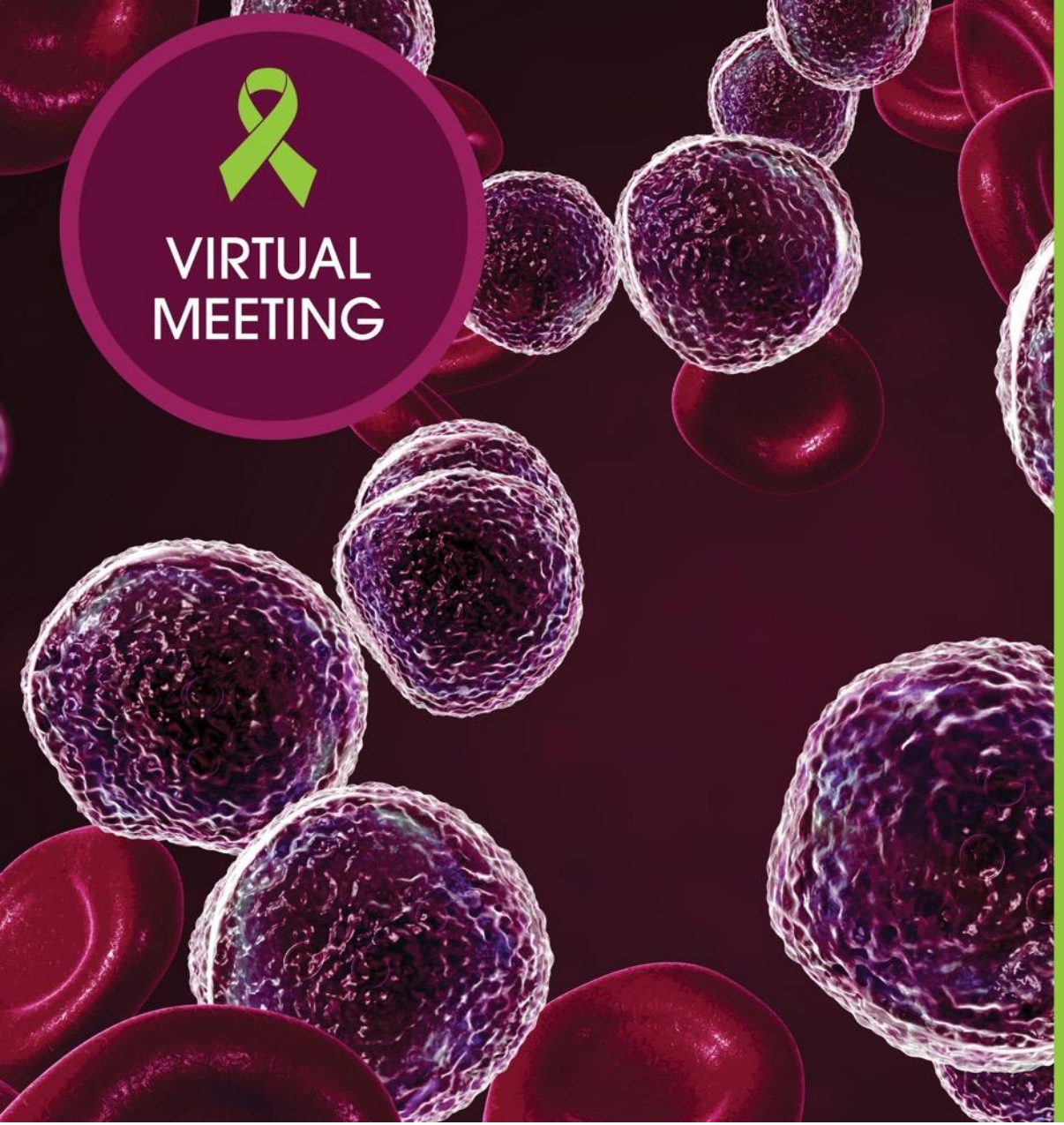
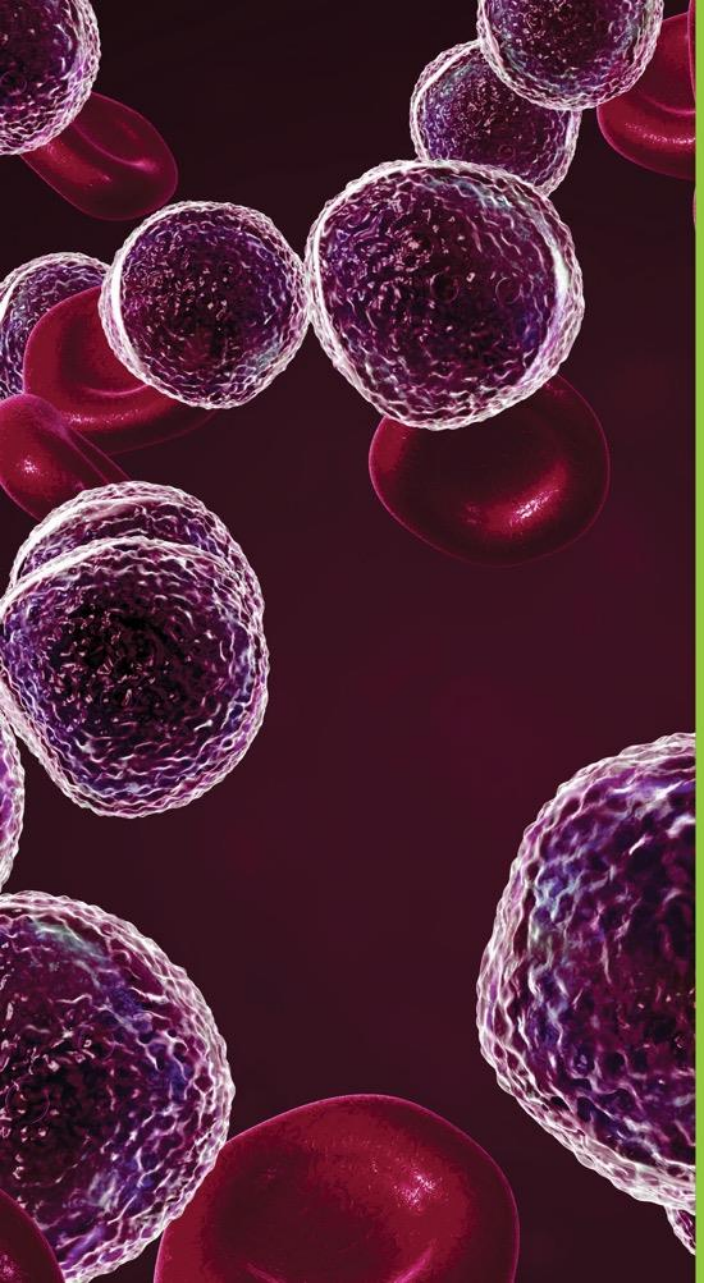


BEYOND THE CONGRESS

Key Conversations from the 2021 Hematology Annual Meeting™

FRIDAY, FEBRUARY 4, 2022

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



Hot Topics in the Management of AML

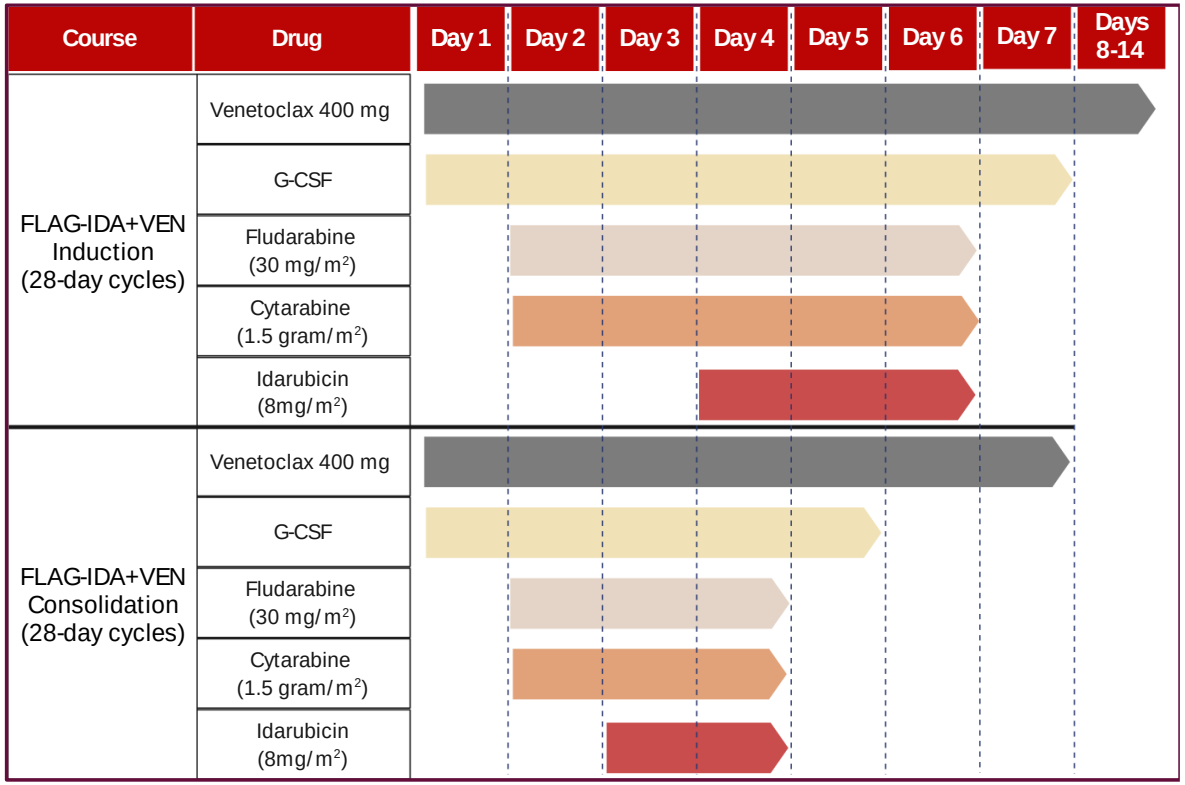
Eunice Wang MD
Roswell Park Comprehensive Cancer Center, Buffalo, NY

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

Hot Topics in the Management of AML

- Does Ven improve intensive chemotherapy?
- What is the best therapy for p53 mutant AML?
- Who should get oral azacitidine maintenance?

Phase 1b/2 trial of Venetoclax + FLAG-IDA



G-CSF: 5 mcg/kg the day prior to and days of IV chemotherapy followed by 1 dose of pegfilgrastim or biosimilar the day following chemotherapy each 28 D cycle

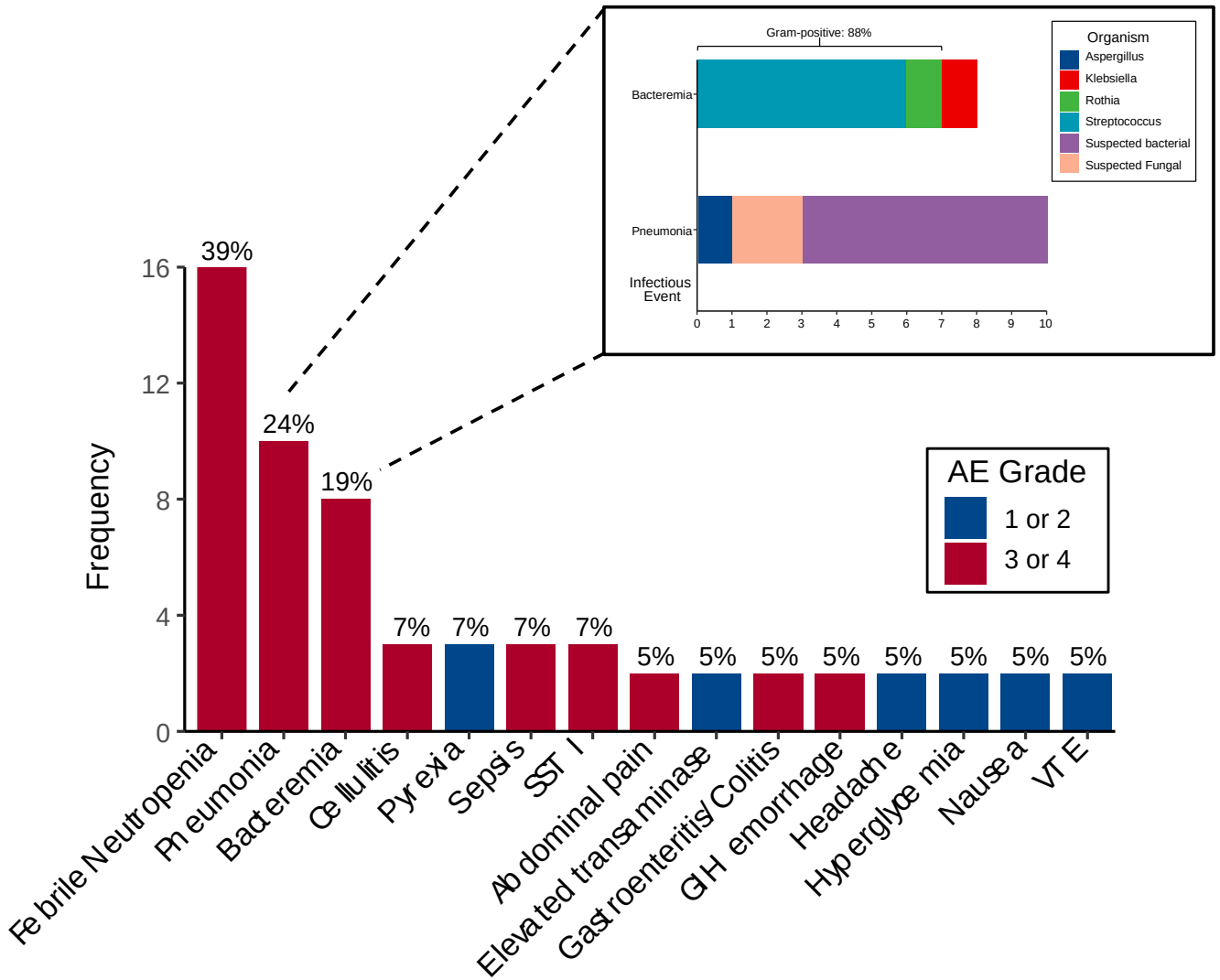
Consolidation: Idarubicin permitted on days 3 and 4 in 2 post-remission cycles (ie. C2 or C3 and C5 or C6) at physician discretion

Patient demographics

Demographic*	N=45
Age, years median (range)	44 (20-65)
Sex, male N(%)	20 (44)
Median blast % at enrollment	46 (4-85)**
AML Type	
De Novo AML	33 (73)
Secondary AML (sAML)	7 (16)
Therapy-related AML (tAML)	5 (11)
Treated sAML/tAML	6 (13)
ELN Risk Group	
Favorable	8 (18)
Intermediate	18 (40)
Adverse	19 (42)
Cytogenetics	
Intermediate risk	32 (71)
Diploid	19
Other intermediate risk	12
KMT2A-rearranged	1
Adverse risk/Complex	12 (27)
Complex karyotype	5
del(7)	1
inv(3)	2
KMT2A-rearranged	4
Insufficient mitoses	1 (2)

Lachowiez CA et al 2021 ASH abstract 701

Phase 1b/2 Ven + FLAG-IDA: Adverse Events



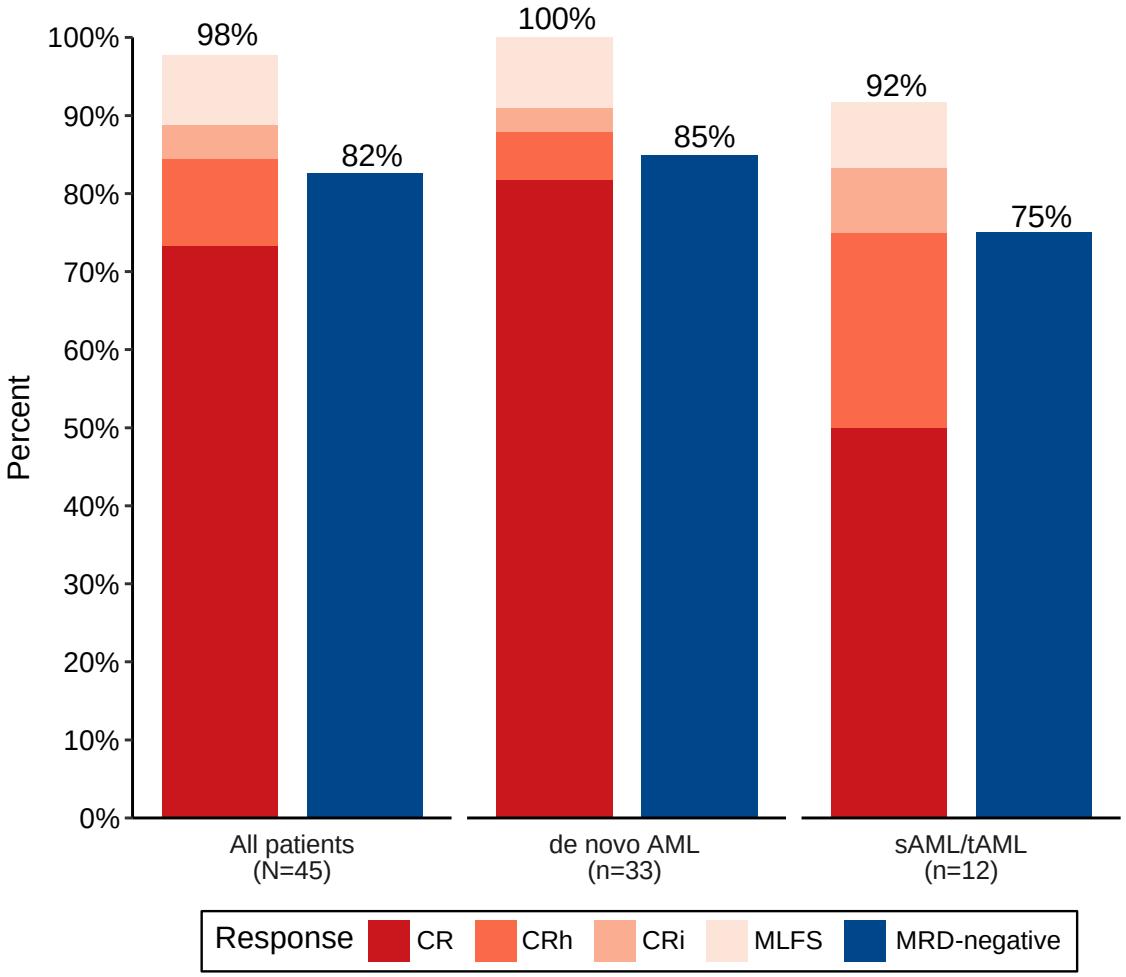
Adverse Event	Total N (%)	Grade 1/2	Grade 3	Grade 4
Febrile Neutropenia	**16 (39%)**	-	16	-
Pneumonia	**10 (24%)**	-	10	-
Bacteremia	**8 (19%)**	-	8	-
Cellulitis	**3 (7%)**	-	3	
Pyrexia	**3 (7%)**	3	-	-
Sepsis	**3 (7%)**	-	-	3
SSTI*	**3 (7%)**	-	3	-
Abdominal pain	**2 (5%)**	-	3	-
Elevated LFT	**2 (5%)**	2	-	-
Gastroenteritis/ Colitis	**2 (5%)**	-	2	-
GI Hemorrhage	**2 (5%)**	-	-	2
Headache	**2 (5%)**	2	-	-
Hyperglycemia	**2 (5%)**	2	-	-
Nausea	**2 (5%)**	2	-	-
VTE	**2 (5%)**	2	-	-

Lachowiez CA et al 2021 ASH abstract 701

Phase 1b/2 Ven + FLAG-IDA: Response Rates

Demographic Median (range)/ N (%)	All (N=45)	De novo AML (n=33)	sAML/tAML (n=12)	*P-value*
Overall Response Rate	44 (98%)	33 (100%)	11 (92%)	0.26
Composite CR	**40 (89%)**	**30 (91%)**	**10 (83%)**	1.0
Complete Response	33 (73%)	27 (82%)	6 (50%)	*0.06*
CRh	5 (11%)	2 (6%)	3 (25%)	-
CRi	2 (4%)	1 (3%)	1 (8%)	-
MRD-Negative CRc*	**37 (93%)**	**28 (93%)**	**9 (90%)**	1.0
MLFS	4 (9%)	3 (9%)	1 (8%)	-
NR/PD	1	-	1 (8%)	-

*Measured using multiparameter flow cytometry in evaluable patients with a sensitivity of 0.1-0.01%. Patients with unavailable or limited specimens were considered positive



MRD-negative rates calculated from total patient population

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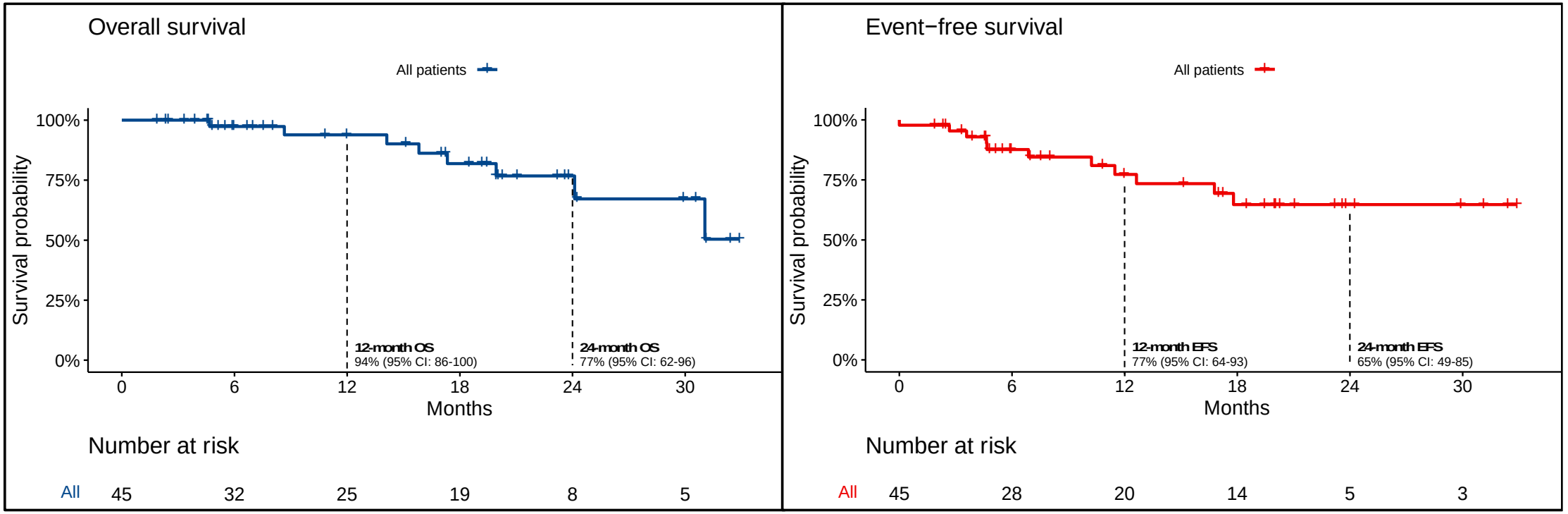
Phase 1b/2 Ven + FLAG-IDA: Adverse Events



Demographic Median (95% CI) or %(SE)	All patients (N=45)	De Novo AML (n=33)	sAML/tAML (n=12)
Median EFS, months	**NR (18-NR)**	**NR (13-NR)**	**NR (18-NR)**
12-Month EFS	77% (8)	72% (10)	83% (11)
24-Month EFS	65% (9)	65% (11)	62% (16)
Median OS	**NR (-)**	**NR (20-NR)**	**31.1 (24-NR)**
12-Month OS	94% (4)	96% (4)	92% (8)
24-Month OS	77% (9)	68% (11)	92% (8)
Median Follow Up, months	19 (11-23)	11 (6-23)	21 (19-NR)

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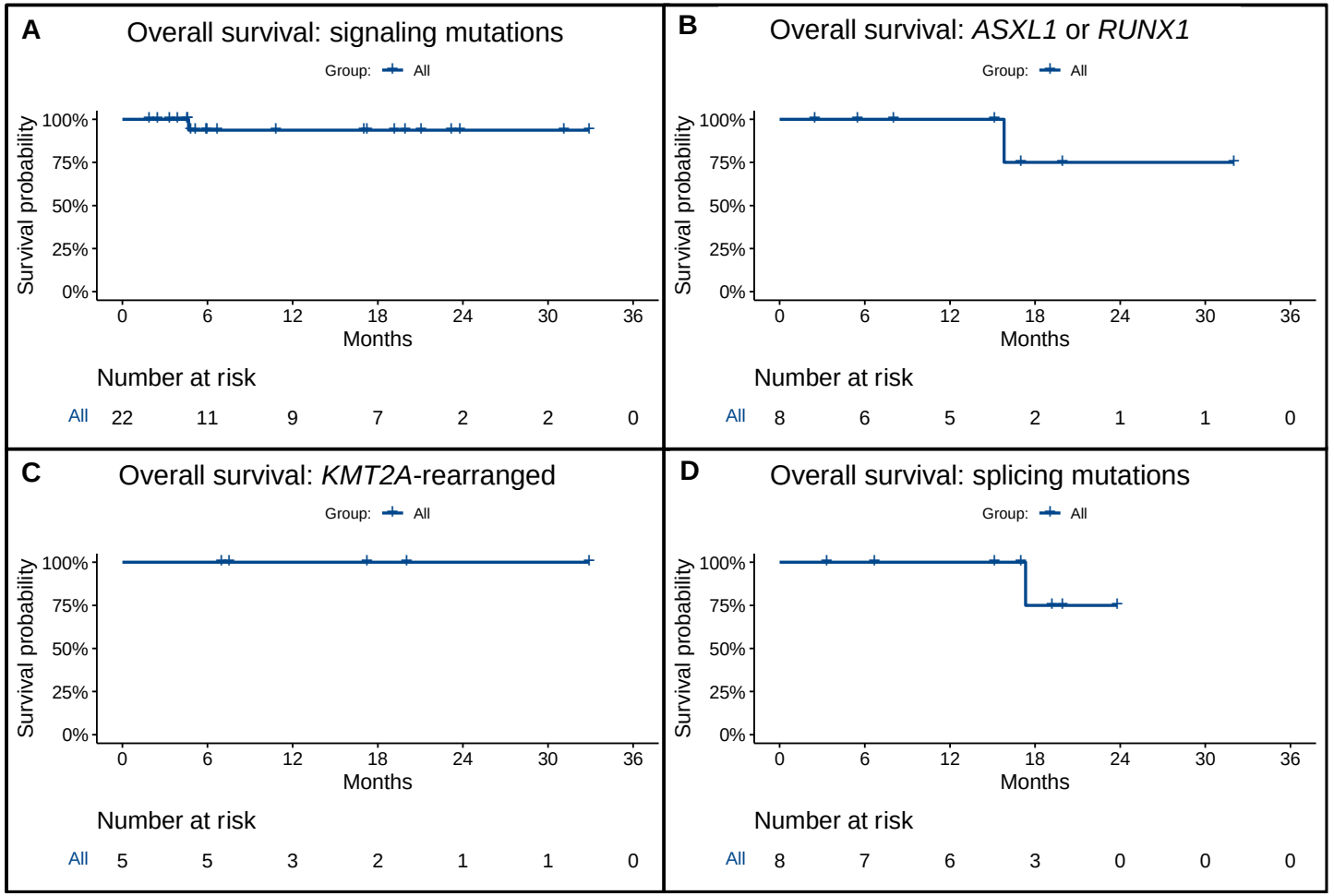
Phase 1b/2 Ven + FLAG-IDA: Adverse Events

FLAG-IDA+VEN associated with favorable outcomes in patients with signaling mutations (**A**) or poor risk cytogenetic/molecular features* (**B-D**)

Overall survival	12-month % (SE)	24-month % (SE)
Signaling mutations (*K/NRAS, PTPN11, FLT3*)	94% (6)	94% (6)
Mutated *ASXL1* or *RUNX1*	100% (-)	75% (22)
***KMT2A*-rearranged**	100% (-)	100% (-)
Splicing mutations (*SRSF2, SF3B1, U2AF1, ZRSR2*)	100% (-)	NA



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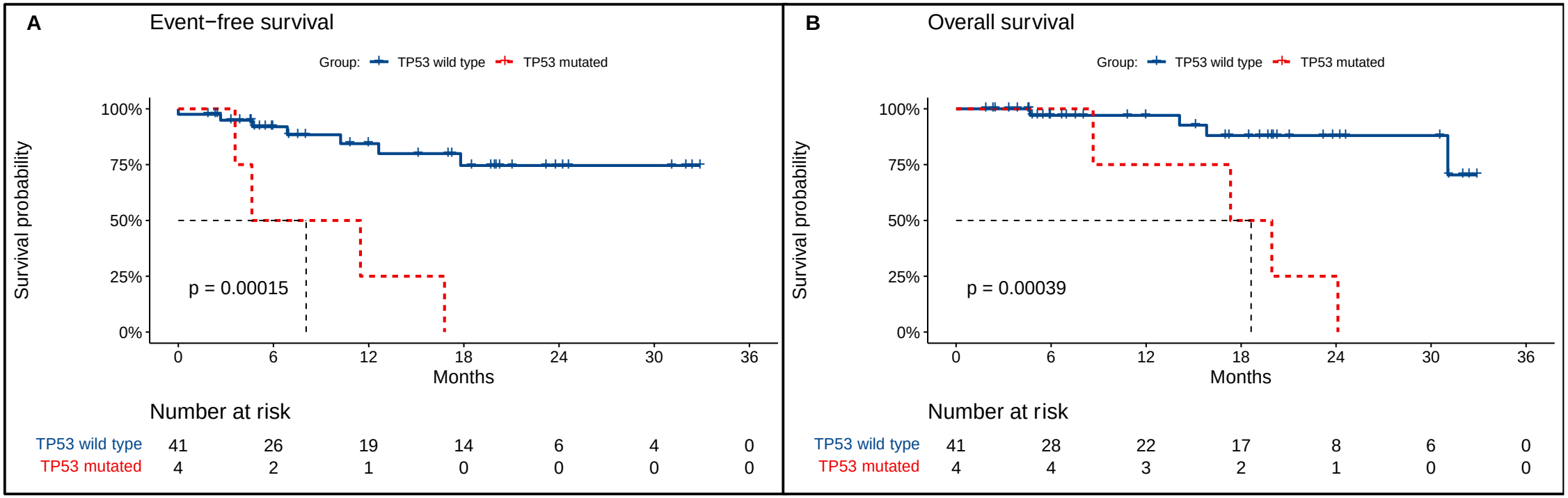
Phase 1b/2 Ven + FLAG-IDA: Adverse Events

TP53 mutations correlated with significantly inferior event-free (**A**) and overall (**B**) survival compared to *TP53* wild type patients



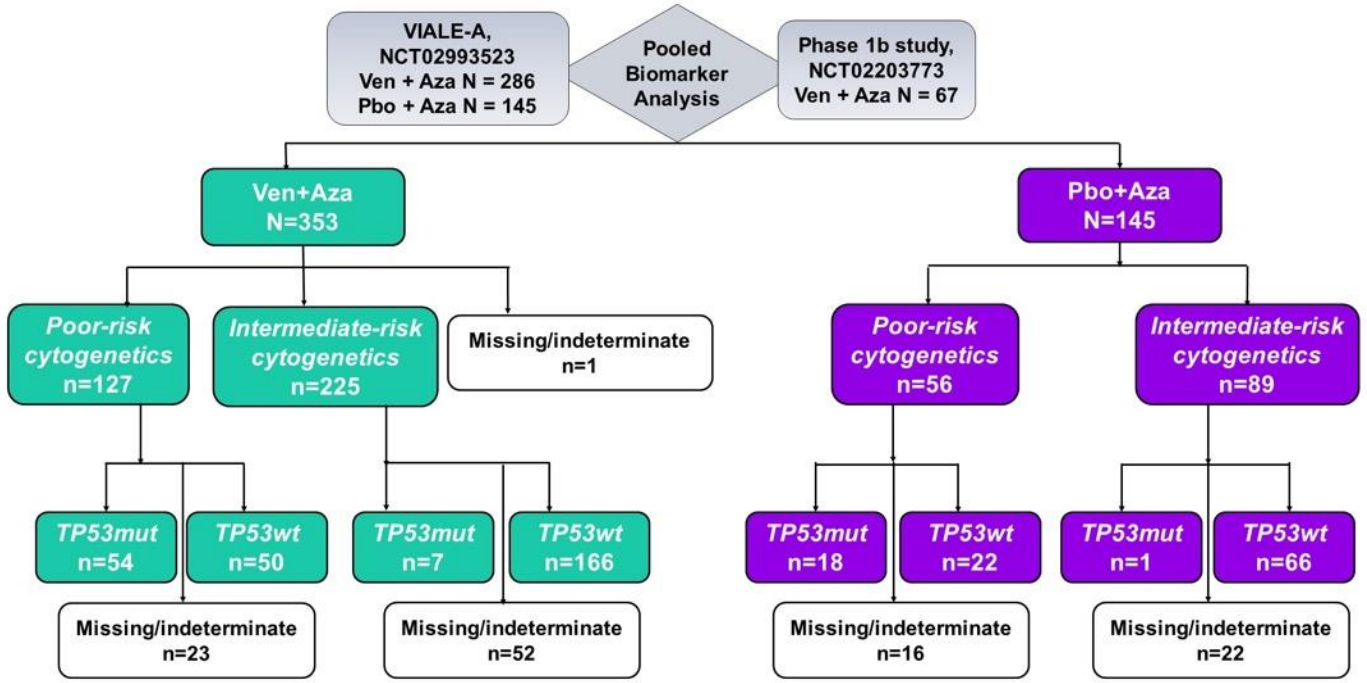
Variable Months (95% CI)	No *TP53* (N=40)	*TP53* (N=4)	*P-value*
Median event-free survival	NR (-)	8 (4-NR)	< *0.001*

Variable Months (95% CI)	No *TP53* (N=40)	*TP53* (N=4)	*P-value*
Median overall survival	NR (31-NR)	19 (9-NR)	< *0.001*

Lachowiez CA et al 2021 ASH abstract 701

Ven/Aza in AML with poor risk cytogenetics and p53 mutation

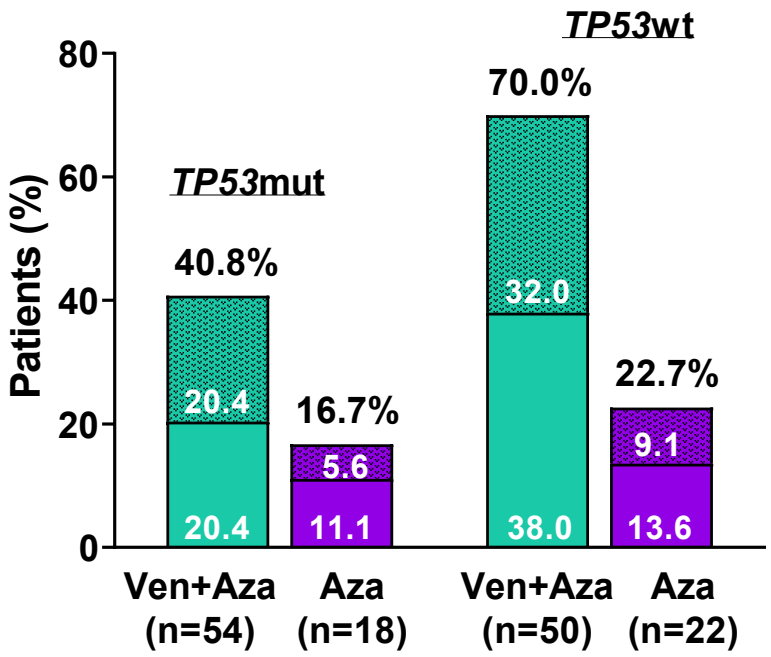
- Design
- Pooled analysis of patients enrolled in the randomized phase 3 VIALE-A trial (NCT02993523) and a prior phase 1b trial (NCT02203773) of Ven+Aza
- Treatment-naïve patients with AML who were unfit for intensive chemotherapy due to co-morbidities and/or age ≥ 75 years
- Analysis of mutations
- Cytogenetics analyzed locally from bone marrow/peripheral blood and categorized per National Comprehensive Cancer Network criteria
- Mutations from MyAML assay (central lab) from bone marrow aspirate at baseline



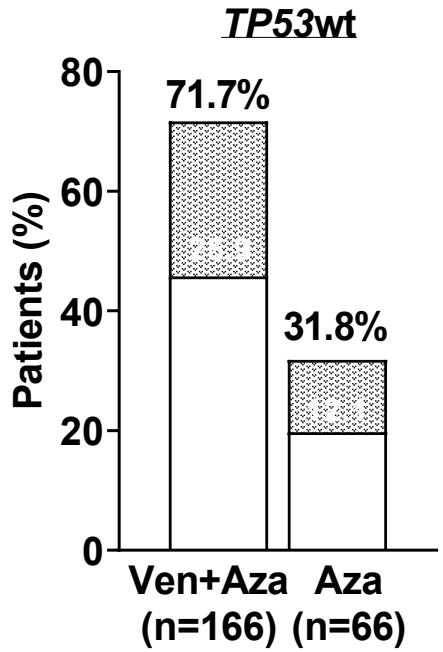
Pollyea et al 2021 ASH abstract

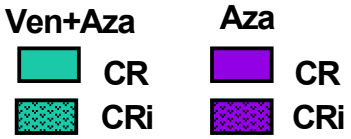
Remission rates of Ven/Aza by cytogenetics and p53 mutation

Poor-risk cytogenetics



Intermediate-risk cytogenetics

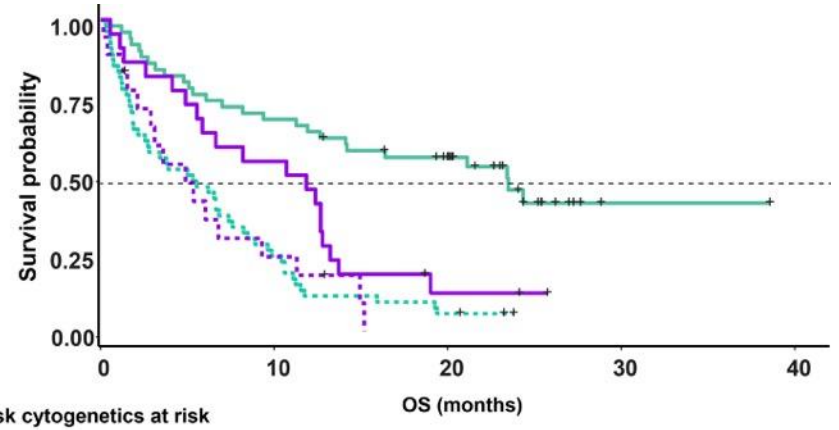




Pollyea et al 2021 ASH abstract

Overall survival of Ven/Aza by cytogenetics and p53 mutation

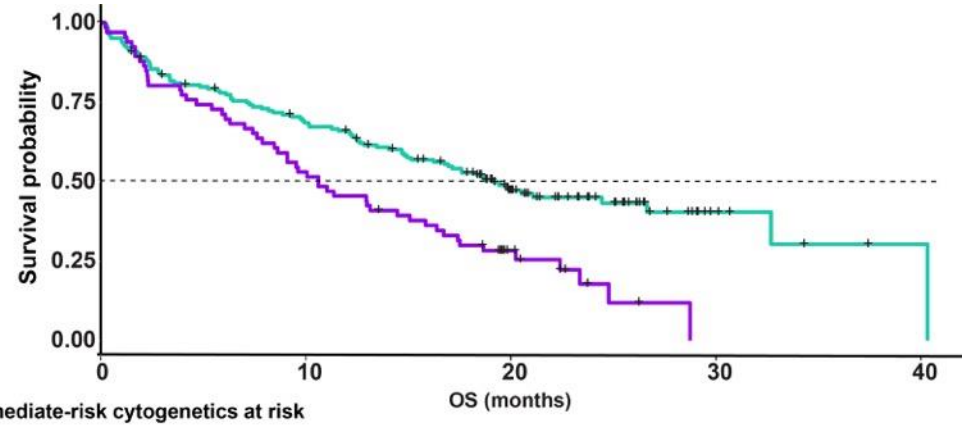
Poor-risk cytogenetics



Patients with poor-risk cytogenetics at risk

Ven+Aza, TP53wt	50	34	24	1	0
Ven+Aza, TP53mut	54	13	3	0	0
Aza, TP53wt	22	12	2	0	0
Aza, TP53mut	18	4	0	0	0

Intermediate-risk cytogenetics



Patients with intermediate-risk cytogenetics at risk

Ven+Aza, TP53wt	166	108	50	6	1
Aza, TP53wt	66	35	11	0	0

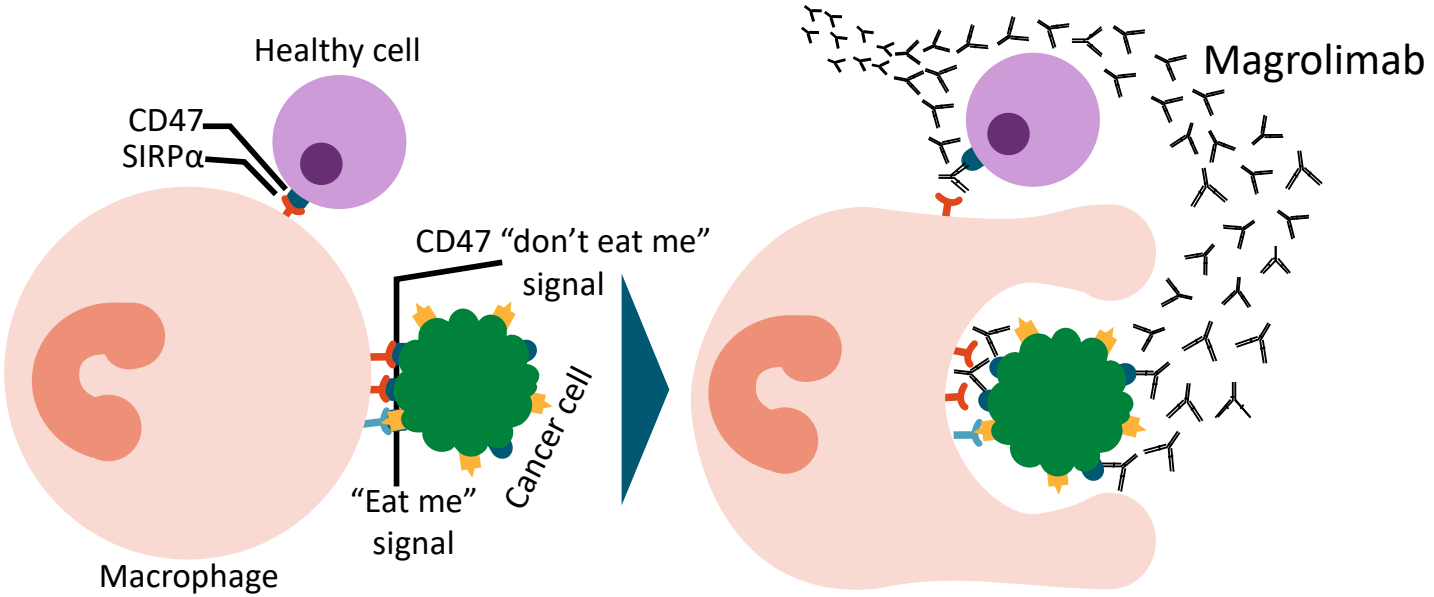
	Median OS, months (95% CI)
Ven+Aza *TP53* wt	23.43 (11.93 — NR)
Ven+Aza *TP53* mut	5.17 (2.17 — 6.83)
Aza *TP53* wt	11.29 (4.9 — 12.78)
Aza *TP53* mut	4.90 (2.14 — 9.30)

	Median OS, months (95% CI)
Ven+Aza *TP53* wt	19.15 (14.95 — 26.64)
Aza *TP53* wt	10.61 (7.89 — 15.08)

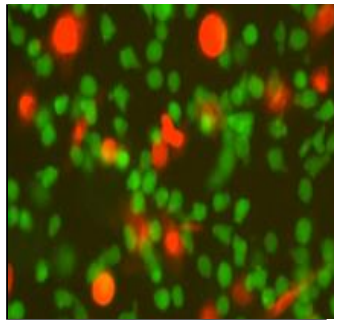
Pollyea et al ASH abstract 2021

Aza, azacitidine; CI, confidence interval; mut, mutation; wt, wild-type; OS, overall survival; Ven, venetoclax

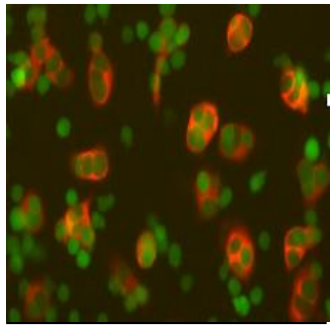
Phase 1b: Magrolimab + Aza for ND-AML



Control mAb: No Phagocytosis



Anti-CD47 mAb: Phagocytosis

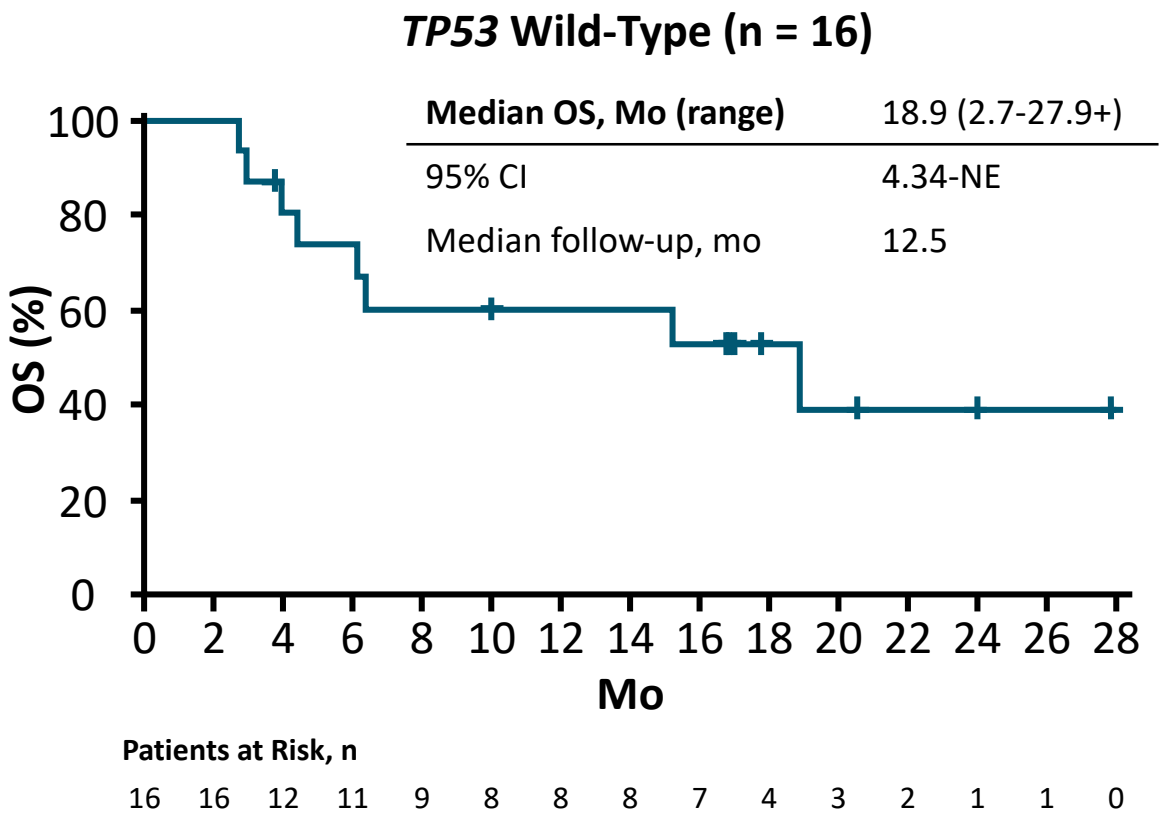


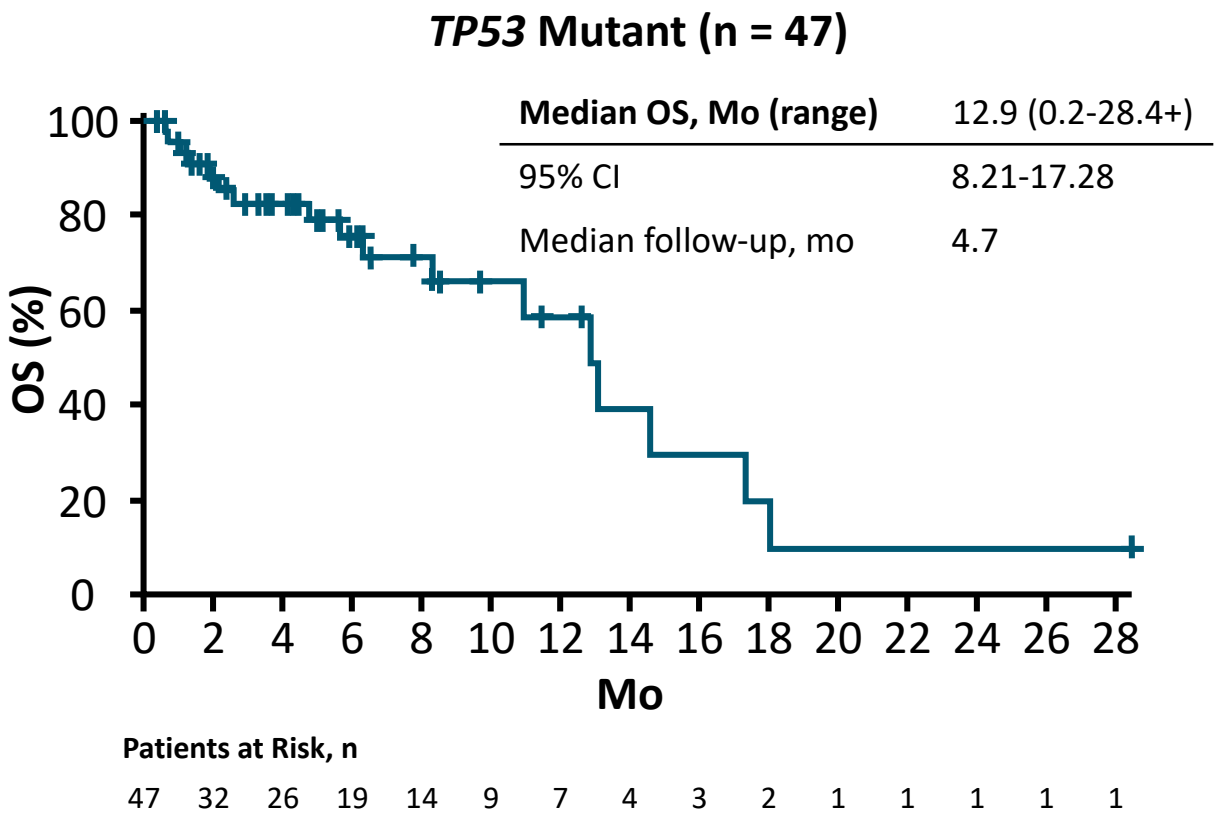
Macrophages
Cancer cells

- Magrolimab is an IgG4 anti-CD47 monoclonal antibody that eliminates tumor cells through macrophage phagocytosis
- Magrolimab is being investigated in multiple cancers with >500 patients dosed

Chao et al Front Oncol 2020;9:1380; Sallman D ASCO 2020 abstract 7507

Phase 1b: Magrolimab + Aza for ND-AML

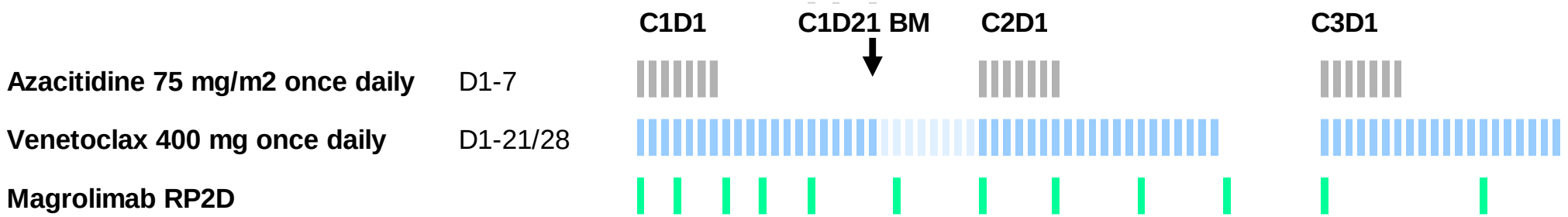




- ENHANCE-2: ongoing phase III trial of magrolimab + azacitidine vs venetoclax/azacitidine or intensive CT in newly diagnosed *TP53*-mutant AML (NCT04778397)

Sallman et al 2020 ASH abstract 330

Phase 1/2: Magrolimab + Ven + Aza for ND/RR-AML



Phase 1 (Dose finding)

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

Phase 2 cohorts

1. Frontline
- ≥ 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

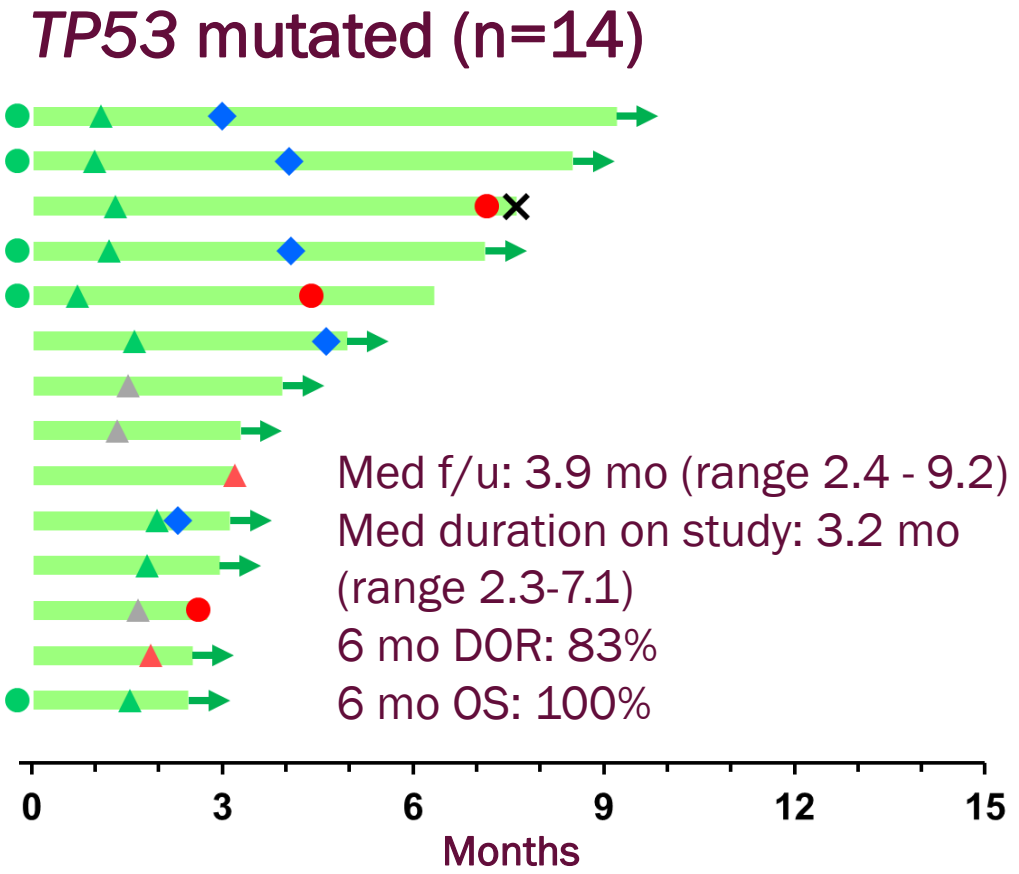
Secondary objectives
- ORR: CR/CRi + PR + MLFS
- Duration of response
- Event-free survival
- Overall survival
- MRD negative rate
- 4- and 8-wk mortality
- No. of pts transitioning to SCT

Exploratory objectives

Daver N et al 2021 ASH abstract 371

Phase 1/2: Magrolimab + Ven + Aza

Outcomes	Frontline Cohort (n=25)	
	TP53 mutated (n=14)	*TP53* wild type (n=11)
ORR	12 (86)	11 (100)
CR/CRi	9 (64)	10 (91)
CR	9 (64)	7 (64)
CRi	0	3 (27)
MLFS / PR[1]	3 (21)	1 (9)
MRD neg FCM	5/9* (55)	4/9 (45)
CCyR	4/9‡ (44)	5/6 (83)
No response	2 (14)	0
TT 1st response	0.7 [0.6-1.9]	0.7 [0.7-1.5]
TT Best response	1.5 [0.7-3.2]	1.1 [0.7-2.9]
Med TT ANC>500	28 (20 – 41) days	
Med TT Plt>50K	24 (18 – 41) days	
8-wk mortality	0	0



Daver N et al 2021 ASH abstract 371

Phase 3 QUAZAR: Oral azacitidine vs placebo following IC

- **Randomized, double-blind, placebo-controlled phase III trial**

Stratified by age, prior MDS or CMML, cytogenetic risk, receipt of consolidation therapy

Patients aged ≥55 yr with AML and intermediate- or poor-risk cytogenetics who achieved CR/CRi after intensive chemotherapy ± consolidation and are transplant-ineligible; ECOG PS ≤3 (N = 472)

Within ≤4 mo (±7 days) of CR/CRi

Oral Aza 300 mg PO
Days 1-14, Q4W
(n = 238)

Placebo PO
Days 1-14, Q4W
(n = 234)

Response assessment every 3 cycles

CR or CRi:
Continue tx

5%-15% BM blasts:
Optional tx escalation*

≥15% BM blasts:
Discontinue tx

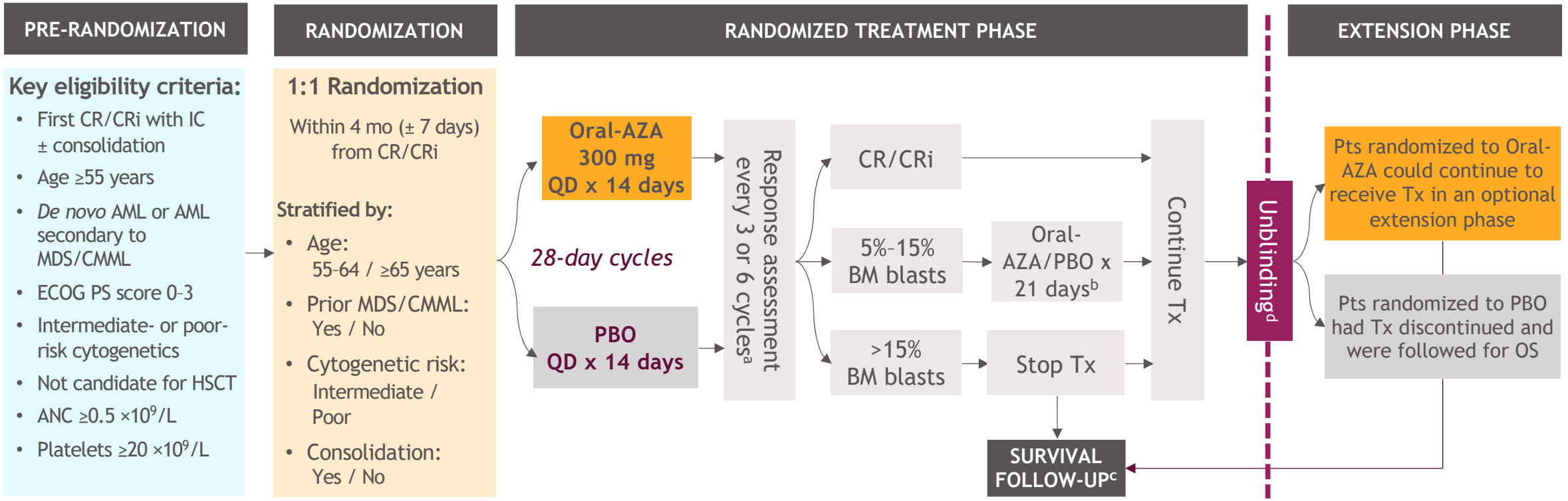
Until death, withdrawal of consent, study end, or loss to f/u

*Escalated dosing schedule for oral Aza or placebo: Days 1-21.

- Primary endpoint: OS
- Key secondary endpoint: RFS

Phase 3 QUAZAR: Oral azacitidine vs placebo following IC

International, multicenter, PBO-controlled, double-blind, randomized, phase 3 trial

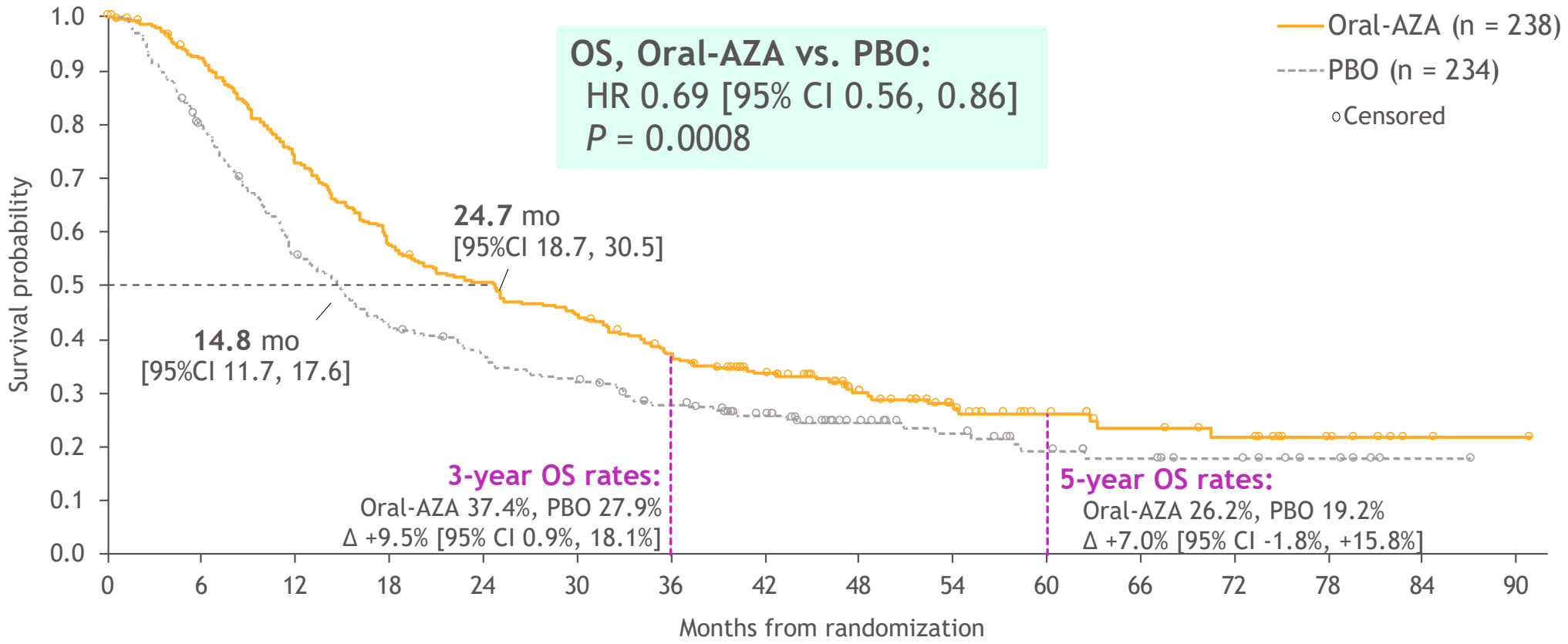


Wei AH, et al. ASH 2021. Abstract 871.

Oral Azacitidine: Long-term survival of QUAZAR

Updated OS at Sep 2020 Data Cutoff

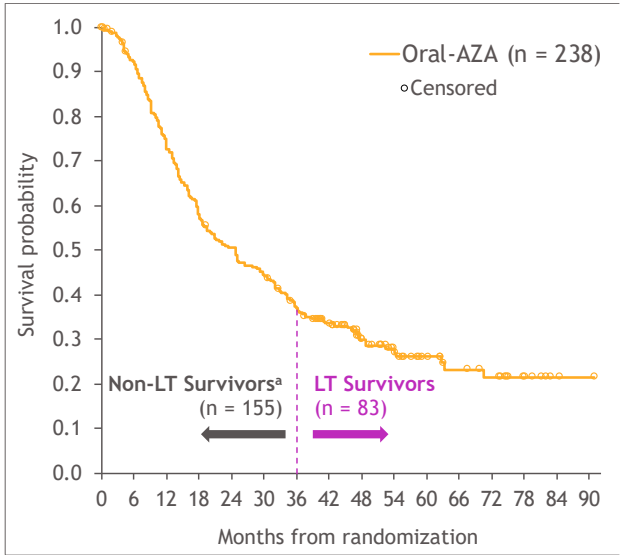
Median follow-up: 51.7 mo

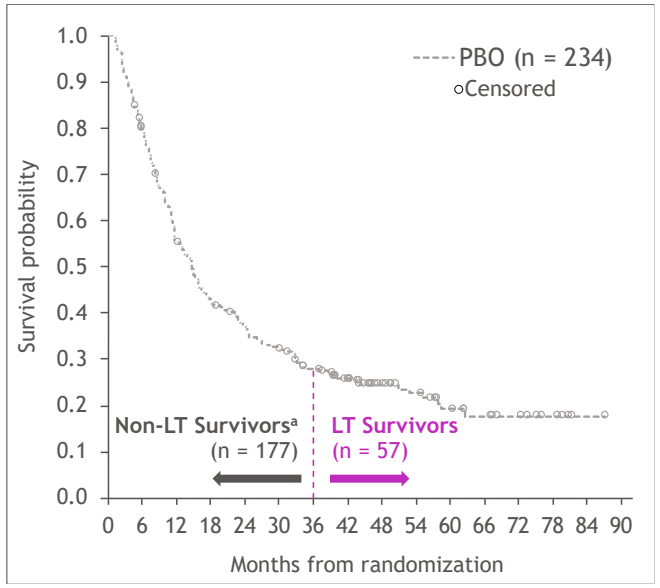


Wei AH, et al. ASH 2021. Abstract 871.

Oral Azacitidine: Long-term survival of QUAZAR

OS for LT vs Non-LT Survivors With Oral Aza and Placebo





- LT Survivors: patients alive in survival follow-up ≥3 years from randomization
- Non-LT Survivors: patients who died or were censored for OS before 3 years

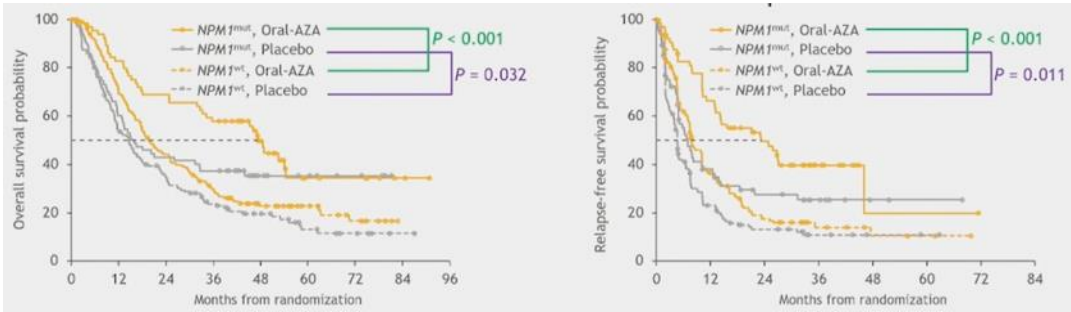
Patient Characteristics by LT Survivor Status	Oral Aza (n=238)		Placebo (n=234)	
	LT (n=83)	Non-LT (n=155)	LT (n=57)	Non-LT (n=177)
Median age (range), years	67 (55-80)	69 (55-86)	67 (55-79)	69 (55-82)
Intermed cytogenetic risk, %	94	81	96	84
*NPM1*mut, %	45	19	46	26
CR/CRi after induction, %	80/20	78/22	84/16	84/16
Received consolidation, %	77	79	88	80
MRD+ at randomization, %	35 (n=29)	48 (n=74)	30 (n=17)	56 (n=99)
Became MRD- on-study, %	76 (22/29)	22 (16/74)	71 (12/17)	10 (10/99)
MRD response,[a] %	37 (38/103)		19 (22/116)	

Wei AH, et al. ASH 2021. Abstract 871.

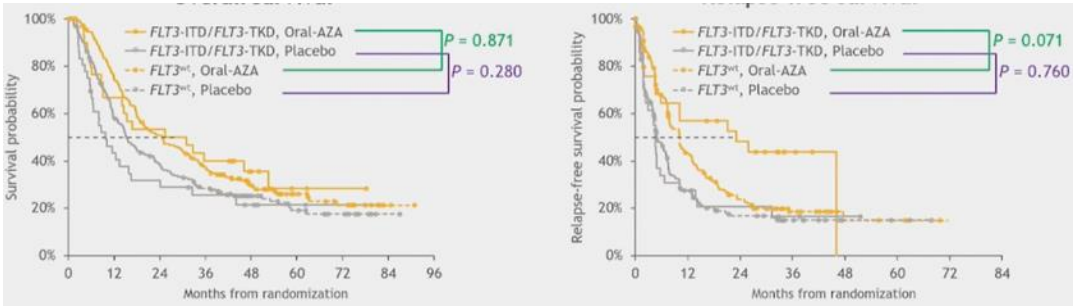
Short N et al Blood Advances

Oral Azacitidine: Mutational and cytogenetic subsets

OS and RFS by *NPM1* Mutation Status at Diagnosis

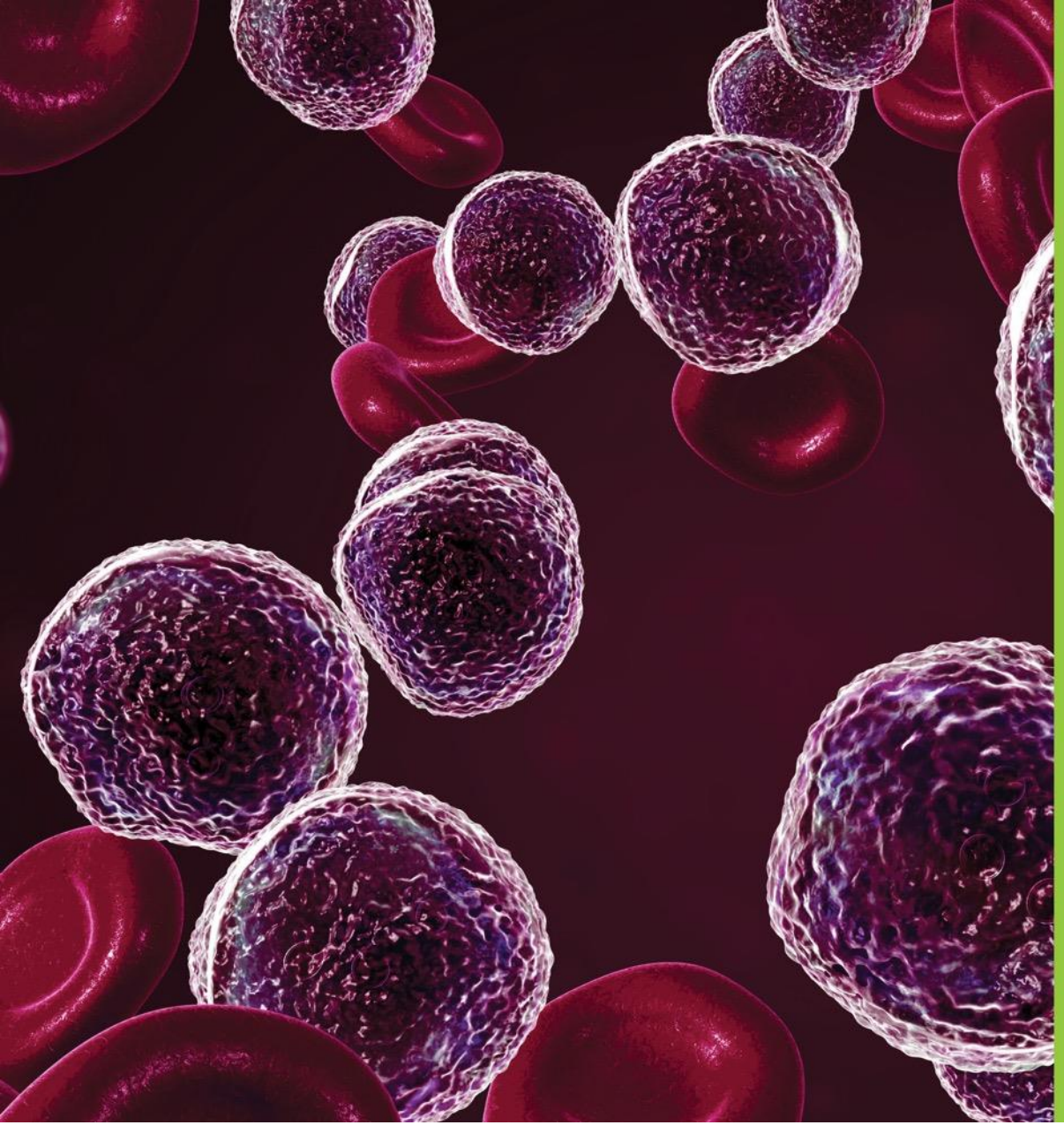


OS and RFS by *FLT3* Mutation Status at Diagnosis



OS via Multivariate Analysis	HR [Exp[coef.)]	*P* Value
Oral Aza vs Placebo	0.78	=0.028
*NPM1*mut vs *NPM1*wt	0.62	=0.002
*FLT3*mut (ITD/TKD) vs. *FLT3*wt	1.48	=0.032
Poor vs intermediate cytogenetic risk	2.01	<0.001
MRD+ vs MRD- at BL (post-IC)	1.65	<0.001
RFS via Multivariate Analysis		
Oral Aza vs Placebo	0.65	<0.001
*NPM1*mut vs *NPM1*wt	0.60	<0.001
*FLT3*mut (ITD/TKD) vs. *FLT3*wt	1.06	=0.737
Poor vs intermediate cytogenetic risk	1.82	<0.001
MRD+ vs MRD- at BL (post-IC)	1.94	<0.001

Wei AH, et al. ASH 2021. Abstract 871.
Dohner H, et al. ASH 2021. Abstract 804.



BEYOND THE CONGRESS

Key Conversations from the 2021 Hematology Annual Meeting™

FRIDAY, FEBRUARY 4, 2022

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