2:20–3:05 PM

AML

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THE 2nd ANNUAL HemOnc Pulse LIVE AUSTIN 2025

AML: Updates and Next Questions

Presenter

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Key Questions for Acute Myeloid Leukemia

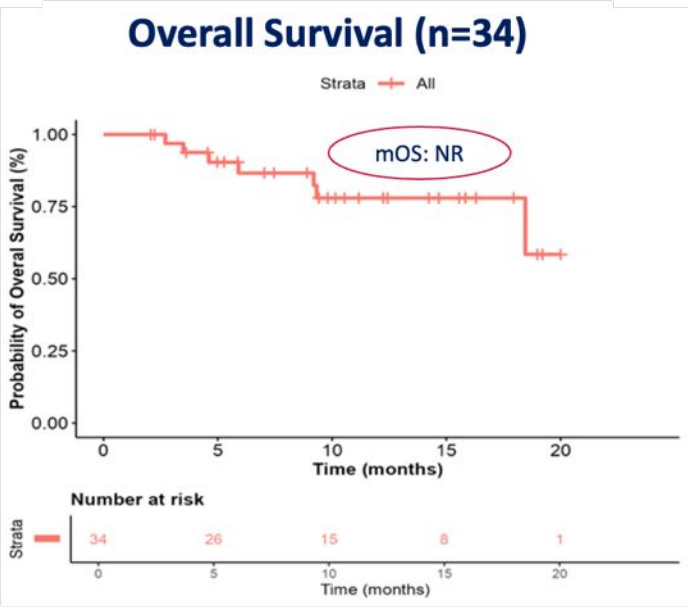
- Q1: Can we improve upon 7+3 induction chemotherapy for young/fit patients with AML?
- Q2: Can Ven/HMA be used instead of intensive chemotherapy in younger patients?
- Q3: Should triplet therapy be used in all patients with IDH1/FLT3-mutant AML?
- Q4: Should MRD be used to determine AML treatment choice?
- Q5: What is the best menin inhibitor? Should menin inhibitor + chemotherapy be used in patients with newly diagnosed NPM1 and KMT2Ar AML?

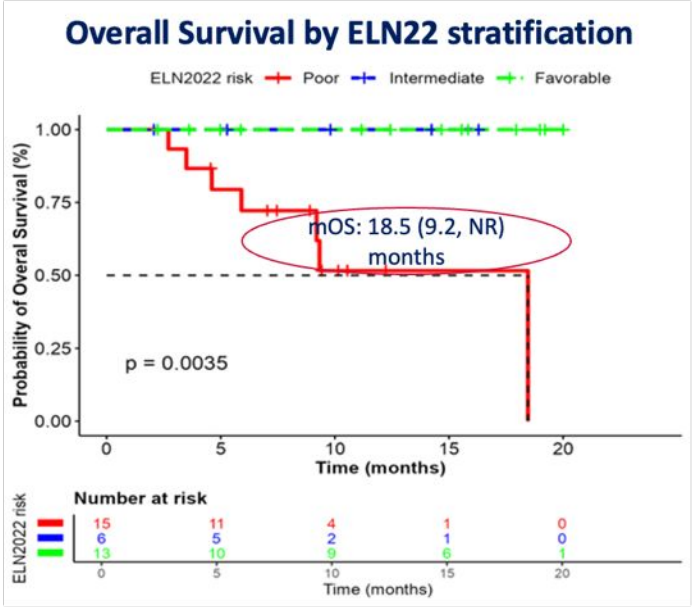
IC: Venetoclax With "7+3" Induction Chemotherapy in ND AML

- 29/34 (**85%**) pts achieved a **CCR** (28 CR + 1 CRh) with single induction
- 25/29 (**86% of CRc**) were **MFC-MRD negative** (LOD 0.02%)

	All Cohorts (n=34)	8-day Venetoclax (n=14)	11-day Venetoclax (n=9)	14-day Venetoclax (n=11)
Response	n (%)			
No response	5 (15)	3 (21)	1 (11)	1 (9)
CR	**28 (82)**	10 (71)	8 (89)	10 (91)
CRh	**1 (3)**	1 (7)	-	-
CRc_{MRD-}	**25/29 (86)**	9/11 (82)	7/8 (87.5)	9/10 (90)

IC: Venetoclax With “7+3” Induction Chemotherapy in ND AML



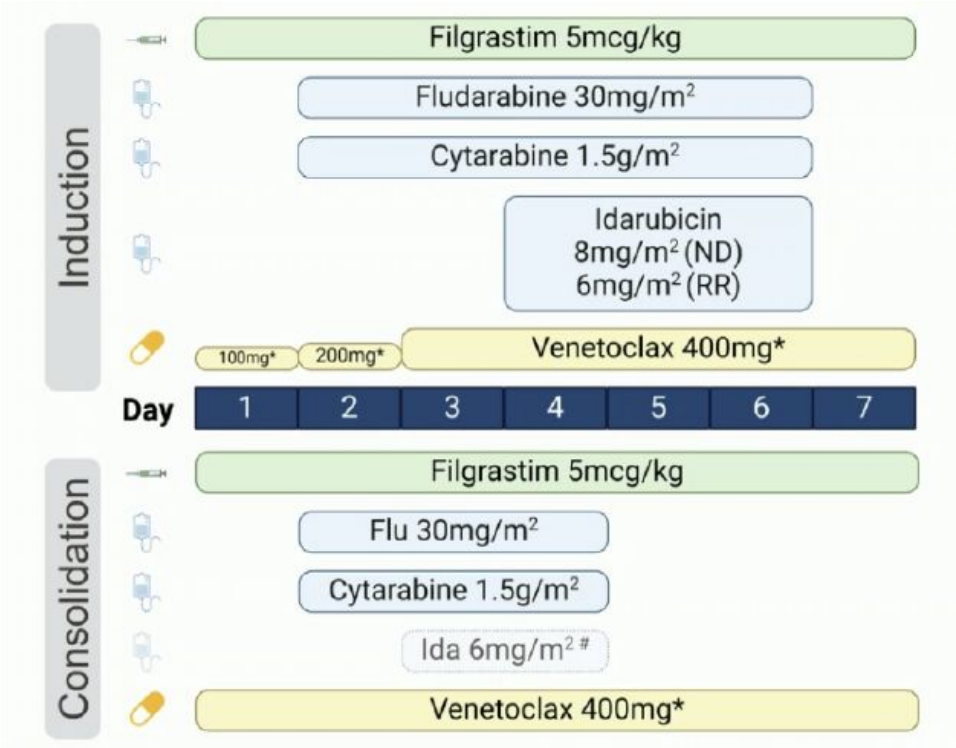


- **Median follow-up = 9.6 (2-20) months**
- **Median DoR, EFS (mEFS) and OS (mOS) were NR**

Mantzaris I et al ASH 2024

- **10 pts (29%) have undergone transplant in CR1**
- **At DOC 27/29 responding pts (93%) were alive and 22/29 (76%) remained in continuous MRD-neg CR**

IC: FLAG-IDA+Ven in Newly Diagnosed or Relapsed/Refractory AML



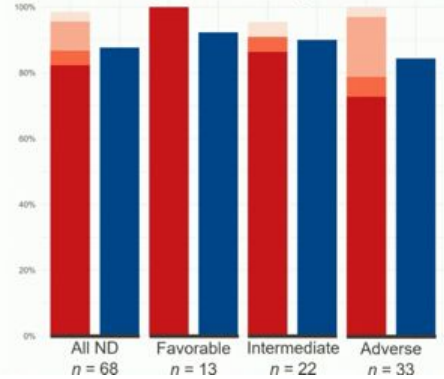
Characteristic		ND AML, n = 68
Age	Median [Range]	44 [20 – 67]
	≥60	10 (15)
Secondary / therapy-related		16 (24)
ELN 2022 Risk Stratification	Favorable	13 (19)
	Intermediate	22 (32)
	Adverse	33 (49)

Characteristic		RR AML, n = 59
Age	Median [Range]	47 [18 – 73]
	≥60	9 (15)
Refractory		15 (25)
Secondary / therapy-related		19 (32)
Prior HSCT		20 (34)

No prior venetoclax exposure

IC: FLAG-IDA+Ven in Newly Diagnosed or Relapsed/Refractory AML

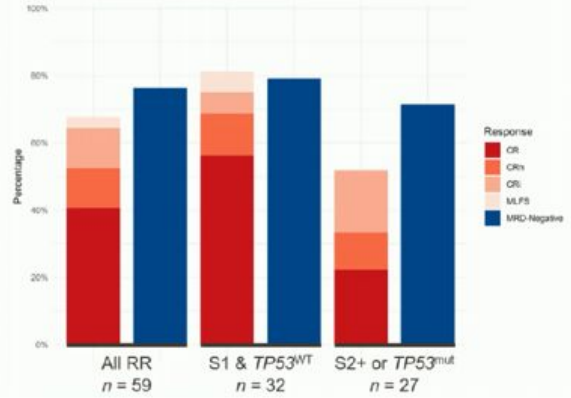
ND AML: Responses by ELN 2022 Risk Stratification



	ND AML n = 68 n (%)
ORR	67 (99)
CRc	65 (96)
CR	56 (82)
CRh	3 (4)
CRi	6 (9)
MLFS	2 (3)
NR	1 (2)
Flow MRD Negative	57 (88)

MRD Assay: MFC (10^{-4})

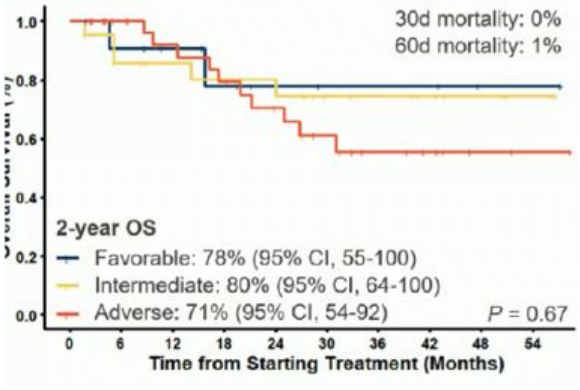
RR AML: Responses

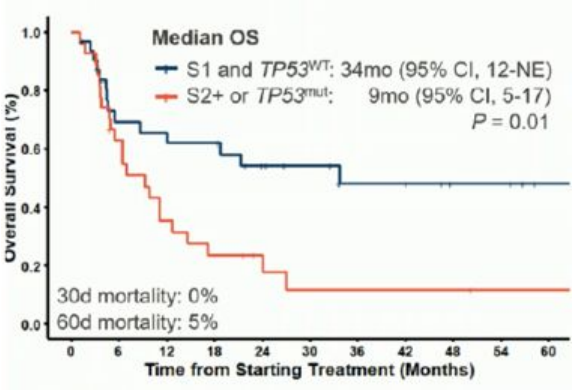


	RR AML n = 59 n (%)
ORR	40 (68)
CRc	38 (64)
CR	24 (41)
CRh	7 (12)
CRi	7 (12)
MLFS	2 (3)
NR	19 (32)
Flow MRD Negative	29 (76)

MRD Assay: MFC (10^{-4})

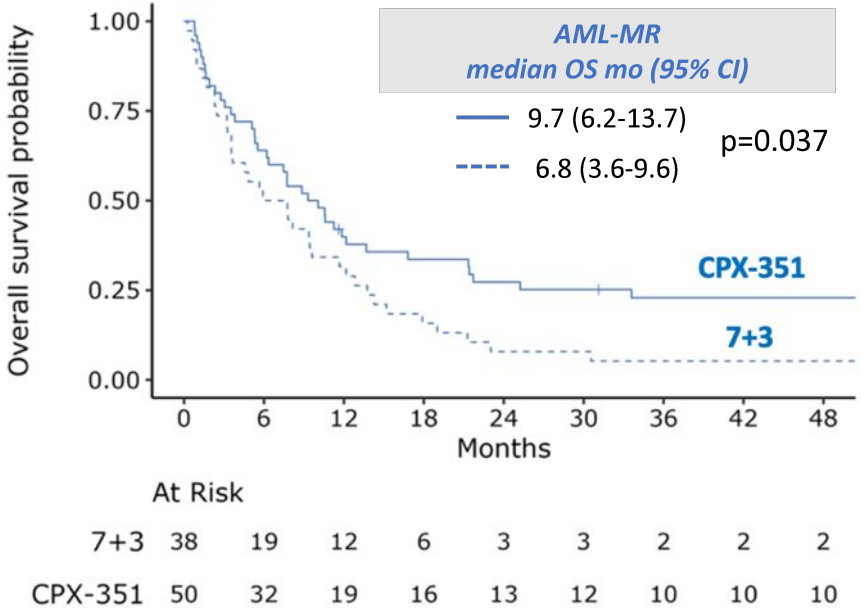
2-year OS; median FU= 27-30 mo



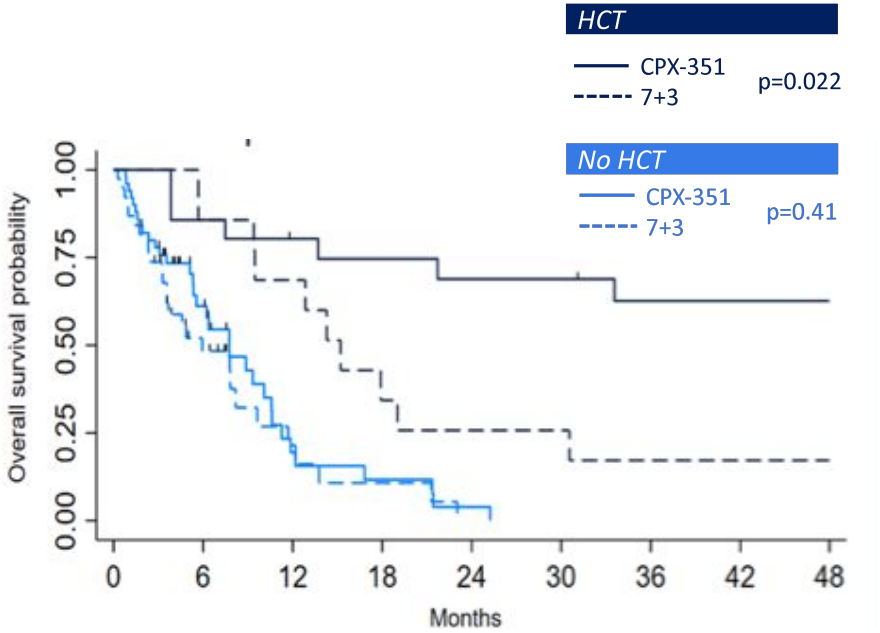


IC: CPX-351 Improves OS vs 7+3 in AML-MR Defined by Mutations

OS in AML-MR with secondary mutations



CPX-351 survival benefit in AML-MR is due to post-CR1 HSCT



Shimony S et al. ASH 2024 abstract.

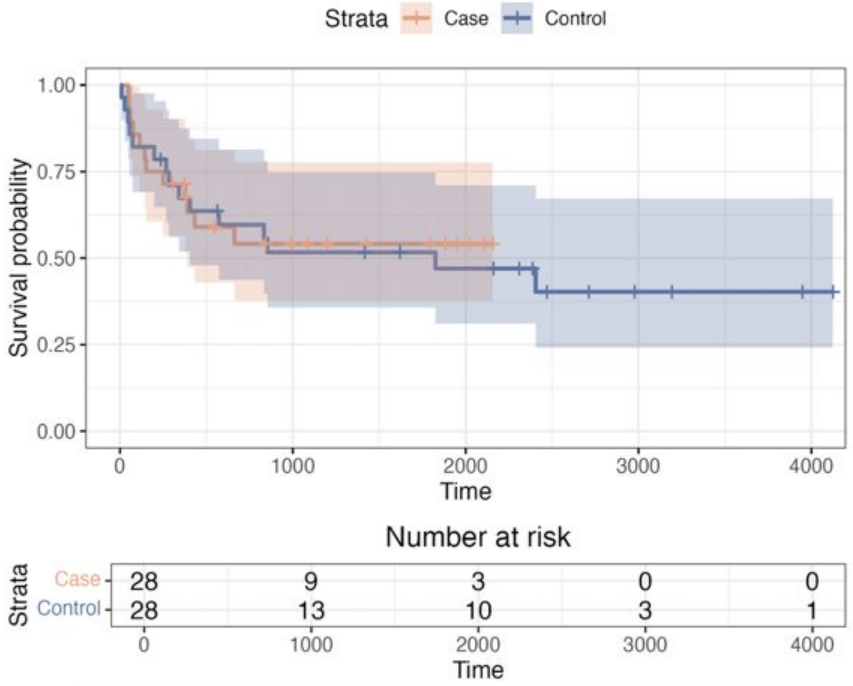
Ven/Aza: Newly Diagnosed Young AML Pts Fit for Intensive Chemotherapy

Response by Patient Subsets

Subset	Overall Response Rate
Monocytic	4/8 (50%)*
Non Monocytic	20/28 (71%)
Myelodysplasia Related	16/21 (76%)
KMT2A Rearranged	3/6 (50%)
mPRS	
Higher Benefit	18/23 (78%)
Intermediate Benefit	5/9 (56%)
Lower Benefit	2/4 (50%)

Median OS= NR (12.6 mo, NR)

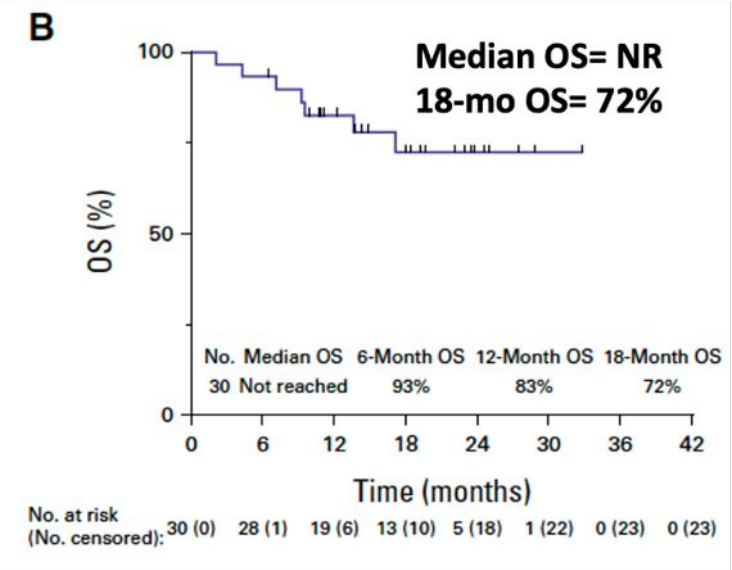
OS of Ven/HMA vs Historic 7+3 patients



Watts J et al. ASH 2024.

Triplet Therapy: Gilteritinib/Ven/Aza in ND FLT3-mutant AML

Frontline AML patients



Short N et al JCO 42: 1499-1508, 2024

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

MRD Response[c]	Frontline Cohort (n = 30)
MRD by flow cytometry (after cycle 1), No. (%)	
Negative	9/16 (56)
Positive	7/16 (44)

Median age = 71 yrs

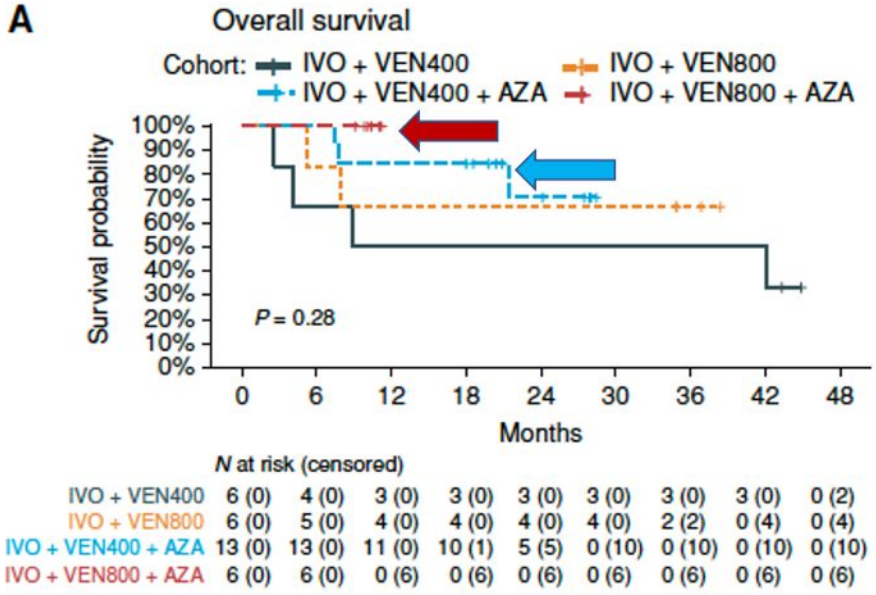
Flow MRD-negativity by cycle 4 = 93%

13 (43%) underwent alloSCT in CR

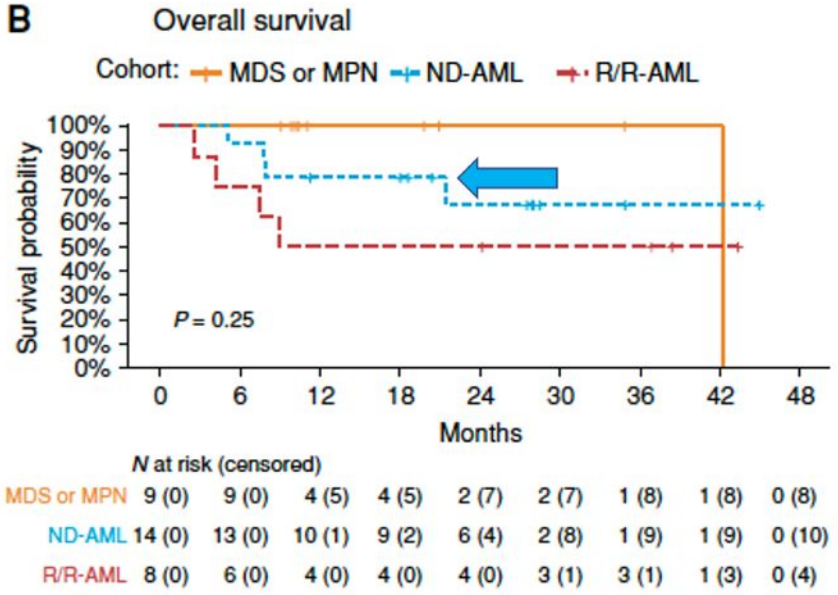
60-day mortality = 0%

Triplet Therapy: Ivo/Ven +/- Aza for ND IDH1m Myeloid Neoplasms

By treatment regimen



By disease type



Lachowiez CA et al Blood Cancer Discov 4: 276-93, 2023

MRD: FLT3m AML: PrECOG R Phase 2 of 7+3/ Gilteritinib vs Midostaurin

- 177 treated pts, Median age 54, 27.7% > age 60
  - Arm A (Gilteritinib) 90, Arm B (Midostaurin) 87
    - 5 (5.6%) vs 6 (6.9%) received 2 cycles induction
  - **CRc (Gilteritinib) 85.6% vs 72.4% (Midostaurin), p=0.042**

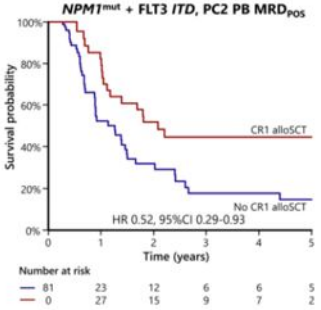
For TKD: LOD 10^{-2} by PCR followed by capillary electropheresis

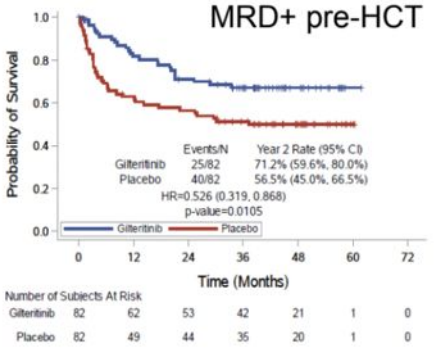
MRD regardless of remission status	Arm A (Gilteritinib) N=90	Arm B (Midostaurin) N=87	Overall N=177
MRD negative	**36 (40.0%)**	**46 (52.9%)**	**82 (46.3%)**
MRD positive	39 (43.3%)	28 (32.3%)	67 (37.9%)
Dropped Out/Unknown	15 (16.7%)	13 (14.9%)	28 (15.8%)

- ***FLT3*m negative CRc post induction**
  - **40% Gilteritinib (A) vs 47.1% Midostaurin (B), p=0.366**

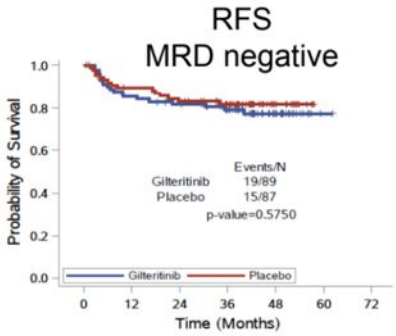
MRD: Post-transplant Gilteritinib Benefits MRD+ FLT3-ITD+ Patients

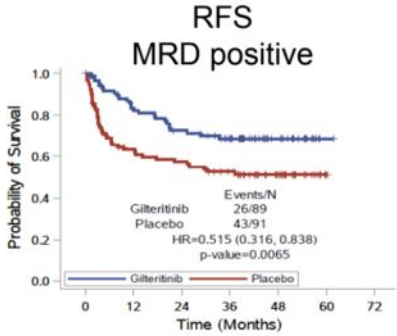
NCRI AML 17&19 (n=286)
median age 51
ND FLT3-ITD+ only
fit for intensive chemo
no FLT3 TKI

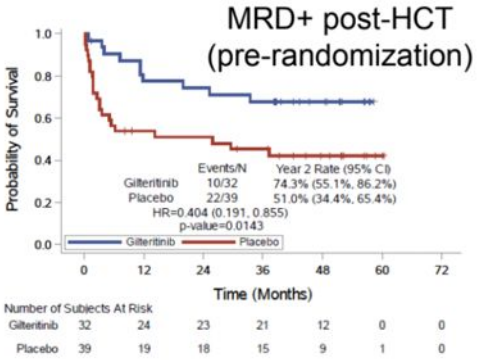




BMT-CTN1506/MORPHO





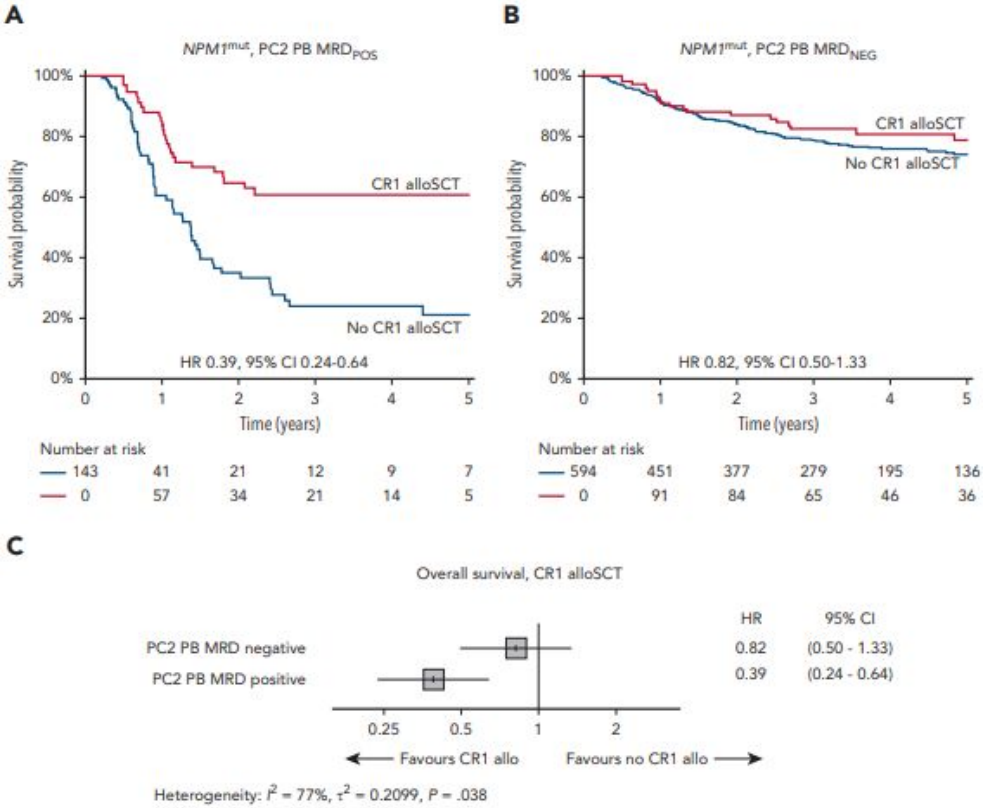


Othman J, et al. Blood. 2024 May 9;143(19):1931-1936.
Levis MJ, et al. J Clin Oncol. 2024 May 20;42(15):1766-1775
Levis MJ, et al. Blood 2025 (epub online)

MRD: Post Induction Identifies NPM1m AML Pts Benefiting From CR1 Transplant

AML17+AML19

- MRD$^-$ - no difference in OS between patients who did or did not receive CR1-allo (3-year OS, 79% vs 82%; HR, 0.82; 95% CI, 0.50-1.33; *P*=0.4)
- MRD$^+$ - OS significantly improved in patients receiving CR1-allo (3-year OS, 61% vs 24%; HR, 0.39; 95% CI, 0.24-0.64; *P*<0.001)



Menin Inhibitors: Efficacy in R/R KMT2Ar and NPM1m AML

Agent (# pts)	Revumenib (n=97)	Ziftomenib (n=20)	Bleximenib (n=33)	Enzomenib (n=40)
Company	**Syndax**	**Kura**	**J&J**	**Sumitomo**
Phase Trial	**Phase 2**	**Phase 1b**	**Phase 1**	**Phase 1**
Drug dose	163 mg bid with CYP450 inhibitor	600 mg qd	90-100 mg bid	200-300 mg bid
KMT2Ar	**97 (100%)**	NA	**19 (58%)**	**23 (57%)**
NPM1^{mut}	NA	**20 (100%)**	**14 (42%)**	**17 (43%)**
CR	15 (15.5%)	7 (35%)	6 (18%)	NA
CR/CRh	**13 (22.7%)**	**7 (35%)**	**7 (21%)**	**15 (37.5%)**
CRc (CR/CRh/CRi)	24(24.7%)	8 (40%)	9 (27%)	19 (42.5%)
ORR (CRc+PR + MLFS)	62 (63.9%)	9 (45%)	15 (46%)	25 (62.5%)

1. Aldoss I et al ASH oral 2024; 2. Wang E et al Lancet Oncol 2024; 3. Jabbour E et al ASH 2024; 4. Zeidner J et al ASH abstract 2024

Updated Jan 2025

Menin Inhibitors: Adverse Events in R/R KMT2Ar and NPM1m AML

Agent (# pts)	Revumenib (n=94)	Ziftomenib (n=83)	Bleximenib (n=146)	Enzomenib (n=84)
Trial	Phase 2	Phase 1/1b	Phase 1	Phase 1
DLT (Y/N)	Ph1: QTc PR	Yes	Yes	No
DLT	Ph1: QTc PR	Gr3 pneumonia Gr4/5 DS	Gr5 DS	NA
DS (all)	26 (28%)	12 (15%)	14% (all doses)	9 (10.7%)
DS (≥Gr3)	15 (16%)	10 (12%)	6-9% (90-150 bid)	None reported*
Febr Np (≥Gr3)	36 (38%)	18 (22%)	27 (18%)	20 (23.8%)
Neutrop (≥Gr3)	27 (28.7%)	7 (8%)	37 (25%)	14 (16.7%)
Thromb (≥Gr3)	20 (21%)	6 (7%)	46 (31%)	18 (21%)
QTc PR (any)	24 (25%)	0 (0%)	0 (0%)	NA
QTc PR (≥Gr3)	13 (14%)	0 (0%)	0 (0%)	1 (1%)

*1. Aldoss I et al ASH 2024; 2. Wang E et al Lancet Oncol 2024; 3. Searle E et al ASH 2024; 4. Zeidner J et al ASH 2024; *No DS mitigation used*

Updated Jan 2025

BEAT AML: Ph1 Trial of Aza/Ven/Revumenib in ND NPM1m/KMT2Ar AML

Adverse Event (n=26)	Any Grade	Grade 3+	Revumenib Dose Holds	Revumenib Dose Reductions/DC
Differentiation Syndrome (DS)	4 (15)	1 (4)	1	0
QTcF Prolongation	12 (46)	3 (12)	3	0

- No non-heme DLT's in dose escalation
- DL2 cohort expanded
- QTcF prolongation and DS self-limiting & resolved w/o complications

Treatment Outcomes	Escalation DL1a (n=7)	Escalation DL2a (n=6)	Expansion DL2a (n=13)	All (n=26)
Response Rates for Evaluable Patients[2]				
Composite CR (CR/CRh/CRi), no. (%)	**7/7 (100)**	**6/6 (100)**	**10/11 (91)**	**23/24 (96)**
Overall (CR/CRh/CRi/MLFS), no. (%)[3]	**7/7 (100)**	**6/6 (100)**	**11/11 (100)**	**24/24 (100)**
MRD[4] Neg., no. (%)	6 (86)	6 (100)	10 (91)	22 (92)
Required Only 1 Induction for marrow remission, no. (%)	7 (100)	5 (83)	9 (82)	21 (88)
Allo-Stem Cell Transplant, no. (%)	1 (14)	1 (17)	4 (31)	6 (23)
Relapse, no. (%)[5]	2 (29)	1 (17)	0 (0)	3 (13)
Survival				
Death, no. (%)	1 (14)	3 (50)	3 (23)	7 (27)
30/60 Day Mortality, no. (%)	0 (0)	0 (0)	1 (8)	1 (4)
12-Month Survival Estimate, % (95% CI)[6]	100 (100-100)	N/A	N/A	62.2 (27.8-83.9)

[1]NE patients: Died of septic shock during cycle 1 (n=1); Withdrew consent for palliative care during cycle 1 (n=1); [2] NE patients are excluded; [3]1 patient achieved marrow remission with hematologic recovery >14 days from last BM Bx; [4] MRD determined by central flow cytometry with sensitivity to 0.01% depending on sample quality; [5]*KMT2Ar* (n=2), *NPM1*mut with extramedullary disease (n=1); Median duration of CRc for relapsed pts = 9 months (Range: 5-11 mos.); [6]Median F/U for DL2a Escalation and Expansion too short to calculate OS estimate but included in All pts.

KOMET-001: Ph1 trial of Ziftomenib /7+3 in ND NPM1m and KMT2Ar AML

- Historically, only 33% of 7+3 treated newly diagnosed Adverse-Risk AML patients achieve CRc, with a median overall survival of ~6 months[1-2]

		NPM1-m				*KMT2A*-r			
Response, n (%)	**All Patients (N=46)**	**200 mg (n=8)**	**400 mg (n=7)**	**600 mg (n=8)**	**Total (n=23)**	**200 mg (n=10)**	**400 mg (n=9)**	**600 mg (n=4)**	**Total (n=23)**
CRc	**42 (91)**	8 (100)	7 (100)	8 (100)	**23 (100)**	9 (90)	6 (67)	4 (100)	**19 (83)**
ORR	**42 (91)**	8 (100)	7 (100)	8 (100)	**23 (100)**	9 (90)	6 (67)	4 (100)	**19 (83)**
CR	**42 (91)**	8 (100)	7 (100)	8 (100)	**23 (100)**	9 (90)	6 (67)	4 (100)	**19 (83)**
CRh	0	0	0	0	0	0	0	0	0
CRi	0	0	0	0	0	0	0	0	0
MLFS	0	0	0	0	0	0	0	0	0
PR	0	0	0	0	0	0	0	0	0
NR	3 (7)	0	0	0	0	0	3 (33)	0	3 (13)
NE	1 (2)	0	0	0	0	1 (10)	0	0	1 (4)
MRD negativity, n/N[b]	**28/37 (76)**	8/8 (100)	4/6 (67)	4/7 (57)	**16/21 (76)**	5/8 (63)	5/6 (83)	2/2 (100)	**12/16 (75)**

[a]Patients who have ≥1 response assessment or who had died.
[b]Among CRc **responders** tested for MRD per local assay (NGS, RT-qPCR, FISH, flow cytometry).

Zeidan A et al oral presentation ASH 2024

THANK YOU