

Newly Diagnosed Fit AML –

**We Are DONE with Intensive
Chemotherapy!**

FLASCO 2026: Malignant Hematology

Jennifer Marvin-Peek, MD

Assistant Professor, Department of Leukemia, MDACC

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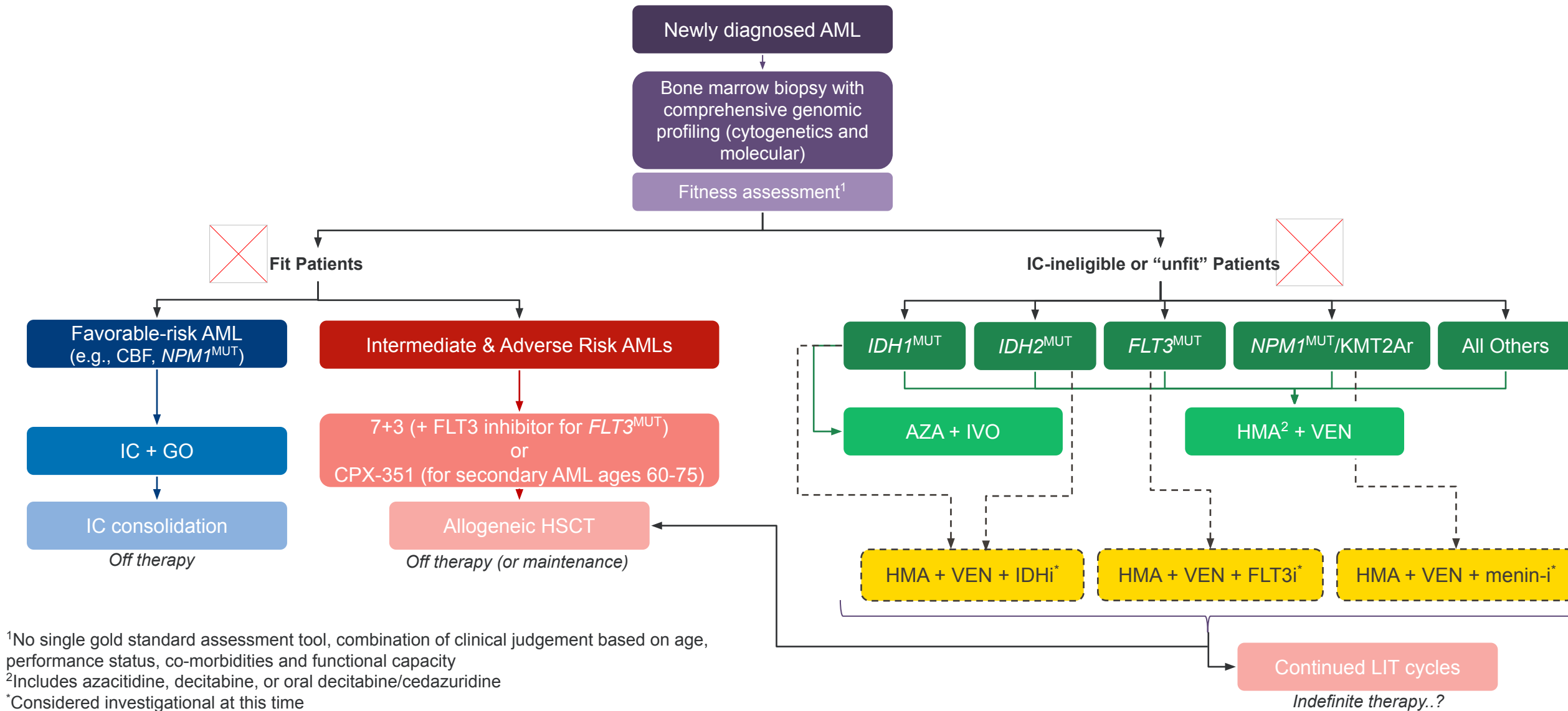
Disclosures

I will be presenting data on investigational combination therapy in this presentation.

The opinions presented during this debate represent my personal interpretation of the available evidence and are intended to stimulate discussion. They do not represent the official positions, policies, or recommendations of my institution.

Current AML Treatment Paradigm

AZA = azacitidine; IC = intensive chemotherapy; IVO = ivosidenib, GO = gemtuzumab ozogamicin; HMA = hypomethylating agent; HSCT = hematopoietic stem cell transplant; IDHi = isocitrate dehydrogenase inhibitor; FLT3i = FLT3 inhibitor; VEN = venetoclax



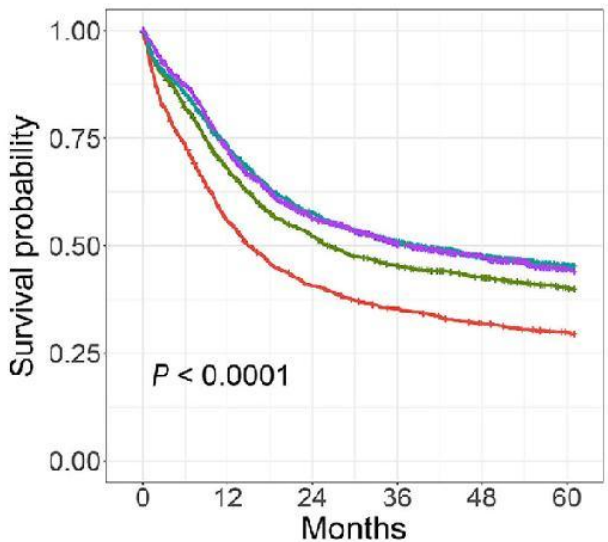
Current AML Treatment Paradigm – Fit Patients

7+3

- CRc rate ~ 50-70%
- 3-year OS: ~50% in more recent years

N=5,359 patients from the HARMONY alliance

- Median age: 53
- 50% HSCT

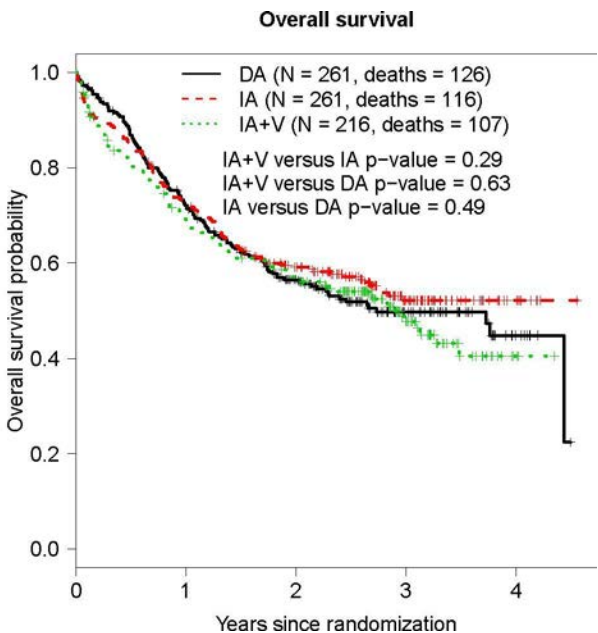


Number of patients

1997-2001	1127	624	452	387	342	310
2002-2006	1294	864	653	556	501	435
2007-2011	1821	1306	1007	871	703	539
2012-2016	1117	774	549	402	305	187

N=738 patients from SWOG1203

- Median age: 49

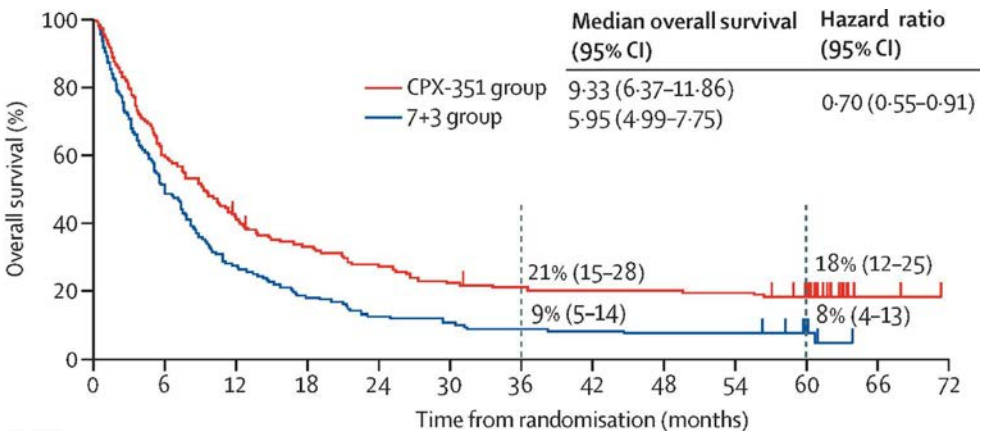


CPX-351

- 60-75 years with secondary AML
- CRc rate: 48% (vs 33% with 7+3)
- 3-year OS: 21%

N=309 patients across 39 centers

- Median age: 68
- 35% HSCT



Number at risk
(number censored)

CPX-351 group	153	92	62	49	40	33	30	29	29	28	22	2	0
	(0)	(0)	(1)	(2)	(2)	(2)	(3)	(3)	(3)	(3)	(7)	(27)	(29)
7+3 group	156	77	43	28	20	17	14	13	12	12	5	0	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(7)	(11)	(11)

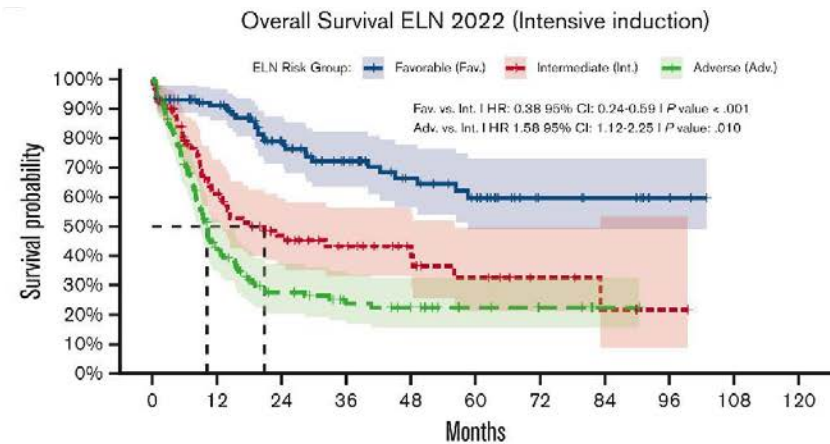
Sobas et al., *Haematologica* 2025 110(5): 285805. Garcia-Manero et al., *Leukemia* 2025, 38(1): 58-66.

Lancet et al., *JCO* 2018 36(26): 2684-2692; Lancet et al., *Lancet Haem* 2021 8(7): E281-E491

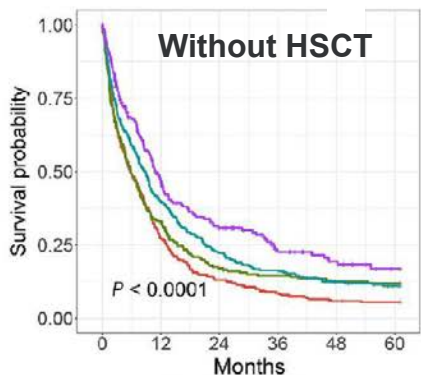
Current AML Treatment Paradigm – adverse risk disease

CR/CRi rate:

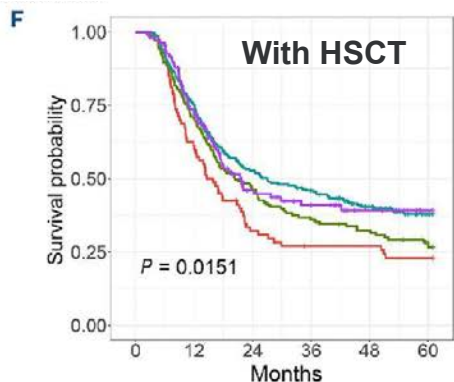
- Favorable: 86%
- Intermediate: 59%
- **Adverse: 49%**



	N at risk (censored)											
Favorable (Fav.)	117 (0)	91 (16)	61 (35)	45 (46)	32 (56)	25 (60)	10 (75)	8 (77)	3 (82)	0 (85)	0 (85)	
Intermediate (Int.)	92 (0)	46 (14)	29 (21)	20 (28)	13 (35)	8 (37)	4 (41)	2 (42)	1 (43)	0 (44)	0 (44)	
Adverse (Adv.)	136 (0)	48 (16)	25 (23)	17 (28)	13 (31)	7 (37)	4 (40)	1 (43)	0 (44)	0 (44)	0 (44)	



	Number of patients				
1997-2001	296	80	38	25	17
2002-2006	221	70	35	29	24
2007-2011	285	108	60	44	30
2012-2016	196	84	49	26	17



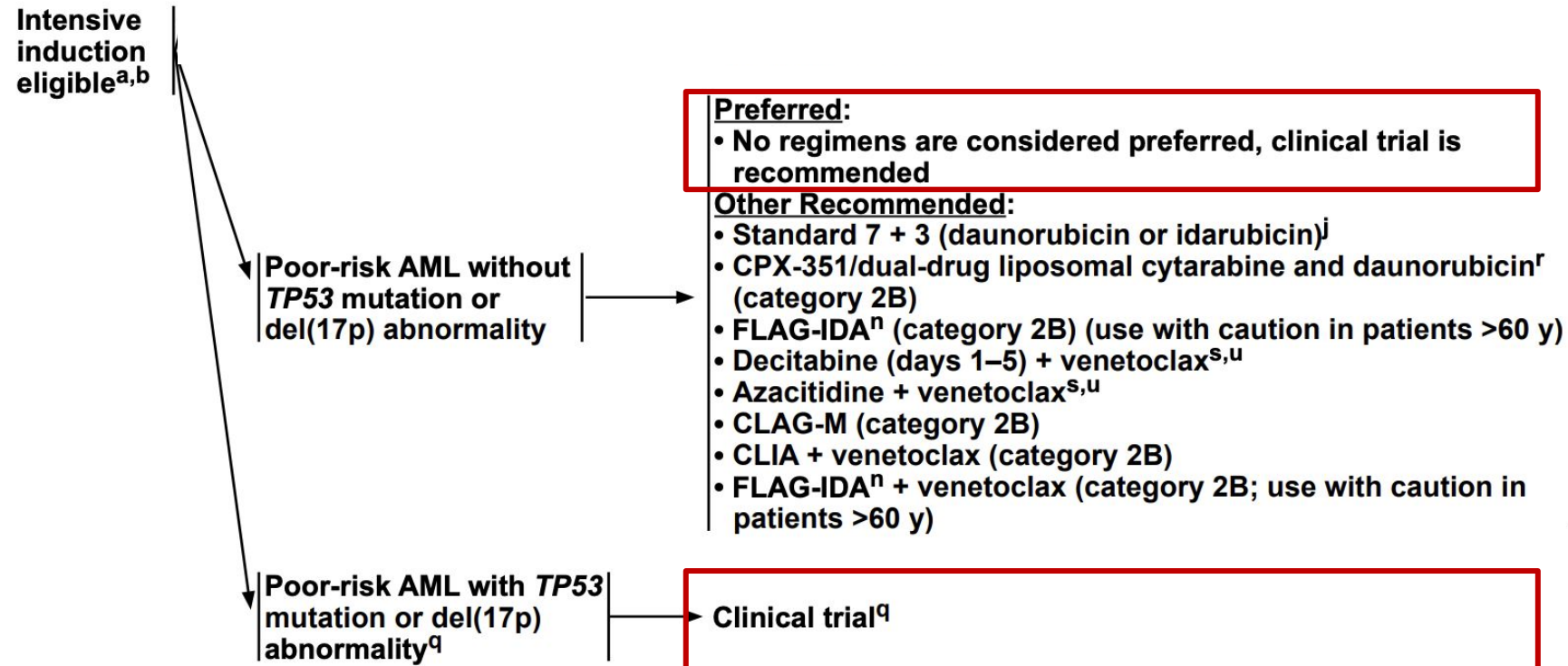
	Number of patients				
1997-2001	80	49	25	20	17
2002-2006	144	99	65	49	32
2007-2011	243	182	124	105	78
2012-2016	108	76	39	29	11

Study	Sample size	Median, months	95% CI
Study design = trial			
Lindsley 2019	35	5.1	[NA; NA]
Prochazka 2019	98	6.5	[5.0; 8.2]
Pooled estimate	133	5.8	[5.1; 6.5]
Study design = retrospective			
Chiche 2021	22	8.5	[NA; NA]
Overall pooled estimate	262	6.5	[5.1; 7.5]

Study	Sample size	Median, months	95% CI
Study design = trial			
DiNardo 2018	36	7.2	[3.7; NR]
DiNardo 2020	37	5.2	[NA; NA]
Pooled estimate	73	6.2	[5.2; 7.2]

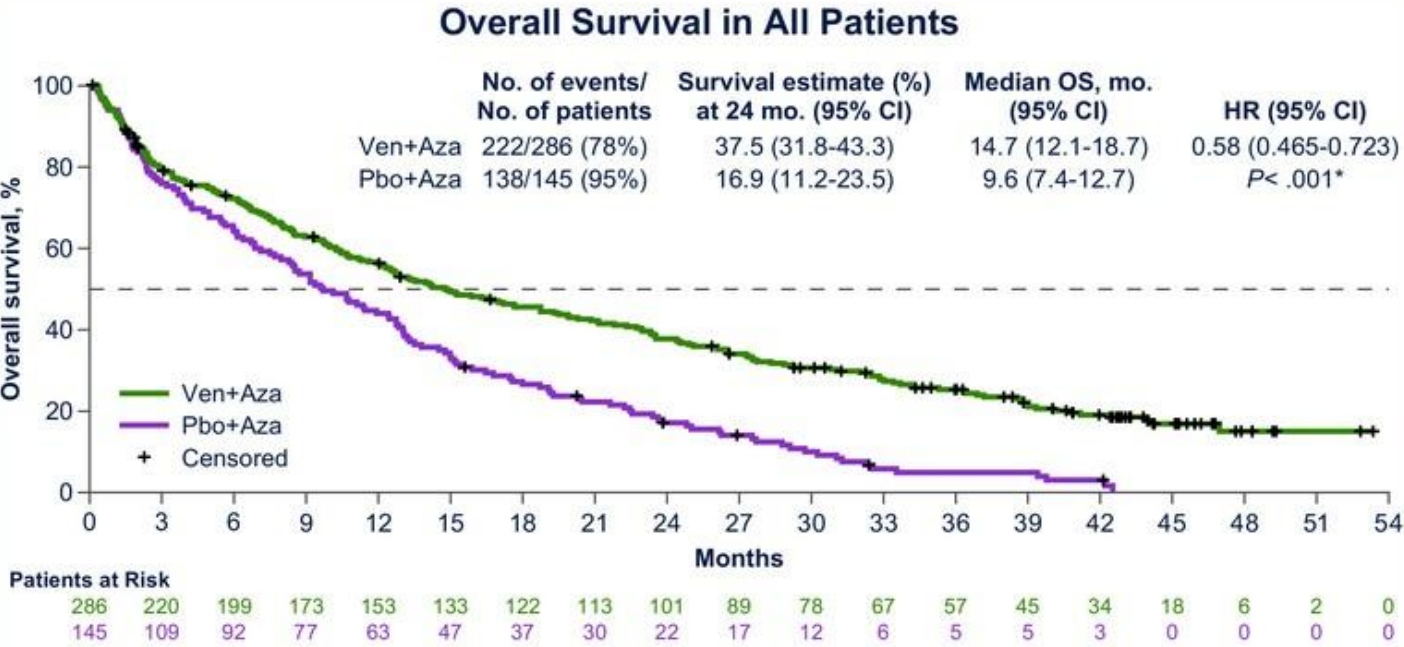
Current AML Treatment Paradigm – adverse risk disease

NCCN Guidelines for AML



Outcomes with HMA-based LIT in older/unfit patients with AML

Outcomes with HMA-VEN doublet



	Venetoclax-Azacitidine (n=286)
Best response, no. (%) [95% CI]	
CR	111 (38.8) [33.1-44.7]
CRi	80 (28) [22.8-33.6]
CRh	75 (26.2) [21.2-31.7]
CR/CRi response, no. (%) [95% CI]	191 (66.8) [61.0-72.2]
CR/CRh response, no. (%) [95% CI]	186 (65.0) [59.2-70.6]

DiNardo et al., *NEJM* 2020 383: 617-629; Pratz et al., *AJH* 2024 99(4): 615-624

Outcomes with IDH inhibitor triplets (HMA+VEN+IDHi)

Table 1. Cohort Characteristics

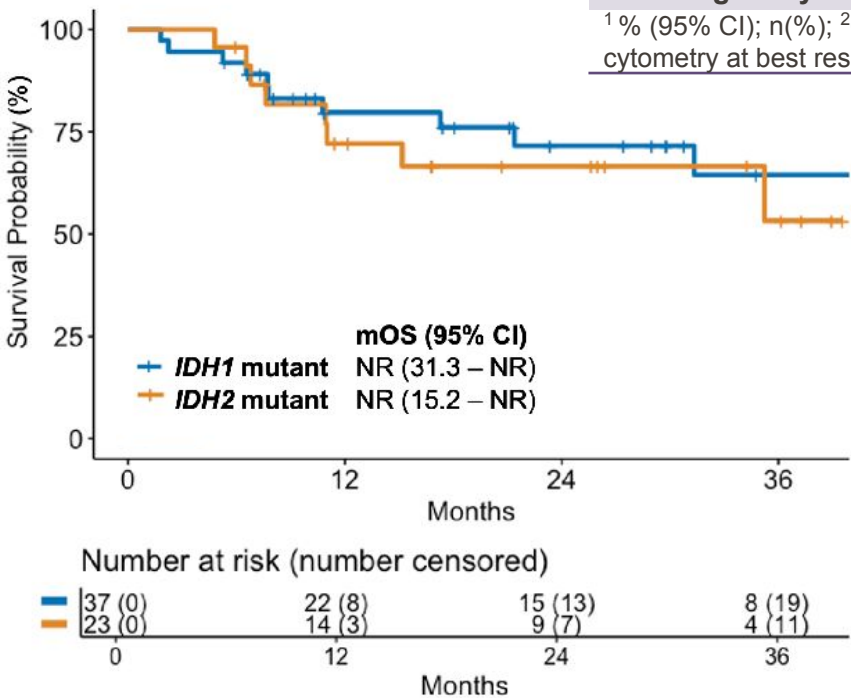
Variable	Overall ¹ (n=60)
Age	71 (62 – 87)
Triplet therapy	--
AZA + VEN + IVO	16 (27)
DAC + VEN + IDHi	44 (73)
DAC + VEN + IVO	21 (48)
DAC + VEN + ENA	23 (52)
Type	--
De novo	35 (58)
Secondary	21 (35)
tsAML	17 (28)
Therapy-related	4 (7)
ELN 2022 Risk	--
Favorable	8 (13)
Intermediate	5 (8)
Adverse	47 (78)
Mutations	--
IDH1	38 (63)
IDH2	26 (43)
FLT3-ITD	2 (3)
K/NRAS	12 (20)
NPM1	13 (22)
TP53	4 (7)
Signaling mutation ²	20 (33)
HSCT	19 (32)

¹ Median (min, max); n (%); ² Including FLT3, JAK2, KIT, KRAS, NF1, NRAS, PTPN11

Table 2. Clinical Outcomes of the Frontline Cohort¹

	All (n=60)	Non-tsAML (n=43)	tsAML (n=17)	IDH1 ^{mut} (n=37)	IDH2 ^{mut} (n=23)
2-year OS	69 (57 – 83)	84 (73 – 97)	34 (16 – 71)	72 (57 – 90)	67 (49 – 91)
2-year CIR ²	24 (6 – 39)	20 (0 – 36)	38 (0 – 65)	26 (0 – 46)	22 (0 – 43)
30-day mortality	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
60-day mortality	1 (2)	0 (0)	1 (6)	0 (0)	1 (4)
CRc ³	55 (92)	42 (98)	13 (71)	32 (86)	23 (100)
MRD negativity	45 (87)	35 (88)	10 (83)	25 (81)	20 (95)

¹ % (95% CI); n(%); ²Censored at SCT; ³Within 5 cycles of treatment; ⁴By multiparameter flow cytometry at best response, sensitivity 10⁻⁴



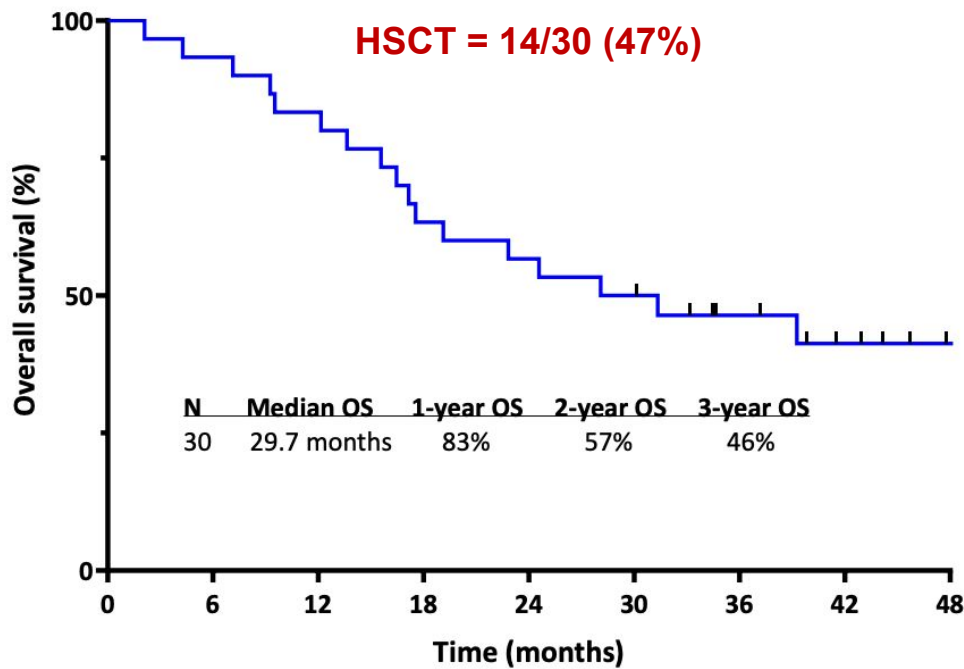
Median follow up: 27.4 months

Outcomes with FLT3 inhibitor triplets

AZA + VEN + GILT

Median age = 71 years

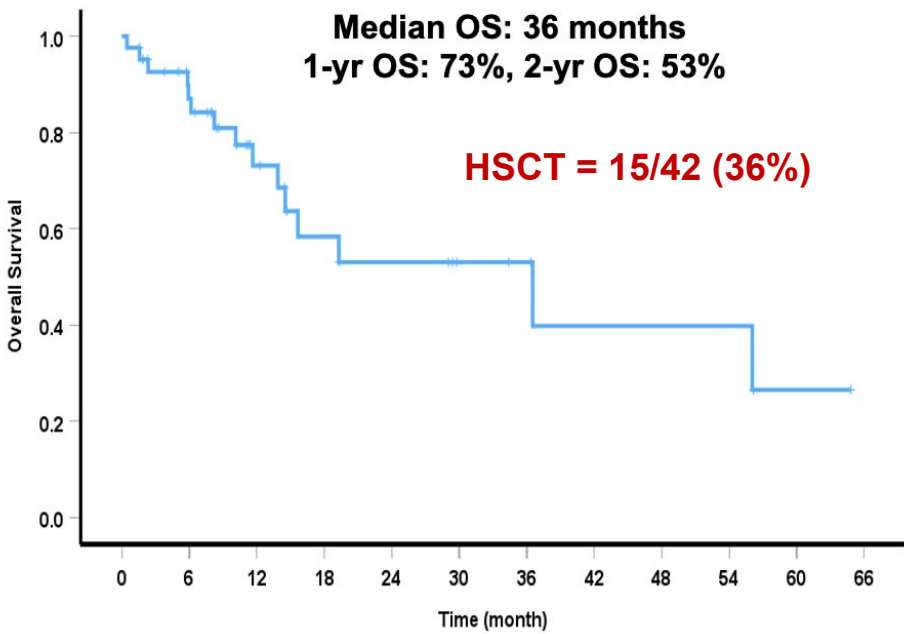
Hematologic Response	Frontline Cohort (n = 30)
mCRc (CR/CRi/MLFS), No. (%)	30 (100)
CR	27 (90)
CRi	2 (6)
MLFS	1 (4)
PR	0
No response	0



DAC + VEN + QUIZ

Median age = 70 years

Response*, N (%)	Newly Diagnosed Cohort (N=42)
Hematologic Response	
mCRc	38 (91)
CR	30 (72)
CRi	7 (17)
MLFS	1 (2)
No response	3 (7)
Induction death	1 (2)



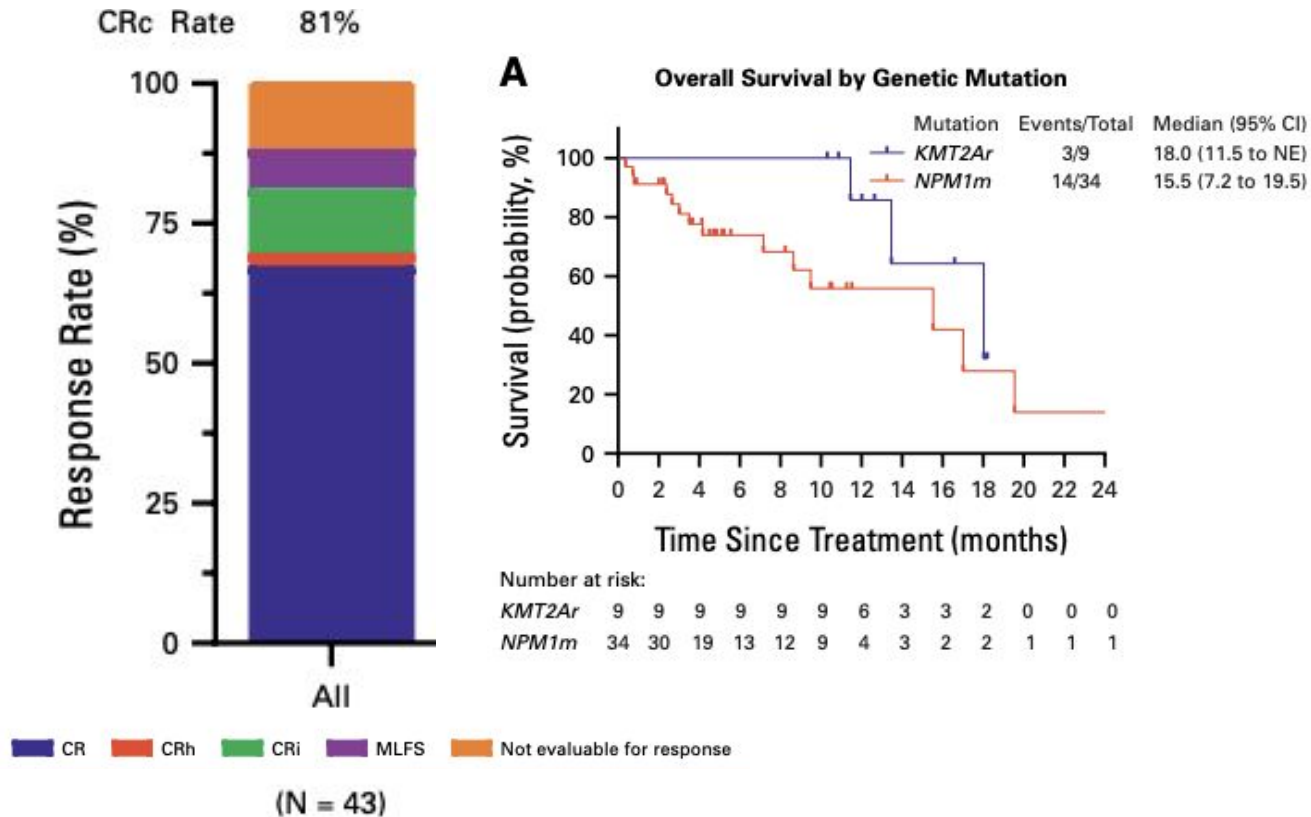
Short et al., *JCO* 2024 42(13): 1499-1508; Short et al., *Blood Adv* 2026, 019841
Yilmaz et al., *JCO* 2026 44(16): Supp 1, ASCO Oral #6504

Outcomes with menin inhibitor triplets

AZA + VEN + REVUMENIB

Median age = 70 years

HSCT = 10/43 (23%)



Oral DAC + VEN + SNDX-5613 (SAVE)

Median age = 70 years

- N=17 patients (11 *NPM1* and 6 *KMT2Ar*)
- **ORR (CR + MLFS) = 94% (16/17)**
- HSCT = 5/17 (29%)

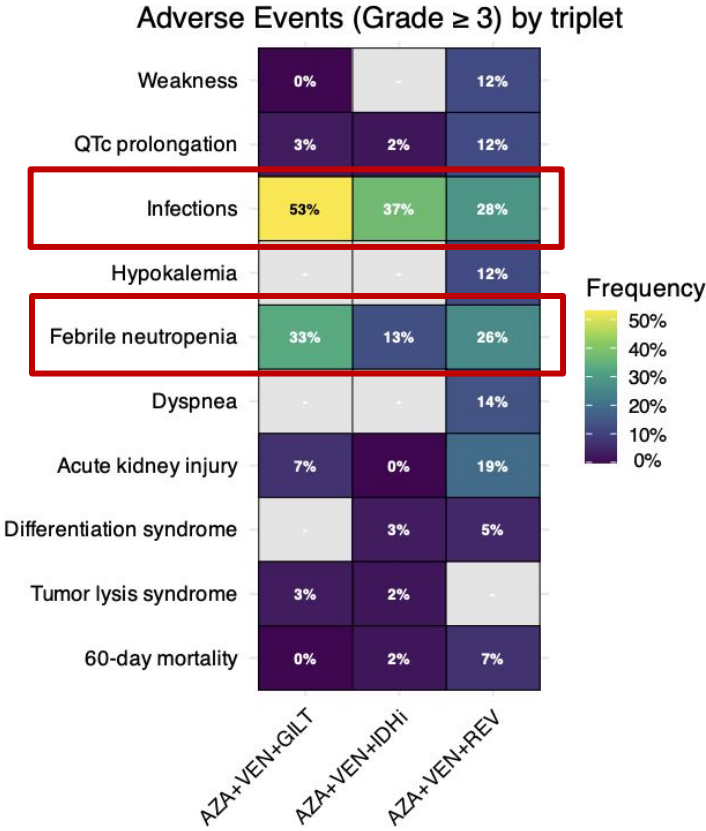
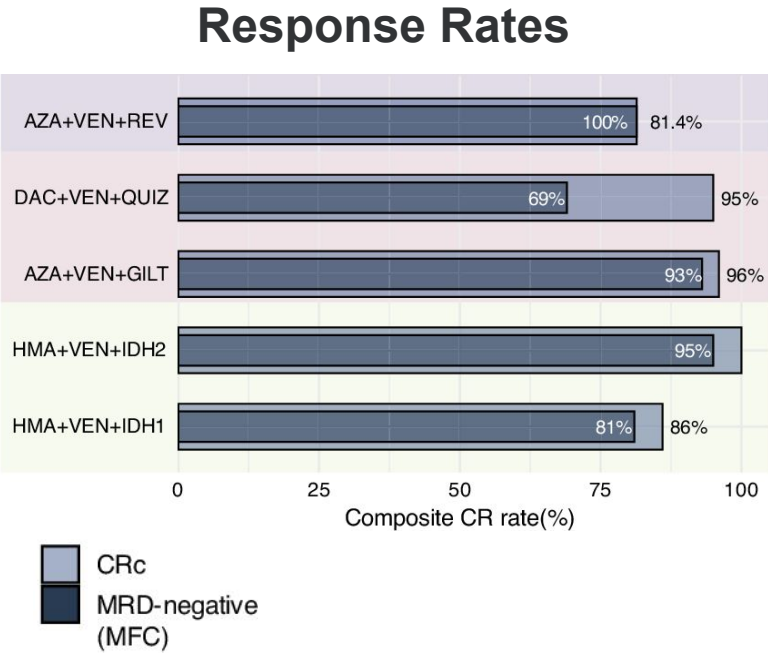
AZA + VEN + ZIFTOMENIB (KOMET-007)

Median age = 75 years

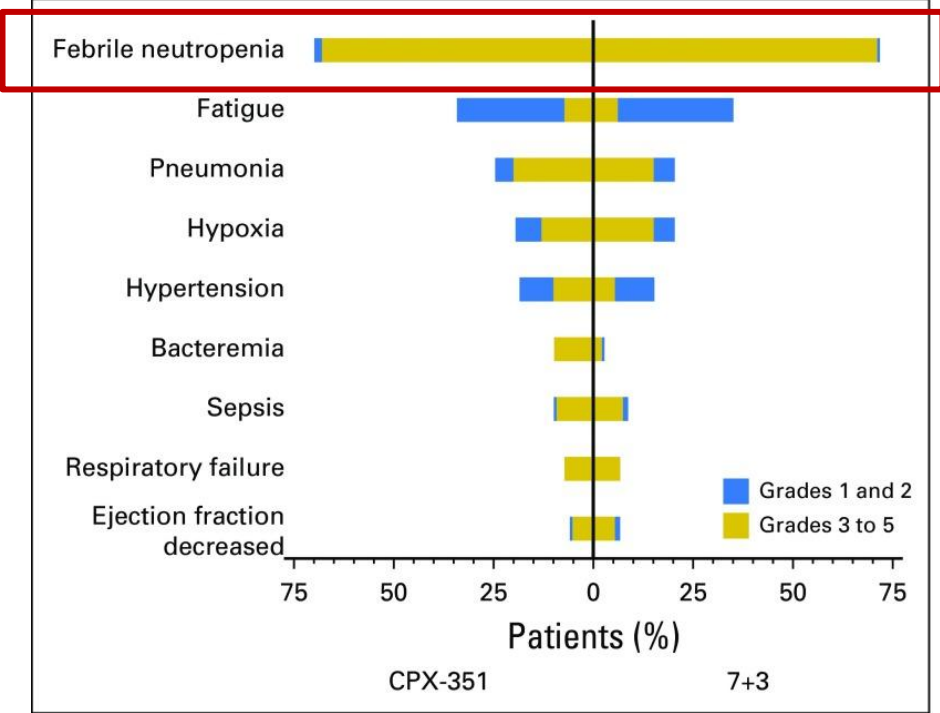
- N=39 patients (All *NPM1*)
- **CRc = 86% (32/37)** with 68% molecular MRD negativity

Zeidner et al., *JCO* 2025 43, 2606-2615; Jen et al., *Blood* 2025 146(1): ASH Oral #47; Roboz et al., *Blood* 2025 146(1): ASH Oral #766

Summary of outcomes and adverse events with HMA-based triplets



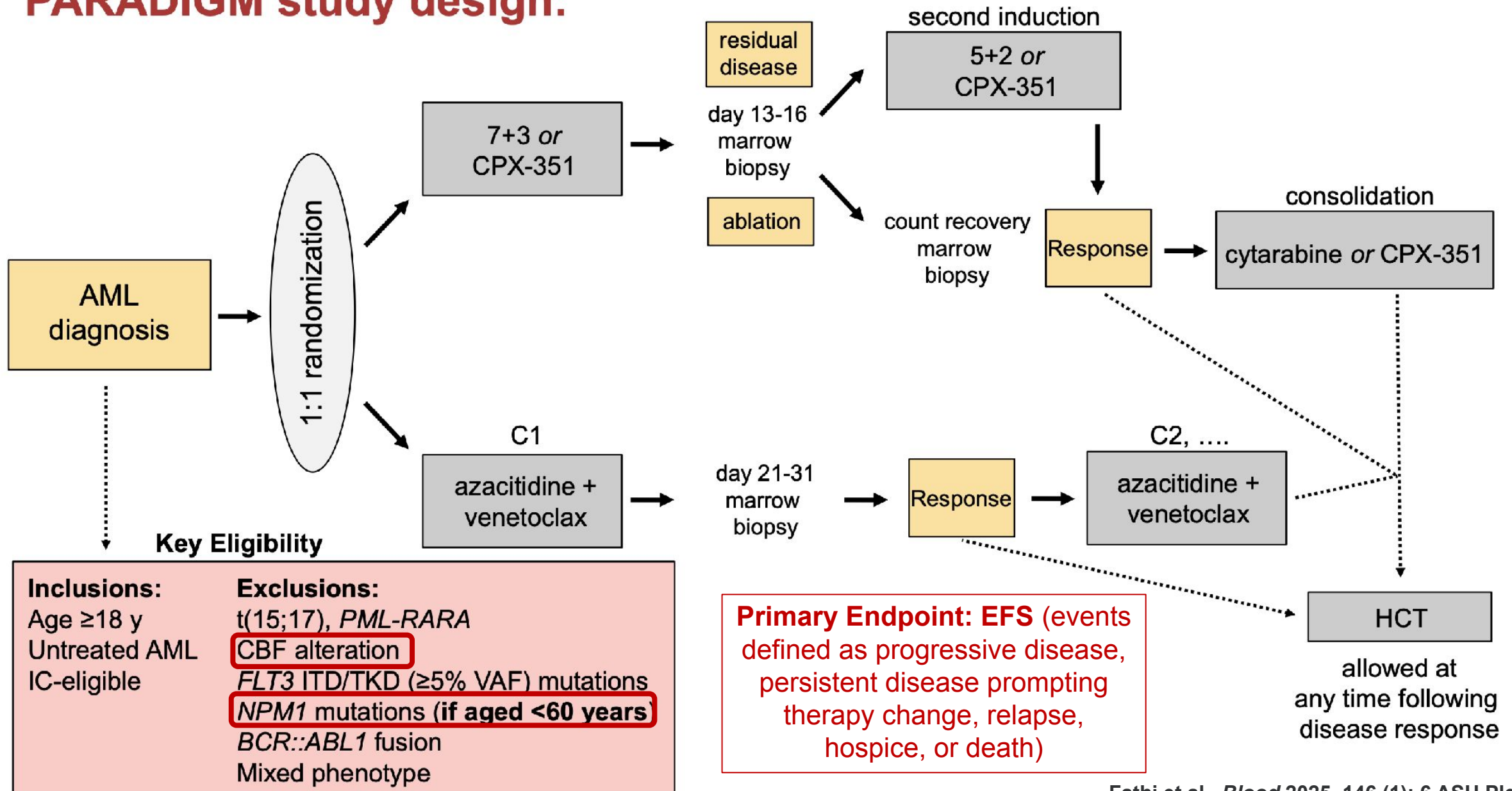
Adverse Events



Jen et al., *Blood Cancer Journal* 2026, 16: Article #6; Lancet et al., *JCO* 2018 36(26): 2684-2692;

Results from the phase 2, multicenter randomized PARADIGM trial in fit / IC-eligible patients

PARADIGM study design:

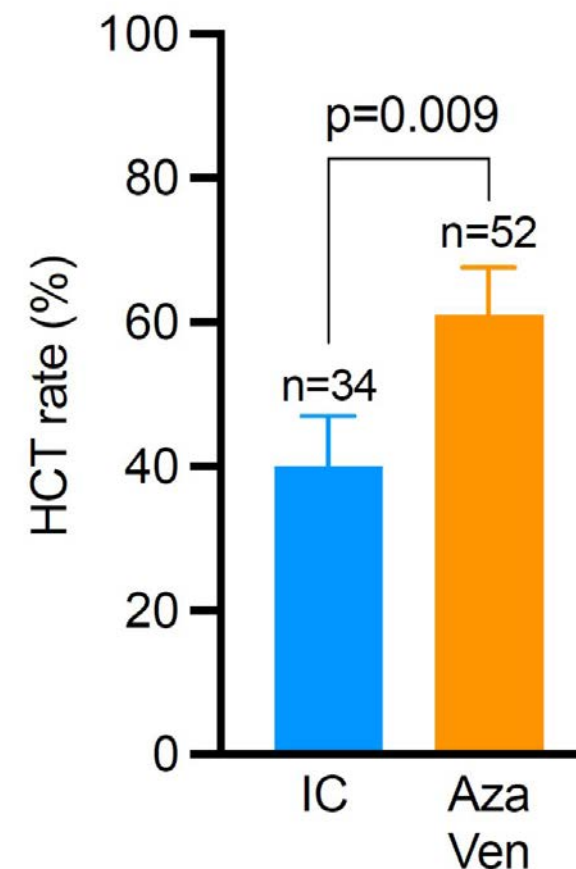
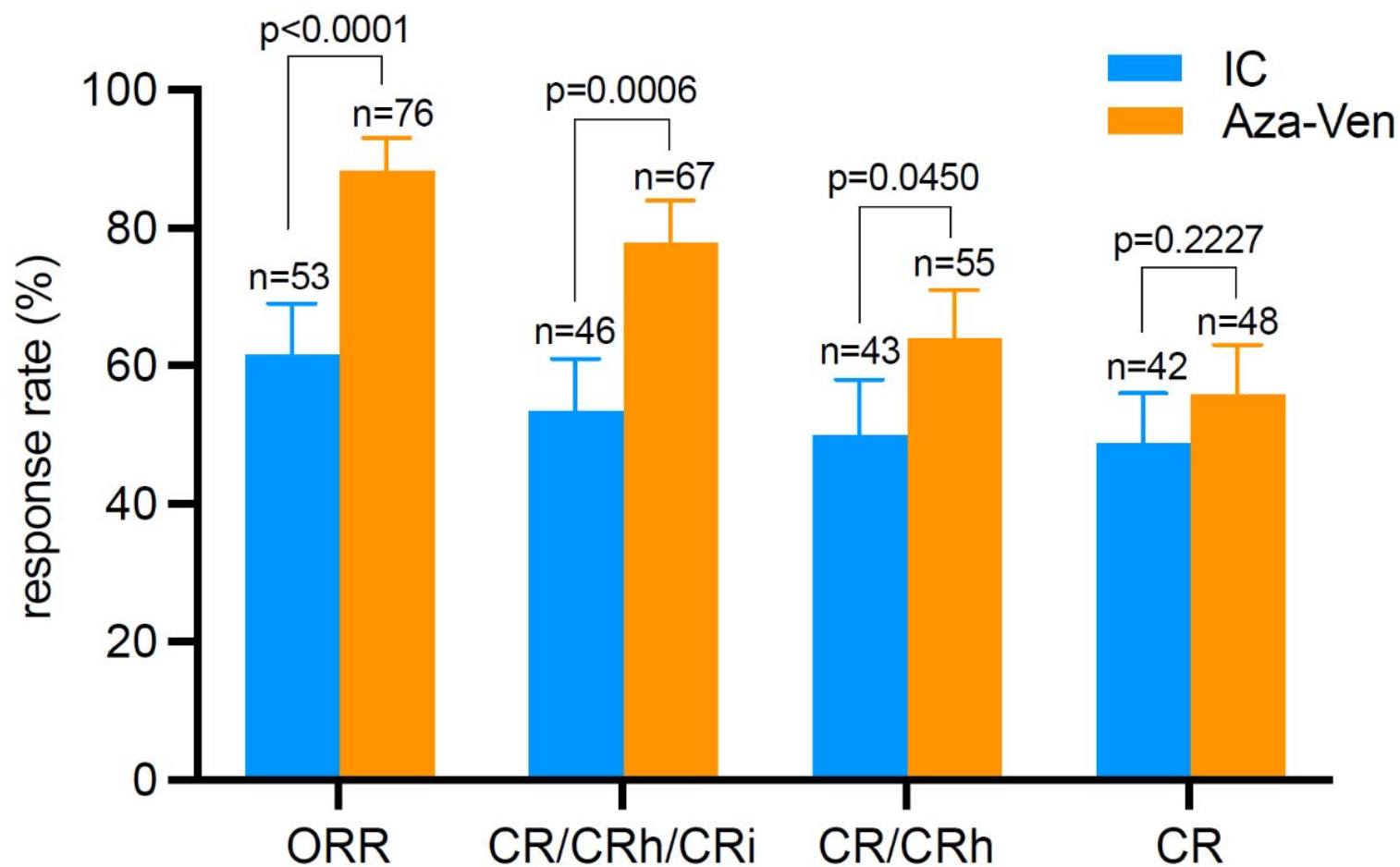


Fathi et al., *Blood* 2025, 146 (1): 6 ASH Plenary

		Total	Aza-Ven	IC
		(N = 172)	(N = 86)	(N = 86)
Age	Median years, (range)	64 (23 - 79)	65 (23 - 79)	64 (28 - 79)
	Less than 65, n (%)	87 (50.6)	43 (50.0)	44 (51.2)
Sex, n (%)				
Male		115 (66.9)	55 (64.0)	60 (69.8)
Race, n (%)				
Caucasian		134 (77.9)	65 (75.6)	69 (80.2)
African American		10 (5.8)	5 (5.8)	5 (5.8)
Hispanic		13 (7.6)	6 (7.0)	7 (8.1)
Asian		15 (8.7)	10 (11.6)	5 (5.8)
ECOG, n (%)				
0/1		161 (93.6)	79 (91.9)	82 (95.4)
2		10 (5.8)	7 (8.1)	3 (3.5)
ELN 2022 risk, n (%)				
Favorable		22 (12.8)	13 (15.1)	9 (10.5)
Intermediate		26 (15.1)	15 (17.4)	11 (12.8)
Adverse		124 (72.1)	58 (67.4)	66 (76.7)
Mutations, n (%)				
NPM1		16 (9.3)	11 (12.8)	5 (5.8)
IDH1		15 (8.7)	8 (9.3)	7 (8.1)
IDH2		28 (16.3)	19 (22.1)	9 (10.5)
TP53		25 (14.5)	9 (10.5)	16 (18.6)
RUNX1		32 (18.6)	14 (16.3)	18 (20.9)
KRAS/NRAS		32 (18.6)	17 (19.8)	15 (17.5)

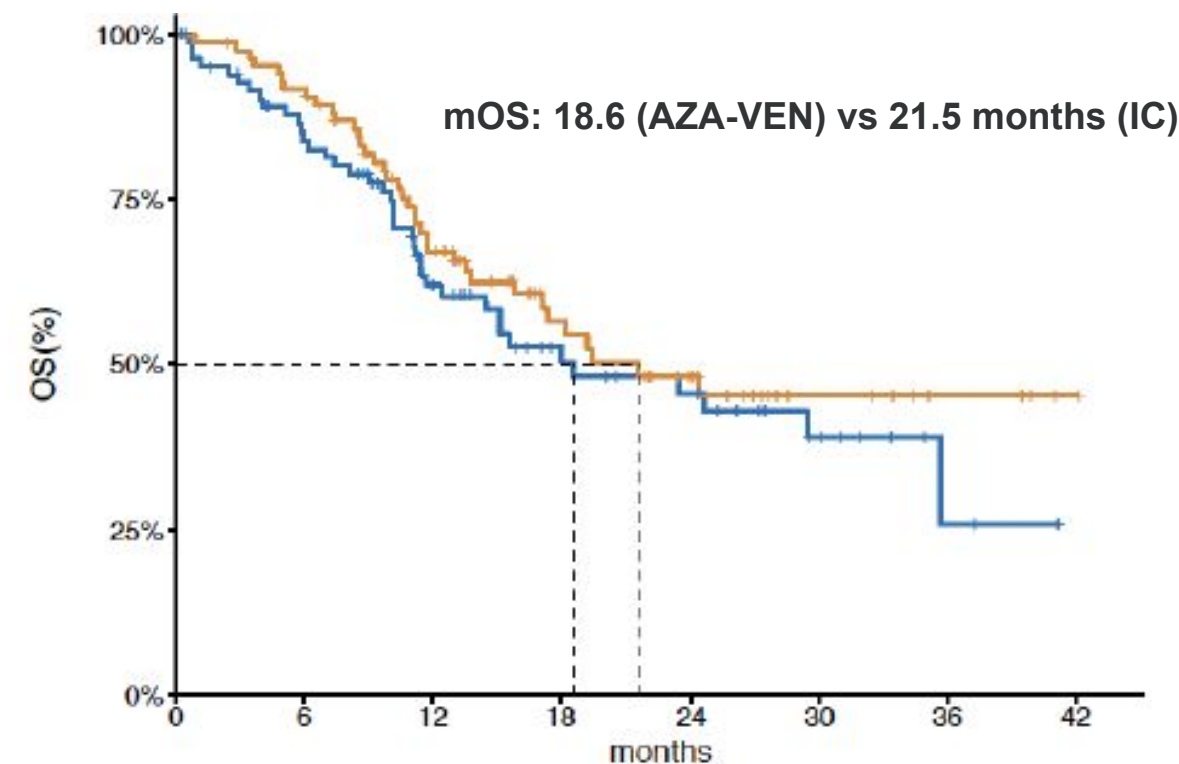
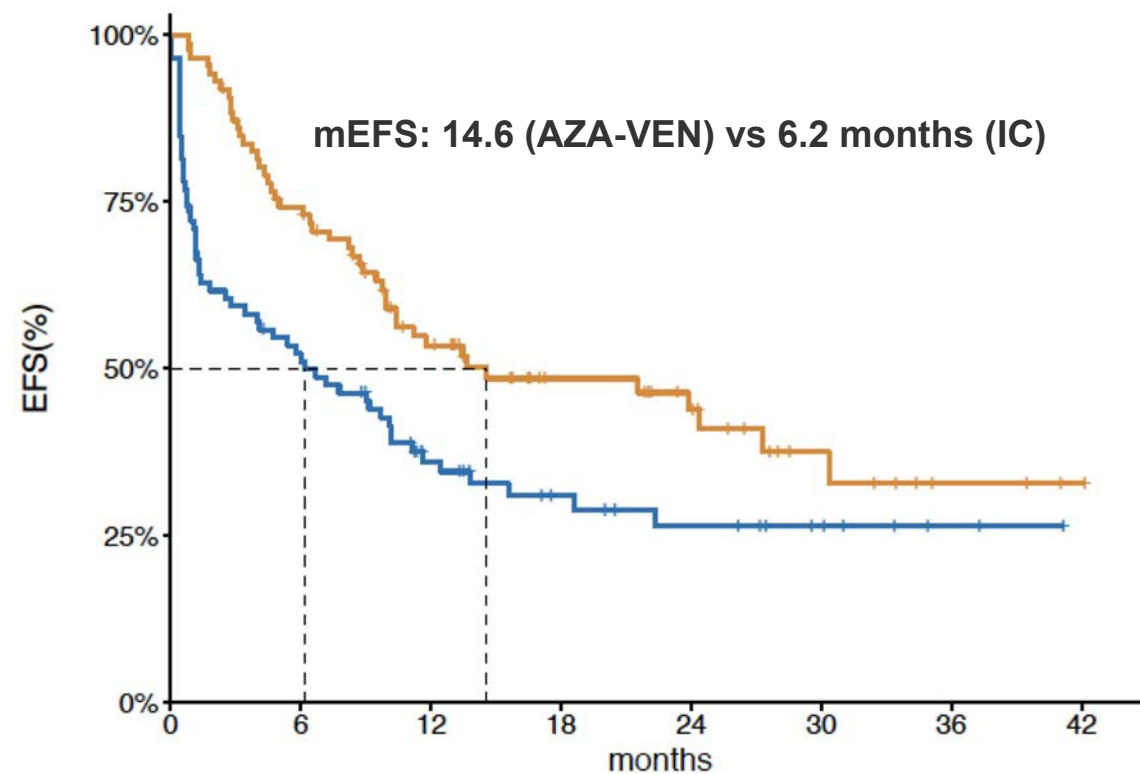
Fathi et al., *Blood* 2025, 146 (1): 6 ASH Plenary

AZA-VEN had higher response rates and H SCT transition than IC



Fathi et al., *Blood* 2025, 146 (1): 6 ASH Plenary

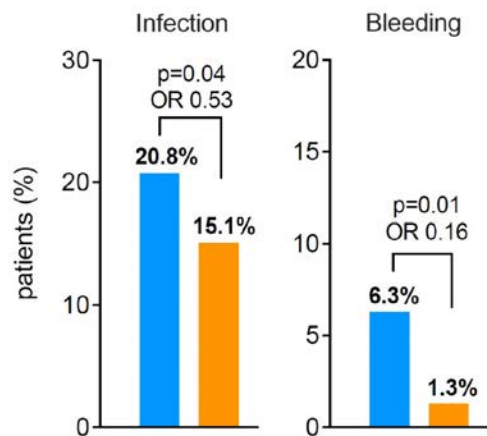
AZA-VEN improved EFS compared to IC



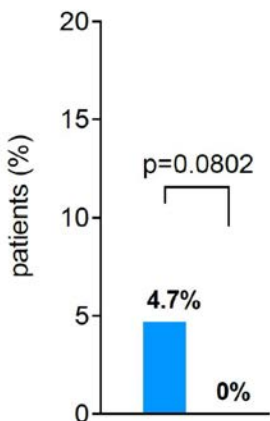
Fathi et al., *Blood* 2025, 146 (1): 6 ASH Plenary

Aza-Ven was associated with less early mortality, improved QOL and symptom burden during initial therapy, with less time in the hospital and ICU.

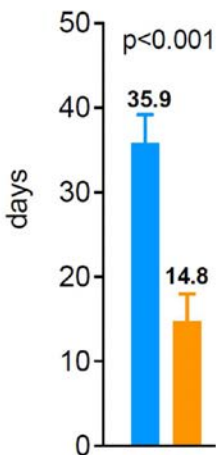
Treatment emergent adverse events (≥ grade 3)



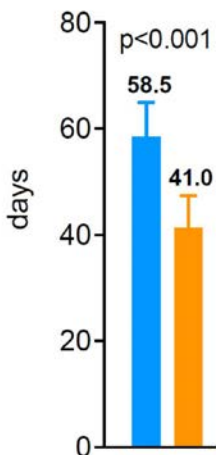
60-day mortality



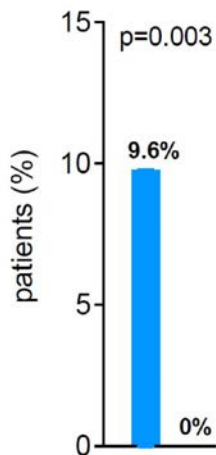
Index hospitalization length of stay



Hospital days in first 6 months



ICU admission in first 30 days



IC
Aza-Ven

PROs at Week-2	Aza-Ven (95%CI)	IC (95%CI)	P-Value
QOL (FACT-Leukemia)	126.1 (121.9 – 130.3)	115.4 (110.7 – 120.2)	0.001
Anxiety Symptoms (HADS)	4.3 (3.6 – 5.0)	4.6 (3.8 – 5.4)	0.565
Depression Symptoms (HADS)	4.8 (4.0 – 5.6)	6.9 (6.0 – 7.9)	0.0007
Symptom Burden (ESAS)	22.2 (18.7 – 26.6)	28.6 (24.6 – 32.6)	0.0186

Fathi et al., *Blood* 2025, 146 (1): 6 ASH Plenary

Conclusions

- Standard-of-care intensive chemotherapy (IC) provides suboptimal long term outcomes, particularly in patients with intermediate and adverse risk disease
- In the randomized phase 2 PARADIGM trial in newly diagnosed fit AML (excluding CBF, young *NPM1*^{MUT}, and *FLT3*^{MUT}), HMA-VEN had superior CRc, EFS, and HSCT rate than IC, with less early mortality and improved QoL
- HMA-based triplet regimens *in older patients* demonstrate impressively high composite CR rates and patients successfully bridged to HSCT, with good safety profiles and low early mortality
- Therefore, future prospective clinical trials should evaluate lower intensity therapy in fit patients with intermediate and adverse risk AML, as a safe and effective way to bridge to curative HSCT, with incorporation of third agents where possible

Newly Diagnosed Fit AML – are we **DONE** with Intensive Chemotherapy?

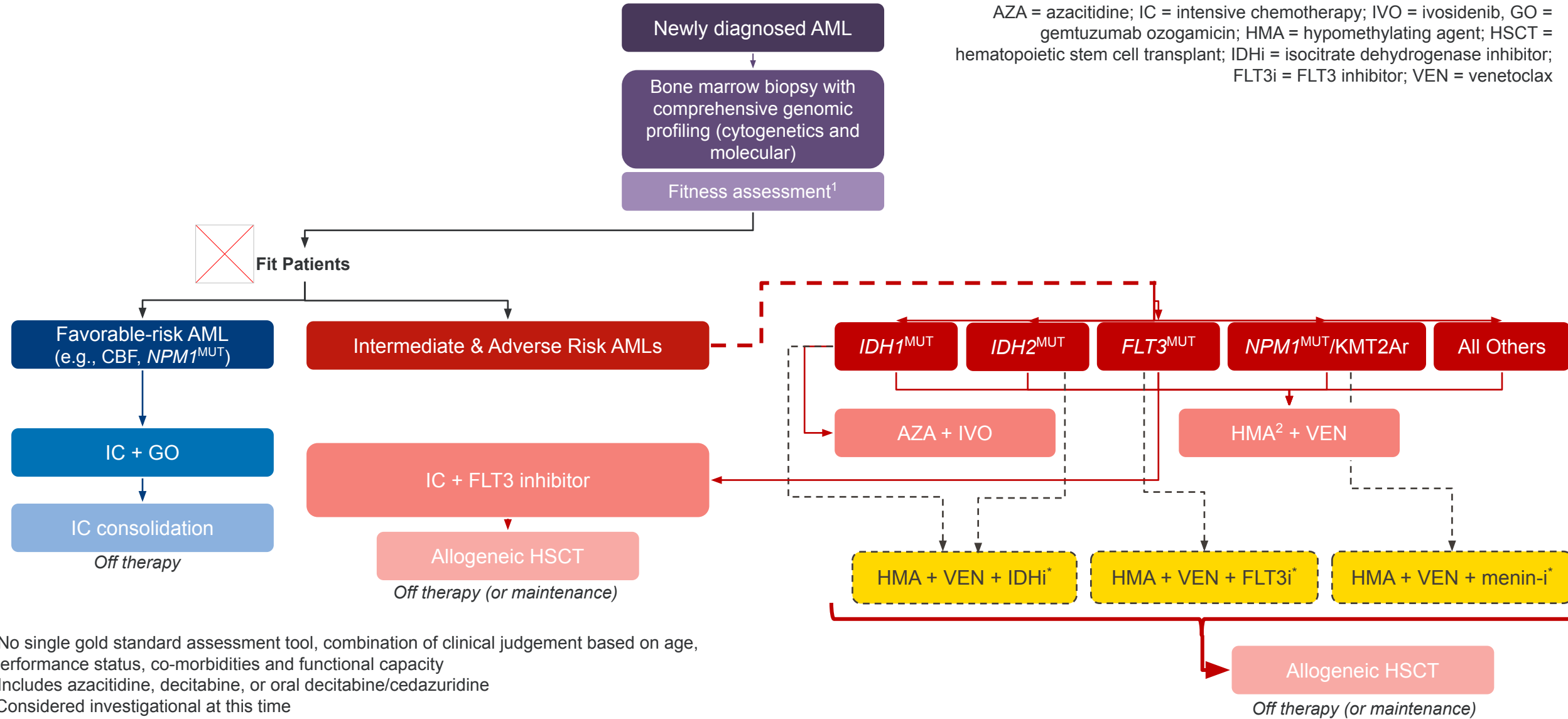
Yes!

Especially for those who are adverse risk

(but excluding favorable risk patients with CBF AML and *NPM1* mutations)

Future (?) AML Treatment Paradigm for Fit Patients

AZA = azacitidine; IC = intensive chemotherapy; IVO = ivosidenib, GO = gemtuzumab ozogamicin; HMA = hypomethylating agent; HSCT = hematopoietic stem cell transplant; IDHi = isocitrate dehydrogenase inhibitor; FLT3i = FLT3 inhibitor; VEN = venetoclax



¹No single gold standard assessment tool, combination of clinical judgement based on age, performance status, co-morbidities and functional capacity

²Includes azacitidine, decitabine, or oral decitabine/cedazuridine

^{*}Considered investigational at this time

Questions or comments?

jmarvin@mdanderson.org