Updates in acute myeloid leukemia

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Curtis Lachowiez, M.D.

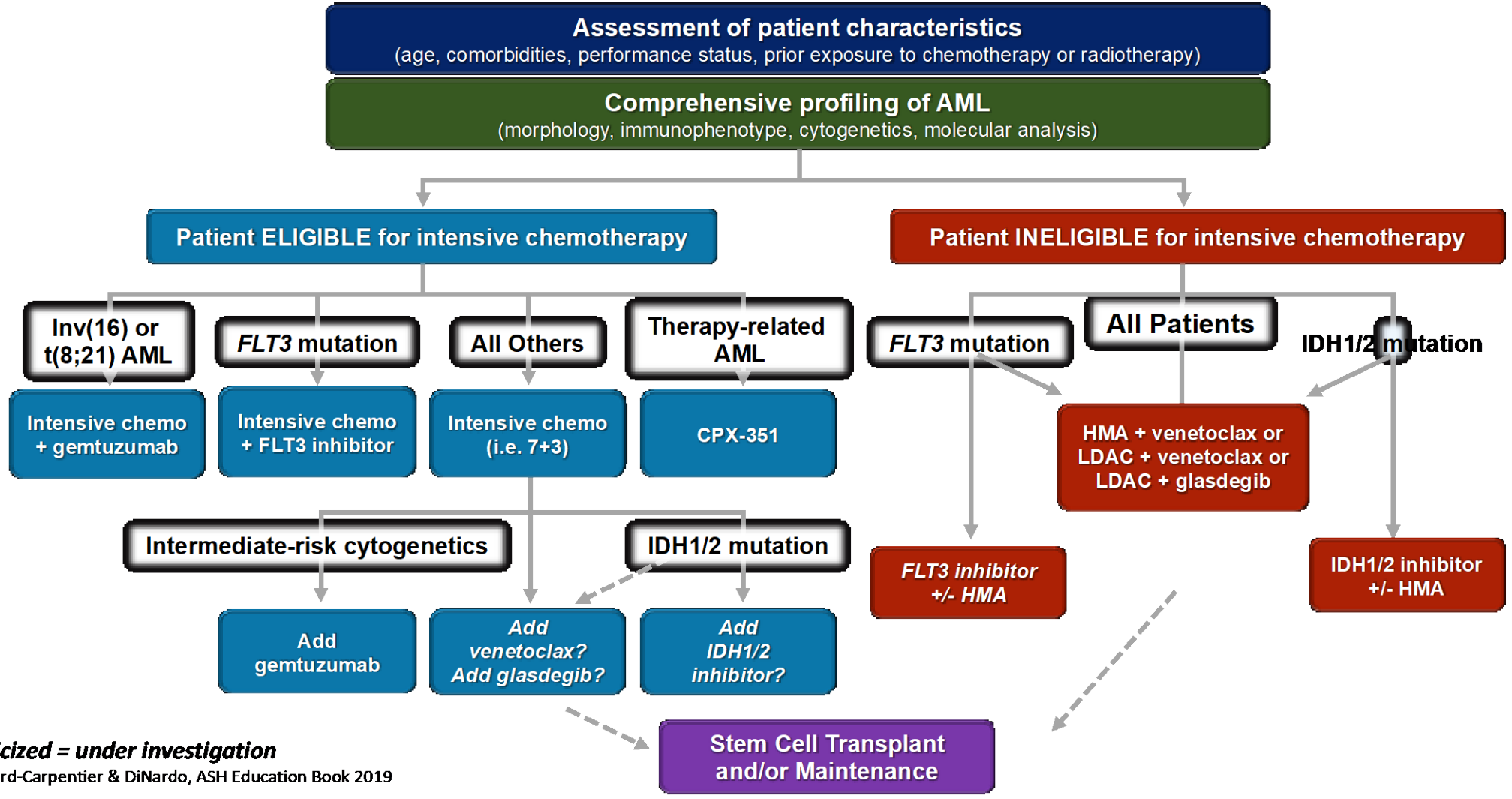
MD Anderson Cancer Center,
Houston, TX

Disclosures

No financial conflict of interest

Will discuss off-label investigational use of commercial agents

Current treatment approach in AML



Italicized = under investigation

Richard-Carpentier & DiNardo, ASH Education Book 2019

Frontline intensive therapy updates

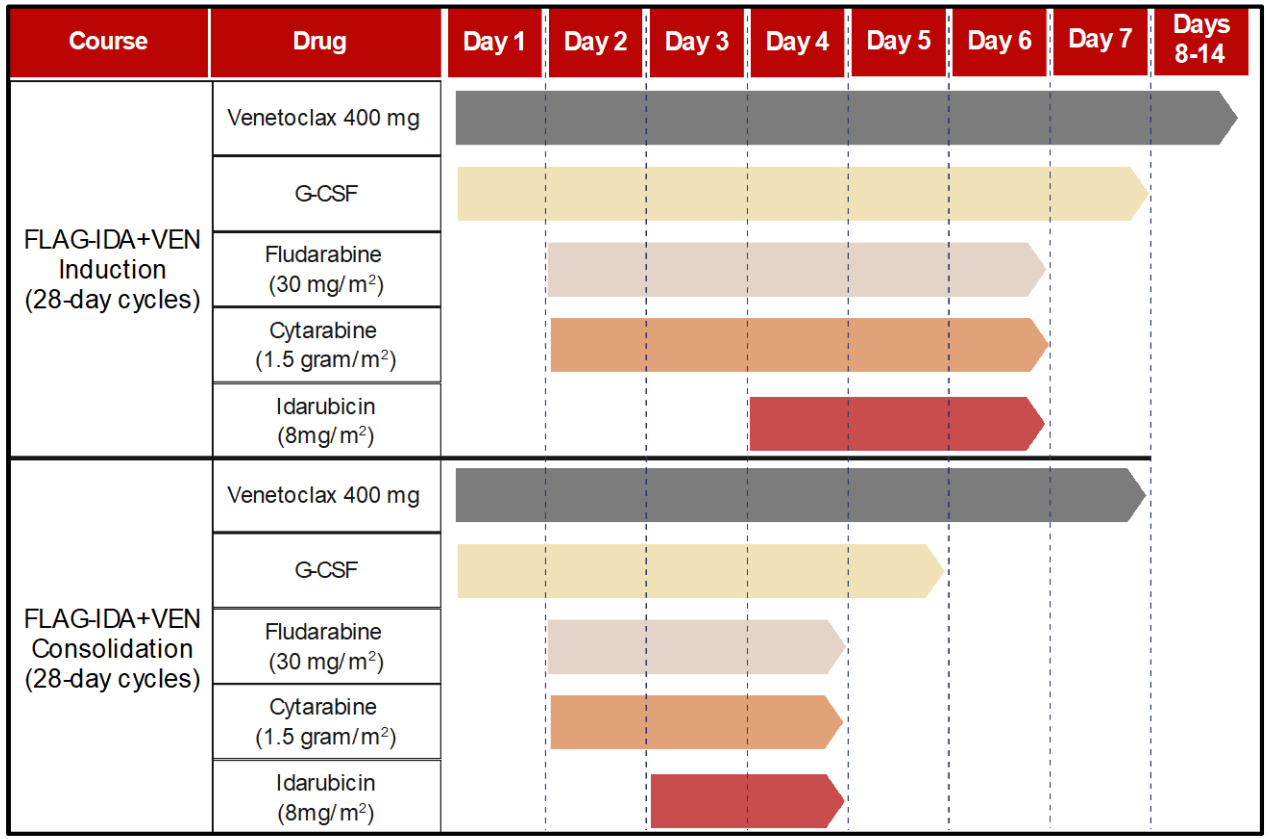
- **FLAG-IDA+Venetoclax**
  - (Lachowiez et. al. ASH abstract 701)

- **Real-world outcomes of CPX-351 vs. HMA+ VEN**
  - (Matthews et. al. ASH abstract 795)

- **Oral AZA (CC-486) maintenance therapy in AML**
  - (Wei et. al. abstract 871)

FLAG-IDA+VEN in AML: Design and demographics

Key Eligibility Criteria
- ND AML, R/R AML, or high-risk MDS (≥ 10% blasts)
- CrCl ≥30 mL/min
- No prior BCL2i



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)

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 28d cycle; **Consolidation**: IDA permitted on days 3 & 4 in 2 post-remission cycles (ie. C2 or C3 and C5 or C6) at physician discretion

Lachowiez et. al. ASH abstract 701

FLAG-IDA+VEN in AML: Treatment characteristics

Treatment characteristics

Demographic Median (range)/ N (%)	All patients (N=45)	De novo AML (n=33)	sAML/tAML (n=12)	P-value
# of treatment cycles	2 (1-6)	2 (1-6)	2 (1-4)	0.94
Median Cycle length*				
Cycle 1	31 (27-59)	31 (27-59)	32 (27-45)	0.26
Cycle 2	41 (27-98)	41 (27-98)	45 (38-60)	0.29
Cycle 3	41 (27-69)	38 (27-51)	46 (36-69)	0.26
Time to best response, days (95% CI)	28 (22-97)	27 (22-97)	32 (25-85)	0.14
Duration of response, months (95% CI)	NR (18-NR)	NR (13-NR)	NR (18-NR)	1.0
Transitioned to alloHSCT	30 (67%)	22 (67%)	8 (67%)	1.0
30-Day Mortality	0%	0%	0%	-
60-Day Mortality	0%	0%	0%	-

Adverse Events

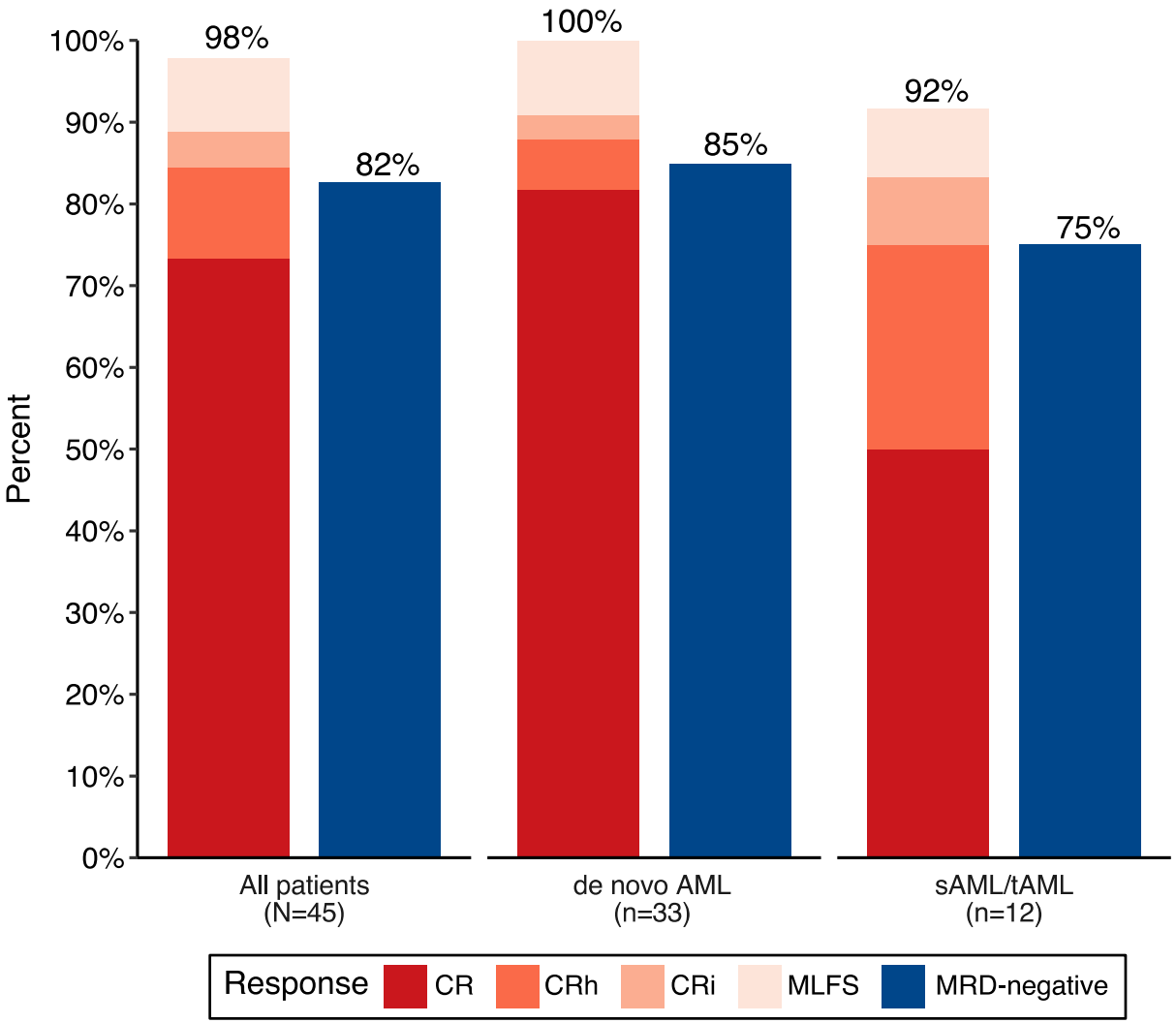
Adverse Event	Total N (%)	Grade 1/2	Grade 3	Grade 4
Febrile Neutropenia	**16 (39%)**	-	16	-
Pneumonia	**10 (24%)**	-	10	-
Bacteremia	**8 (19%)**	-	8	-
Cellulitis	**3 (7%)**	-	3	
Pyrexia	**3 (7%)**	3	-	-
Sepsis	**3 (7%)**	-	-	3
SSTI*	**3 (7%)**	-	3	-
Abdominal pain	**2 (5%)**	-	3	-
Elevated LFT	**2 (5%)**	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 et. al. ASH abstract 701

FLAG-IDA+VEN in AML: Response

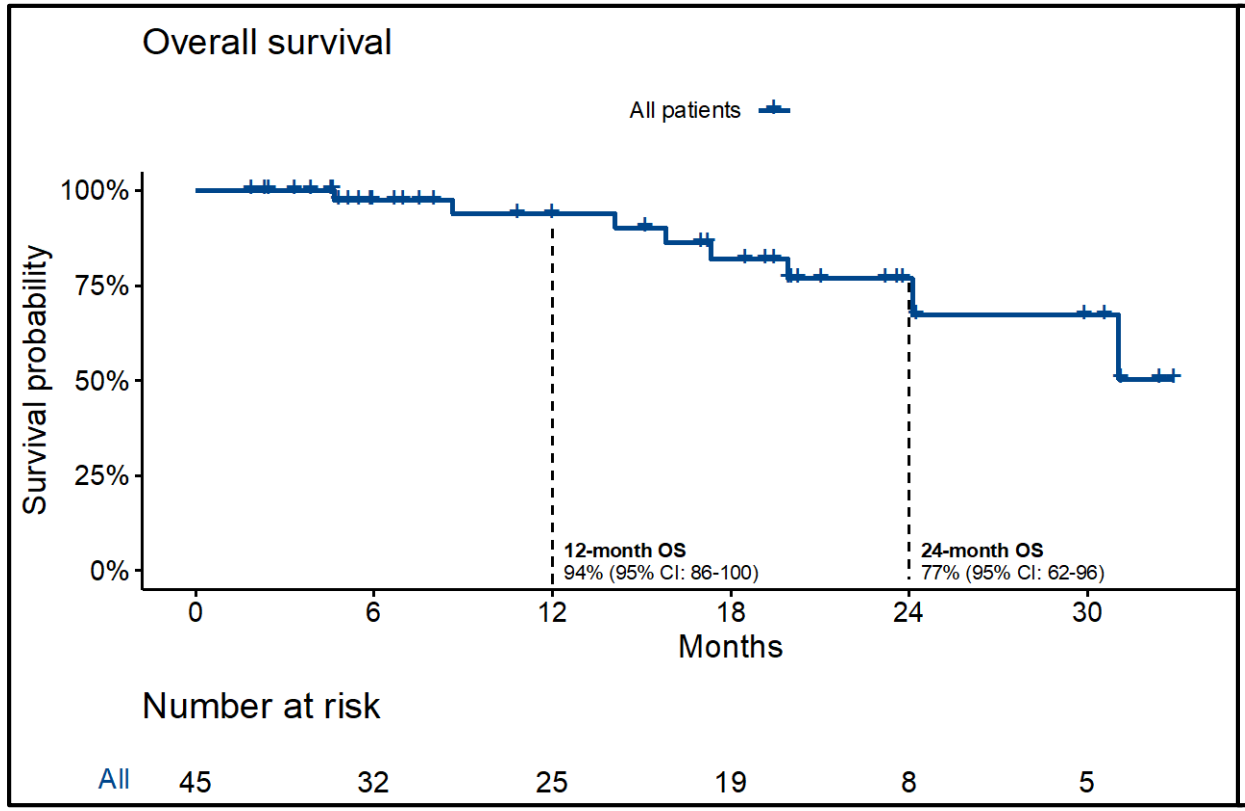
Treatment response

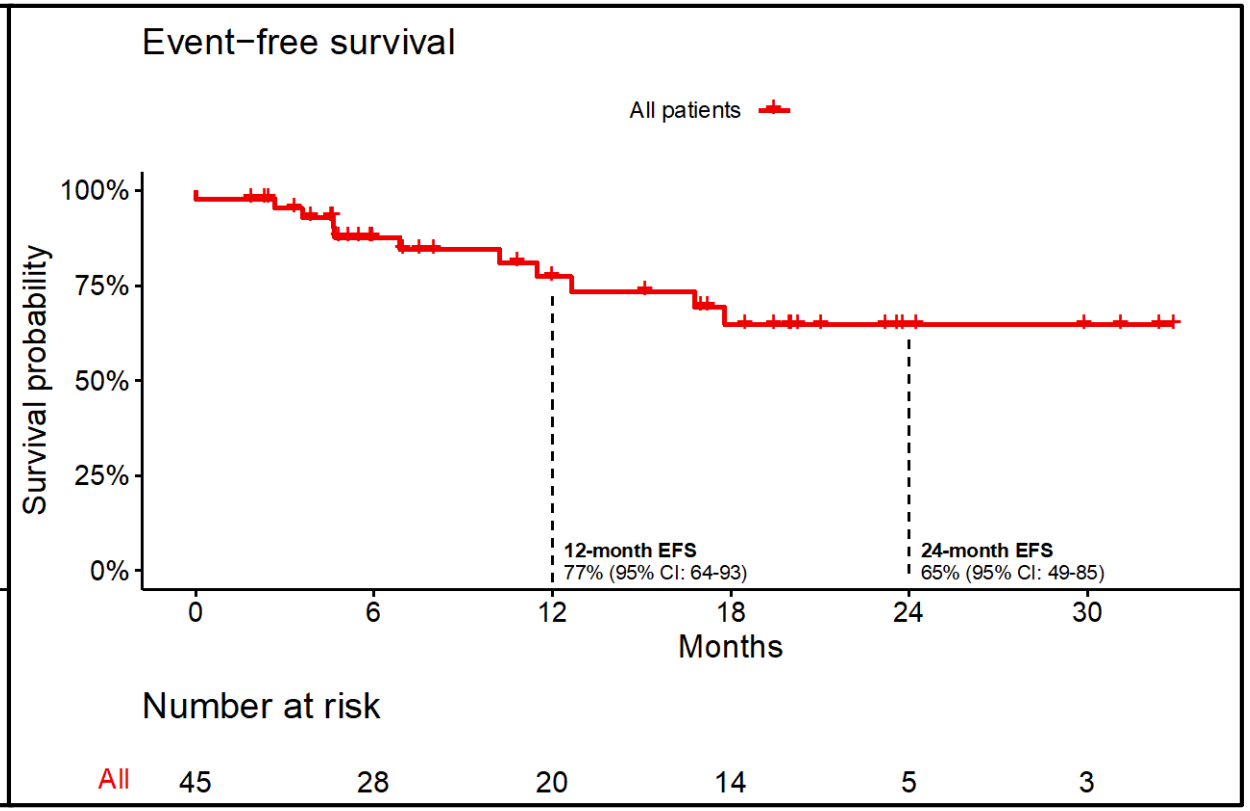
Demographic Median (range)/ N (%)	All (N=45)	De novo AML (n=33)	sAML/tAML (n=12)	P-value
Overall Response Rate	44 (98%)	33 (100%)	11 (92%)	0.26
Composite CR	**40 (89%)**	**30 (91%)**	**10 (83%)**	1.0
Complete Response	33 (73%)	27 (82%)	6 (50%)	0.06
CRh	5 (11%)	2 (6%)	3 (25%)	-
CRi	2 (4%)	1 (3%)	1 (8%)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



Lachowiez et. al. ASH abstract 701

FLAG-IDA+VEN in AML: Survival





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)

Lachowiez et. al. ASH abstract 701

Frontline intensive therapy updates

- **FLAG-IDA+Venetoclax**
  - (Lachowiez et. al. ASH abstract 701)

- **Real-world outcomes of CPX-351 vs. HMA+ VEN**
  - (Matthews et. al. ASH abstract 795)

- **Oral AZA (CC-486) maintenance therapy in AML**
  - (Wei et. al. abstract 871)

HMA+VEN vs. CPX-351 in AML: Study Design

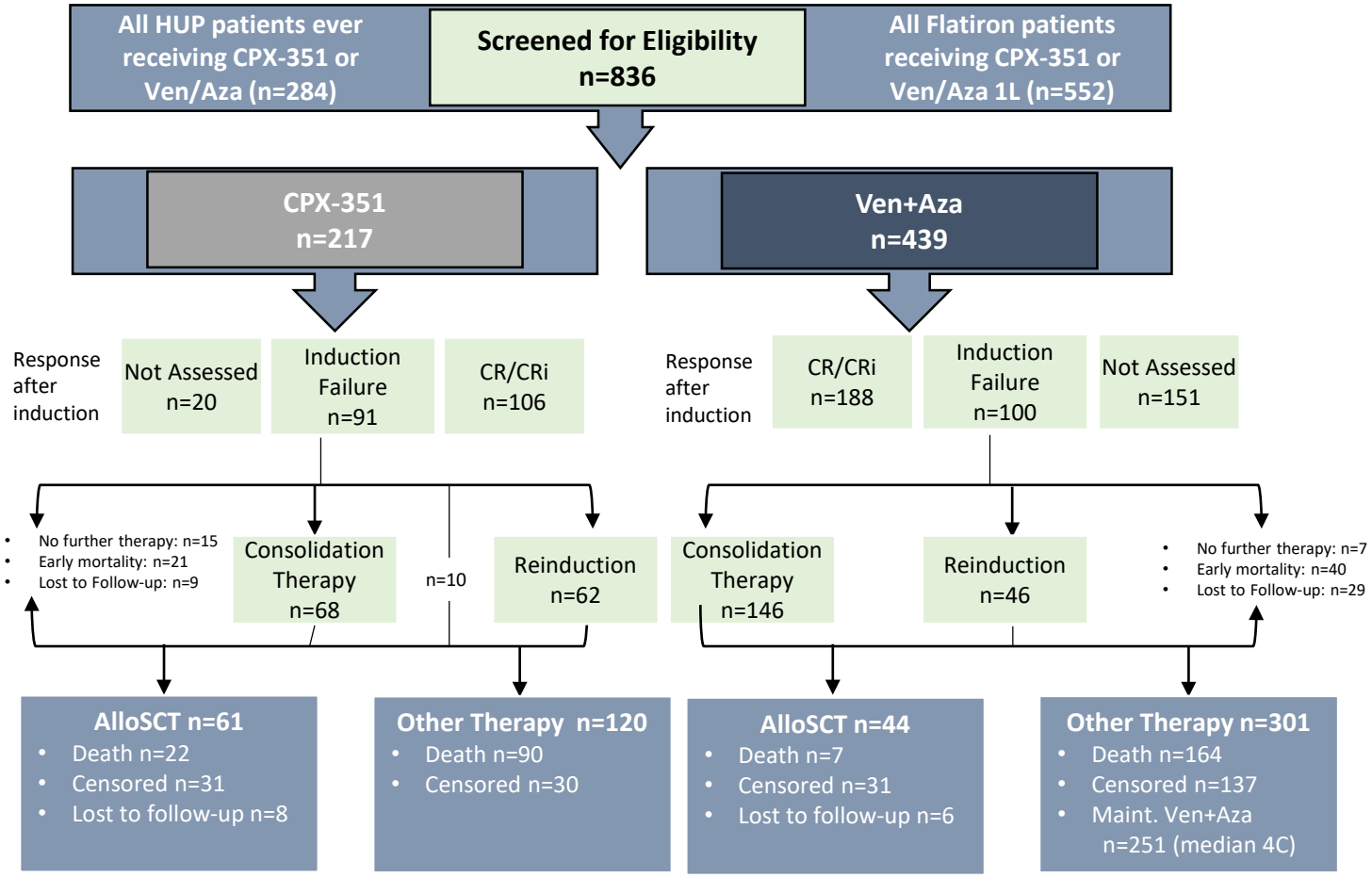
Key Eligibility Criteria

- AML (based on BM or PB blasts > 20%)
- Therapy started between 1/1/2017 to 12/31/2020
- 1L with Ven+Aza or CPX-351
- No mixed-phenotype leukemia or APL
- ECOG PS 0-2

2 data sources

1. UPHS (HUP) HER: a 5-hospitals system spanning inpatient and outpatient settings
2. Flatiron Health database: a nationwide compilation of de-identified EHR-derived clinical, biomarker, treatment and mortality data for 2.2 million patients at 800 sites of care

Primary endpoint: OS (time 0 at diagnosis)



Matthews et. al. ASH abstract 795

HMA+VEN vs. CPX-351 in AML: Demographics

Patient Characteristics		Ven+Aza (n=439)	CPX-351 (n=217)	P value
Median age (range), years		**75 (36-88)**	**67 (21-82)**	<0.001
Gender, n (%)	Female	191 (44)	112 (52)	0.056
	Male	248 (56)	105 (48)	
Practice type, n (%)	Academic	149 (34)	103 (47)	<0.001
	Community	290 (66)	114 (53)	
AML type, n (%)	De Novo	**226 (51)**	**63 (29)**	<0.001
	Prior MDS/MPN	150 (34)	104 (48)	
	Therapy-related	63 (14)	50 (23)	
ELN risk group, n (%)	Favorable	34 (8)	15 (7)	0.84
	Intermediate	117 (27)	64 (29)	
	Adverse	172 (39)	92 (42)	
	Favorable	34 (8)	15 (7)	

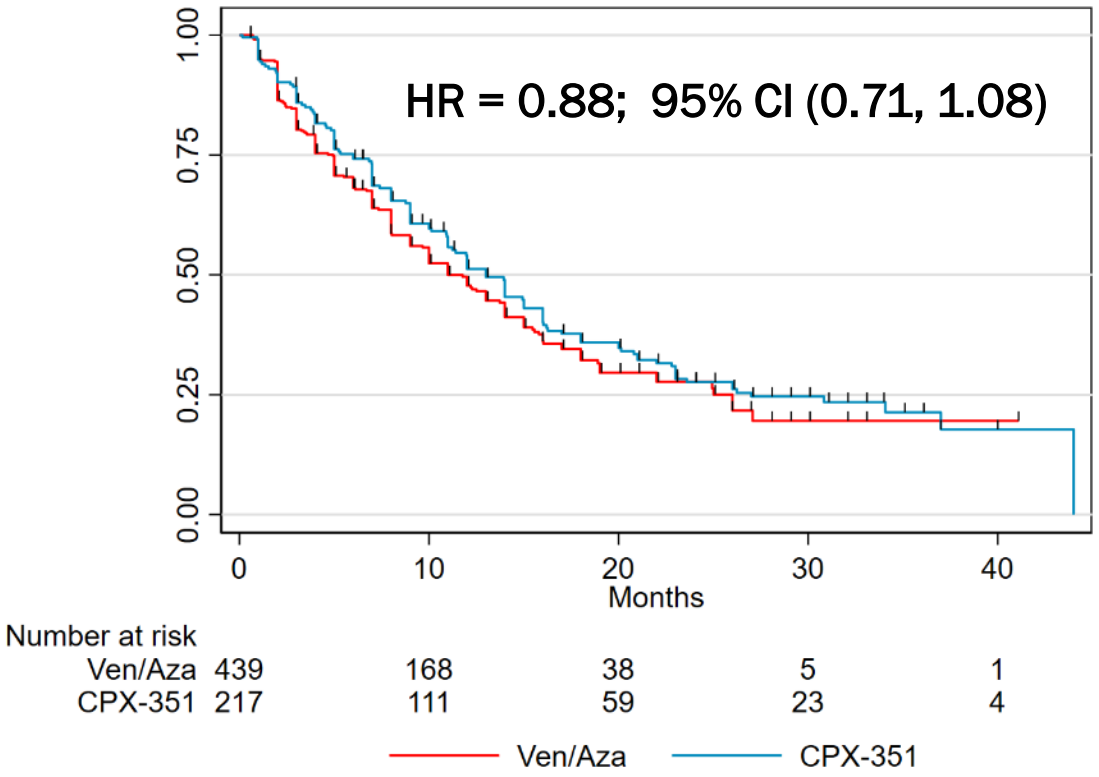
Patient Characteristics		Ven+Aza (n=439)	CPX-351 (n=217)	P value
HCT comorbidity index, n (%)	0	116 (26)	69 (32)	0.28
	1-2	156 (36)	69 (32)	
	≥3	82 (19)	35 (16)	
ECOG PS, n (%)	0-1	62 (14)	31 (14)	0.23
	2-4	196 (45)	72 (33)	
High-risk mutations, n (%)	Negative	201 (46)	90 (41)	0.17
	RUNX1	29 (7)	22 (10)	
	ASXL1	42 (10)	14 (6)	
	TP53	57 (13)	33 (15)	

VEN treated patients were older, CPX-351 treated patients with increased sAML/tAML as anticipated

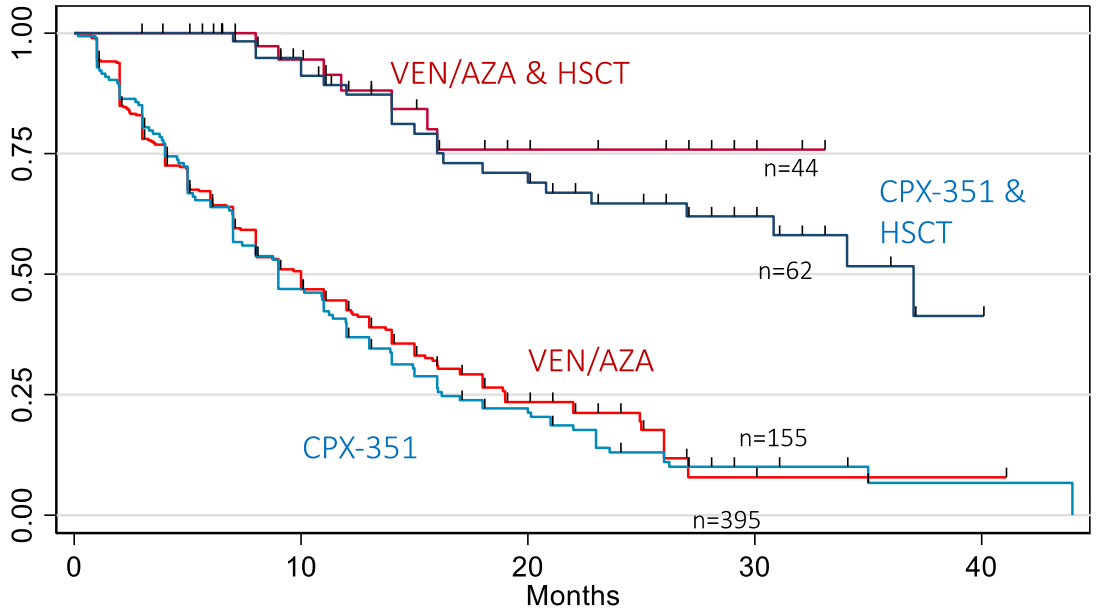
Matthews et. al. ASH abstract 795

HMA+VEN vs. CPX-351 in AML: Survival

Similar OS observed from diagnosis



HSCT remains essential component of therapy



	VEN/AZA	CPX-351
Number (%)	44 (10%)	61 (28%)
Median Time to Transplant (range)	186 days (87 to 578)	171 days (34 to 903)
Median OS w/ HSCT	NR	37 months
Median OS w/o HSCT	10 months	9 months

Matthews et. al. ASH abstract 795

HMA+VEN vs. CPX-351 in AML: Safety

- **CPX-351 treated patients with increased rates of infectious complications compared to HMA+VEN**
- **30 and 60-day mortality were similar between CPX-351 and VEN+AZA**

Flatiron & UPHS	CPX-351 (n=217)	Ven+Aza (n=439)	P value
Median cycles (range)	2 (1-5)	4 (1-28)	N/A
30-day mortality, % (95% CI)	5 (2-8)	5 (3-7)	0.51
60-day mortality, % (95% CI)	10 (6-14)	13 (10-16)	0.10
Diagnosis of infection, % (95% CI)	**51 (42-61)**	20 (15-25)	<0.00005

UPHS Only	CPX-351 (n=52)	Ven+Aza (n=59)	P value
Febrile neutropenia, % (95% CI)	**90 (82 -98)**	54 (42-67)	<0.00005
Culture positive infection, % (95% CI)	**67 (55-80)**	36 (23-48)	0.0004
Mean inpatient stay, days (95% CI)	**41 (37-45)**	15 (10-20)	<0.00005

Matthews et. al. ASH abstract 795

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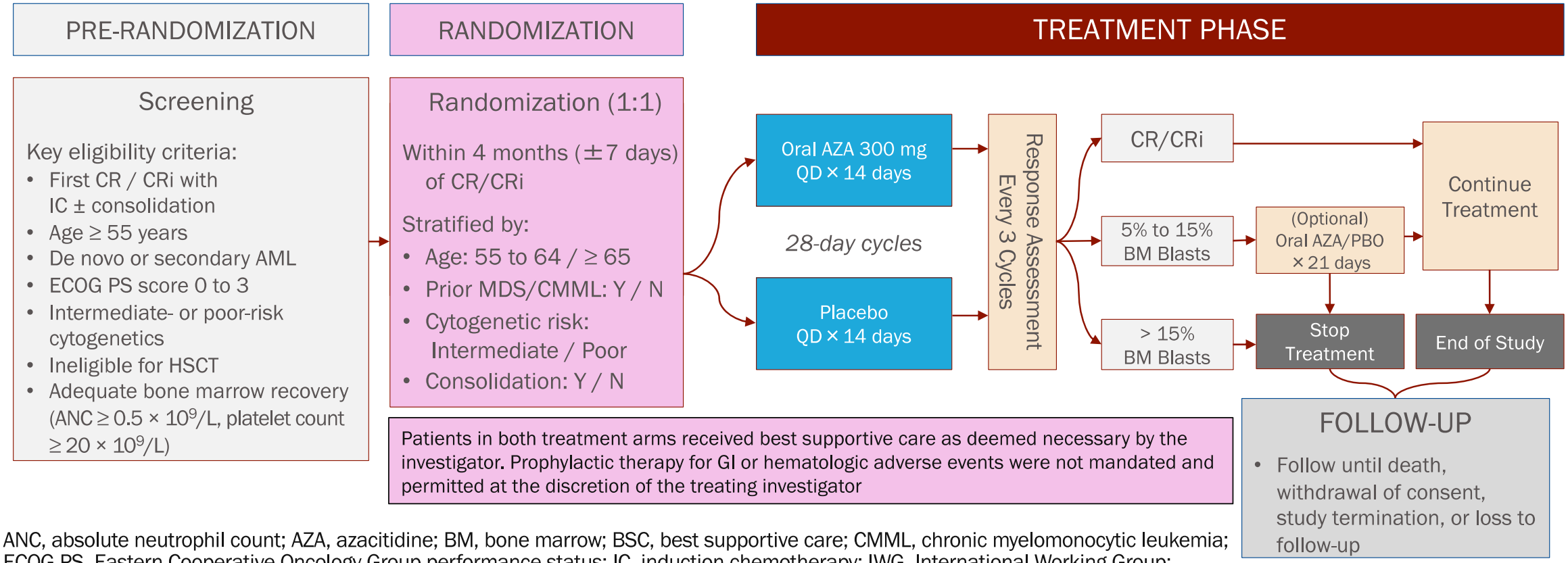
- **Oral AZA (CC-486) maintenance therapy in AML**
  (Wei et. al. abstract 871; Dohnner et. al. abstract 804)

QUAZAR AML-001: Study Design

Objectives: OS following >1 additional year on AZA; OS and RFS in *NPM1*/*FLT3* pt subgroups, and influence of post-IC MRD on outcomes



Patients in both treatment arms received best supportive care as deemed necessary by the investigator. Prophylactic therapy for GI or hematologic adverse events were not mandated and permitted at the discretion of the treating investigator

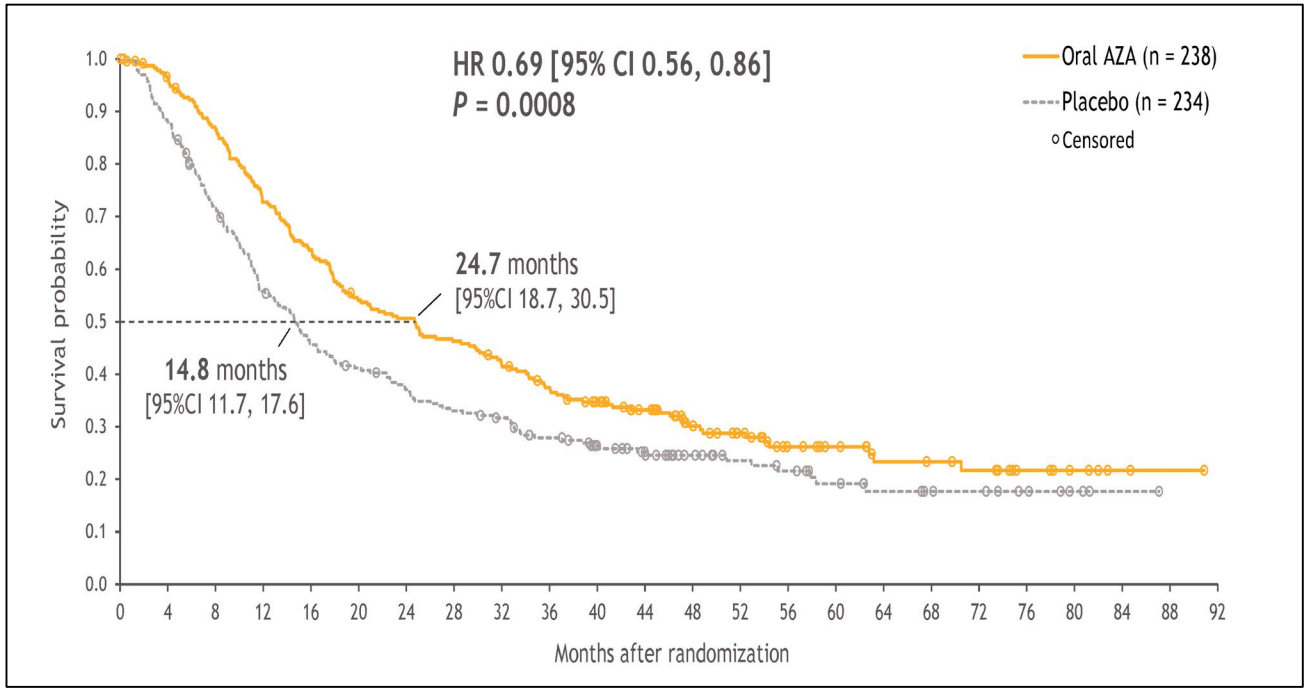
ANC, absolute neutrophil count; AZA, azacitidine; BM, bone marrow; BSC, best supportive care; CMML, chronic myelomonocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, induction chemotherapy; IWG, International Working Group; MDS, myelodysplastic syndrome; PBO, placebo; QD, once daily.

Wei AH, et al. N Engl J Med. 2020;383:2526-2537.

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

QUAZAR AML-001: Survival Outcomes

With extended follow-up, OS favors oral AZA vs. PBO arm



- **Median follow-up:** 51.7 months
- **Estimated 3-year survival:** 37.4% vs. 27.9% in the Oral-AZA and PBO arms, respectively (95% CI 0.9%, 18.1%)

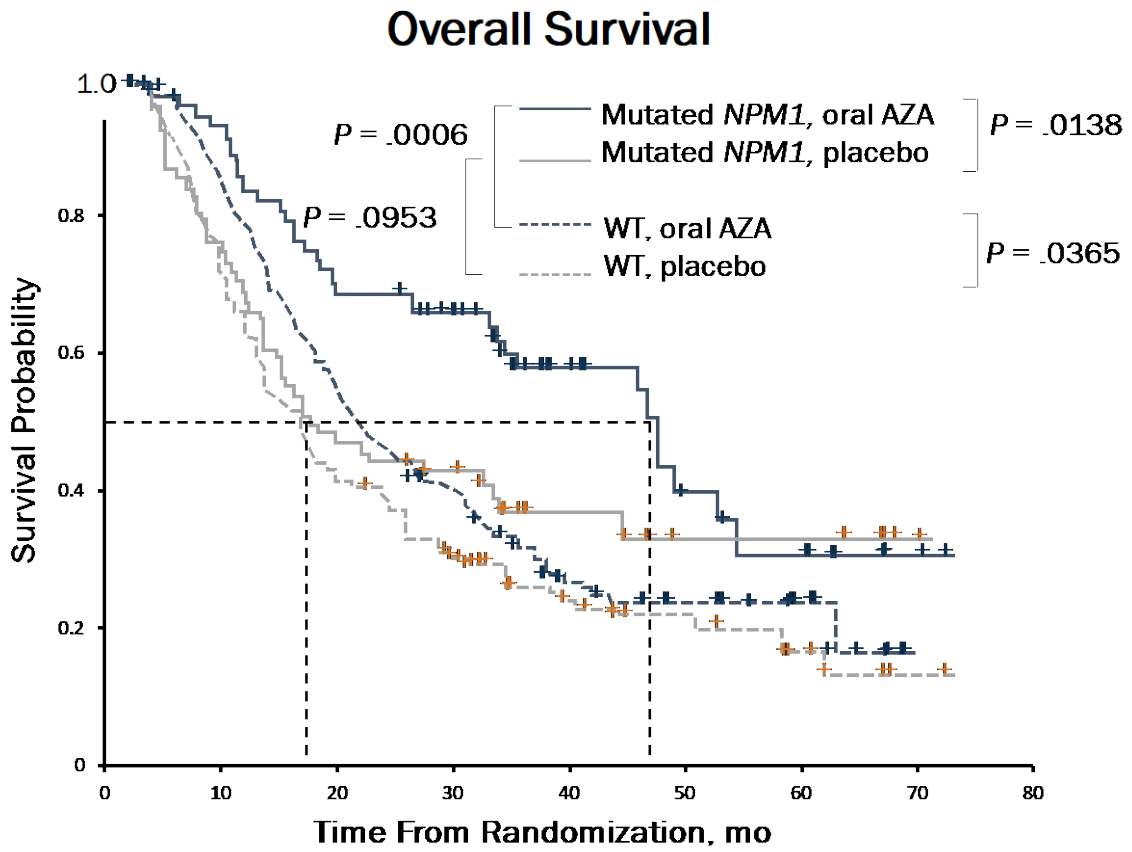
Long-term survivor cohort: 140 patients (29.7%) who were known to be alive for ≥ 3 years, including:

- **Oral-AZA: n = 83**
- **PBO: n = 57**

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)
Intermediate CG risk, %	94	81	96	84
NPM1mut, %	**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 A, et. al. ASH 2021. Abstract 871

QUAZAR AML-001: Molecular Outcomes



OS benefit of more than 2.5 years vs placebo (OS for all patients in QUAZAR AML-001 was lengthened by 9.9 mo with oral AZA)

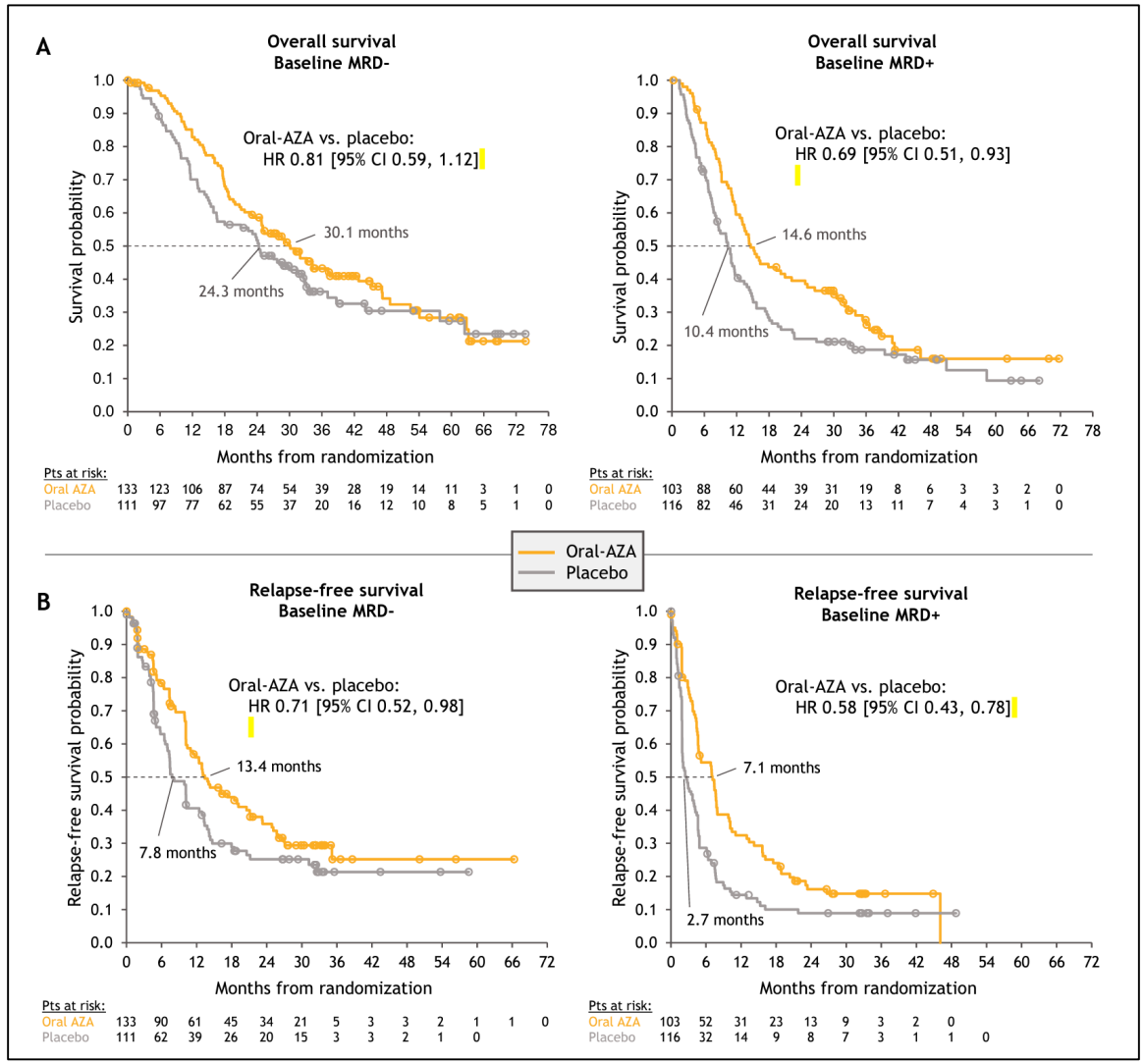
Improved OS and RFS observed in:

- *NPM1*-mutated AML
- MRD-negative post IC
- Oral AZA vs. PBO arm

OS via Multivariate Analysis	HR [Exp[coef.)]	P Value
Oral Aza vs Placebo	0.78	=0.028
NPM1mut vs NPM1wt	0.62	=0.002
FLT3mut (ITD/TKD) vs. FLT3wt	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
NPM1mut vs NPM1wt	0.60	<0.001
FLT3mut (ITD/TKD) vs. FLT3wt	1.06	=0.737
Poor vs intermediate cytogenetic risk	1.82	<0.001
MRD+ vs MRD- at BL (post-IC)	1.94	<0.001

Dohner H, et. al. ASH 2021. Abstract 804

QUAZAR AML-001: MRD Outcomes



- **Improved OS and RFS with oral AZA vs. PBO**
  - Independent of MRD status
- **Oral AZA increased conversion to MRD-negative remission**
  - Oral AZA: 37% vs. PBO: 19%

OS via Multivariate Analysis	HR [95%CI]	P Value
Baseline MRD status		
MRD+ vs. MRD-	1.85 [1.49-2.31]	<0.0001
Treatment Arm		
Oral-AZA vs. placebo	0.74 [0.59-0.92]	0.0067
RFS via Multivariate Analysis		
Baseline MRD status		
MRD+ vs. MRD-	2.04 [1.65-2.53]	<0.0001
Treatment Arm		
Oral-AZA vs. placebo	0.63[0.51-0.78]	<0.001

Roboz GJ et. al. Blood. 2022 Jan 11.

Frontline lower-intensity therapy updates

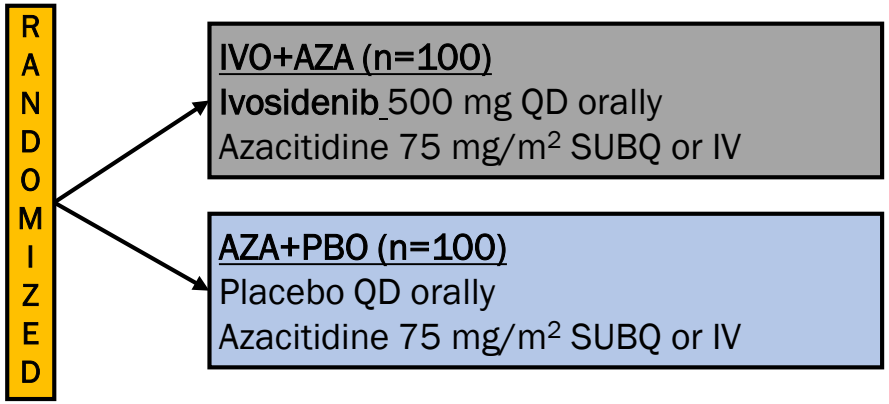
- **AGILE Phase 3 study of IVO+AZA vs. AZA in *IDH1*-mutated AML**
  - (Montesinos, et al. ASH abstract 697)

- **LACEWING Phase 3 study of Gilteritinib+AZA vs. AZA**
  - (Wang, et al. ASH abstract 700)

- **Molecular outcomes with HMA+VEN**
  - *FLT3:* (Konopleva, et al. ASH abstract 1904)
  - *TP53*+ Cytogenetics (Pollyea, et al. ASH abstract 224)

IVO+AZA vs. AZA: Study Design and demographics

Key Eligibility Criteria
- Newly diagnosed m*IDH1* AML
- ECOG PS ≤2
- Ineligible for intensive induction chemotherapy



- Cutoff date (March 18, 2021)
- IDMC halted enrollment (unrelated to safety) based on a noted difference in clinical importance
- 148 patients were enrolled at 155 sites in 20 countries

Primary endpoint: EFS with ~173 events (52 months)
Key secondary endpoints: CR rate, OS, CR + CRh rate, ORR

Patient Characteristics		Ivo+Aza (n=72)	Pbo+Aza (n=74)
Median age (range), years		76 (58-84)	75.5 (45-94)
ECOG PS, n (%)	0	14 (19.4)	10 (13.5)
	1	32 (44.4)	40 (54.1)
	2	26 (36.1)	24 (32.4)
Disease history per INV, n (%)	De novo AML	54 (75.0)	53 (71.6)
	Secondary AML	18 (25.0)	21 (28.4)
Median mIDH1 VAF in BMA (range),[a] %		36.7 (3.1-50.5)	35.5 (3.0-48.6)
Cytogenetic risk n, %	Favorable	3 (4.2)	7 (9.5)
	Intermediate	48 (66.7)	44 (59.5)
	Poor	16 (22.2)	20 (27.0)
Median BM blasts, % (range)		54 (20-95)	48.0 (17-100)

Montesinos et. al. ASH abstract 697

IVO+AZA vs. AZA: Response Outcomes

Response Rates		Ivo+Aza (n=72)	Pbo+Aza (n=74)
CR	Rate, n (%) [95% CI]	**34 (47.2) [35.3-59.3]**	**11 (14.9) [7.7-25.0]**
	Odds ratio (95% CI); 1-sided P value	**4.8 (2.2-10.5); P<0.0001**	
	Median DOR (95% CI), months	NE (13.0-NE)	11.2 (3.2-NE)
	Median time to CR (range), months	4.3 (1.7-9.2)	3.8 (1.9-8.5)
CR+CRh	Rate, n (%) [95% CI]	**38 (52.8) [40.7-64.7]**	**13 (17.6) [9.7-28.2]**
	Odds ratio (95% CI); 1-sided P value	**5.0 (2.3-10.8); P<0.0001**	
	Median DOR (95% CI), months	NE (13.0-NE)	9.2 (5.8-NE)
	Median time to CR+CRh (range), months	4.0 (1.7-8.6)	3.9 (1.9-7.2)
ORR	n (%) [95% CI]	**45 (62.5) [50.3-73.6]**	**14 (18.9) [10.7-29.7]**
	Odds ratio (95% CI); 1-sided P value	**7.2 (3.3-15.4); P<0.0001**	
	Median DOR (95% CI), months	22.1 (13.0-NE)	9.2 (6.6-14.1)
	Median TTFR (range), months	2.1 (1.7-7.5)	3.7 (1.9-9.4)

mIDH1 Clearance[a] in BMMCs by Response, n/N (%)	Ivo+Aza (n=43)	Pbo+Aza (n=34)
CR+CRh	17/33 (51.5)	3/11 (27.3)
CR	14/29 (48.3)	2/10 (20)
CRh	3/4 (75)	1/1 (100)
Non-CR+CRh responders	2/4 (50)	0/2 (0)
Nonresponders	1/6 (16.7)	0/21 (0)

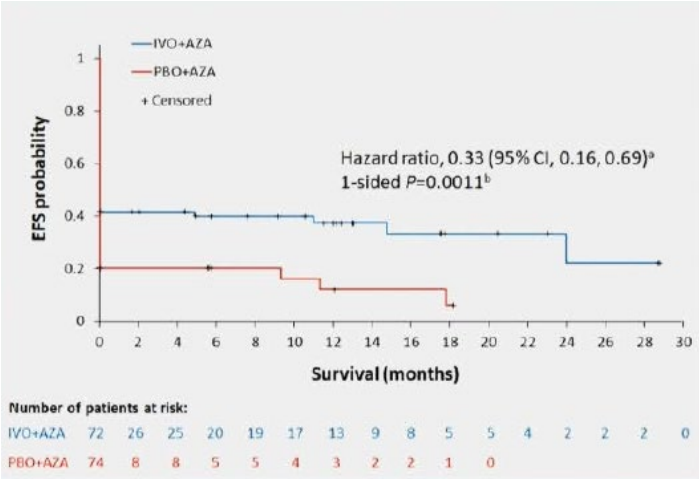
[a]Assessed by BEAMing Digital PCR (limit of detection 0.02-0.04%) in patients with ≥1 on-treatment sample

- **IVO+AZA resulted in improved ORR, CR, CR+CRh rates compared to AZA+PBO**
- **IDH1 clearance was higher in patients treated with IVO+AZA vs. AZA**

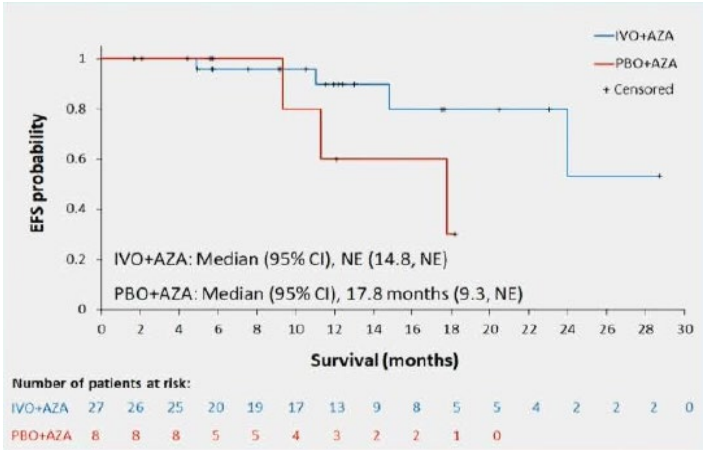
Montesinos et. al. ASH abstract 697

IVO+AZA vs. AZA: Survival Outcomes

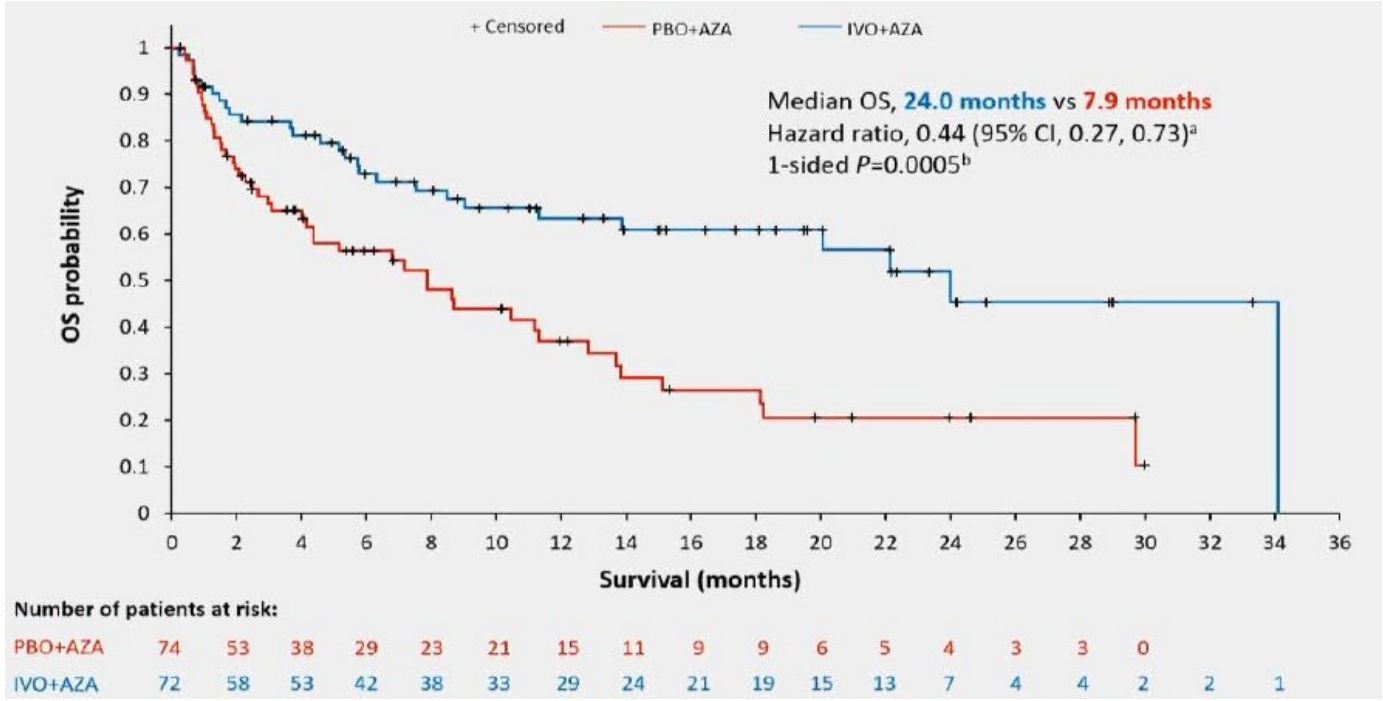
EFS: ITT Population



EFS: Patients With CR by 24-weeks



Overall Survival



- **EFS and OS favored IVO+AZA vs. AZA+PBO**
- **Patients without a CR by week 24 were considered to have had an event at day 1 of randomization**

[a]HR estimated using Cox's proportional hazards model stratified by the randomization stratification factors.
[b]*P* value was calculated from the 1-sided log-rank test stratified by the randomization stratification factors.

Montesinos et. al. ASH abstract 697

IVO+AZA vs. AZA: Safety Outcomes

- **Non-hematologic and hematologic treatment emergent adverse events (TEAE) were similar with IVO+AZA vs. AZA**

Adverse Events, n (%)		Ivo+Aza (n=71)		Pbo+Aza (n=73)	
		Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any TEAE		70 (98.6)	66 (93.0)	73 (100)	69 (94.5)
Most common TEAEs, (>20%)	**Nausea**	30 (42.3)	2 (2.8)	28 (38.4)	3 (4.1)
	Vomiting	29 (40.8)	0	19 (26.0)	1 (1.4)
	Diarrhea	25 (35.2)	1 (1.4)	26 (35.6)	5 (6.8)
	Pyrexia	24 (33.8)	1 (1.4)	29 (39.7)	2 (2.7)
	Constipation	19 (26.8)	0	38 (52.1)	1 (1.4)
	Pneumonia	17 (23.9)	16 (22.5)	23 (31.5)	21 (28.8)
Any hematologic TEAE		55 (77.5)	50 (70.4)	48 (65.8)	47 (64.4)
Most common hematologic TEAEs (>20%)	**Anemia**	22 (31.0)	18 (25.4)	21 (28.8)	19 (26.0)
	Febrile neutropenia	20 (28.2)	20 (28.2)	25 (34.2)	25 (34.2)
	Neutropenia	20 (28.2)	19 (26.8)	12 (16.4)	12 (16.4)
	Thrombocytopenia	20 (28.2)	17 (23.9)	15 (20.5)	15 (20.5)
	Bleeding	29 (40.8)	4 (5.6)	21 (28.8)	5 (6.8)
	Infections	20 (28.2)	15 (21.1)	36 (49.3)	22 (30.1)

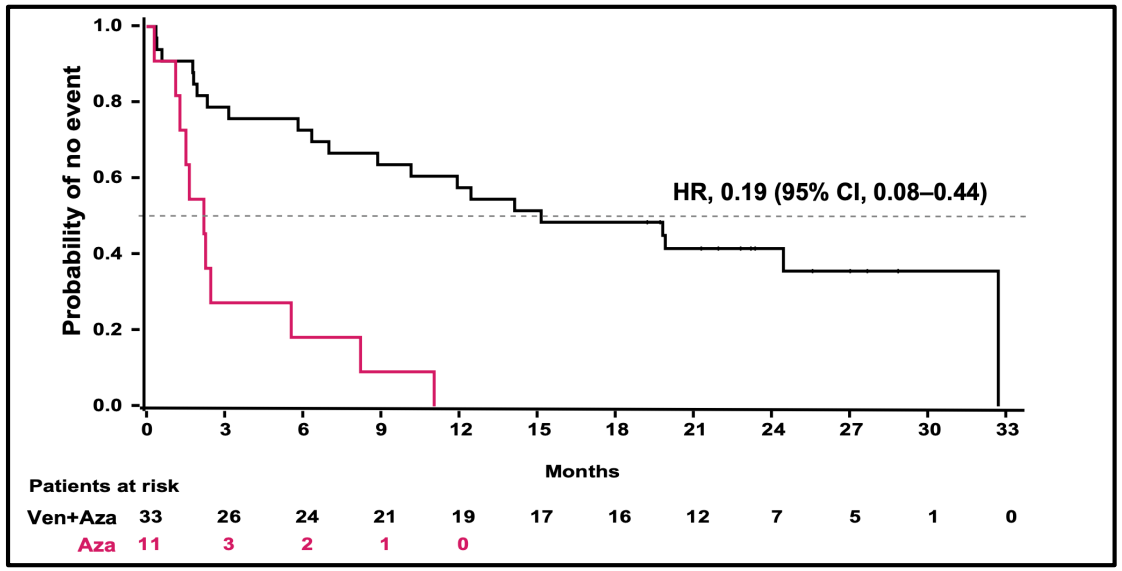
- **Patients who received IVO+AZA vs AZA had higher rates of:**
  - Grade ≥2 differentiation syndrome (14.1% vs 8.2%)
  - Grade ≥3 QT prolongation (9.9% vs 4.1%)

- Clinically meaningful improvements were observed in global health status/QoL and fatigue EORTC QLQ-C30 subscales in the IVO+AZA arm vs. AZA

Montesinos et. al. ASH abstract 697

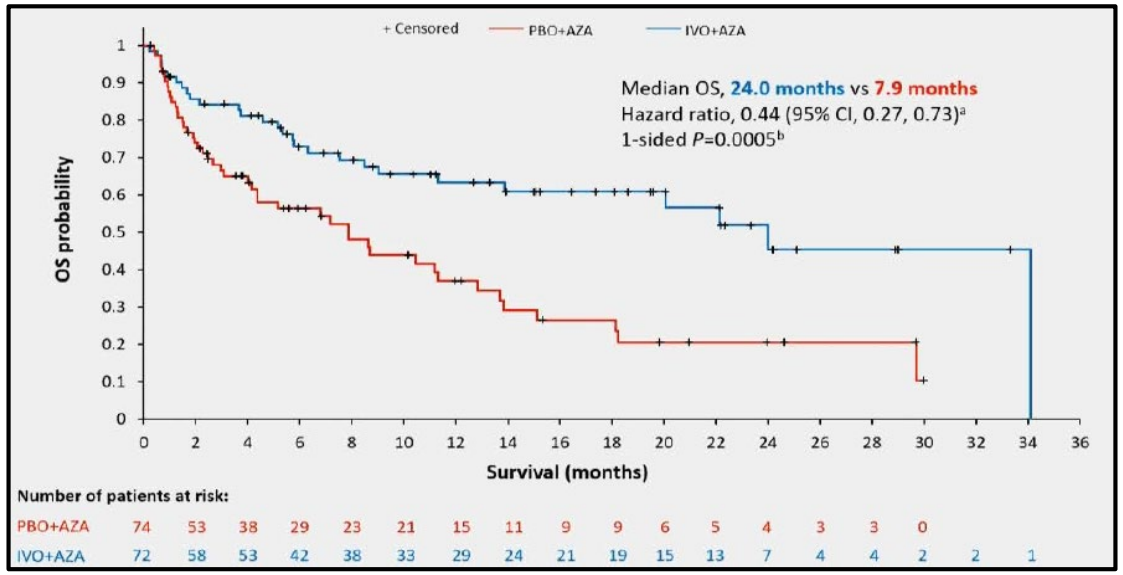
AZA+VEN vs. IVO+AZA: Is one preferred?

HMA+VEN: Post-hoc analysis of P1b and P3 studies



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

AGILE: Prospective randomized P3 trial



- Median OS: 24 months
- 24-month OS: 50%

- Key questions: 1. Sequencing of therapy; 2. Adverse event profile of combinations; 3. Durability of response

Pollyea et. al. Clinical Cancer Research 2022; Montesinos et. al. ASH abstract 697

Frontline lower-intensity therapy updates

- **AGILE Phase 3 study of IVO+AZA vs. AZA in *IDH1*-mutated AML**
  - (Montesinos, et al. ASH abstract 697)

- **LACEWING Phase 3 study of Gilteritinib+AZA vs. AZA**
  - (Wang, et al. ASH abstract 700)

- **Molecular outcomes with HMA+VEN**
  - *FLT3:* (Konopleva, et al. ASH abstract 1904)
  - *TP53*+ Cytogenetics (Pollyea, et al. ASH abstract 224)

Gilt+AZA vs. AZA: Study design and demographics

Key Eligibility Criteria
- Newly diagnosed *FLT3*$^{mut+}$ AML
- Not eligible for intensive induction chemotherapy

Administered over 28-day cycles

RANDOMIZED

2:1*

Gilteritinib 120 mg PO daily on days 1 to 28

Gilteritinib + Azacitidine Gilt 120 mg PO daily, days 1 to 28, Aza 75 mg/m^2 IV or SUBQ daily, days 1 to 7

Azacitidine (Aza) 75 mg/m^2 IV or SUBQ daily, days 1 to 7

30-day follow-up → then every 3 months for ≤3 years

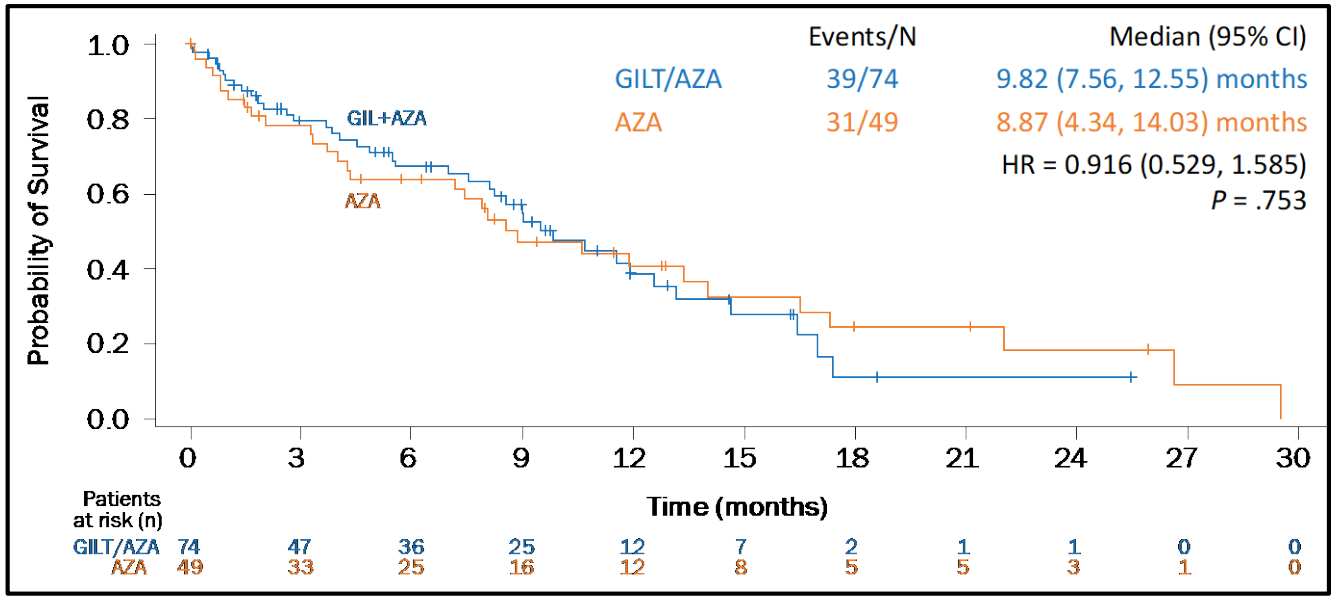
Primary endpoint: OS
Key secondary endpoint: EFS
Other secondary endpoints: Response, safety/tolerability
Exploratory endpoint: PK

Patient Characteristics		GILT/AZA (n=74)	AZA (n=49)
Mean age (SD), years		77.4 (5.6)	76.7 (5.3)
Age group, n (%)	<75 years	21 (28.4)	13 (26.5)
	≥75 years	53 (71.6)	36 (73.5)
ECOG PS, n (%)	0 to 1	38 (51.4)	32 (65.3)
	≥2	35 (47.3)	16 (32.7)
	Missing	1	1
FLT3 mutation type, n (%)	**ITD alone**	**58 (78.4)**	**40 (81.6)**
	TKD alone	14 (18.9)	7 (14.3)
	ITD with TKD	2 (2.7)	2 (4.1)
FLT3 mutation status, n (%)	ITD allelic ratio <0.5	25 (33.8)	18 (36.7)
	ITD allelic ratio ≥0.5	35 (47.3)	24 (49.0)
	TKD	14 (18.9)	7 (14.3)
Cytogenetic risk status,† n (%)	Favorable	2 (2.7)	0
	Intermediate	51 (68.9)	36 (73.5)
	Unfavorable	8 (10.8)	5 (10.2)

Wang et al. ASH abstract 700

Gilt+AZA vs. AZA: Survival and subsequent therapy

No significant OS difference observed with GILT+AZA vs. AZA



Median follow-up: 9.76 months for GILT/AZA and 17.97 months for AZA

More patients in the AZA arm received subsequent therapy, including FLT3 directed therapy

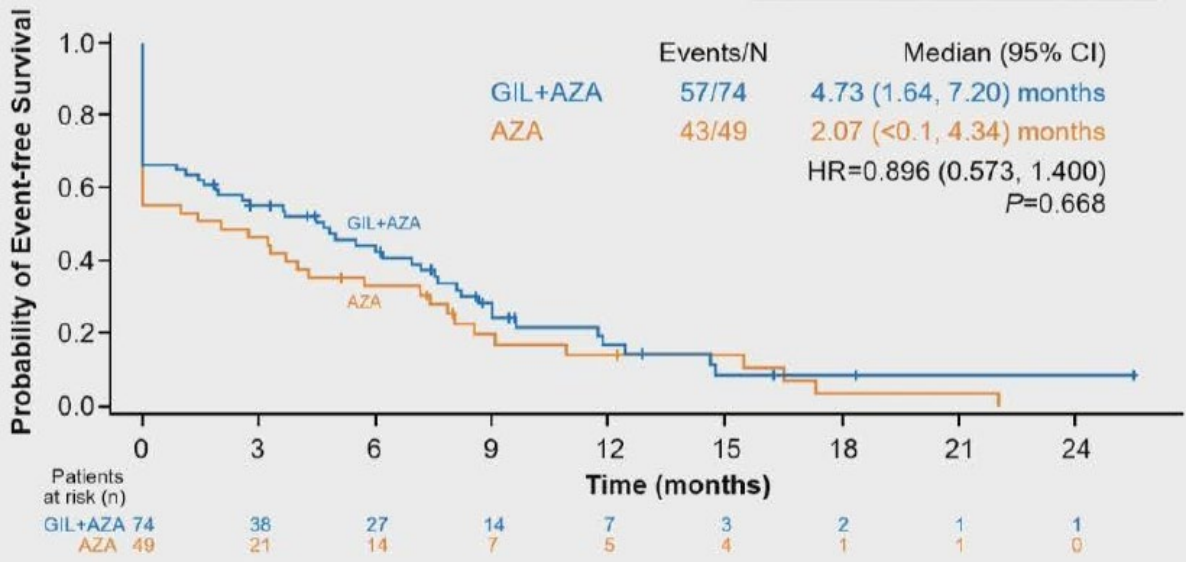
Regimen*	GIL+AZA (n=74) n (%)	AZA (n=49) **n (%)**
Any treatment	15 (20.3)	22 (44.9)
FLT3 inhibitor–containing regimen†	3 (4.1)	**14 (28.6)**

Types of FLT3 Inhibitor-containing regimens‡	GIL+AZA (n=3) n† (%)	AZA (n=14) **n† (%)**
Azacitidine and gilteritinib	1 (33.3)	0
Azacitidine and sorafenib	0	1 (7.1)
Gilteritinib	**2 (66.7)**	**10 (71.4)**
Quizartinib	0	2 (14.2)
Sorafenib	0	3 (21.4)

*Subsequent AML regimens are as reported by study investigators.
†Regimens only displayed for those receiving FLT3 inhibitor as the subsequent therapy; patients could have received non-FLT3 inhibitor–containing therapy.
‡Regimens are not mutually exclusive; a given patient may have received >1 subsequent antileukemic treatment regimen.
Wang ES, et al. ASH abstract 700.

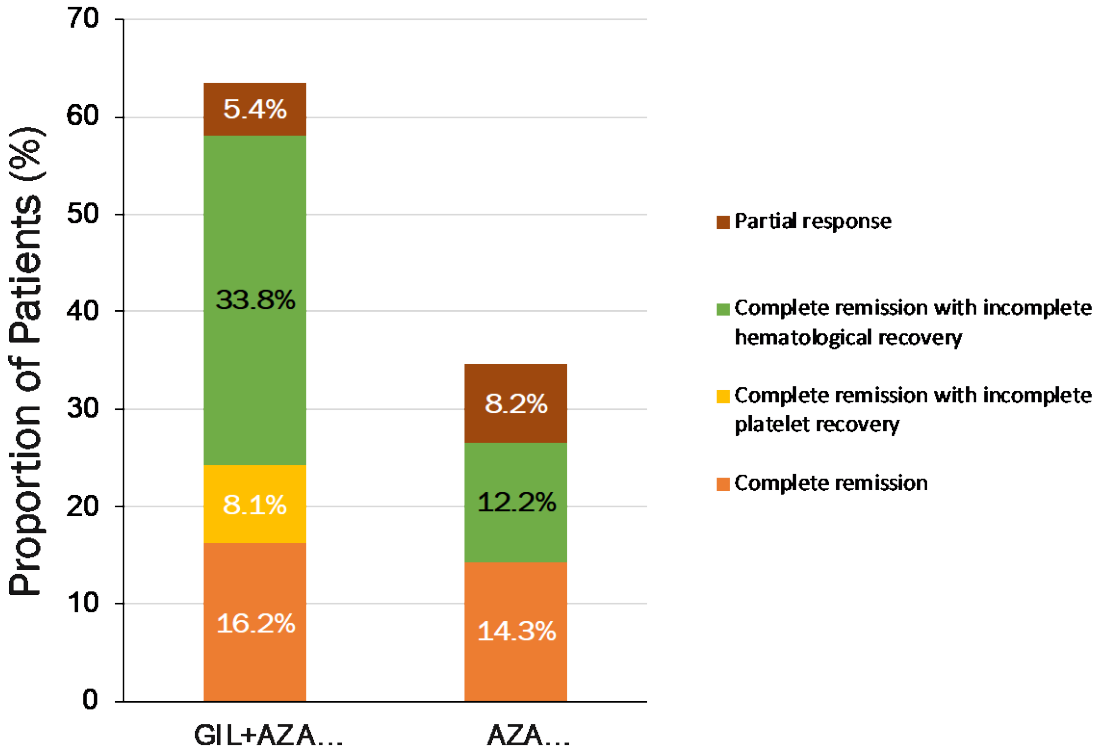
Gilt+AZA vs. AZA: EFS and response outcomes

Event-free survival



- **Median EFS**
  - 0.03 months in both arms
  - HR: 1.175 (95% CI: 0.764-1.807); *P*=0.459
- **Median EFS based on CRc instead of CR**
  - Gilt+Aza: 4.73 months vs. AZA: 2.07 months
  - HR: 0.896 (95% CI: 0.57-1.40), *P*= 0.668

Overall Response rate



CRc difference: 31.4% (95% CI: 13.1, 49.7); *P* < .001

Wang et al. ASH abstract 700

Gilt+AZA vs. AZA: Safety outcomes

Grade 3 Adverse events similar between treatment arms

Grade ≥3 AEs, n (%)	Gilt+Aza (n=73)	Aza (n=47)
Overall	70 (95.9)	42 (89.4)
Pyrexia	7 (9.6)	0
Diarrhea	5 (6.8)	0
Febrile neutropenia	26 (35.6)	9 (19.1)
Nausea	1 (1.4)	1 (2.1)
Anemia	18 (24.7)	13 (27.7)
Thrombocytopenia	20 (27.4)	9 (19.1)
Pneumonia	15 (20.5)	8 (17.0)
Neutropenia	16 (21.9)	10 (21.3)
AST increased	4 (5.5)	0
Vomiting	2 (2.7)	0
Asthenia	5 (6.8)	0
Hyopkalemia	6 (8.2)	4 (8.5)
Decreased appetite	3 (4.1)	1 (2.1)
Decreased neutrophil count	14 (19.2)	4 (8.5)
Decreased platelet count	13 (17.8)	9 (19.1)
Hyponatremia	9 (12.3)	1 (2.1)
Sepsis	4 (5.5)	5 (10.6)

Wang et al. ASH abstract 700

Frontline lower-intensity therapy updates

- **AGILE Phase 3 study of IVO+AZA vs. AZA in *IDH1*-mutated AML**
  - (Montesinos P, et al. ASH abstract 697)

- **LACEWING Phase 3 study of Gilteritinib+AZA vs. AZA**
  - (Wang E, et al. ASH abstract 700)

- **Molecular outcomes with HMA+VEN**
  - *FLT3:* (Konopleva M, et al. ASH abstract 1904)
  - *TP53* +/- adverse cytogenetics (Pollyea D, et al. ASH abstract 224)

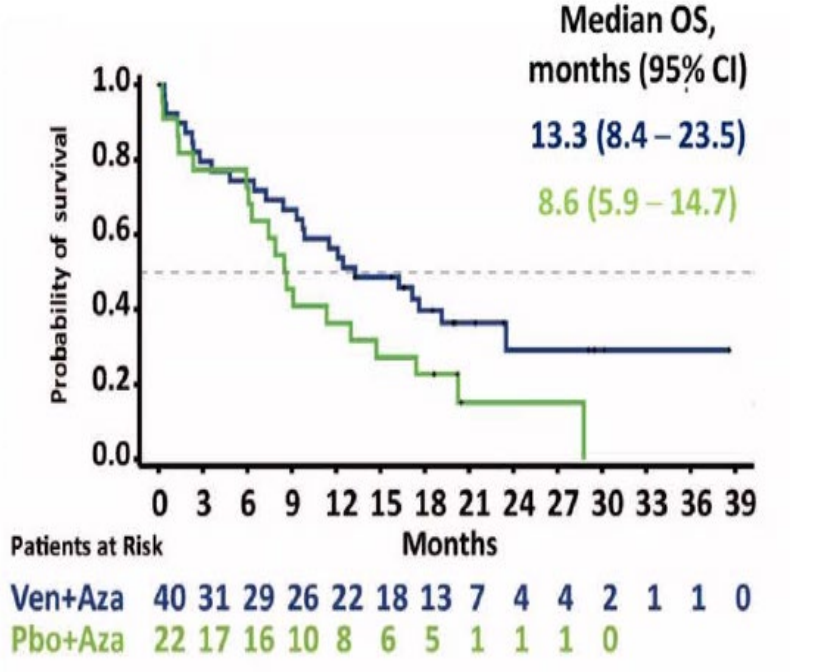
HMA+VEN in FLT3-mutated AML

CR/CRi rates and OS are improved in *FLT3*-mutated AML with AZA+VEN vs. AZA (OS driven mainly by *FLT3*-TKD mutations)

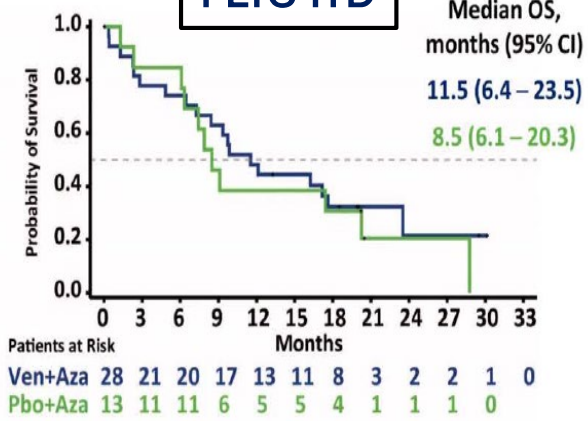
CR+CRi, n/N (%)	VEN + AZA	PBO + AZA
FLT3^{mut+}	**28/40 (70)**	**8/22 (36)**
FLT3^{WT}	150/227 (66)	21/86 (24)
FLT3-ITD	**19/28 (68)**	**6/13 (46)**
FLT3-ITD AR < 0.5	14/19 (74)	4/8 (50)
FLT3-ITD AR ≥ 0.5	5/9 (56)	2/5 (40)
FLT3-TKD	10/13 (77)	3/10 (30)
FLT3 and NPM1 co-mutation	10/14 (71)	2/7 (29)

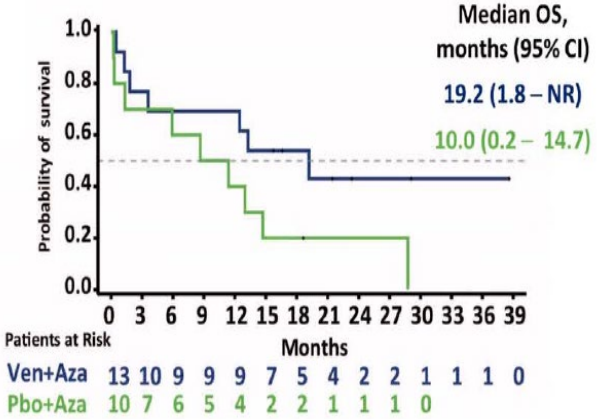
Median Duration of CR+CRi	VEN + AZA		PBO + AZA	
	N	Months (95% CI)	N	Months (95% CI)
FLT3^{mut+}	28	17.3 (10.1; NR)	8	5.0 (1.0; 15.9)
FLT3^{WT}	150	18.2 (14.0; NR)	21	13.4 (5.8; 15.6)

FLT3-mutated



FLT3-ITD





FLT3-TKD

Konopleva M, et al. ASH abstract 1904

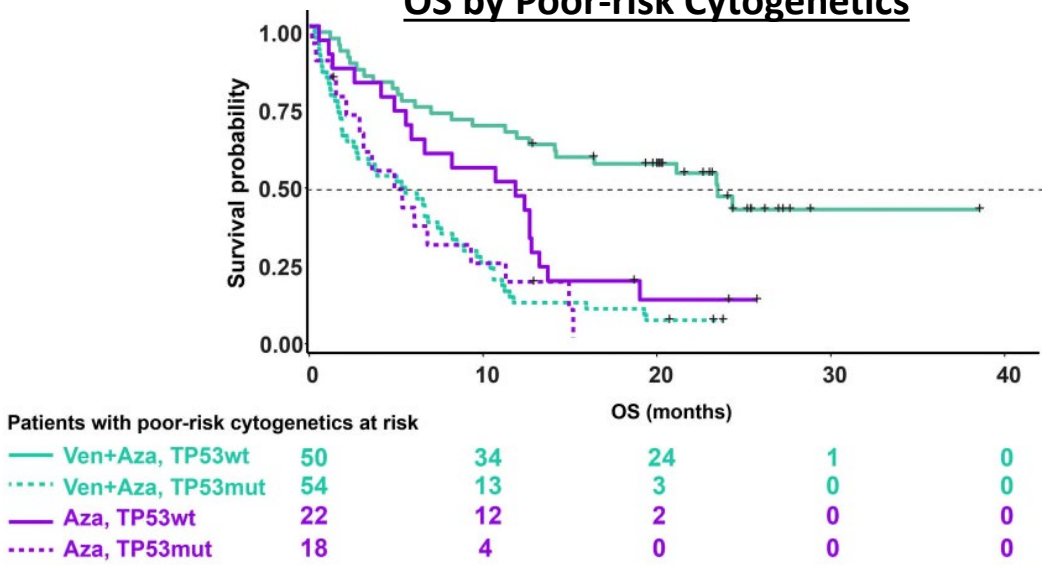
HMA+VEN in adverse-risk CG/TP53-mutated AML

HMA+VEN improved OS in patients with poor-risk CG *without* concurrent *TP53* mutation

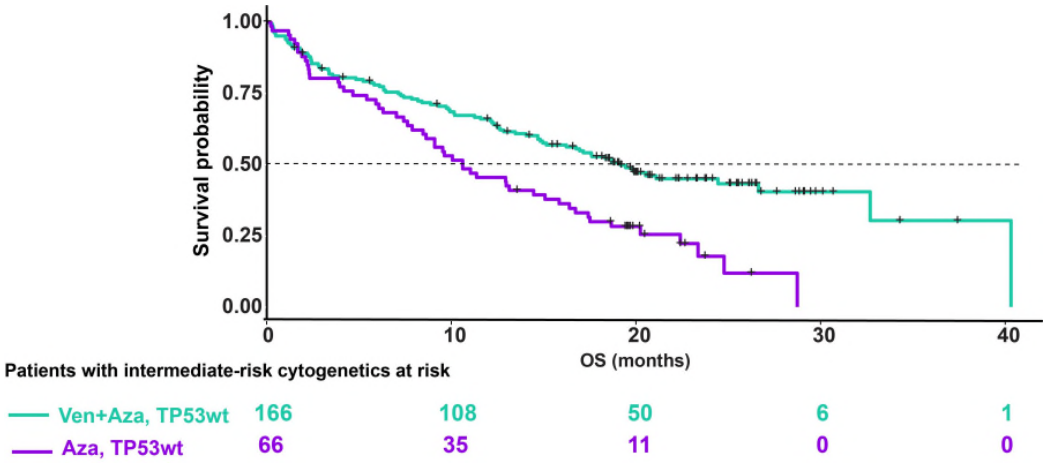
OS by CG. Risk	Poor Risk				Intermediate Risk	
	VEN+AZA		AZA		VEN+AZA	AZA
	***TP53* mut (n=54)**	***TP53* wt (n=50)**	***TP53* mut (n=18)**	***TP53* wt (n=22)**	***TP53* wt (n=166)**	***TP53* wt (n=66)**
Median, months (95% CI)	5.17 (2.17-6.83)	23.43 (11.93-NR)	4.9 (2.14-9.3)	11.29 (4.90-12.78)	19.15 (14.95-26.64)	10.61 (7.89-15.08)

Efficacy by VAF of *TP53* for Patients Who Received Ven+Aza[a]	VAF <20% (n=6)	VAF 20%-40% (n=5)	VAF >40% (n=42)	WT (n=50)
Median OS (95% CI), months	6.18 (0.59-NE)	1.22 (0.56-NE)	5.17 (2.17-6.64)	23.43 (11.93-NE)

OS by Poor-risk Cytogenetics



OS by Intermediate-risk Cytogenetics



Pollyea D, et al. ASH abstract 224

Frontline triplet regimens in AML

- **HMA+VEN+FLT3 inhibitor in ND-AML**
  - (Yilmaz M, et al. ASH 2021 abstract 798)

- **AZA+VEN+Magrolimab in ND-AML**
  - (Daver et al. ASH abstract 371)

HMA+VEN+FLT3 inhibitor: Study design and demographics

Key Eligibility Criteria
- ND *FLT3*-mutated AML (ITD and/or TKD)
- Unfit for intensive chemotherapy

Induction	Consolidation
Doublets: Low-intensity chemo + FLT3i **Dec (20 mg/m² IV D1-5 to D10), *or* Aza (75 mg/m² IV/SUBQ D1-7), *or* Cladribine (5 mg/m² IV D1-5) + LDAC (20 mg/m² SUBQ D1-10 or LDAC alone) + FLT3i (D1-28)**	**Dec (20 mg/m² IV D1-5 to D10), *or* Aza (75 mg/m² IV/SUBQ D1-5 to D7), *or* Cladribine (5 mg/m² IV D1-3) + LDAC (20 mg/m² SUBQ D1-3; alt. w/Dec or LDAC alone) + FLT3i (D1-28)**
Triplets: Low-intensity chemo + FLT3i + Ven **Dec (20 mg/m² IV D1-10), *or* Aza (75 mg/m² IV/SC D1-7) + Ven 400 mg/day (D1-14 to D28) + FLT3i (D1-14 to D28)**	**Dec (20 mg/m² IV D1-5 to D10), *or* Aza (75 mg/m² IV/SC D1-5 to D7) + Ven 400 mg/day (D1-14 to D28) + FLT3i (D1-14 to D28)**

Primary endpoint: OS, response rates, MRD-negative response rates

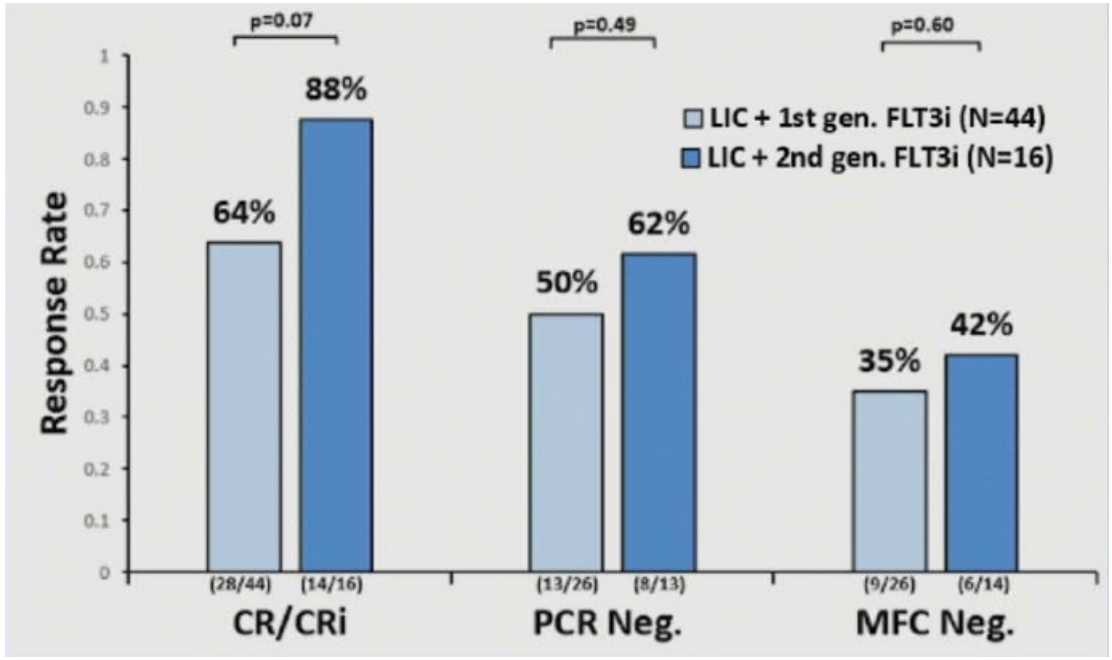
Patient Characteristics		Doublet (n=60)	Triplet (n=27)
Median age (range), years		71 (51-83)	69 (40-85)
≥75 years old, n (%)		22 (37)	7 (26)
De novo AML, n (%)		43 (71)	20 (74)
Median WBC (range), x10^9/L		5.3 (0.3-164)	4.2 (1-201)
Median Hgb (range), g/dL		9.2 (7-13)	9.0 (6-12)
Median Plt (range), x10^9/L[a]		27 (3-326)	53 (9-116)
Median PB blasts (range), %		26 (0-98)	19 (0-89)
Median BM blasts (range), %		70 (22-97)	60 (22-85)
Cytogenetics, n (%)	Diploid	37 (62)	13 (48)
	Complex/-5/-7	6 (10)	5 (19)
FLT3 mut,[b] n (%)	ITD	53 (88)	21 (78)
	D835	0 (0)	5 (18)
	ITD and D835	7 (12)	1 (4)
Median basline allelic ratio (range)	ITD	0.71 (0.06-4.1)	0.41 (0-3.34)
	D835[b]	0 (0-0.41)	0 (0-0.46)

[a]P=0.01. [b]P<0.01.

Yilmaz M, et al. ASH 2021. Abstract 798.

HMA+VEN+FLT3 inhibitor: Response outcomes

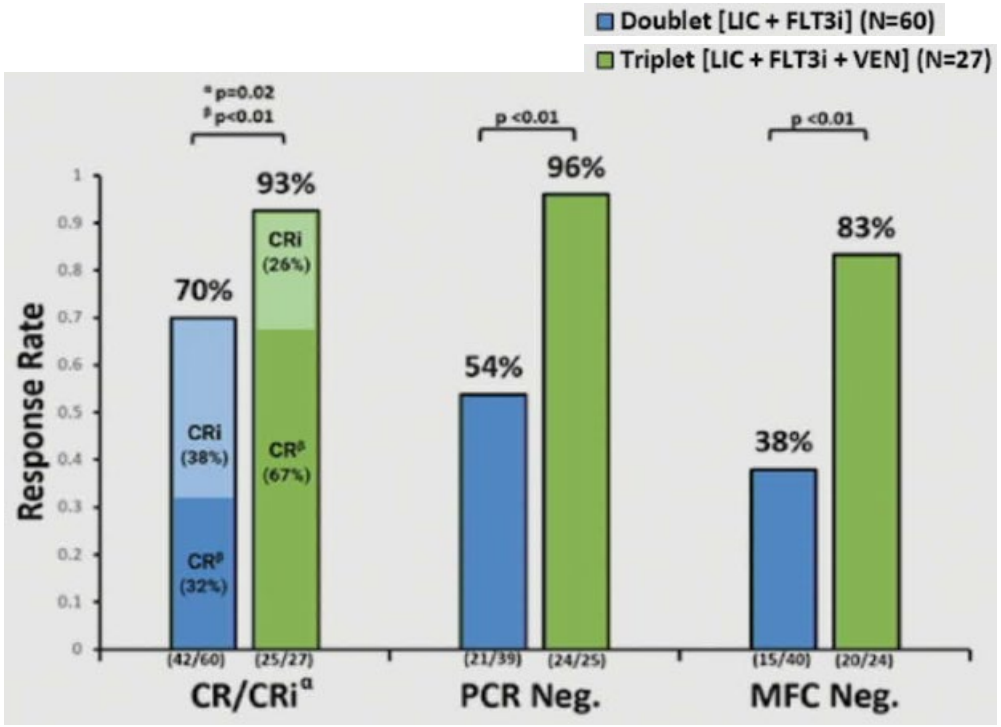
Higher CR/CRi rates observed with 2nd generation FLT3i



Doublet (n=60)

- 1st generation FLT3i: 73% (n=44)
- 2nd generation FLT3i: 16% (n=27)

Higher CR/CRi and MRD-negative CR rates with triplet



Median cycles to best response

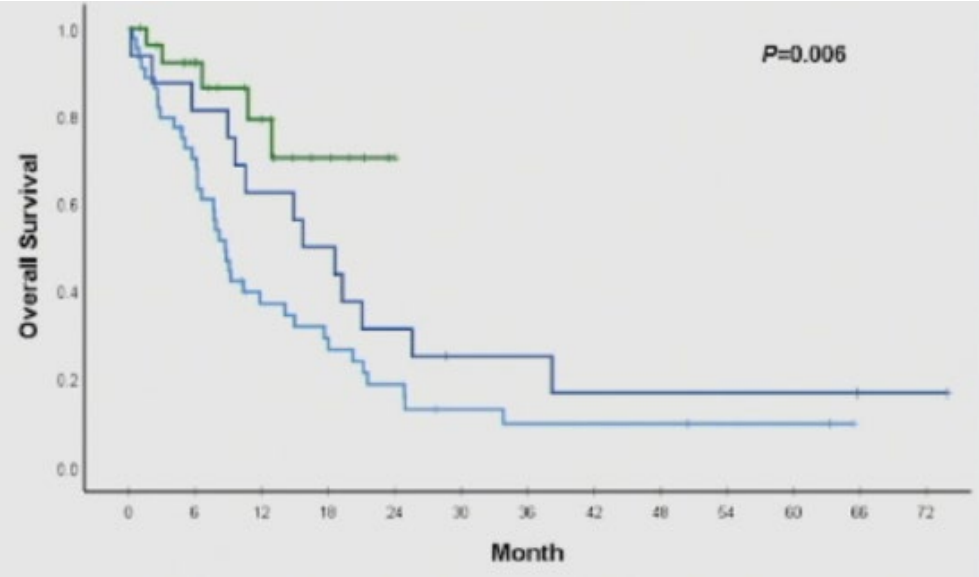
- Triplet (n=27): 1 cycle (range, 1-4)
- Doublet (n=60): 2 cycles (range, 1-5)

[a]*P*=0.01. [b]*P*<0.01.

Yilmaz M, et al. ASH 2021. Abstract 798.

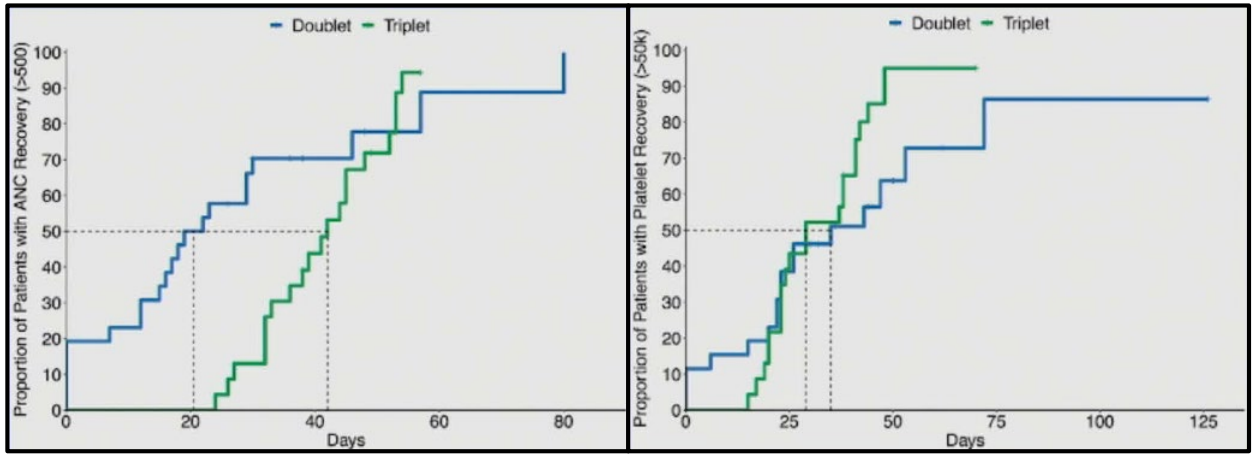
HMA+VEN+FLT3 inhibitor: Survival outcomes

Incremental increases in OS observed with successive iteration of treatment



OS by Treatment	n	Median Follow-up, months	Median OS, months
Triplet	27	12	NR
Doublet: 1st gen FLT3i	44	50	8.7
Doublet: 2nd gen FLT3i	16	65	15.7

Median time to ANC recovery prolonged with triplets compared to doublets at end of cycle 1; 60-day mortality similar



60-day mortality	N	%
Doublet	6	10
Triplet	2	7

AlloSCT in CR1		n	Median OS, months
Doublets	Yes	6	NR
	No	23	18.5
Triplets	Yes	8	NR
	No	13	NR

Frontline triplet regimens in AML

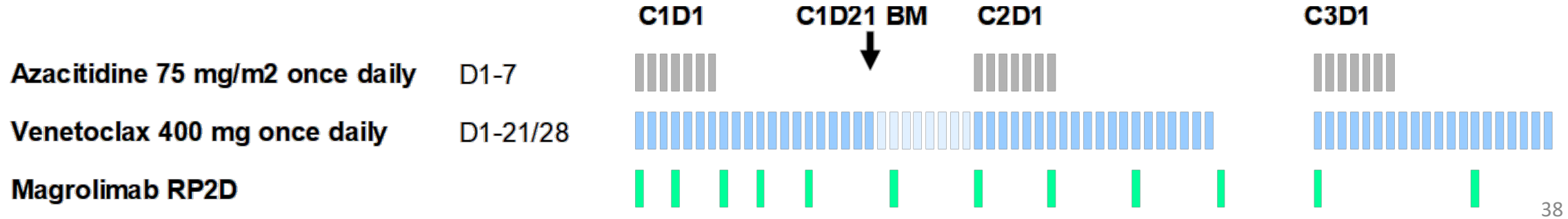
- **HMA+VEN+FLT3 inhibitor in ND-AML**
  - (Yilmaz M, et al. ASH 2021 abstract 798)

- **AZA+VEN+Magrolimab**
  - (Daver et al. ASH abstract 371)

AZA+VEN+Magrolimab: Demographics

Characteristics	Frontline Cohort (n=25)		R/R Cohort (n=23)	
	TP53 mutated (n=14)	TP53 wild type (n=11)	VEN-naïve (n=8)	Prior VEN (n=15)
Age, yrs	67 [46 to 77]	71 [32 to 82]	51 [28 to 74]	70 [35 to 79]
BM blasts, %	37 (9 to 96)	33 (16 to 92)	29 (11 to 87)	57 (6 to 85)
Diagnosis				
De novo AML	4 (29)	6 (55)	4 (50)	5 (33)
Secondary AML	10 (71)	5 (45)	4 (50)	10 (67)
ELN 2017 CG				
Intermediate	2 (14)	6 (55)	2 (25)	4 (27)
Adverse	11 (86)	5 (45)	6 (75)	11 (73)
Prior therapies	0	0	2 (1 to 3)	2 (1 to 5)

Results expressed as no. (%) or median [range], unless specified.



Daver N, et al. ASH abstract 371.

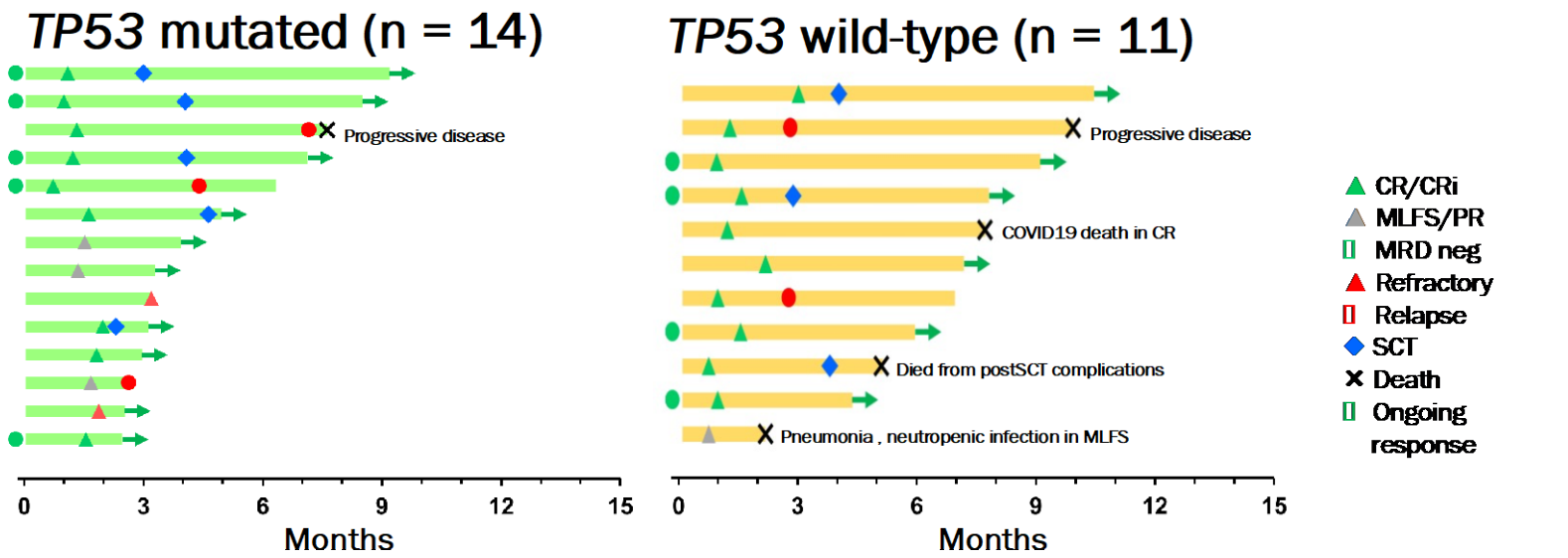
AZA+VEN+Magrolimab: Response outcomes

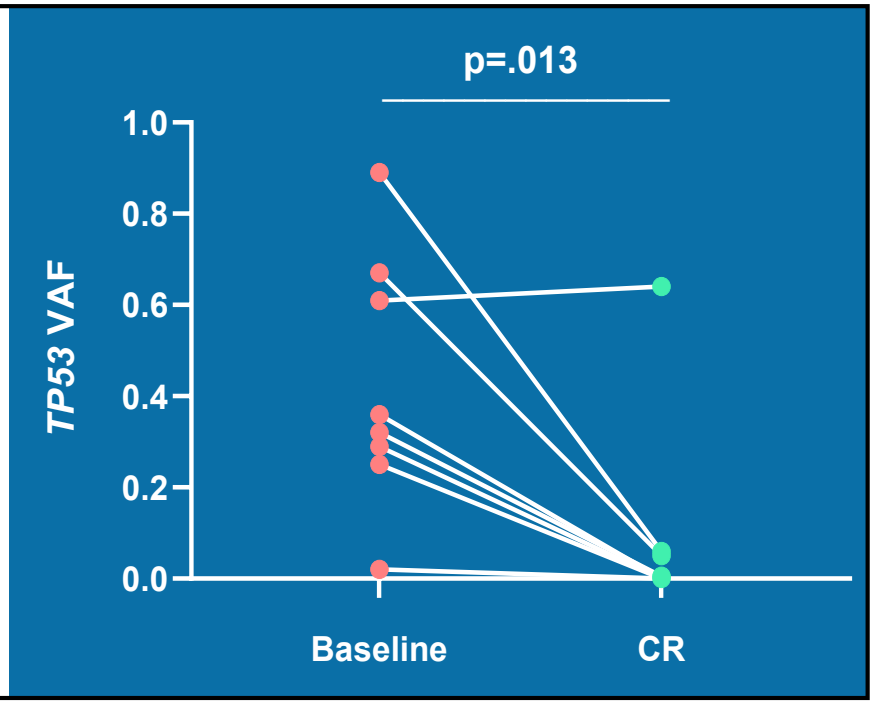
Outcomes	Frontline Cohort (n=25)		R/R Cohort (n=23)	
	TP53 mutated (n=14)	TP53 wild type (n=11)	VEN-naïve (n=8)	Prior VEN (n=15)
ORR	**12 (86)**	**11 (100)**	**6 (75)**	**3 (20)**
CR/CRi	9 (64)	10 (91)	5 (63)	3 (20)
CR	**9 (64)**	**7 (64)**	**3 (38)**	**0**
CRi	0	3 (27)	2 (25)	3 (20)
MLFS / PR[1]	3 (21)	1 (9)	1 (13)	0
MRD neg FCM	5/9* (55)	4/9 (45)	2/6 (33)	0
CCyR	4/9‡ (44)	5/6 (83)	3/5 (60)	1/2 (50)
No response	2 (14)	0	2 (25)	12 (80)
TT First response	**0.7 [0.6 to 1.9]**	**0.7 [0.7 to 1.5]**	0.7 [0.6 to 4.1]	2.2 [1.8 to 2.6]
TT Best response	1.5 [0.7 to 3.2]	1.1 [0.7 to 2.9]	1.5 [1.0 to 4.1]	2.0 [1.2 to 3.9]
Med TT ANC > 500	**28 (20 to 41) days**			
Med TT Plt > 50K	**24 (18 to 41) days**			
8-wk mortality	**0**	**0**	**1 (13)**	**3 (20)**

Results expressed as n (%), n/N (%) or median [range]. FCM = multiparametric FCM, sensitivity 0.1 to 0.01%, *Only among pts with evaluable longitudinal samples; ‡Only among patients with baseline cytogenetic aberrations and longitudinal cytogenetic samples; [1]2 with PR per ELN2017

Daver N, et al. ASH abstract 371.

AZA+VEN+Magrolimab: Survival outcomes





OS by Treatment	*TP53* Mutated (N=14)	*TP53* wild-type (N=11)
Median follow-up	3.9 (range: 2.4-9.2)	7.0 (range: 2.1-10.3)
6-month DOR	83%	80%
6-month OS	100%	81%

Magrolimab appears active in *TP53* AML. Longer follow-up needed to confirm early efficacy signal

Daver N, et al. ASH abstract 371.

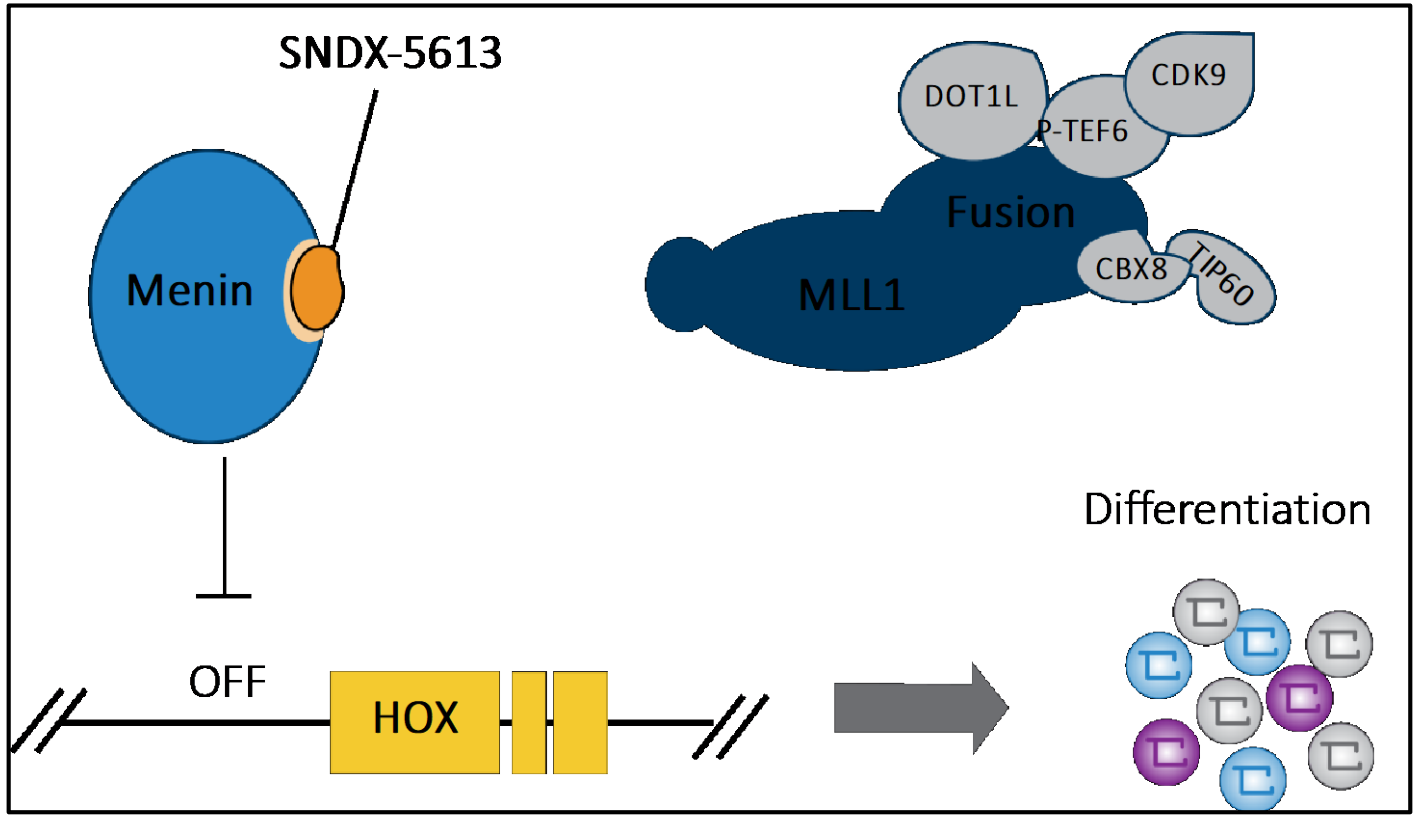
Treatment of relapsed/refractory AML

- **SNDX-5613 in *MLLr* or *NPM1*-mutated R/R-AML**
  - (Stein E, et al. ASH abstract 699)

- **IDHentify Phase 3 Study of Enasidenib vs Other Lower-Intensity Therapies in Patients With IDH2-Mutated R/R AML**
  - (DiNardo C, et al. ASH abstract 1243)

SNDX-5613 in MLLr or NPM1-mutated AML: Demographics

*MLL*r occurs in ~ 15% of pediatric and 5% to 10% of adult leukemias and is associated with poor prognosis: spontaneous translocations at the *MLL1* gene locus[a,b]



Patient Characteristics		Safety Population (n=59)
Median age (range), years		47 (1-78)
ELN risk, n (%)	Favorable	4 (7)
	Intermediate	9 (15)
	Adverse	23 (39)
Leukemia type, n (%)	AML	49 (83)
	ALL	9 (15)
	MPAL	1 (2)
Genetics, n (%)	MLLr	38 (64)
	NPM1 mut	13 (22)
	Non MLLr/Non NPM1 mut	8 (14)
Prior therapies	Median (range)	4 (1-12)
	SCT, n (%)	25 (42)
	Venetoclax, n (%)	35 (59)

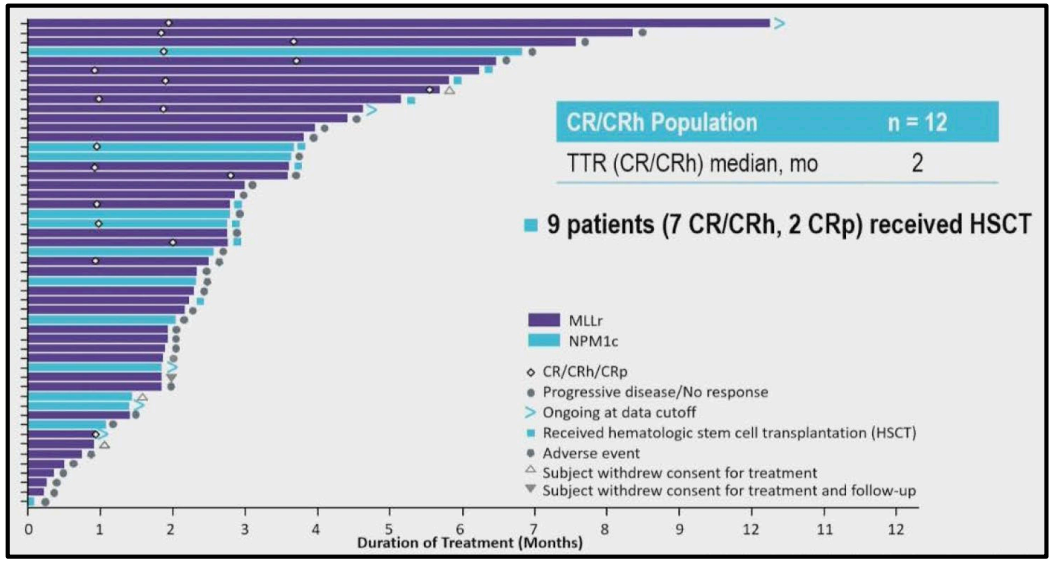
MLLr, mixed lineage leukemia-rearranged.

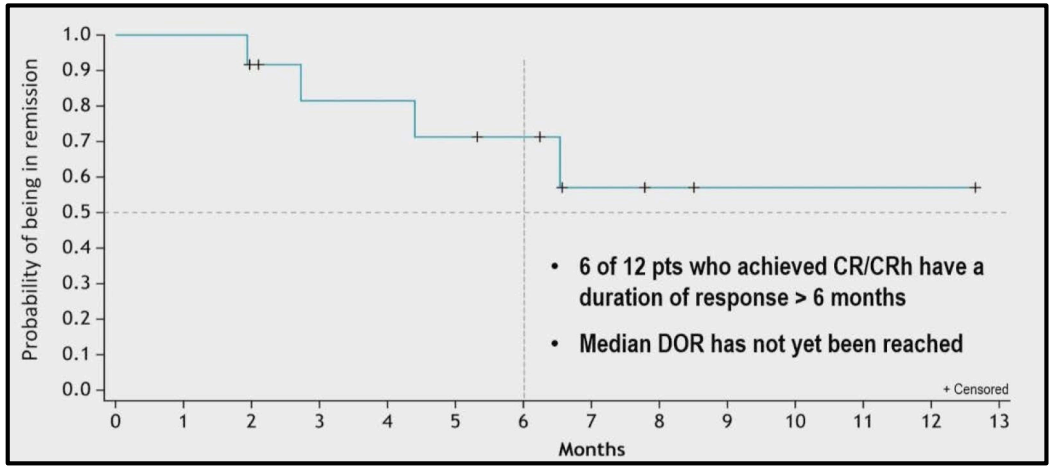
a. Uckelmann HJ, et al. Blood. 2018;132:546; b. Kuhl MW, Armstrong SA. Cancer Cell. 2015;27:431-433.

Stein E, et al. ASH abstract 699.

SNDX-5613 in MLLr or NPM1-mutated AML: Response and survival

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





Stein E, et al. ASH abstract 699.

SNDX-5613 in MLLr or NPM1-mutated AML: Safety

- 7% (N=3/43) of patients treated at RP2D reported G2 QTc prolongation
- Differentiation syndrome occurred in 14% (N=8) of patients, none grade 3 or greater

Any Grade TRAE (≥5%), n (%)	Safety Population (n=59)
Patients with ≥1 TRAE	46 (78)
ECG QTc prolonged	29 (49)
Nausea	16 (27)
Vomiting	10 (17)
Differentiation syndrome	8 (14)
Diarrhea	7 (12)
Dysgeusia	5 (8)
Decreased appetite	4 (7)
Fatigue	3 (5)
Hyperphosphatemia	3 (5)
Neutropenia	3 (5)
Thrombocytopenia	3 (5)

Grade ≥3 TRAE, n (%)	Safety Population (n=59)
Patients with grade≥3 TRAE	11 (19)
ECG QTc prolonged	7 (12)
Diarrhea	2 (3)
Anemia	1 (2)
Asthenia	1 (2)
Fatigue	1 (2)
Febrile neutropenia	1 (2)
Hypokalemia	1 (2)
Neutropenia	1 (2)
Thrombocytopenia	1 (2)
TLS	1 (2)

Stein E, et al. ASH abstract 699.

Treatment of relapsed/refractory AML

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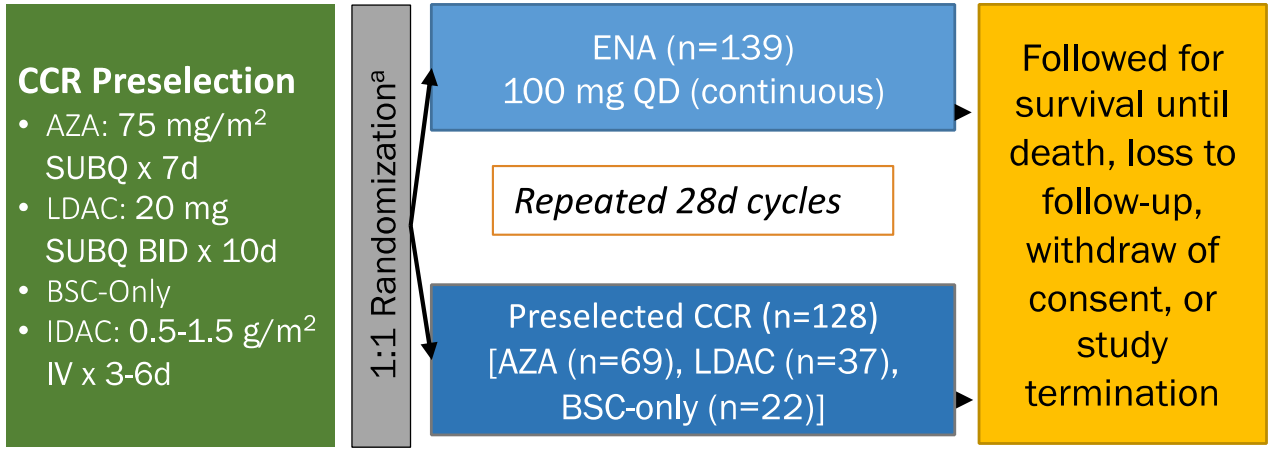
  - (DiNardo C, et al. ASH abstract 1243)

ENA vs. CCR in AML: Design and demographics

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



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

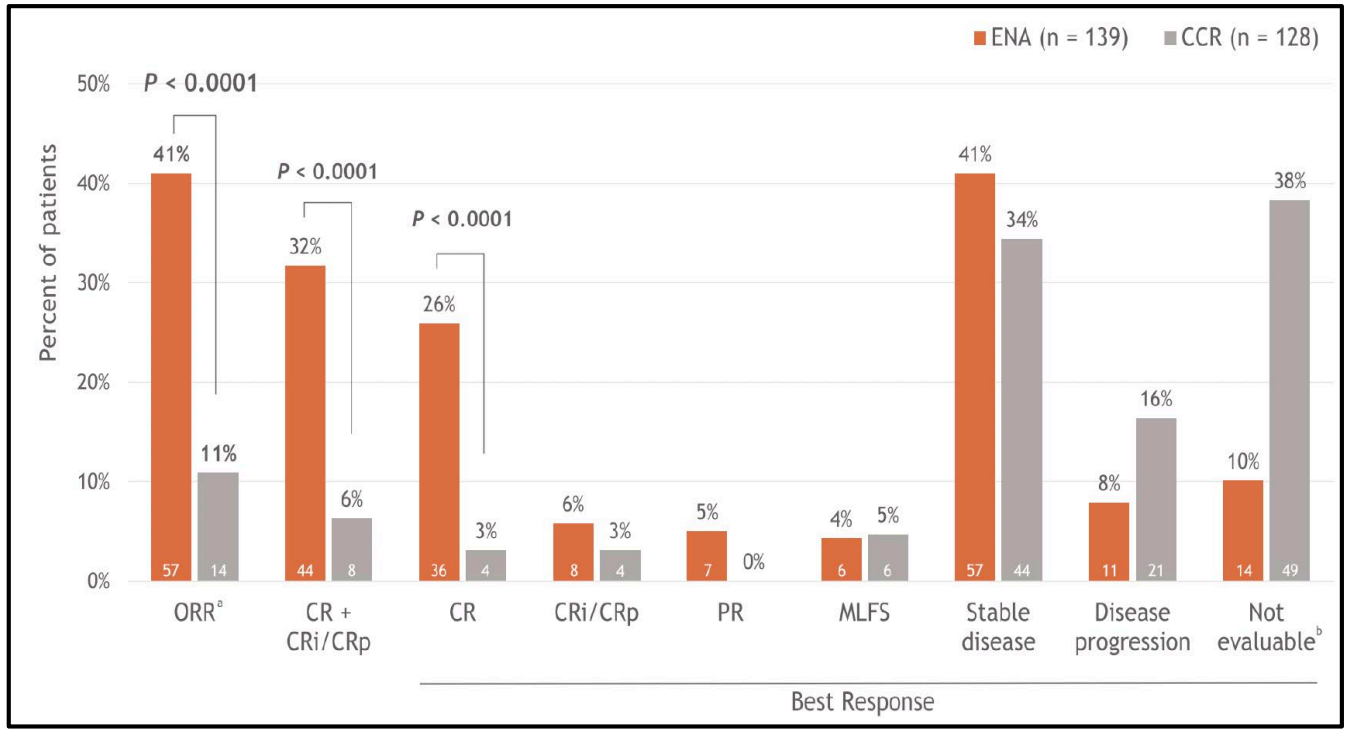
Primary endpoint: OS
Secondary endpoints: ORR, EFS, TTF, HI & TI, safety

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

DiNardo C, et al. ASH abstract 1243.

ENA vs. CCR in AML: Response outcomes

Clinical Response Rates

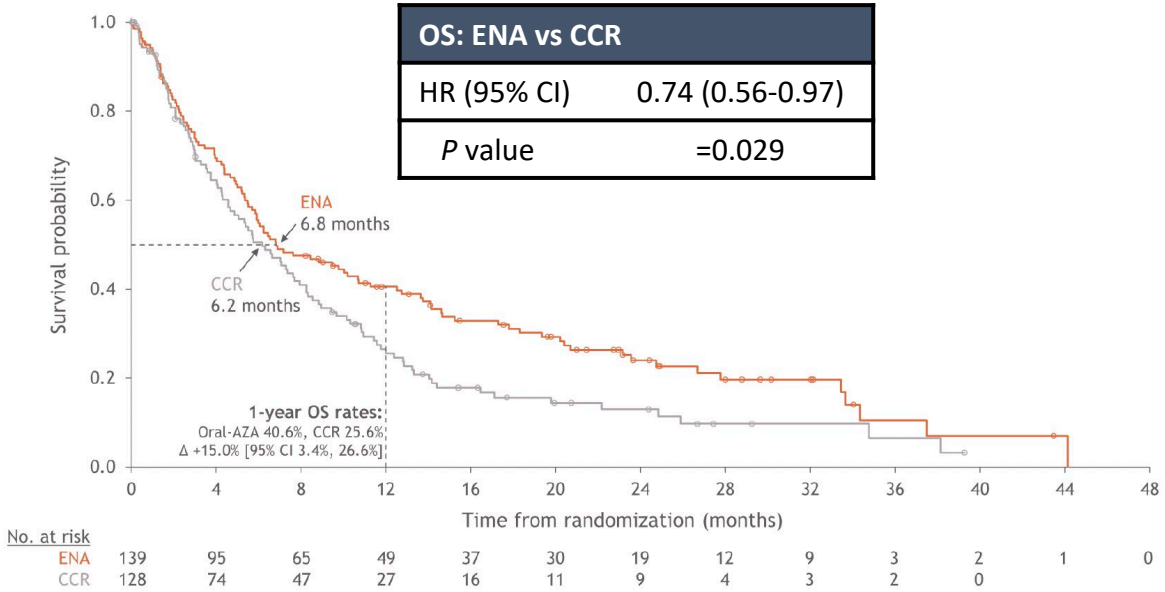


Hematologic Response		ENA (n=139)	CCR (n=128)
RBC TI, n/N (%)	RBC TD at BL, achieved TI on-study	29/93 (31.2)	8/76 (10.5)
	RBC TI at BL, retained TI on-study	28/45 (62.2)	7/37 (18.9)
Platelet TI, n/N (%)	Platelet TD at BL, achieved TI on-study	24/80 (30.0)	6/57 (10.5)
	Platelet TI at BL, retained TI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

DiNardo C, et al. ASH abstract 1243.

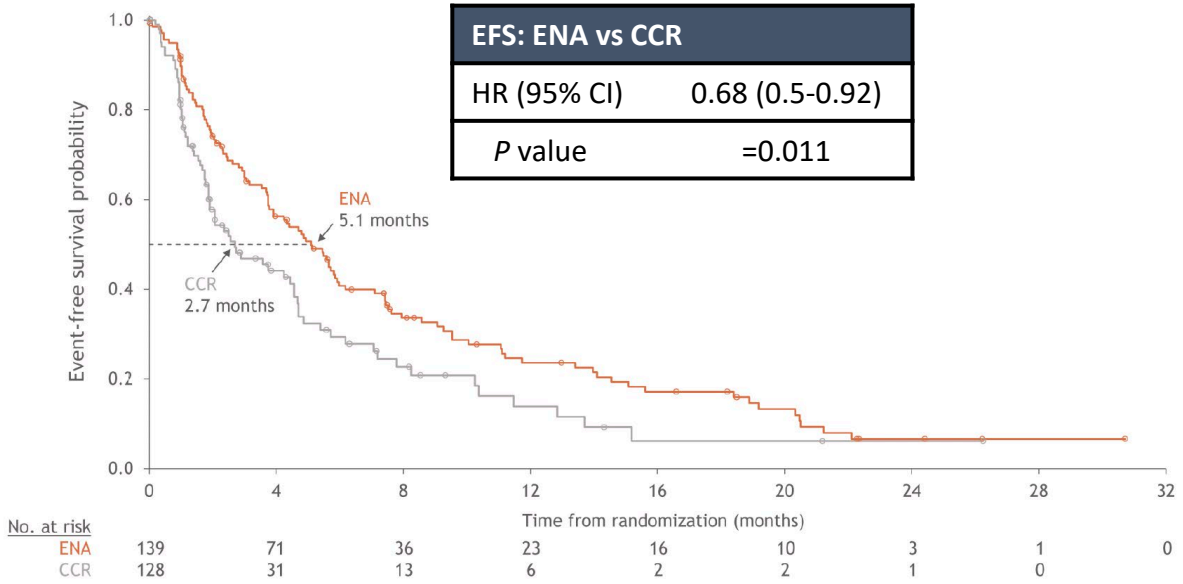
ENA vs. CCR in AML: Survival outcomes

OS



OS: ENA vs CCR	
HR (95% CI)	0.74 (0.56-0.97)
P value	=0.029

EFS



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

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

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

DiNardo C, et al. ASH abstract 1243.

ENA vs. CCR in AML: Treatment and safety outcomes

Safety	ENA (n=139)	CCR (n=128)
Median treatment duration (range), days	143 (3-1270)	49 (1-1166)
ENA-related differentiation syndrome, %	13	-
TX-related hyperbilirubinemia, %	26	-
Treatment discontinuation, n (%)[a]	128 (92)	109 (85)
Disease progression	41 (29)	26 (20)
Death	29 (21)	19 (15)
No benefit from treatment	-	24 (19)
AML relapse	25 (18)	-
AE	15 (11)	10 (8)
Patient decision	9 (6)	22 (17)
HSCT	6 (4)	2 (2)
Transition to other treatment	1 (<1)	-
Other	2 (1)	3 (2)

Safety profile of ENA in this patient subgroup was
- Similar to that of all ENA-randomized patients in this trial
- Consistent with previous reports of ENA monotherapy in patients with R/R AML

DiNardo C, et al. ASH abstract 1243.

Thank You!

Questions:

clachowiez@mdanderson.org