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Acute Myeloid Leukemia

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Disclosures

In compliance with ACCME policy, ASH requires disclosures to the session audience:

Speaker

Geoffrey L. Uy, MD

Disclosures

Consultancy: Jazz Pharmaceuticals; Novartis

Research Funding: Genzyme

Membership on a Board or Advisory Committee: Jazz; Novartis

Speakers Bureau: Genzyme

Discussion of off-label drug use: Gilteritinib for initial treatment of FLT3 mutated AML



Learning Objectives

Upon participation in this activity, attendees will be able to:

- Summarize the efficacy of patients treated with azacitidine and venetoclax
- Discuss and describe novel combination therapies with azacitidine +/- venetoclax for
 - FLT3 mutated
 - TP53 mutated AML
- Discuss and describe emerging therapies for NPM1 mutated / KMT2A rearranged AML with menin inhibitors



Patient Case:

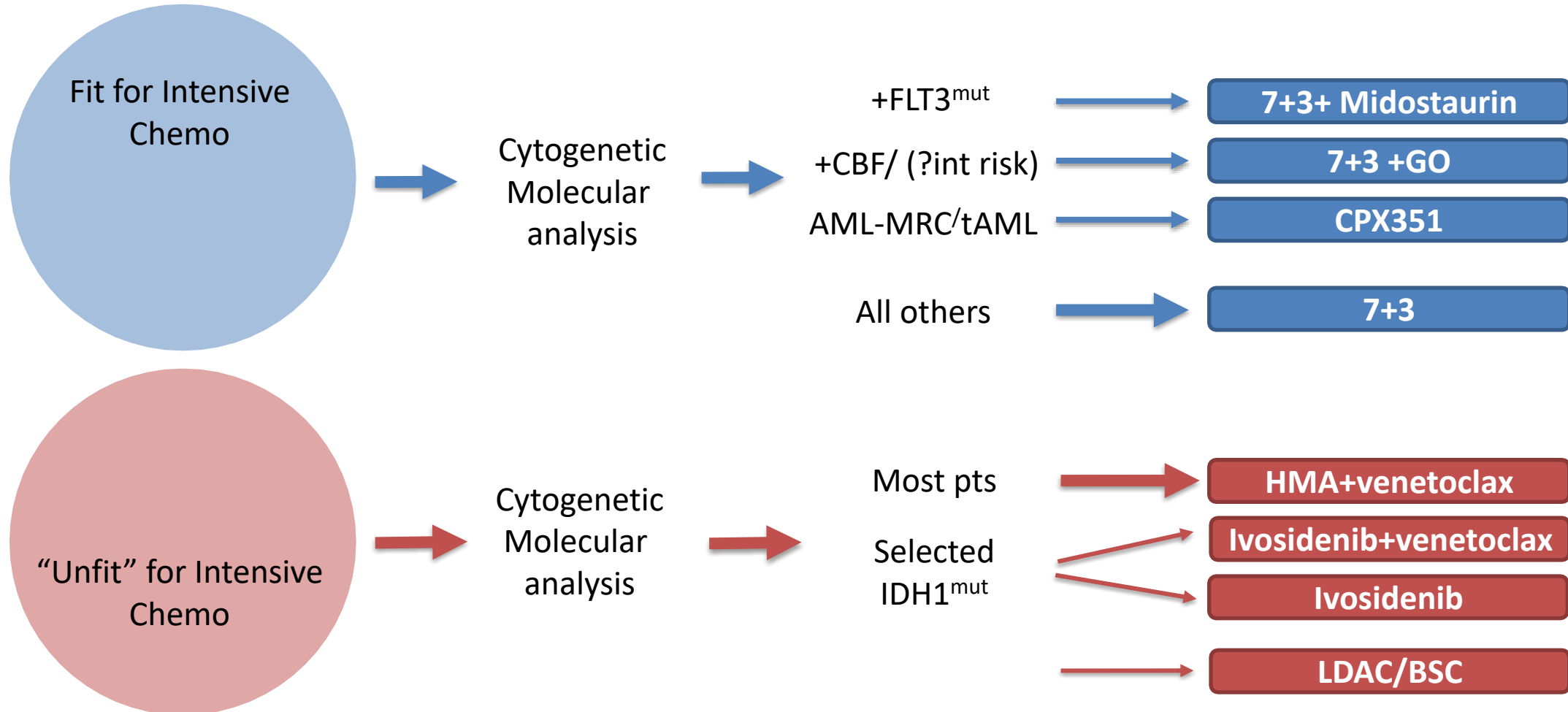
68 y/o male presents with 2 week history of increasing fatigue, generalized weakness, and now has a fever to 38.5 C. Initial CBC shows a WBC 28K with 20% circulating blasts, hemoglobin of 6.8 g/dL and platelet count of 18 k/cumm. A bone marrow biopsy shows a 90% cellular marrow with 70% blasts +MPO, CD13, CD33, CD34, and CD117. Multilineage dysplasia is observed with hypo granulated neutrophils, multinucleated erythroid precursors, and micromegakaryocytes. Cytogenetic / FISH as well as NGS molecular testing is sent.

What is your choice of initial chemotherapy?

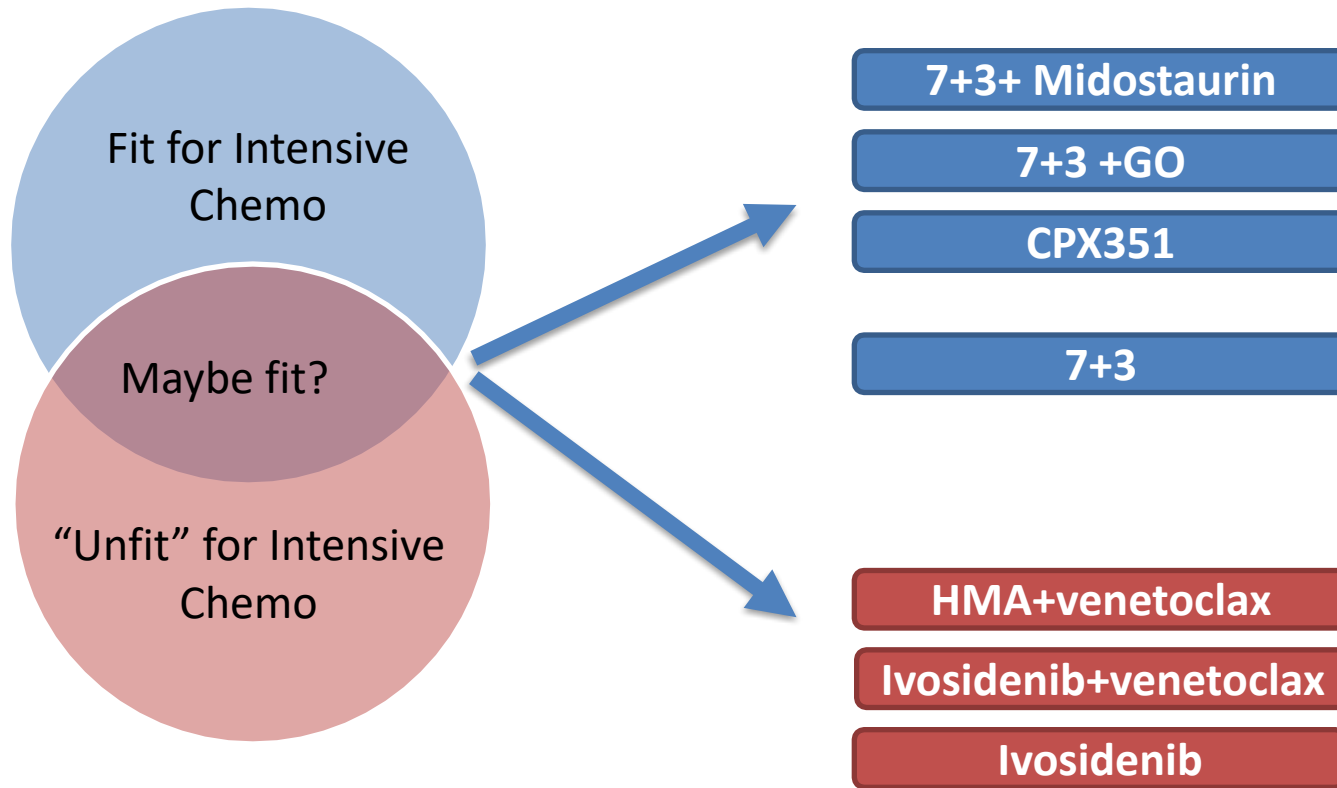
- A. 7+3
- B. 7+3 + GO
- C. CPX-351
- D. Azacitidine + venetoclax
- E. Wait for additional cytogenetic and molecular data



Management of AML in 2023



Management of AML in 2023



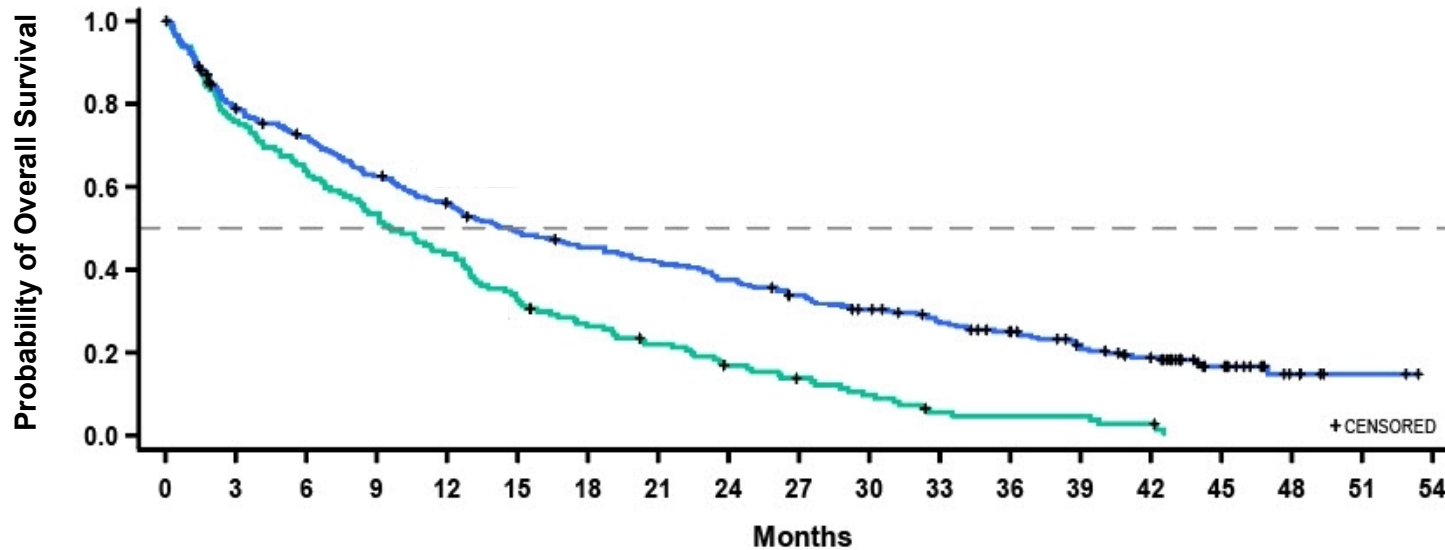
The reality

- Decisions for initial treatment of AML are frequently made with incomplete information
- Age is a poor predictor of treatment tolerance and validated measures of fitness and frailty do not exist
- Assessment of who is “appropriate” for what therapy is an evolving target
 - Outcomes of “less intensive” treatments are improving
 - “less intensive” treatments are becoming more “intense”
 - Improved understanding of how biologic subsets respond to specific treatments



Patients treated with Ven+Aza continue to show OS benefit over those on Aza monotherapy

Median follow-up time: 43.2 months (range: < 0.1 - 53.4)



	No. of events/No. of patients (%)	OS (months) median (95% CI)
Ven+Aza	222/286 (77.6)	14.7 (12.1 - 18.7)
Pbo+Aza	138/145 (95.2)	9.6 (7.4 - 12.7)

Hazard ratio: 0.58 (95% CI, 0.465 - 0.723), P < 0.001

HR reduction from 0.66 (95% CI, 0.52 - 0.85) at 75% OS analysis

Patients at Risk

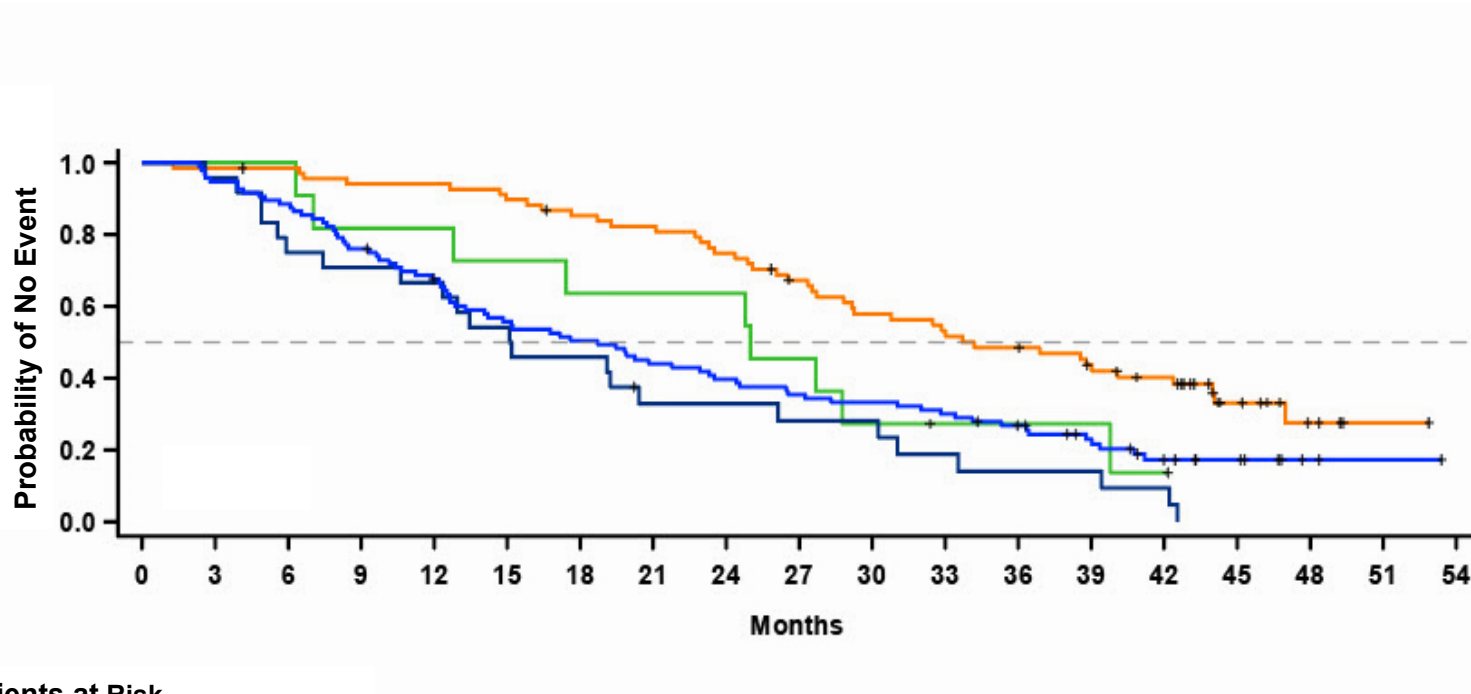
Ven+Aza	286	220	199	173	153	133	122	113	101	89	78	67	57	45	34	18	6	2	0
Pbo+Aza	145	109	92	77	63	47	37	30	22	17	12	6	5	5	3	0	0	0	0

The distributions were estimated for each treatment arm using Kaplan-Meier methodology and compared using the log-rank test stratified by age (18-<75, ≥75 years) and cytogenetic risk (intermediate risk, poor risk); The hazard ratio between treatment arms were estimated using the Cox proportional hazards model with the same stratification factors used in the log-rank test; Data cutoff: 01 Dec 2021

Abbreviations: Aza, azacitidine; Pbo, placebo; Ven, venetoclax



Median OS is longer for MRD 10^{-3} than MRD $\geq 10^{-3}</math> in patients who achieved CR+CRi on Ven+Aza$



	No. of events/No. of patients (%)	OS (months) median (95% CI)
Ven+Aza MRD 10^{-3}	43/69 (62)	34.2 (27.7 - 44.0)
Ven+Aza MRD $\geq 10^{-3}</math>$	76/96 (79)	18.7 (12.9 - 23.5)

Patients at Risk

Ven+Aza MRD 10^{-3}	69	68	67	64	64	61	57	55	50	43	37	34	31	26	22	10	4	1	0
Ven+Aza MRD $\geq 10^{-3}</math>$	96	91	85	73	63	52	47	41	37	33	31	28	23	17	10	7	2	1	0
Pbo+Aza MRD 10^{-3}	11	11	11	9	9	8	7	7	7	5	3	2	2	2	1	0			
Pbo+Aza MRD $\geq 10^{-3}</math>$	24	23	18	17	16	13	11	7	7	6	6	4	3	3	2	0			

The distributions were estimated for each treatment arm using Kaplan-Meier methodology; Data cutoff: 01 Dec 2021; Abbreviations: Aza; azacitidine; Pbo, placebo; MRD, minimal residual disease; Ven, venetoclax

American Society of Hematology 2022

Real World Effectiveness of “7 + 3” Intensive Chemotherapy Vs Venetoclax and Hypomethylating Agent for Initial Therapy in Adult Acute Myeloid Leukemia

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December 11, 2022

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All UPHS patients 60-75 ever receiving 7 and 3 or Ven/HMA as first treatment at UPHS n = 253

Screened for Eligibility n = 1,774

All Flatiron patients receiving 7 and 3 or Ven/HMA 1st line n = 1,521

7 and 3 n = 312

Ven/HMA n = 488

Survived Initial Therapy n = 296

Survived Initial Therapy n = 441

Intensive Reinduction n = 91

Ven/HMA n = 62

Consolidation / Other n = 143

Intensive Therapy n = 25

Ven/HMA n = 238

Other n = 178

Transplant n = 98

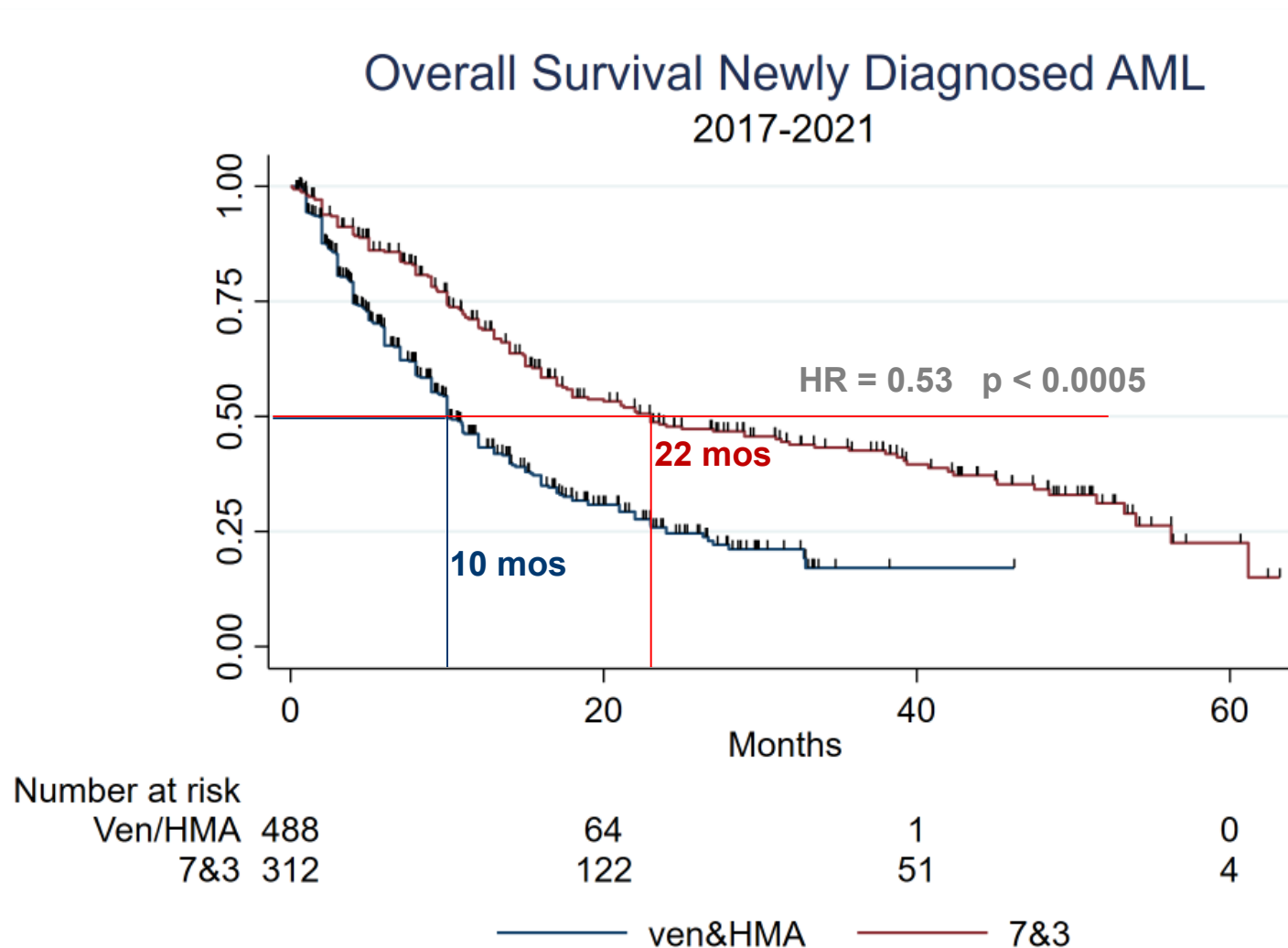
Transplant n = 73

164 Died
126 Alive at end of observation period
22 Lost to follow-up

280 Died
185 Alive at end of observation period
23 Lost to follow-up

"Intensive therapy" defined as regimens including: cytarabine, idarubicin, daunorubicin, fludarabine, mitoxantrone, etoposide, cladribine, hydroxycarbamide, methotrexate. "Other" included monotherapy with azacitidine, decitabine, CC-486, decitabine and cedazuridine, gilteritinib, midostaurin, ivosidenib, enasidenib, best supportive care,

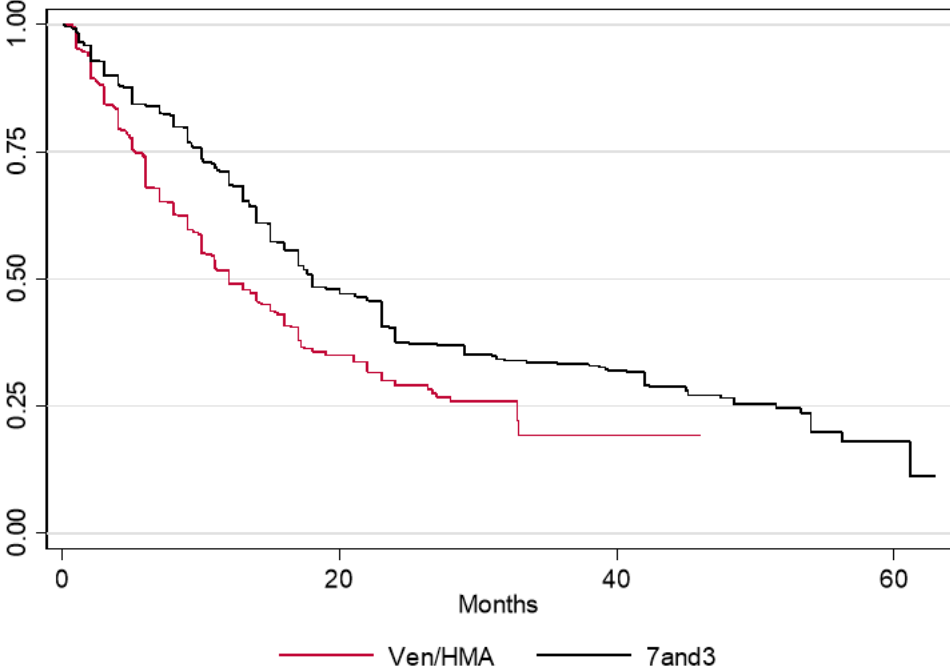
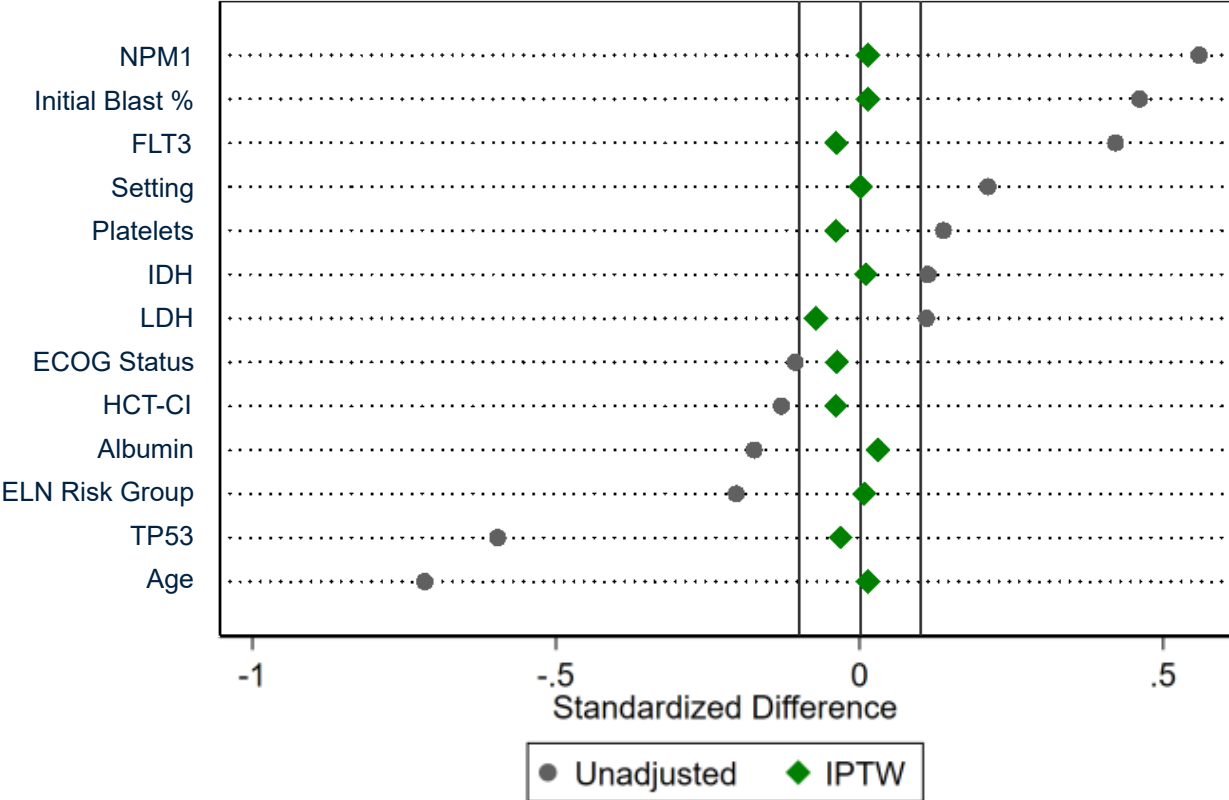
Patients Receiving 7&3 Had Improved Overall Survival vs Ven/HMA



Ven/HMA patients were older, sicker and had worse disease biology

Multiple Imputation (MI) and Inverse Probability of Treatment Weighting (IPTW) Balanced Baseline Covariates

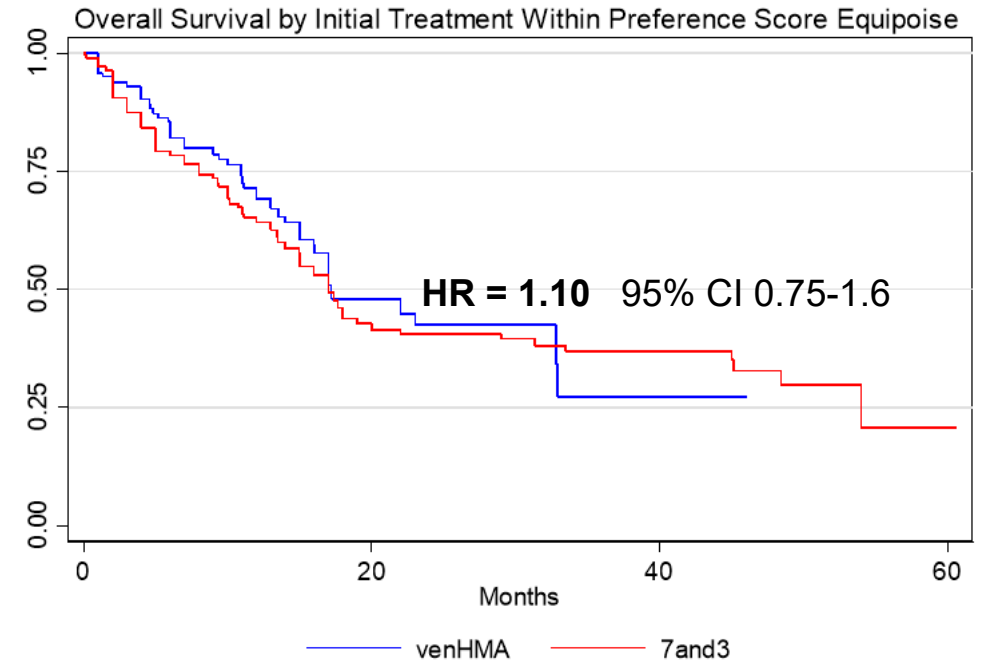
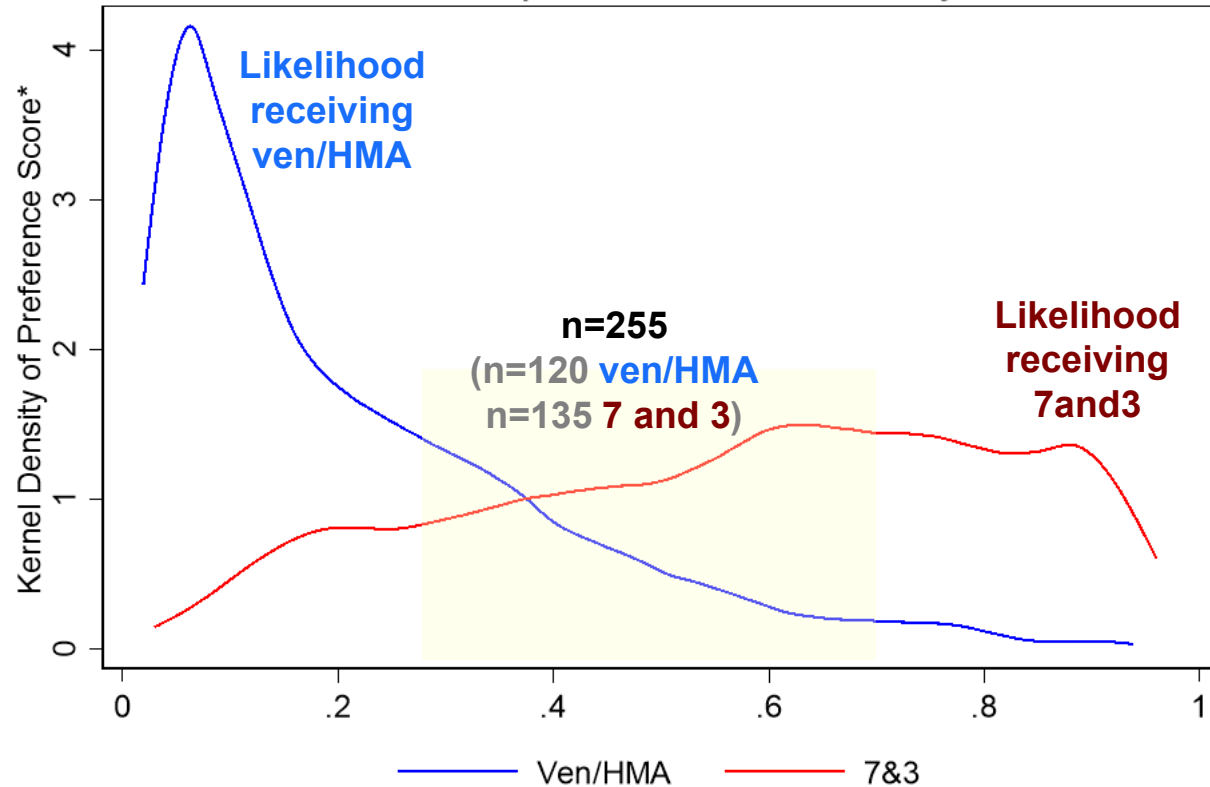
Covariate Balance Pre- and Post-IPTW



- ▶ Survival remained improved with 7&3 after balancing covariates
 - HR 0.71, p-value 0.026, 95% CI 0.53-0.94

Instead of Looking Across All Patients, it is Possible to Focus on a Narrower Subgroup of Clinical Equipoise

Distributional Overlap Preference Score by Treatment



*preference score defined as $\text{Logit}(\text{preference score}) = \text{logit}(\text{propensity score}) - \text{logit}(\text{treatment prevalence})$. Walker AM et al A tool for assessing the feasibility of comparative effectiveness research. Comp Eff Res 2013; 3:11-20.

ELN Risk Stratification and Outcomes Among Treatment-Naïve Patients With Acute Myeloid Leukemia Treated With Venetoclax and Azacitidine

Hartmut Döhner¹, Keith W. Pratz², Courtney D. DiNardo³, Brian A. Jonas⁴, Vinod A. Pullarkat⁵, Michael J. Thirman⁶, Christian Recher⁷, Andre C. Schuh⁸, Sunil Babu⁹, Monique Dail¹⁰, Grace Ku¹⁰, Yan Sun¹¹, Jalaja Potluri¹¹, Brenda Chyla¹¹, Daniel A. Pollyea¹²

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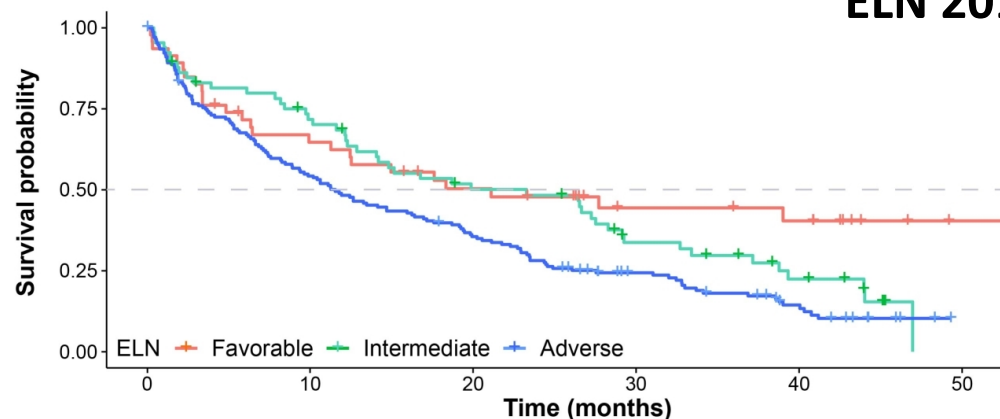
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⁶Section of Hematology and Oncology, Department of Medicine, University of Chicago Medicine, Chicago, IL, USA; ⁷CHU de Toulouse; Institut Universitaire du Cancer de Toulouse Oncopole, Toulouse, France; ⁸Princess Margaret Cancer Centre, Toronto, Canada; ⁹Fort Wayne Medical Oncology and Hematology, Fort Wayne, IN, USA;

¹⁰Genentech Inc., South San Francisco, CA, USA; ¹¹AbbVie Inc., North Chicago, IL, USA; ¹²University of Colorado Division of Hematology, School of Medicine, Aurora, CO, USA

ELN recommendations do not provide clinically meaningful outcome stratification for patients treated with Ven+Aza

ELN 2017



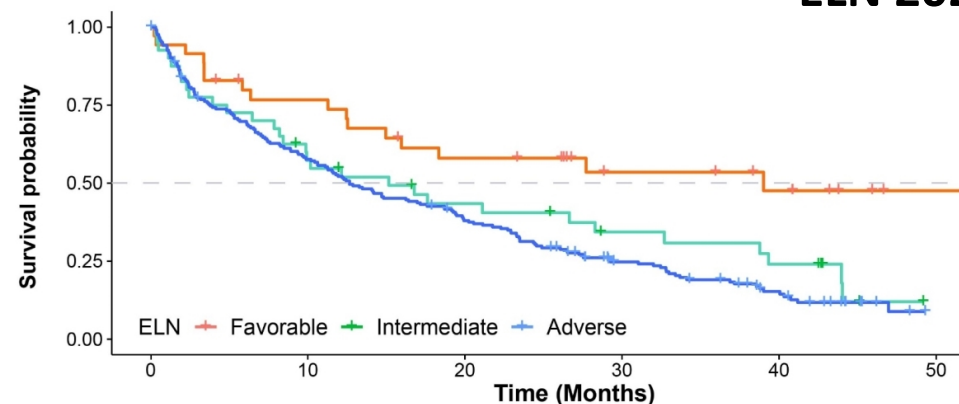
Patients at risk

ELN	Favorable	Intermediate	Adverse
46	28	20	12
65	44	29	17
168	90	58	31
			10
			9
			14
			0
			0
			0

ELN 2017	n	Events	Median OS, mo (95% CI)
Favorable	46	25	21.09 (9.92 – NE)
Intermediate	65	48	23.26 (12.85 – 28.29)
Adverse	168	141	11.53 (8.87 – 16.23)

- Overlapping outcomes to Ven+Aza for favorable and intermediate-risk patients

ELN 2022



Patients at Risk

ELN	Favorable	Intermediate	Adverse
35	25	18	11
40	22	15	10
204	115	74	39
			8
			7
			18
			2
			0
			0

ELN 2022	n	Events	Median OS, mo (95% CI)
Favorable	35	16	39.0 (12.52 – NE)
Intermediate	40	30	15.15 (8.18 – 28.29)
Adverse	204	168	12.65 (10.41 – 17.15)

- Overlapping outcomes to Ven+Aza for intermediate and adverse-risk pts;
- A small population of favorable-risk pts, primarily with *NPM1* mutations, show prolonged mOS of 39 months

Pooled analysis of Ven+Aza treated patients to evaluate prognostic subgroups

Objective

Divide patients treated with Ven+Aza into three distinct groups based on OS, and then determine how these groups differ with respect to baseline cytogenetic/molecular data

Approach

Sequential-BATting method¹ to derive algorithm

- Subgroup identification method to define subgroups as distinctive as possible from the remainder of the population.
- Minimize the *P* value of HR between the selected subgroup versus the remainder of the population

30 genetic markers as candidate predictors

- Included in the ELN 2022 recommendations and/or
- Genes with prevalence $\geq 10\%$ in the analysis population of patients in the Ven+Aza arm

Limitation: 11 of the genetic markers have prevalence $< 10\%$ and may be too small to identify a signal

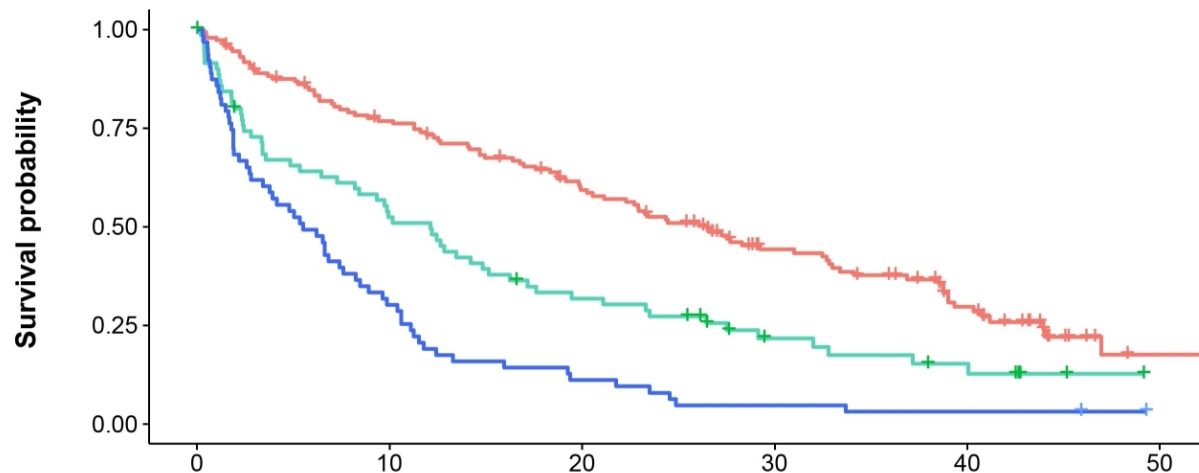
Cytogenetics	Ven+Aza (N=279)	Prev. (%)
Com. karyotype	72	25.8
del(5q)	49	17.6
del(7q)	48	17.2
del(17p)	15	5.4
t(v;11q23)	7	2.5
inv(3)	6	2.1

Mol. mutations detected	Ven+Aza (N=279)	Prevalence (%)
<i>TET2</i>	81	29.0
<i>IDH1/2</i>	77	27.6
<i>DNMT3A</i>	72	25.8
<i>RUNX1</i>	70	25.1
<i>TP53</i>	63	22.6
<i>SRSF2</i>	62	22.2
<i>FLT3-TKD</i>	59	21.1
<i>IDH2</i>	47	16.8
<i>NPM1</i>	46	16.5
<i>FLT3-ITD</i>	43	15.4
<i>N/KRAS</i>	42	15.0
<i>ASXL1</i>	35	12.5
<i>STAG2</i>	34	12.2
<i>IDH1</i>	32	11.5
<i>BCOR</i>	29	10.4
<i>EZH2</i>	16	5.7
<i>SF3B1</i>	23	8.2
<i>U2AF1</i>	26	9.3
<i>CEBPA</i>	13	4.7
<i>ZRSR2</i>	6	2.1
<i>CEBPA-bZip</i>	4	1.4

¹Huang et. al. Stat. Med., 2017; Favorable-risk pts with CBF-AML [inv(16), t(8;21)] were excluded from the trials, except for one patient who was enrolled with poor cytogenetic risk; inv(6) and t(8;21) were included in the thirty genetic markers that were analyzed; Abbreviations: Aza, azacitidine; ELN, European LeukemiaNet; HR, hazard ratio; OS, overall survival; Ven, venetoclax

Patients receiving Ven+Aza are distinguishable into three efficacy subgroups by OS benefit

- First a higher benefit group was identified, with a median OS > 24 months
- Subsequently a lower benefit group was determined, with a median OS < 6 months
- Patients fitting neither criteria were categorized as the intermediate benefit group, with a median OS of 12 months



Benefit Group

Patients at Risk

Benefit Group	0	10	20	30	40	50
Higher Benefit	145	107	79	47	25	2
Interm. Benefit	71	36	21	10	6	0
Lower Benefit	63	19	7	3	2	0

Ven + Aza (N = 279)	n	Events	Median OS, months (95% CI)
Higher Benefit	145	96	26.51 (20.24, 32.69)
Intermediate Benefit	71	57	12.12 (7.26 – 15.15)
Lower Benefit	63	61	5.52 (2.79 – 7.59)

- Majority of patients in the Ven+Aza arm are in the higher benefit group: 52% (145/279)
- The remainder of the patients are distributed equally between the intermediate and lower benefit groups: 25.4% (71/279) and 22.6% (63/279), respectively

Prognostic risk signatures for each subgroup are derived based on the mutational status of 4 genes in patients receiving Ven+Aza

Group	Higher Benefit		Intermediate Benefit		Lower Benefit	
	Ven+Aza (n=145)	Pbo+Aza (n=64)	Ven+Aza (n=71)	Pbo+Aza (n=28)	Ven+Aza (n=63)	Pbo+Aza (n=21)
Mutations, n (%)						
<i>FLT3</i> -ITD	0	0	39 (54.9)	21 (75)	4 (6.3)	0
<i>NRAS</i>	0	0	28 (39.4)	7 (25)	5 (7.9)	1 (4.8)
<i>KRAS</i>	0	0	11 (15.5)	2 (7.1)	2 (3.2)	0
<i>TP53</i>	0	0	0	0	63 (100)	21 (100)
<i>NPM1</i>	22 (15.2)	13 (20.3)	23 (32.4)	7 (25)	1 (1.6)	0
<i>IDH1/2</i>	53 (36.6)	19 (29.7)	21 (29.6)	4 (14.3)	3 (4.8)	0
<i>IDH1</i>	22 (15.2)	7 (10.9)	9 (12.7)	2 (7.1)	1 (1.6)	0
<i>IDH2</i>	32 (22.1)	13 (20.3)	13 (18.3)	2 (7.1)	2 (3.2)	0
<i>FLT3</i> -TKD	12 (8.3)	9 (14.1)	3 (4.2)	2 (7.1)	1 (1.6)	1 (4.8)
<i>DNMT3A</i>	40 (27.6)	15 (23.4)	25 (35.2)	13 (46.4)	7 (11.1)	4 (19)
<i>TET2</i>	48 (33.1)	24 (37.5)	29 (40.8)	8 (28.6)	4 (6.3)	3 (14.3)
<i>ASXL1</i>	18 (12.4)	18 (28.1)	12 (16.9)	7 (25)	5 (7.9)	2 (9.5)
<i>BCOR</i>	15 (10.3)	9 (14.1)	13 (18.3)	5 (17.9)	1 (1.6)	1 (4.8)
<i>EZH2</i>	8 (5.5)	6 (9.4)	6 (8.5)	0	2 (3.2)	0
<i>RUNX1</i>	43 (29.7)	17 (26.6)	25 (35.2)	9 (32.1)	2 (3.2)	4 (19)
<i>SF3B1</i>	16 (11.0)	5 (7.8)	6 (8.5)	3 (10.7)	1 (1.6)	1 (4.8)
<i>SRSF2</i>	42 (29.0)	22 (34.4)	16 (22.5)	8 (28.6)	4 (6.3)	4 (19)
<i>STAG2</i>	21 (14.5)	13 (20.3)	11 (15.5)	7 (25)	2 (3.2)	4 (19)
<i>U2AF1</i>	16 (11.0)	3 (4.7)	7 (9.9)	3 (10.7)	3 (4.8)	0
<i>ZRSR2</i>	4 (2.8)	2 (3.1)	2 (2.8)	0	0	0

Group	Higher Benefit		Intermediate Benefit		Lower Benefit	
	Ven+Aza (n=145)	Pbo+Aza (n=64)	Ven+Aza (n=71)	Pbo+Aza (n=28)	Ven+Aza (n=63)	Pbo+Aza (n=21)
Cytogenetics^a						
Com. karyotype	19 (13.1)	6 (9.4)	3 (4.2)	1 (3.6)	50 (79.4)	18 (85.7)
del(5q)	9 (6.2)	4 (6.2)	0	0	40 (63.5)	15 (71.4)
del(7q)	20 (13.9)	11 (17.2)	6 (8.5)	2 (7.1)	22 (34.9)	8 (38.1)
del(17p)	2 (1.4)	0	0	1 (3.6)	13 (20.6)	4 (19)
t(v;11q23)	2 (1.4)	2 (3.1)	0	0	5 (7.9)	1 (4.8)

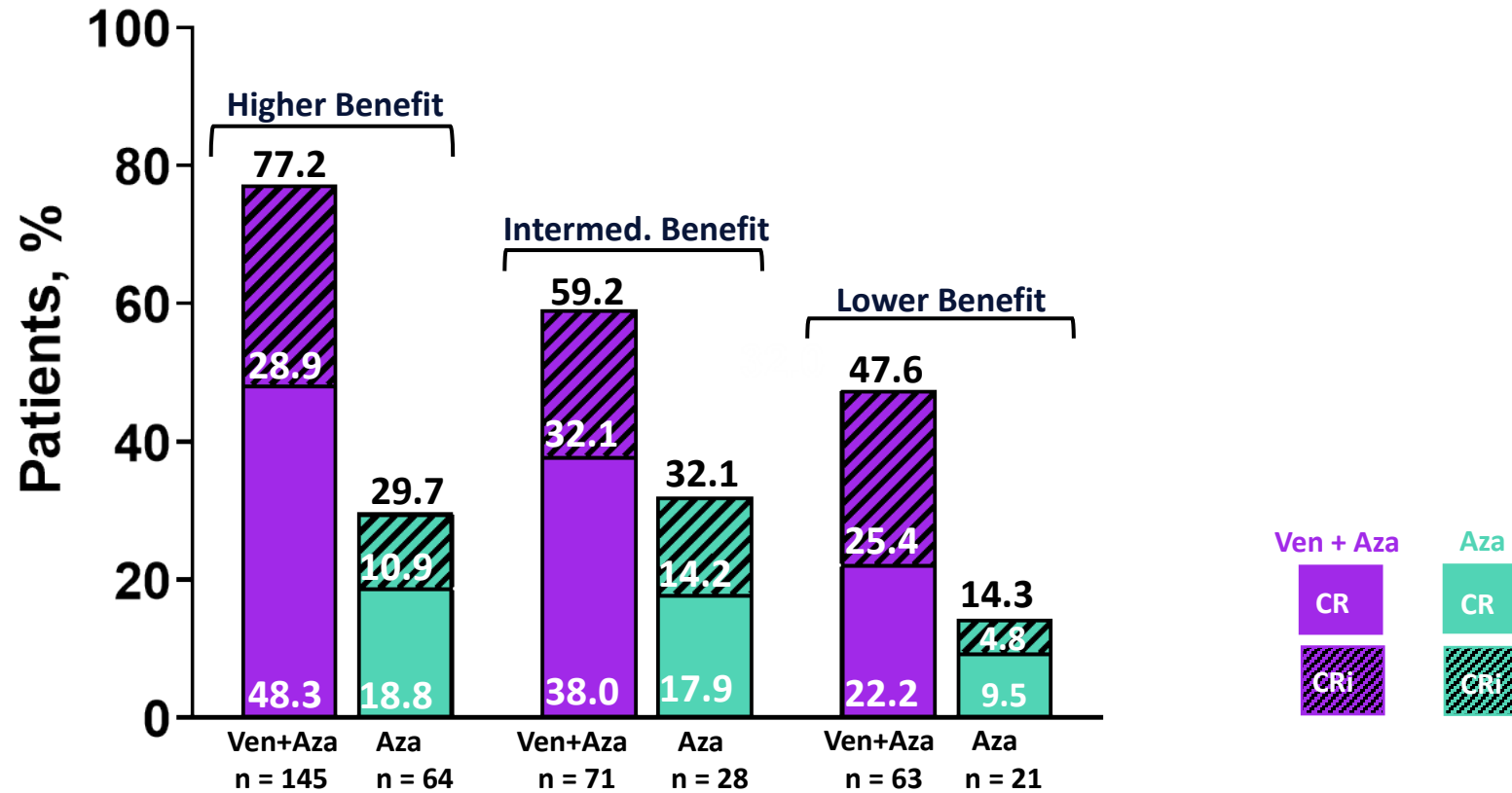
Higher Benefit Group - *TP53*^{WT}, No *FLT3*-ITD, *K/NRAS*^{WT}

Intermediate Benefit Group - *TP53*^{WT} and *FLT3*-ITD or *K/NRAS* mutated

Lower Benefit Group - *TP53* mutated

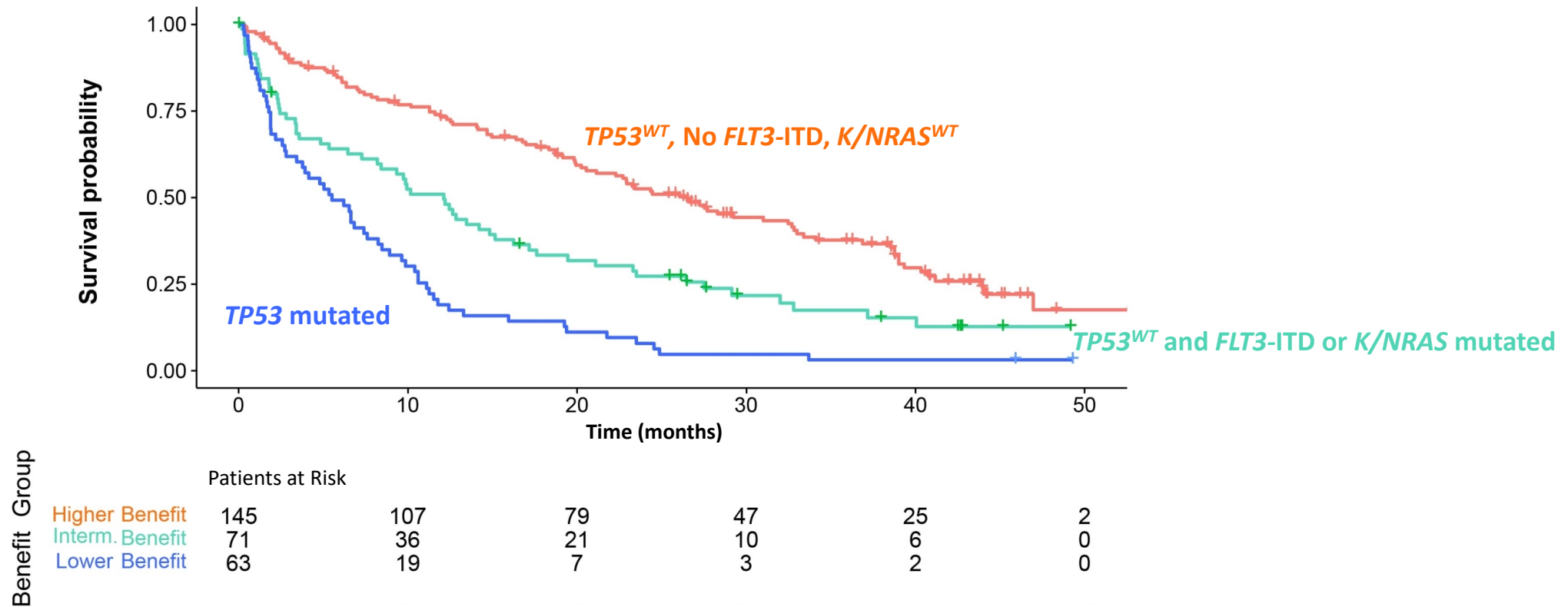
t(6;9), t(9;11), and t(8;11) were not detected in any of the subgroups; ^aCytogenetics were classified per National Comprehensive Cancer Network (NCCN) criteria; Abbreviations: Aza, azacitidine; Com., complex; Pbo, placebo; Ven, venetoclax

Remission rates were higher with Ven+Aza than with Aza monotherapy across all 3 groups



- CR and CR/CRi rates were highest in the higher benefit group
- Higher MRD negativity rates were achieved with Ven+Aza than with Aza monotherapy across all 3 groups

Three prognostic risk signatures derived to indicate higher, intermediate, and lower benefit from treatment with Ven+Aza



Can we improve on the outcomes of Aza/ven?

- Addition of a targeted agent
 - FLT3, IDH1, IDH2
- Nontargeted novel agents for high risk subsets (*TP53*)
 - Anti-CD47 Ab (Magrolimab)





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Updated results from a phase I/II study of the triplet combination of azacitidine, venetoclax and gilteritinib for patients with *FLT3*-mutated acute myeloid leukemia

NJ Short, CD Dinardo, N Daver, W Macaron, M Yilmaz, G Borthakur, G Montalban-Bravo, G Garcia-Manero, GC Issa, K Sasaki, P Thompson, J Burger, A Maiti, Y Alvarado, M Kwari, R Delumpa, J Thankachan, E Mayor, C Loiselle, A Milton, G Banks, T Kadia, M Konopleva, H Kantarjian, F Ravandi

Department of Leukemia

The University of Texas MD Anderson Cancer Center, Houston, TX

Aza+Ven+Gilteritinib in FLT3-mutated AML: Regimen

Induction

- Relapsed/refractory *FLT3*-mutated* AML or high-risk MDS or CMML

or

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

Azacitidine
75 mg/m² IV/SC on D1-7

Venetoclax[#]
D1-28 (bone marrow on D14)[%]

Gilteritinib
80-120 mg on D1-28

Consolidation (up to 24 cycles)

Azacitidine
75 mg/m² IV/SC on D1-5

Venetoclax
400mg on D1-7

Gilteritinib
80-120 mg on D1-28

[#] Venetoclax ramp-up during cycle 1:
100mg on D1, 200mg on D2, 400mg on D3+

[%] If <5% blasts or insufficient on C1D14, venetoclax held
(both cohorts) and gilteritinib held (frontline only)

Primary endpoints: MTD of gilteritinib in combination (phase I), CR/CRi rate (phase II)

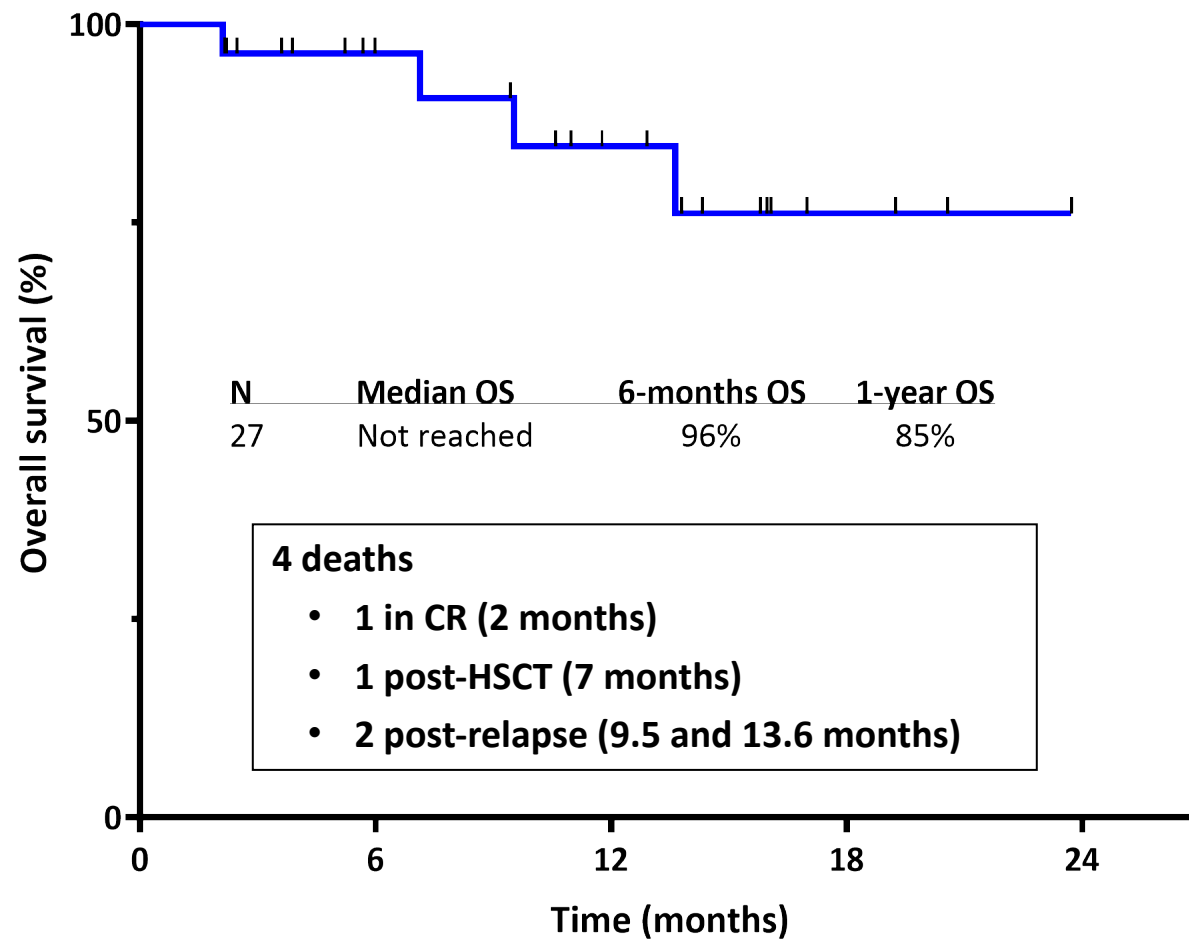
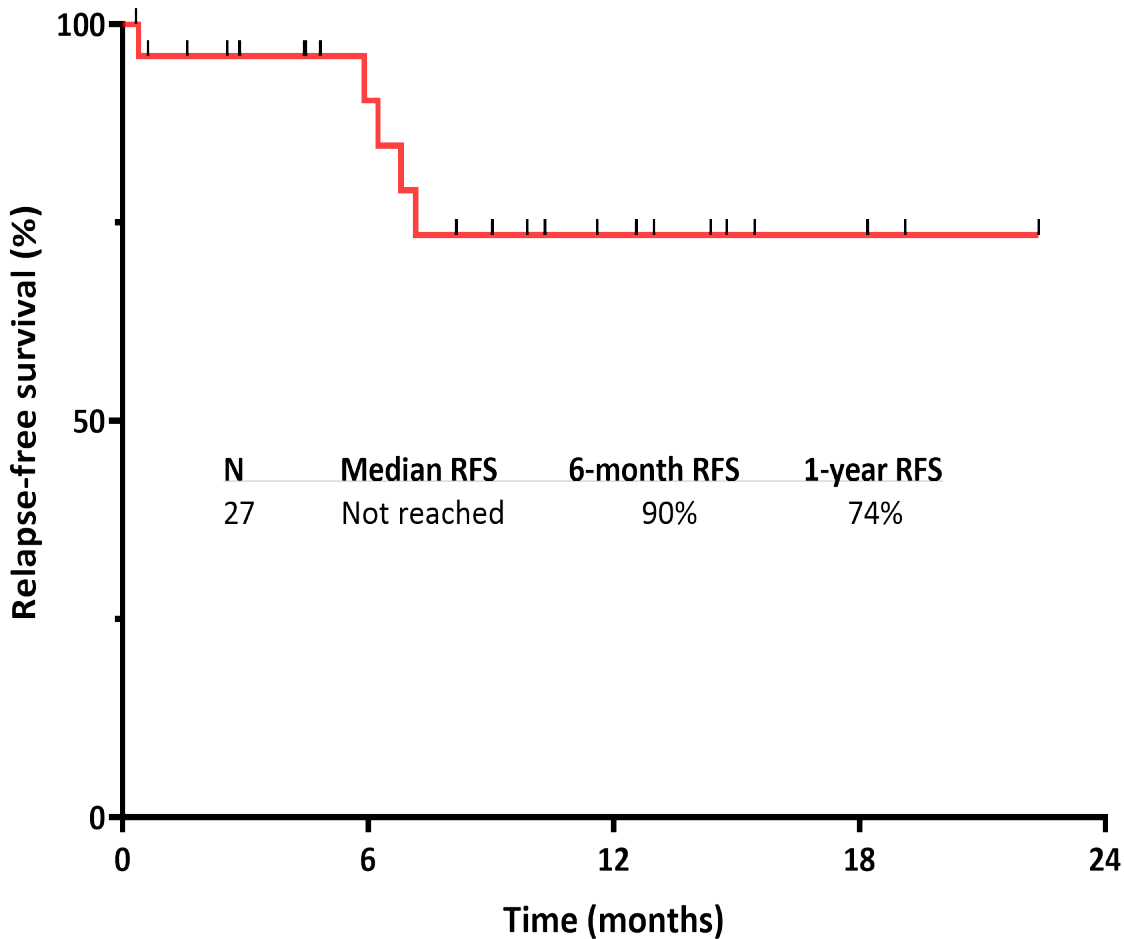
Secondary endpoints: CR rate, MRD negativity rate, duration of response, OS, safety

Aza+Ven+Gilteritinib in FLT3-mutated AML: Responses

Response, n/N (%)	Frontline N = 27	R/R N = 20
mCRc (CR/CRi/MLFS)	27 (100)	14 (70)
CR	25 (92)	4 (20)
CRi	1 (4)	3 (15)
MLFS	1 (4)	7 (35)
PR*	0	1 (5)
No response	0	5 (25)
Early death	0	0

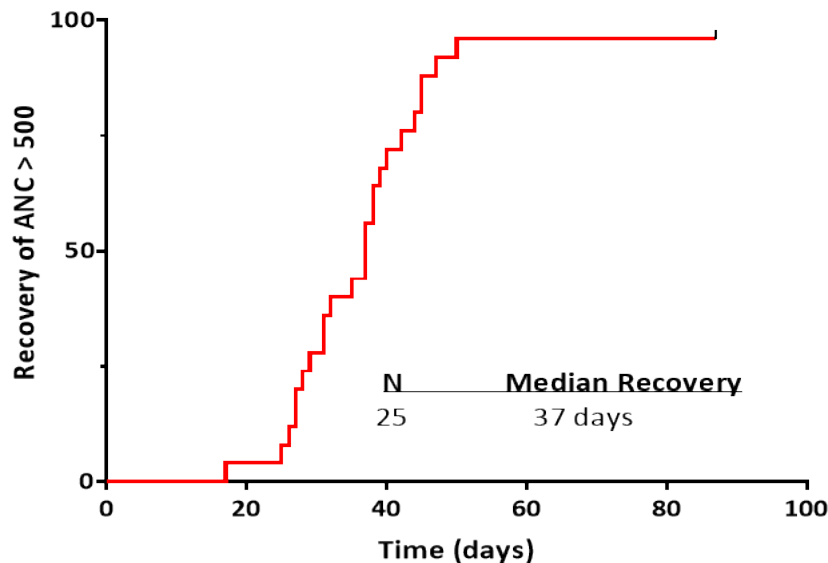
Aza+Ven+Gilteritinib in FLT3-mutated AML: RFS and OS in Frontline Cohort

Median follow-up: 12 months (range, 1.5-24+ months)

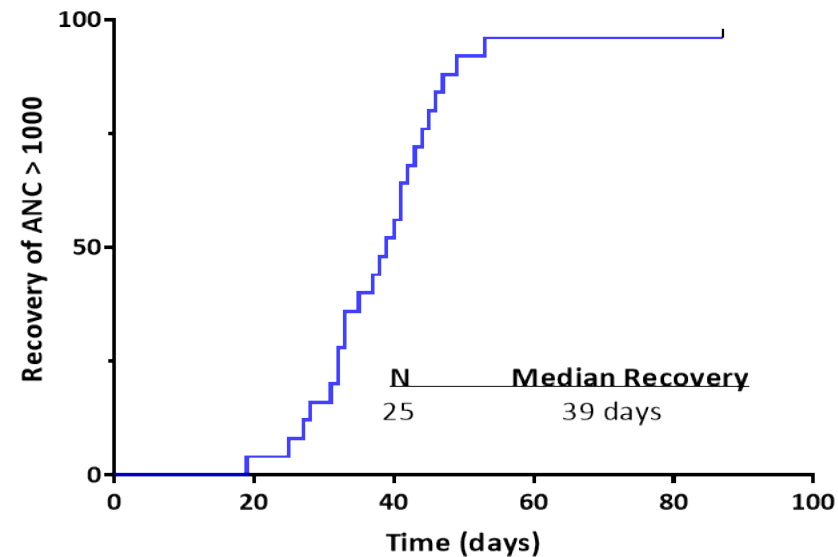


Aza+Ven+Gilteritnib in FLT3-mutated AML: Hematologic Recovery in Cycle 1 (Frontline Cohort)

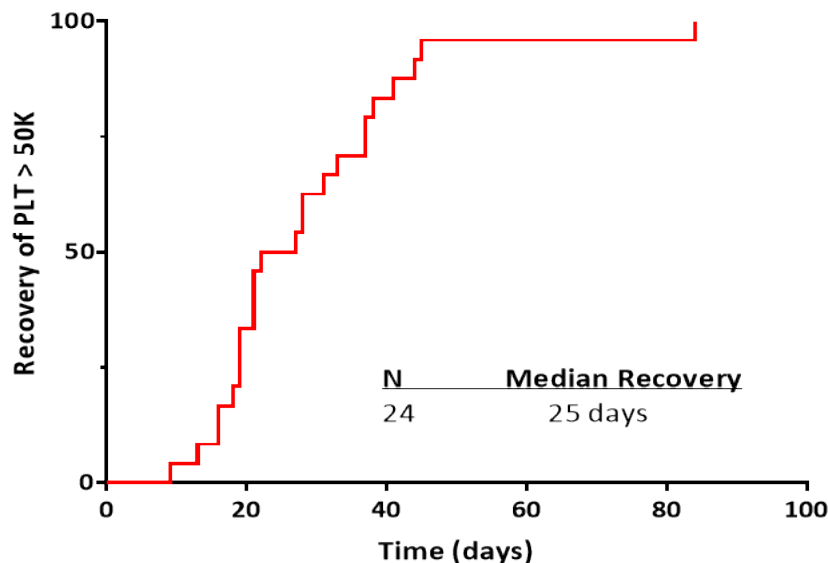
**ANC
>500**



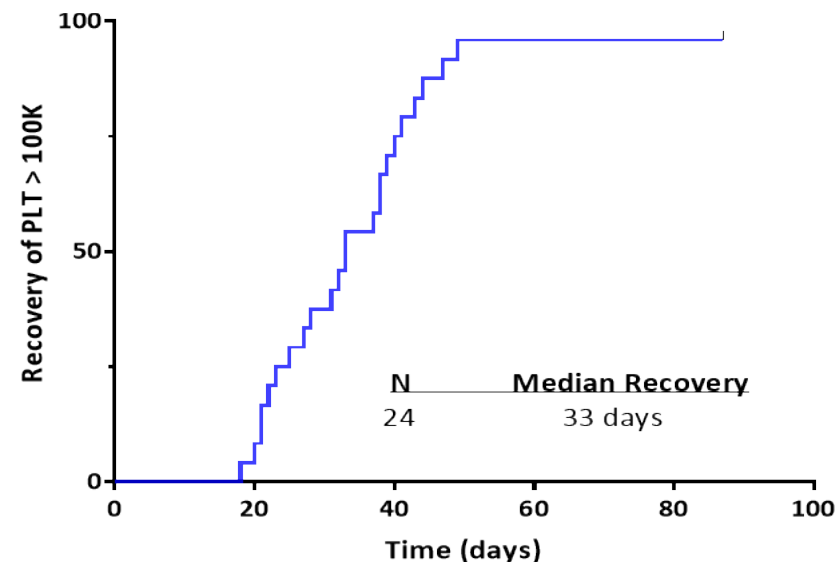
**ANC
>1000**



**Platelets
>50K**



**Platelets
>100K**



TP53 mutations in AML patients

- Epidemiology
 - Occurs in 5-10% of patients with de novo AML
 - 20-30% of patients with therapy-related AML
 - Often associated with complex / monosomal karyotype
- Poor outcomes irrespective of treatment with median OS (<1 yr)
 - No clear benefit with newer approved agents
 - AlloHCT still the best modality but post-transplant outcomes are also poor with a median posttransplant OS of <1 year and 2 year OS rate of <30%

1. Bowen D, et al Leukemia 2009
2. Grossman V, et al Blood 2012
3. Short NJ, et al. Lancet Haematol 2019
4. Ciurea SO, et al Blood 2018

sAML therapy options

Regimen	Response rates		Overall survival	
	All groups	TP53	All groups	TP53
Intensive regimens				
7+3 (cytarabine and anthracycline) ^{2,11,12,37}	CR: 35%-71% CR/CRi: 40%-71% <u>sAML subset:</u> CR: 26%-52% CR/CRi: 33%-55%	CR: 30%-34% CR/CRi: 40%	<u>sAML subset:</u> 5-10 mo	5-6 mo
CPX-351 (liposomal cytarabine and daunorubicin) ^{12,16,37}	<u>sAML subset:</u> CR: 7%-12% CR/CRi: 45%-48%	CR: 29% CR/CRi: 29%	<u>sAML subset:</u> 10-13 mo	4-6 mo
Nonintensive regimens				
Azacitidine and venetoclax ^{16,17,21}	CR: 40% CR/CRi: 65% <u>sAML subset:</u> CR/CRi: 60%	CR: NA CR/CRi: 50%-55%	11-16 mo <u>sAML subset:</u> 11-16 mo	5-7 mo
Azacitidine or decitabine monotherapy ^{21,38}	CR: 13%-24% CR/CRi: 18%-27% <u>sAML subset:</u> CR/CRi: 25%	CR: 24%-40% CR/CRi: 0%-40%	6-11 mo <u>sAML subset:</u> 7-8 mo	2-7 mo



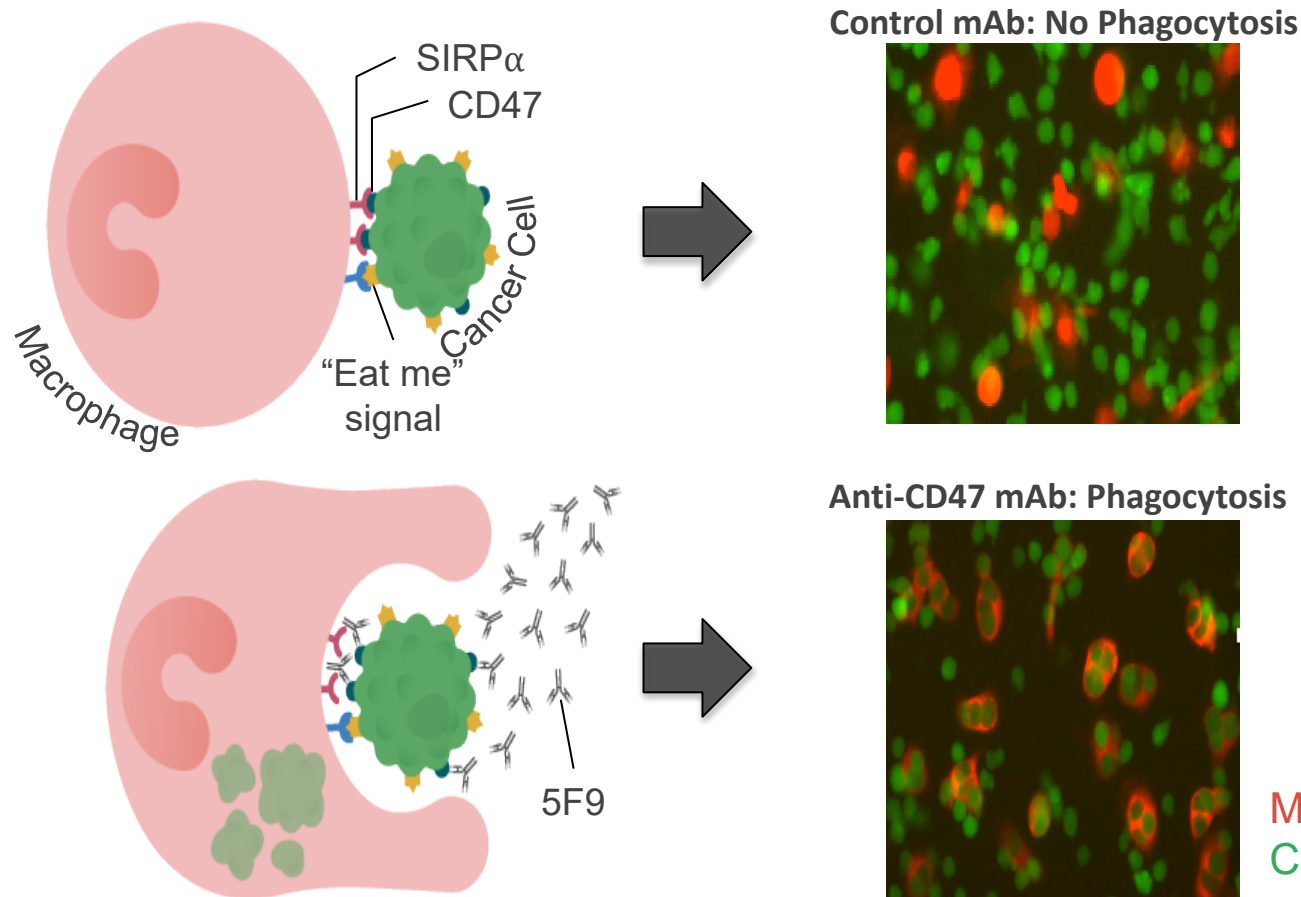
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Phase I/II Study of Azacitidine, Venetoclax and Magrolimab for Newly Diagnosed and Relapsed/Refractory AML

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Magrolimab is a Macrophage Immune Checkpoint Inhibitor Targeting CD47



- Magrolimab enables macrophages to phagocytose cancer cells by blocking the binding of the “don’t eat me” signal CD47 to its receptor SIRP α
- Normal cells are not phagocytosed as they do not express “eat me” signals, except for aged red blood cells

Macrophages
Cancer cells

Methods: Study Design

Phase 1 (Dose finding)

- R/R AML
- ≥ 18 yrs
- ECOG PS ≤ 2
- adequate organ function
- WBC ≤ 15x10⁹/L

Phase 2 cohorts

1. Frontline (De Novo and Secondary AML cohorts)

- ≥ 75 yrs or
- <75 yrs, ineligible for intensive therapy
- ≥ 18 yrs with *TP53*^{mut} or adverse risk CG, regardless of 'fitness'

2. R/R venetoclax-naïve (Salvage 1 and 2)

3. R/R prior venetoclax (Salvage 1 and 2)

Primary objectives

- Determine MTD and RP2D
- CR/CRi rate

Secondary objectives

- ORR: CR/CRi + PR + MLFS
- Duration of response
- Event-free survival
- Overall survival
- MRD negative rate
- 4- and 8-wk mortality
- No. of pts transitioning to SCT

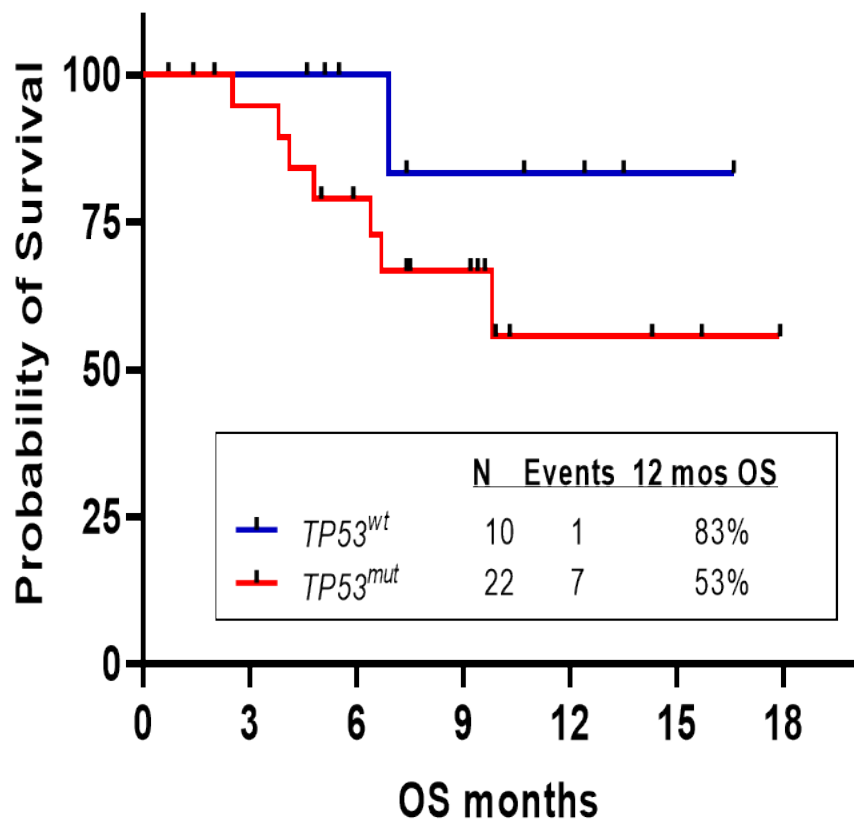
Exploratory objectives

Responses per ITT FRONTLINE (n=43): CR/CRI rates similar in TP53m and TP53wt

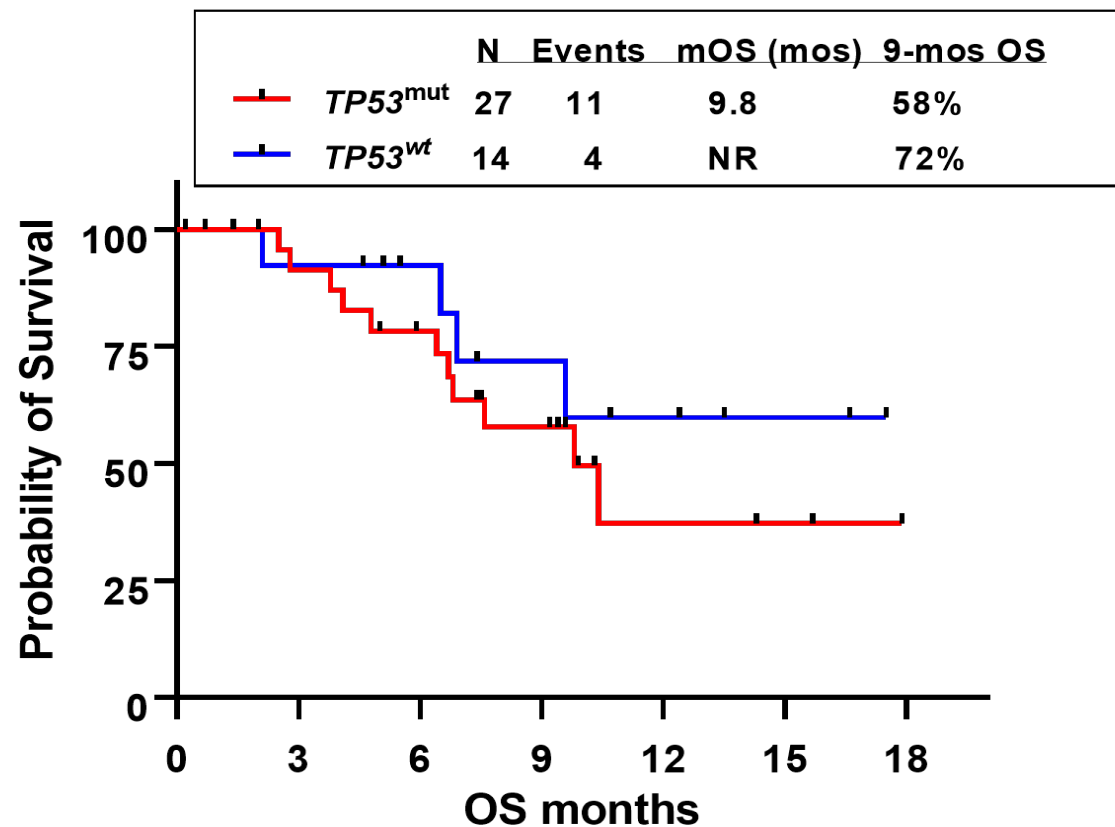
Parameters		Full Frontline		De novo		Secondary AML	
		N=43	TP53 ^{mut} (N=22)	TP53 ^{WT} (N=11)	TP53 ^{mut} (N=5)	TP53 ^{WT} (N=5)	
		N (%), Median [range]					
Overall response	CR	21 (49)	10 (46)	6 (55)	2 (40)	3 (60)	
	CRI	10 (23)	4 (18)	4 (36)	1 (20)	1 (20)	
	CR + CRI	31 (72)	14 (64)	10 (91)	3 (60)	4 (80)	
	MLFS	4 (9)	1 (5)	1 (9)	2 (40)	0 (0)	
MRD-ve best responses[#]	FCM-CR/CRI	16/28 (67) [#]	8/14 (64)	6/10 (60)	0 (0)	2/4 (50)	
Time to response (days)	First response	23 [19-105]	24 [20-81]	20 [20-29]	20 [19-105]	27 [20-73]	
	Best response	51 [20-130]	49 [20-130]	33 [20-63]	48 [20-105]	62 [20-88]	
Counts recovery (days)	ANC ≥ 500/cu mm	36 [16-88]	36 [16-88]	34 [26-62]	34 [31-36]	39 [23-59]	
	Platelet ≥ 100 x 10 ⁹ /L	32 [0-74]	31 [15-55]	33 [19-74]	28 [22-49]	33 [0-46]	
Cycles on therapy		3 [1-17]	3 [2-6]	3 [1-17]	1 [1-3]	2 [1-3]	
Mortality:							
-	4 week	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
-	8 week	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	

Results: Survival outcomes FRONTLINE (n=41)* cohort

Median OS in frontline De Novo population (N=32)*



Median OS in FRONTLINE population (N=41)*



Results: Impact of SCT in the frontline setting in $TP53^{mut}$ patients

No. of $TP53^{mut}$ patients transplanted

8 (7 denovo+ 1 secondary untreated)

Age of the SCT patients

64 years (range, 46-69 years)

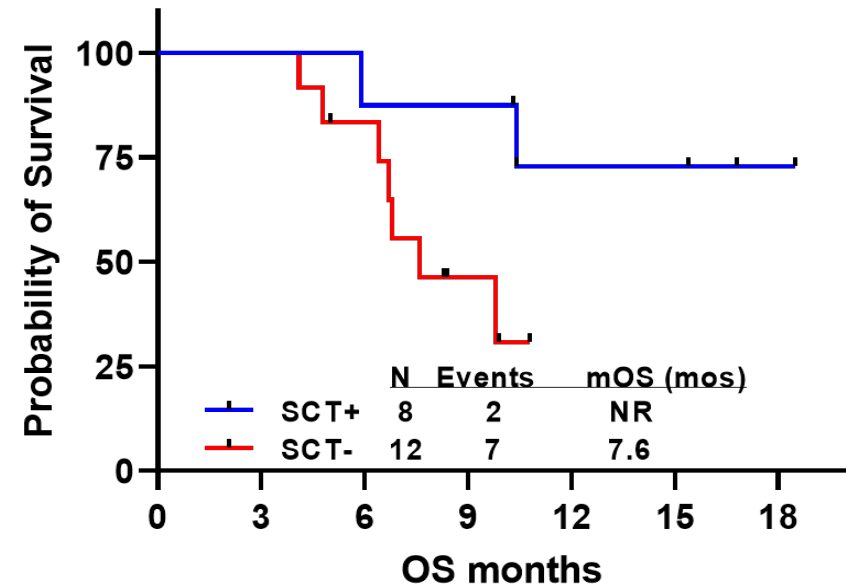
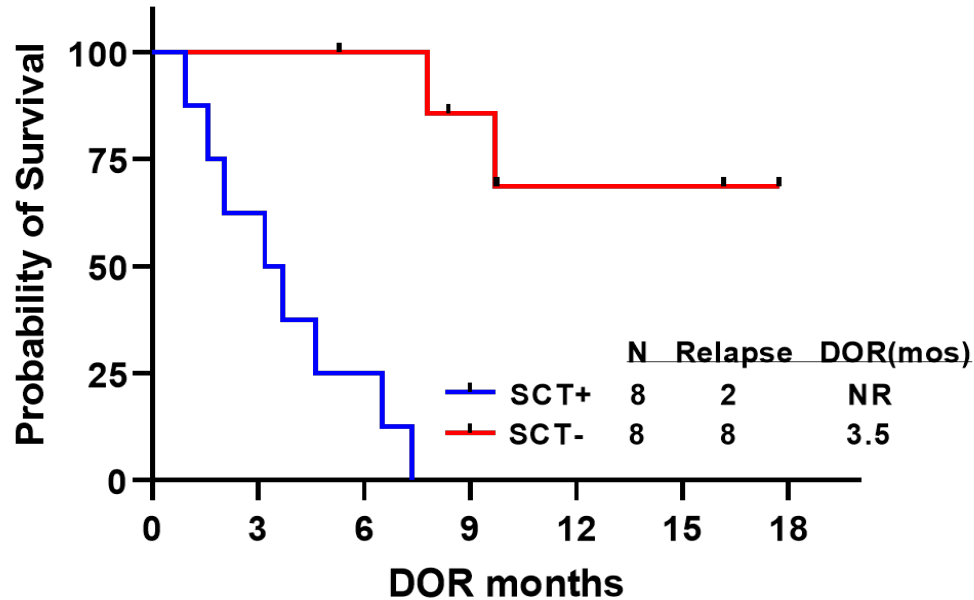
Median time to SCT from trial therapy initiation

4.2 months (range, 2.6-5.8 months)

Median cycles on therapy to SCT

3 (range, 2-4 cycles)

CR

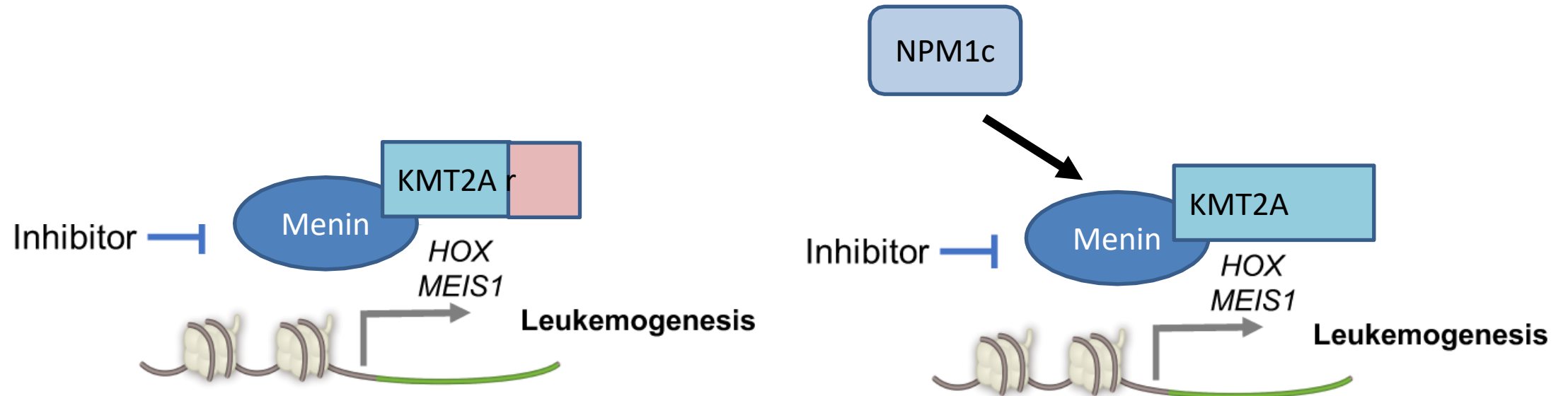


Landmark analysis of SCT vs. No SCT in frontline setting with $TP53^{mut}$ mutated AML

*Median age of landmark comparator "No SCT" arm= 67 years (range, 32-84 years)

Menin inhibitors for KMT2Ar and NPM1

- KMT2Ar represent ~10% of acute leukemias
 - 70-80% of infantile leukemias
 - t-AML following exposure to topoisomerase II inhibitors
 - Targets and dysregulates expression of HOXA9 and MEIS1





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The Menin Inhibitor Revumenib (SNDX-5613) Leads to Durable Responses in Patients with *KMT2A*-Rearranged or *NPM1* Mutant AML: Updated Results of a Phase 1 Study

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Adverse Events across all doses of revumenib

Any-grade treatment-related AE (≥5%)	Safety Population N=68
Patients with ≥1 treatment-related AE, n (%)	53 (78)
ECG QTc prolonged	36 (53)
Nausea	18 (27)
Vomiting	11 (16)
Differentiation syndrome	11 (16)
Diarrhea	7 (10)
Dysgeusia	5 (7)
Decreased appetite	5 (7)

No treatment discontinuations for QTc prolongations, or associated arrhythmias

≥Grade 3 treatment-related AE	Safety Population N=68
Patients with ≥Gr 3 treatment-related AE, n (%)	11 (16)
ECG QTc prolonged	9 (13)
Diarrhea	2 (3)
Anemia	2 (3)
Asthenia	1 (2)
Fatigue	1 (2)
Hypercalcemia	1 (2)
Hypokalemia	1 (2)
Neutropenia	1 (2)
Thrombocytopenia	1 (2)
Tumor lysis syndrome	1 (2)

10% of patients (5/52) had Gr 3 QTc prolongation at doses meeting criteria for RP2D

ECG, electrocardiogram; QTc, corrected QT interval.

Data cutoff: 31 March 2022

Revumenib demonstrates promising antileukemic activity in relapsed/refractory *KMT2Ar* and *mNPM1* leukemias

Best Response, n (%)	Efficacy Population n=60	
ORR*	32/60 (53%)	
Best Response		
CR	12 (20%)	
CRh	6 (10%)	
CRp	5 (8%)	
MLFS	9 (15%)	
MRD^{neg} rate[†]	18/32 (56%)	
CR/CRh MRD ^{neg}	14/18 (78%)	
CR/CRh/CRp MRD ^{neg}	18/23 (78%)	
Genetic alteration	<i>KMT2Ar</i> n=46	<i>mNPM1</i> n=14
ORR	27/46 (59%)	5/14 (36%)
CR/CRh	15 (33%)	3 (21%)
CR/CRh/CRp MRD ^{neg} rate	11/15 (73%)	3/3 (100%)

CR/CRh
18 (30%)

*Overall Response Rate = CR + CRh + CRp + MLFS; MRD status assessed locally by PCR or MCF.
CR, complete remission; CRh, complete remission with partial hematologic recovery; CRp, complete remission with incomplete platelet recovery; MLFS, morphologic leukemia free state; MRD, measurable residual disease; ORR, objective response rate.

Data cutoff:
31 March 2022



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Update on a Phase 1/2 First-in-Human Study of the Menin-KMT2A (MLL) Inhibitor Ziftomenib (KO-539) in Patients with Relapsed or Refractory Acute Myeloid Leukemia

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Phase 1a Dose Escalation – Safety

≥Gr3 TEAEs (All Causality) Preferred Term	50 mg (N = 1) n (%)	100 mg (N = 1) n (%)	200 mg (N = 6) n (%)	400 mg (N = 5) n (%)	600 mg (N = 5) n (%)	800 mg (N = 11) n (%)	1000 mg (N = 1) n (%)
Anemia	0	0	2 (33.3)	1 (20.0)	3 (60.0)	2 (18.2)	0
Pneumonia	1 (100.0)	0	2 (33.3)	1 (20.0)	0	3 (27.3)	0
Thrombocytopenia	0	0	1 (16.7)	1 (20.0)	3 (60.0)	0	0
Neutropenia	0	1 (100.0)	1 (16.7)	0	0	3 (27.3)	0
Febrile neutropenia	0	0	0	1 (20.0)	1 (20.0)	1 (9.1)	0
Decreased appetite	0	0	2 (33.3)	0	0	1 (9.1)	0

No drug-induced QT/QTc prolongation reported

Two DLTs were reported:

- 400 mg cohort (pneumonitis, post-aspiration pneumonia)
- 1000 mg cohort (differentiation syndrome)
 - Per protocol, the DLT in first patient at 1000 mg resulted in de-escalation to 800 mg

Ziftomenib Demonstrates Encouraging Antileukemic Activity at 600 mg

Best Overall Response	200 mg	600 mg
<i>NPM1-m</i> Phase 1a + 1b	(n=6)	(n=20)
CR	1 (16.7)	6 (30.0)
CR/CRh	1 (16.7)	6 (30.0)
CRc	1 (16.7)	7 (35.0)
MRD negativity	1 (100.0)	3 (42.9) ¹
ORR	2 (33.3)	8 (40.0)
<i>KMT2A-r</i> Phase 1a + 1b	(n=14)	(n=18)
CR/CRh	0	1 (5.6)
CRc	0	2 (11.1)
MRD negativity	0	2 (100.0)
ORR	0	3 (16.7)

- 2 pts had concurrent *IDH1/2*
- 2 pts had both *IDH1/2* and *FLT3-ITD/TKD*

Of *IDH1/2* co-mutants (7), 57% experienced a CR

¹ MRD was assessed for 5/7 CRc patients; 3 of those 5 patients (60%) tested were MRD negative

CRc includes CR, CRh, CRi, CRp

ORR includes CR, CRh, CRi, CRp, MLFS

Conclusions

- Emerging data with novel triplet combinations of targeted agents with azacitidine/venetoclax
 - High response rates
 - Increased myelosuppression, unknown long term tolerability
- AML with *TP53* mutation continues to demonstrate inferior outcomes with conventional and HMA/venetoclax-based therapies
 - Novel strategies are warranted
 - CD47 targeting being explored in this subset
 - Transplant continues to be the best strategy for cure.
- Emergence of targeted therapy for MLL and NPM1 subsets with menin inhibitors

