%)	
On maintenance post-HSCT	2 (22%)	
HSCT	5 (56%)	
Progression	1 (11%)	
Death (unrelated)	2 (22%)	Sepsis ARDS post-HSCT
Adverse event (unrelated)	1 (11%)	
Treatment-related adverse event	0	

Data Cutoff 11/01/2023

Adverse Events – Ph1 SAVE

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TEAEs (any grade, ≥20%)	N = 9
Febrile neutropenia	5 (56%)
Nausea	5 (56%)
Hyperphosphatemia	5 (56%)
Vomiting	4 (44%)
QTc prolongation	3 (33%)
Hypokalemia	3 (33%)
Thrombocytopenia	2 (22%)
Neutropenia	2 (22%)
Elevated ALT/AST	2 (22%)
Lung infection	2 (22%)
Abdominal pain	2 (22%)

TEAEs: treatment emergent adverse event regardless of attribution.

TRAEs (≥Grade 3)	N = 9
Febrile neutropenia	5 (56%)
Neutropenia	2 (22%)
Thrombocytopenia	2 (22%)
Lung infection	2 (22%)
TRAEs (Grades 1-2)	
Nausea	5 (56%)
Hyperphosphatemia	5 (56%)
Vomiting	4 (44%)
QT prolongation	3 (33%)
Differentiation syndrome	2 (22%)

TRAEs: treatment-related adverse event. **Related to any of the agents used.**

No Grade 3 or higher ↑QTc

Leukocytosis in 1 patient

Data Cutoff 11/01/2023

High response rate with SAVE combination

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Abstract #58 SAVE

Best Response n (%)	All patients (N = 9)	*KMT2Ar* (N=5)	*NUP98r* (N=3)	*NPM1mt* (N=1)
ORR	9 (100%)	5 (100%)	3 (100%)	1 (100%)
CR/CRh	**4 (44%)**	3 (60%)	1 (33%)	0
CR	**3 (33%)**	3 (60%)	0	0
CRh	1 (11%)	0	1 (33%)	0
CRp	3 (33%)	2 (40%)	0	1 (100%)
PR	1 (11%)	0	1 (33%)	0
MLFS	1 (11%)	0	1 (33%)	0
MRD neg by MFC	6/9 (67%)	4/5 (80%)	1/3 (33%)	1/1 (100%)
Within CR/CRh	4/4 (100%)	3/3 (100%)	1/1 (100%)	1/1 (100%)
Complete cytogenetic remission by FISH	5/8 (63%)	4/5 (80%)	1/3 (33%)	NA

Overall Response Rate (ORR) = CR + CRh + CRp + PR + MLFS. Complete cytogenetic remission in which fusions were not detectable by fluorescence in situ hybridization (FISH).

Data Cutoff 11/01/2023

SAVE leads to rapid responses in refractory cases

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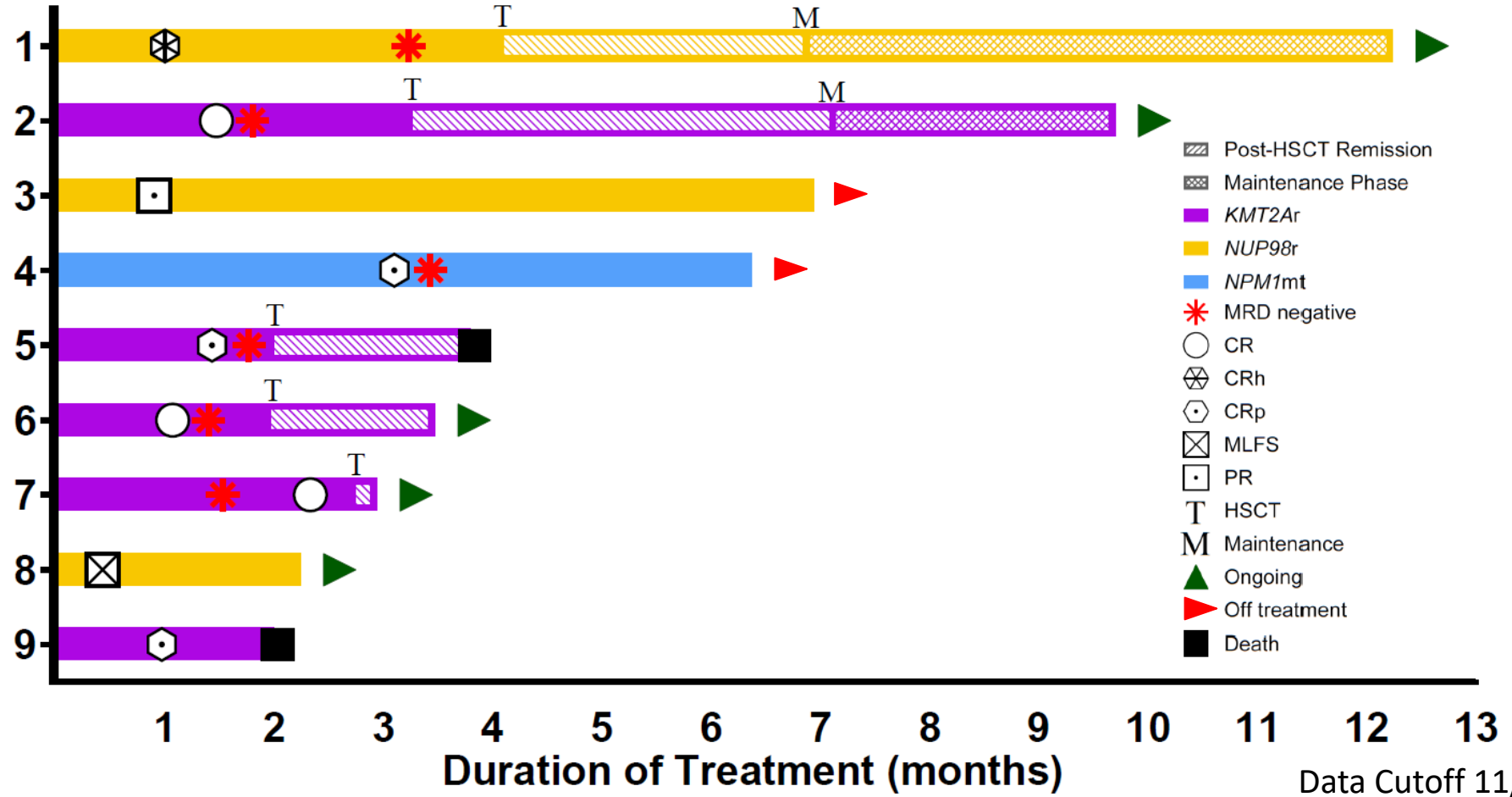
Abstract #58 SAVE

Median follow-up of 6.4 months (range 0.4 to 12.3)

Median time to response 28 days (range 14 to 55); BM D14 <5% in 6/6 patients

Prior Therapies			
HSCT	HMA	Ven	Menin-I
+	-	-	-
-	-	+	-
+	+	+	-
+	+	+	+
-	+	+	-
+	+	-	-
-	-	-	-
+	+	-	-
+	+	+	-



Data Cutoff 11/01/2023

SAVE early results indicate durable remissions

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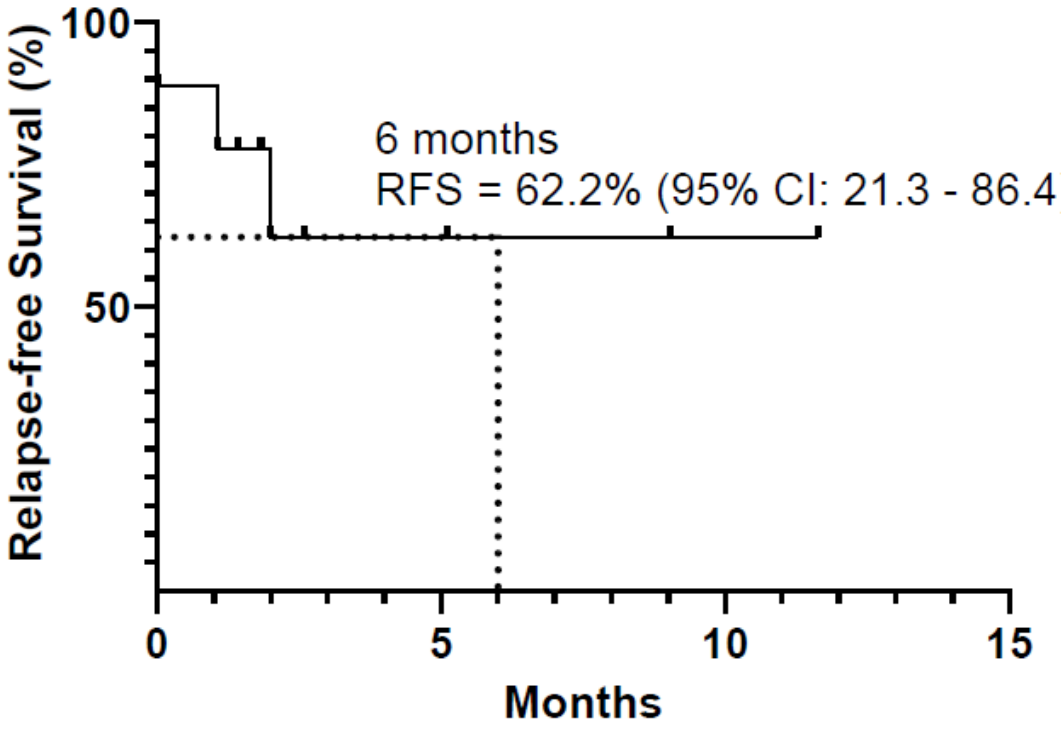
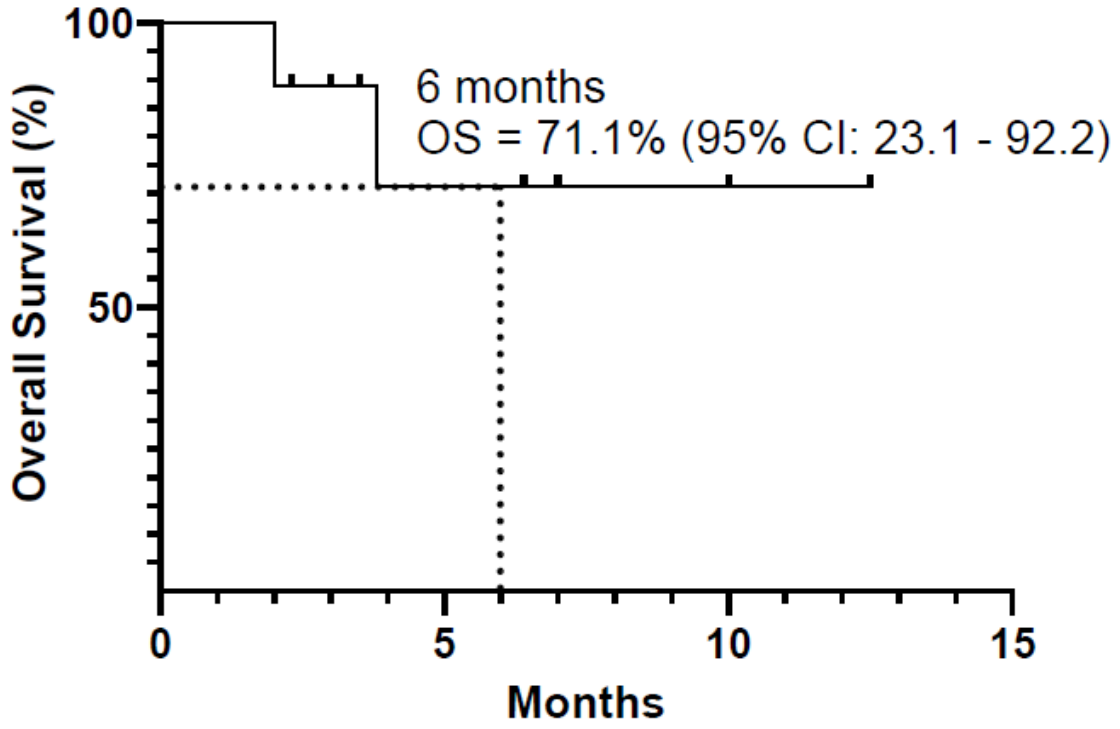
Abstract #58 SAVE

Median follow-up of 6.4 months (range 0.4 to 12.3) (N=9)





Median RFS and OS not reached with 2 patients having ongoing remission beyond 11 months

Data Cutoff 11/01/2023

Differentiation Syndrome on SAVE

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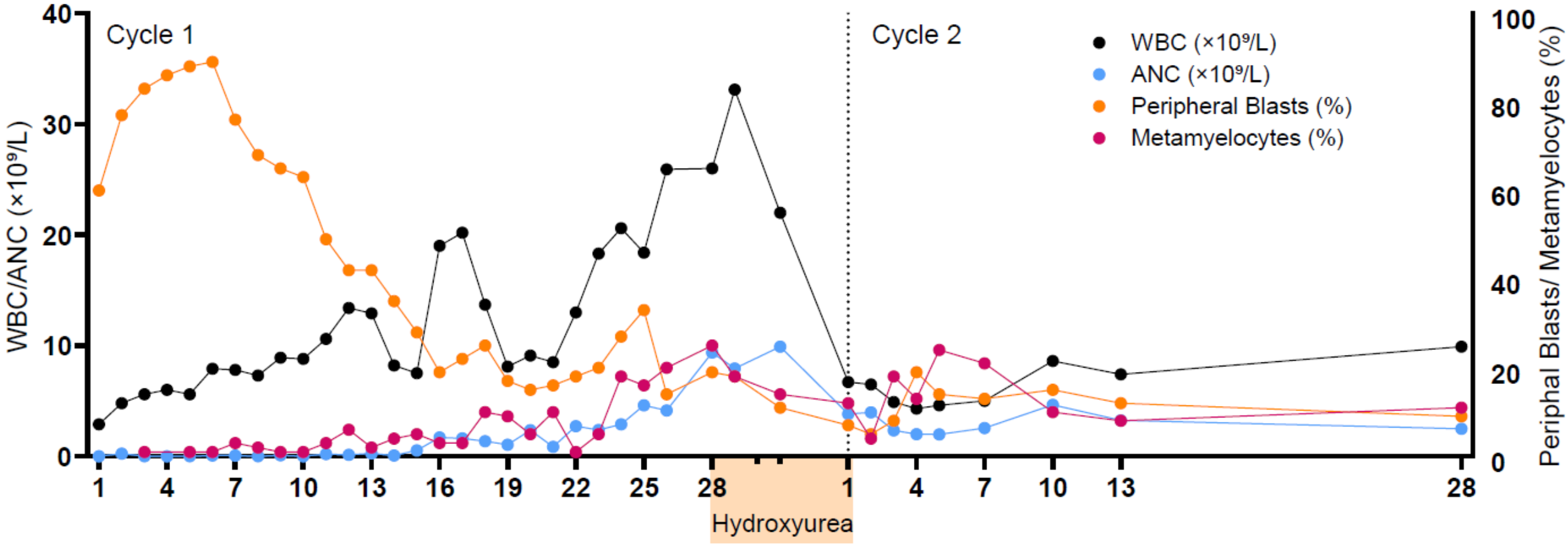
Abstract #58 SAVE

Asymptomatic leukocytosis with hallmarks of differentiation in *NUP98r*

BM Blasts 66% → 8% with platelet count recovery (PR)



Conclusions

- Early results **of all-oral SAVE** [**revumenib (SNDX-5613)**, **oral decitabine (ASTX727)** and **VEnetoclax**] → acceptable safety and high efficacy in **children and adults** with R/R AML susceptible to menin inhibition
- High rates of response in heavily pretreated population
  - **ORR 100%** (9/9), **CR/CRh 44%** (4/9), **MRD-neg 67%** (6/9)
  - 5/9 patients HSCT consolidation, 2 resumed revumenib maintenance with ongoing remission > 11 months
- No severe differentiation syndrome or ≥Grade 3 QT prolongation
- Myelosuppression, confounded by expected risk with HMA + Ven in R/R AML
  - Future mitigation measures to include intermittent revumenib dosing, without compromising efficacy given clearance of leukemia by day 14
- This study continues to accrue patients

Phase I/II Study of Quizartinib, Venetoclax, and Decitabine Triple Combination in FLT3-ITD Mutated AML

Musa Yilmaz, Muharrem Muftuoglu, Hagop Kantarjian, Courtney DiNardo, Tapan Kadia, Marina Konopleva, Gautam Borthakur, Naveen Pemmaraju, Nicholas J. Short, Yesid Alvarado, Abhishek Maiti, Lucia Masarova, Guillermo Montalban-Bravo, Carissa Jurisprudencia, Allison Pike, Sanam Loghavi, Keyur Patel, Guillin Tang, Jairo Matthews, Steven Kornblau, Elias Jabbour, Guillermo Garcia-Manero, Farhad Ravandi, Michael Andreeff, Naval Daver

Department of Leukemia, MD Anderson Cancer Center
Houston, Texas, USA

DAC + VEN + Quizartinib in FLT-ITD mutated AML

Primary Objective:

- To establish RP2D of quizartinib in combination with DAC + VEN in pts with FLT3m AML

Secondary Objective:

- To determine complete remission (CR), CR with incomplete count recovery (CRi), minimal residual disease (MRD), and overall survival (OS)

Patients

- Relapsed/Refractory FLT3-mutated* AML or high-risk MDS (≥10% blasts)

or

- Newly diagnosed FLT3-mutated* AML unfit for intensive chemoRx

*FLT3-ITD with/without TKD mutations allowed

Induction

Decitabine
20 mg/m^2 IV on D1-10

Venetoclax 400 mg/day**
D1-D21 (BM biopsy on D14)

Quizartinib
30-40 mg/day on D1-28#

**Venetoclax discontinued on D14 in pts with BM blasts ≤5% or hypoplastic BM
#Amendment - reduced quizartinib to 14 days in C1

Consolidation

Decitabine
20 mg/m^2 IV on D1-5

Venetoclax* 400 mg/day**
D1-D14

Quizartinib
30-40 mg/day on D1 to 28

Up to 12 cycles. ***Venetoclax duration reduced to 14 > 10 >7 days in subsequent cycles for pts in CR based on count recovery durations. Quizartinib dose reduced to 14 days in pts with prolonged count recovery

Baseline Clinical Characteristics

Characteristics	Relapse/Refractory (N=43)	Frontline (N=14)
	N (%), Median [Range]	N (%), Median [Range]
Age-years	59 [19-86]	70 [62-85]
Gender- Male	26 (60)	7 (50)
Diagnosis, AML		
De novo	31 (72)	6 (43)
Secondary	9 (21)	6 (43)
Therapy related	3 (7)	2 (14)
Prior therapies, median	3 [1-5]	n/a
HMA + VEN	24 (56)	n/a
≥1 prior FLT3i	36 (83)	n/a
≥ 2 prior FLT3i	9 (23)	n/a
Prior Gilteritinib	21 (74)	n/a
ASCT, yes	16 (37)	n/a
Karyotype		
Diploid	17 (40)	8 (56)
Adverse	13 (30)	3 (22)
Other	13 (30)	3 (22)

Baseline Molecular Characteristics

Characteristics	Relapse/Refractory (N=43)	Frontline (N=14)
	N (%), Median [Range]	N (%), Median [Range]
FLT3 mutations		
ITD	43 (100)	14 (100)
ITD allelic ratio	0.45 [0.01-23]	0.44 [0.19-4.04]
ITD + D835	1 (2)	0 (0)
ITD + F691L	1 (2)	0 (0)
Other mutations*		
DNMT3A	19 (44)	4 (29)
NPM1	13 (30)	3 (21)
WT1	17 (40)	1 (7)
RAS/MAPK	12 (28)	1 (7)
RUNX1	11 (25)	5 (35)
TET2	10 (23)	3 (21)
SRSF2	2 (5)	3 (21)

-1 pt with no baseline molecular data excluded from molecular subcategory, mutations with >20% incidence in R/R or frontline cohort are shown
*RAS/MAPK pathway mutations: RAS/PTPN11/CBL/NF1/BRAF

R/R cohort - Response Rates

Response*, N (%)	All Patients (n=43)
CRc	**28 (65)**
CR	5 (12)
CRi	8 (19)
MLFS	15 (34)
Day 14 BM blasts ≤5%¥	**18 (42)**
Best MRD, anytime	
Flow Cytometry (-)	8/27 **(30)**
FLT3 PCR (-)	9/25 **(36)**
30-day mortality	0 (0)
60-day mortality	**3 (7)**
Bridge to ASCT	**17 (40)**

*Response assessment by modified IWG criteria – Cheson et al. J Clin Oncol. 2003 Dec 15;21(24):4642-9
¥Including acellular or aplastic bone marrow

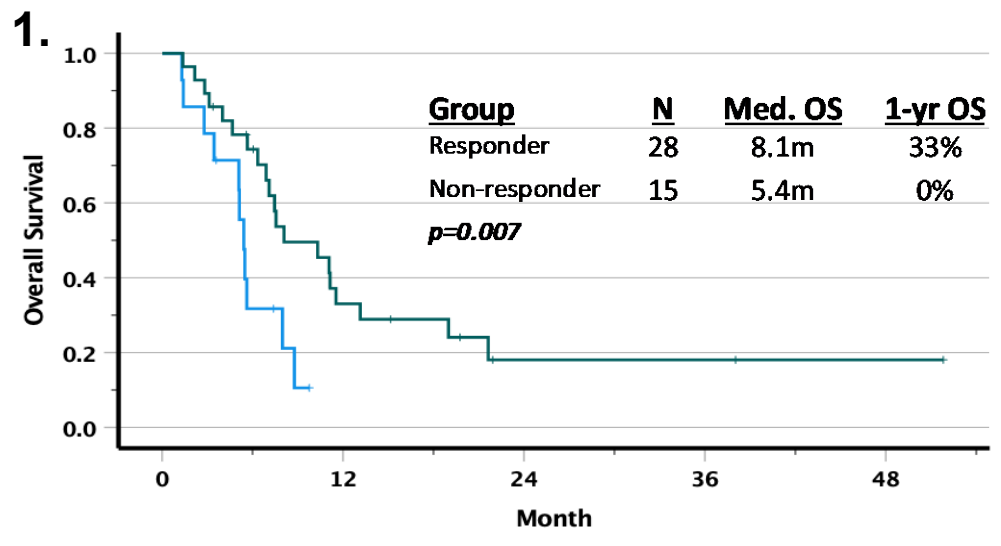
CRc Rates in Subgroups	n/N (%)
Prior Gilteritinib	**20/32 (63)**
No Prior Gilteritinib	8/11 (72)
Prior HMA + VEN	**14/24 (58)**
No Prior HMA + VEN	14/19 (74)
RAS/MAPK* positive	**6/12 (50)**
RAS/MAPK negative	22/30 (73)
DNMT3A positive	**14/20 (70)**
DNMT3A negative	14/22 (64)
NPM1 positive	**10/13 (77)**
NPM1 negative	18/29 (62)

-1 pt with no baseline molecular data excluded from molecular subcategory
*RAS/MAPK pathway mutations: RAS/PTPN11/CBL/NF1/BRAF

Relapse/Refractory cohort (Median OS 7.5m)

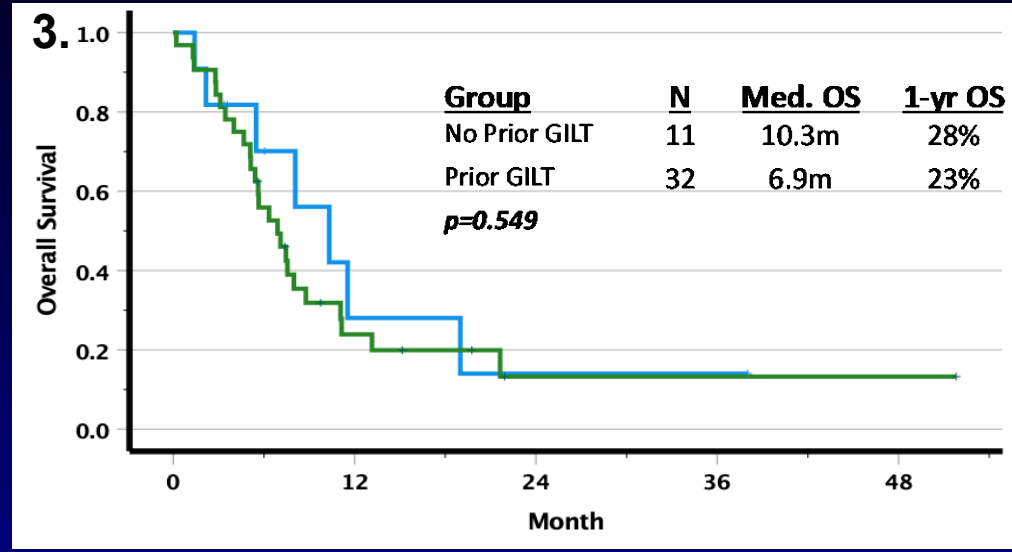
Responder vs. Non-responder

1.



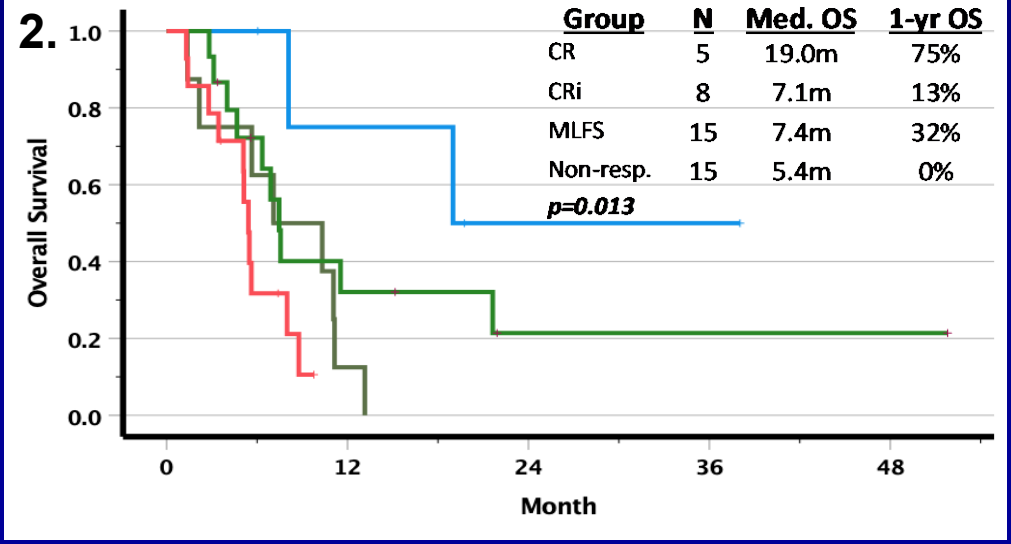
Prior Gilteritinib

3.



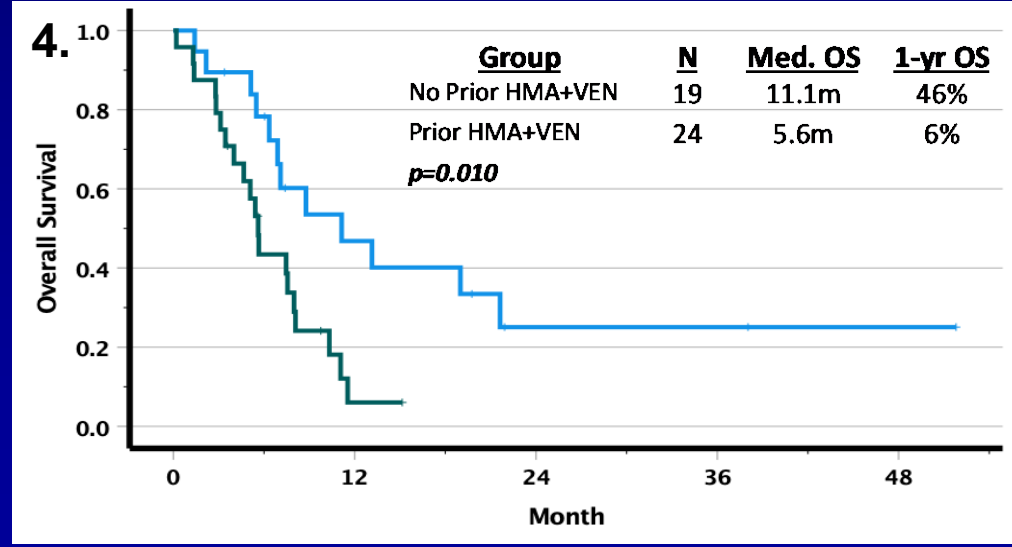
CR, CRi, MLFS vs. Non-responder

2.



Prior HMA + Venetoclax

4.



Median follow-up: 21 months

Frontline Cohort - Response Rates

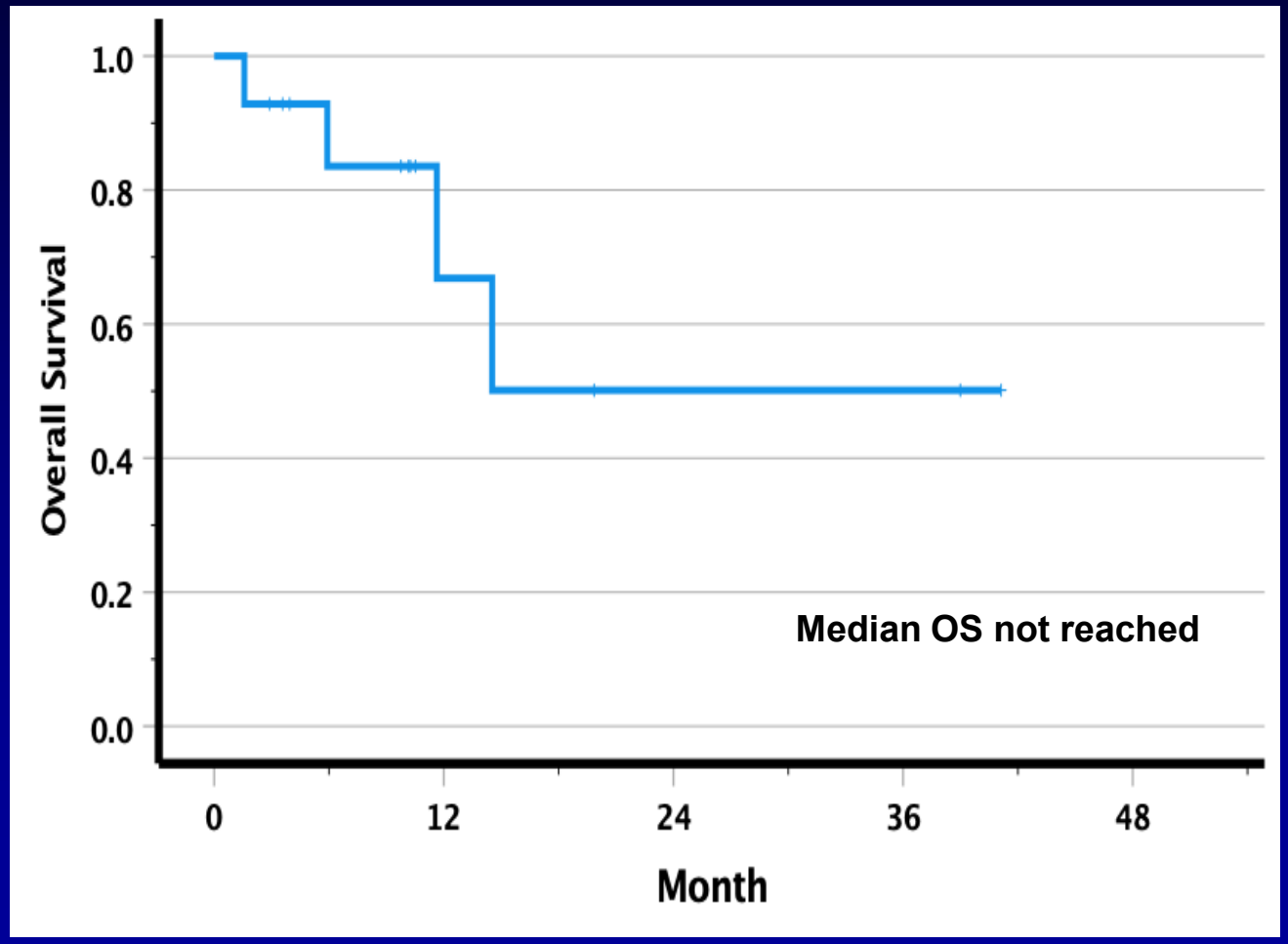
Response*, N (%)	All Patients (N=14)
CRc	**14 (100)**
CR	11 (79)
CRi	3 (21)
MLFS	0 (0)
Day 14 BM blasts ≤5%¥	**14 (100)**

Response*, N (%)	All Patients (N=14)
Best MRD, anytime	
Flow Cytometry (-)	9/12 (75)
FLT3 PCR (-)	12/14 (86)
30-day mortality	0 (0)
60-day mortality	**1 (7)**
Bridge to ASCT	**4 (19)**

*Response assessment by modified IWG criteria – Cheson et al. J Clin Oncol. 2003 Dec 15;21(24):4642-9
¥Including acellular or aplastic bone marrow

Frontline Cohort

Overall Survival



Median follow-up: 11 months

Last follow-up

2 relapses:

- 1 TP53, complex (FLT3-)
- 1 MECOM (FLT3-)

4 deaths:

- 2 deaths in CR (1 post-SCT)
- 2 deaths after relapse

10 alive:

- All in CR
  - 2 post-SCT
  - 8 no SCT, on Rx

Adverse Events (all patients)

Non-hematological	Grade 3-5	Grade 1-2
Febrile Neutropenia	26 (42)	1 (2)
Lung infection	22 (35)	0 (0)
Infection - other	10 (16)	6 (10)
Sepsis	6 (10)	0 (0)
Hypermagnesemia	2 (3)	8 (13)
Syncope	2 (3)	0 (0)
Hyperbilirubinemia	2 (3)	18 (29)
Hypocalcemia	1 (2)	33 (53)
Hypokalemia	0 (0)	37 (60)
Hyponatremia	0 (0)	34 (55)
Dyspnea	0 (0)	26 (42)
Diarrhea	0 (0)	26 (42)
Hypophosphatemia	0 (0)	26 (42)
Hypoalbuminemia	0 (0)	25 (40)
Hypomagnesemia	0 (0)	19 (31)
QTcF Prolongation	1 (2)	6 (10)

A total of 62 patients were evaluated for toxicity (including 5 patients who were not evaluable for response). Only grade 3-5 (=/>5%) and grade 1-2 (=/ >30%) frequencies are shown (except QTcF, and overlapping toxicities between groups).

Prolonged Myelosuppression

Frontline Cohort (N=14)

Quizartinib D1-D28 in C1
6 patients: 3CR, 3CRi

Median time to ANC >500: 43 days [36-56 d]
Median time to PLT >50K: 42 days [21-46 d]

⇩

Reduced Quizartinib to D1-D14 in C1
8 patients: 8CR

Median time to ANC >500: 36 days [28-41 d]
Median time to PLT >50K: 35 days [27-71 d]

Conclusion

- **DAC + VEN + Quizartinib is active in heavily pretreated pts R/R FLT3-ITDm pts**
  - All patients - CRc 65%, med OS 7.5 m, 1-yr OS 25%
  - Prior Gilteritinib – CRc 63%, med OS 6.9m, 1-yr OS 23%
- **High remission rates in newly diagnosed FLT3-ITDm**
  - CRc 100% (CR 79%), med OS not reached (median f/u 11m)
- **Delayed ANC recovery can be mitigated by reducing VEN and Quizartinib to 14 days**
  - **Time to ANC recovery (500 cells/mcL) – 43 days to 36 days**
- **Grade 3 QTcF prolongation is uncommon (2%)**
- **This clinical trial continuous to accrue and expansion planned (NCT03661307)**

Conclusions

Thank you!!!

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