Acute Leukemia Review 2023

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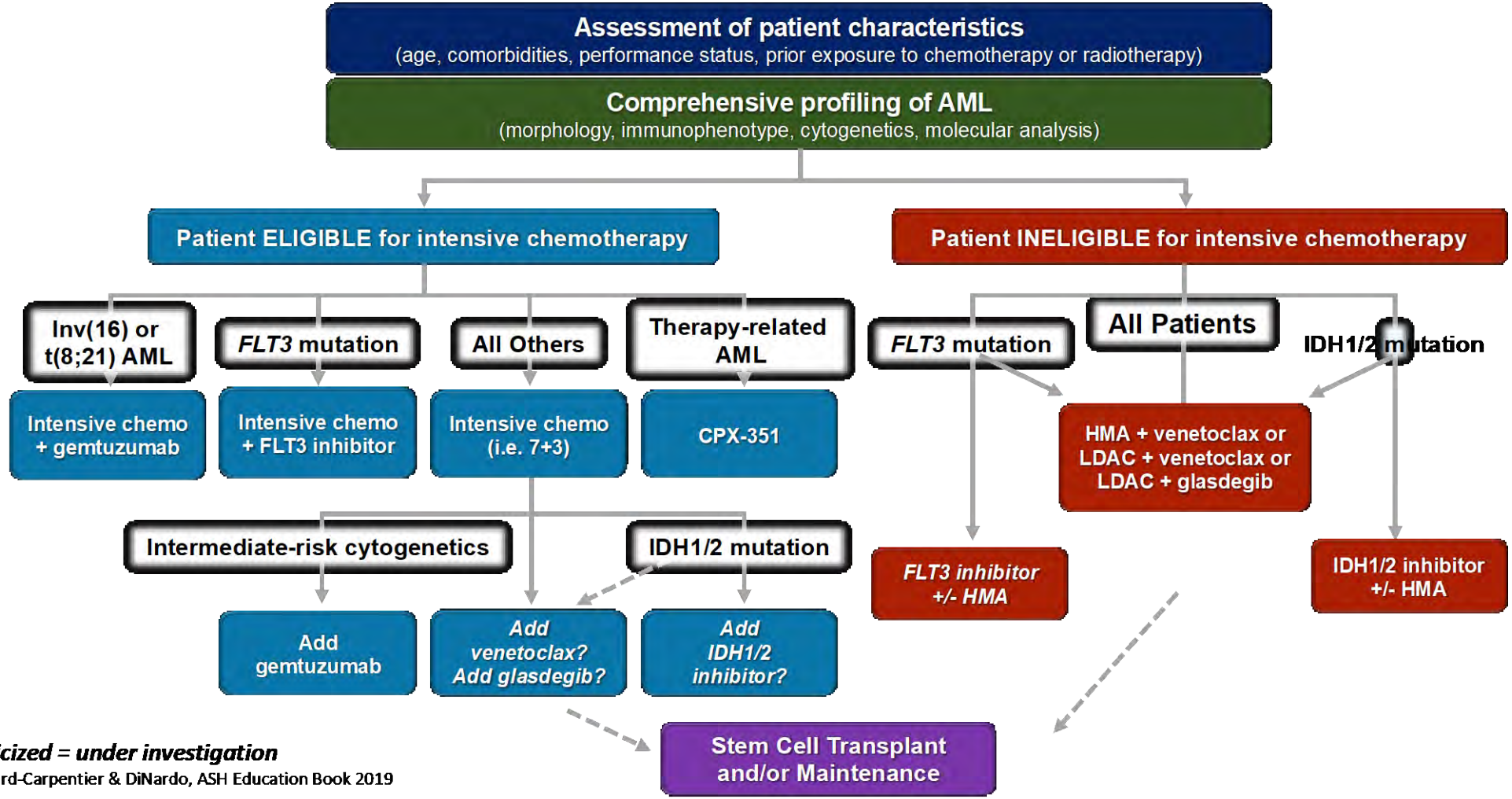
Conflict of interest

No relevant COI to disclose

AML Treatment approach



Italicized = under investigation

Richard-Carpentier & DiNardo, ASH Education Book 2019

Discussion outline

- Long term outcomes VIALE—A
- Risk stratification with AZA+VEN

AZA+VEN updates

- AZA+VEN vs. ‘7+3’
- CLIA+VEN updates
- ‘7+3’+quizartinib

Intensive induction treatment

- AZA+VEN+magrolimab
- AZA+VEN+gilteritinib
- Cladribine/LDAC/VEN

Lower-intensity treatment

- Menin inhibitor *KMT2A*/*NPM1* AML

New therapies for AML

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Long-Term Follow-Up of the Phase 3 VIALE-A Clinical Trial of Venetoclax Plus Azacitidine for Patients With Treatment-Naïve Acute Myeloid Leukemia Ineligible for Intensive Chemotherapy

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American Society for Hematology 2022, New Orleans, LA, USA

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VIALE-A study design

Eligibility

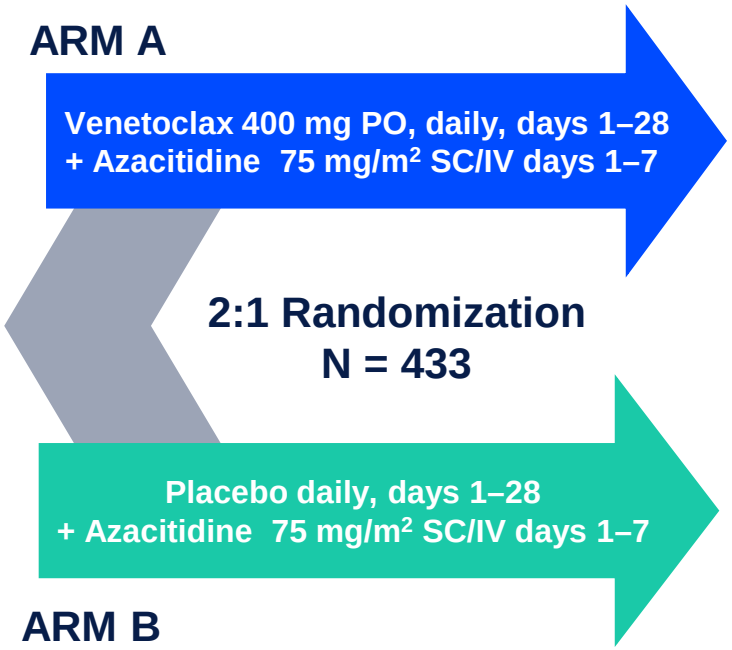
Key Inclusion Criteria

● AML previously untreated ● Age ≥ 75 years or 18-74 years with co-morbidities ineligible for standard induction regimens ● ECOG of 0-2 for pts ≥ 75 years or 0 to 3 for pts ≥ 18-74 years

Key Exclusion Criteria

● Prior receipt of any HMA, Ven, or chemotherapy for MDS ● Favorable risk cytogenetics per NCCN 2016 ● AML secondary to MPN, CML ● Acute promyelocytic leukemia ● Active CNS involvement

Treatment



Randomization Stratification Factors	Age (< 75 vs. ≥ 75 years); Cytogenetic Risk (intermediate, poor); Region
Venetoclax dosing ramp-up	**Cycle 1 ramp-up** Day 1: 100 mg, Day 2: 200 mg, Day 3 - 28: 400 mg **Cycle 2** Day 1-28: 400 mg

Key Endpoints

Key Primary Endpoints:

● Overall survival (OS)*

Key Secondary Endpoints:

● CR+CRi rate*, CR rate

● OS, CR+CRi in mol. subgroups

● MRD negativity remission rate

*For US and US reference countries, OS is the single endpoint and CR+CRi rate is one of the ranked secondary endpoints; CR+CRi rate is co-primary endpoint for EU and EU reference countries;
Abbreviations: AML, acute myeloid leukemia; CML, chronic myelogenous leukemia; CNS, central nervous system; CR, complete remission; CRi, CR with incomplete count recovery; ECOG, Eastern Cooperative Oncology Group; HMA, hypomethylating agent; Ven, venetoclax; MDS, myelodysplastic syndrome; mol., molecular; MPN, myeloproliferative neoplasms; MRD, minimal residual disease; NCCN, National Comprehensive Cancer Network; OS; overall survival

Patient demographics and baseline disease characteristics

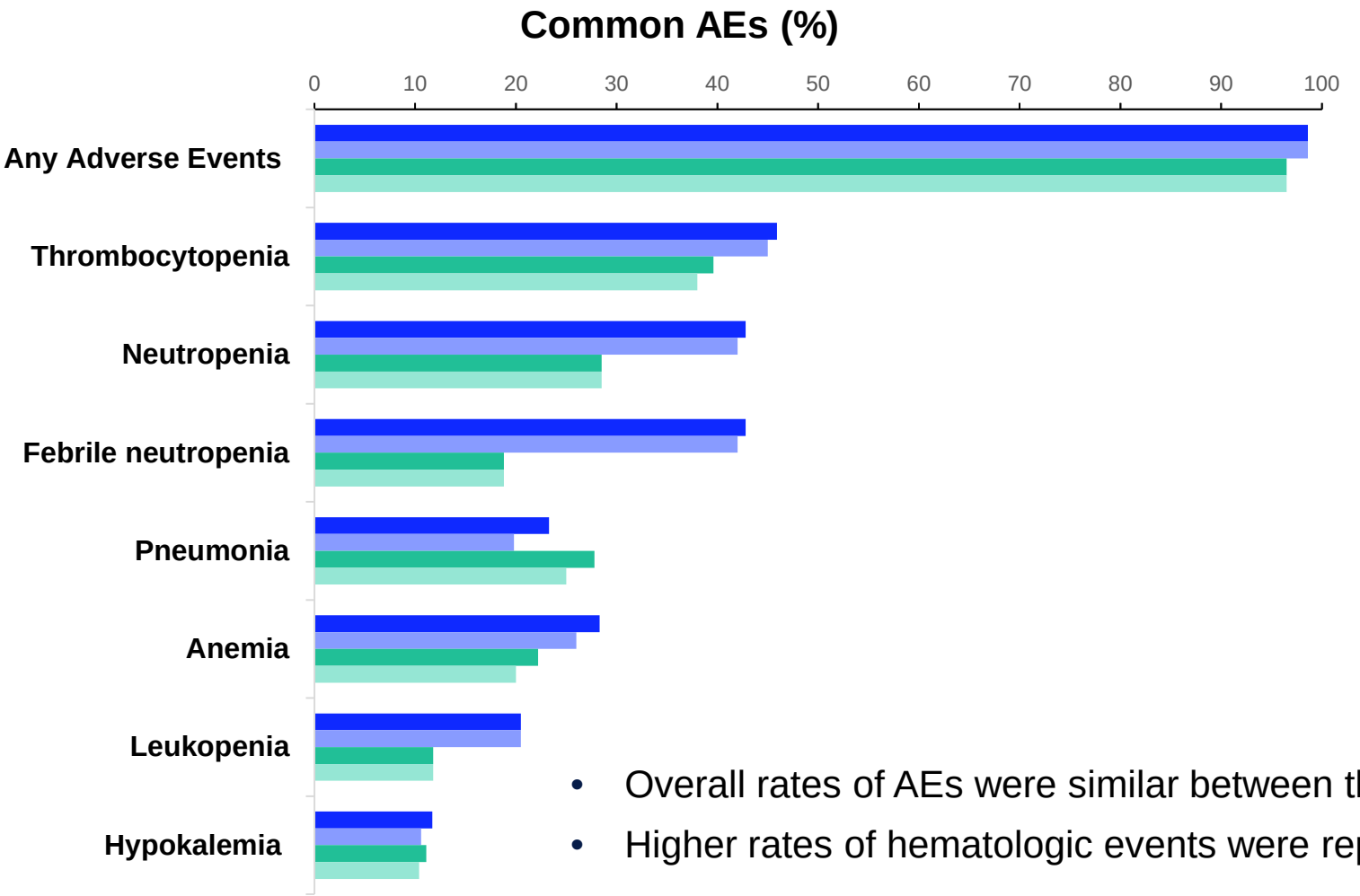
	Ven+Aza (N=286)	Pbo+Aza (N=145)
Median age, years (range)	76.0 (49.0 - 91.0)	76.0 (60.0 - 90.0)
Age categories, n (%)		
18 - < 65	10 (3.5)	5 (3.4)
65 - < 75	102 (35.7)	53 (36.6)
≥ 75	174 (60.8)	87 (60.0)
AML types, n (%)		
De novo	214 (74.8)	110 (75.9)
Secondary	72 (25.2)	35 (24.1)
Types of secondary AML		
Therapy related to AML	26 (36.1)	9 (25.7)
Post MDS/CMML	46 (63.9)	26 (74.3)
AML-MRC, n (%)	92 (32.2)	49 (33.8)

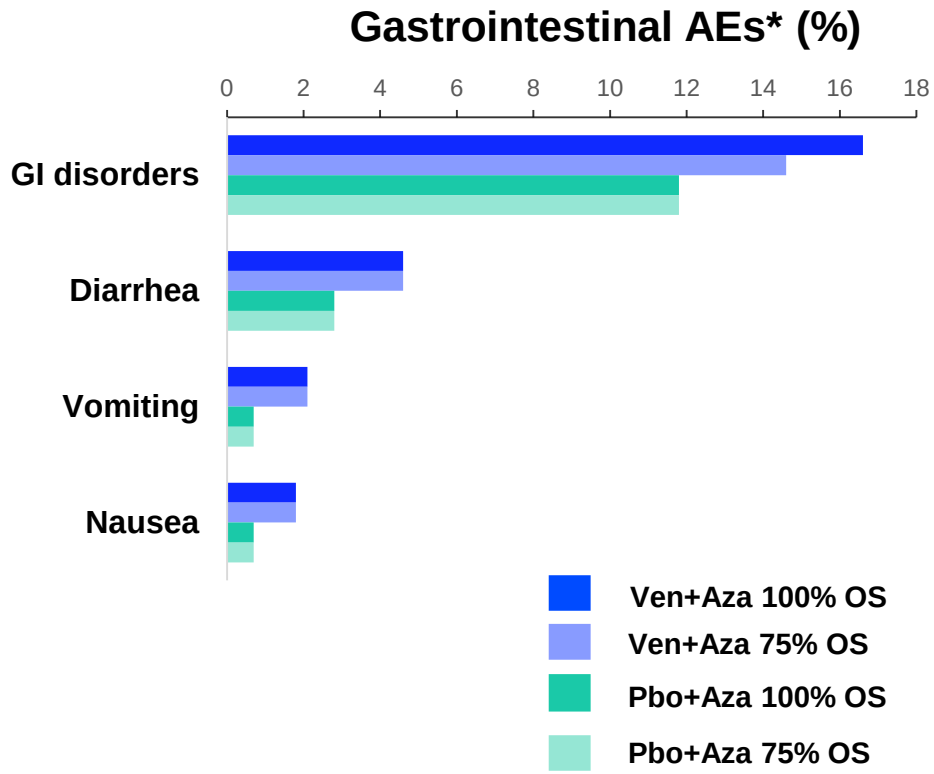
	Ven+Aza (N=286)	Pbo+Aza (N=145)
Blast count, n (%)		
< 30%	85 (29.6)	41 (28.1)
≥ 30 - < 50%	61 (21.3)	33 (22.6)
≥ 50%	140 (49.1)	71 (49.3)
ECOG score, n (%)		
0 - 1	157 (54.9)	81 (55.9)
2 - 3	129 (45.1)	64 (44.1)
Cytogenetic risk categ.		
Intermediate	182 (63.6)	89 (61.4)
Poor	104 (36.4)	56 (38.6)
Somatic mutations, n/N (%)		
FLT-3	29/206 (14.1)	22/108 (20.4)
IDH1/2	61/245 (24.9)	28/127 (22.0)
TP53	38/163 (23.3)	14/86 (16.3)
NPM1	27/163 (16.6)	17/86 (19.8)

Data cutoff: 01 Dec 2021;

Abbreviations: AML, acute myeloid leukemia; AML-MRC, AML with myelodysplasia-related changes; Aza, azacitidine; CMML, chronic myelomonocytic leukemia; ECOG, Eastern Cooperative Oncology Group; MDS, myelodysplastic syndrome; Ven, venetoclax

With longer follow up on treatment, grade ≥ 3 TEAEs reported in ≥ 10% are slightly higher than at 75% OS analysis





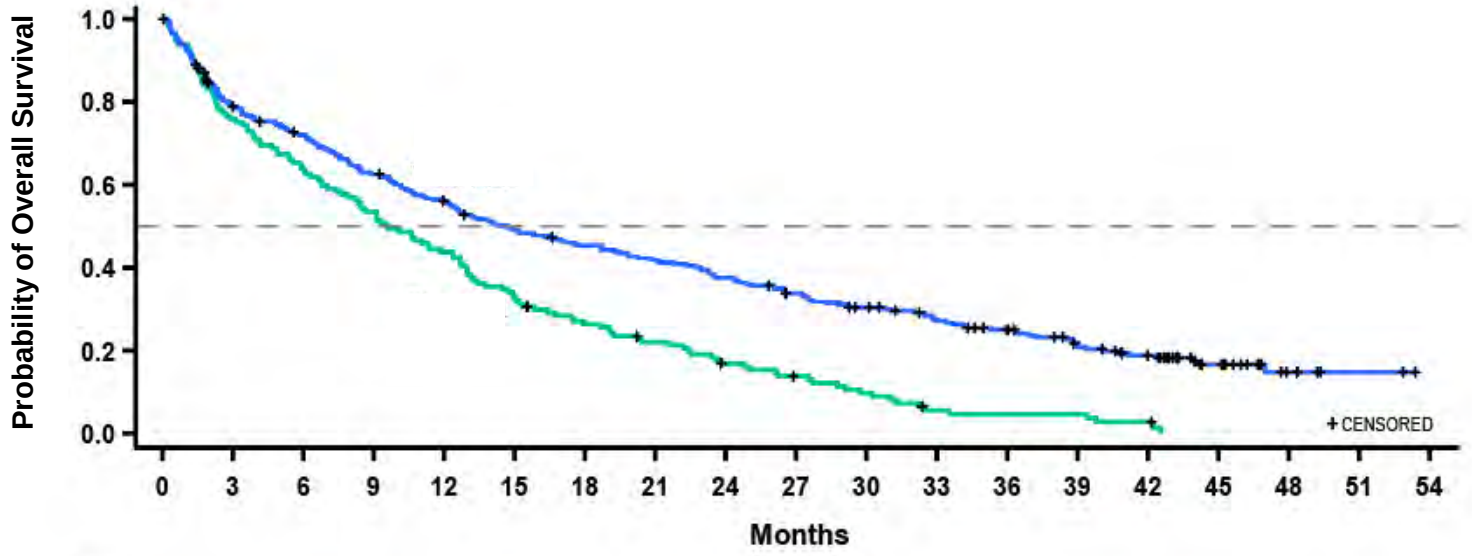
- Overall rates of AEs were similar between the two arms
- Higher rates of hematologic events were reported in the Ven+Aza arm

Data cutoff: 01 Dec 2021; *Gastrointestinal AEs reported are in < 10% pts.

Abbreviations: AE, adverse event; Aza, azacitidine; GI, gastrointestinal; OS, overall survival; Pbo, placebo; TEAE, treatment-emergent adverse event; Ven, venetoclax

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)



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

	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

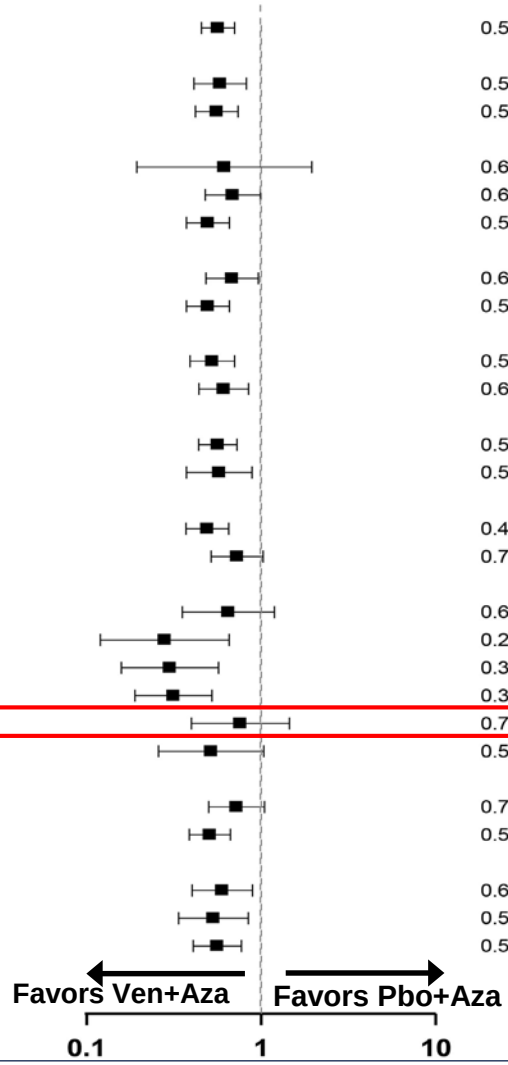
HR reduction from 0.66 (95% CI, 0.52 - 0.85) at 75% OS analysis

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

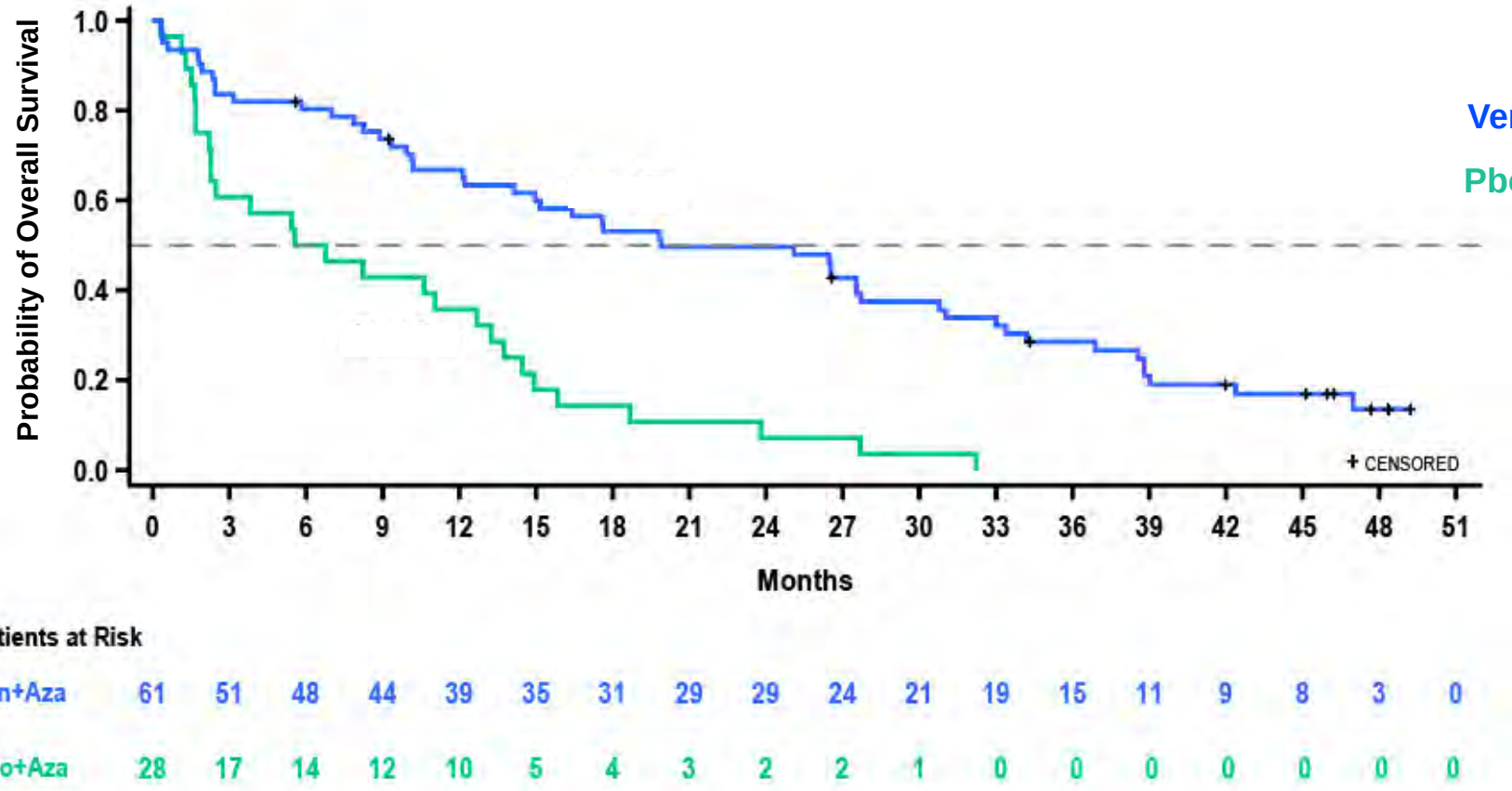
All subgroups of patients treated with Ven+Aza demonstrate continued OS benefit over Aza monotherapy

	Ven+Aza n/N (%)	Pbo+Aza n/N (%)	HR (95% CI)
All Patients	222/286 (77.6)	138/145 (95.2)	0.57 (0.45, 0.70)
Gender			
Female	88/114 (77.2)	55/ 58 (94.8)	0.58 (0.41, 0.82)
Male	134/172 (77.9)	83/ 87 (95.4)	0.56 (0.42, 0.74)
Age (Years)			
18 - < 65	8/ 10 (80.0)	5/ 5 (100.0)	0.61 (0.19, 1.95)
65 - < 75	79/102 (77.5)	49/ 53 (92.5)	0.69 (0.48, 0.99)
≥ 75	135/174 (77.6)	84/ 87 (96.6)	0.50 (0.37, 0.66)
Age (Years)			
< 75	87/112 (77.7)	54/ 58 (93.1)	0.68 (0.48, 0.96)
≥ 75	135/174 (77.6)	84/ 87 (96.6)	0.50 (0.37, 0.66)
Baseline ECOG			
Grade < 2	127/157 (80.9)	78/ 81 (96.3)	0.52 (0.39, 0.70)
Grade ≥ 2	95/129 (73.6)	60/ 64 (93.8)	0.61 (0.44, 0.85)
Type of AML			
De Novo	162/214 (75.7)	104/110 (94.5)	0.56 (0.44, 0.73)
Secondary	60/ 72 (83.3)	34/ 35 (97.1)	0.57 (0.37, 0.89)
Cytogenetic risk			
Intermediate	130/182 (71.4)	84/ 89 (94.4)	0.49 (0.37, 0.65)
Poor	92/104 (88.5)	54/ 56 (96.4)	0.73 (0.52, 1.02)
Molecular Marker			
FLT3	23/ 29 (79.3)	20/ 22 (90.9)	0.65 (0.35, 1.19)
IDH1	21/ 23 (91.3)	11/ 11 (100.0)	0.28 (0.12, 0.65)
IDH2	30/ 40 (75.0)	18/ 18 (100.0)	0.30 (0.16, 0.57)
IDH1/2	49/ 61 (80.3)	28/ 28 (100.0)	0.31 (0.19, 0.52)
TP53	36/ 38 (94.7)	13/ 14 (92.9)	0.76 (0.40, 1.45)
NPM1	17/ 27 (63.0)	17/ 17 (100.0)	0.52 (0.26, 1.03)
AML-MRC			
Yes	81/ 92 (88.0)	46/ 49 (93.9)	0.72 (0.50, 1.04)
No	141/194 (72.7)	92/ 96 (95.8)	0.51 (0.39, 0.67)
Bone marrow blast count			
< 30%	72/ 85 (84.7)	40/ 41 (97.6)	0.60 (0.40, 0.89)
30 -< 50%	47/ 61 (77.0)	32/ 33 (97.0)	0.53 (0.34, 0.84)
≥ 50%	103/140 (73.6)	66/ 71 (93.0)	0.56 (0.41, 0.77)



The hazard ratio between treatment arms were from unstratified Cox proportional hazards model; *TP53* and *NPM1* data are from the central lab using MyAML panel; *IDH1/2* and *FLT3* data are by CDX method; Data cut-off: 01 Dec 2021;
Abbreviations: Aza, azacitidine; AML, acute myeloid leukemia; AML-MRC; AML with myelodysplasia-related changes; HR, hazard ratio; Pbo, placebo; Ven, venetoclax

Median OS is achieved in patients with *IDH1/2* mutations



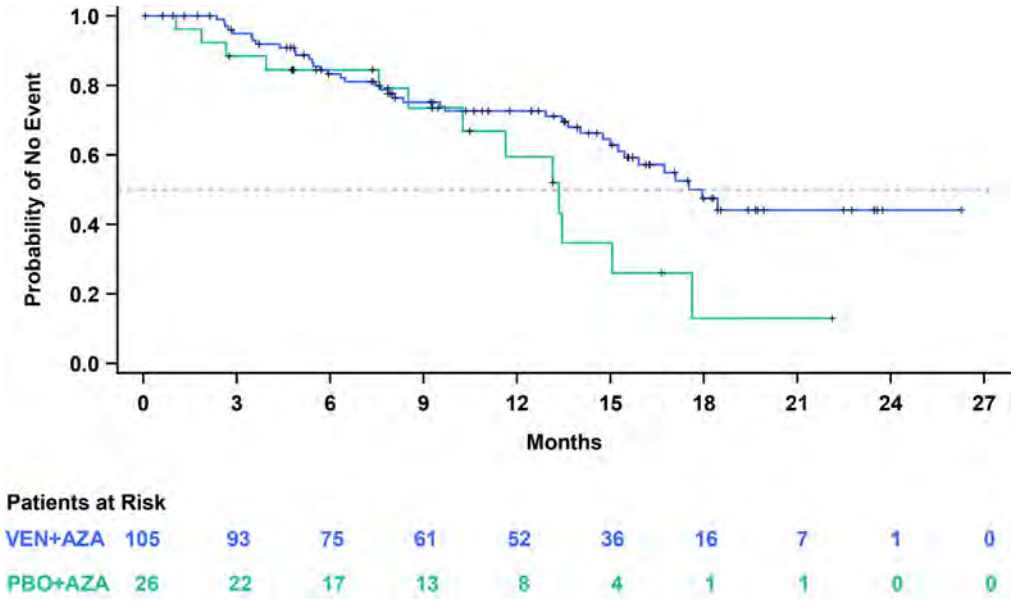
	No. of events/No. of patients (%)	OS (months) median (95% CI)
Ven+Aza	49/61 (80.3)	19.9 (12.2 - 27.7)
Pbo+Aza	28/28 (100)	6.2 (2.3 - 12.7)

HR: 0.314 (95% CI, 0.189 - 0.522), P < 0.001

The distributions were estimated for each treatment arm using Kaplan-Meier methodology. Unstratified log-rank test and hazard ratio was estimated using unstratified Cox model; IDH1/2 data are by CDX method; Data cutoff: 01 Dec 2021; Abbreviations: Aza, azacitidine; Pbo, placebo; Ven, venetoclax

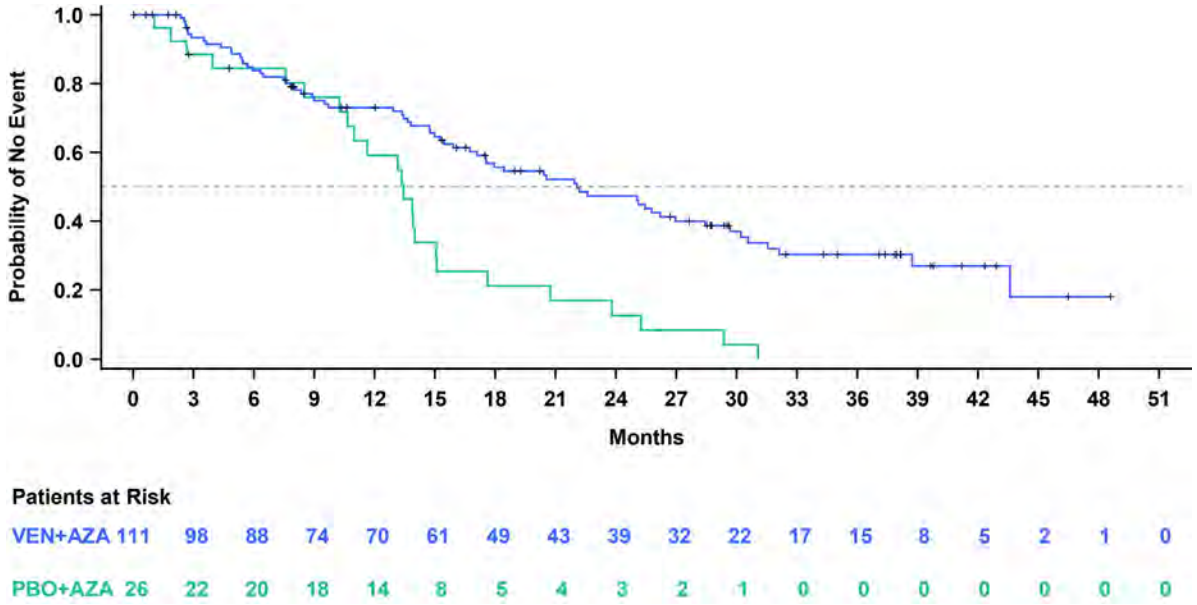
Median duration of CR for patients on Ven+Aza is ~5 months longer at 100% OS analysis than at primary analysis

Duration of CR at median follow-up of 20.5 months[1]



	DOR at 75% OS analysis (months) median (95% CI)
Ven+Aza (n=105)	17.5 (15.3 – NE)
Pbo+Aza (n=26)	13.3 (8.5 – 17.6)

Duration of CR at median follow-up of 43.2 months

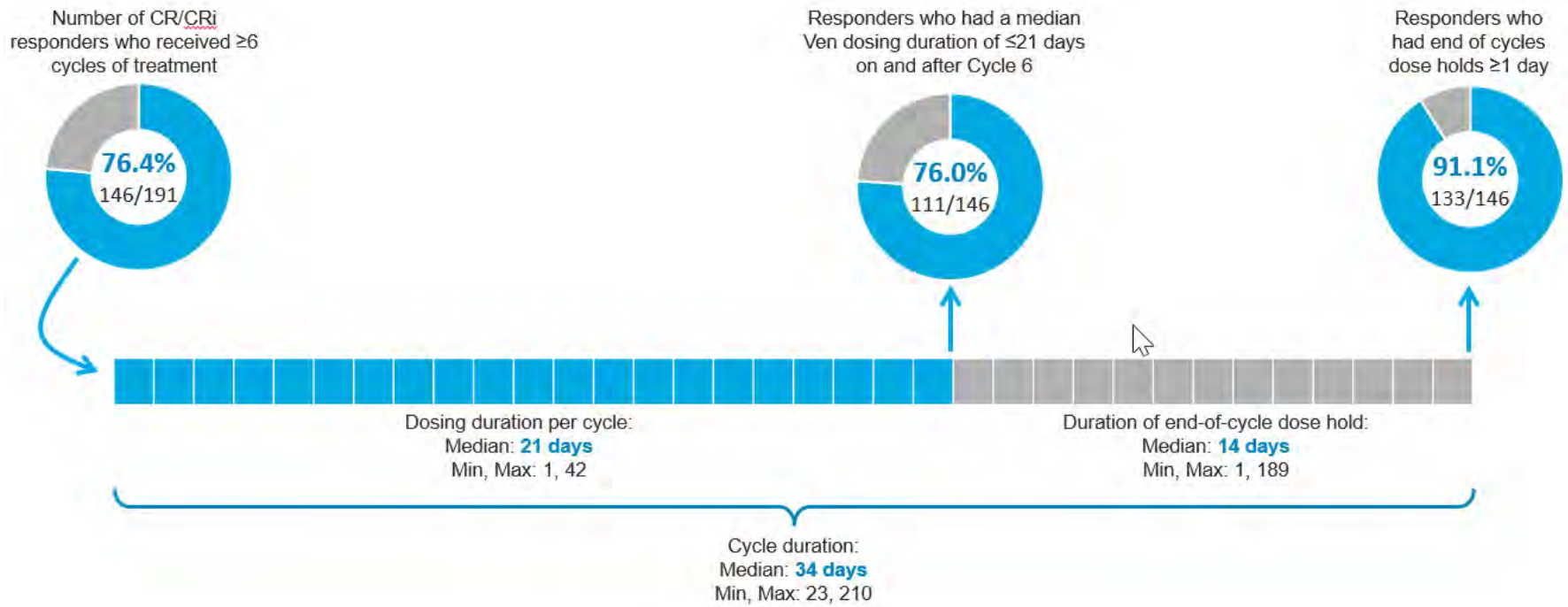


	DOR at 100% OS analysis (months) median (95% CI)
Ven+Aza (n=111)	22.1 (16.7 – 27.0)
Pbo+Aza (n=26)	13.4 (10.3 – 15.1)

[1]DiNardo et. al. NEJM, 2020; The distributions were estimated for each treatment arm using Kaplan-Meier methodology; 75% OS interim analysis data cut-off: 04 Jan 2020; 100% final overall survival data cut-off: 01 Dec 2021; Abbreviations: Aza, azacitidine; CR, complete remission; DOR, duration of response; NE, non-evaluable; OS, overall survival; Pbo, placebo; Ven, venetoclax

Treatment duration and Ven dosing schedule among CR+CRi responders who received ≥ 6 cycles of treatment

	Ven+Aza (N = 282*)
No. of patients who achieved CR+CRi as best response, n (%)	**191 (67.7)**
Duration of treatment (in cycles) among responders (CR+CRi) Median (range)	**13.0 (1 - 46)**
Responders who had ≥ 6 cycles of treatment (n/N, %)	**146/191 (76.4)**



*Excludes 1 patient who was randomized from an earlier protocol by stratification factors of age and region, not cytogenetic risk; Data cut-off: 01 Dec 2021;
Abbreviations: Aza, azacitidine; CR, complete remission; CRi, CR with incomplete count recovery; Ven, venetoclax

The VIALE-A study demonstrates favorable benefit risk of Ven+Aza in newly diagnosed AML patients who are ineligible to receive intensive chemotherapy

The 100% OS analysis shows that the OS benefit from Ven+Aza continues to be observed

No new safety signals are found for Ven+Aza or Aza monotherapy from the previous analysis

Duration of CR, CR+CRi, and OS in some subgroups are longer at the 100% OS analysis than at the 75% OS analysis

AbbVie and the authors thank the participants, study sites, and investigators who participated in this clinical trial.

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

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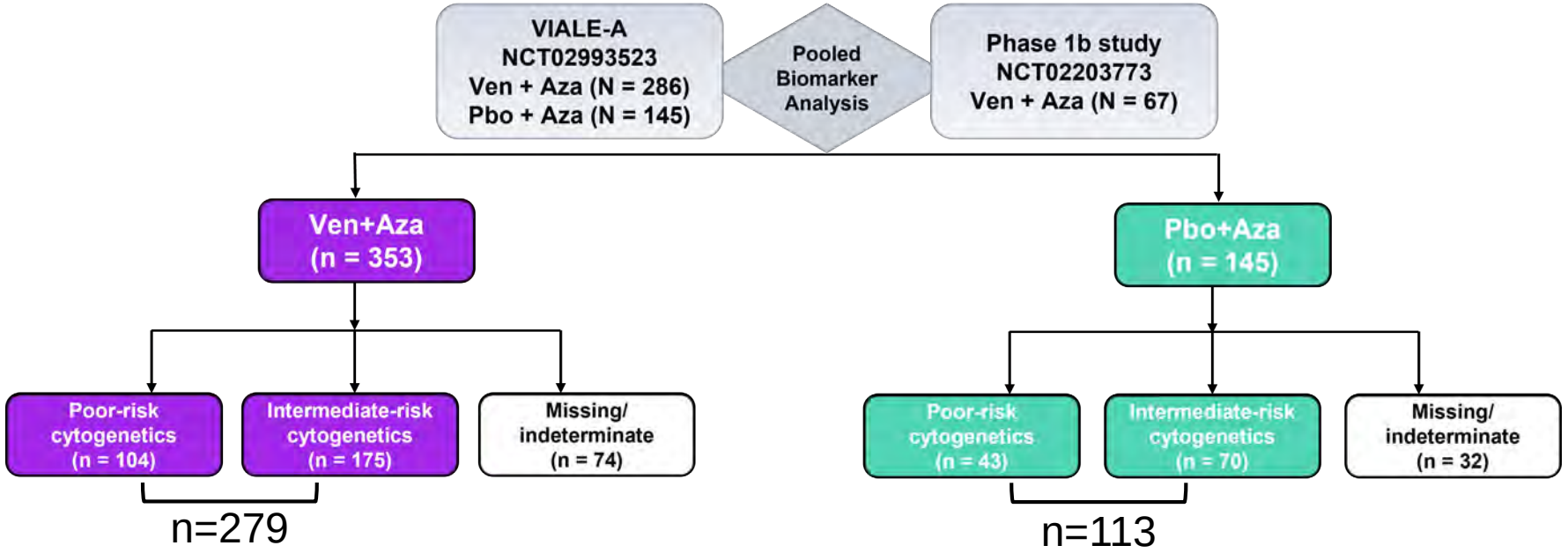
Pooled analysis of chemotherapy ineligible patients in a phase 3 and a phase 1b study

Design: Pooled analysis of treatment-naïve, chemotherapy-ineligible patients enrolled in the phase 3 VIALE-A trial and a prior phase 1b trial of Ven+Aza



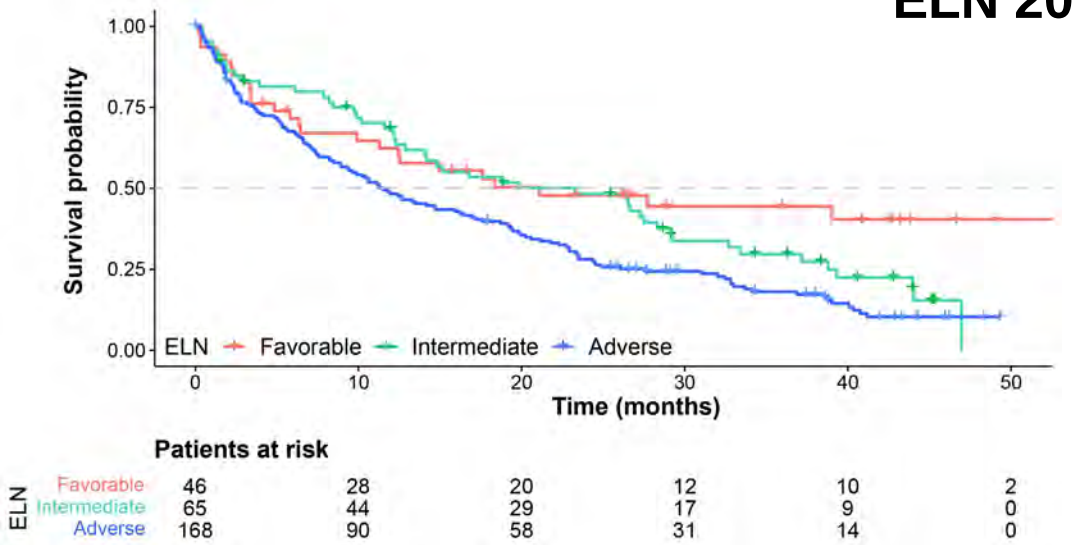
Analysis of genetic features:

- Cytogenetics analyzed locally and categorized per NCCN criteria
- Mutations analyzed from BM aspirate at baseline using the MyAML assay (central lab)
- Inclusion of central molecular data allowed the reclassification of patients according to ELN recommendations

Data cut-off: VIALE-A, 01 Dec 2021; Phase 1b, 19 Jul 2019; Median follow-up duration for patients included in the pooled analysis was 42.7 months (40.8-44.2);
Abbreviations: Aza, azacitidine; BM, bone marrow; ELN, European LeukemiaNet; Pbo, placebo; NCCN, National Comprehensive Cancer Network; Ven, venetoclax (400 mg)

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

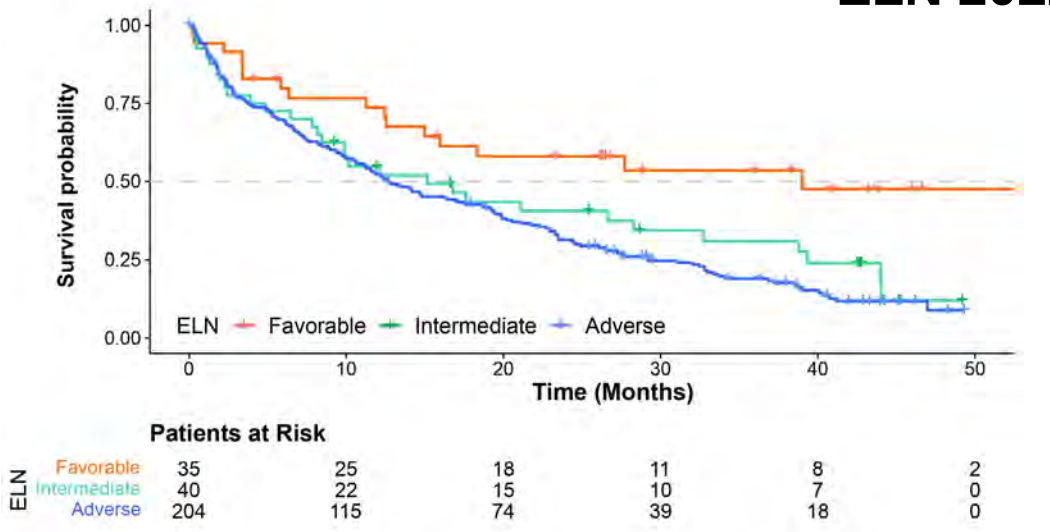
ELN 2017



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



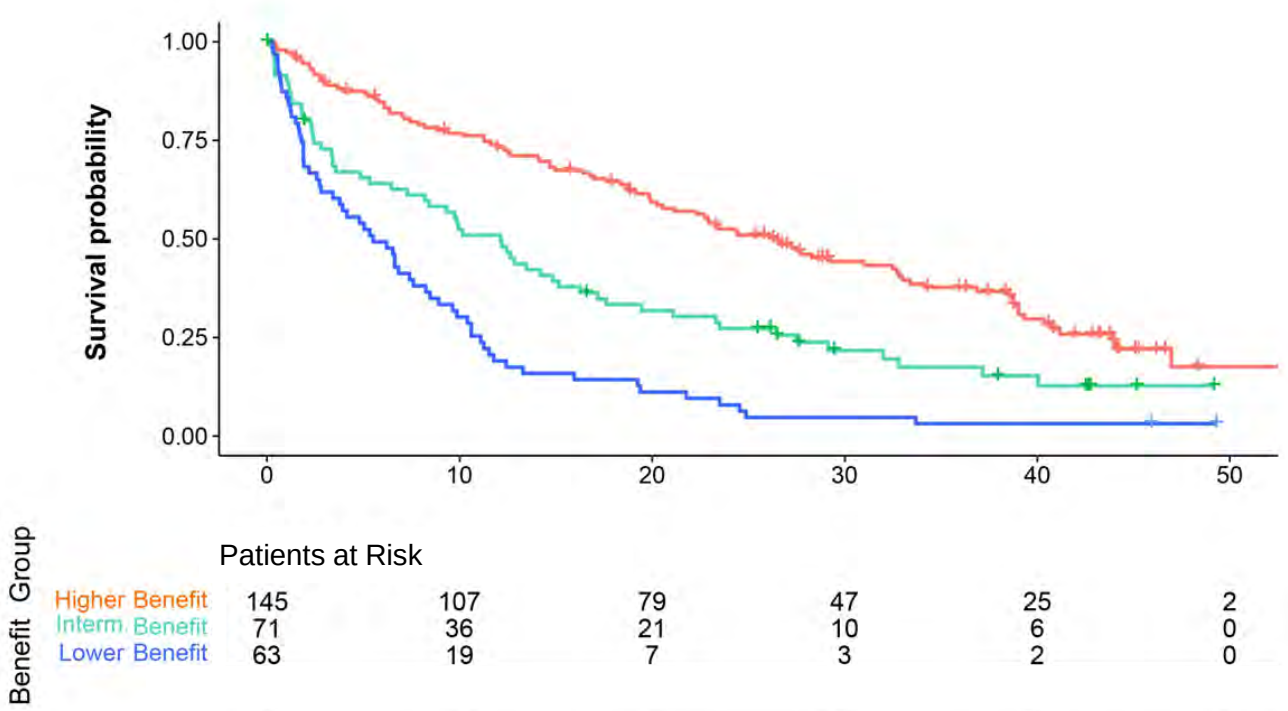
ELN 2022	n	Events	Median OS, mo (95% CI)
Favorable	35	16	39.0 (12.52 – NE)
Intermediate	40	30	15.15 (8.18 – 28.29)
Adverse	204	168	12.65 (10.41 – 17.15)

- 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

Abbreviations: Aza, azacitidine; CI, confidence interval; ELN, European LeukemiaNet; HR, hazard ratio; mo, months; Pbo, placebo; NCCN, National Comprehensive Cancer Network; 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

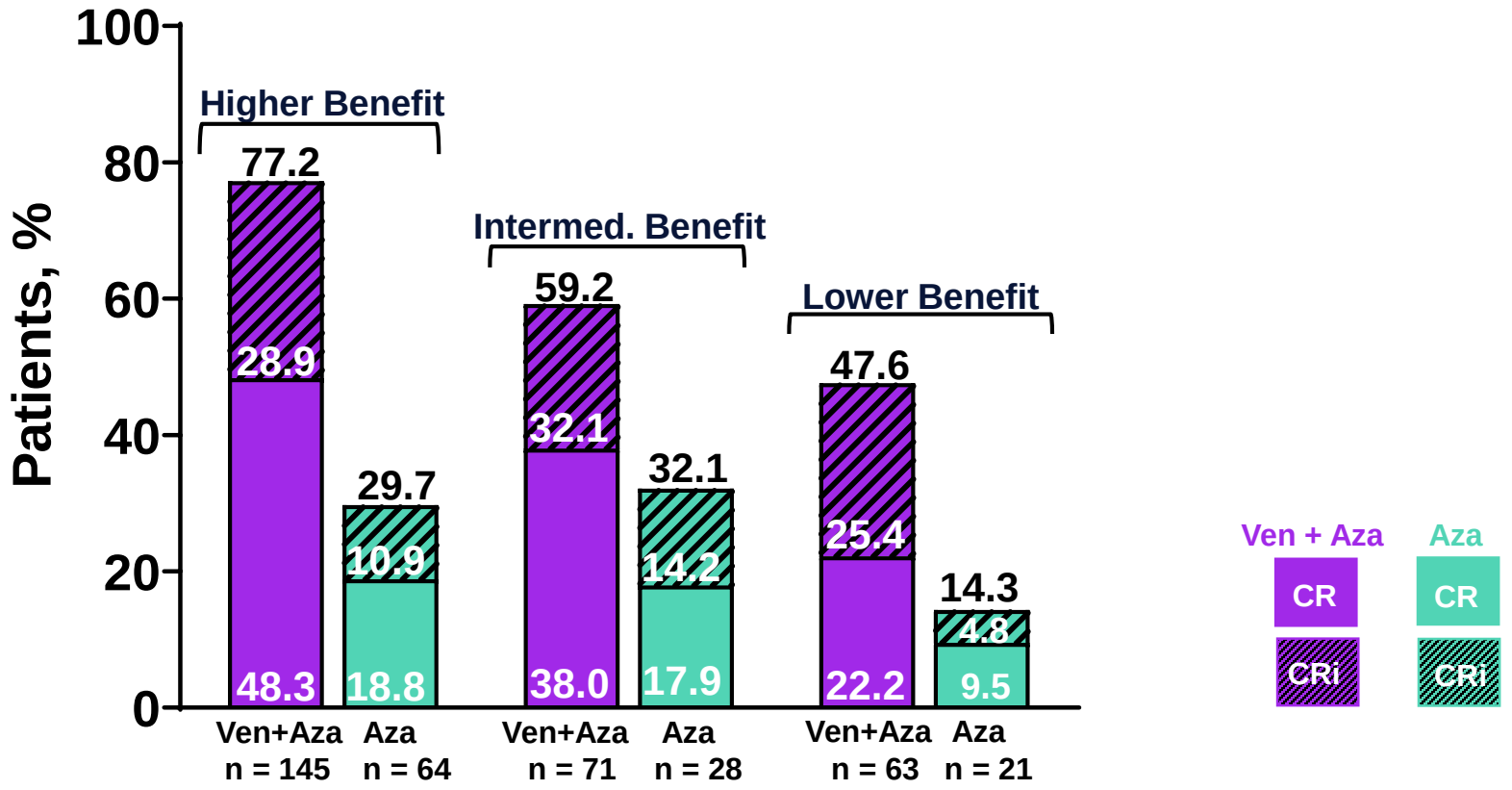


Ven + Aza (N = 279)	n	Events	Median OS, months (95% CI)
Higher Benefit	145	96	26.51 (20.24, 32.69)
Intermediate Benefit	71	57	12.12 (7.26 – 15.15)
Lower Benefit	63	61	5.52 (2.79 – 7.59)

- 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

Abbreviations: Aza, azacitidine; OS, overall survival; Ven, venetoclax

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



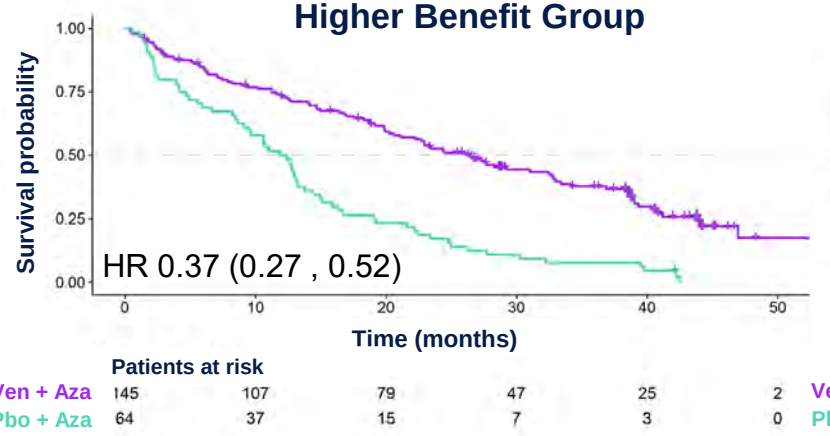
- CR and CR/CRi rates were highest in the higher benefit group
- Higher MRD negativity rates were achieved with Ven+Aza than with Aza monotherapy across all 3 groups

Abbreviations: Aza, azacitidine; CR, complete remission; CRi, CR with incomplete count recovery; Intermed., intermediate; MRD, minimal residual disease; Ven, venetoclax

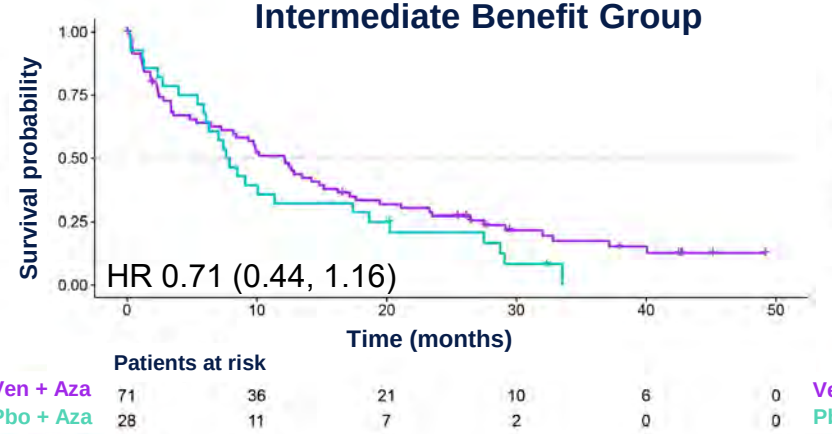
Median OS was higher with Ven+Aza than Aza monotherapy in patients with higher and intermediate benefit signatures

Ven + Aza **Pbo + Aza**

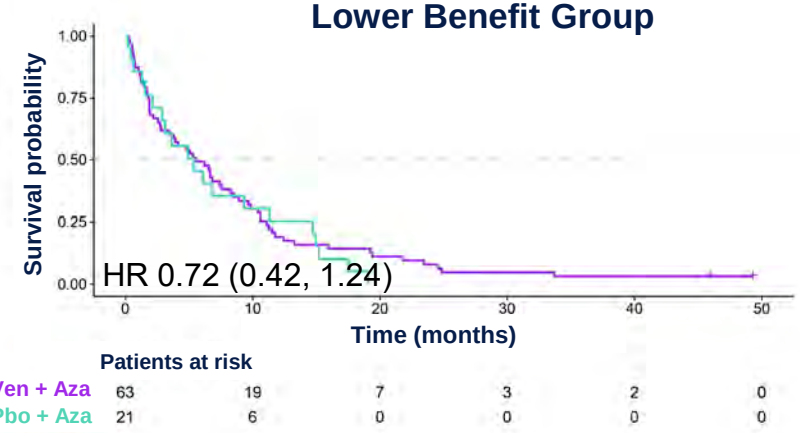
Higher Benefit Group



Intermediate Benefit Group



Lower Benefit Group



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

Higher Benefit Group	n	Events	Median OS, months (95% CI)
Ven + Aza	145	96	26.51 (20.24 , 32.69)
Pbo + Aza	64	63	12.12 (8.64 – 13.24)

mOS with Ven+Aza is double that for Aza alone

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

Intermed. Benefit Group	n	Events	Median OS, months (95% CI)
Ven + Aza	71	57	12.12 (7.26 – 15.15)
Pbo + Aza	28	26	7.75 (5.88 – 11.37)

~ 5 month longer mOS if treated with Ven+Aza vs Aza alone

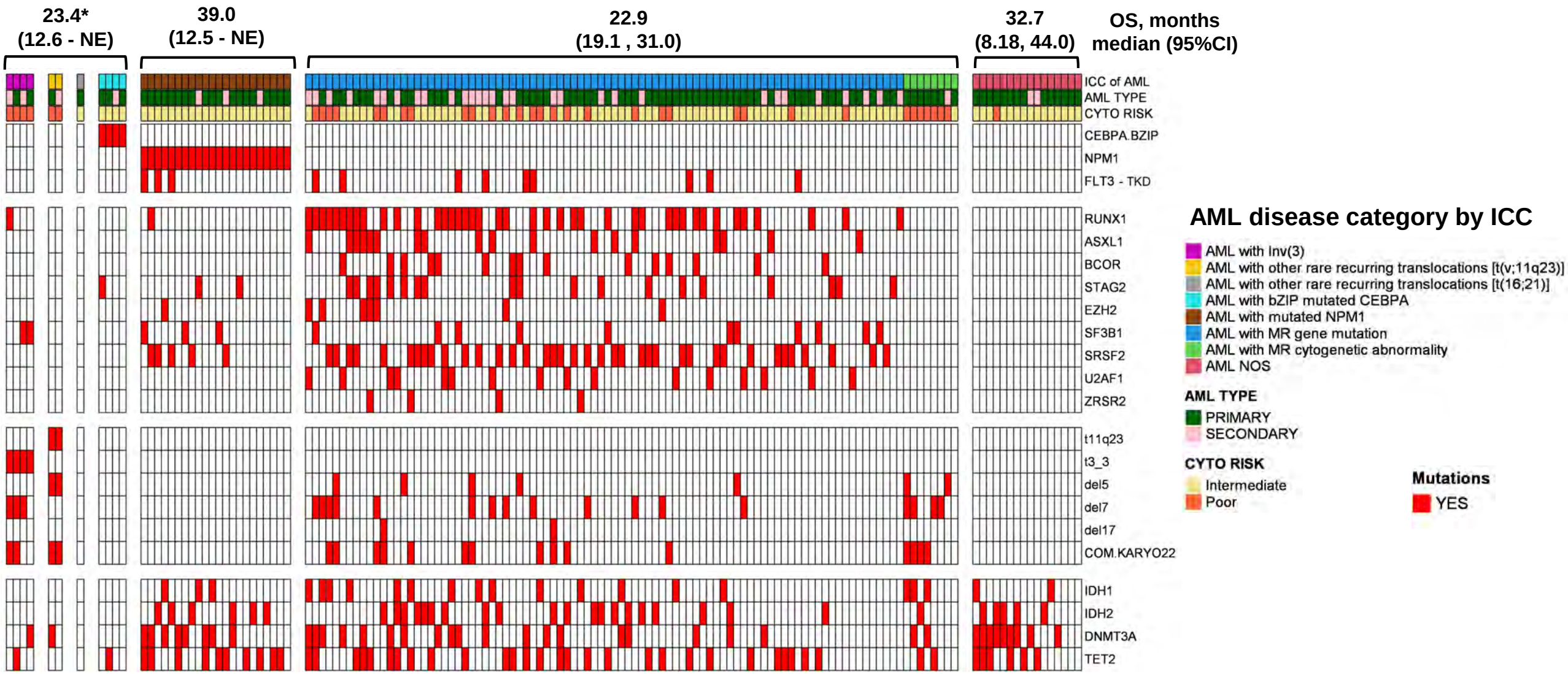
***TP53* mutated**

Lower Benefit Group	n	Events	Median OS, months (95% CI)
Ven + Aza	63	61	5.52 (2.79 – 7.59)
Pbo + Aza	21	20	5.36 (2.14 – 11.3)

Patients with *TP53* mutations have similar mOS with Ven+Aza and Aza alone

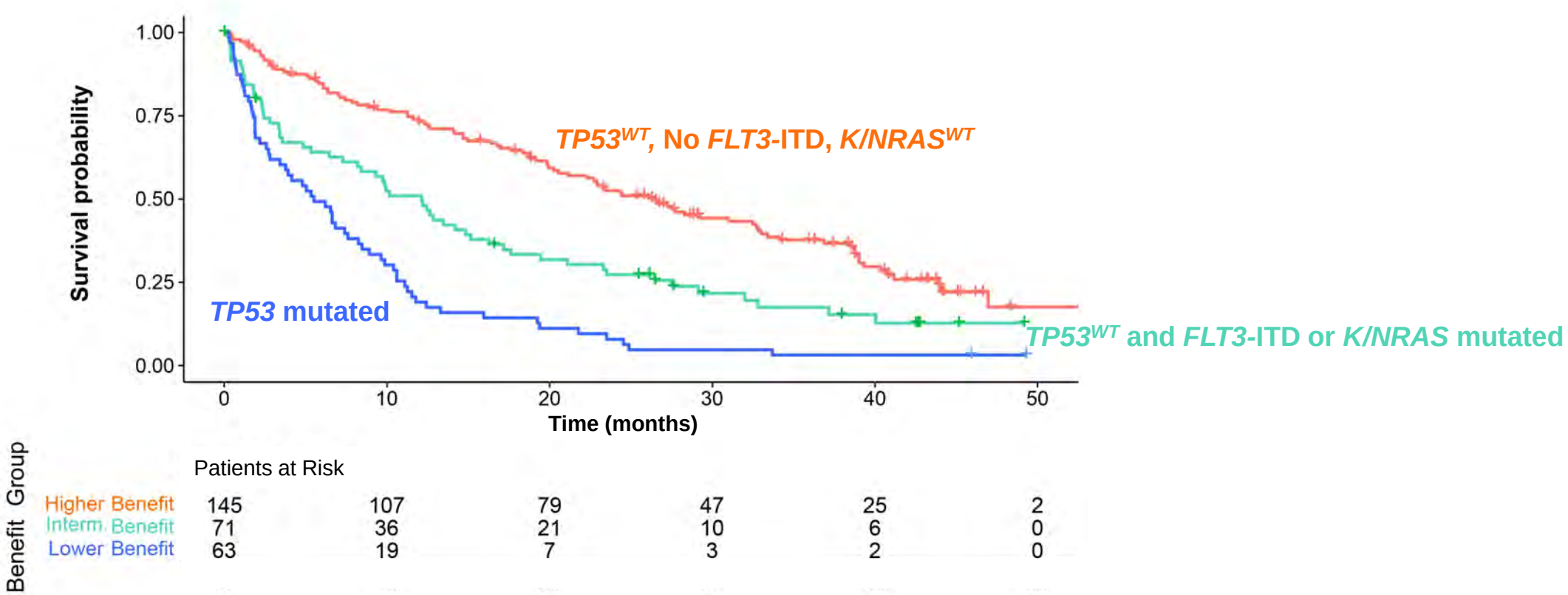
Abbreviations: Aza, azacitidine; HR, hazard ratio; Intermed., intermediate; mOS, median overall survival; Ven, venetoclax; WT, wild-type

The higher benefit group includes patients with diverse biological drivers of AML



*Combination of 4 groups with < 10 pts/group; Abbreviations: AML, acute myeloid leukemia; Aza, azacitidine; cyto, cytogenetic; ICC, International Consensus Classification; MR, myelodysplasia-related; NE, non-evaluable; NOS, not otherwise specified; OS, overall survival; Ven, venetoclax

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



Abbreviations: Aza, azacitidine; OS, overall survival; Ven, venetoclax; WT, wild-type

Conclusions

2017 and 2022 ELN genetic risk groups do not provide clinically meaningful stratification of outcomes for chemotherapy-ineligible treatment-naïve AML patients treated with Ven+Aza

Three prognostic risk signatures, derived based on the mutational status of 4 genes: *FLT3*-ITD, *KRAS*, *NRAS* and *TP53*, indicate higher benefit, intermediate benefit and lower benefit from Ven+Aza treatment

The predictive value of the 4-gene prognostic signature is demonstrated by improved outcome in patients on Ven+Aza compared to Aza monotherapy in the higher benefit group

These findings require validation in a larger independent dataset

AbbVie and the authors thank the participants, study sites, and investigators who participated in this clinical trial.

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Penn Medicine

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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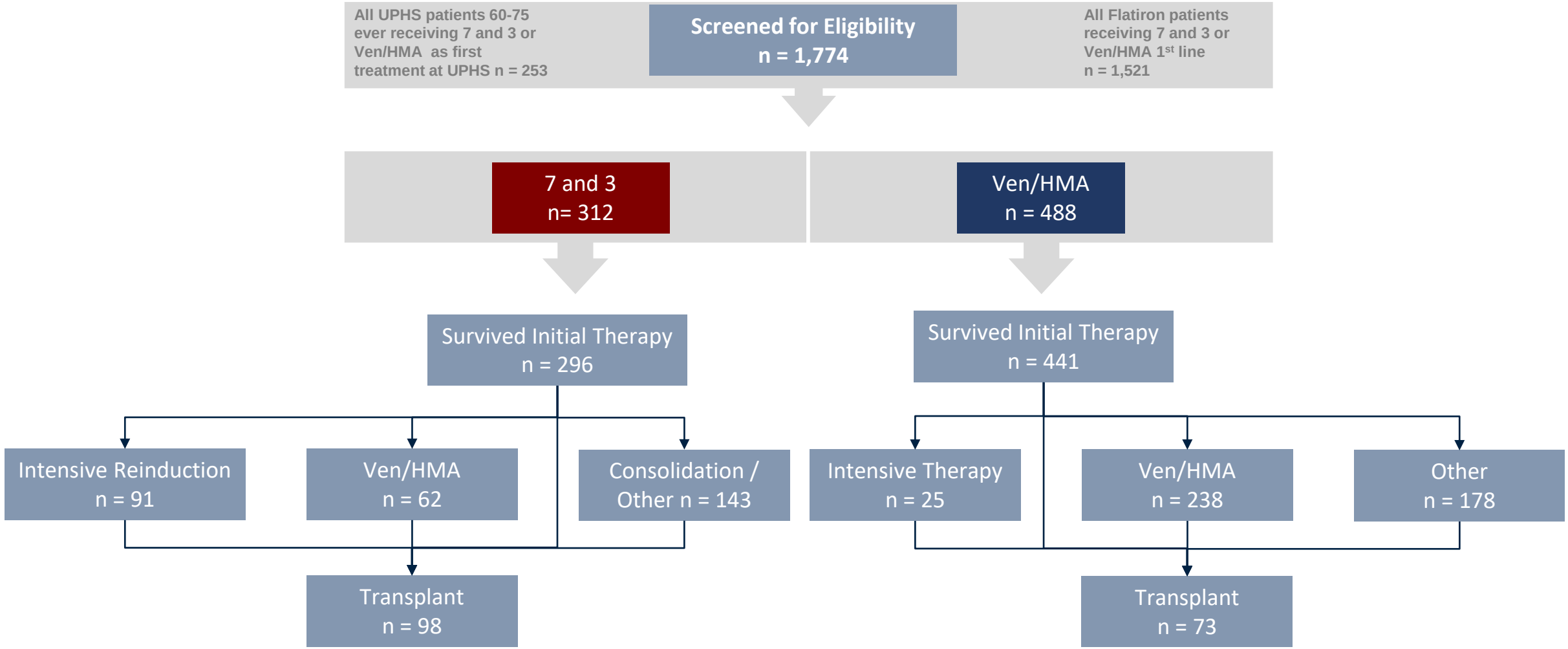


164 Died
126 Alive at end of observation period
22 Lost to follow-up

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,

Patient Characteristics Show Major Imbalances at Baseline

	Ven/HMA N=488	7&3 N=312	p-value
Age	71 (60-75)	67 (60-75)	<0.001
Gender			0.56
Female	204 (42%)	137 (44%)	
Male	284 (58%)	175 (56%)	
Practice Type			0.004
Academic	175 (36%)	144 (54%)	
Community	313 (64%)	168 (46%)	
Type			<0.001
De Novo	104 (21%)	160 (51%)	
Secondary AML[1]	**312 (64%)**	**139 (46%)**	
Prior MDS	153 (31%)	42 (13%)	
Prior MPN[2]	58 (12%)	25 (8%)	
Therapy-Related	72 (15%)	13 (4%)	
ELN 2022 Risk Group			<0.001
Favorable	40 (7%)	48 (15%)	
Intermediate	140 (42%)	158 (59%)	
Adverse	**255 (50%)**	**91 (26%)**	
Missing	53 (11%)	15 (5%)	

	Ven/HMA N=488	7&3 N=312	p-value
HCT-Comorbidity Index			0.008
0	198 (41%)	138 (44%)	
1-2	74 (15%)	70 (22%)	
>=3	98 (20%)	45 (14%)	
Missing	118 (24%)	59 (19%)	
ECOG Performance Status			0.17
0-1	287 (59%)	178 (57%)	
2	94 (19%)	39 (13%)	
Missing	107 (22%)	95 (30%)	
Selected Mutations or Cytogenetic Changes			
CBF	11 (2%)	11 (4%)	0.55
NPM1	33 (7%)	79 (25%)	<0.001
FLT3	49 (10%)	80 (26%)	<0.001
TP53	98 (20%)	12 (4%)	<0.001

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

*Data are presented as median (range) for continuous measures, and n (%) for categorical measures. *Includes AML-MR (myelodysplasia related) by WHO 2022 criteria and ICC MR mutations or cytogenetic changes regardless of prior diagnosis of MDS/MPN as listed; 2. MPN includes MDS/MPN CMML as well as PV, ET, MF, CML*

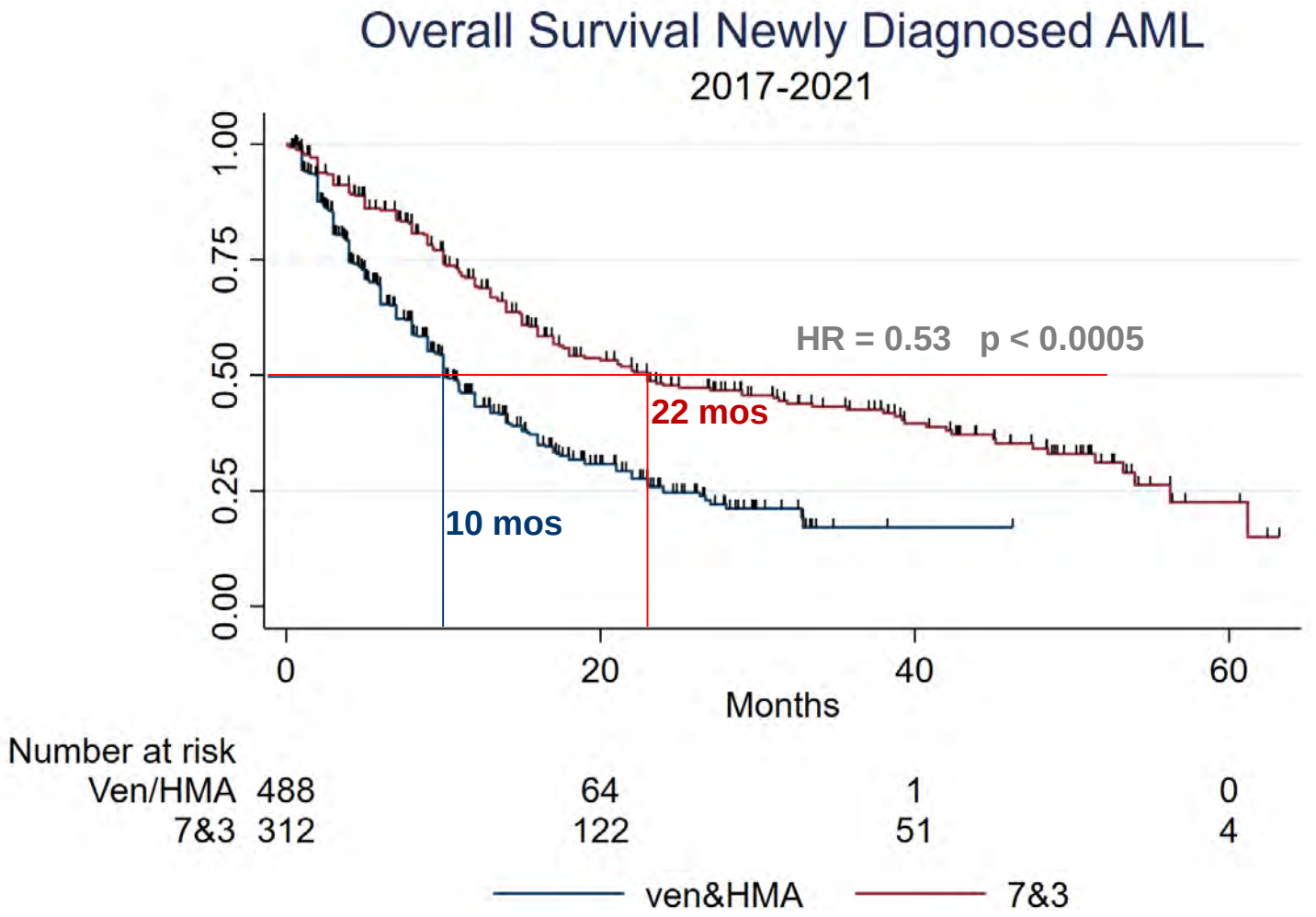
Early Mortality Higher for Ven/HMA but Length of Stay and Infections Higher for 7 and 3.

	Ven/HMA N = 488	7&3 n = 312	p-value
30 Day Mortality (95% CI)	5% (3-7%)	3% (1-5%)	0.20
60 Day Mortality (95% CI)	15% (11-17%)	6% (4-9%)	<0.001
Febrile Neutropenia % (95% CI)[1]	47% (37-57%)	93% (87-98%)	<0.001
Culture Positive Infection % (95% CI)[1]	21% (12-28%)	44% (35-56%)	0.004
Median Days Inpatient Induction[2] (Range)[1,2]	15.5 (0-90)	31.5 (6-82)	<0.001

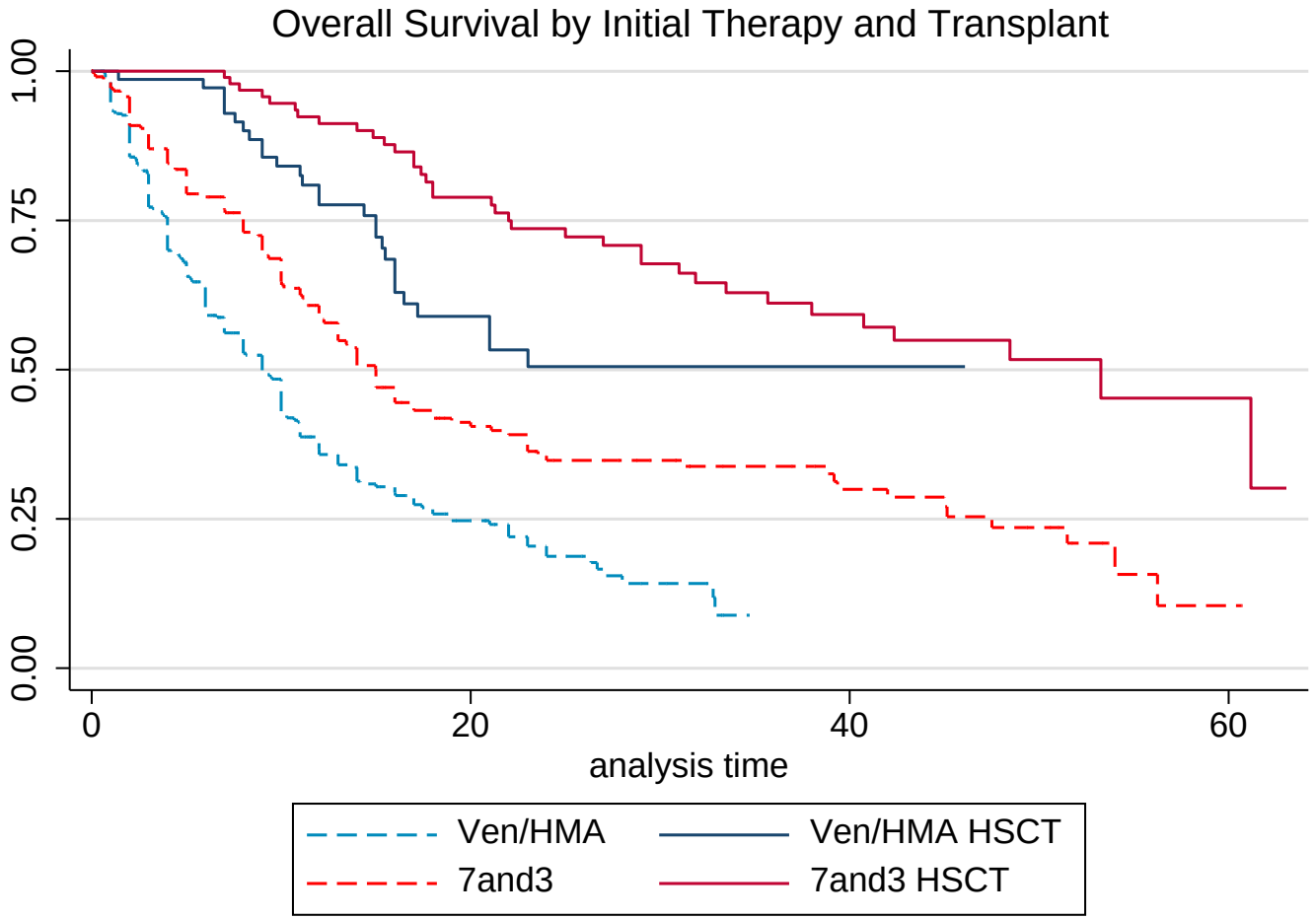
Grade 3-4 Adverse Events by Common Terminology Criteria for Induction Adverse Events[1,3]			
UPHS Only (n = 179)	**Ven/HMA n = 94**	**7&3 n = 85**	**p-value**
Hypokalemia	6%	25%	<0.001
Alanine aminotransferase increased	7%	6%	0.77
Aspartate aminotransferase increased	8%	8%	1.00
Blood Bilirubin increased	6%	2%	0.44
Anemia	89%	99%	0.018
Median Transfusions in Induction	12	18	0.006
Platelet Count Decreased	86%	99%	<0.001
Median Transfusions in Induction	6	20	<0.001

1. UPHS Only, confirmed with manual chart review; culture positive infections includes urine cultures, blood cultures, sputum cultures or c. diff positivity between treatment initiation and next cycle of consolidation therapy. 2 Includes readmission before second cycle of therapy. P-values by Fisher's exact test. 3. CTCAE version 4

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



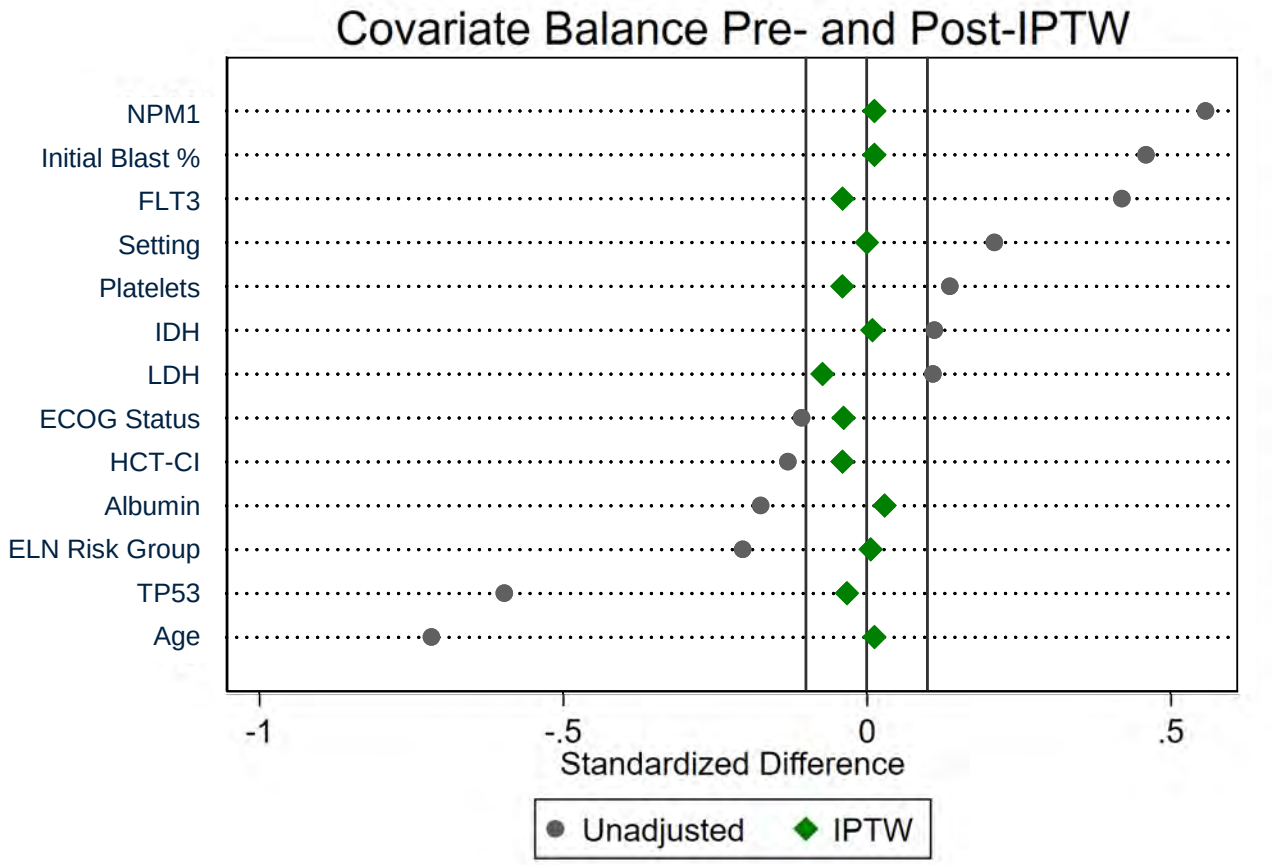
Transplant is Critical for Survival Regardless of Initial Treatment

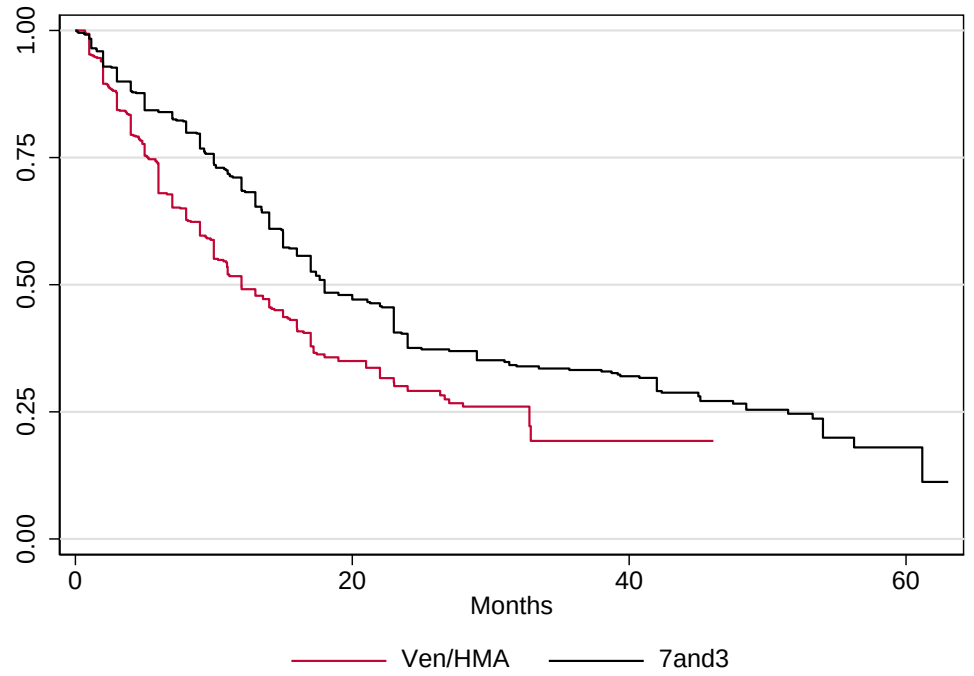


	Ven/HMA	7&3
Number (%)	72 (15%)	96 (31%)
Median Time to Transplant (range)	169 (78-415)	168 (75-983)
Median OS w/ HSCT	NR	53.3 mos
Median OS w/o HSCT	9 mos	15 mos

- HR of HSCT with transplant as a time-varying covariate is 0.44 (95% CI 0.33 to 0.58, p-value <0.0005)

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





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

Limitations

- Selection bias & Confounding by Indication
  - Major baseline imbalance in secondary AML likely impacted by availability of CPX-351
  - Higher transplant rates and overall survival for patients selected to receive 7 and 3 compared to historical studies
- Unmeasured Confounding
  - Multiple imputation and inverse probability treatment weighting can only correct measured confounders
- Depth of Response Unclear
  - Molecular or flow-based MRD unavailable
  - Assessment bias would complicate EFS or RFS comparisons
- Cross-over May Confound Overall Survival Results
  - 20% of patients initially selected to receive 7 and 3 went on to receive ven/HMA

Conclusions

- Patients selected for intensive chemotherapy with “7&3” had superior overall survival compared to patients selected for venetoclax & HMA

- After adjusting for measured baseline covariates, “7&3” remains superior to ven/HMA
  - One can select a group of patients with equipoise between the two treatments

- Unmeasured confounding may drive this study’s outcome:
  - These two groups had different baseline characteristics
  - Imbalance in ***measured*** baseline characteristics appears to account for half of survival difference
  - Uneven cross-over, differences in transplant rates likely reflect confounding by indication

- This question requires a prospective randomized trial
  - Prospective Trials (e.g., NCT04801797)
  - Additional Retrospective Replication

Fathi et al
ClinicalTrials.gov

Abstract #709

Venetoclax combined with Cladribine, Idarubicin, Cytarabine (CLIA) as Induction Therapy in Patients with Newly Diagnosed Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Patrick K Reville, Hagop M. Kantarjian, Gautam Borthakur, Musa Yilmaz, Naval Daver, Nicholas Short, Courtney DiNardo, Steven Kornblau, Naveen Pemmaraju, Nitin Jain, Yesid Alvarado, Prithviraj Bose, Elias Jabbour, Kelly Chien, Hussein Abbas, Lucia Masarova, Sa A Wang, Rebecca S. S. Tidwell, Michael Andreeff, Guillermo Garcia-Manero, Marina Konopleva, Farhad Ravandi, Tapan M. Kadia

Department of Leukemia at MD Anderson Cancer Center

Patient Selection

- Previously untreated AML or high-risk MDS (≥ 10% blasts or IPSS ≥ 2).
  - Hydroxyurea, hematopoietic growth factors, ATRA, or a total dose of cytarabine up to 2g (for emergency use for stabilization) is allowed.
- Age ≤ 65 years.
- ECOG performance status of ≤ 2.
- No prior therapy with venetoclax
- Adequate organ function (bilirubin < 2mg/dL, AST and/or ALT < 3 x ULN, creatinine < 1.5 x ULN, LVEF ≥ 45%)
- Patients with APL and known CBF were excluded

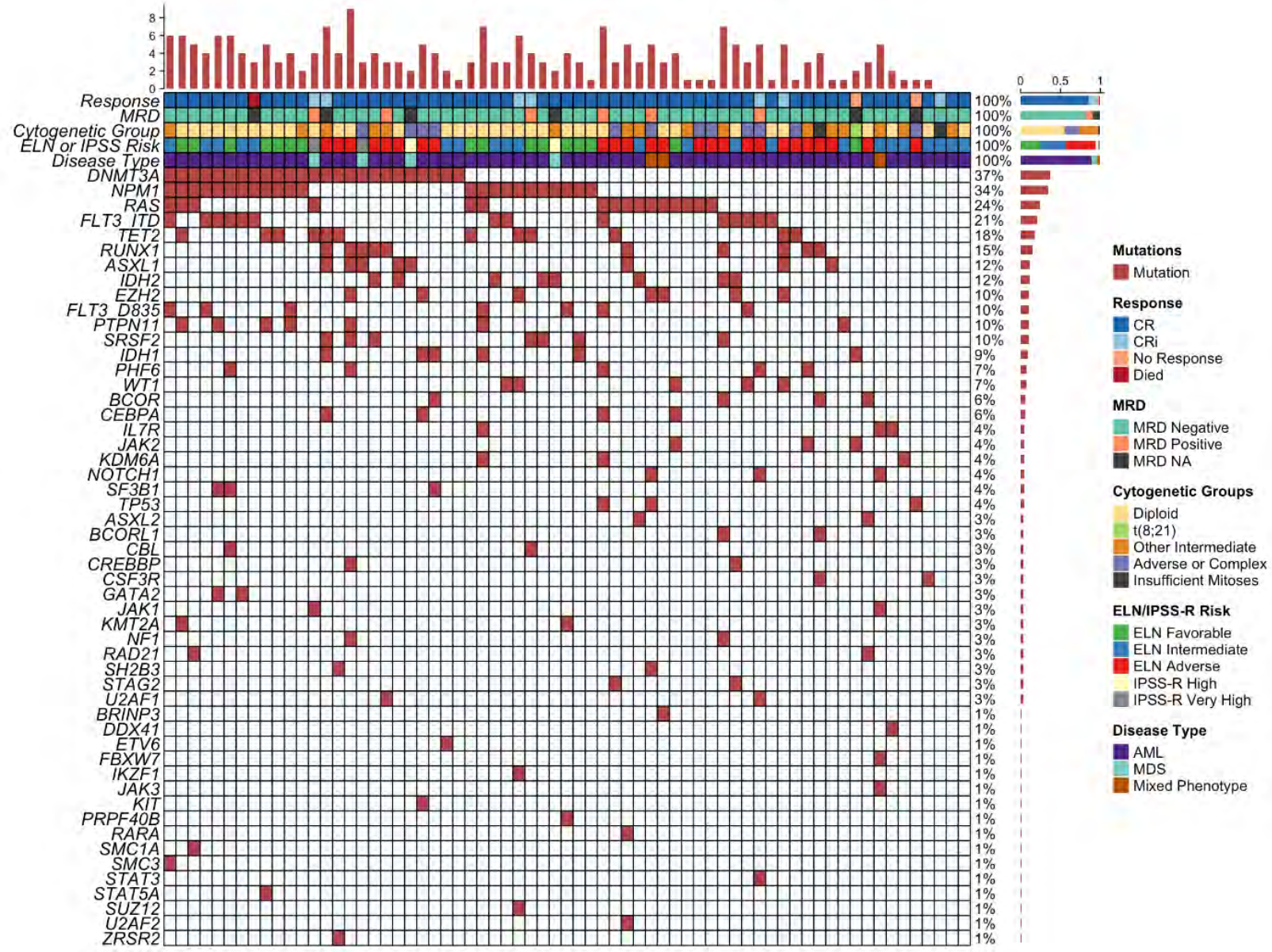
Baseline Characteristics

N = 67	n / N (%); Median [Range]
Age	**48** [18 – 64]
Diagnosis	
AML	60 / 67 (90)
MDS	4 / 67 (6.0)
MPAL	3 / 67 (4.5)
Sex	
Female	31 / 67 (46)
Male	36 / 67 (54)
Therapy Related AML	5 / 63 (8)
Secondary AML	6 / 63 (10)
Treated Secondary AML	3 / 63 (5)
Cytogenetic Group	
Diploid	36 / 66 (55)
Other Intermediate	16 / 66 (24)
Adverse/Complex	12 / 66 (18)
Insufficient Mitoses	2 / 66 (3)
ELN Risk	
Favorable	16 / 63 (25)
Intermediate	22 / 63 (35)
Adverse	25 / 63 (40)

Response

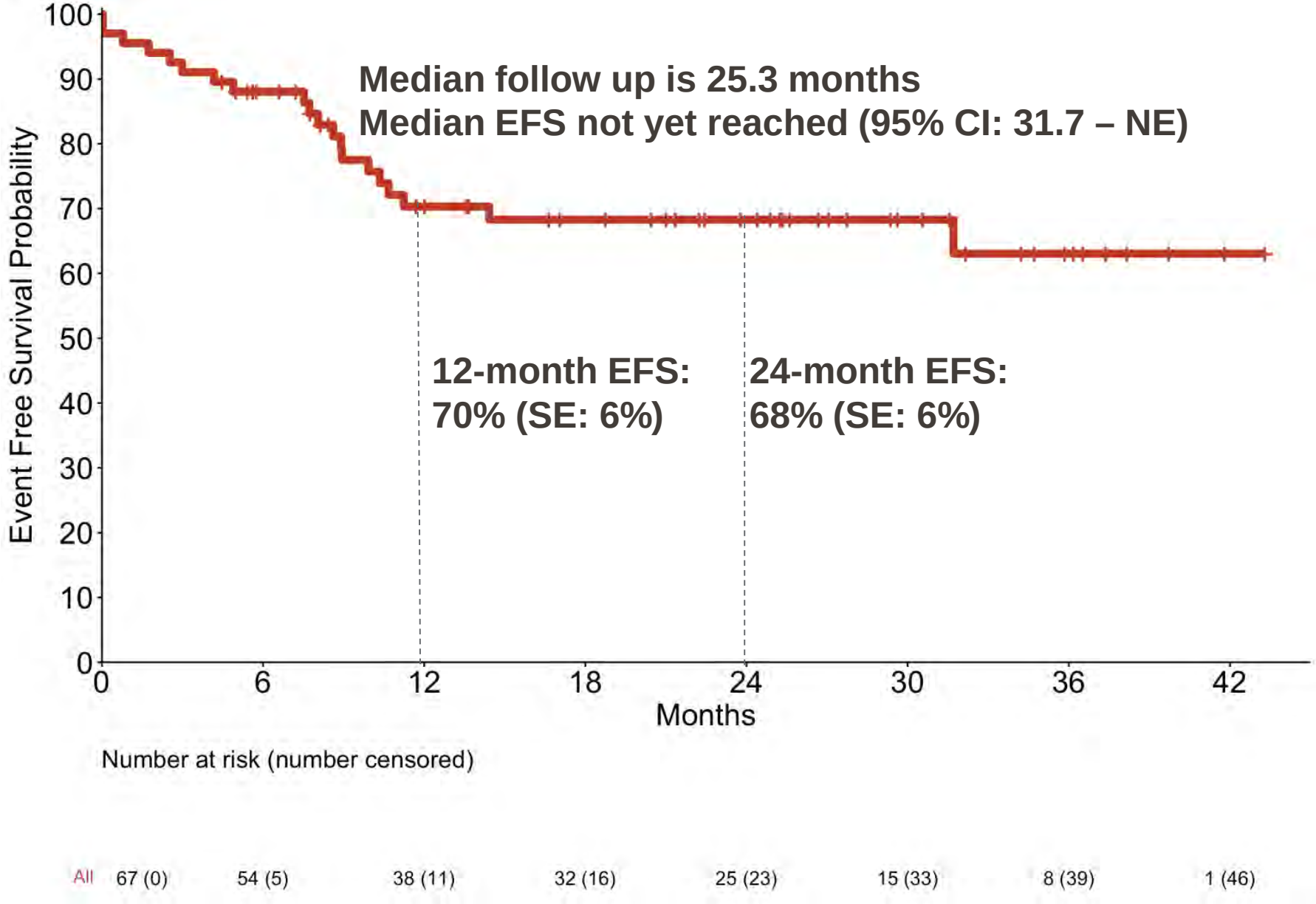
N = 67	n / N (%); Median [Range]
Composite CR Rate (CR+CRi)	**64 / 67 (96)**
Best Response	
CR	**57 / 67 (85)**
CRi	**7 / 67 (10)**
NR	2 / 67 (3)
Died	1 / 67 (1.5)
MRD Negative at First Response Assessment (by flow)	47 / 61 (**77**)
MRD Negative on Study (by flow)	55 / 61 (**90**)
Positive	6 / 61 (10)
Total Number of Course Given, Median (IQR)	2.0 [2.0 – 3.0]
Responders that Received alloSCT	45 / 64 (**70**)
Mortality Rate at 4 Weeks	1 / 67 (1.5)
Mortality Rate at 8 Weeks	2 / 67 (3)

Genomic Landscape and Response

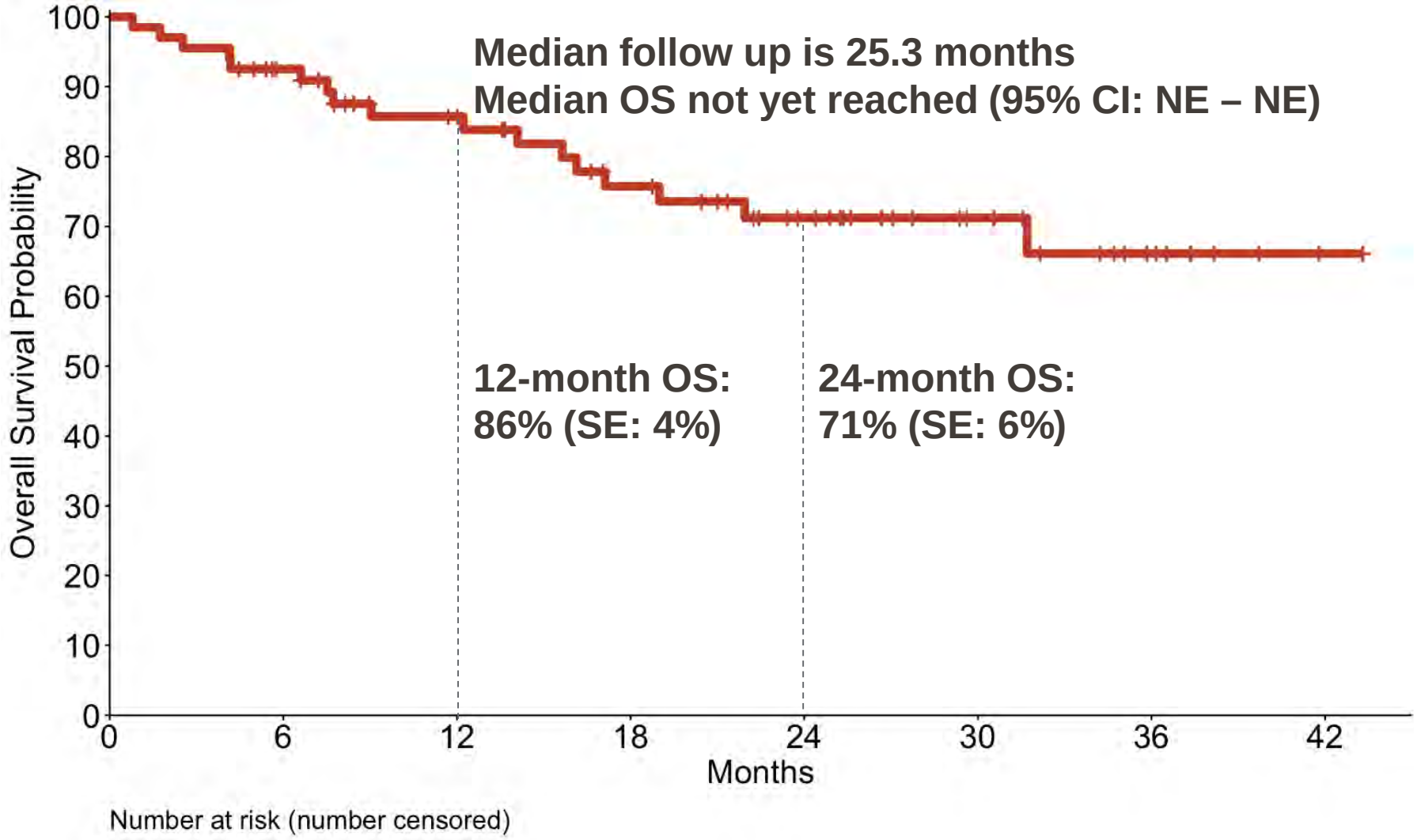


	Response
ELN Favorable (n=16)	94%
ELN Intermediate (n=22)	95%
ELN Adverse (n=25)	96%
Diploid Cytogenetics (n=36)	97%
Other Intermediate Cytogenetics (n=16)	100%
Complex/Adverse Cytogenetics (n=12)	92%
TP53 Mutated (n=3)	**67%**
NPM1 Mutated (n=23)	96%
FLT3 ITD Mutated (n=14)	93%

Event-Free Survival

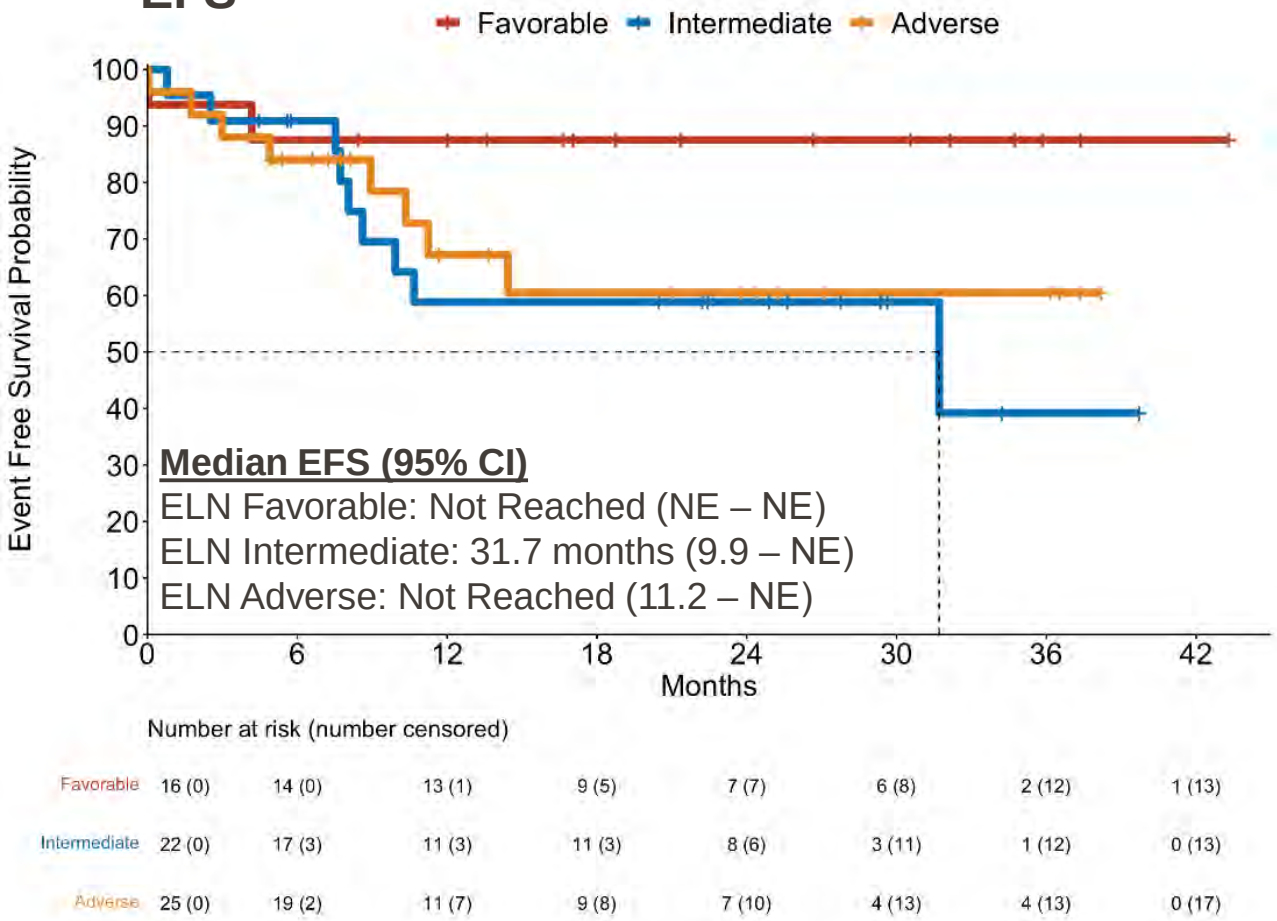


Overall Survival

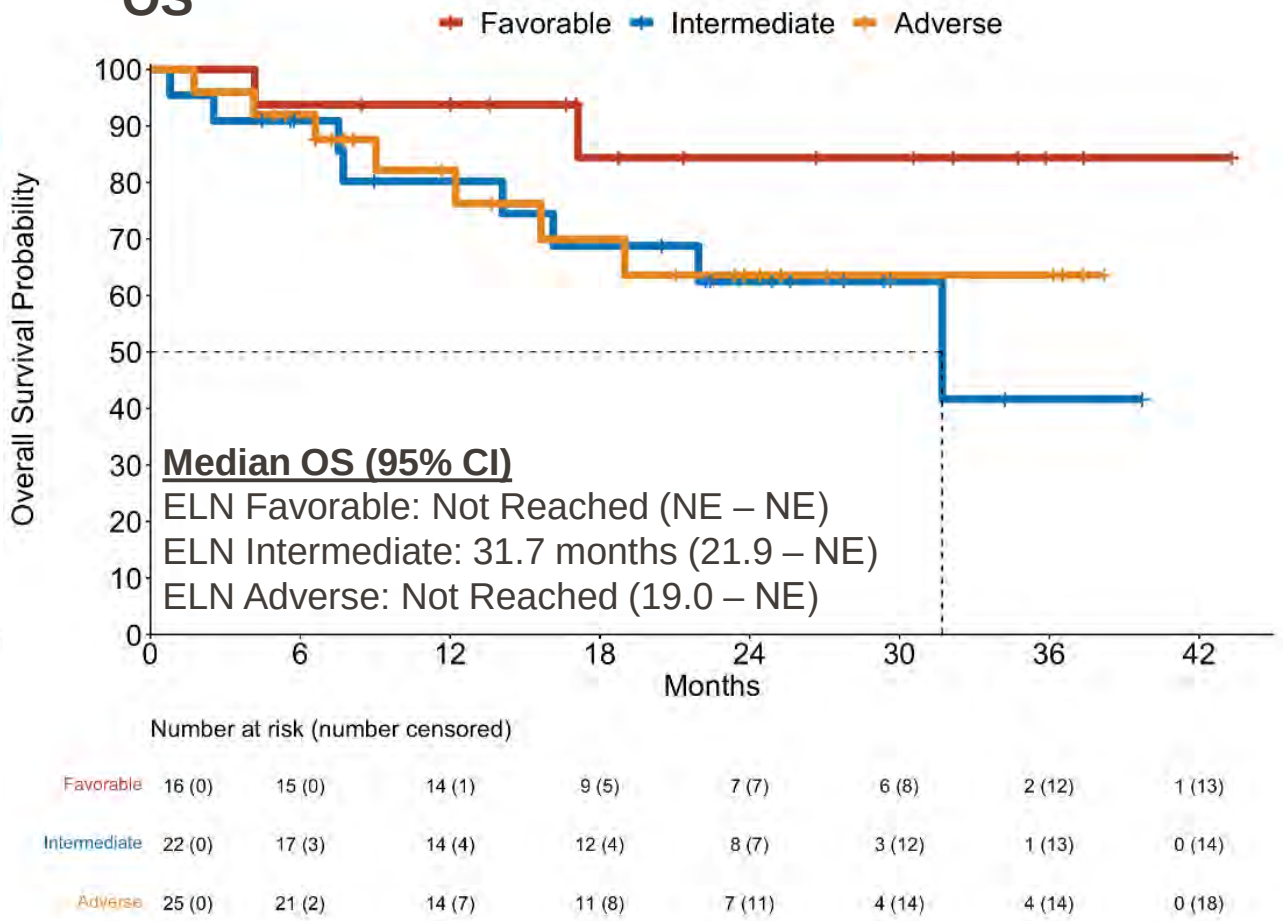


EFS and OS by ELN Risk

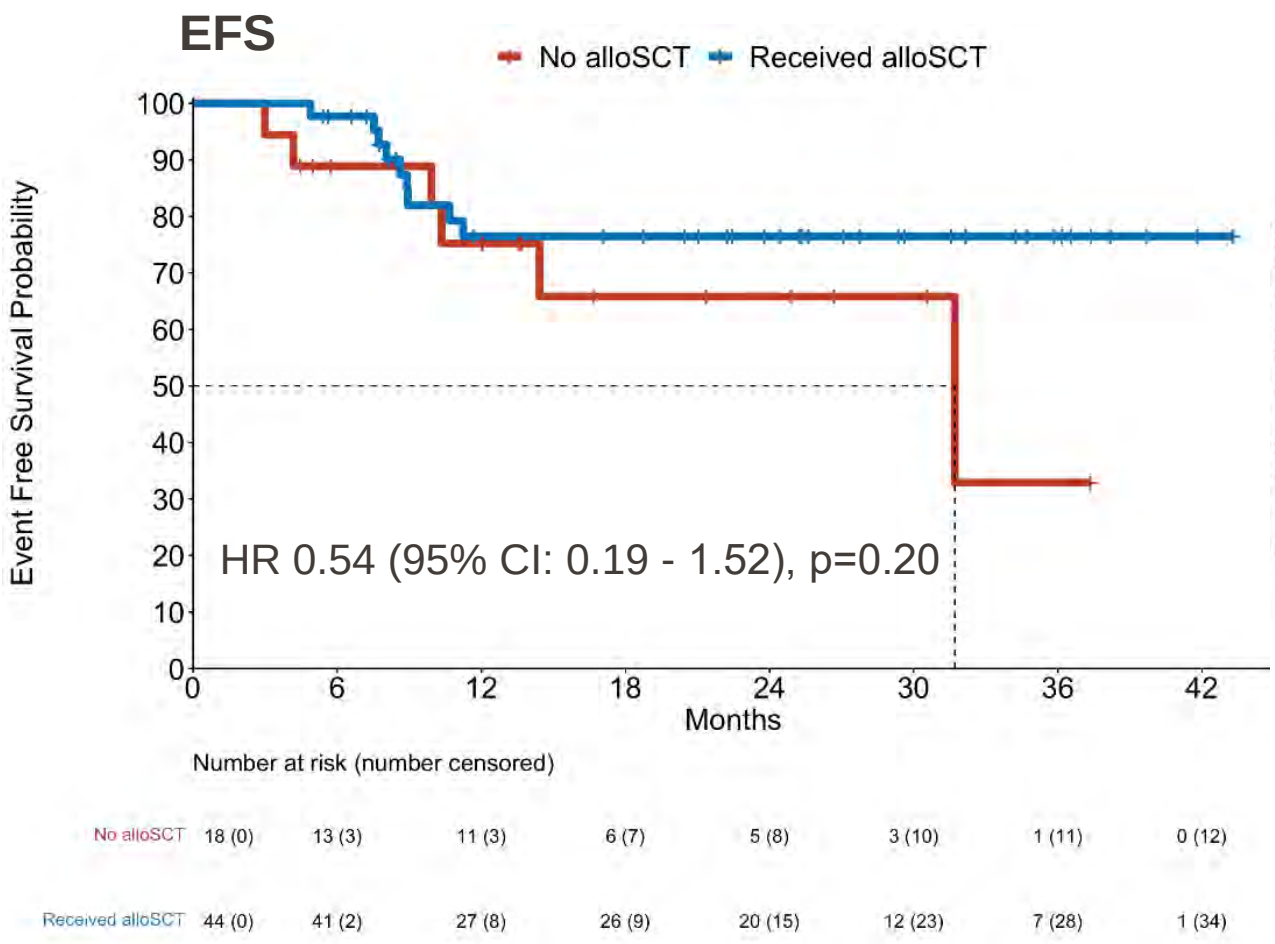
EFS

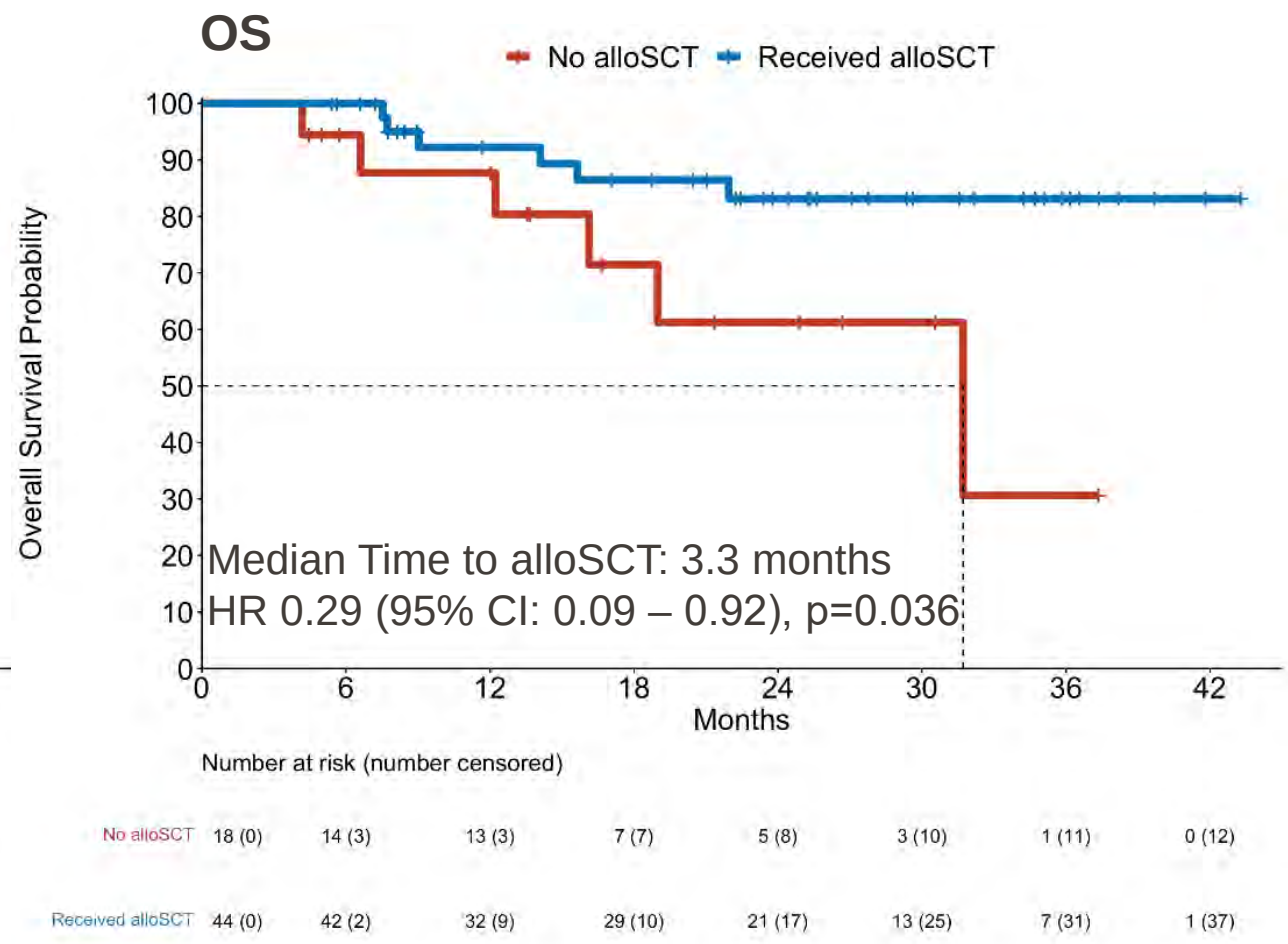


OS

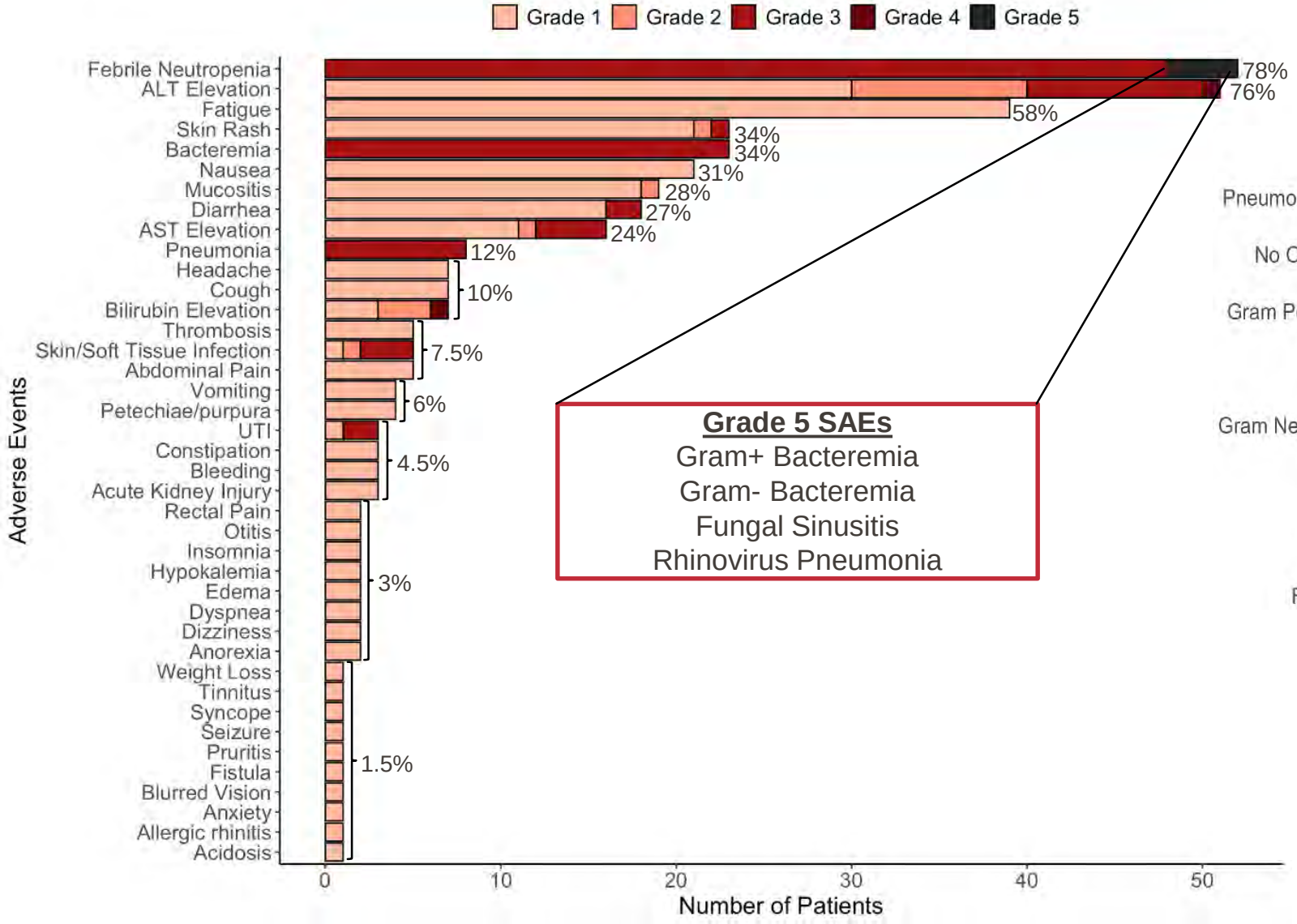


Landmark EFS and OS by Receipt of SCT

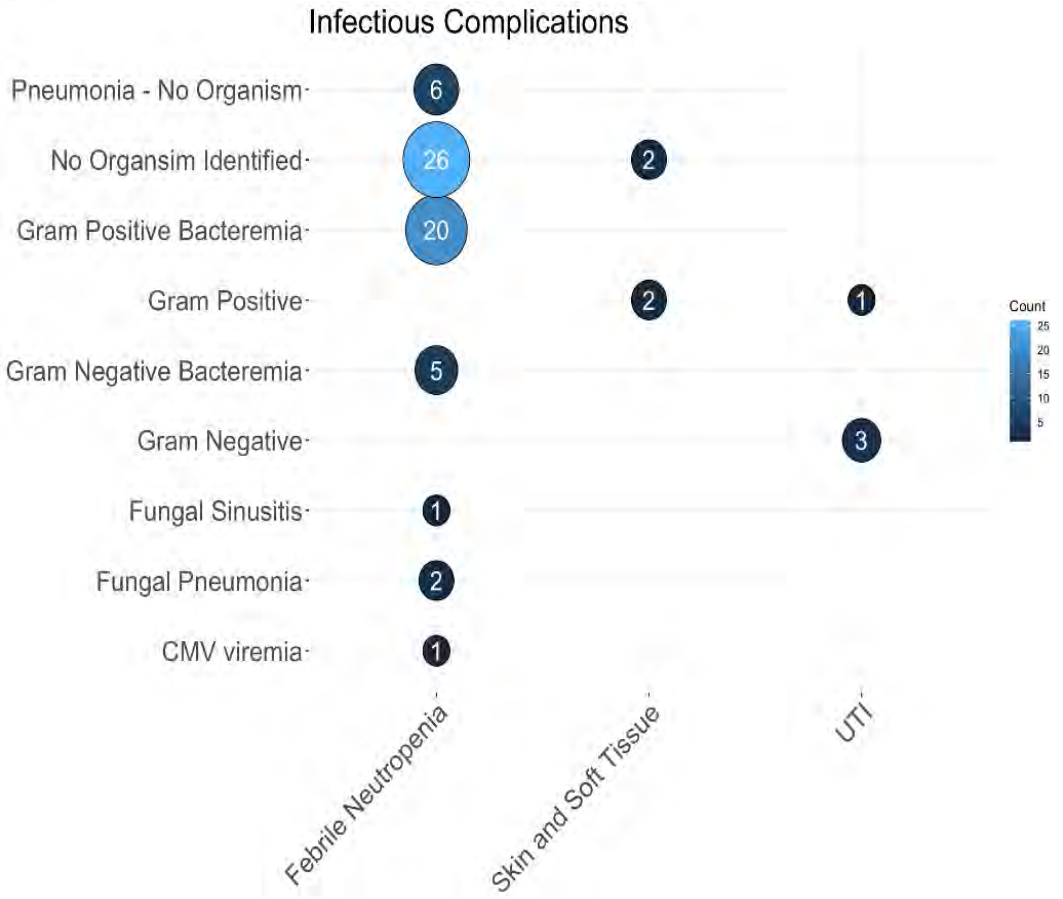




Adverse Events

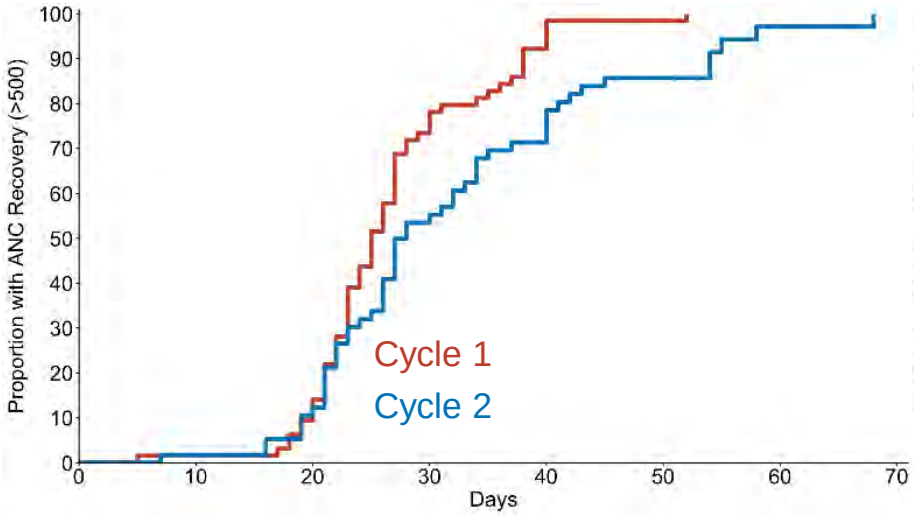


Grade 5 SAEs
Gram+ Bacteremia
Gram- Bacteremia
Fungal Sinusitis
Rhinovirus Pneumonia

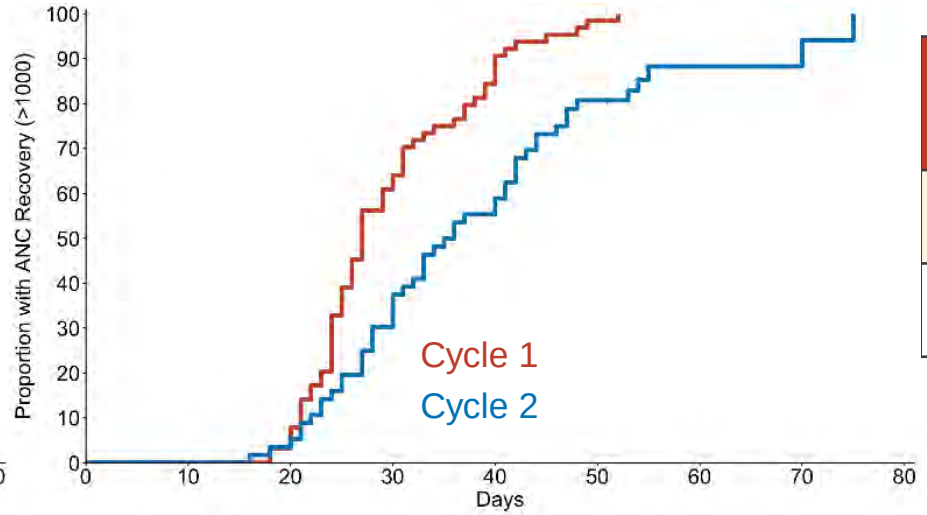


Blood Count Recovery During Cycle 1 and 2

ANC > 500

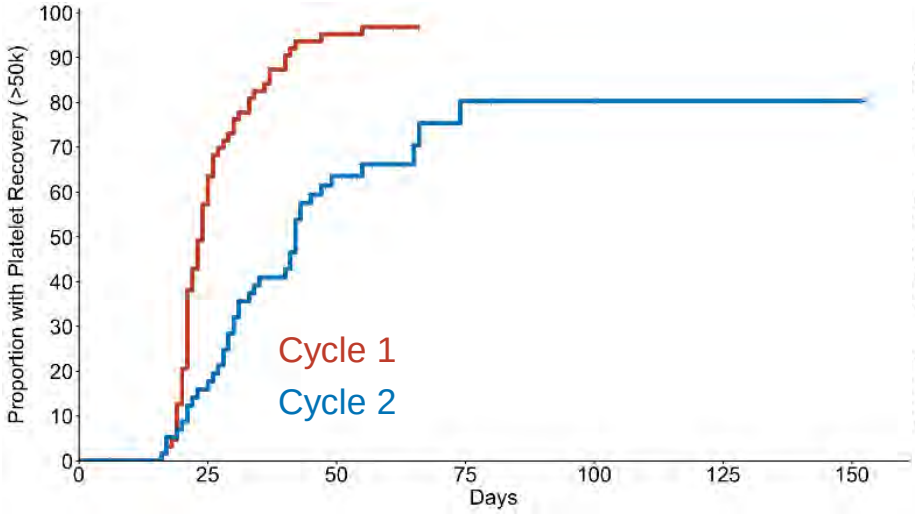


ANC > 1000

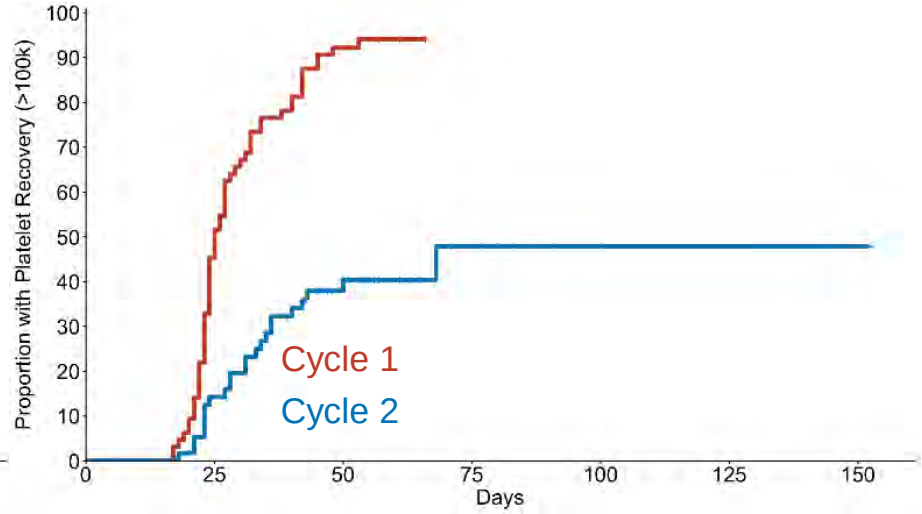


Median Time to Count Recovery	C1	C2
ANC > 500	25	28
ANC > 1000	27	36

Platelet > 50k



Platelet > 100k



Median Time to Count Recovery	C1	C2
Platelet > 50,000	24	42
Platelet > 100,000	25	NA

Quizartinib Prolonged Survival vs Placebo Plus Intensive Induction and Consolidation Therapy Followed by Single-Agent Continuation in Patients Ages 18-75 Years With Newly Diagnosed *FLT3*-ITD+ AML

Harry P. Erba,[1] Pau Montesinos,[2] Radovan Vrhovac,[3] Elzbieta Patkowska,[4] Hee-Je Kim,[5] Pavel Zak,[6] Po-Nan Wang,[7] Tsvetomir Mitov,[8] James Hanyok,[9] Li Liu,[9] Aziz Benzohra,[9] Arnaud Lesegretain,[9] Jorge Cortes,[10] Alexander Perl,[11] Mikkael Sekeres,[12] Hervé Dombret,[13] Sergio Amadori,[14] Jianxiang Wang,[15] Mark Levis,[16] Richard F. Schlenk[17]

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QuANTUM-FIRST STUDY

AML, acute myeloid leukemia; FLT3, fms related receptor tyrosine kinase 3; ITD+, internal tandem duplication positive.

QuANTUM-First Phase 3 Trial (NCT02668653): Quizartinib Plus Standard Induction Chemotherapy and Consolidation Followed by Single-Agent Quizartinib

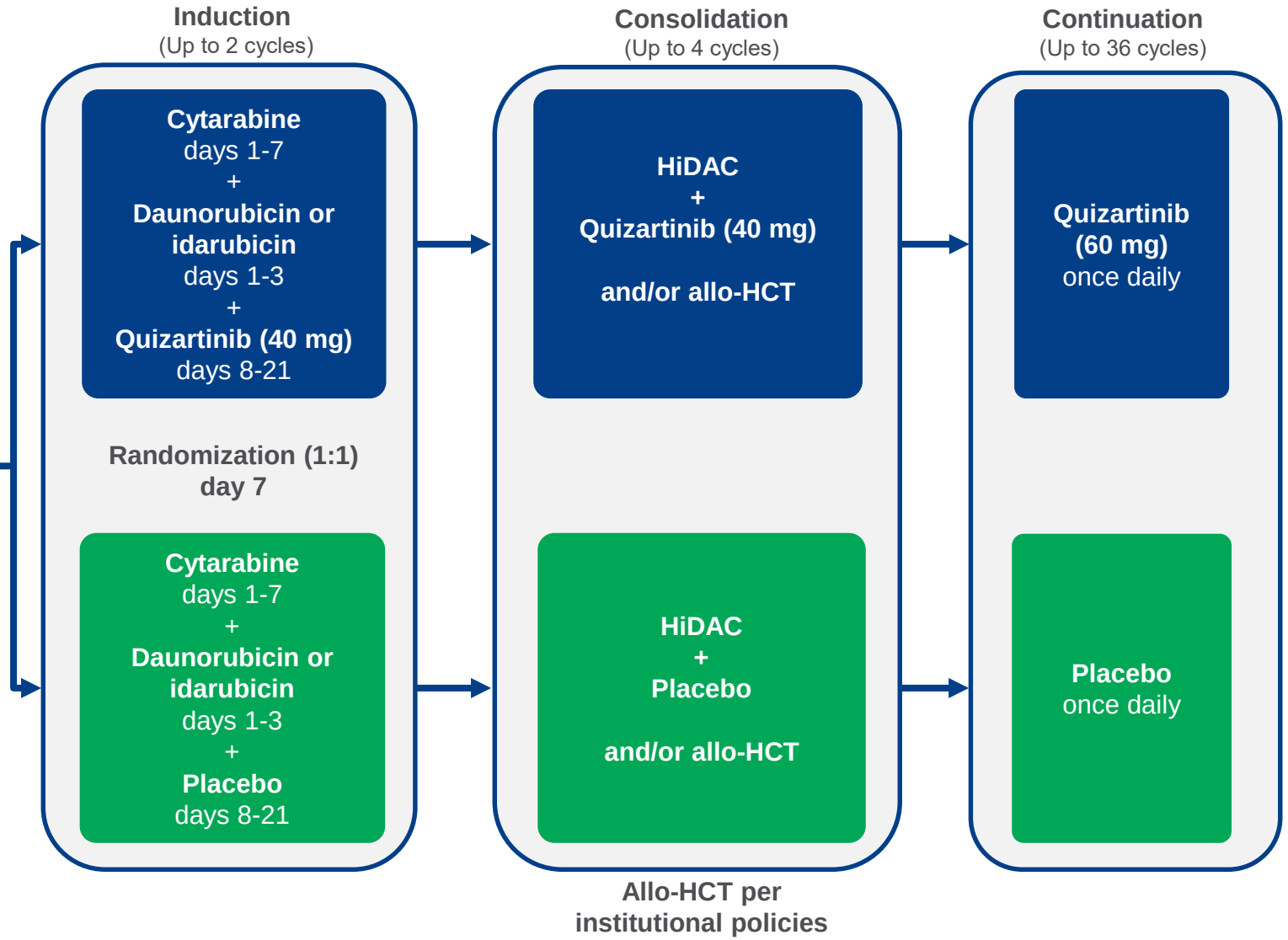
Enrollment dates: September 2016 to August 2019
Data cutoff: August 13, 2021

Stratification factors
- **Region**: NA, EU, and Asia/other regions
- **Patient age**: <60 years, ≥60 years
- **WBC**[a]: $<40\times10^9$/L, $\geq40\times10^9$/L

- Newly diagnosed *FLT3*-ITD+ AML
- 18-75 years of age
- ≥3% *FLT3*-ITD allelic frequency
- Patients begin 7+3 chemotherapy during screening

Selected endpoints
- **Primary endpoint**: OS
- **Secondary endpoints**: EFS, CR/CRc, Safety
- **Exploratory endpoints**: RFS, DoCR

A hierarchical testing procedure was used to test the primary endpoint of OS, followed by EFS, CR and CRc.



AML, acute myeloid leukemia; CR, complete remission; CRc, composite complete remission; DoCR, duration of complete remission; EFS, event-free survival; EU, Europe; HiDAC, high-dose cytarabine; NA, North America, OS, overall survival; RFS, relapse-free survival; WBC, white blood cell.
[a] WBC count was measured at the time of AML diagnosis.

Baseline Patient Characteristics

Patient Characteristics	Quizartinib (N=268)[a]	Placebo (N=271)[a]
Age, years		
Median (range)	56 (23-75)	56 (20-75)
≥60 years, %	39.9	40.2
Sex, n %		
Male	46.3	44.6
Female	53.7	55.4
Race, %		
Asian	29.9	28.8
Black or African American	0.7	1.8
American Indian or Alaska Native	0	0.4
White	59.3	60.1
Other	10.1	8.9
Region, %		
North America	6.0	6.6
Europe	60.8	60.1
Asia/other regions	33.2	33.2

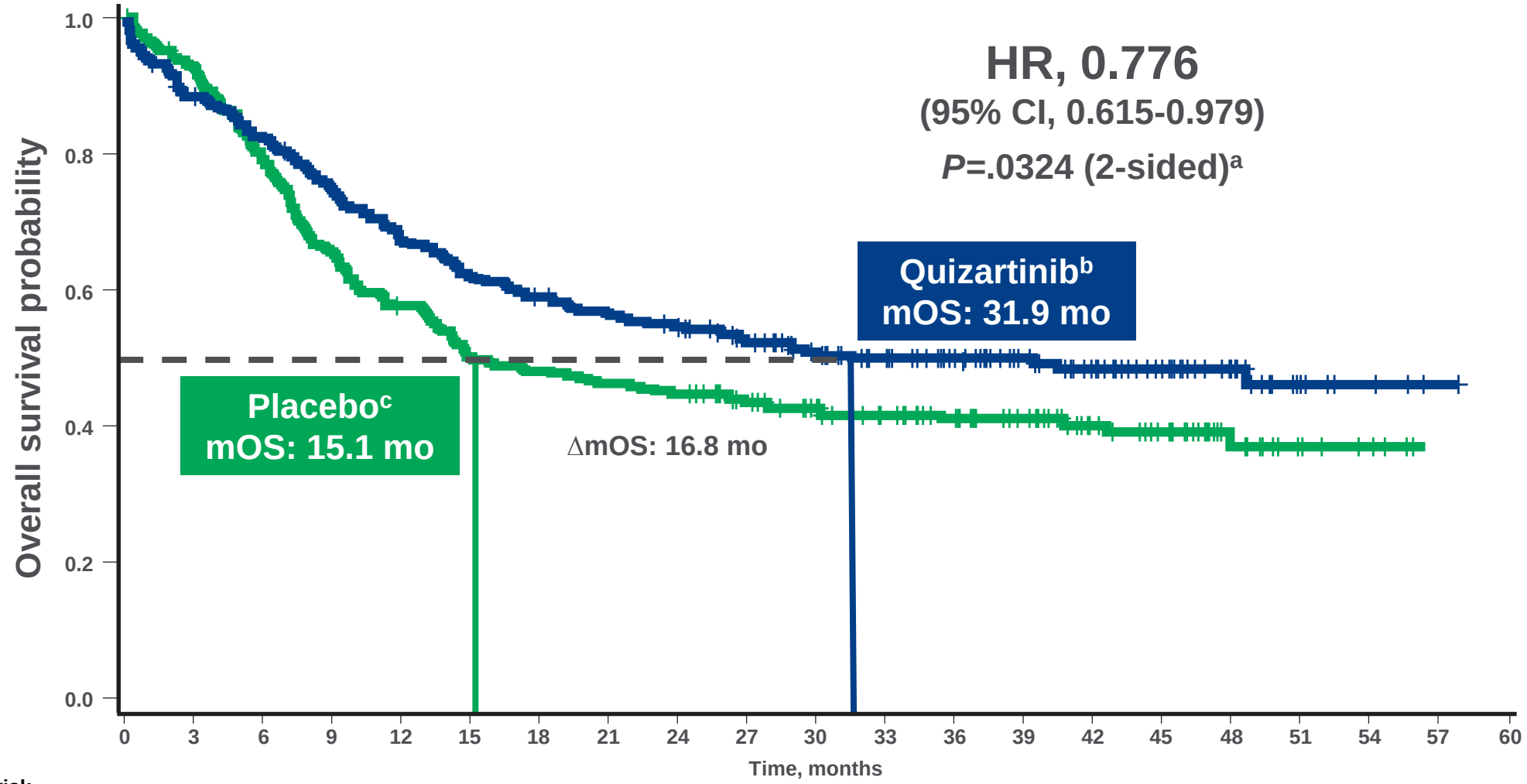
ITT, intention to treat.
[a] Three patients in the ITT set were randomized but not treated.

Baseline Disease Characteristics

Disease Characteristics	Quizartinib (N=268)[a]	Placebo (N=271)[a]
ECOG performance status, %[b]		
0	32.5	36.2
1	50.0	50.2
2	17.5	13.3
Cytogenetic risks, %		
Favorable	5.2	7.0
Intermediate	73.5	71.2
Unfavorable	7.1	10.0
Unknown	14.2	11.4
Missing	0	0.4
Mutated *NPM1*	53.0	51.7
***FLT3*-ITD/total *FLT3*, %[c,d]**		
≥3% to ≤25%	35.1	36.2
>25% to ≤50%	53.4	50.9
>50%	11.2	12.9
WBC count at diagnosis of AML, %		
$<40\times10^9$/L	50.4	50.6
$\geq40\times10^9$/L	49.6	49.4

AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; FLT3, fms related receptor tyrosine kinase 3; ITD, internal tandem duplication; *NPM1*, nucleophosmin; WBC, white blood cell.
[a] Three patients in the ITT set were randomized but not treated in each arm. [b] One patient in the placebo group was missing an ECOG status. [c] Variant allele frequency was assessed by central lab testing. [d] One patient with unknown *FLT3*-ITD/total *FLT3* was positive per local laboratory testing.

Primary Endpoint: Overall Survival

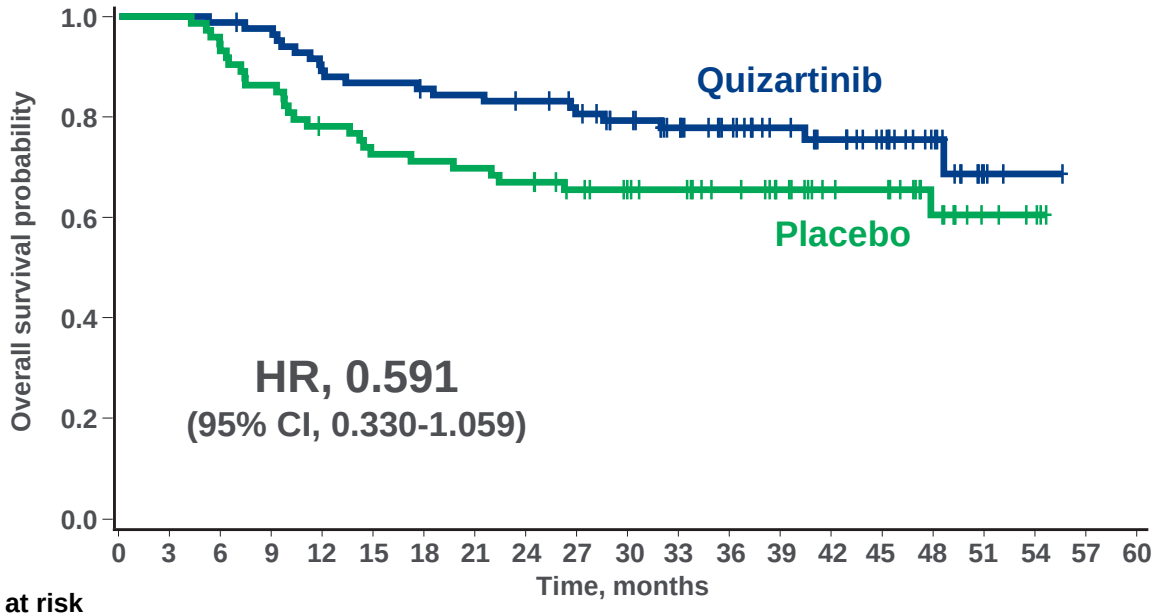


No. at risk																					
Quizartinib	268	233	216	195	176	162	153	145	139	126	110	96	83	68	53	36	24	8	4	1	0
Placebo	271	249	211	175	151	131	126	121	117	103	97	81	70	56	39	31	17	8	5	0	0

HR, hazard ratio; mOS, median overall survival.
[a] *P* value was calculated using a stratified log-rank test. [b] Median follow-up time for quizartinib arm, 39.2 months. [c] Median follow-up time for placebo arm, 39.2 months.

Post-hoc Analysis: OS in Patients Who Achieved CR[a]

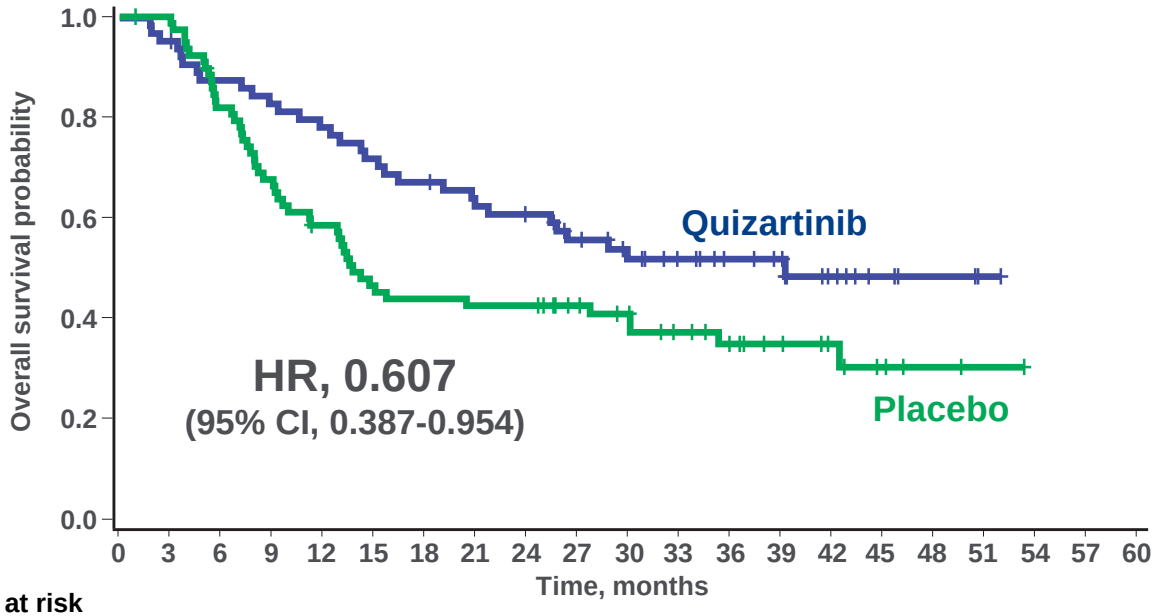
OS – Patients With CR Who Received Allo-HCT in CR1



No. at risk

Quizartinib	84	84	83	81	74	72	70	69	67	63	57	50	42	34	29	22	14	3	1	0	0
Placebo	73	73	68	63	56	52	51	50	48	43	39	37	32	27	21	20	12	5	3	0	0

OS – Patients With CR NOT Receiving Allo-HCT in CR1



No. at risk

Quizartinib	63	60	54	51	48	44	41	37	35	30	25	21	17	15	9	5	3	1	0	0	0
Placebo	77	76	61	50	42	33	31	30	30	25	22	17	14	10	7	4	2	1	0	0	0

- Subgroup analysis for descriptive purposes only

Allo-HCT, allogeneic hematopoietic cell transplantation; CR, complete remission; HR, hazard ratio; IRC, independent review committee; OS, overall survival.
[a] By end of induction by IRC.

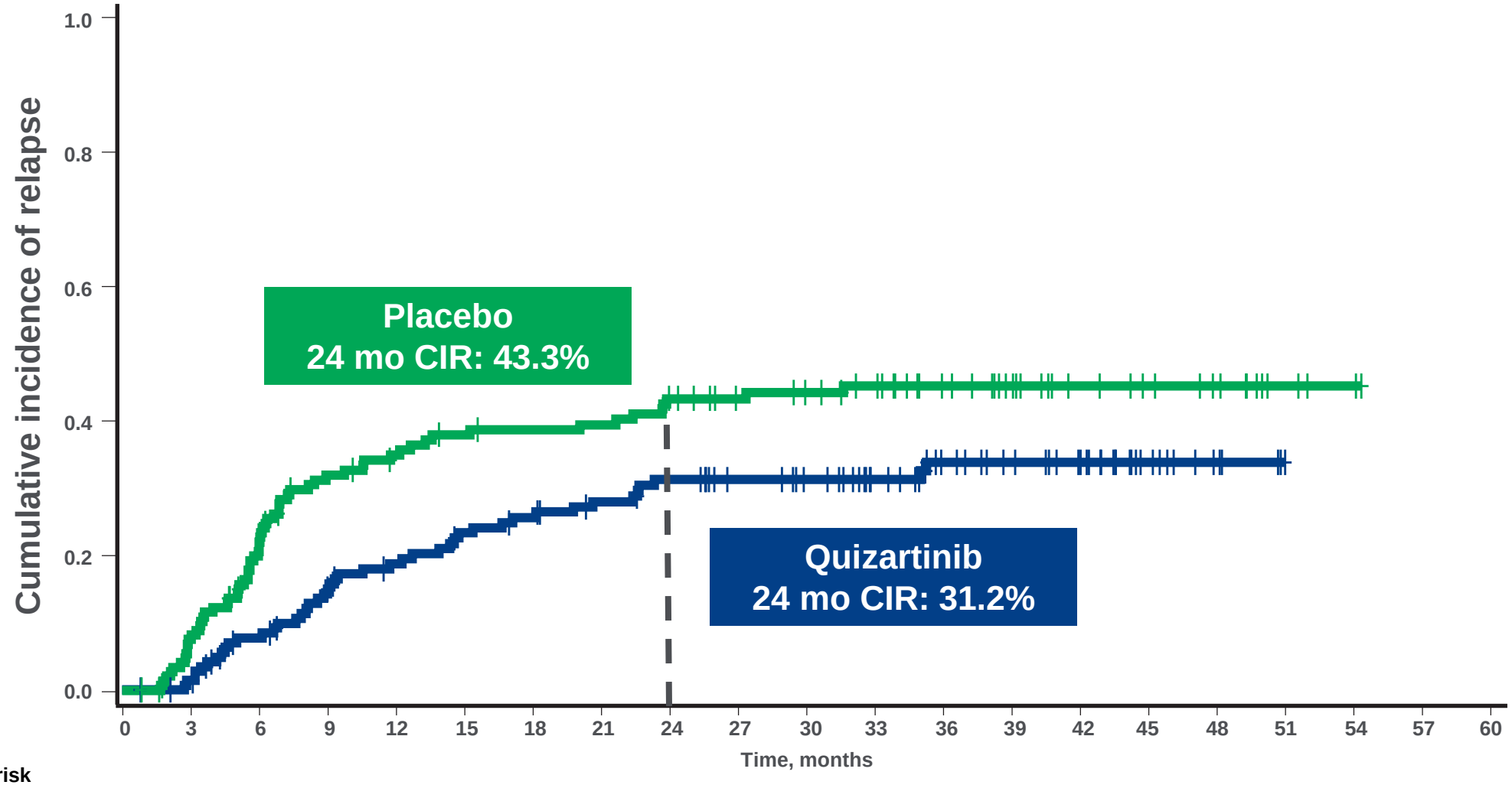
Response and Duration of CR[a]

Parameter	Quizartinib (N=268)	Placebo (N=271)
CRc % 95% CI	 71.6 (65.8-77.0)	 64.9 (58.9-70.6)
CR % 95% CI	 54.9 (48.7-60.9)	 55.4 (49.2-61.4)
CRi % 95% CI	 16.8 (12.5-21.8)	 9.6 (6.4-13.7)
Duration of CR Median, months 95% CI	 38.6 (21.9-NE)	 12.4 (8.8-22.7)

CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete neutrophil or platelet recovery; IRC, independent review committee; NE, not evaluable.

[a] By end of induction by IRC.

Post-Hoc Analysis: Cumulative Incidence of Relapse in Patients Who Achieved CR[a]



No. at risk																					
Quizartinib	147	140	123	111	97	90	84	77	71	63	57	48	36	31	24	13	6	0	0	0	0
Placebo	150	136	103	82	70	63	60	58	52	47	44	39	31	24	18	14	10	4	2	0	0

CIR, cumulative incidence of relapse; CR, complete remission; IRC, independent review committee.

[a] By end of induction by IRC.

Summary of TEAEs Occurring in ≥20% of Patients

TEAEs, %	Quizartinib (N=265)[a]		Placebo (N=268)[a]	
Hematologic adverse events	All Grades	Grade ≥3	All Grades	Grade ≥3
Febrile neutropenia	44.2	**43.4**	42.2	41.0
Neutropenia	20.4	**18.1**	10.1	8.6
Non-hematologic adverse events	All Grades	Grade ≥3	All Grades	Grade ≥3
Pyrexia	42.3	4.5	40.7	4.9
Diarrhea	37.0	3.8	35.1	3.7
Hypokalemia	35.1	18.9	35.8	16.4
Nausea	34.0	1.5	31.3	1.9
Headache	27.5	0	19.8	0.7
Rash	26.0	3.0	24.6	1.1
Vomiting	24.5	0	19.8	1.5
Stomatitis	21.5	4.5	20.9	3.0
Constipation	21.1	0.4	25.7	0

TEAE, Treatment Emergent Adverse Event.
[a] Three patients in each group were not treated and not included in the safety analysis.

QT Prolongation by Central ECG and Select Cardiac Events by TEAE

Parameter	Quizartinib (N=265)	Placebo (N=268)
QTcF interval based on central ECG data (ms), %		
New > 450 ms	34.3	17.9
New > 480 ms	7.5	2.2
New > 500 ms	2.3	0.7
QTcF increase from baseline > 30 ms	55.1	32.5
QTcF increase from baseline > 60 ms	10.1	4.9
Select cardiac events by TEAE (PT), %		
ECG QT prolonged	13.6	4.1
Cardiac arrest/ventricular fibrillation	0.8	0
Ventricular tachycardia	0.4	0.4

- Two patients (0.8%) treated with quizartinib had cardiac arrest (grade 4 [n=1], grade 5 [n=1]), with recorded ventricular fibrillation in the setting of severe hypokalemia
- One patient (0.4%) died in their sleep (PT ‘death’) in the quizartinib arm
- Two patients (0.8%) discontinued quizartinib due to QT prolongation

ECG, electrocardiogram; PT, preferred term; QTcF, corrected QT interval by Fridericia’s formula; TEAE, Treatment Emergent Adverse Event.

Conclusions

- In this pivotal phase 3 trial, QuANTUM-First, quizartinib improved OS when combined with standard induction and consolidation therapy and continued for up to 3 years as a single agent in patients ages 18-75 with newly diagnosed *FLT3*-ITD+ AML
  - Clinically meaningful improvements in RFS, reduced CIR, and longer duration of CR may underpin the OS benefit
- Safety of quizartinib combined with intensive chemotherapy and as continuation monotherapy was generally manageable, with no new safety signals
- These data have the potential to change the standard of care for the treatment of adult patients with newly diagnosed *FLT3*-ITD+ AML

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

N.G. Daver[1], J. Senapati[1], A. Maiti[1], M.Y. Konopleva[1], C.D. DiNardo[1], G. Borthakur[1], K. Chien[1], G.C. Issa[1], E.J. Jabbour[1], S.M. Kornblau[1], L. Masarova[1], T.M. Kadia[1], Y. Alvarado[1], N. Jain[1], S. Loghavi[2], K. Sasaki[1], N. Pemmaraju[1], H. Abbas[1], P. Bose[1], J.A. Burger[1], A. Ferrajoli[1], G. Montalban-Bravo[1], M. Yilmaz[1], M. Ohanian[1], N.J. Short[1], K. Takahashi[1], P.A. Thompson[1], W.W. Weirda[1], G. Tang[2], M. Golez[1], K.P. Patel[2], S. Pierce[1], G. Nogueras-Gonzalez[3], J. Ning[3], F. Ravandi[1], M. Konopleva[1], G. Garcia-Manero[1], H.M. Kantarjian[1].

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ABSTRACT#616

American Society of Hematology Meeting, 2022

Methods: Study Design

Phase 1 (Dose finding)

- R/R AML
- ≥ 18 yrs
- ECOG PS ≤ 2
- adequate organ function
- WBC ≤ $15x10^9$/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

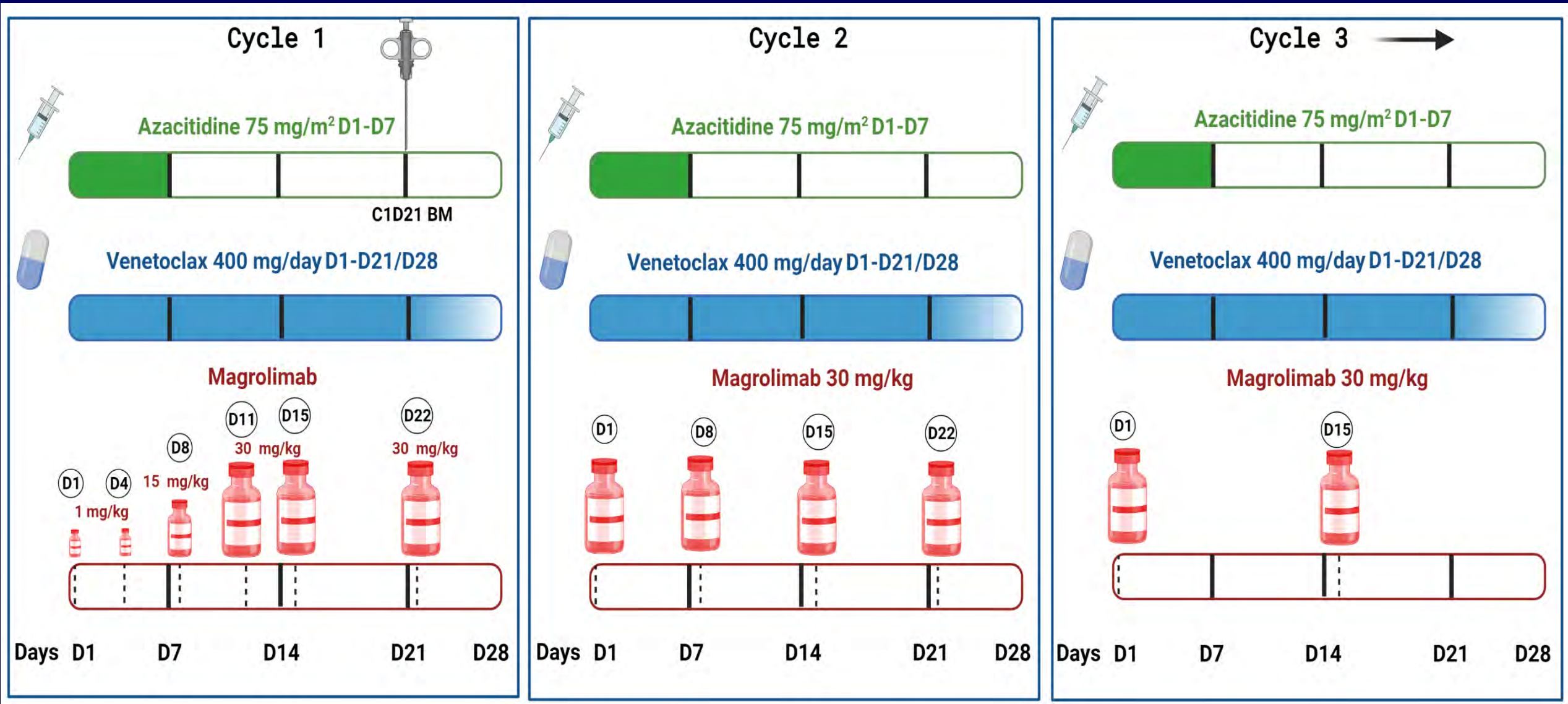
- Determine MTD and RP2D
- CR/CRi rate

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

Treatment Schema



Characteristics FRONTLINE (n=43): A very high risk cohort

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]			
Age (yrs)		70 [32-84]	65 [33-81]	76 [67-80]	75 [61-84]	72 [69-82]
Age >65 years		30 (70)	11 (50)	10 (100)	4 (80)	5 (100)
Gender	Females	16 (37)	10 (45)	4 (36)	1 (20)	1 (25)
ECOG PS	0	2 (5)	2 (10)	0 (0)	0 (0)	0 (0)
	1-2	40 (93)	20 (90)	11 (100)	5 (100)	4 (100)
Therapy (for non-hematological cancer) related AML		16 (37)	10 (45)	1 (9)	2 (40)	3 (75)
ELN 2017 risk stratification	Intermediate	4 (9)	0 (0)	4 (36)	0 (0)	0 (0)
	Adverse	39 (91)	22 (100)	7 (64)	5 (100)	4 (100)
CTG per ELN 2017	Intermediate	15 (35)	4 (18)	8 (73)	1 (20)	1 (25)
	- Diploid	10	3	6	1	0
	- Others	4	1	2	0	1
	Adverse	28 (65)	18 (82)	3 (27)	4 (80)	3 (75)
	- CK	23	17	1	4	1
	- Isolated -5/5q- or -7/7q-	4	1	2	0	1
	- Other adverse	1	0	0	0	1
Mutations	*IDH1/IDH2*	7 (16)	4 (18)	3 (27)	0 (0)	0 (0)
	FLT3 ITD/TKD	1 (2)	1 (5)	0 (0)	0 (0)	0 (0)
	NPM1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	ASXL1	7 (16)	2 (9)	5 (45)	0 (0)	0 (0)
	RUNX1	5 (12)	2 (9)	3 (27)	0 (0)	0 (0)

**This includes treated and untreated sAML, except prior HMA treatment (such as targeted Rx, investigational agents, LDAC-based, growth factors, ImiDs, etc)*

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)
Cytogenetic responses*	CCyR	11/21 (52)*	5/10 (50)	4/6 (67)	2/5 (40)	
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)

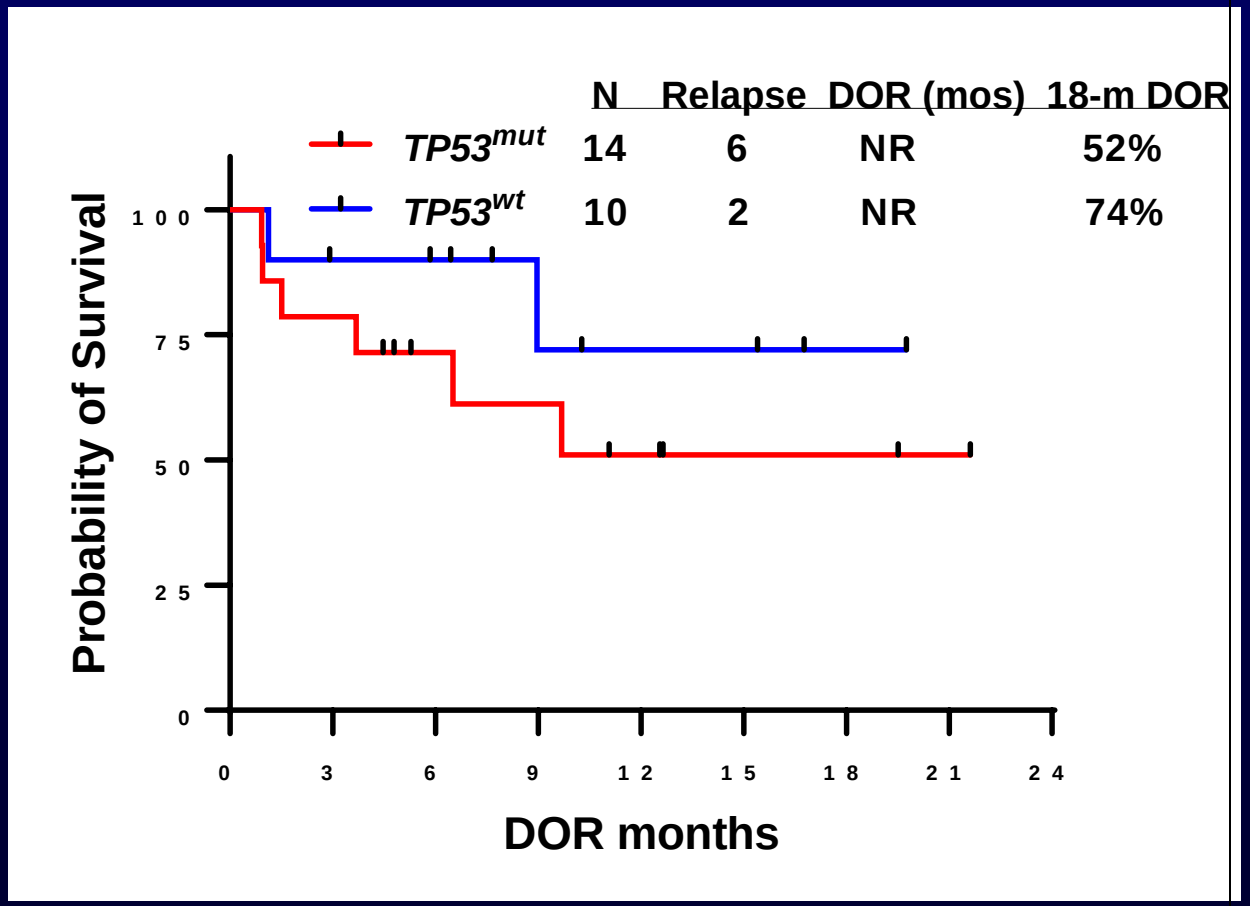
Amongst CR/CRi patients with longitudinally MRD evaluable samples

* Amongst responders with baseline clonal CTG abnormality

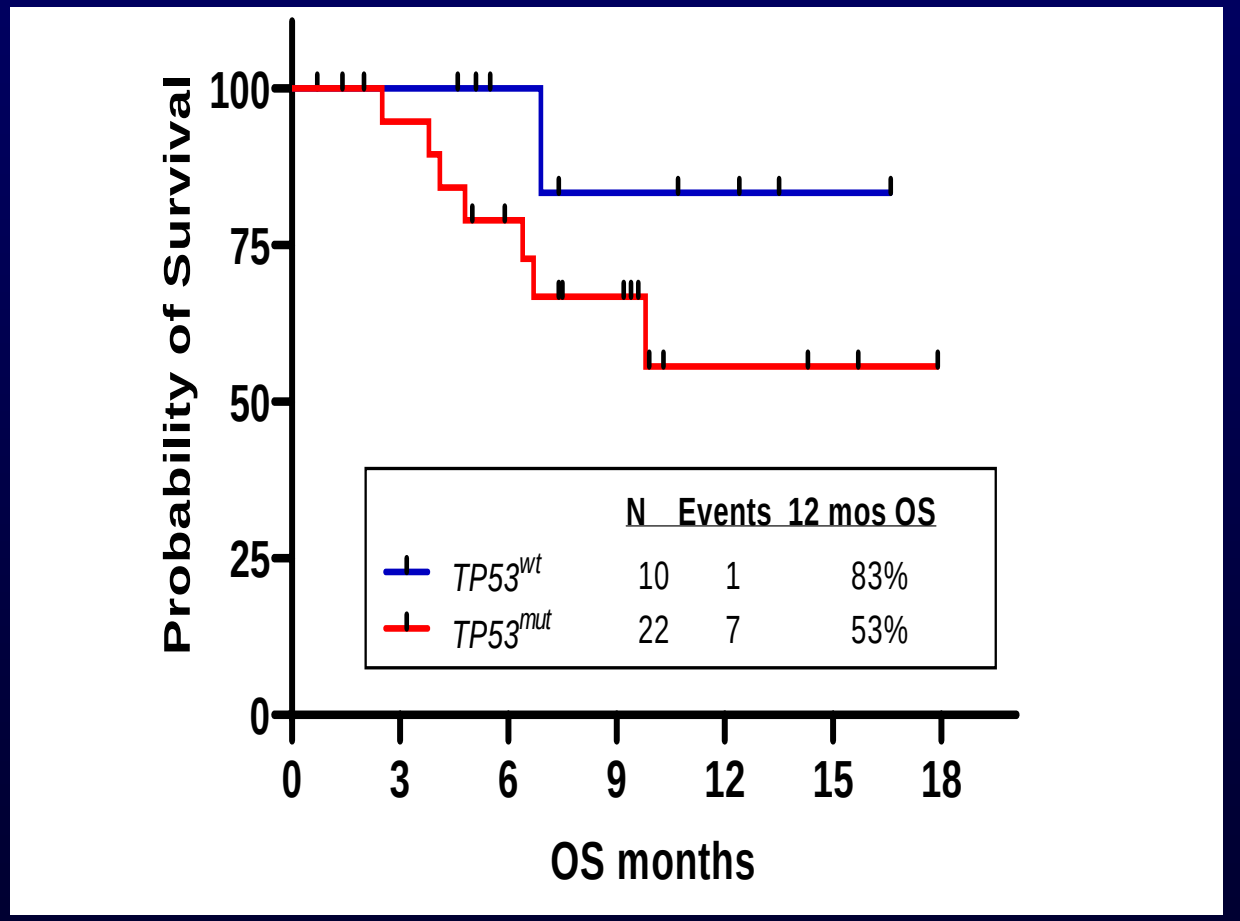
Duration of response and OS in FRONTLINE De Novo cohort

Median follow-up: 14.5 months

DOR (De Novo patients, N=33)



Overall Survival (De Novo patients, n=33)



Survival comparison with Aza-Ven-Magrolimab to HMA-Ven combination: *TP53* mutated arm

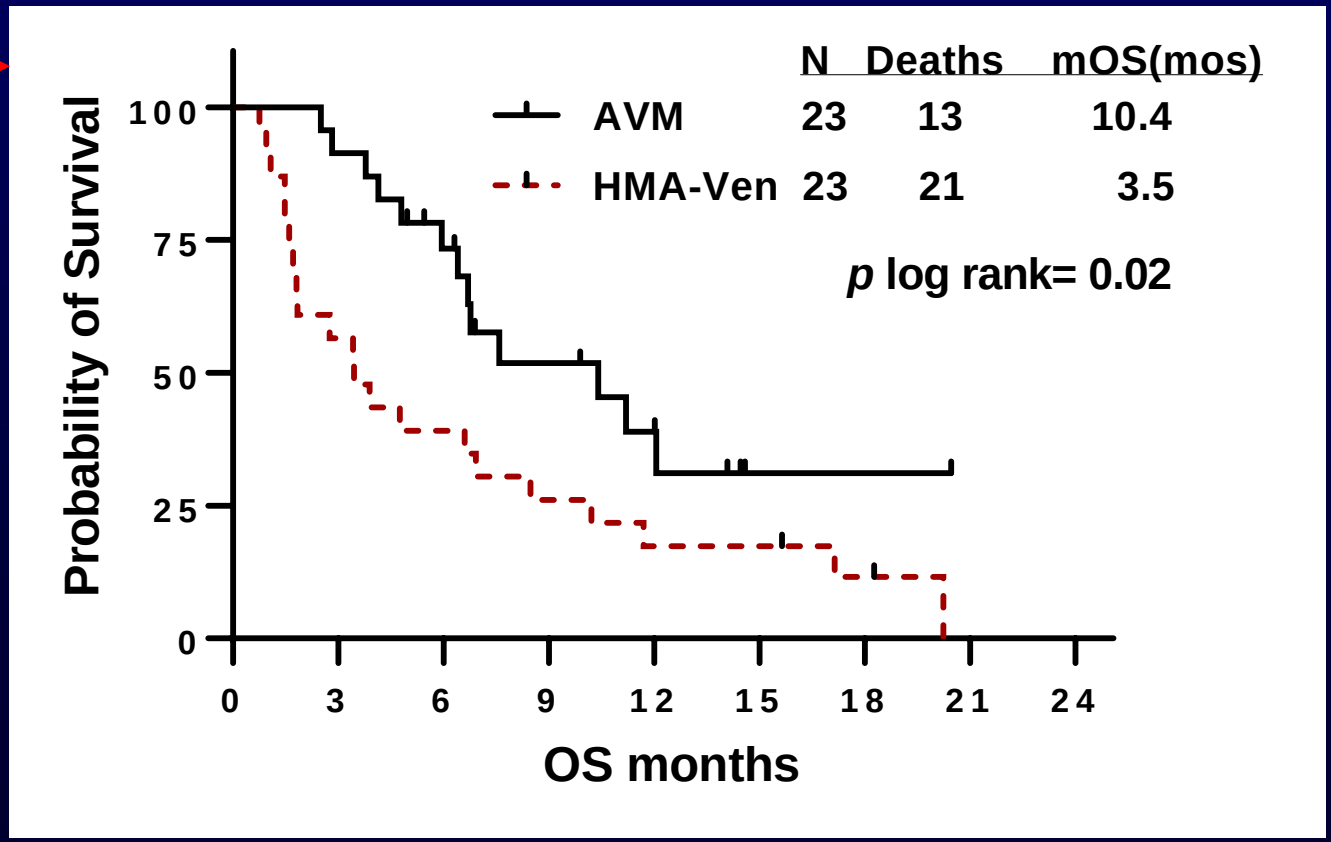
Propensity matched analysis: 1:1 (nearest neighbor)

Comparison of baseline characteristics of propensity matched groups

Parameters	AVM (n=23)*	HMA-VEN (n=45)	HMA-Ven Propensity matched (n=23)
Age, years	64 [38-81]	74 [61-86]	75 [61-86]
t-AML	11 (48)	17 (38)	11 (48)
CTG- HR CTG-CK	21 (91) 21 (91)	43 (96) 41 (91)	21 (91) 19 (83)
ASXL1	2 (9)	2 (4)	2 (9)
RUNX1	2 (9)	2 (4)	2 (9)

*23 propensity matching pts identified among total n=27
TP53m on AVM

Comparison of overall survival of matched population



Results: Safety analysis (N= 79)

- All patients had at least one any grade adverse event
- 71 patients (90%) had at least one ≥ grade 3 adverse event
- No patient had any immunological adverse event
- **No study treatment discontinuations due to TRAEs**
- Infusion reactions noted: in 8 (10%) patients (3 patients had grade 3 reaction)
  - ✓ effectively mitigated with dexamethasone pre-med for subsequent doses

- Eighteen patients (23%) had a ≥ grade 3 anemia while on study.

- No anemia related life-threatening events or deaths.
- The median drop in Hb post first infusion of magrolimab in the frontline cohort (n=43) was **1.2 g/dl (range, 0 - 3.9 g/dl)**.

Results: Treatment emergent adverse events* (non-hematological)

Adverse Event	Overall		≥ Grade 3	
	N	%	N	%
Febrile neutropenia	35	44	**35**	**44**
Lung infection	34	43	**28**	**35**
Sepsis	12	15	**12**	**15**
Hyperbilirubinemia	41	52	**9**	**11**
Hypokalemia	48	61	**6**	**8**
Inc. Creatinine /AKI	28	35	**6**	**8**
ALT elevation	31	39	**5**	**6**
Skin infection	9	11	**5**	**6**
Hypotension	26	33	**4**	**5**
Hyperuricemia	13	16	**4**	**5**
Urinary tract infection	4	5	**4**	**5**
Fatigue	19	24	**3**	**4**
Hyperglycemia	13	16	**3**	**4**
Respiratory failure	3	4	**3**	**4**
Mucositis	18	23	**2**	**3**
Infusion reaction	8	10	**2**	**3**
Hematuria	6	8	**2**	**3**
Syncope	2	3	**2**	**3**
Hypophosphatemia	40	51	**1**	**1**
Hypocalcemia	32	41	**1**	**1**

Adverse Event	Overall		≥ Grade 3	
	N	%	N	%
Diarrhea	29	41	**1**	**1**
ALP elevation	27	34	**1**	**1**
Hypomagnesemia	23	29	**1**	**1**
Dyspena	23	29	**1**	**1**
Abdominal pain	22	28	**1**	**1**
Pruritis	18	23	**1**	**1**
Hyperkalemia	9	11	**1**	**1**
Hypernatremia	6	8	**1**	**1**
Bone pain	4	5	**1**	**1**
Bladder spasm	1	1	**1**	**1**
Atrial fibrillation	1	1	**1**	**1**
Myocarditis	1	1	**1**	**1**
QTc prolongation	1	1	**1**	**1**
Rash	1	1	**1**	**1**
SVT	1	1	**1**	**1**
Pulmonary edema	1	1	**1**	**1**
Cholecystitis	1	1	**1**	**1**
Constipation	32	41	**0**	**0**
Nausea	28	35	**0**	**0**
Hypercalcemia	11	14	**0**	**0**

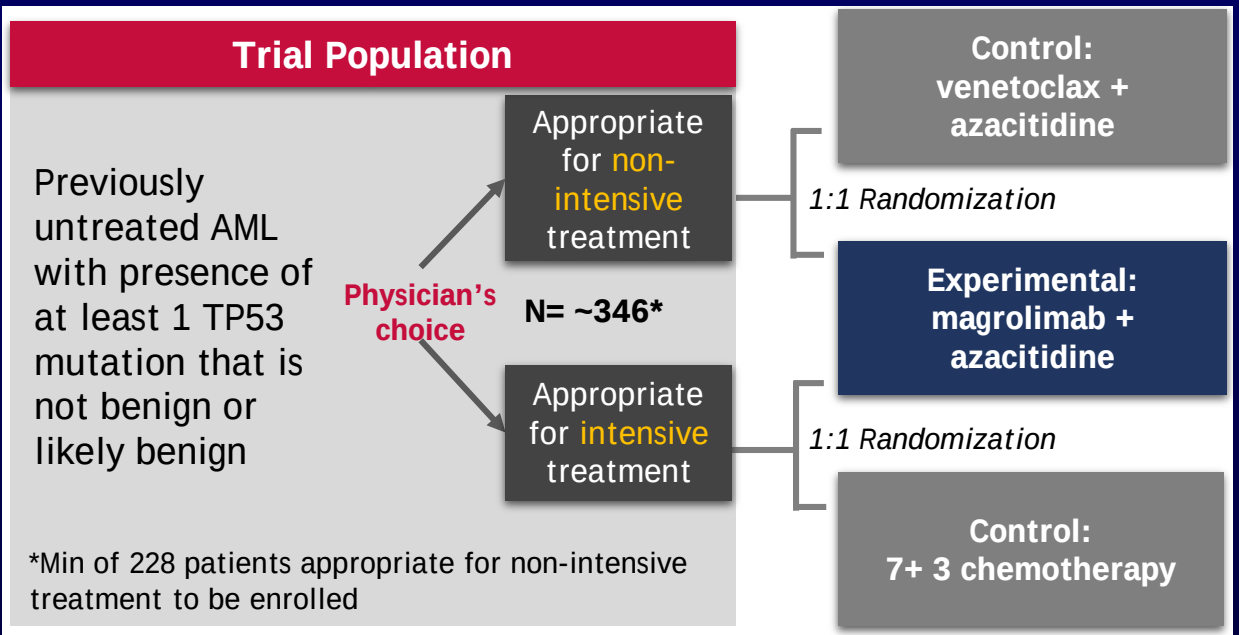
* Unique highest grade adverse event/patient. All ≥ grade 3 events and all any grade AE regardless of attribution seen in ≥10% study patients tabulated

Conclusions

- Combination of AZA VEN magrolimab was safe in the frontline setting in this very high risk population
- CR rates in overall frontline (De Novo and Secondary cohorts) population were :
  - Frontline *TP53^{mut}* AML (n=27) CR/CRi rate = 63%, CR rate = 42%
  - Frontline *TP53^{wt}* AML **(64% ELN adverse risk) (n=16)** CR/CRi rate = 88%, CR rate = 56%
  - 8-week mortality in frontline = 0
- On propensity matching OS appeared to be better than HMA-VEN FL historical protocol patients for TP53m but median f/u and numbers remain small. Numbers too low currently to conduct this in the TP53wt
- Activity in R/R AML was modest
- No unexpected adverse events → Careful monitoring of Hemoglobin pre-magrolimab infusion (espescially between C1D1=C1D10)
- **Randomized study initiated to assess whether AVM can improve on AV in frontline patients**

Ongoing Phase III Studies with Magrolimab in Frontline AML

Phase III AZA+Magro vs Investigator Choice in TP53^{mut} AML (ENHANCE-2)



Stratification:
1) Appropriateness for non-intensive therapy vs intensive therapy
2) Age (<75 vs ≥ 75)
3) Geographic region (US vs. outside the US)

Primary Endpoint: OS in patients appropriate for non-intensive therapy
Key Secondary Endpoint: OS in all patients
Other Secondary Endpoints: EFS, CR/CR^{MRD-}, duration of response, transfusion independence, rate of SCT

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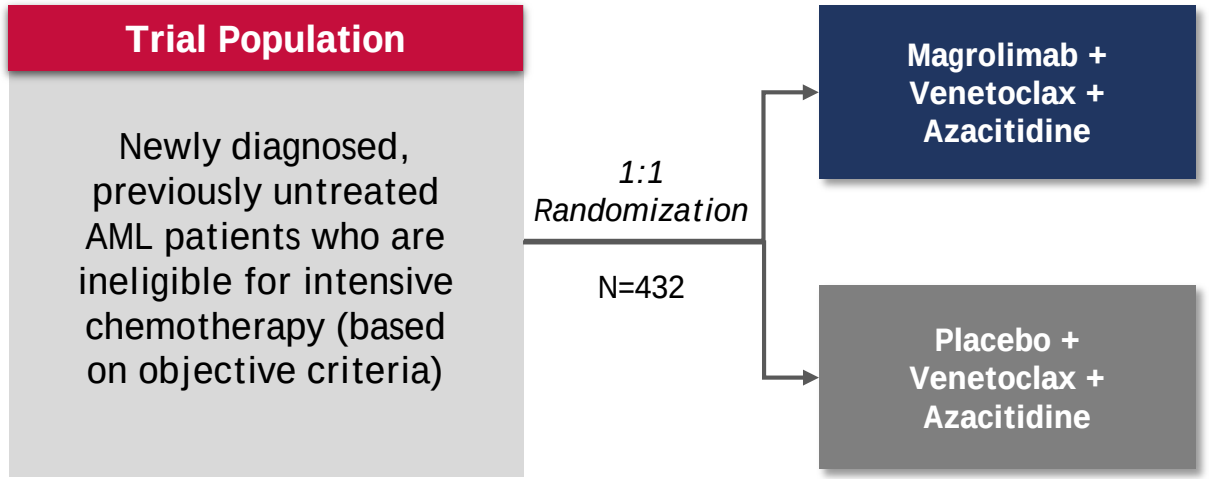
Phase III AZA+ VEN+ Magro vs AZA+VEN in older/unfit AML (ENHANCE-3)



Stratification:
1) Age (<75 vs ≥ 75)
2) Cytogenetic risk (favorable/intermediate vs. adverse vs. unknown)
3) Geographic region (US vs. outside the US)

Dual Primary Endpoint:
- CR rate within 6 cycles of treatment as determined by the investigator
- OS

Secondary Endpoints: CR^{MRD-}, CR/CRh, duration of response, transfusion independence, EFS, QOL

NCT05079230

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

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

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

or

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

Induction

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

* FLT3-ITD or FLT3 D835 mutations allowed

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: Patients

		Frontline (N=27)	Relapsed/Refractory (N=20)
Characteristic	**Category**	**N (%) / median [range]**	**N (%) / median [range]**
Age (years)		70 [18-86]	69 [19-90]
	≥60 years	26 (96)	16 (80)
	≥75 years	8 (30)	4 (20)
Diagnosis	AML	27 (100)	19 (95)
	MDS/CMML	0	1 (5)
Cytogenetics	Diploid	18 (67)	8 (40)
	Adverse risk	3 (11)	7 (35)
	Others	6 (22)	5 (25)
FLT3 mutation type	ITD	19 (70)	9 (45)
	TKD	8 (30)	7 (35)
	ITD+TKD	0	4 (20)
FLT3 allelic ratio	ITD	0.21 [0.04-3.35]	0.36 [0.03-15.7]
	TKD	0.65 [0.03-1.34]	0.59 [0.01-1.81]
Number of prior therapies		---	2 [1-5]
Prior FLT3 inhibitor		---	6 (30)
Prior gilteritinib		---	2 (10)
Prior HMA + venetoclax		---	8 (40)
Prior HSCT		---	5 (25)

Aza+Ven+Gilteritinib in FLT3-mutated AML: Phase I Safety

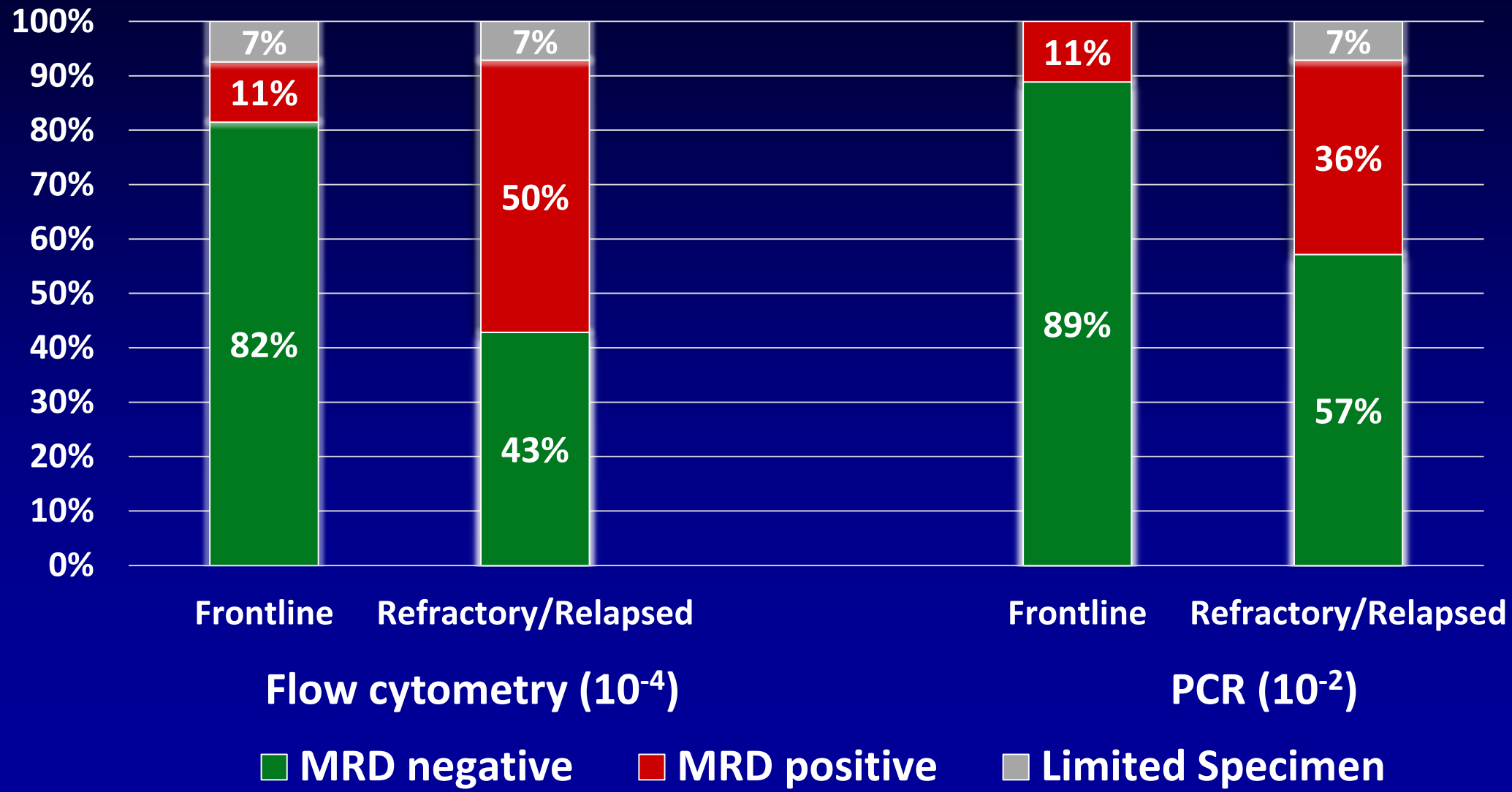
- 10 pts treated in Phase I cohort
  - Gilteritinib 80mg daily in 6 pts
  - Gilteritinib 120mg daily in 4 pts (1 pt not evaluable for DLT)
- No non-hematologic DLTs observed
- Myelosuppression appeared greater with gilteritinib 120mg dosing
  - 1/3 DLT at 120mg (grade 4 myelosuppression); 0/6 DLTs at 80mg
  - Among 3/4 responding pts at 120mg dose, MLFS was best response
  - 3/6 pts (50%) at 80mg dose responded → 1 CR and 2 CRi
  - Gilteritinib 80mg chosen as phase II expansion dose

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

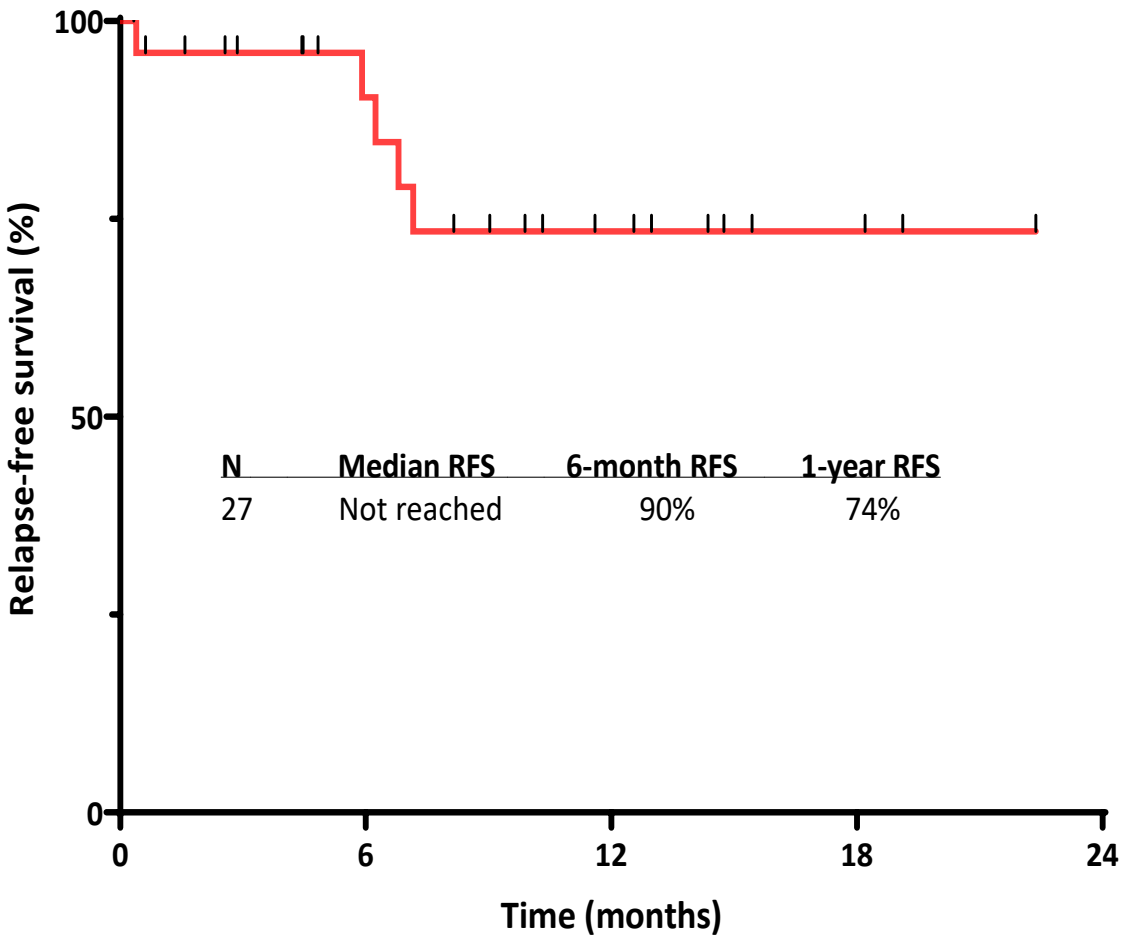
* PR in 1 patient with extramedullary-only disease (assessed by PET scan)

Aza+Ven+Gilteritinib in FLT3-mutated AML: Best MRD Response

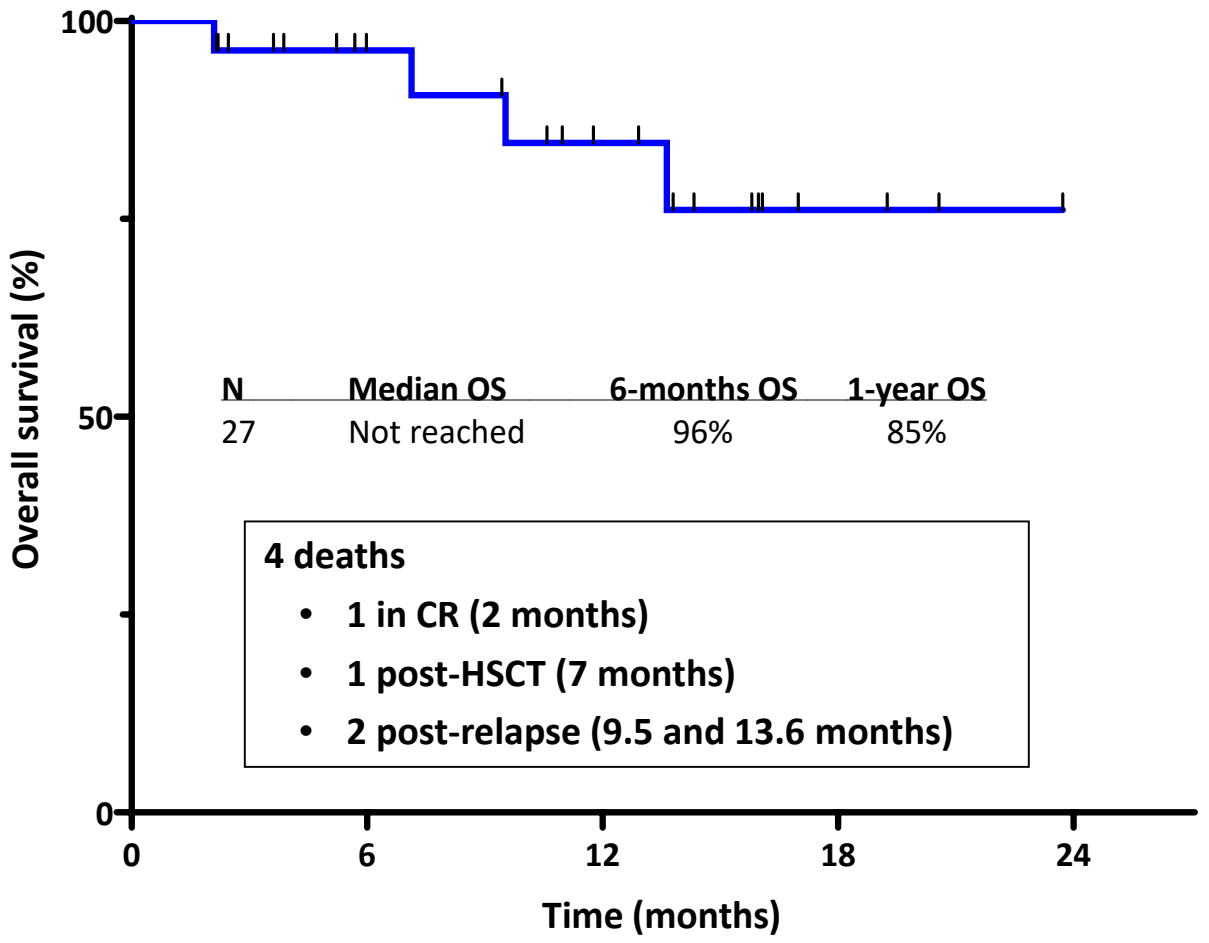


Aza+Ven+Gilteritinib in FLT3-mutated AML: RFS and OS in Frontline Cohort

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



N	Median RFS	6-month RFS	1-year RFS
27	Not reached	90%	74%



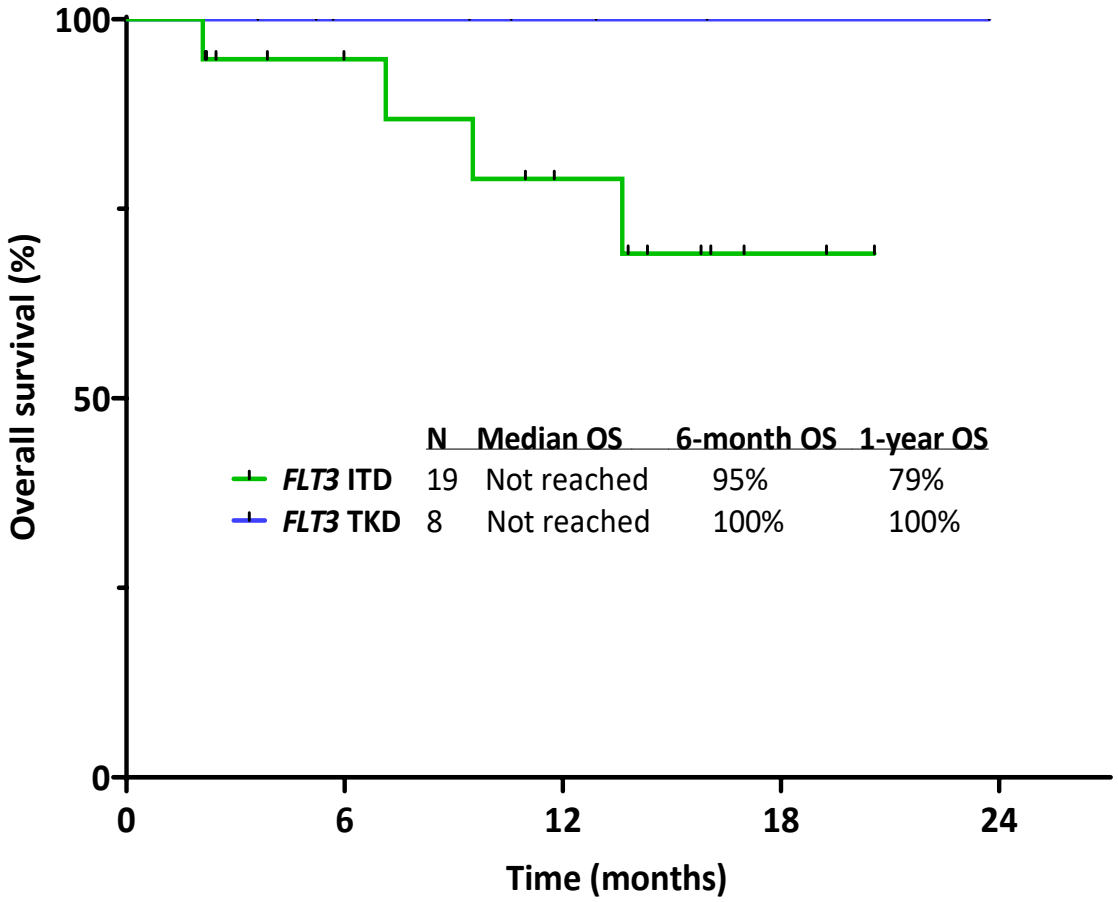
N	Median OS	6-months OS	1-year OS
27	Not reached	96%	85%

4 deaths

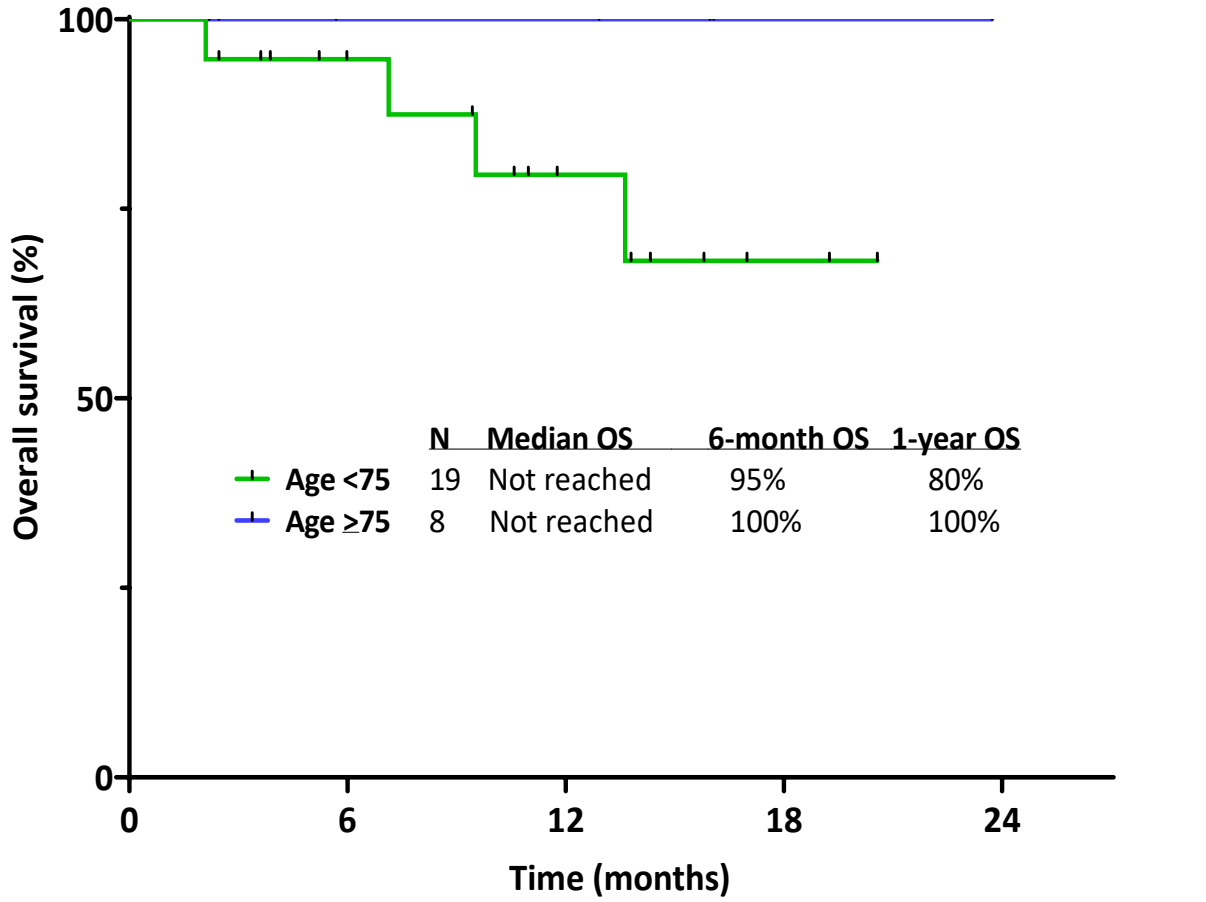
- **1 in CR (2 months)**
- **1 post-HSCT (7 months)**
- **2 post-relapse (9.5 and 13.6 months)**

Aza+Ven+Gilteritinib in FLT3-mutated AML: OS in Frontline Cohort by Subgroups

Type of *FLT3* Mutation

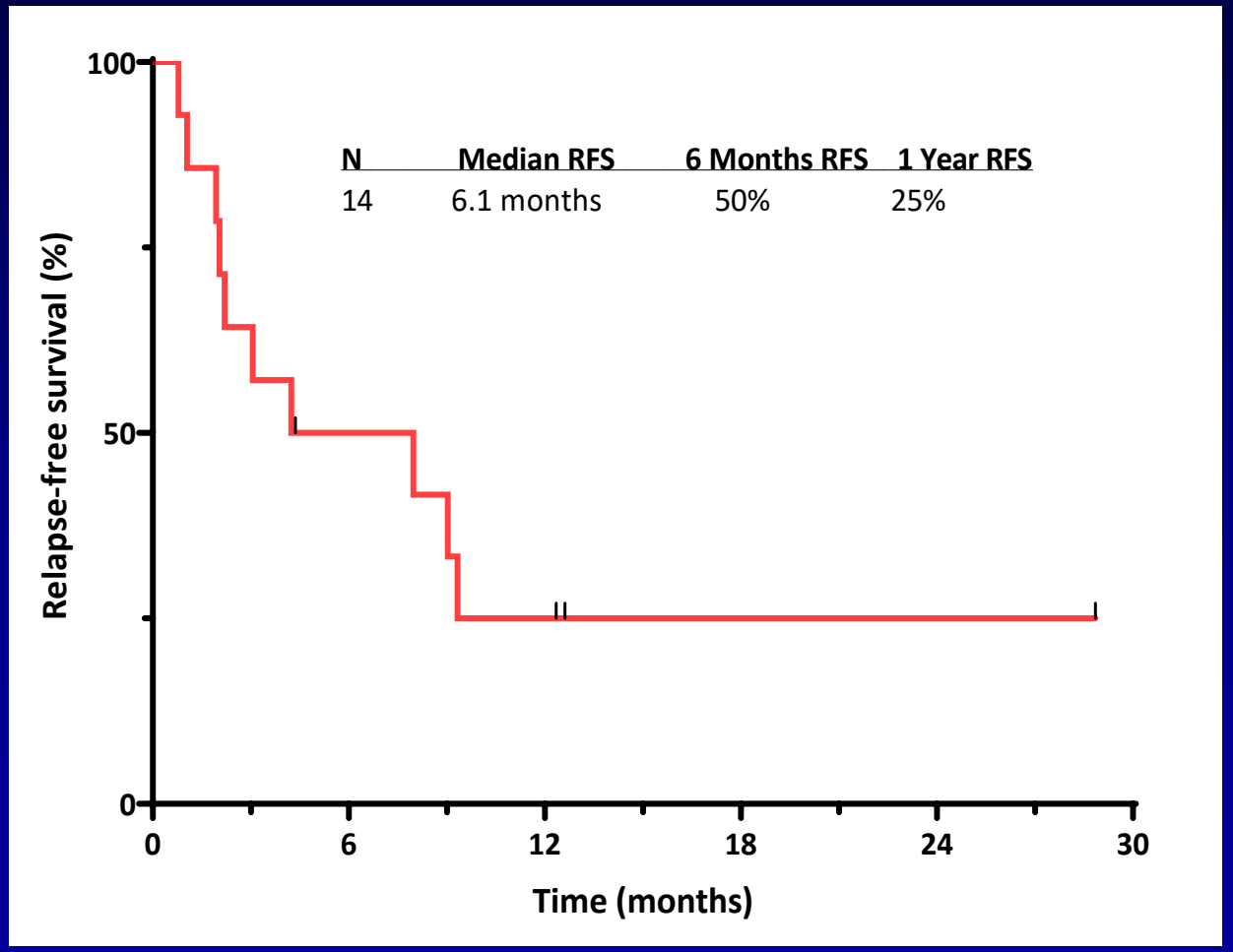


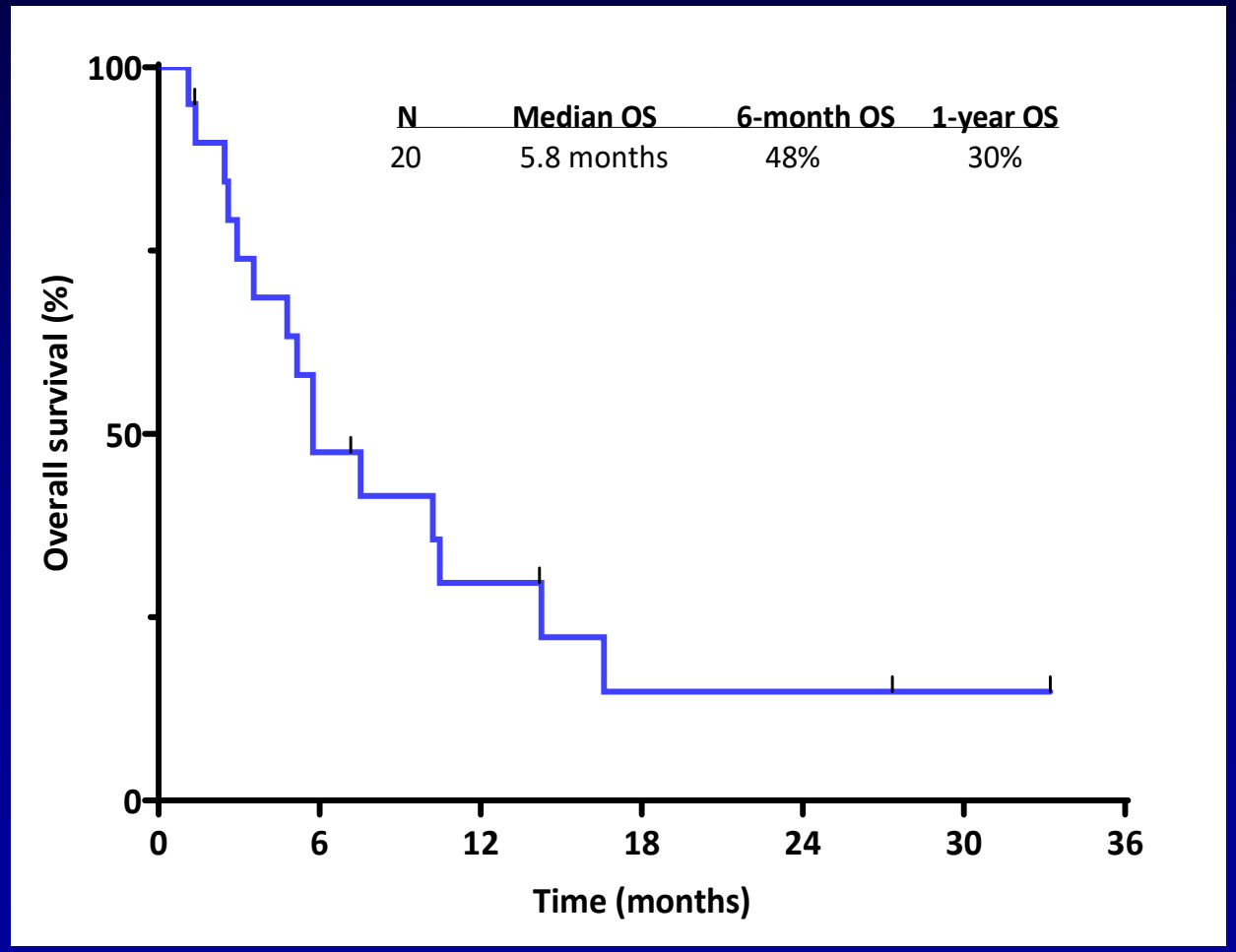
Age



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

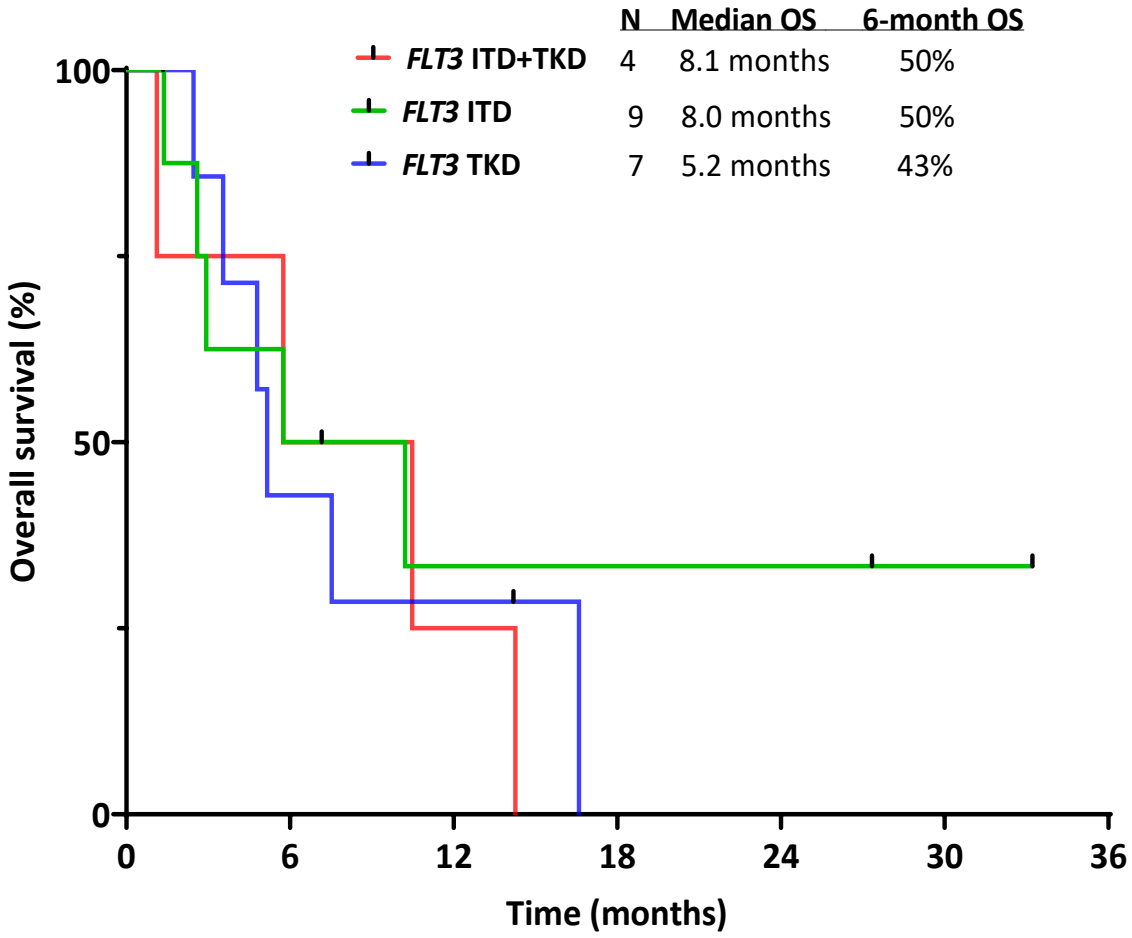
Median follow-up: 27 months (range, 1.1-33.2+ months)



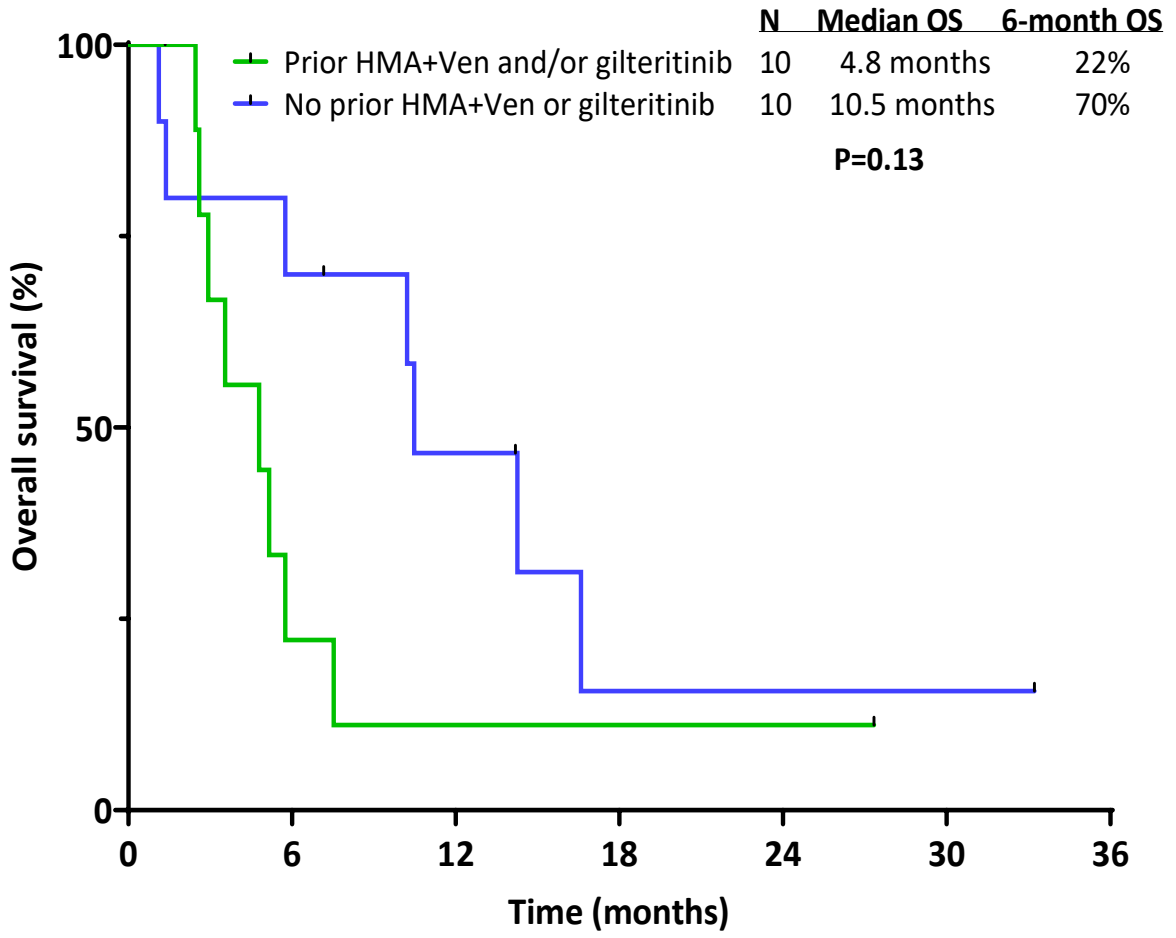


Aza+Ven+Gilteritinib in FLT3-mutated AML: OS in R/R Cohort by Subgroups

Type of *FLT3* Mutation



Prior Therapies

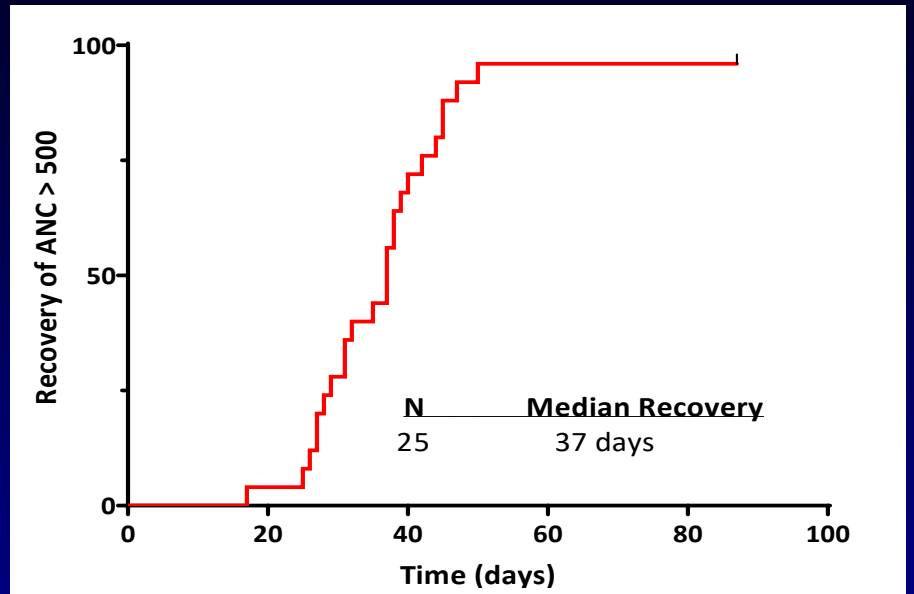


Aza+Ven+Gilteritinib in FLT3-mutated AML: Safety

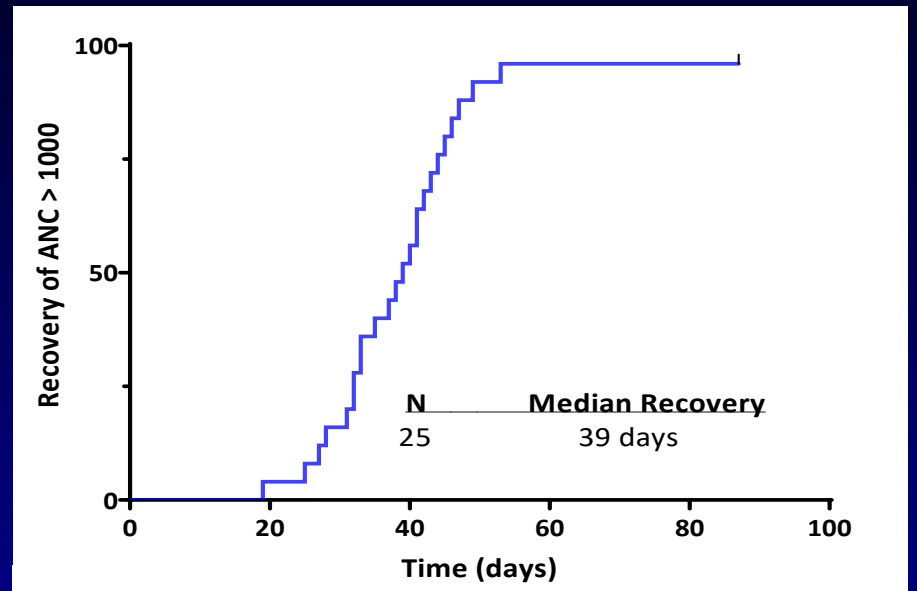
	Frontline (N=27)			Refractory/Relapsed (N=20)		
Adverse events	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)
Acute kidney injury	1 (4)	0	0	1 (5)	0	0
Altered mental status	0	0	0	1 (5)	0	0
Atrial fibrillation	0	0	0	1 (5)	0	0
Cardiac enzyme elevation	0	0	0	1 (5)	0	0
DIC	0	0	0	0	0	1 (5)
Febrile neutropenia	1 (4)	0	0	5 (25)	0	0
GU bleeding	0	0	0	2 (11)	1 (5)	0
Hypotension	0	0	0	2 (10)	1 (5)	0
Infection	5 (18)	0	1 (4)	9 (45)	0	2 (10)
Intracranial hemorrhage	0	0	0	0	0	1 (5)
Nausea/vomiting	1 (4)	0	0	0	0	0
QT prolongation	1 (4)	0	0	0	0	0
Sepsis	0	0	0	4 (20)	1 (5)	0
Small bowel obstruction	1 (4)	0	0	0	0	0
Tumor lysis syndrome	1 (4)	0	0	1 (5)	0	0

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

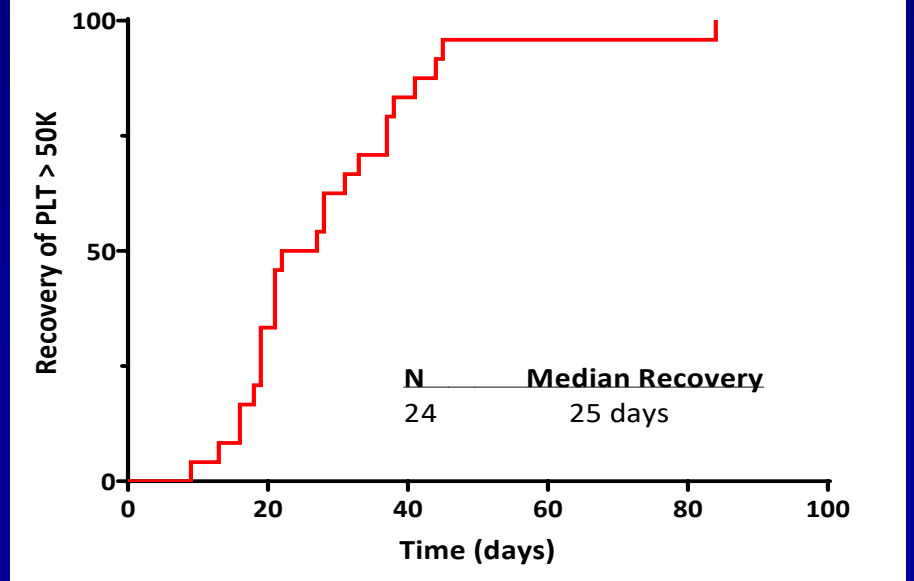
ANC >500



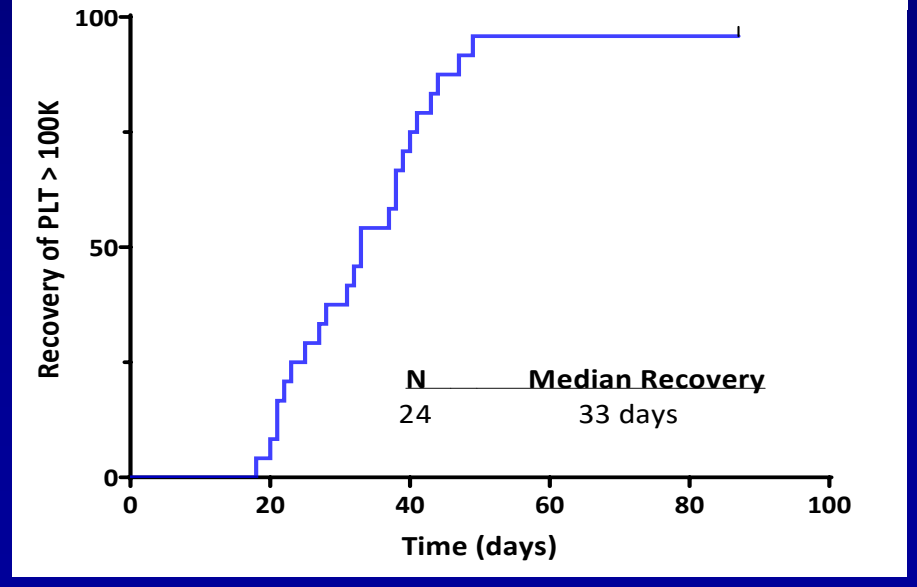
ANC >1000



Platelets >50K



Platelets >100K



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

- Azacitidine + venetoclax + gilteritinib results in high rates of mCRc in newly diagnosed (100%) and R/R (70%) *FLT3*-mutated AML
  - CR rate 92% and flow MRD negativity rate 82% in newly diagnosed pts
- Durability of responses encouraging in newly diagnosed pts, regardless of age of type of *FLT3* mutation
  - 3 relapses to date; estimated 1-year OS: 85% (vs. 40-60% in VIALE-A)
- Myelosuppression manageable with mitigation strategies
  - Use of gilteritinib 80mg
  - Day 14 bone marrow to determine course of venetoclax/gilteritinib
  - Attenuation of azacitidine/venetoclax in consolidation

Publication #4074:

Venetoclax added to cladribine (CLAD) + low dose AraC (LDAC) alternating with azacitidine (AZA) is highly active as frontline therapy in older patients with newly diagnosed acute myeloid leukemia in a phase 2 study

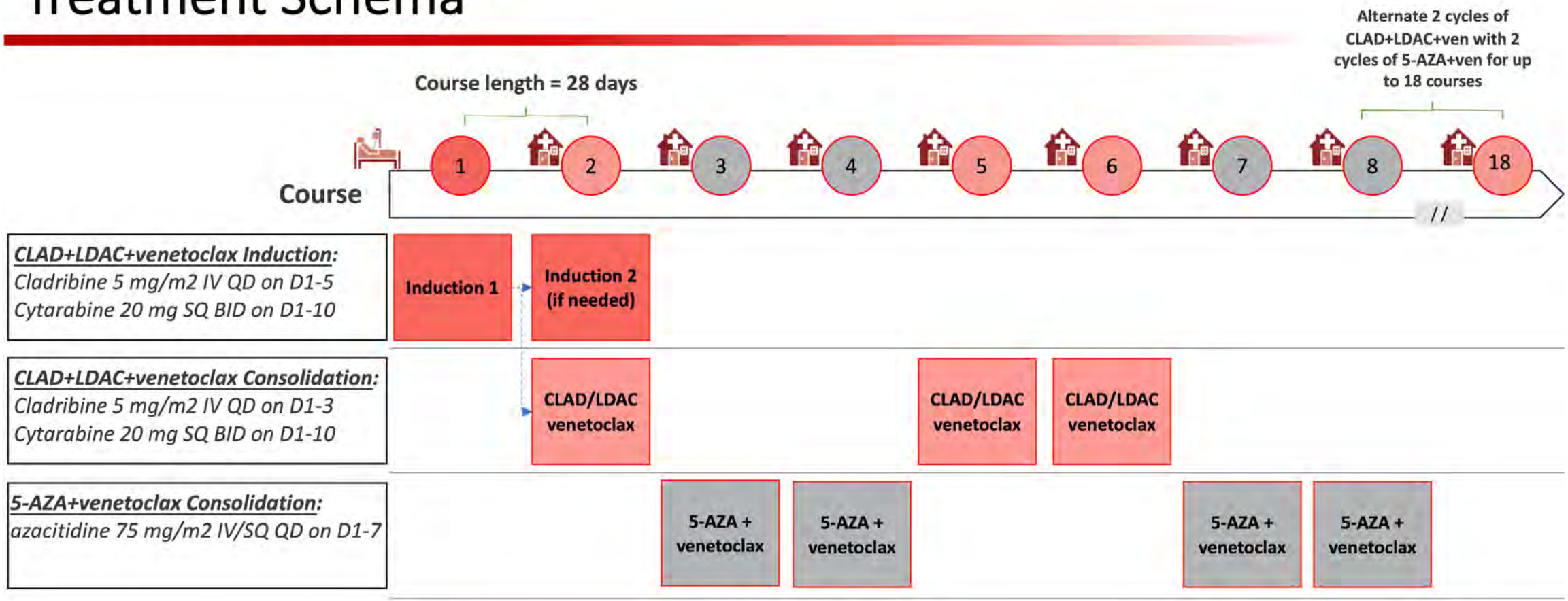
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Patrick K Reville (@patrickreville), Hagop Kantarjian, Gautam Borthakur, Naveen Pemmaraju, Naval Daver, Courtney DiNardo, Koji Sasaki, Nicholas Short, Ghayas Issa, Maro Ohanian, Elias Jabbour, Guillermo Montalban-Bravo, Abhishek Maiti, Nitin Jain, Alessandra Ferrajoli, Kapil Bhalla, Koichi Takahashi, Caitlin R. Rausch, Danielle Hammond, Rashmi Malla, Kelly Quagliato, Mark Brandt, Uday Popat, Marina Konopleva, Guillermo Garcia-Manero, Farhad Ravandi, and Tapan M. Kadia

Patient Selection

- Previously untreated AML.
  - Hydroxyurea, hematopoietic growth factors, ATRA, or a total dose of cytarabine up to 2g (for emergency use for stabilization) is allowed.
- Age **≥ 60 years**. Patients aged < 60 years who are unsuitable for standard induction therapy may be eligible (*1 patient <60 years was enrolled, 57 years old*)
- Adequate organ function (bilirubin < 2mg/dL, AST and/or ALT <3 x ULN and creatinine < 1.5 x ULN)
- ECOG performance status of ≤ 2.
- No prior therapy with venetoclax
- Patients with acute promyelocytic leukemia were excluded

Treatment Schema



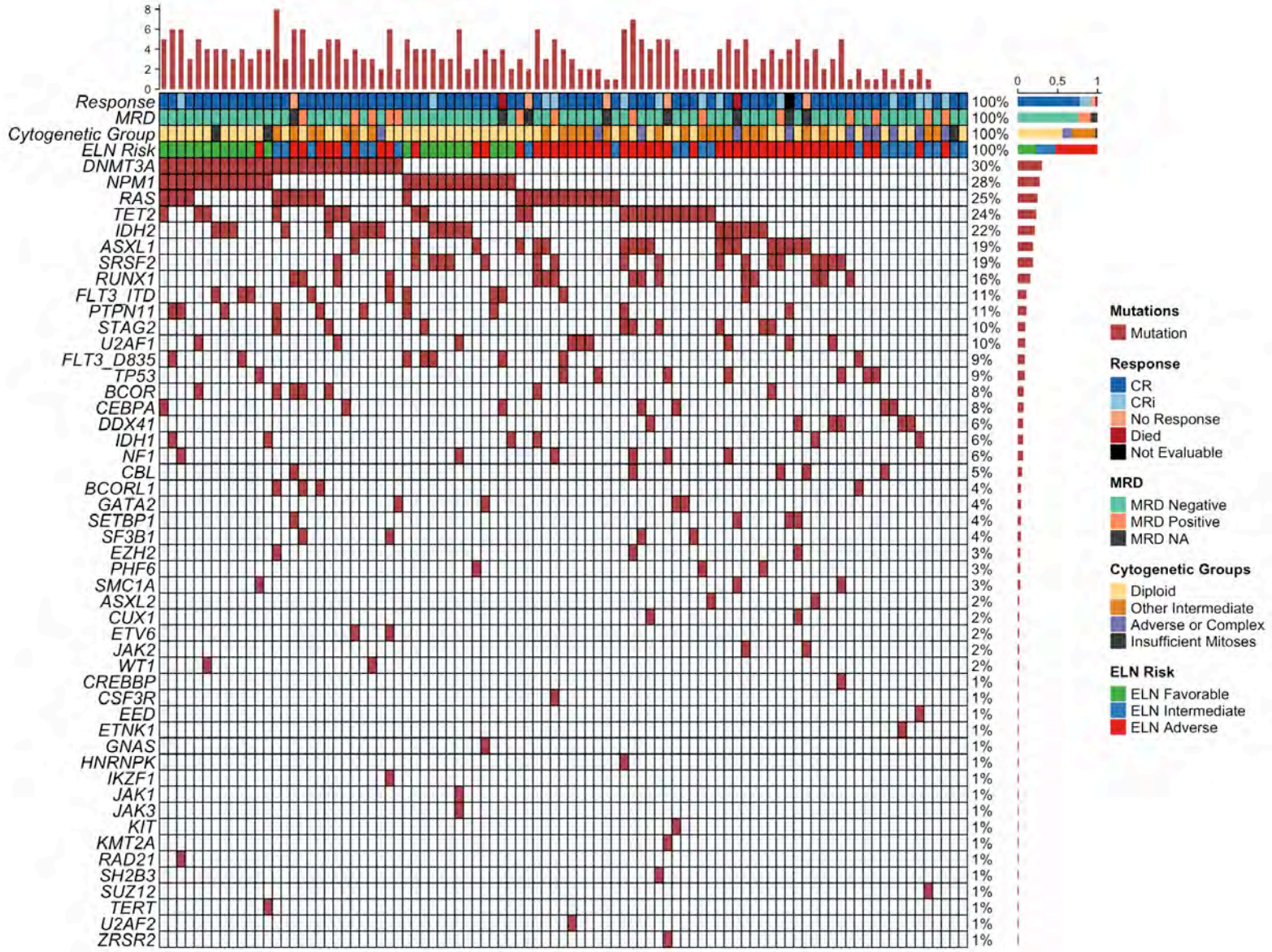
	Suggested Ramp Up for Venetoclax			
	Day 1	Day 2	Day 3	Target Dose
Strong CYP3A4 Inhibitor	50mg	50 mg	100 mg	**100 mg**
Moderate CYP3A4 Inhibitor	50mg	100 mg	200 mg	**200 mg**
No CYP3A4 Inhibitor	100mg	200 mg	400 mg	**400 mg**

Venetoclax dosing:

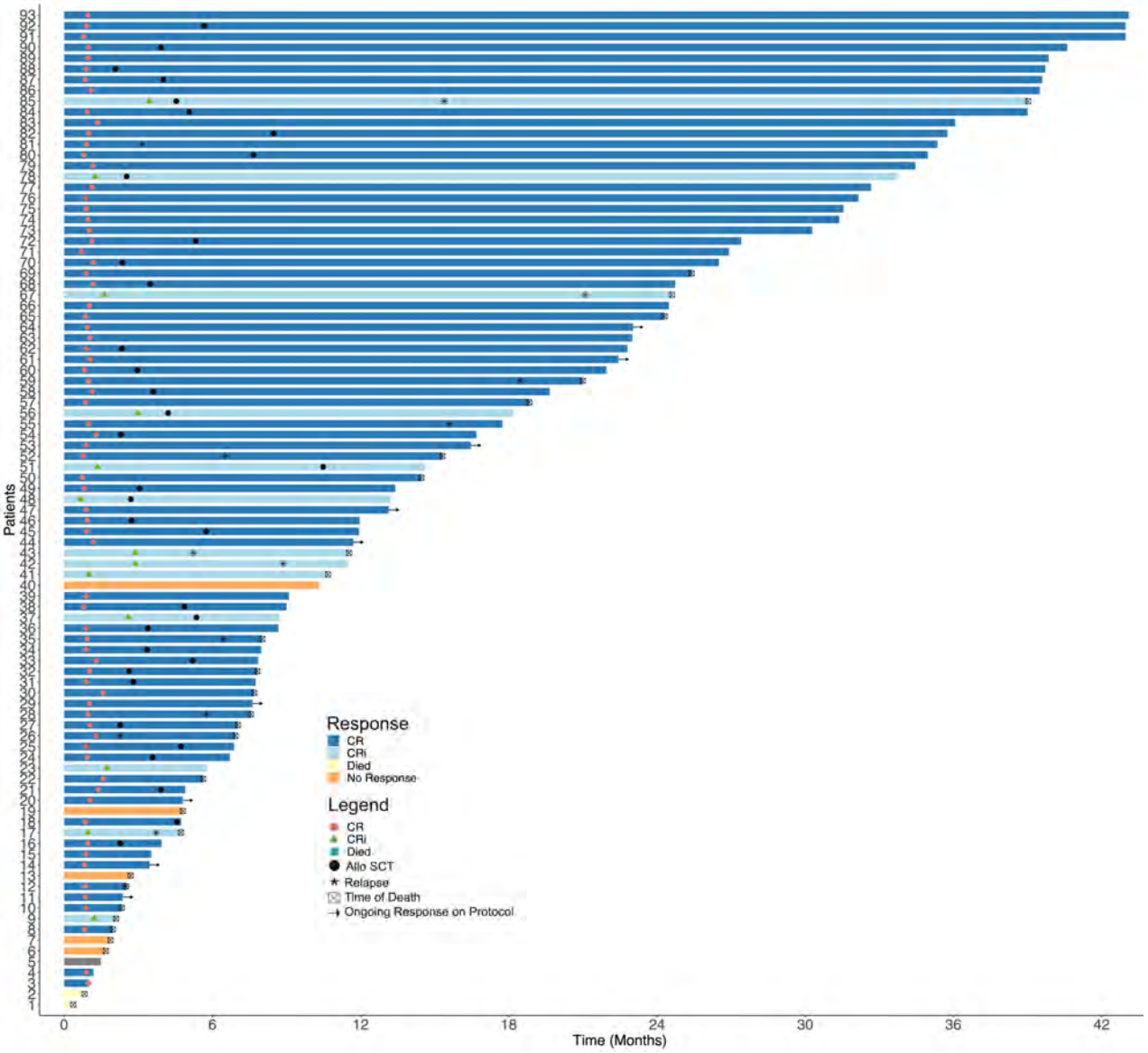
- Cycle 1: 21 days
- Cycle 2+: 7 – 14 days, based on MRD and tolerability

Baseline Characteristics

N = 93	N (%); Median [Range]
Age	**68 [57 – 84]**
Therapy Related AML	10 / 93 (11%)
Secondary AML	19 / 93 (20%)
Treated Secondary AML	4 / 93 (4.3%)
Cytogenetic Group	
Diploid	52 / 93 (56%)
Other Intermediate	27 / 93 (29%)
Complex/Adverse	11 / 93 (12%)
Insufficient Mitoses	3 / 93 (3.2%)
ELN Risk	
Favorable	22 / 93 (24%)
Intermediate	22 / 93 (24%)
Adverse	49 / 93 (53%)

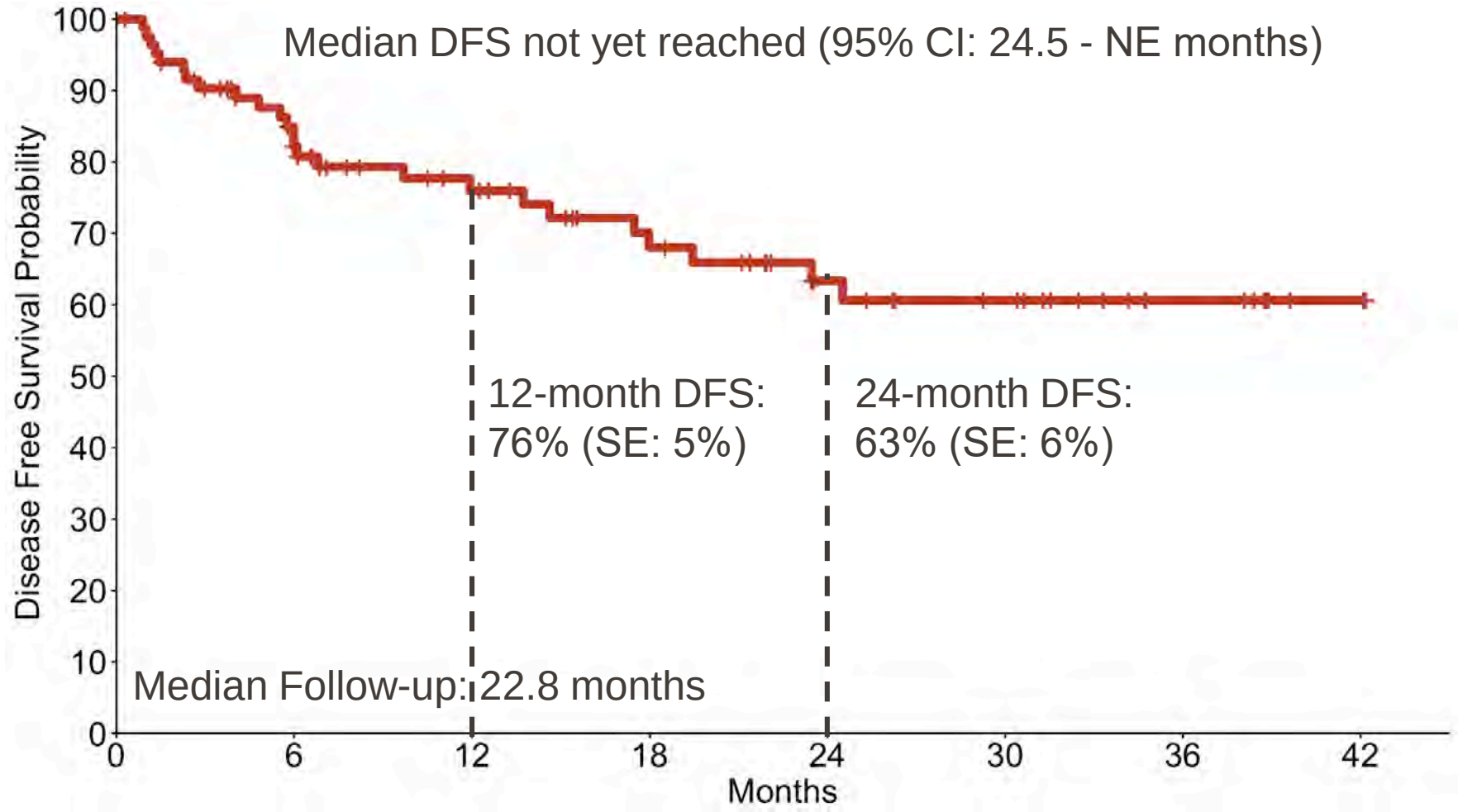


Response

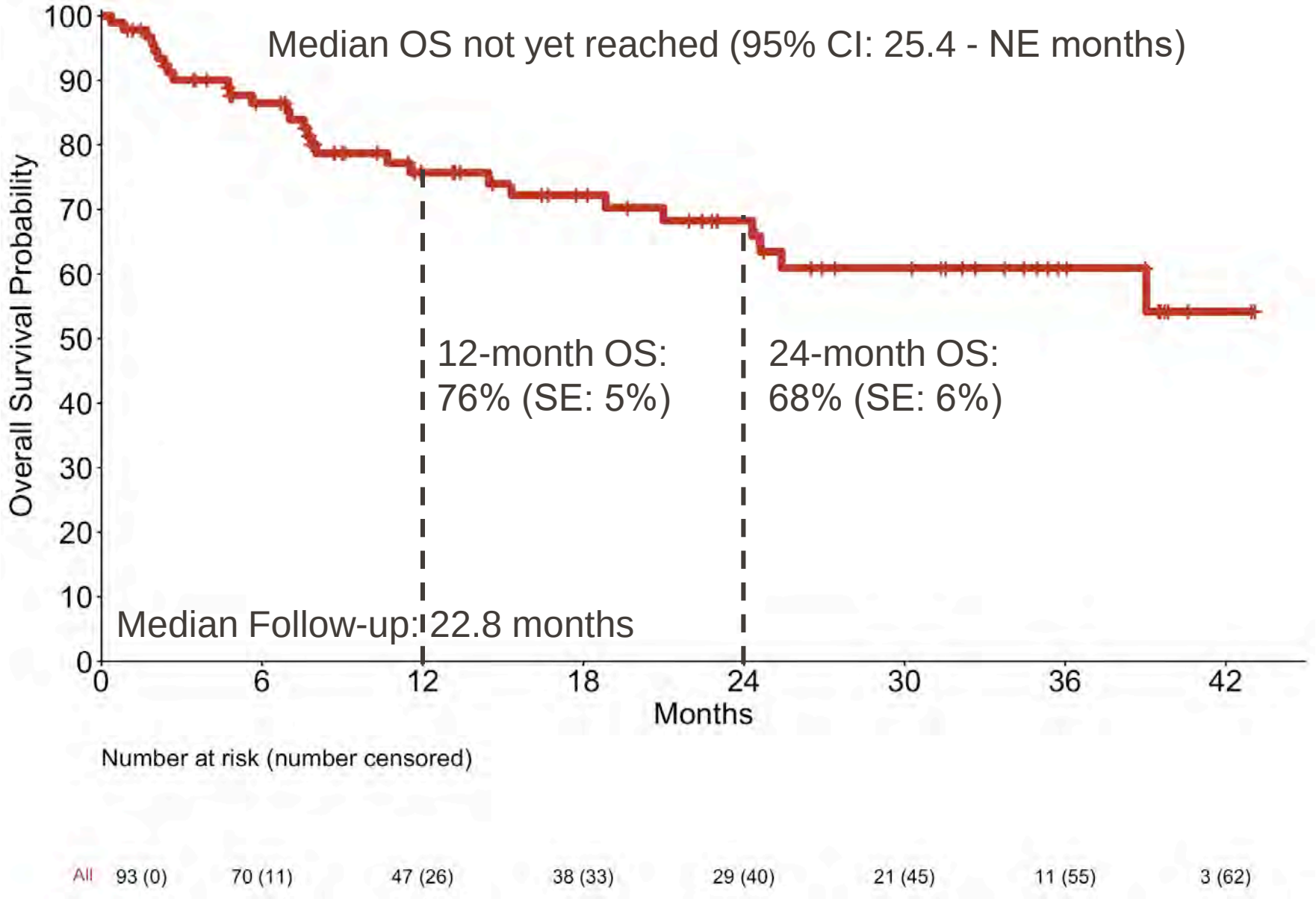


N = 93	N (%); Median [Range]
Composite CR Rate (CR+CRi)	**85 / 92 (92%)**
Best Response	
CR	**72 / 92 (78%)**
CRi	**13 / 92 (14%)**
NR	5 / 92 (5.4%)
Died	2 / 92 (2.2%)
MRD Negative at Response Assessment (by flow)	66 / 81 (81%)
MRD Negative on Study (by flow)	71 / 85 (**84%**)
Total Number of Course Given, Median (IQR)	3 [1 – 18]
Responders that Received alloSCT	35 / 85 (41%)
Mortality Rate at 4 Weeks	2 / 93 (2.2%)
Mortality Rate at 8 Weeks	5 / 93 (5.4%)

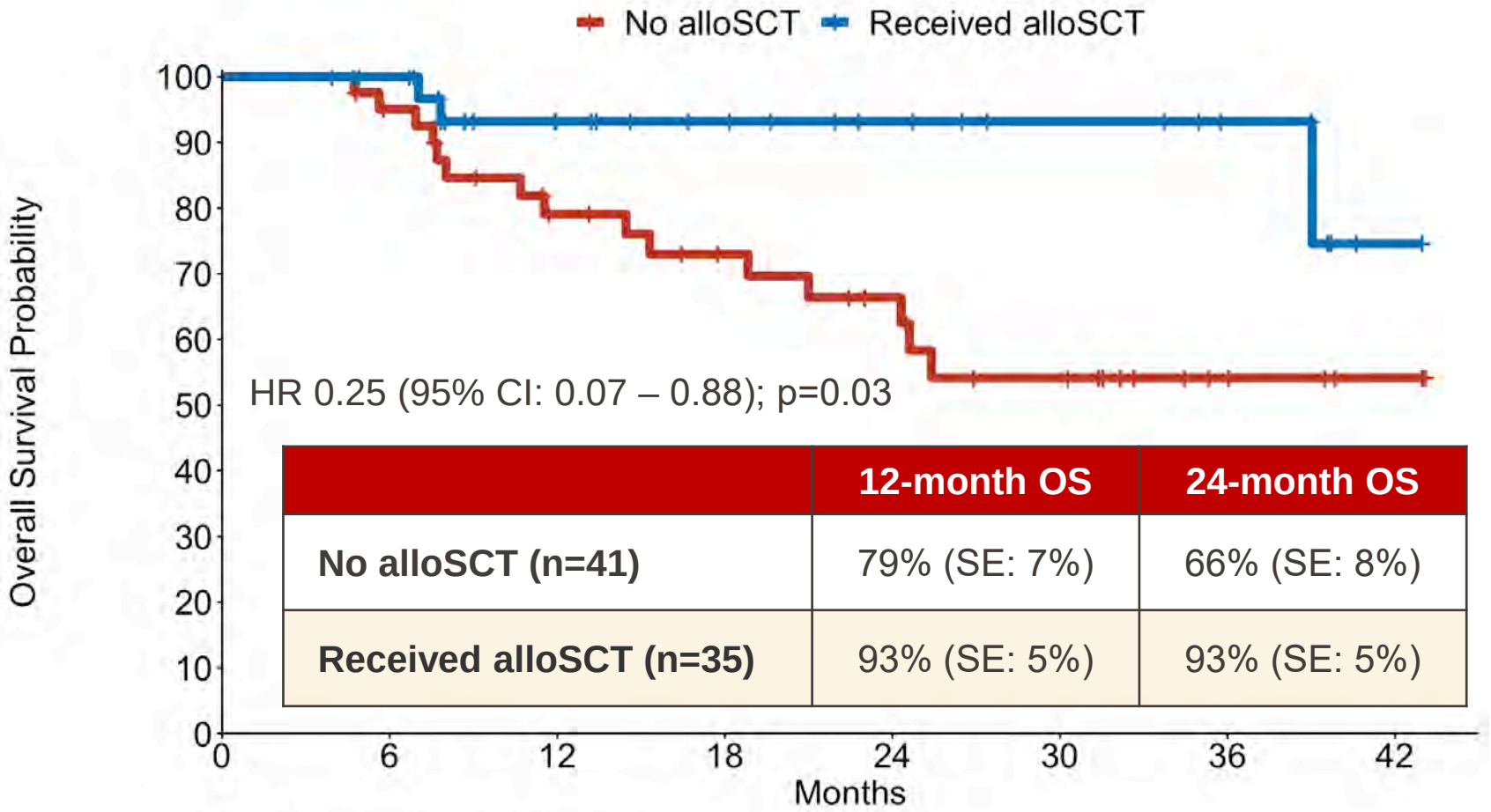
Disease-Free Survival



Overall Survival

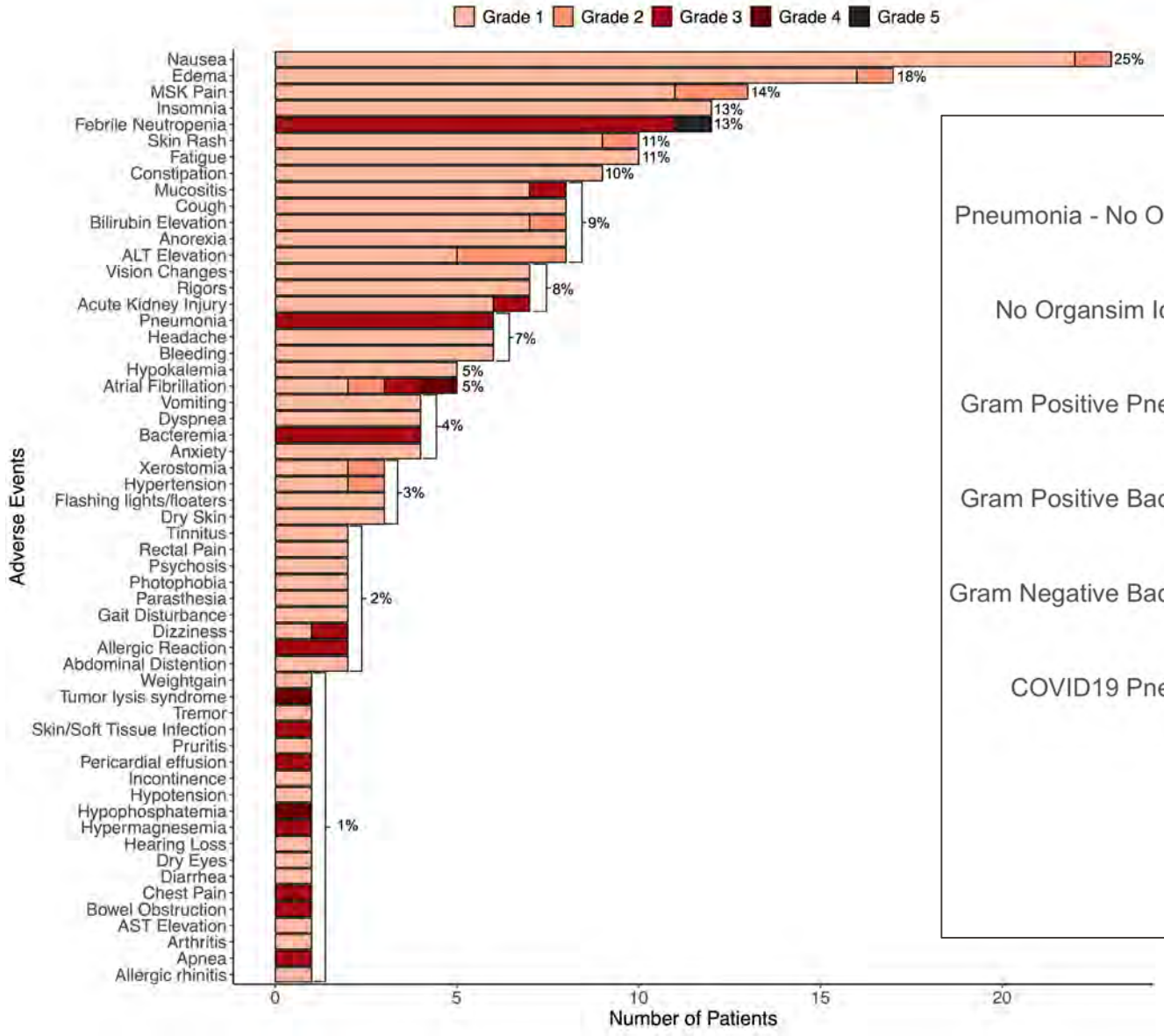


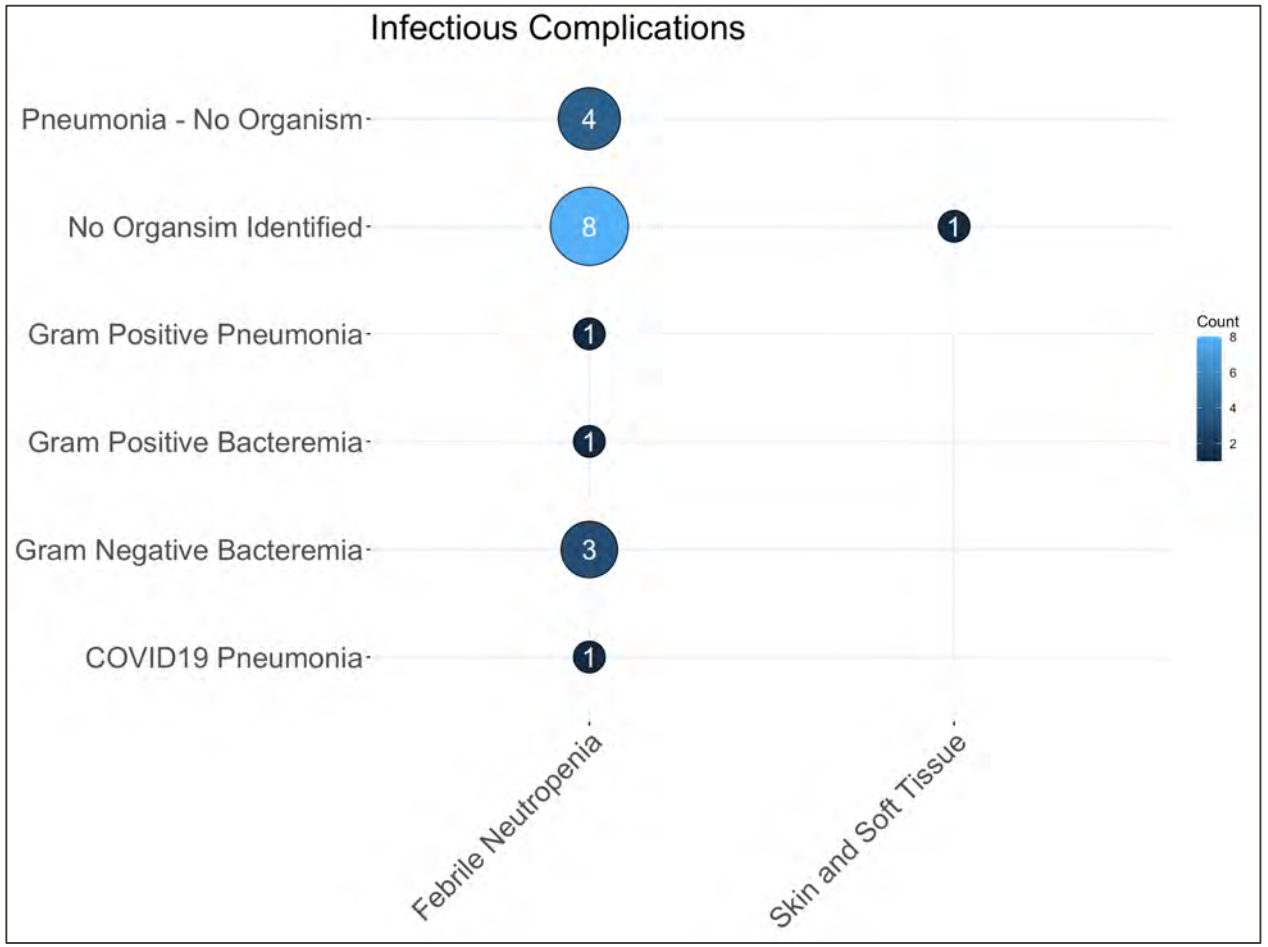
OS by Receipt of SCT



	12-month OS	24-month OS
No alloSCT (n=41)	79% (SE: 7%)	66% (SE: 8%)
Received alloSCT (n=35)	93% (SE: 5%)	93% (SE: 5%)

Adverse Events





American Society of Hematology
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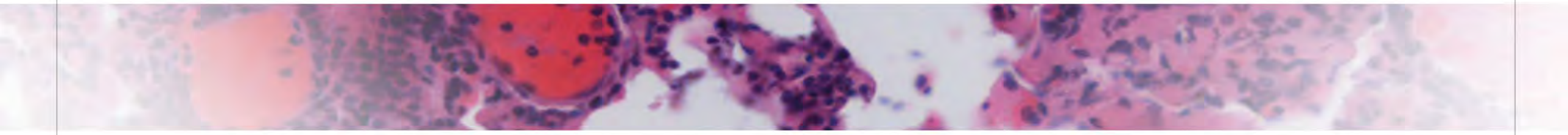


The Menin Inhibitor Revumenib (SNDX-5613) Leads to Durable Responses in Patients with *KMT2A*-Rearranged or *NPM1* Mutant AML: Updated Results of a Phase 1 Study

Ghayas C. Issa, MD,[1] Ibrahim Aldoss, MD,[2] John F. DiPersio, MD, PhD,[3] Branko Cuglievan, MD,[1] Richard M. Stone, MD,[4] Martha L. Arellano, MD,[5] Michael Thirman, MD,[6] Manish R. Patel, MD,[7] David Dickens, MD,[8] Shalini Shenoy, MD,[3] Neerav Shukla, MD,[9] Galit Rosen, MD,[10] Rebecca G. Bagley, MA,[10] Michael L. Meyers, MD, PhD,[10] Kate Madigan, MD,[10] Peter Ordentlich, PhD,[10] Yu Gu, PhD,[10] Steven Smith, BS,[10] Gerard M. McGeehan, PhD,[10] and Eytan M. Stein, MD[9]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]City of Hope, Duarte, CA; [3]Washington University School of Medicine, St. Louis, MO; [4]Dana-Farber Cancer Institute, Boston, MA; [5]Emory University School of Medicine, Atlanta, GA; [6]University of Chicago, Chicago, IL; [7]Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL; [8]University of Iowa, Iowa City, IA; [9]Memorial Sloan Kettering Cancer Center, New York, NY; [10]Syndax Pharmaceuticals, Inc., Waltham, MA

AUGMENT-101 patients are heavily pretreated with a poor prognosis

Baseline Characteristics	Safety Population N=68
Median age, years (range)	42.5 (0.8, 79)
Adult (n=60)	50.5
Pediatric (n=8)	2.5
Female, n (%)	42 (62)
Leukemia type, n (%)	
AML	56 (82)
ALL	11 (16)
MPAL	1 (2)
Median prior therapies (range)	4 (1,12)
Stem cell transplant, n (%)	31 (46)
Venetoclax, n (%)	41 (60)

Baseline Characteristics	Safety Population N=68
***KMT2Ar*, n (%)**	46 (68)
t(9;11)	10 (15)
t(11;19)	9 (13)
t(4;11)	6 (9)
t(6;11)	3 (4)
t(11;17)	2 (3)
Other	16 (24)
***mNPM1*, n (%)**	14 (21)
***KMT2A* and *NPM1* wild type, n (%)**	8 (12)
Co-occurring mutations*, n (%)	
FLT3	14 (25)
RAS	12 (29)
TP53	4 (10)

*In patients for whom co-occurring mutation data were available.
MPAL, mixed-phenotype acute leukemia

Data cutoff: 31 March 2022

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

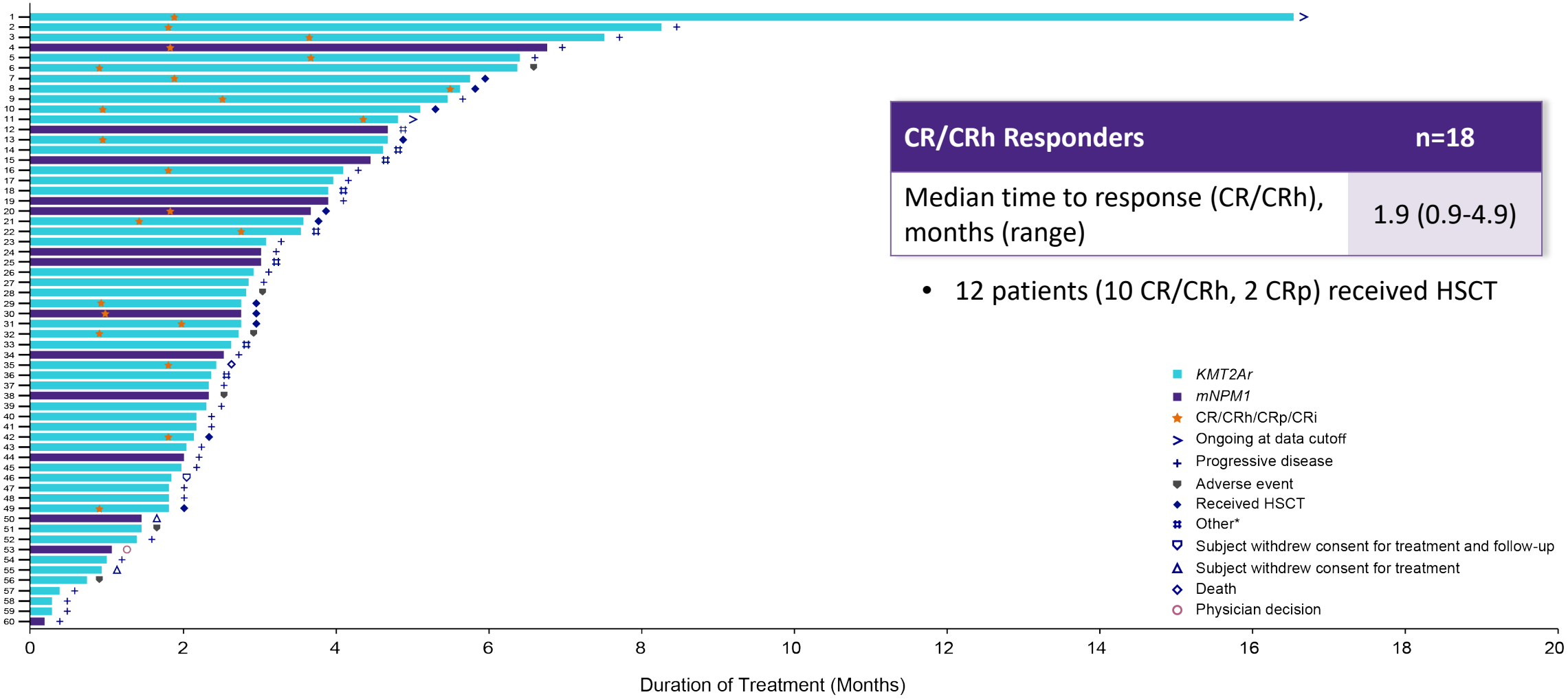
Best Response, n (%)	Efficacy Population n=60		Efficacy Population Doses Meeting Criteria for RP2D n=48	
ORR*	**32/60 (53%)**		**25/48 (52%)**	
Best Response				
CR	12 (20%)		8 (17%)	
CRh	6 (10%)		5 (10%)	
CRp	5 (8%)		5 (10%)	
MLFS	9 (15%)		7 (15%)	
MRD^{neg} rate†	**18/32 (56%)**		**14/25 (56%)**	
CR/CRh MRD^{neg}	14/18 (78%)		10/13 (77%)	
CR/CRh/CRp MRD^{neg}	18/23 (78%)		14/18 (78%)	
Genetic alteration	***KMT2Ar* n=46**	***mNPM1* n=14**	***KMT2Ar* n=37**	***mNPM1* n=11**
ORR	**27/46 (59%)**	**5/14 (36%)**	**20/37 (54%)**	**5/11 (46%)**
CR/CRh	15 (33%)	3 (21%)	10 (27%)	3 (27%)
CR/CRh MRD^{neg} rate	11/15 (73%)	3/3 (100%)	7/10 (70%)	3/3 (100%)

Data cutoff: 31 March 2022

*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.

Duration of revumenib therapy in patients with *KMT2Ar* or *mNPM1*



CR/CRh Responders	n=18
Median time to response (CR/CRh), months (range)	1.9 (0.9-4.9)

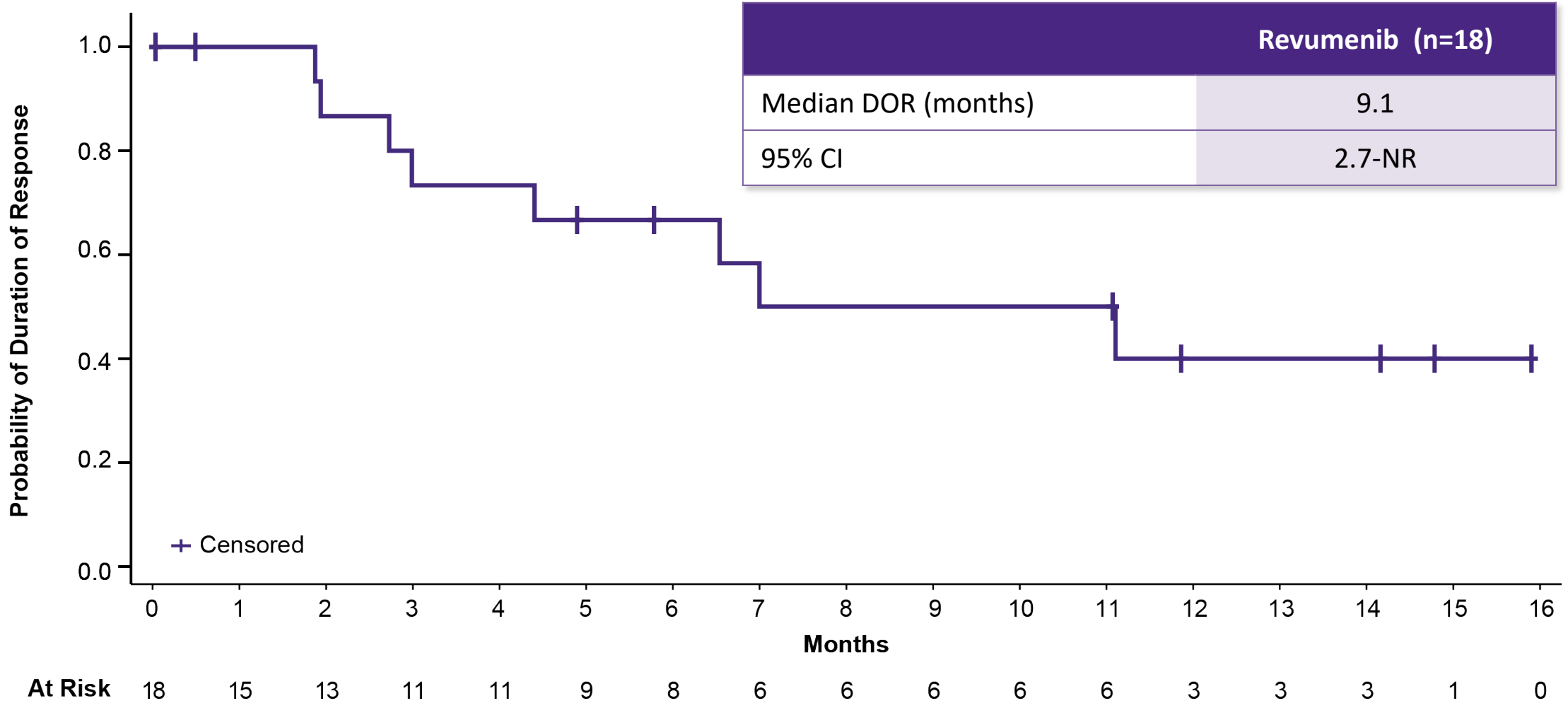
- 12 patients (10 CR/CRh, 2 CRp) received HSCT

*Other reasons for treatment discontinuation included no response, relapse, death, and donor lymphocyte infusion.

Data cutoff: 31 March 2022

Duration of CR/CRh response with revumenib treatment

	Revumenib (n=18)
Median DOR (months)	9.1
95% CI	2.7-NR

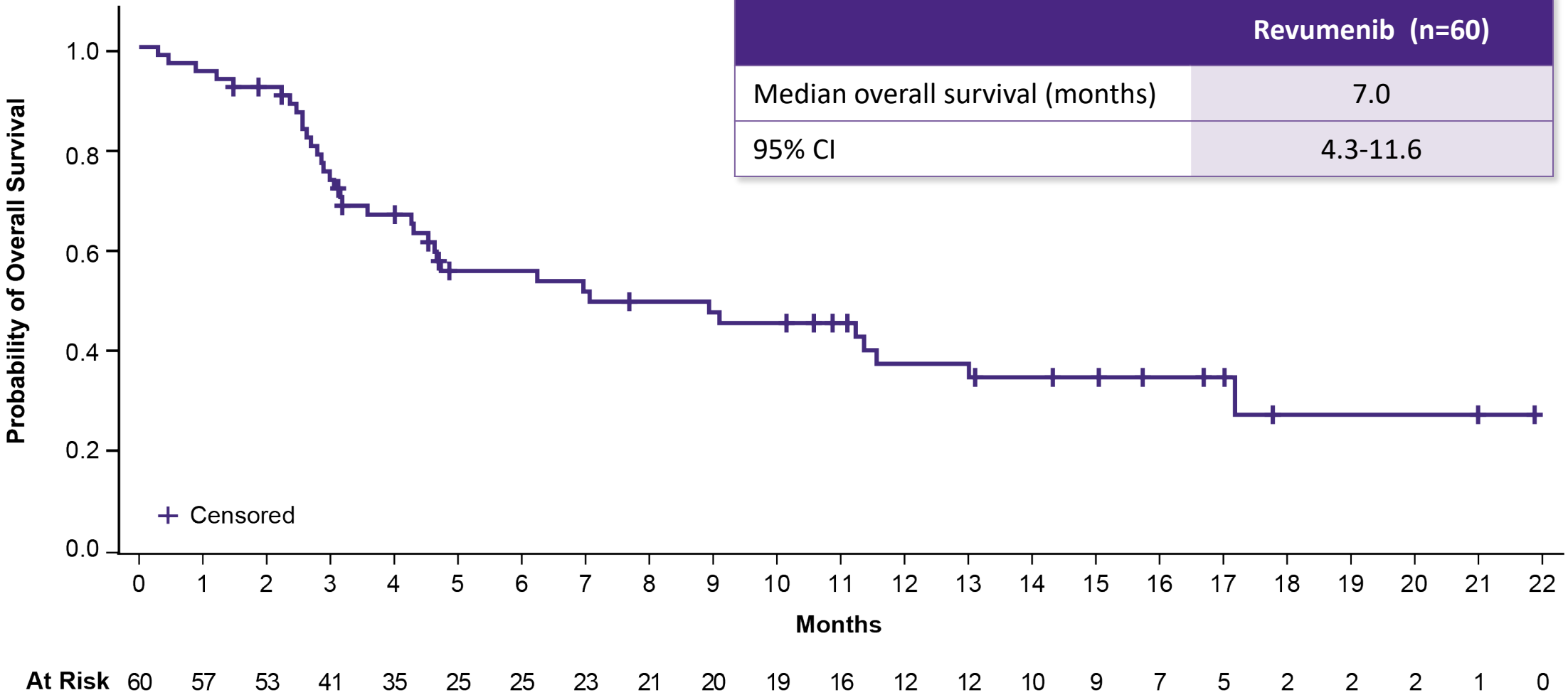


DOR, duration of response; NR, not reached.

Data cutoff: 31 March 2022

Overall survival in revumenib treated patients with *KMT2Ar* or *mNPM1*

	Revumenib (n=60)
Median overall survival (months)	7.0
95% CI	4.3-11.6



Data cutoff: 31 March 2022

Conclusions

- Revumenib resulted in deep, durable responses in heavily pre-treated R/R *KMT2Ar* and *mNPM1* patients, and demonstrated a clinically manageable safety profile
- 30% of patients attained CR/CRh with a median duration of 9.1 months
  - 78% of patients with CR/CRh attained MRD negativity
- 38% of responders proceeded to transplant
- Median OS was 7 months in this R/R population
- The only DLT, and the only common (≥5%) ≥Grade 3 related TEAE, was asymptomatic Grade 3 QTc prolongation
  - 10% in patients treated at doses meeting criteria for RP2D; 13% in patients treated at all doses tested
- Differentiation syndrome occurred in 16% of patients
  - All cases were Grade 2 and responded to management with steroids with or without hydroxyurea

AUGMENT-101 Phase 2 pivotal trials underway in 3 distinct patient populations

AUGMENT-101

R/R
KMT2Ar (MLLr)
or *mNPM1*
acute leukemia

Dose:
Revumenib 163 mg q12h
with a strong CYP3A4 inhibitor

Independent, pivotal trials

64 adults + up to 20 peds	**AUGMENT-101-2A: *KMT2Ar* ALL**
64 adults + up to 20 peds	**AUGMENT-101-2B: *KMT2Ar* AML**
64 adults + up to 20 peds	**AUGMENT-101-2C: *mNPM1* AML**

Primary objective: CR/CRh*
Secondary objectives: Durability of CR/CRh, OS, transfusion independence

*Patients taken to HSCT can restart treatment with revumenib post-transplant.

Conclusion

Thank you!!!

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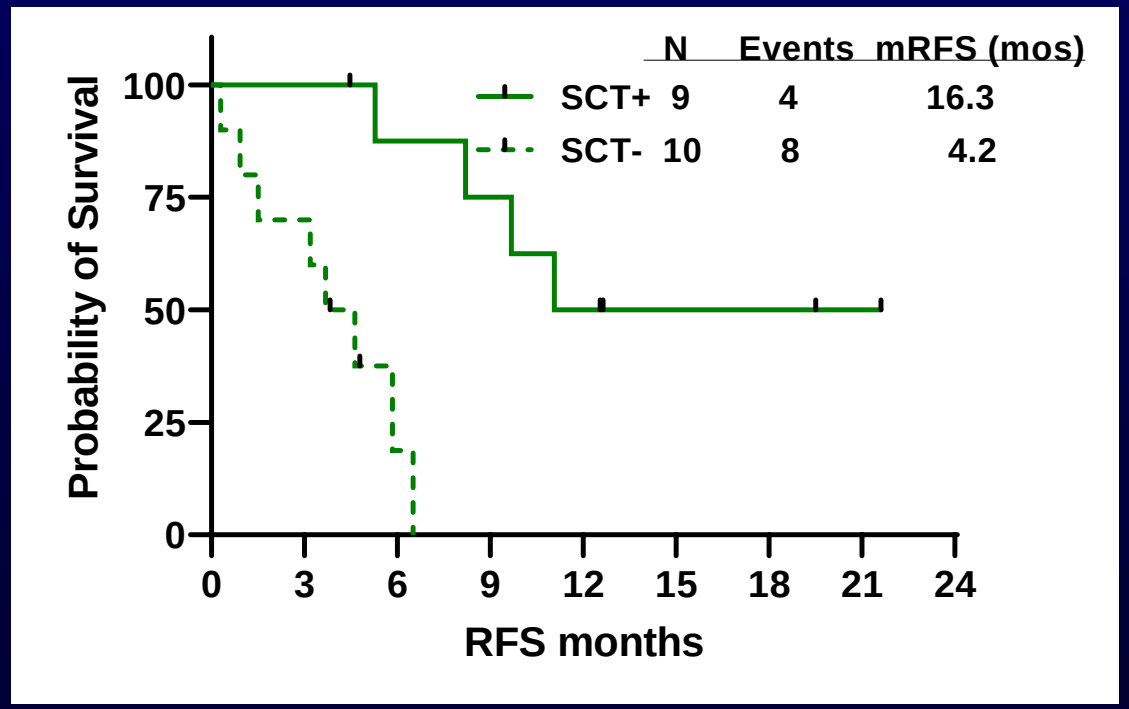
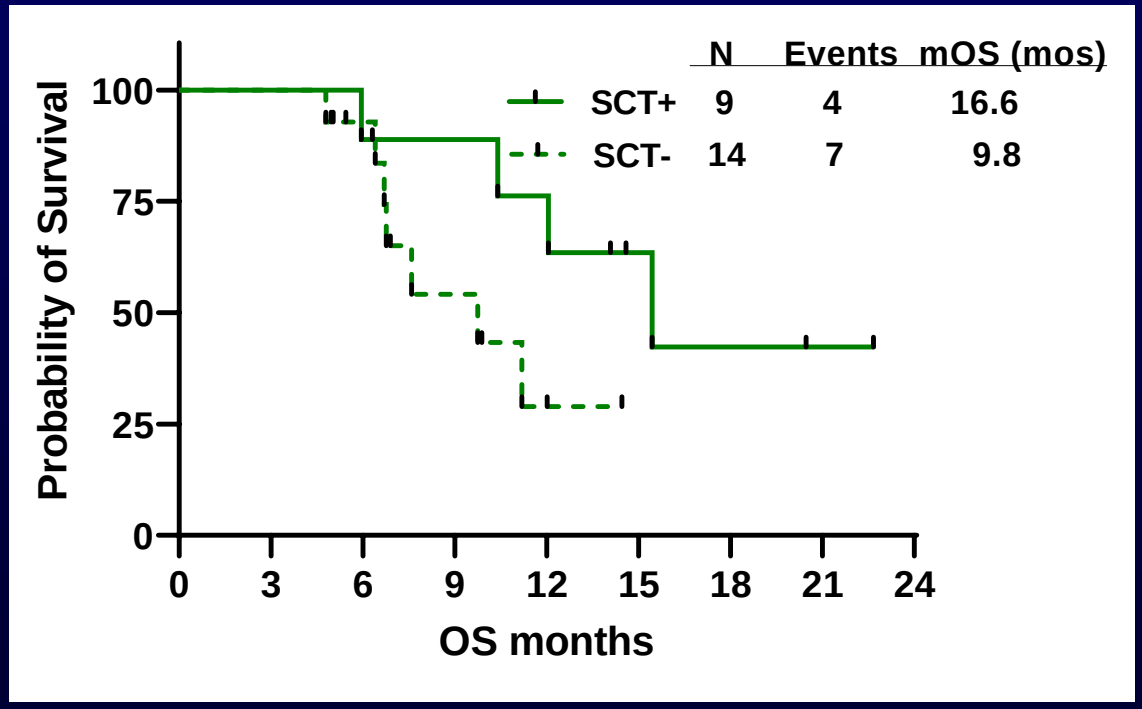
Results: Impact of SCT in the frontline setting in *TP53*^{mut} patients

No. of *TP53*^{mut} patients transplanted	9 (8 denovo+ 1 secondary untreated)
Age of the SCT patients	64 years (range, 46-69 years)
Median time to SCT from trial therapy initiation	4.3 months (range, 2.6-5.8 months)
Median cycles on therapy to SCT	3 (range, 2-4 cycles)
Disease status at SCT *	CR=7; CRi=2; MRD-ve=5





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)