How I Treat R/R AML

Boaz Nachmias MD PhD
Director of Leukemia Service
Hadassah University Hospital
Jerusalem Israel

Topics

- **Are there different relapses?**
  - D14/ primary refractory
  - Persistent MRD
  - Molecular relapse

- **Treatment goals**
  - Bridge to transplant
  - MRD eraser
  - Maintenance

- **Treatment approaches**
  - Salvage chemotherapy
  - Vidaza-venetoclax
  - Novel agents as monotherapy and in combination
  - Sequential therapy

D14 Residual Disease

- >5% blasts has a low specificity for not achieving CR, especially in the context of a hypocellular marrow (<20%)
- Up to 35-50% of patients would achieve CR with no additional treatment
- No statistically significant difference in median OS or RFS based on D14 when survival analysis was stratified by ELN risk group (*Balev et al. ASH abstract 2022*)

D14 Residual Disease

- **J Rowe et al. Cancer 2010-** Patients with residual leukemia on day 10–14 received a second course of therapy with similar long-term outcome in those who achieved CR
- **LAM-2001 trial-** a second cycle with IDAC was administered to patients with >5% bone marrow blast, with no difference in outcome
- Possibly higher treatment-related mortality with 2nd induction

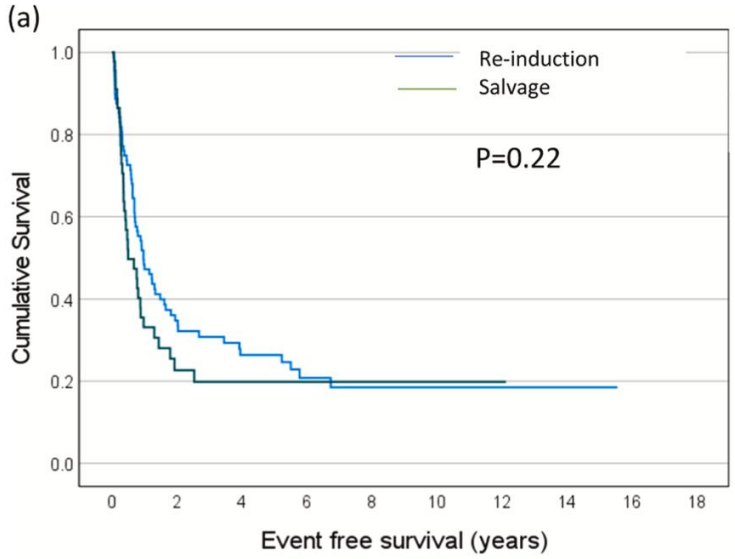
- Cancer. 2010 Nov 1; 116(21): 5012–5021
- Haematologica. 2014 Jan;99(1):46-53.

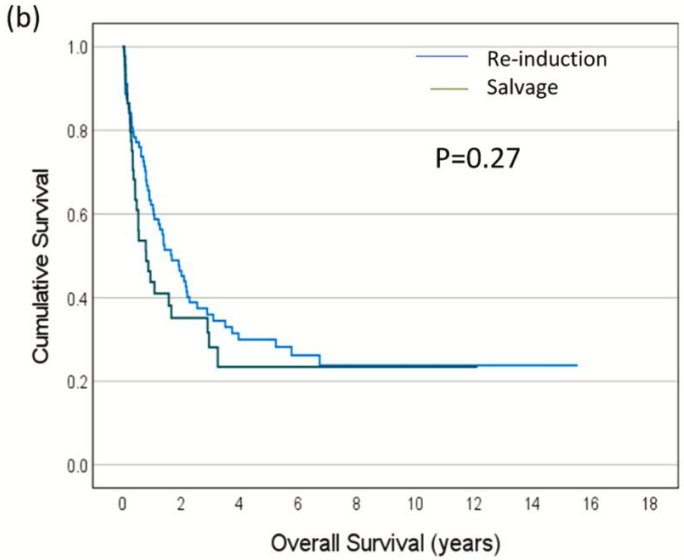
Re-induction versus salvage for D14-resiudal acute myeloid leukemia: A retrospective multi-center study

Avraham Frisch [a,b,1], Shlomzion Aumann [d,1], Tsila Zuckerman [a,b], Ronit Leiba [c], Noa Gross Even-Zohar [d], Moshe E. Gatt [d], Vladimir Vainstein [d], Adir Shaulov [d], Alexander Gural [d], Eran Zimran [d], Yaniv Zohar [b,e], Yishai Ofran [f,1], Boaz Nachmias [d,*,1]

Table 1
Patients characteristics.

	All (N = 133)	Salvage (N = 44)	Re-induction (N = 89)	p
Age median (range)	52 (17–74)	52 (17–73)	52 (18–74)	P = 0.84
Gender				P = 0.37
Male	73 (55 %)	22 (50 %)	51 (57 %)	
Female	60 (45 %)	22 (50 %)	38 (43 %)	
ECOG Performance Status				P = 0.06
0	128 (96 %)	40 (91 %)	88 (99 %)	
1	3 (2 %)	2 (4.5 %)	1 (1 %)	
2	2 (2 %)	2 (4.5 %)	0	
WBC	6.05 [2.67–26.25]	6.2 [2.45–46.15]	6.0 [2.65–24.4]	P = 0.61
ELN Cytogenetic category				
Favorable	13 (10 %)	3 (7 %)	10 (11 %)	
Intermediate	71 (53 %)	14 (32 %)	57 (64 %)	
Adverse	49 (37 %)	27 (61 %)	22 (25 %)	P < 0.001
17p abnormality	10(7.5 %)	5 (11 %)	5 (5.6 %)	P = 0.2





Molecular Failure Definitions

- **Molecular persistence:** MRD > 1 copy/100 copies ABL1 after the completion of induction and consolidation chemotherapy
- **Molecular relapse:** conversion of MRD negativity to positivity
- **Molecular progression:** a rise of ≥1 log10 in transcript levels from low-level positivity

Table 5. Definitions for MRD response categories and MRD relapse

Response category	Abbreviation	Defining criteria
CR with negative MRD	$CR_{MRD}-$	1. Complete morphologic remission and 2. MRD^- in all MRD technologies that were used: a. FC-MRD^- in BM (if MFC-MRD was used). b. qPCR-MRD^- in BM (or in PB after cycle 2 for *NPM1*- and CBF-MRD) (if qPCR-MRD was used). c. NGS-MRD^- in BM (if NGS-MRD was used).
CR with positive MRD	$CR_{MRD}+$	1. Complete morphologic remission, and 2. MFC-MRD^+ in PB and/or BM, or 3. NGS-MRD^+ in PB and/or BM, or 4. qPCR-MRD^+ in PB and/or BM.
CR with molecular MRD detection at low level	CR-MRD-LL	1. Morphologic CR, and 2. Molecular MRD detectable at low level in PB and/or BM (ie, qPCR for *NPM1* <2% or NGS-MRD <0.1%, but above the detection limit of the assay).
MRD relapse	—	1. Conversion of MRD negativity to MRD positivity independent of the MRD technique, or 2. increase in MRD copy numbers ≥1 $\log_{10}$ between any 2 positive samples in patients with CR-MRD-LL who are monitored by qPCR. 3. The result of (1) or (2) should be rapidly confirmed in a second consecutive sample, preferably from the BM.

MRD IN AML: ELN MRD WORKING PARTY CONSENSUS

Persistent MRD

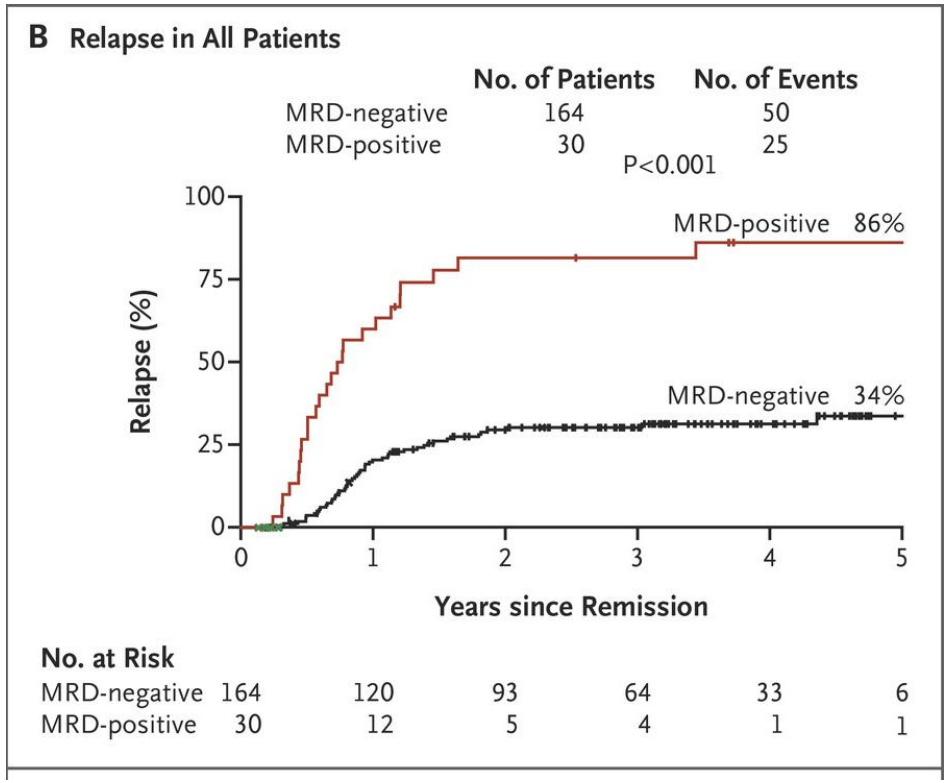


Table 2. UniAllogeneic Stem Cell Transplantation

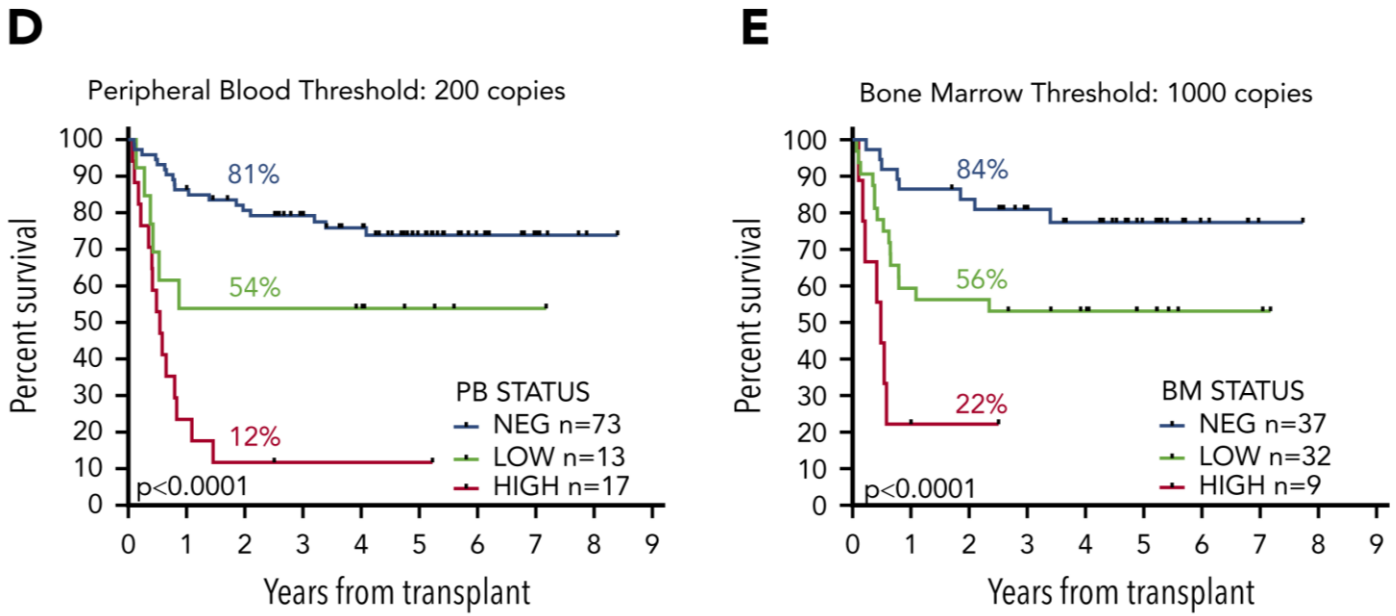
Variable	Multivariate SHR	95% CI	*P*
Age*	—	—	—
log(WBC)*	—	—	—
Abn. karyotype	7.63	2.75 to 21.17	< .001
FLT3-ITD	2.52	1.04 to 6.08	.04
FLT3-TKD	—	—	—
*DNMT3A*m	—	—	—
*IDH1/2*m	—	—	—
*TET2*m	—	—	—
*WT1*m	2.60	0.72 to 9.44	.15
MRD < 4-log reduction	5.14	2.28 to 11.58	< .001

Abbreviations: —, not appl
*Continuous variable.

Ivey et al. N Engl J Med 2016; 374:422-433
J Clin Oncol. 2017;35:185–93

Persistent MRD

Core-binding factor *AML*	If levels remain below these thresholds, monitor closely with no intervention[14] t(8;21) BM 500 copies or PB 100 copies/10^5 *ABL* inv(16) BM 50 copies or PB 10 copies/10^5 *ABL* Otherwise see next column
NPM1 mutation *FLT3* unmutated	If level in BM <200 copies/10^5 *ABL*, monitor BM every 4 weeks and ensure donors in place[8]



Dillon et al. Blood 2020
Dillon et al. BJH 2020

Case #1: Low positive

- 25 Y old male
- DN AML FLT3-ITD/NPM1
- 7+3+ mido…. 12%
- S/P IDAC+mido….0.04% Low positive

What do you want to do?

(a) Continue IDAC as consolidation

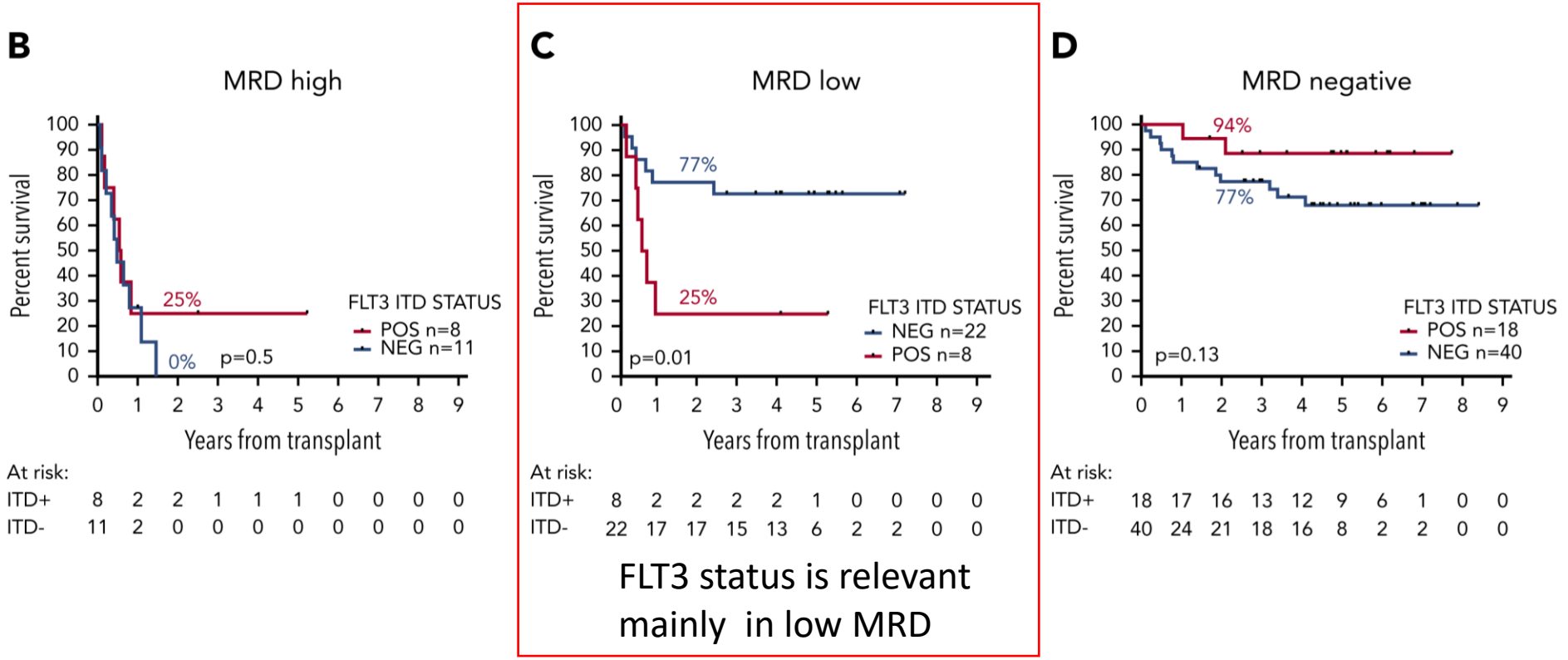
(b) alloSCT

(c) Gilteritinib

(d) Ven-Aza as a bridge to transplant

The Relevance of FLT3-ITD

34 patients were positive for FLT3-ITD at diagnosis, and 73 were negative
Pre-transplant MRD



FLT3 status is relevant mainly in low MRD

Relapse in patients with pretransplant MRD positivity below these levels is largely restricted to those with FLT3-ITD

Dillon et al. Blood 2020

UK AML Trials

AML17

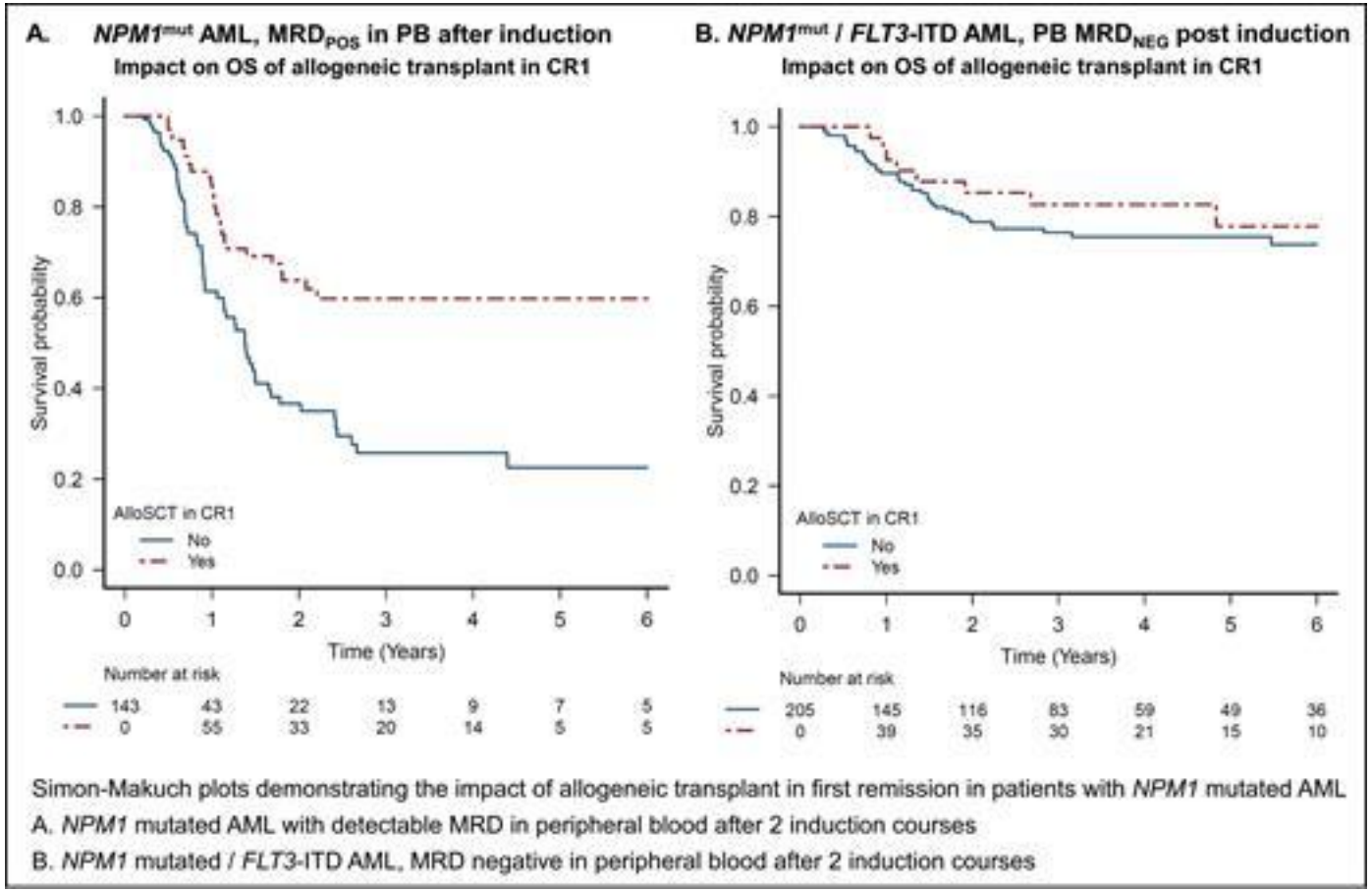
Decisions regarding CR1-allo were made using baseline factors and response to induction

AML19

NPM1^{mut} CR1-allo only in patients testing MRD positive PC2 PB, regardless of other baseline risk factors such as *FLT3* ITD

The Benefit of Allogeneic Transplant in 1st CR in c*NPM1* AML with or without FLT3 ITD

- Of the <u>MRD-positive patients</u> CR1-allo was performed in 16/60 (27%) in AML17 compared to 50/83 (60%) in AML19
- CR1-allo was associated with a significant survival benefit in MRD+ patients (3y OS 61% vs 24%)



Simon-Makuch plots demonstrating the impact of allogeneic transplant in first remission in patients with *NPM1* mutated AML

A. *NPM1* mutated AML with detectable MRD in peripheral blood after 2 induction courses

B. *NPM1* mutated / *FLT3*-ITD AML, MRD negative in peripheral blood after 2 induction courses

Blood (2023) 142 (Supplement 1): 425

European Journal of Haematology

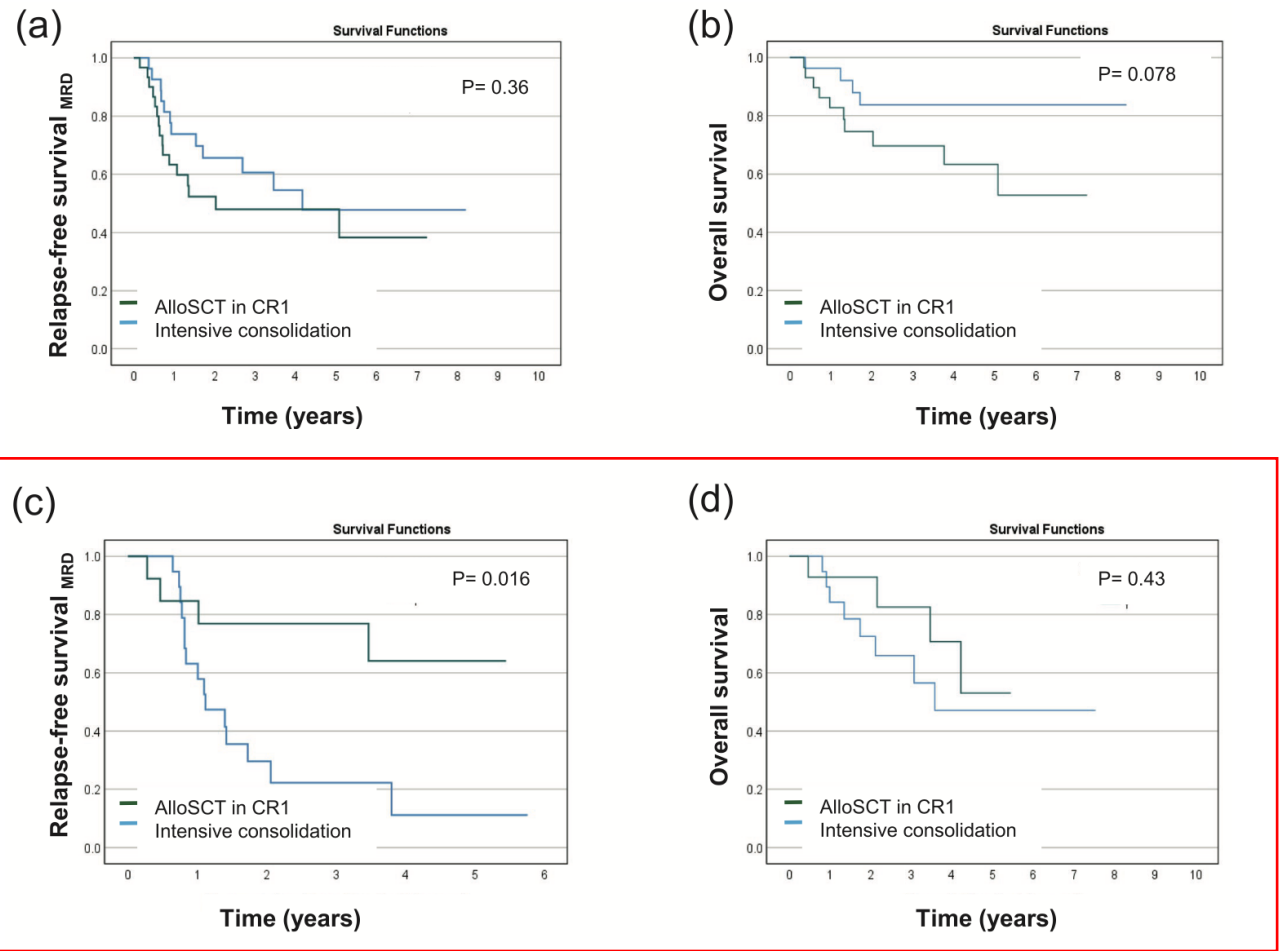
ORIGINAL ARTICLE OPEN ACCESS

Post-Relapse Outcomes of Older Patients With *NPM1*-Mutated AML Are Favorable With Allo Transplant in Second Remission

Avraham Frisch[1] | Chezi Ganzel[2] | Yishai Ofran[2] | Baher Krayem[1] | Arnon Haran[3] | Vladimir Vainstein[3] | Shlomzion Aumann[3] | Noa Gross Even-Zohar[3] | Boaz Nachmias[3]

- Patients over 60 years and patients with FLT3–ITD co- mutation had significantly lower RFS with intensive consolidation
- In all subgroups, the lower RFS did not translate into OS difference
- Relapsed NPM1 patients can often be salvaged and consequently achieve long- term remission

Above 60 years



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What do you want to do?

(a) Continue IDAC as consolidation?

(b) alloSCT

(c) Gilteritinib

(d) Ven-Aza as a bridge to transplant

Case #2: Persistent MRD

- A 57-year-old patient with AML **INV16**, RAS mutation
- The patient received 7+3+GO in induction and achieved CR (2-log reduction)
- After C1 3-log reduction with no change after C2 (200 copies)

What do you want to do?

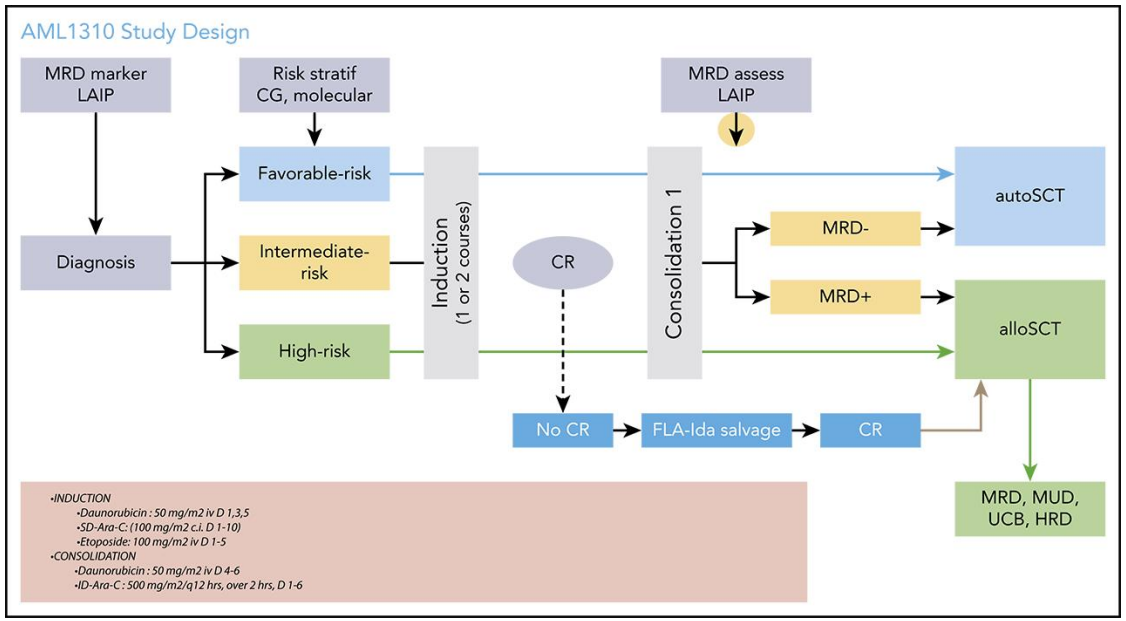
(a) Continue 2 more IDAC as consolidation

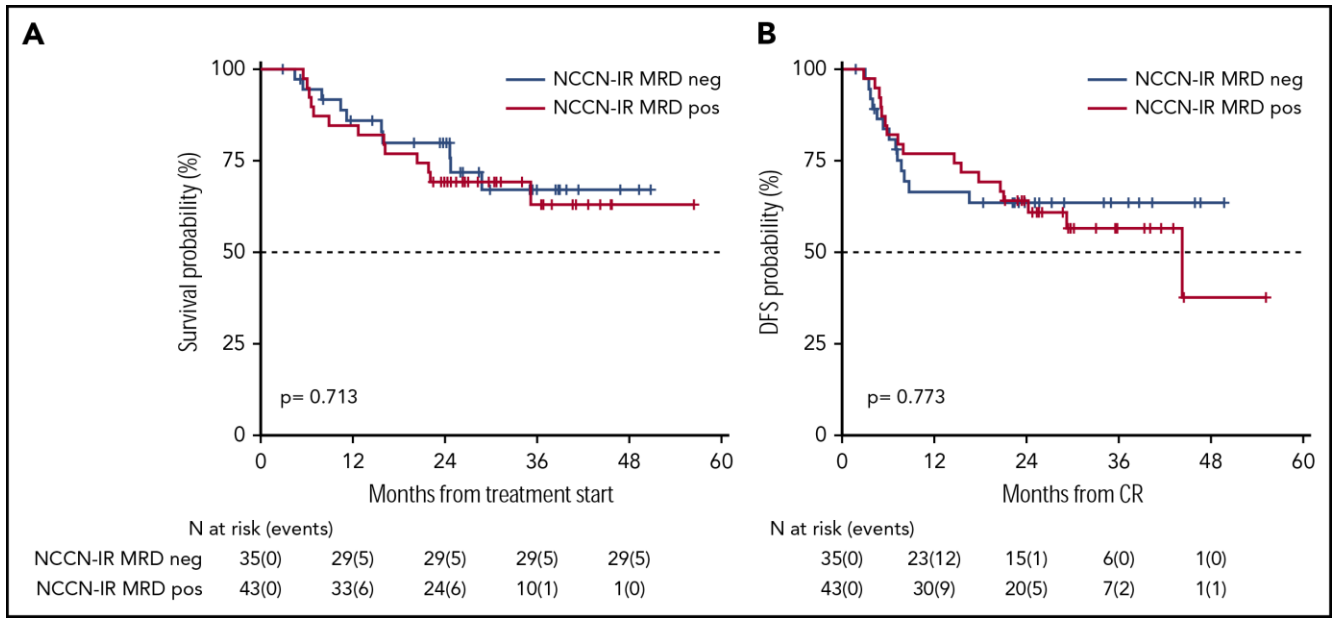
(b) Salvage

(c) Allo SCT

(d) Ven-Aza

GIMEMA AML1310 trial of risk-adapted, MRD-directed therapy for young adults with newly diagnosed acute myeloid leukemia





Two-year OS and DFS were:

74% and 61% in the **FR** category

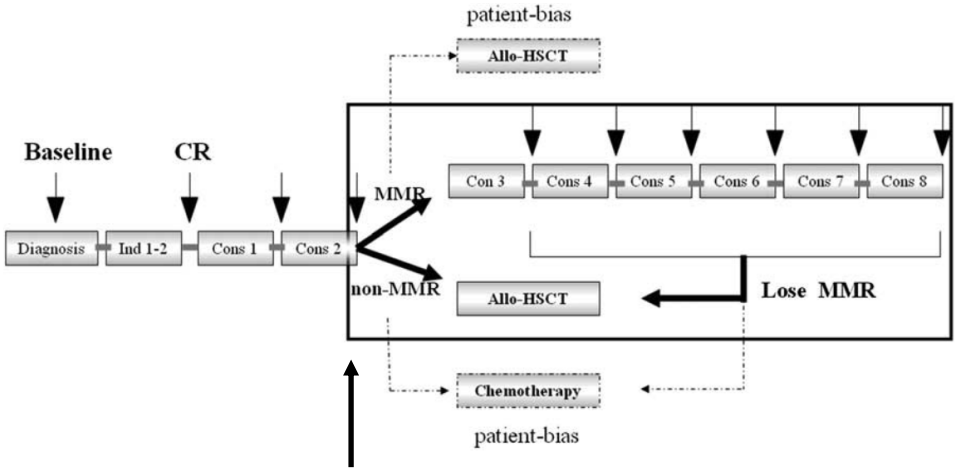
79% and 61% in the **IR** MRD-negative category

70% and 67% in the **IR** MRD-positive category ⟶ Allo might be a good strategy for MRD-positive pts?

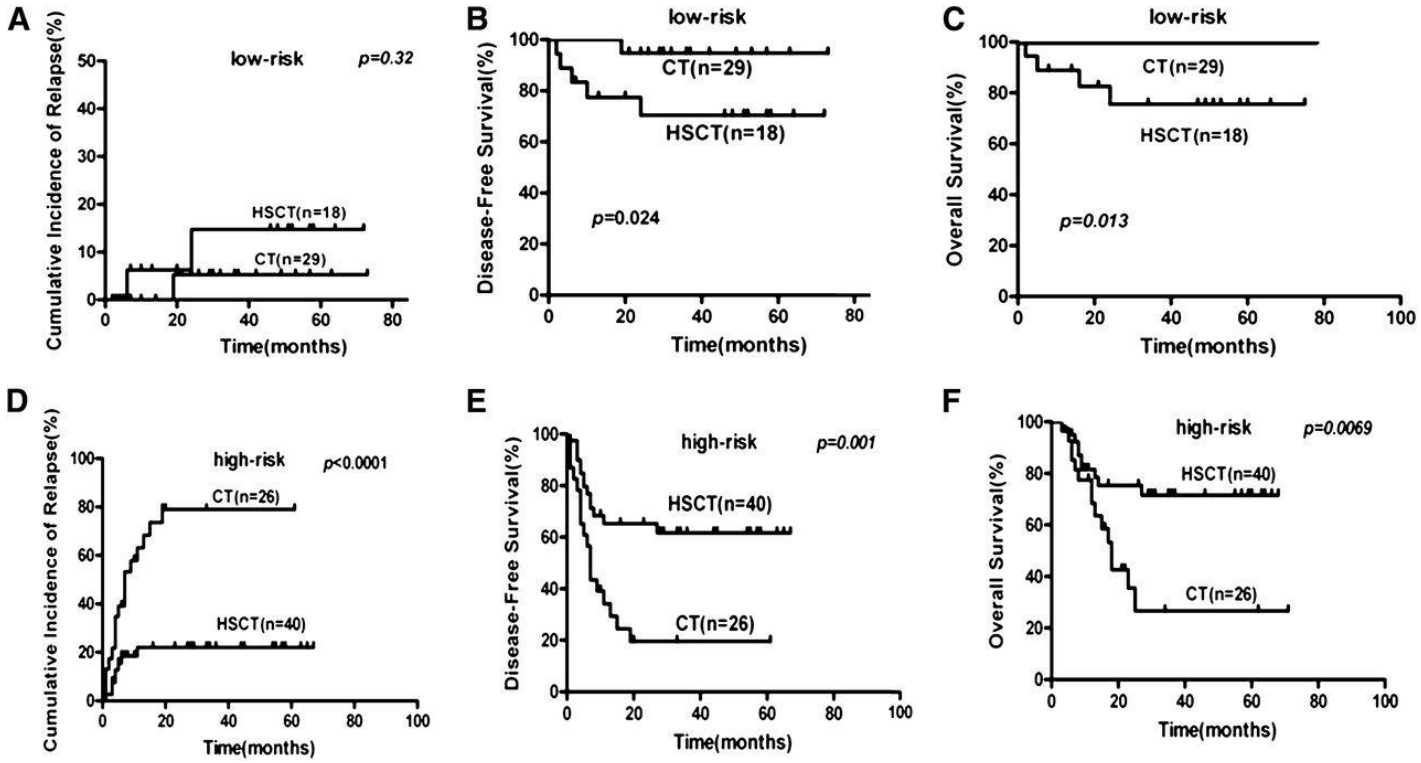
Similar signal from the AML17 trial in low MRD patients

MRD-directed risk stratification treatment may improve outcomes of t(8;21) AML in the first complete remission: results from the AML05 multicenter trial

t(8;21) MRD positive patients benefit from allo transplant



After 2nd consolidation
MMR was defined as a >3-log reduction in *RUNX1/RUNX1T1*



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(d) Ven-Aza

ARTICLE OPEN

Check for updates

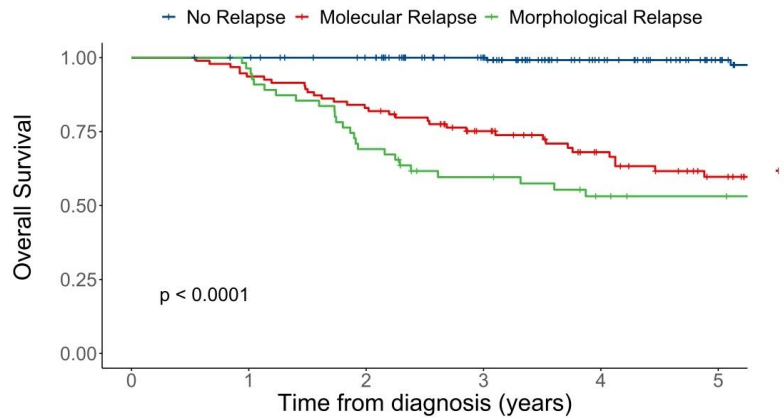
ACUTE MYELOID LEUKEMIA

Molecular relapse after first-line intensive therapy in patients with CBF or *NPM1*-mutated acute myeloid leukemia – a FILO study

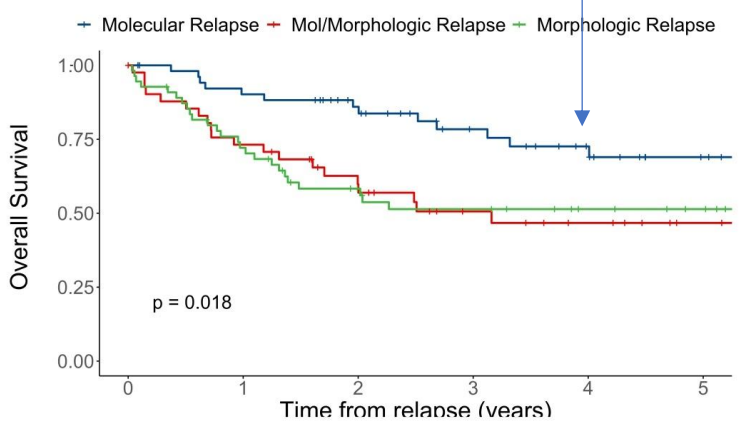
Corentin Orvain[1,2,3], Sarah Bertoli[4], Pierre Peterlin[5], Yohann Desbrosses[6], Pierre-Yves Dumas[7], Alexandre Iat[8], Marie-Anne Hospital[9], Martin Carre[10], Emmanuelle Tavernier[11], Jérémie Riou[12], Anne Bouvier[13], Audrey Bidet[14], Sylvie Tondeur[15], Florian Renosi[16], Marie-Joelle Mozziconacci[17], Pascale Flandrin-Gresta[18], Bérengère Dadone-Montaudié[19], Eric Delabesse[20], Arnaud Pigneux[7], Mathilde Hunault-Berger[1,2,3] and Christian Recher[4]✉

With preemptive therapy

- OS was significantly different according to whether patients never relapsed, had molecular relapse, or had upfront morphological relapse
- Patients who received preemptive therapy had a better OS than those who received salvage therapy after having progressed from molecular to morphologic relapse
- Preemptive therapy included upfront allogeneic HCT (n=19), intensive chemotherapy (n=21), and non-intensive therapy (n=13) with different OS rates that did not reach statistical significance



No Relapse	153	151	144	123	89	64
Molecular Relapse	94	88	78	59	43	30
Morphological Relapse	55	53	38	29	23	21



Molecular Relapse	53	46	38	27	20	12
Mol/Morphologic Relapse	42	30	21	13	9	4
Morphologic Relapse	55	38	26	22	17	14

Leukemia (2024) 38:1949 – 1957

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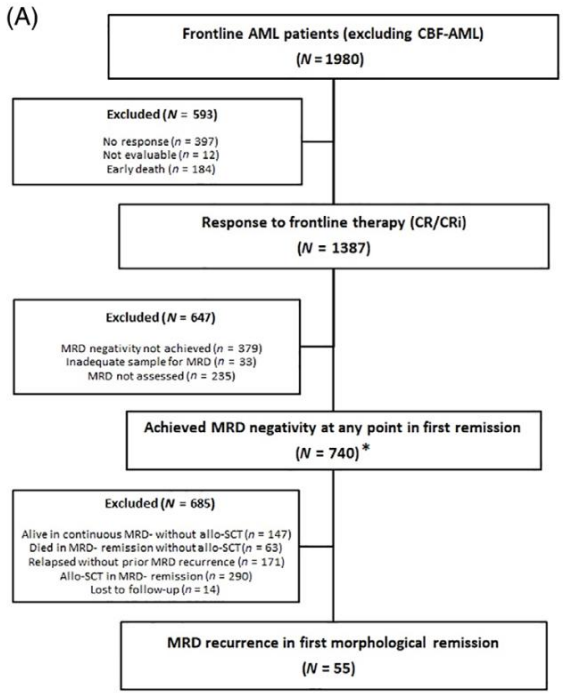
DOI: 10.1002/ajh.26698

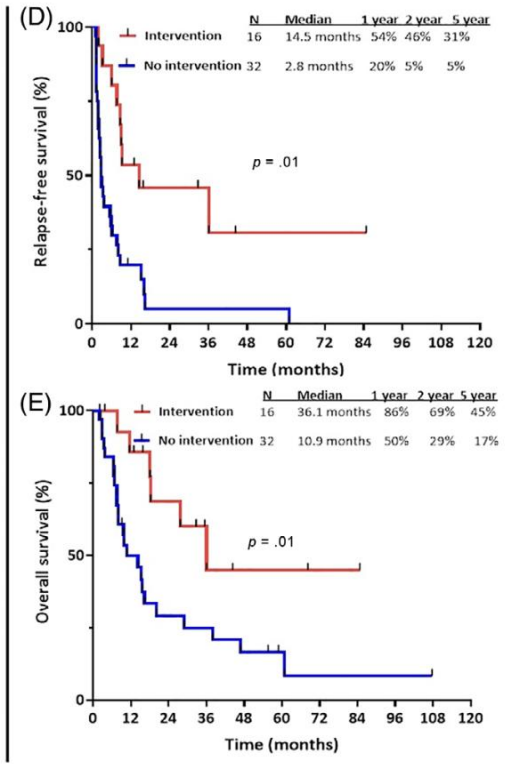
CORRESPONDENCE

Clinical outcomes and impact of therapeutic intervention in patients with acute myeloid leukemia who experience measurable residual disease (MRD) recurrence following MRD-negative remission

The median RFS for intervention versus continuation of current therapy was 14.5 and 2.8 months

There was no difference in outcomes between patients who proceeded directly to allo-SCT at the time of MRD recurrence and those who changed chemotherapy regimens



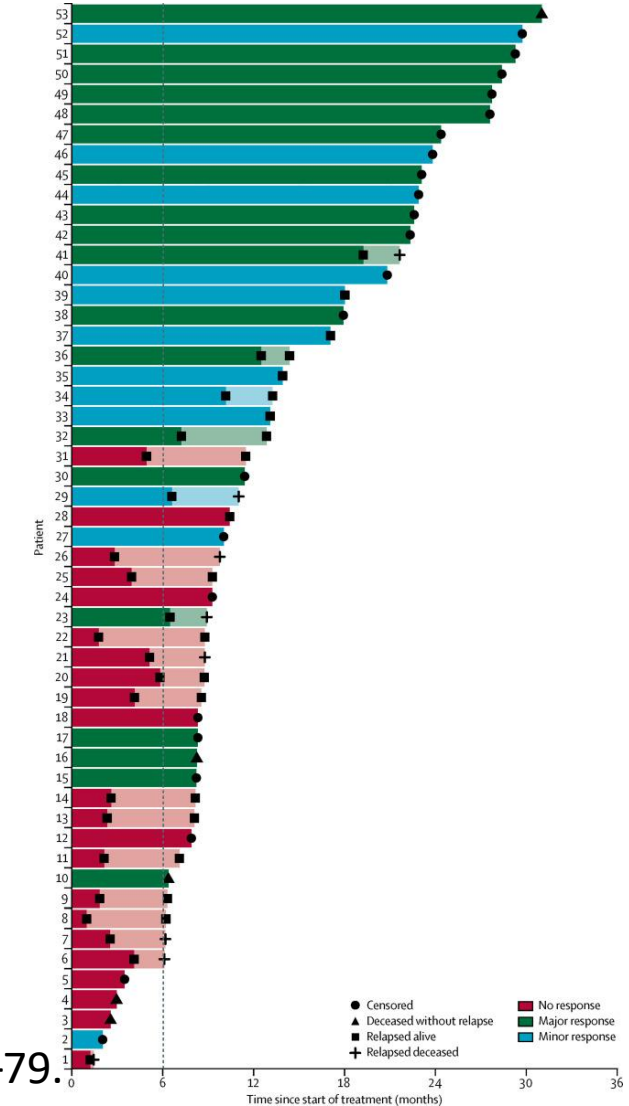


Am J Hematol, 97: E408-E411.

Measurable residual disease-guided treatment with azacitidine to prevent haematological relapse in patients with myelodysplastic syndrome and acute myeloid leukaemia (RELAZA2): an open-label, multicentre, phase 2 trial

- 53 (AML, n = 48; MDS, n = 5) became MRD-positive and were eligible for treatment with azacitidine
- 19 of the 31 patients achieved MRD-negativity
- At 12 months- RFS was 46%, and OS was 75%

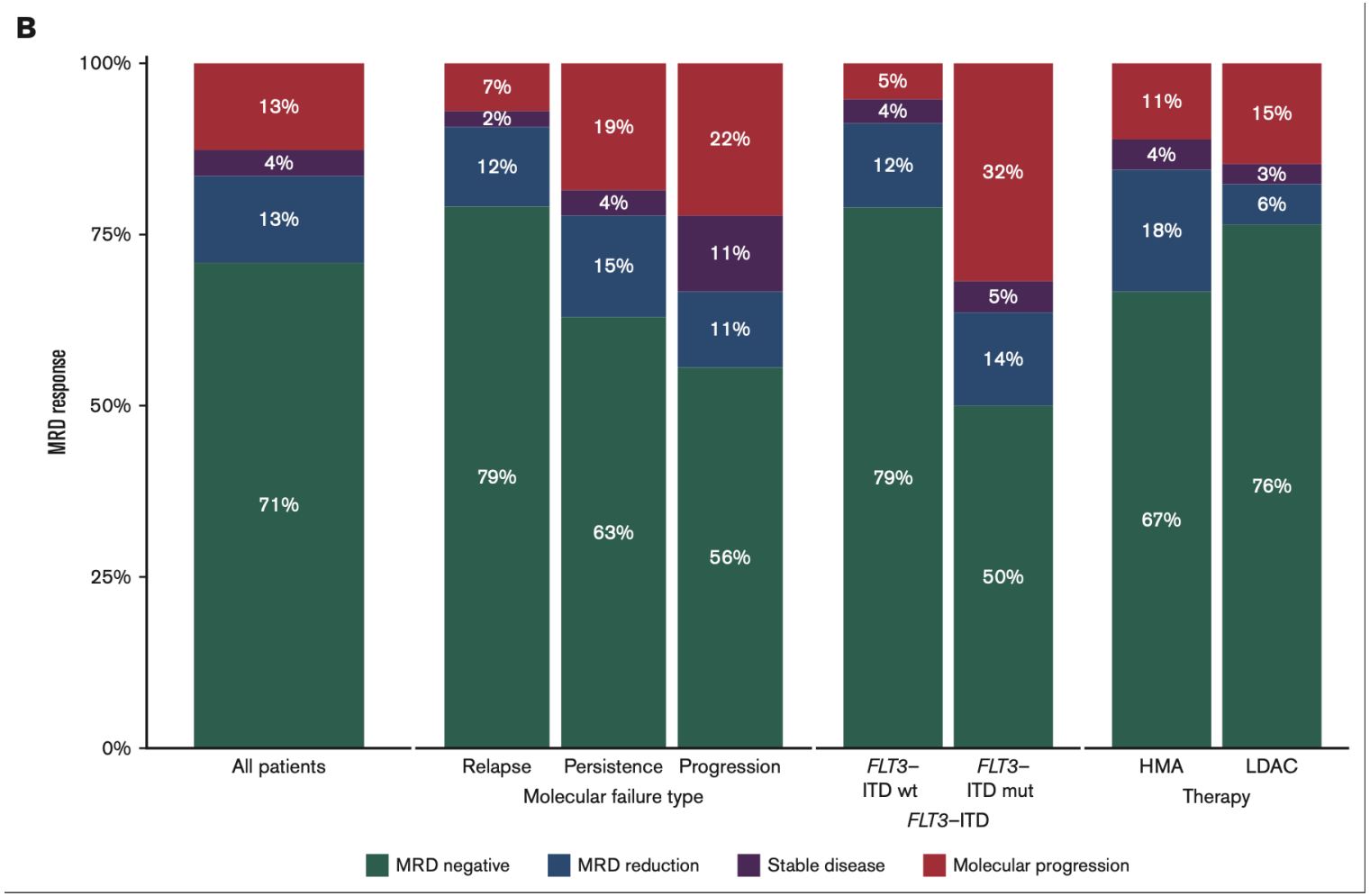
- MRD negative 12-month RFS was 88% and OS was 91%
- **Post-hoc analysis comparing outcomes between MRD-responders and non-responders showed no difference in OS at 6 months**



Lancet Oncol (2018) 19(12):1668–79.

Venetoclax–based low intensity therapy in molecular failure of *NPM1*-mutated AML

Carlos Jimenez-Chillon,[1,2] Jad Othman,[2-4] David Taussig,[5] Carlos Jimenez-Vicente,[6] Alexandra Martinez-Roca,[6,7] Ing Soo Tiong,[8-10] Manish Jain,[11] James Aries,[12] Seda Cakmak,[12] Steven Knapper,[13] Daniel Tuyet Kristensen,[14] Vidhya Murthy,[15] Joy Zacharoula Galani,[16] Charlotte Kallmeyer,[17] Loretta Ngu,[18] David Veale,[18] Simon Bolam,[19] Nina Orfali,[20] Anne Parker,[21] Cara Manson,[21] Jane Parker,[22] Thomas Erblich,[23] Deborah Richardson,[24] Katya Mokretar,[25] Nicola Potter,[2] Ulrik Malthe Overgaard,[26,27] Anne Stidsholt Roug,[14,28] Andrew H. Wei,[8] Jordi Esteve,[7] Martin Jädersten,[29,30] Nigel Russell,[3] and Richard Dillon[2,3]



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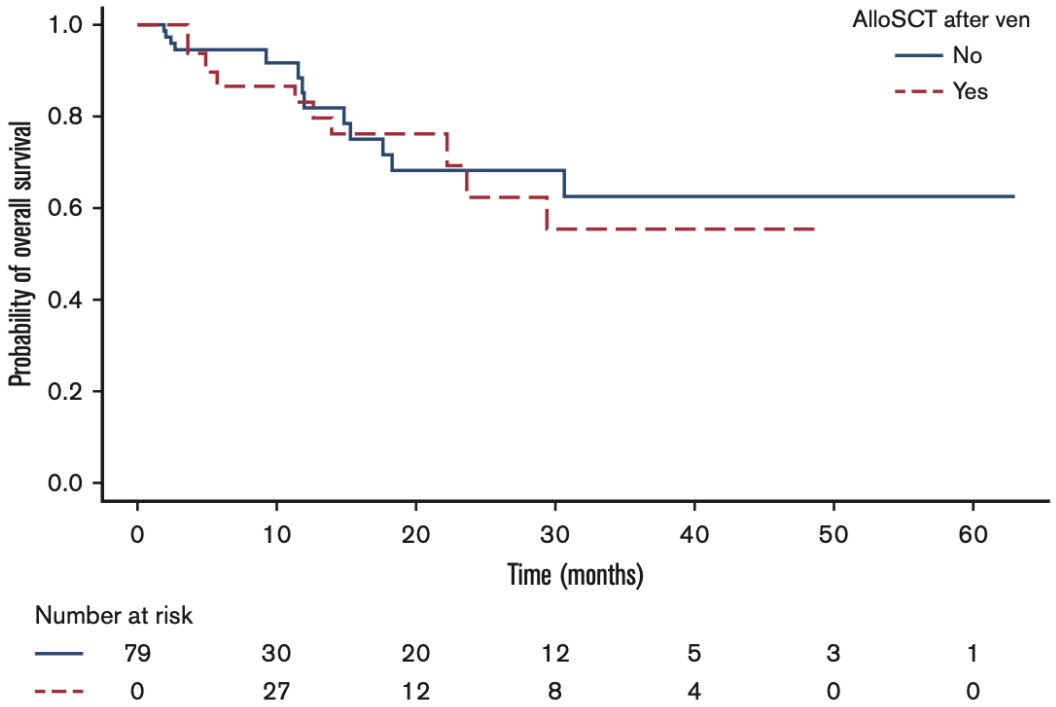
44 of 79 patients (56%) underwent allograft
41 of 44 (93%) without further therapy (only HMA-Ven)
25 of 41 (57%) were MRD negative before transplant

MRD negativity before HSCT did not have an impact on OS or EFS



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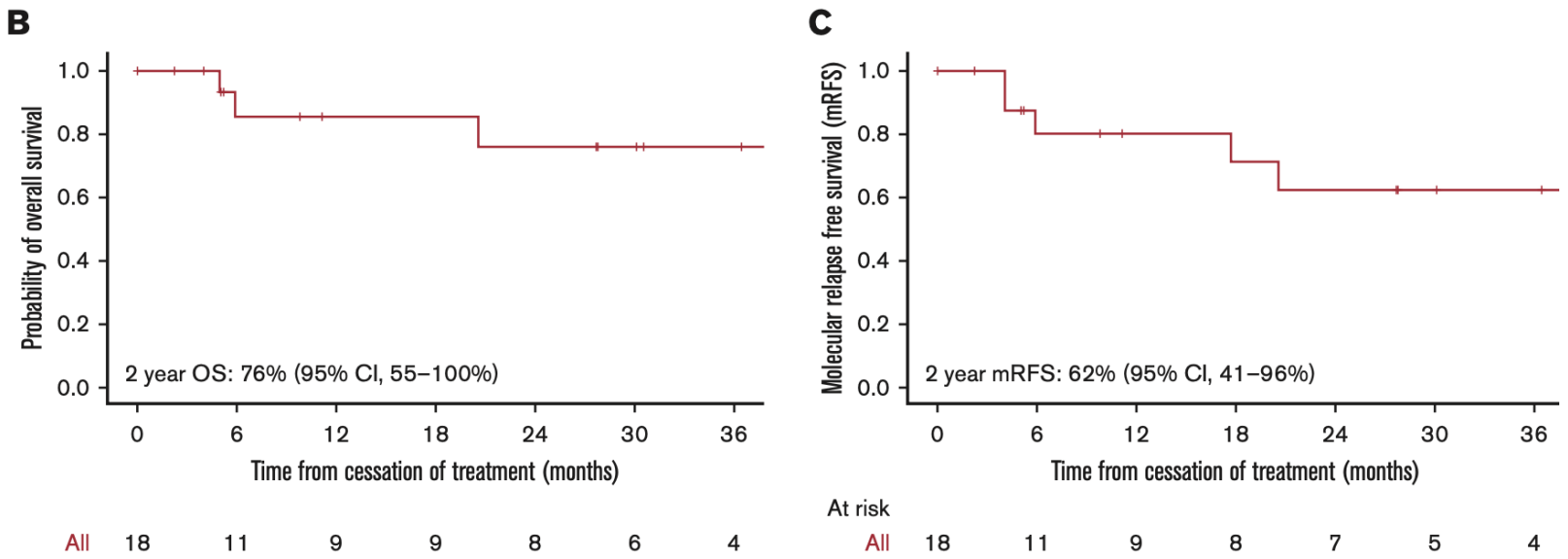
18 patients who ceased treatment after achieving MRD negativity had good outcomes, with molecular RFS at 4 years of 62%.



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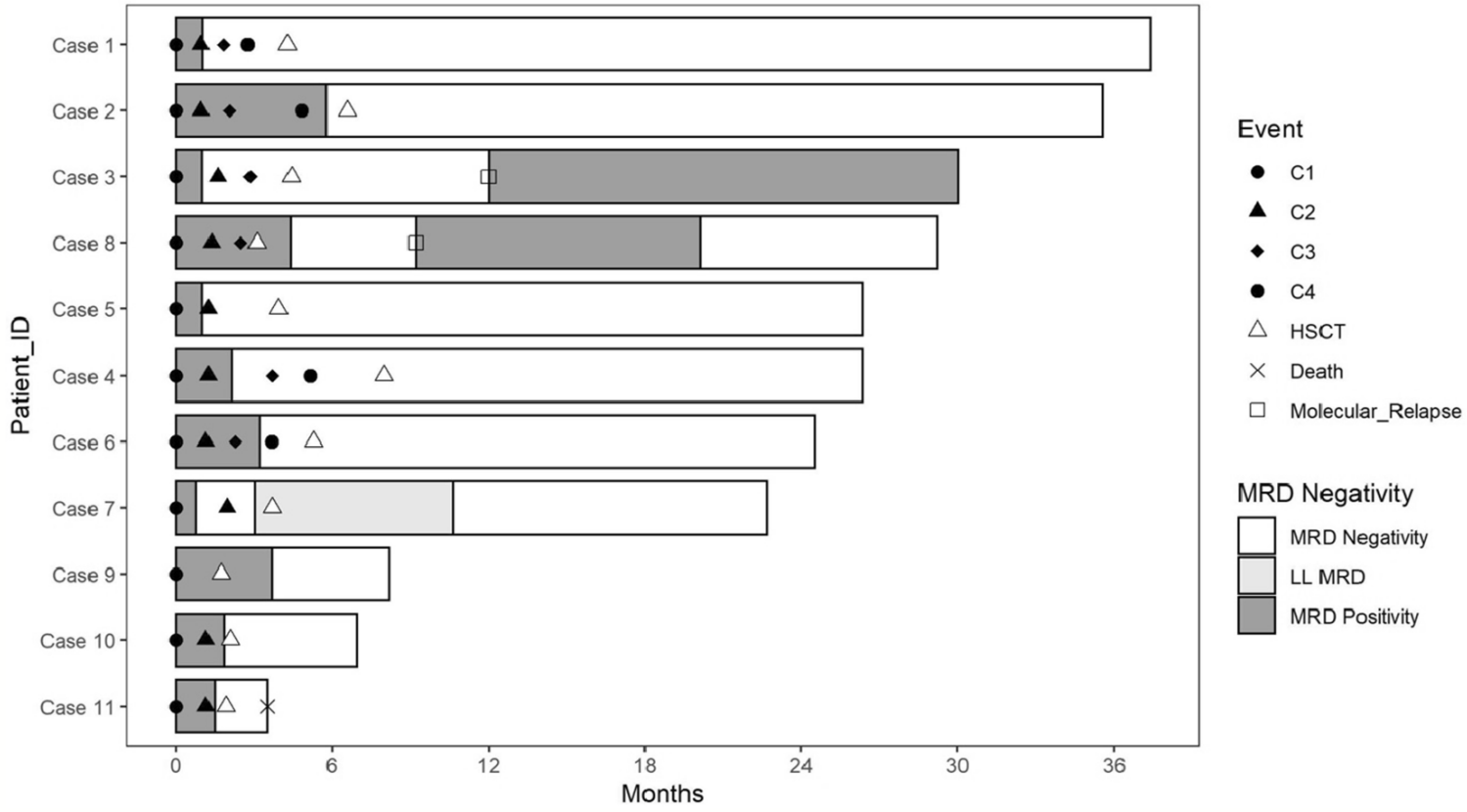
BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

ORIGINAL PAPER

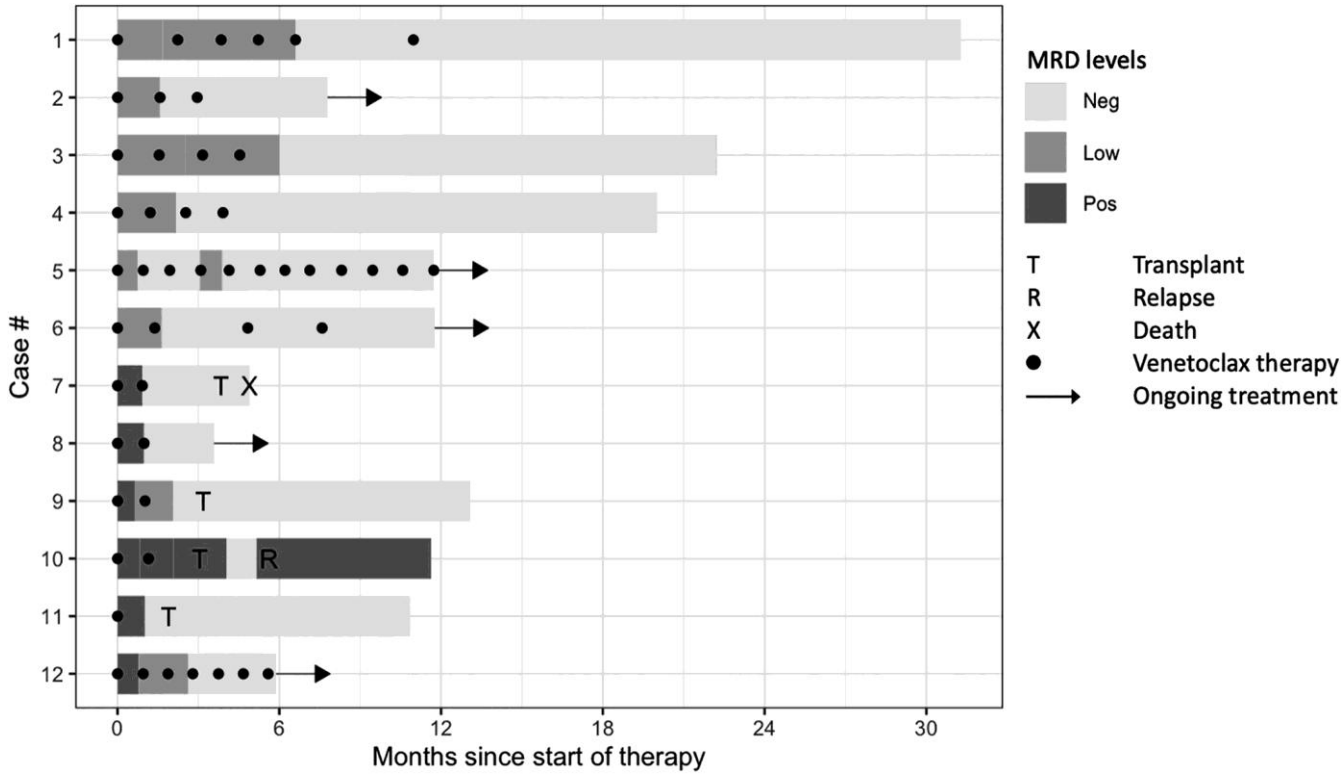
A venetoclax and azacitidine bridge-to-transplant strategy for *NPM1*-mutated acute myeloid leukaemia in molecular failure

- 82% achieved MRD negativity
- In the UK NCRI AML17 study, 27 patients received salvage chemotherapy for MRDpos in the with 56% MRDneg



bjh short report

Venetoclax induces rapid elimination of *NPM1* mutant measurable residual disease in combination with low-intensity chemotherapy in acute myeloid leukaemia



92% patients achieved MRDneg
4 proceeded to HSCT

Can we avoid transplant in patients who achieve MRD negativity?

Consider:
Transplant risk
Donor
Additional mutations

Br J Haematol, Volume: 192, Issue: 6, Pages: 1026-1030 2020

FLT3 inhibitors as MRD-guided salvage treatment for molecular failure in *FLT3* mutated AML

Jad Othman[1,2,3], Nicola Potter[1], Katya Mokretar[4], David Taussig[5], Anjum Khan[6], Pramila Krishnamurthy[7], Anne-Louise Latif[8], Paul Cahalin[9], James Aries[10], Mariam Amer[11], Edward Belsham[12], Eibhlin Conneally[13], Charles Craddock[14], Dominic Culligan[15], Mike Dennis[16], Caroline Duncan[17], Sylvie D. Freeman[18], Caroline Furness[5], Amanda Gilkes[19], Paraskevi Gkreka[20], Katherine Hodgson[21], Wendy Ingram[22], Manish Jain[6], Andrew King[23], Steven Knapper[24], Panagiotis Kottaridis[25], Mary Frances McMullin[26], Unmesh Mohite[27], Loretta Ngu[28], Jenny O'Nions[25], Katharine Patrick[29], Tom Rider[30], Wing Roberts[31], Marianne Tang Severinsen[32], Neill Storrar[33], Tom Taylor[34], Nigel H. Russell[2] and Richard Dillon[1,2]✉

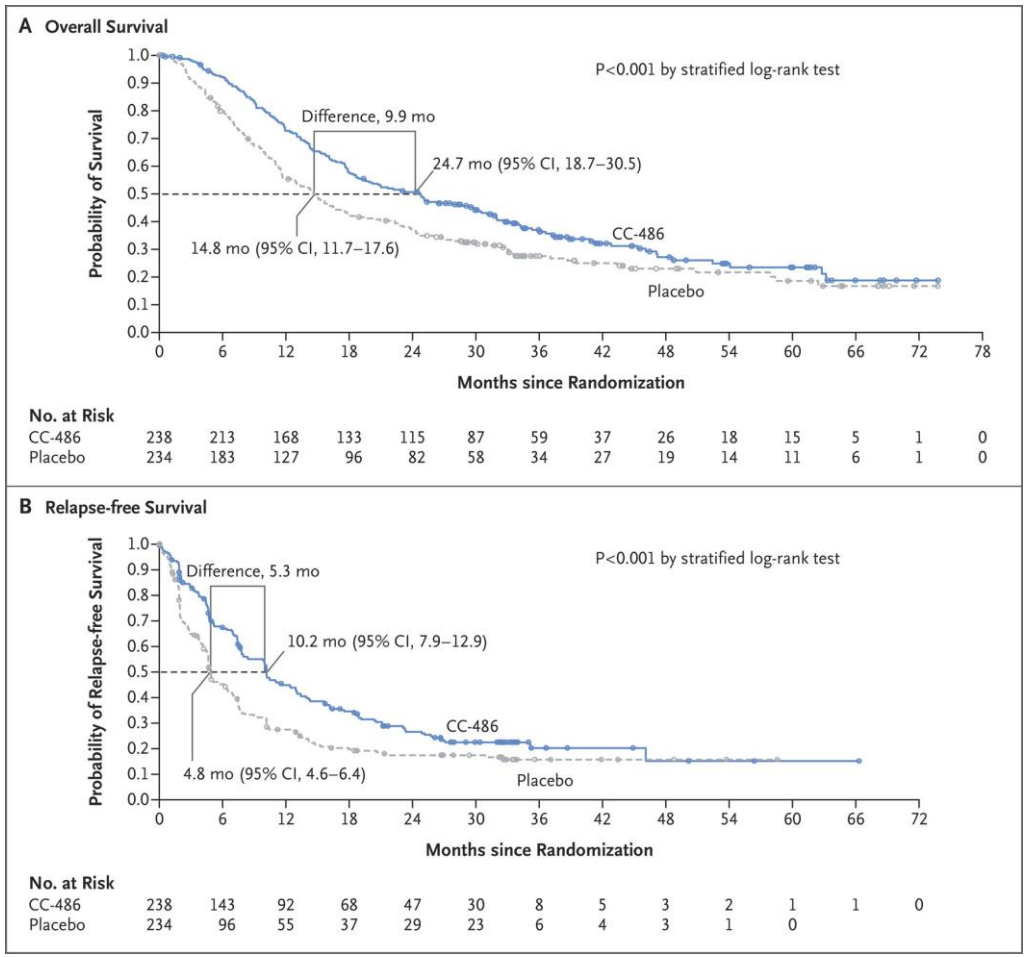
MRD-directed pre-emptive treatment in patients with molecular failure

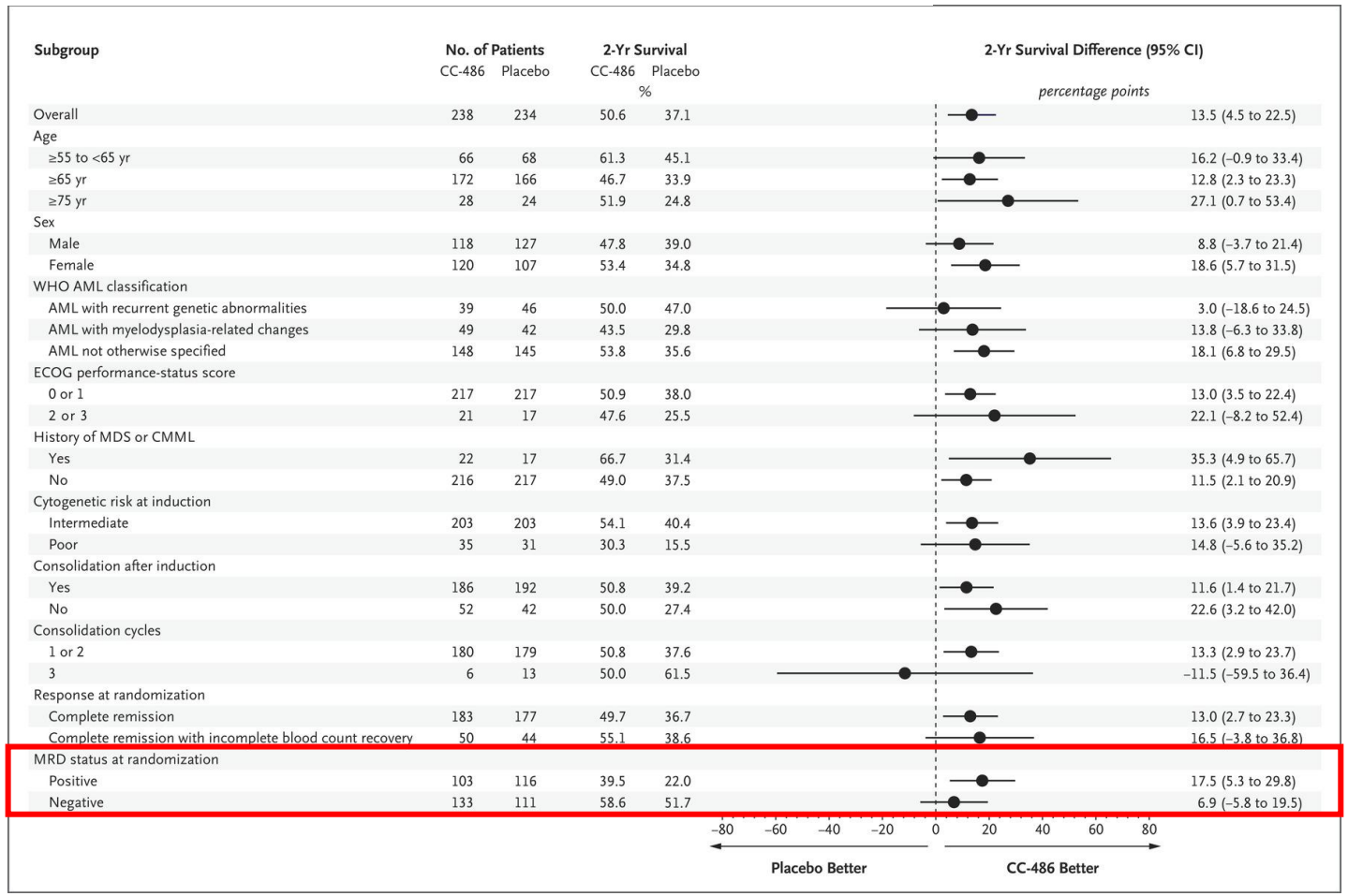
- The deepest MRD response achieved with FLT3 inhibitor occurred after a median of 50 days
- In the 28 patients who were bridged to allo-SCT or DLI, responses improved after cellular therapy, with CR MRD-neg increasing from 48% to 96%
- Treatment at molecular relapse had a higher response rate of 75% compared to treatment at molecular progression (50%) or persistence (44%, p = 0.46)
- 24-month OS was 91% in patients who achieved MR with vs 60% in those who did not

Previous midostaurin	29 (52%)
On midostaurin at time of molecular failure	17 (30%)
Previous allo-SCT	17 (30%)
In first remission	12
In CR2 or at relapse	5
Type of molecular failure	
Molecular relapse	26 (46%)
Molecular persistence	9 (16%)
Molecular progression	21 (38%)
FLT3 inhibitor used for molecular failure	
Gilteritinib	38 (68%)
Quizartinib	7 (12%)
Sorafenib	11 (20%)

Leukemia (2023) 37:2066 – 2072

Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission

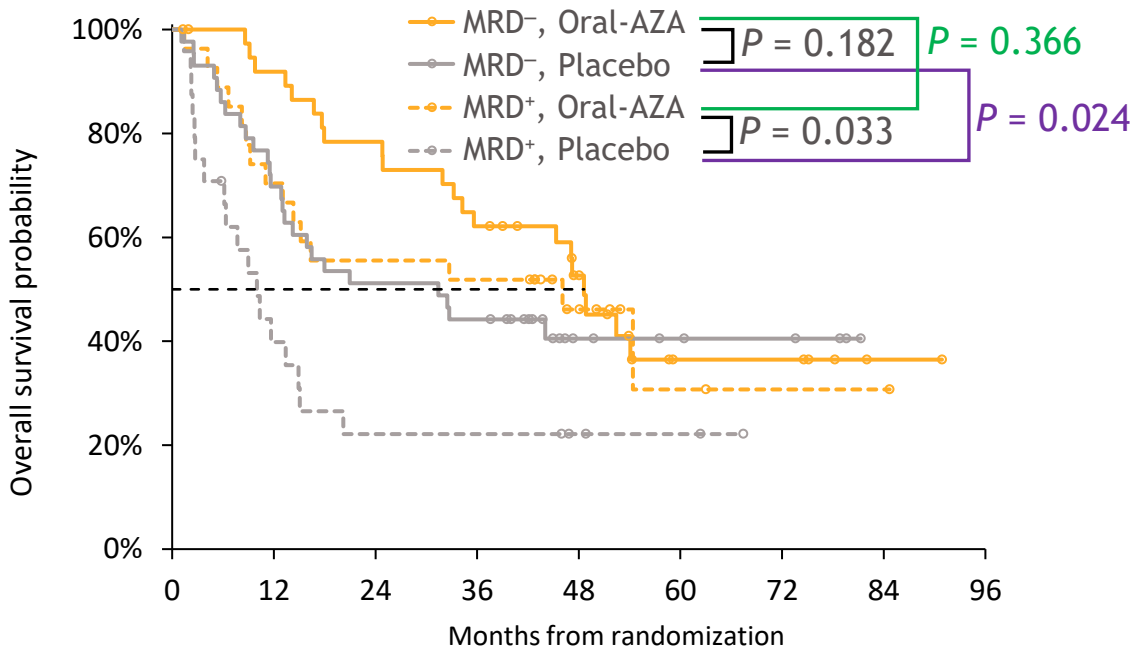




Flow based 0.1%

Oral-AZA prolongs OS and RFS vs. placebo in patients with NPM1mut mainly in positive post-IC MRD status

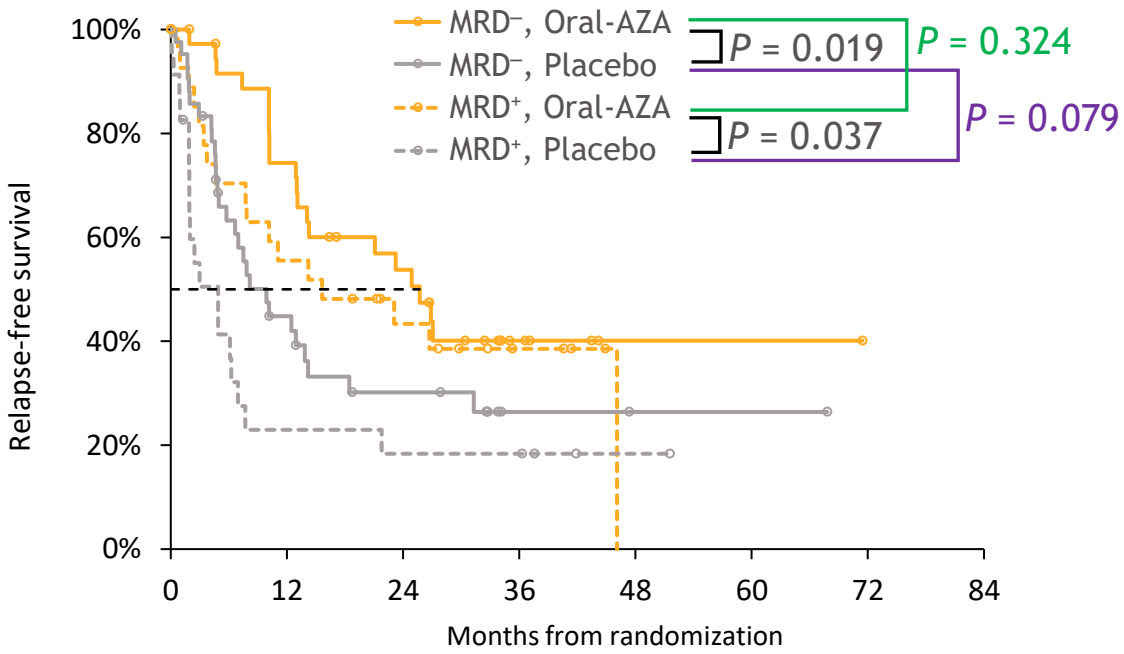
OS for patients with *NPM1*^{mut} at Dx, by post-IC MRD status



Median OS, months

MRD⁻, Oral-AZA (n=39)	**48.6**	MRD⁺, Oral-AZA (n=27)	**46.1**
MRD⁻, Placebo (n=43)	**31.4**	MRD⁺, Placebo (n=24)	**10.0**

RFS for patients with *NPM1*^{mut} at Dx, by post-IC MRD status



Median RFS, months

MRD⁻, Oral-AZA (n=39)	**25.7**	MRD⁺, Oral-AZA (n=27)	**15.6**
MRD⁻, Placebo (n=43)	**9.9**	MRD⁺, Placebo (n=24)	**4.9**

- MRD determined at study entry by MFC using a "different-from normal" method with a 0.1% positivity threshold.

Döhner et al. Oral Presentation at ASH 2021. Presentation 804.

Case #3: Persistent MRD

- 29 y old patient, **NPM1+** FLT3-TKD AML
- The patient received 7+3 +Midostaurin
- D28 CR by morphology and flow, still neutropenic
- NPM1 MRD PB 18% (1800 copies)

What do you want to do?

(a) AZA VEN

(b) Salvage

(c) Consolidation

(d) allo-BMT

Case #4: Molecular Relapse

- A 50-year-old patient with AML **NPM1**, FLT3-ITD mutation
- The patient completed 7+3+MIDO in induction 3 IDACs as consolidation with MRD negativity at the end of C2
- 3 months post consolidation, NPM1 was detected at 0.1% and in a following test (1-month apart) 4%

What do you want to do?

(a) alloSCT

(b) Salvage

(c) Gilt

(d) Ven-Aza- Gilt

(e) Ven-Gilt

Case #4: Molecular Relapse

- A 50-year-old patient with AML **NPM1**, FLT3-ITD mutation
- The patient completed 7+3+MIDO in induction 3 IDACs as consolidation with MRD negativity at the end of C2
- 3 months post consolidation, NPM1 was detected at 0.1% and in a following test (1-month apart) 4%

What do you want to do?

(a) alloSCT – do you need to buy time?

(b) Salvage

(c) Gilt

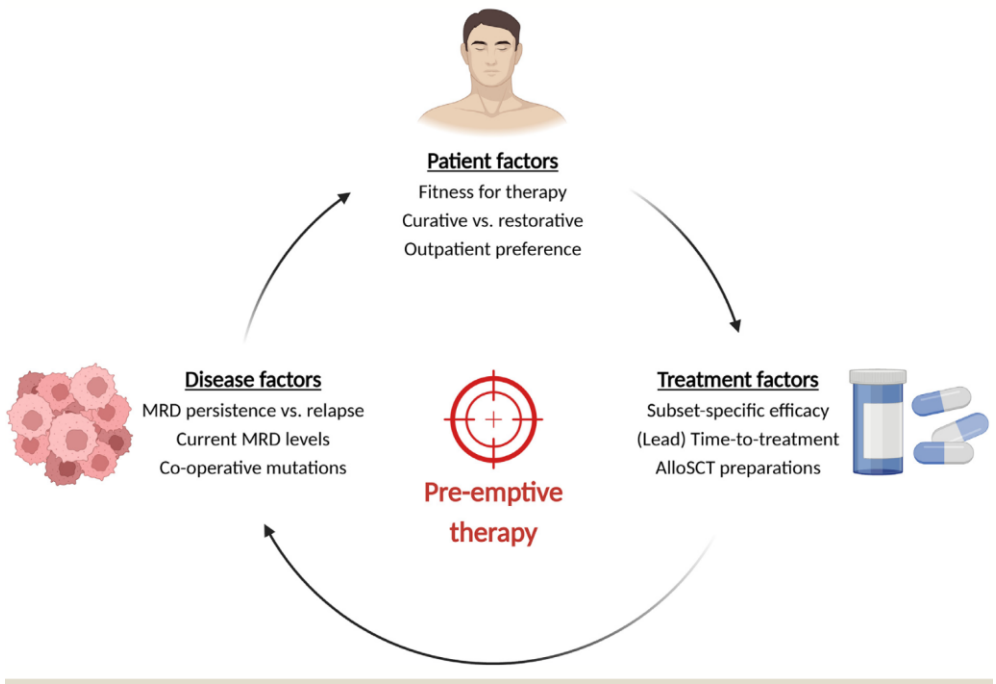
(d) Ven-Aza- Gilt

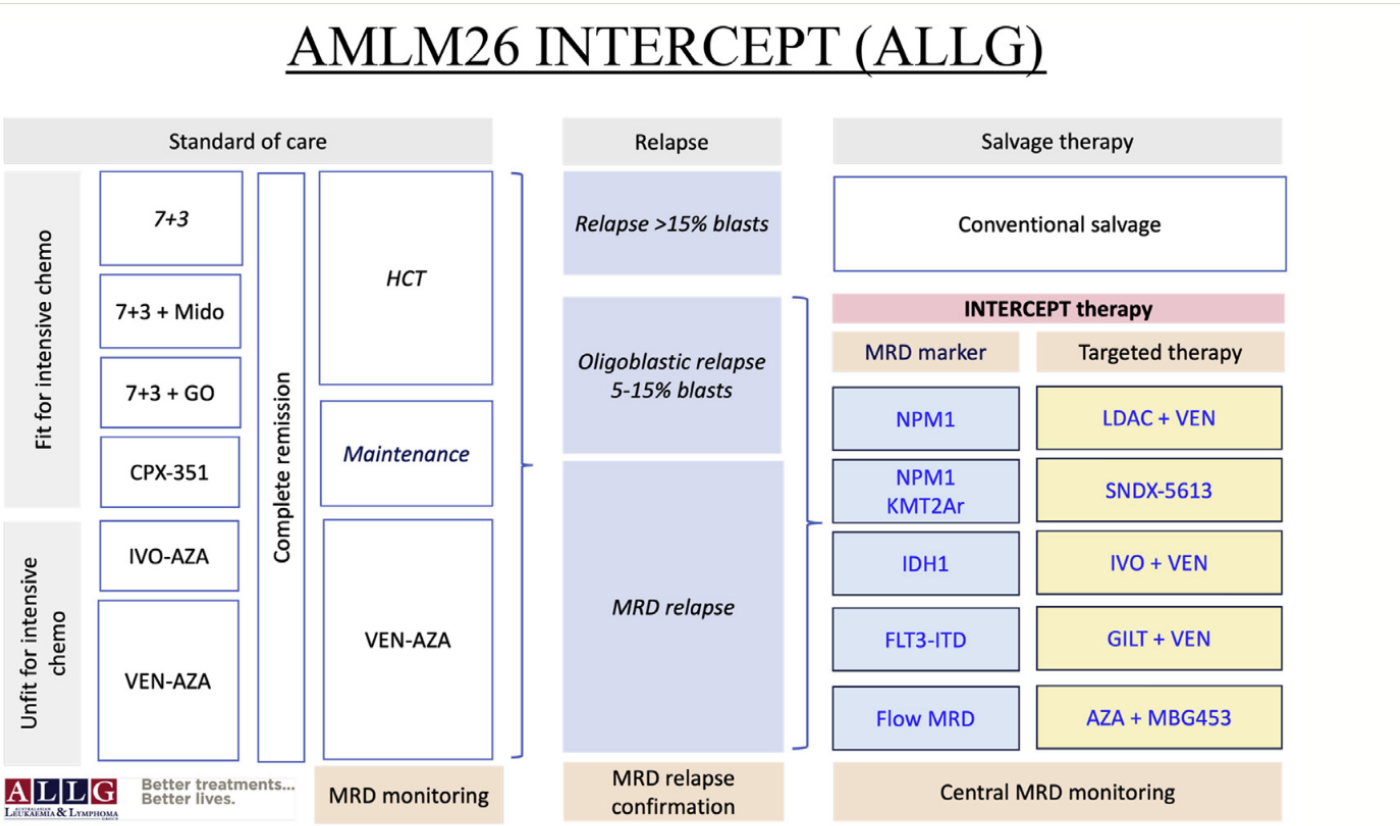
(e) Ven-Gilt

Review Article

SOHO State of the Art Updates and Next Questions: Pre-emptive Therapy at Molecular Measurable Residual Disease Failure in Acute Myeloid Leukemia

Aditya Tedjaseputra,[1,2,3] Nigel Russell,[1] Richard Dillon[1,2]





Summary

D14

- Inconclusive- wait
- clear disease with partial response-re-induction
- Refractory disease- salvage/novel agents

MRD persistence (low)

- Consider other risk factors (FLT3, cytogenetics)
- Consider treatment augmentation
- Monitor closely
- Oral Aza?
- Allo-SCT is currently the only MRD-converter with supporting clinical evidence

MRD persistence (high)/relapse

- **Pre-emptive treatment improves outcome**
- Allo-SCT
- Consider salvage/ven-aza/FLT3i
- Not enough data supporting pte-transplant on pre-transplant MRD erasing

Case #5: Morphological Relapse

- A 39-year-old patient with AML trisomy 8 and TET2 mutation
- The patient received 7+3+ induction with CR on D28
- The patient received 3 cycles of IDAC
- 12-months later BM revealed 35% blasts

What do you want to do?

(a) FLAG-IDA-VEN

(b) 7+3

(c) Ven-Aza

Venetoclax Combined With FLAG-IDA Induction and Consolidation in Newly Diagnosed and Relapsed or Refractory Acute Myeloid Leukemia

Courtney D. DiNardo, MD, MSCE[1]; Curtis A. Lachowiez, MD[2]; Koichi Takahashi, MD, PhD[1]; Sanam Loghavi, MD[3]; Lianchun Xiao, MS[4];

FLAG-IDA

- CR was obtained in 24 of 46 patients (52.1%)
- 3 of 46 (6.6%) died during reinduction therapy

(Annals of Hematology volume 82, 231–235, 2003)

Parameter	Phase IIA ND-AML (n = 29)	Phase IB R/R-AML (n = 16)	Phase IIB R/R-AML (n = 23)
Age, years	45 (20-65)	51 (20-73)	47 (22-66)
Sex (male)	13	10	14
VEN dose level			
Dose level −1 (VEN 200 mg, D1-21)	—	8	—
Alternate dose level −1 (VEN 200 mg, D1-14)	—	5	—
Dose level 0 (VEN 400 mg, D1-14)	29	3	23
Median No. of prior therapies	—	2 (1-6)	1 (1-3)
Prior HSCT	—	7	7
ELN risk group			
Favorable	5	6	6
Intermediate	13	2	3
Adverse	11	8	14
Cytogenetic group			
Favorable	—	4	2
Diploid	13	2	8
Other intermediate	8	2	3
Adverse-risk or complex	4	4	9
Insufficient mitoses	1	1	—
KMT2A-rearranged	3	3	1

Venetoclax Combined With FLAG-IDA Induction and Consolidation in Newly Diagnosed and Relapsed or Refractory Acute Myeloid Leukemia

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FLAG-IDA-VEN

- CRc of about 60%
- 12m OS 68%
- NPM1, IDH1/2-mutated AML had favorable responses, whereas tumor suppressor mutations, in particular TP53, resulted in resistance like signaling mutations
- No early mortality

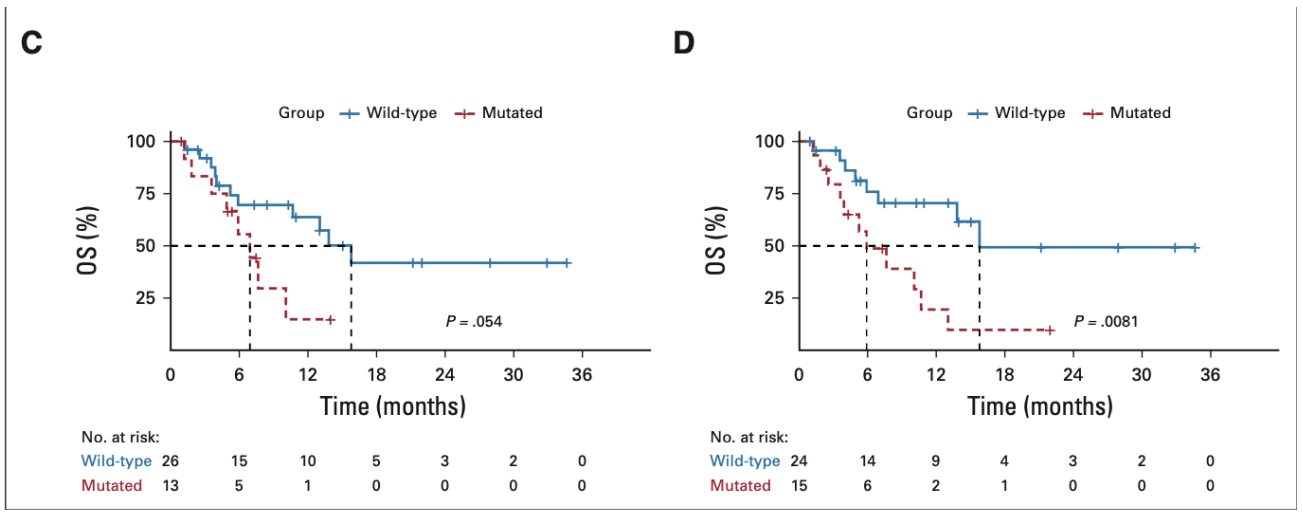

TABLE 2. Patient Outcomes

Outcome	Phase IB R/R-AML (n = 16)	Phase IIB R/R-AML (n = 23)
ORR, No. (% [CI])	12 (75 [48 to 93])	16 (70 [47 to 83])[a]
CRc (CR + CRi + CRh), No. (% [95% CI])	12 (75 [48 to 93])	14 (61 [39 to 80])
CR, No. (%)	6 (38)	11 (48)
CRh, No. (%)	2 (13)	3 (13)
CRi, No. (%)	4 (25)	—
MRD⁻ CR (flow cytometry), No. (% [95% CI])	7 (58 [28 to 85])	11 (79 [49 to 95])
MLFS	—	2
No response	4	7
DOR (median, months)	6 (3 to NE)	NR
EFS		
Median, months (95% CI)	6 (3 to NE)	11 (2 to NE)
6-month, % (95% CI)	50 (31 to 82)	59 (41 to 84)
12-month, % (95% CI)	31 (15 to 65)	41 (21 to 77)
OS		
Median, months (95% CI)	9 (4.9 to NE)	NR (6 to NE)
6-month, % (95% CI)	63 (43 to 91)	68 (49 to 94)
12-month, % (95% CI)	38 (20 to 71)	68 (49 to 94)

Venetoclax in combination with FLAG-IDA-based protocol for patients with acute myeloid leukemia: a real-world analysis

Ofir Wolach[1,2] · Avraham Frisch[3] · Liat Shargian[1,2] · Moshe Yeshurun[1,2] · Arie Apel[2,4] · Vladimir Vainstein[5] · Yakir Moshe[6] · Shai Shimony[1,2,7] · Odelia Amit[6] · Yael Bar-On[6] · Yishai Ofran[8] · Pia Raanani[1,2] · Boaz Nachmias[5] · Ron Ram[6]

- R/R 24 patients
- 44% adverse risk
- CRc 72%

Age, years (range)	53.4 (30.1, 72)
Sex (male, %)	16 (64)
Median prior lines of therapy	1 (0, 3)
Treatment context (*n*, %)	
Upfront	1 (4)
Relapsed/refractory	24 (96)
AML type (*n*, %)	
De novo AML	13 (52)
Secondary AML	12 (48)
t-AML	8 (32)
AML-AHD	4 (16)
Prior HCT (*n*, %)	11 (44)
ELN risk group (*n*, %)	
Favorable	6 (24)
Intermediate	8 (32)
Adverse	11 (44)
Cytogenetic group (*n*, % of total assessed)	
Favorable	1 (4)
Diploid	12 (48)
Other intermediate	3 (12)
Adverse-risk or complex	4 (16)
KMT2A-rearranged	4 (16)
Insufficient mitoses/NA	1 (4)
Molecular mutations(*n*, % of total assessed)	
NPM1	4/25 (16)
FLT3-ITD	5/25 (25)
TP53/del17p	3/13 (23)
IDH1/2	4/15 (26)

Response (FLAG-IDA-VEN) (*n*, %)	
ORR	19/25 (76)
No transplant	9/14 (64)
Post-transplant	10/11 (91)
CRc	18/25 (72)
No transplant	8/14 (57)
Post-transplant	10/11 (91)
MLFS	1 (4)
Persistent disease	3 (12)
NA	3 (12)
Subsequent therapy (*n*, %)	
Allo SCT	10 (40)
DLI	4 (16)
Maintenance^	5 (20)
None	4 (16)
NA	2 (8)

Venetoclax in combination with FLAG-IDA-based protocol for patients with acute myeloid leukemia: a real-world analysis

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- High rate of invasive fungal infection
- Significant early mortality

	Grades 3–4 AE
Blood stream infection	12 (48)
Invasive fungal infection	8 (32)
Gastro-intestinal	4 (16)
Pulmonary	3 (12)
Hepatic	1 (2)
CNS	0 (0)
TLS	0 (0)
Time to neutrophil recovery* (median, days, range)	23 (95% *CI* 20–28)
Time to platelet recovery** (median, days, range)	31 (95% *CI* 17.6–38.3)
Duration of admission *** (median, days, range)	26 (18–72)
Early death, 30 days (*n*, %)	3 (12)
Early death, 60 days (*n*, %)	3 (12)

DOI: 10.1111/bjh.18229

LETTER TO THE EDITOR

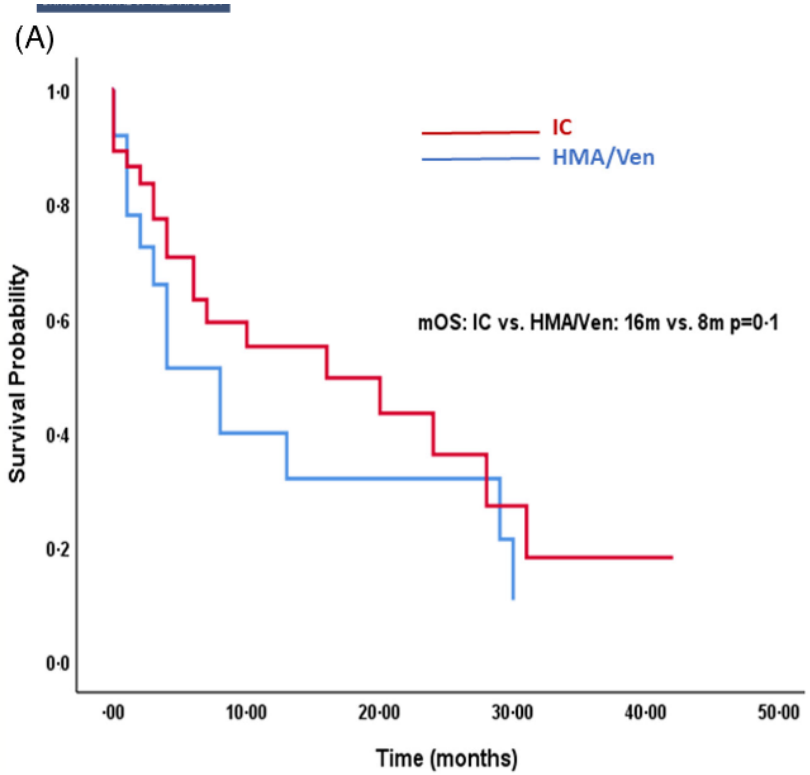
BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

Hypomethylating agent/venetoclax versus intensive chemotherapy in adults with relapsed or refractory acute myeloid leukaemia

- There was no difference in composite CR rates (IC 57% vs 59% HMA/Ven, $p = 0.8$)
- More patients in the IC cohort (41%), compared to the HMA/Ven (20%) cohort proceeded to transplant ($p = 0.04$).

TABLE 1 Baseline characteristics

	HMA/Ven ($n = 53$)	Intensive chemotherapy ($n = 53$)	p-Value
Age (median, range)	62 (22–75)	57 (24–72)	0.06
Male (n, %)	30 (57)	29 (55)	0.4
Bone marrow blast % (median, range)	39 (6–94)	59 (6–93)	**0.03**
Cytogenetics (n, %)			
Poor	22 (41)	21 (39)	0.7
Intermediate	31 (59)	31 (59)	
ELN 2017 risk stratification (n, %)			
Poor/adverse	31 (59)	27 (51)	0.5
Intermediate	16 (30)	20 (38)	
Favourable	6 (11)	6 (11)	
Mutations (n, %)			
NPM1	9 (16)	12 (22)	0.5
FLT3-ITD/TKD	10 (19)	14 (27)	
IDH1/2s	14 (27)	10 (19)	
TP53	12 (22)	8 (15)	
Time to relapse			
<6 months	28 (52)	29 (54)	0.8
≥6 months	25 (48)	24 (46)	
Prior transplant (n, %)	12 (22)	6 (11)	0.2
Prior intensive chemotherapy	51 (97%)	53 (100%)	0.6
Line of therapy (median, range)	2 (2–6)	2 (2–4)	0.9



HMA-Ven

Graveno et al. (2022) Leukemia & Lymphoma, 63:7, 1645-1650

- 77 patients with a median of 1 prior therapy
- The median overall survival (OS) was 13.1 months
- CR/CRi of 53%.

Mohassel et al. ASH abstract 2022

- Common chemotherapy regimens included MEC (74%), ME (12%), and FLAG ± IDA (11%)
- Similar efficacy, better safety

Table 1. Primary and Secondary Outcomes

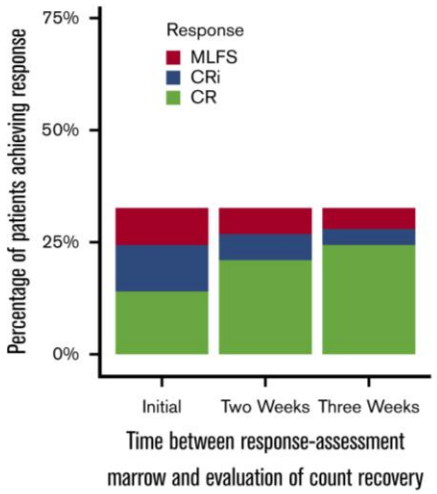
	VEM/HMA (n = 25)	SC (n = 38)	p-value
Primary outcome			
Overall response rate*	13 (52)	16 (42)	0.44
CR	7 (28)	9 (24)	
CRi	2 (8)	5 (13)	
MLFS	4 (16)	2 (5)	
Secondary outcomes			
Overall survival, days (median, 95% CI)	287 (139-562)	285 (183-444)	0.99
Relapse-free survival, days (median, 95% CI)†	304 (205-NA)	325 (151-468)	0.38
Received stem cell transplant	5 (20)	11 (29)	0.55
30-day induction mortality	1 (4)	0	0.39
60-day induction mortality	3 (12)	2 (5)	0.37
Length of hospital stay, days	13 (8-38)	34 (27-41)	0.04
Induction completed as outpatient	15 (60)	0	< 0.00001
Toxicities (Grade ≥ 3)¶			
Neutropenia	25 (100)	38 (100)	1
Thrombocytopenia	24 (96)	38 (100)	1
Anemia	20 (80)	37 (97)	0.02
Nausea	0	4 (11)	0.14
Diarrhea	2 (8)	5 (13)	0.69
Mucositis	1 (4)	10 (26)	0.03
Transaminitis/hyperbilirubinemia	1 (4)	1 (3)	1
Febrile neutropenia	10 (40)	37 (97)	<0.00001
Tumor lysis syndrome‡	3 (12)	4 (11)	1
Incidence of bacterial infections	6 (24)	19 (50)	0.03
Bacterial infection, site			
Blood	2 (8)	14 (37)	0.01
Lungs	0	1 (3)	1
GI (*Clostridium difficile*)	1 (4)	5 (13)	0.38
Sinus	1 (4)	1 (3)	1
Oral cavity	2 (8)	0	0.15
Other	4 (16)	2 (5)	0.20
Incidence of fungal infections§	7 (28)	16 (42)	0.25
Fungal infection, site			
Blood	1 (4)	1 (3)	1
Lungs	3 (12)	14 (37)	0.04
Sinus	1 (4)	0	0.39
Oral cavity	2 (8)	2 (5)	1
Skin	1 (4)	0	0.39

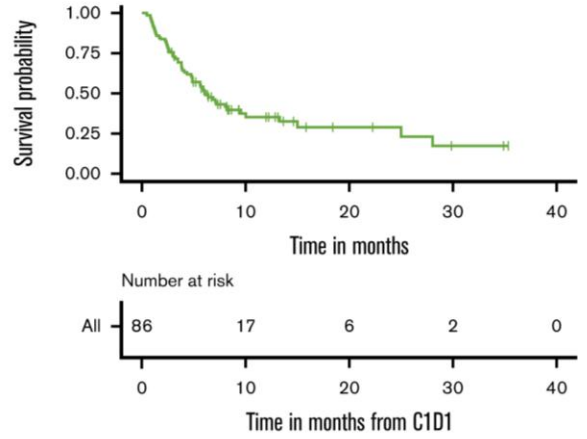
Data reported as median (interquartile range) or n (%) unless otherwise noted. *Assessed by the 2017 European LeukemiaNet response criteria.
†Evaluated in responders: VEN/HM, n = 13 and SC, n = 16. ¶Defined per Common Toxicity Criteria for Adverse Events v.5.0. ‡No clinical tumor lysis syndrome reported
§Defined per 2020 European Organization for Research and Treatment of Cancer & Mycoses Study Group Education and Research Consortium consensus definitions.
Abbreviations: CR, complete response; CRi, complete response with incomplete hematologic recovery; MLFS, morphologic leukemia-free state; NA, not available.

Clinical and molecular predictors of response and survival following venetoclax therapy in relapsed/refractory AML

Maximilian Stahl,[1,2,*] Kamal Menghrajani,[1,2,*] Andriy Derkach,[3] Alexander Chan,[4] Wenbin Xiao,[4] Jacob Glass,[1,2] Amber C. King,[5] Anthony F. Daniyan,[1,2] Christopher Famulare,[1,2] Bernadette M. Cuello,[1] Troy Z. Horvat,[5] Omar Abdel-Wahab,[1,2,6,7] Ross L. Levine,[1,2,6,7] Aaron D. Viny,[1,6] Eytan M. Stein,[1,2] Sheng F. Cai,[1,2] Mikhail Roshal,[4] Martin S. Tallman,[1,2] and Aaron D. Goldberg[1,2]

- CR/CRi rate was 24%
- Azacitidine- ven resulted in higher response rates compared with low-dose cytarabine- ven (49% vs 15%; P= 0.008)
- Median OS was significantly longer with azacitidine- ven compared with low-dose cytarabine- ven (25 vs 3.9 months; P= 0.003)
- This survival advantage persisted when patients were censored for subsequent allogeneic stem cell transplantation (8.1 vs 3.9 months; P= 0.035)
- Mutations in NPM1 were associated with higher response rates, whereas adverse cytogenetics and mutations in TP53, KRAS/NRAS, and SF3B1 were associated with worse OS





Blood Adv 2021

Case #5: FLT3-Mutated AML

- A 39-year-old patient with AML FLT3-ITD
- The patient received 7+3+ midostaurin induction with active disease on D28

What do you want to do?

(a) FLAG-IDA-VEN

(b) Gilteritinib

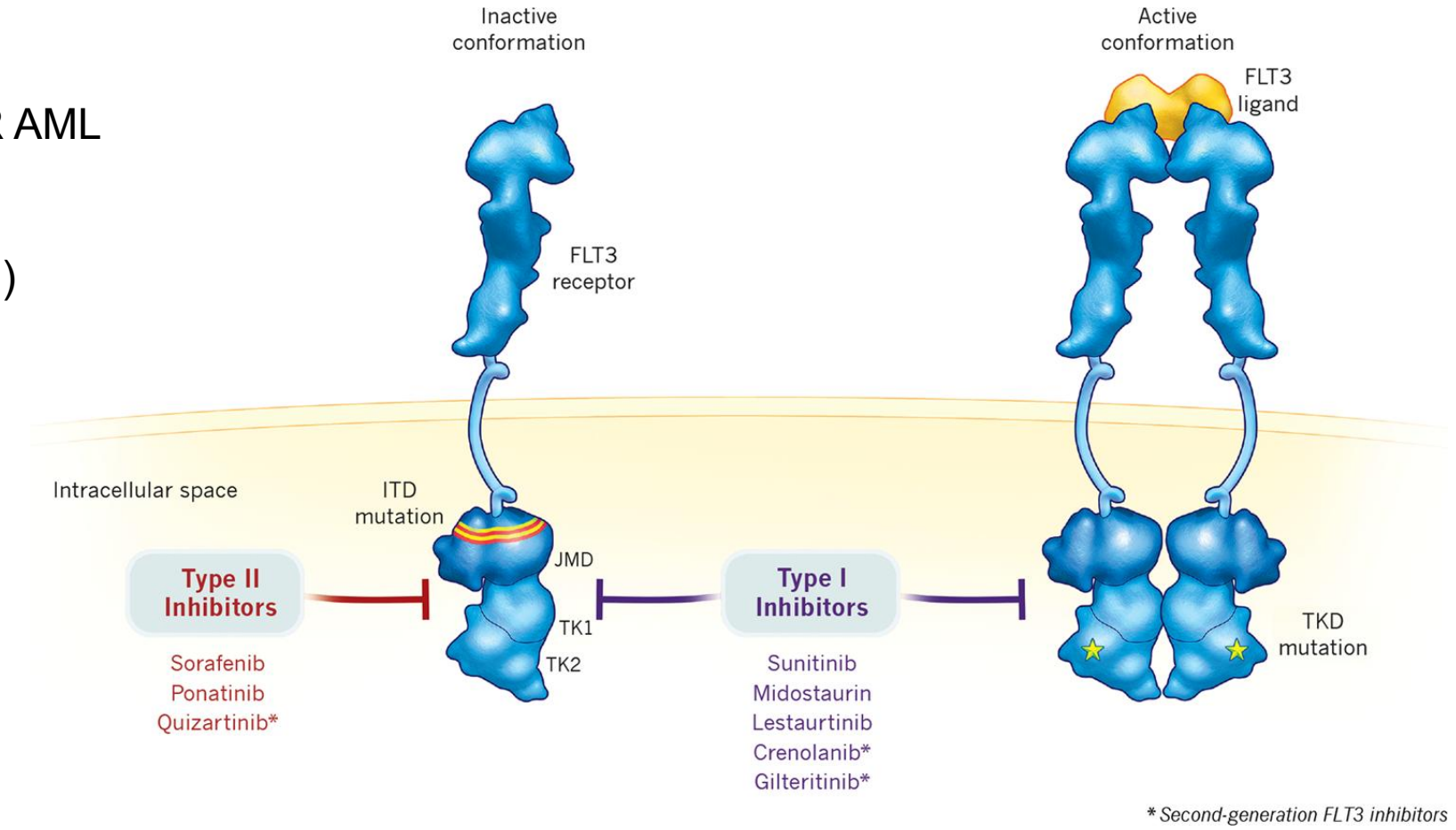
(c) Gilteritinib-venetoclax

(d) Ven-Aza-Gilteritinib

Relapsed FLT3-Mutated AML

- Azacitidine with Sorafeninb in R/R AML
- 37 patients- CR/CRi 43%

(Blood. 2013 Jun 6;121(23):4655–62)



Gilteritinib or Chemotherapy for Relapsed or Refractory *FLT3*-Mutated AML

A.E. Perl, G. Martinelli, J.E. Cortes, A. Neubauer, E. Berman, S. Paolini, P. Montesinos, M.R. Baer, R.A. Larson, C. Ustun, F. Fabbiano, H.P. Erba, A. Di Stasi, R. Stuart, R. Olin, M. Kasner, F. Ciceri, W.-C. Chou, N. Podoltsev, C. Recher, H. Yokoyama, N. Hosono, S.-S. Yoon, J.-H. Lee, T. Pardee, A.T. Fathi, C. Liu, N. Hasabou, X. Liu, E. Bahceci, and M.J. Levis

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	All Patients (N=371)	Gilteritinib (N=247)	Salvage Chemotherapy (N=124)
Age — yr			
Median	62.0	62.0	61.5
Range	19.0–85.0	20.0–84.0	19.0–85.0
Female sex — no. (%)	201 (54.2)	131 (53.0)	70 (56.5)
Cytogenetic risk status — no. (%)			
Favorable	5 (1.3)	4 (1.6)	1 (0.8)
Intermediate	271 (73.0)	182 (73.7)	89 (71.8)
Unfavorable	37 (10.0)	26 (10.5)	11 (8.9)
Unknown	58 (15.6)	35 (14.2)	23 (18.5)
Previous therapy for AML — no. (%)			
Anthracycline	311 (83.8)	205 (83.0)	106 (85.5)
FLT3 inhibitor	49 (13.2)	34 (13.8)	15 (12.1)
HSCT	74 (19.9)	48 (19.4)	26 (21.0)
Response to first-line therapy before enrollment — no. (%)†			
Relapse	225 (60.6)	149 (60.3)	76 (61.3)
Primary refractory disease without HSCT	146 (39.4)	98 (39.7)	48 (38.7)
Preselected salvage chemotherapy per IRT — no. (%)			
High-intensity chemotherapy	224 (60.4)	149 (60.3)	75 (60.5)
Low-intensity chemotherapy	147 (39.6)	98 (39.7)	49 (39.5)
FLT3 mutation subtype — no. (%)‡			
ITD only	328 (88.4)	215 (87.0)	113 (91.1)
TKD only	31 (8.4)	21 (8.5)	10 (8.1)
ITD and TKD	7 (1.9)	7 (2.8)	0

Table 2. Antileukemic Responses (Intention-to-Treat Population).*

Variable	Gilteritinib (N=247)	Salvage Chemotherapy (N=124)	Hazard Ratio or Risk Difference (95% CI)†
Median overall survival (95% CI) — mo	9.3 (7.7–10.7)	5.6 (4.7–7.3)	0.64 (0.49–0.83)
Median event-free survival (95% CI) — mo	2.8 (1.4–3.7)	0.7 (0.2–NE)	0.79 (0.58–1.09)
Response — no. (%)			
Complete remission	52 (21.1)	13 (10.5)	10.6 (2.8–18.4)
Complete remission or complete remission with partial hematologic recovery	84 (34.0)	19 (15.3)	18.6 (9.8–27.4)
Complete remission with partial hematologic recovery	32 (13.0)	6 (4.8)	ND
Complete remission with incomplete hematologic recovery	63 (25.5)	14 (11.3)	ND
Complete remission with incomplete platelet recovery	19 (7.7)	0	ND
Partial remission	33 (13.4)	5 (4.0)	ND
No response	66 (26.7)	43 (34.7)	ND
Composite complete remission‡	134 (54.3)	27 (21.8)	32.5 (22.3–42.6)
Overall response	167 (67.6)	32 (25.8)	
Median duration of remission (95% CI) — mo§	11.0 (4.6–NE)	NE (NE–NE)	NE
Time to composite complete remission — mo	2.3±1.9	1.3±0.5	NA
Median leukemia-free survival (95% CI) — mo	4.4 (3.6–5.2)	6.7 (2.1–8.5)	NE

Annals of Hematology (2022) 101:2001–2010
https://doi.org/10.1007/s00277-022-04895-8

ORIGINAL ARTICLE

Gilteritinib monotherapy for relapsed/refractory *FLT3* mutated acute myeloid leukemia: a real-world, multi-center, matched analysis

Shai Shimony[1,2,3] · Jonathan Canaani[4] · Eitan Kugler[1,2] · Boaz Nachmias[5] · Ron Ram[2,6] · Israel Henig[7] · Avraham Frisch[7] · Chezi Ganzel[8] · Vladimir Vainstein[5] · Yakir Moshe[2,6] · Shlomzion Aumann[5] · Moshe Yeshurun[1,2] · Yishai Ofran[8] · Pia Raanani[1,2] · Ofir wolach[1,2]

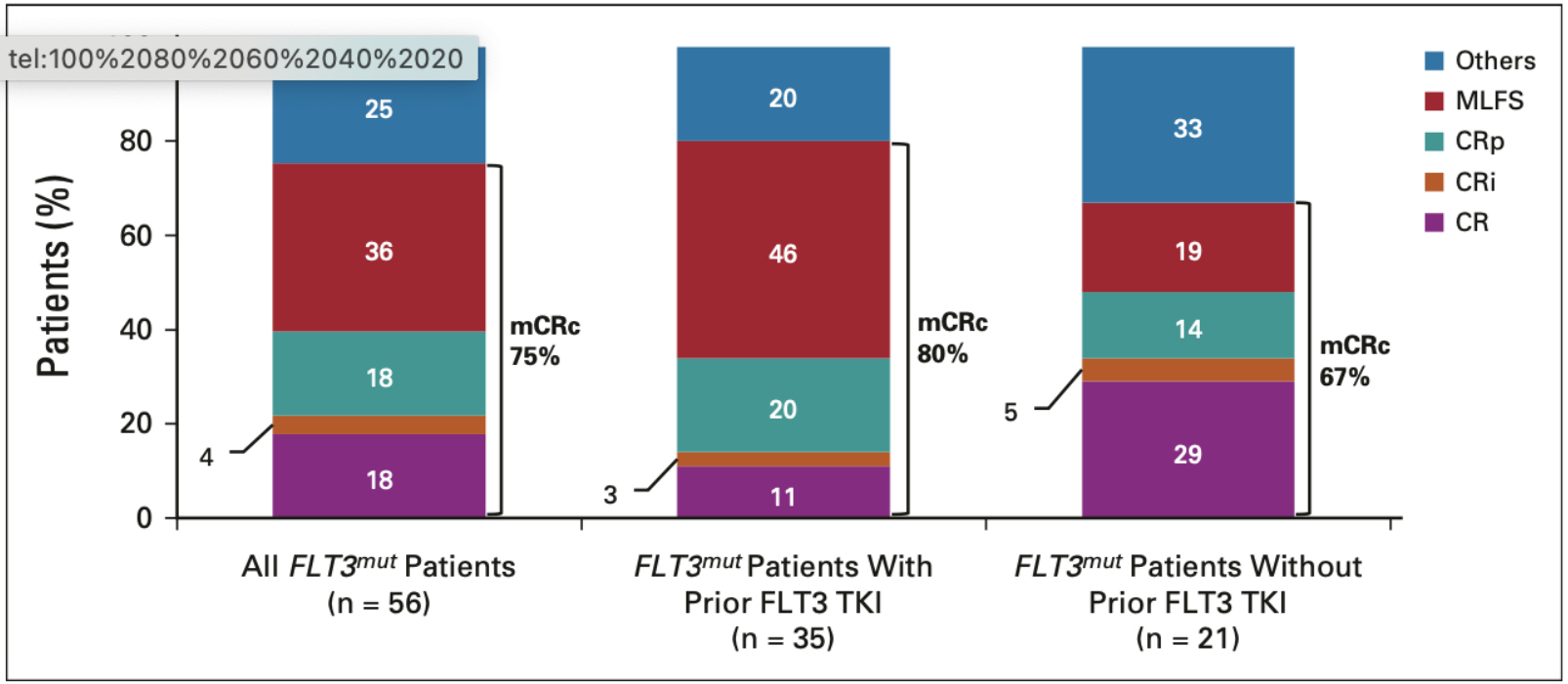
- CR rate was 48%
- 12% proceeded to allo-SCT
- Patients who achieved CR had a higher median OS than patients who did not (16.3 vs. 2.6 months)
- The major hematological toxicity was thrombocytopenia, and the main non-hematological toxicity was grade II elevated liver enzymes
- No clinically meaningful QT interval prolongations or differentiation syndrome were reported

Venetoclax Plus Gilteritinib for *FLT3*-Mutated Relapsed/Refractory Acute Myeloid Leukemia

Naval Daver, MD[1]; Alexander E. Perl, MD[2]; Joseph Maly, MD[3]; Mark Levis, MD, PhD[4]; Ellen Ritchie, MD[5]; Mark Litzow, MD[6]; James McCloskey, MD[7]; Catherine C. Smith, MD[8]; Gary Schiller, MD[9]; Terrence Bradley, MD[10,11]; Ramon V. Tiu, MD[12]; Kiran Naqvi, MD[13]; Monique Dail, PhD[13]; Deanna Brackman, PhD[14]; Satya Siddani, PhD[14]; Jing Wang, PhD[14]; Brenda Chyla, PhD[14]; Paul Lee, MD, PhD[14]; and Jessica K. Altman, MD[15]

- The median age was 63 years
- 30% received prior alloSCT
- 16% received prior venetoclax
- 64% had prior FLT3 TKIs

- The CRc rate was 39%
- Median DOR of 4.9 months
- The median time to first CRc was 2.1 (range, 0.7-4.6) months
- 50% FN, 15% 17% sepsis



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Blood Cancer Journal

CORRESPONDENCE Open Access

Triplet therapy with venetoclax, FLT3 inhibitor and decitabine for *FLT3*-mutated acute myeloid leukemia

Abhishek Maiti[1], Courtney D. DiNardo[1], Naval G. Daver[1], Caitlin R. Rausch[2], Farhad Ravandi[1], Tapan M. Kadia[1], Naveen Pemmaraju[1], Gautam Borthakur[1], Prithviraj Bose[1], Ghayas C. Issa[1], Nicholas J. Short[1], Musa Yilmaz[1], Guillermo Montalban-Bravo[1], Alessandra Ferrajoli[1], Elias J. Jabbour[1], Nitin Jain[1], Maro Ohanian[1], Koichi Takahashi[1], Philip A. Thompson[1], Sanam Loghavi[3], Kathryn S. Montalbano[1], Sherry Pierce[1], William G. Wierda[1], Hagop M. Kantarjian[1] and Marina Y. Konopleva[1]

Among 8 patients with R/R AML and prior exposure to a FLT3i the CRc rate was 63%

Same group JCO 2024

- 22 R/R patients
- The recommended phase II dose was gilteritinib 80 mg once daily in combination with azacitidine and venetoclax.
- In the relapsed/refractory cohort, the CR/CRi rate was 27%

Case #5: FLT3-Mutated AML

- A 39-year-old patient with AML FLT3-ITD
- The patient received 7+3+ midostaurin induction with active disease on D28

What do you want to do?

(a) **FLAG-IDA-VEN**

(b) **Gilteritinib**

(c) **Gilteritinib-venetoclax**

(d) **Ven-Aza-Gilteritinib**

Case #6: p53-mutated R/R AML

- A 45-year-old patient with AML with del17p and complex karyotype
- The patient received CPX-351 with no response
- Similar no response to FLAG-IDA-VEN

What do you want to do?

(a) Sequential

(b) Ven-Aza

(c) MEC

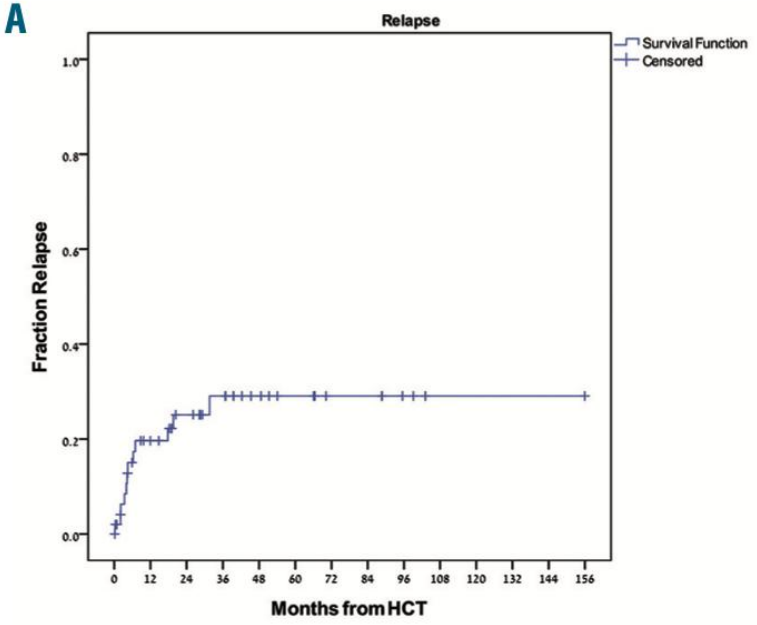
Sequential therapy for patients with primary refractory acute myeloid leukemia: a historical prospective analysis of the German and Israeli experience

Ron Ram,[1] Christof Scheid,[2] Odelia Amit,[1] Jens Markus Chemnitz,[2] Yakir Moshe,[1] Michael Hallek,[2] Dominik Wolf,[3] Irit Avivi[1] and Udo Holtick[2]

- 3-years OS of 61%
- Non-relapse mortality at 3 months and 3-years were 6% and 16%
- Relapse incidences were **6%** and 29%

Age, median, range (years)	54, 18-73
Median days to HCT, range	84 (25-183)
Cytogenetics	
Normal karyotype	28 (55%)
Complex karyotype	13 (26%)
Other	10 (19%)
Molecular	
FLT3-ITD	14 (28%)
JAK2	2 (4%)
BCRABL	1 (2%)
FLT3-TKD	6 (12%)
MLL	1 (2%)
RUNX1	3 (6%)
Prior Chemotherapy	
TAD/HAM	7 (14%)
sHAM	23 (45%)
7+3 only	11 (22%)
7+3 plus salvage	8 (13%)
Azacitidine only	3 (6%)
% blasts in marrow prior to HCT (range)	24 (5-93) %
Preparative regimen	
FLAMSA-TBI-based	13 (26%)
FLAMSA-Treo-based	17 (33%)
FITCy-TBI-based	21 (41%)
ATG	30 (59%)

A



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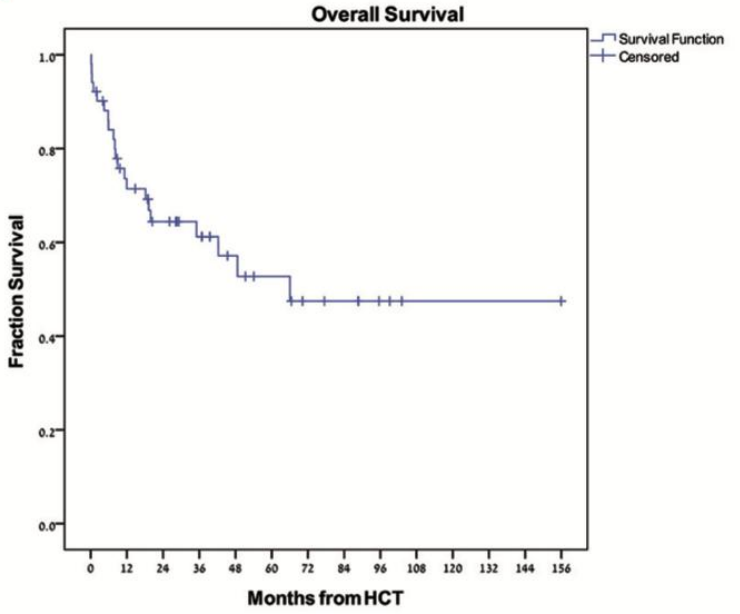


Remission induction versus immediate allogeneic haematopoietic stem cell transplantation for patients with relapsed or poor responsive acute myeloid leukaemia (ASAP): a randomised, open-label, phase 3, non-inferiority trial

Matthias Stelljes, Jan Moritz Middeke*, Gesine Bug*, Eva-Maria Wagner-Drouet, Lutz P Müller, Christoph Schmid, Stefan W Krause, Wolfgang Bethge, Edgar Jost, Uwe Platzbecker, Stefan A Klein, Jörg Schubert, Judith Niederland, Martin Kaufmann, Kerstin Schäfer-Eckart, Markus Schaich, Henning Baldauf, Friedrich Stölzel, Cathleen Petzold, Christoph Röllig, Nael Alakel, Björn Steffen, Beate Hauptrock, Christoph Schliemann, Katja Sockel, Fabian Lang, Oliver Kriege, Judith Schaffrath, Christian Reicherts, Wolfgang E Berdel, Hubert Serve, Gerhard Ehninger, Alexander H Schmidt, Martin Bornhäuser*, Jan-Henrik Mikesch*, Johannes Schetelig* on behalf of the Study Alliance Leukemia and the German Cooperative Transplant Study Group*

- RIST-arm- intensive remission induction with HAM and subsequent alloHCT
- DISC-arm- disease control prior to sequential conditioning and alloHCT
- In the DISC-arm, 76% were kept on w&w
- In the RIST-arm all pts received HAM
- The primary endpoint CR D56 after alloHCT was reached by 84.1% of pts in the DISC-arm and 81.3% of pts in the RIST-arm

all patients were scheduled for sequential conditioning consisting of intensive chemotherapy followed by reduced-intensity conditioning. FLAMSA-reduced-intensity conditioning consisted of fludarabine, amsacrine, and cytarabine on days –12 to –9 followed by fludarabine-alkylator-based reduced intensity conditioning before transplantation. Melphalan–fludarabine and total body irradiation consisted of high-dose melphalan on day –11 combined with fludarabine plus cumulative total body irradiation with 8 Gray before allogeneic HSCT. Graft-

Case #6: p53 mutated R/R AML

- A 45-year-old patient with AML with del17p and complex karyotype
- The patient received CPX-351 with no response
- Similar no response to FLAG-IDA-VEN

What do you want to do?

(a) Sequential

(b) Ven-Aza

(c) MEC

Case #7: Non-Fit Patients

- A 50-year-old patient with AML with and IDH1 and RUNX1 mutations
- Medical Hx is relevant for compensated liver cirrhosis
- The patient received Aza-ven with CR lasting 7 months
- Due to reduction in counts (ANC-1000, PLT-85K) BM was done showing 15% blasts

What do you want to do?

(a) Ivosidenib

(b) 5+2

(c) Maintenance ven-aza

ORIGINAL ARTICLE

Durable Remissions with Ivosidenib in *IDH1*-Mutated Relapsed or Refractory AML

- 21% CR
- Median time to response around 2 months

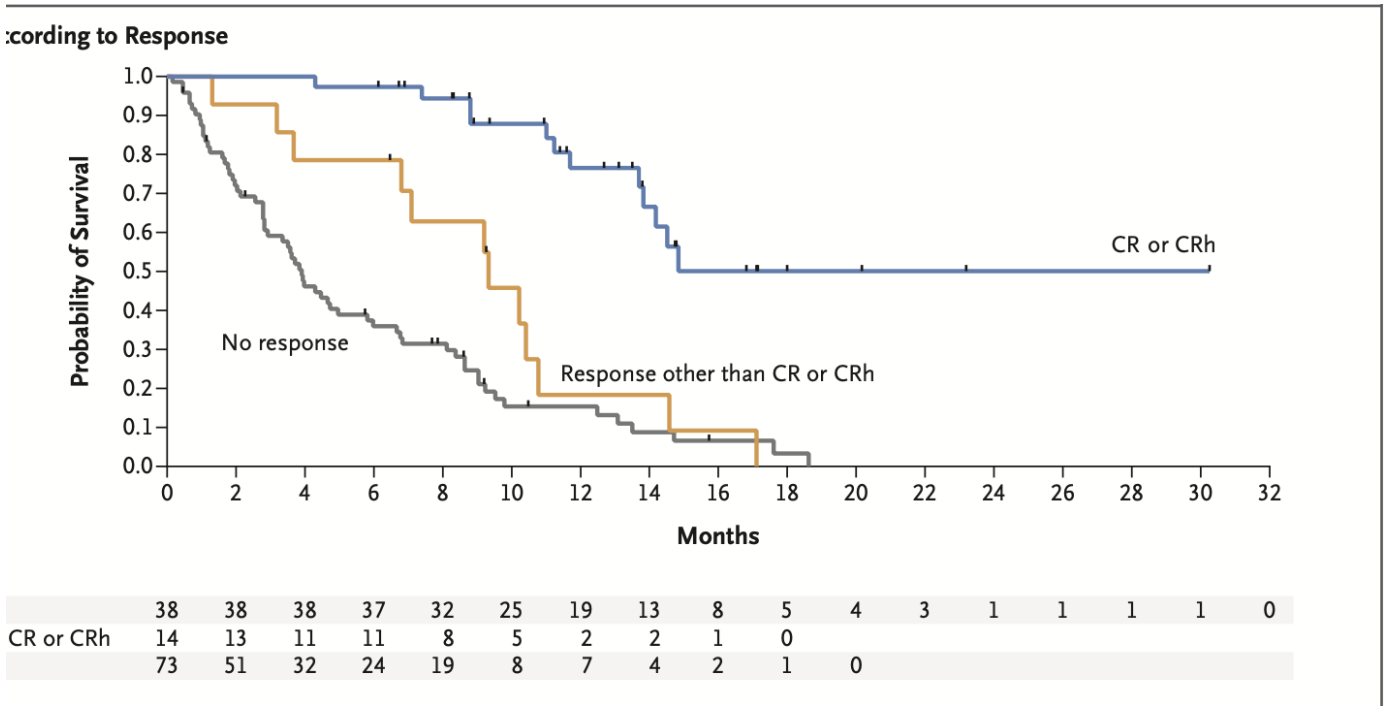


Table 2. Treatment-Related Adverse Events of Grade 3 or Higher Occurring in More than

Event	Relapsed or Refractory AML and Starting Dose of Ivosidenib of 500 mg Daily (N=179)
	no. of pa
≥1 Treatment-related adverse event of grade 3 or higher	37 (20.7)
Prolongation of the QT interval on ECG	14 (7.8)
IDH differentiation syndrome†	7 (3.9)
Anemia	4 (2.2)
Thrombocytopenia	3 (1.7)
Leukocytosis	3 (1.7)
Febrile neutropenia	1 (0.6)
Diarrhea	1 (0.6)
Platelet count decreased	3 (1.7)
Hypoxia	2 (1.1)

Enasidenib vs conventional care in older patients with late-stage mutant-*IDH2* relapsed/refractory AML: a randomized phase 3 trial

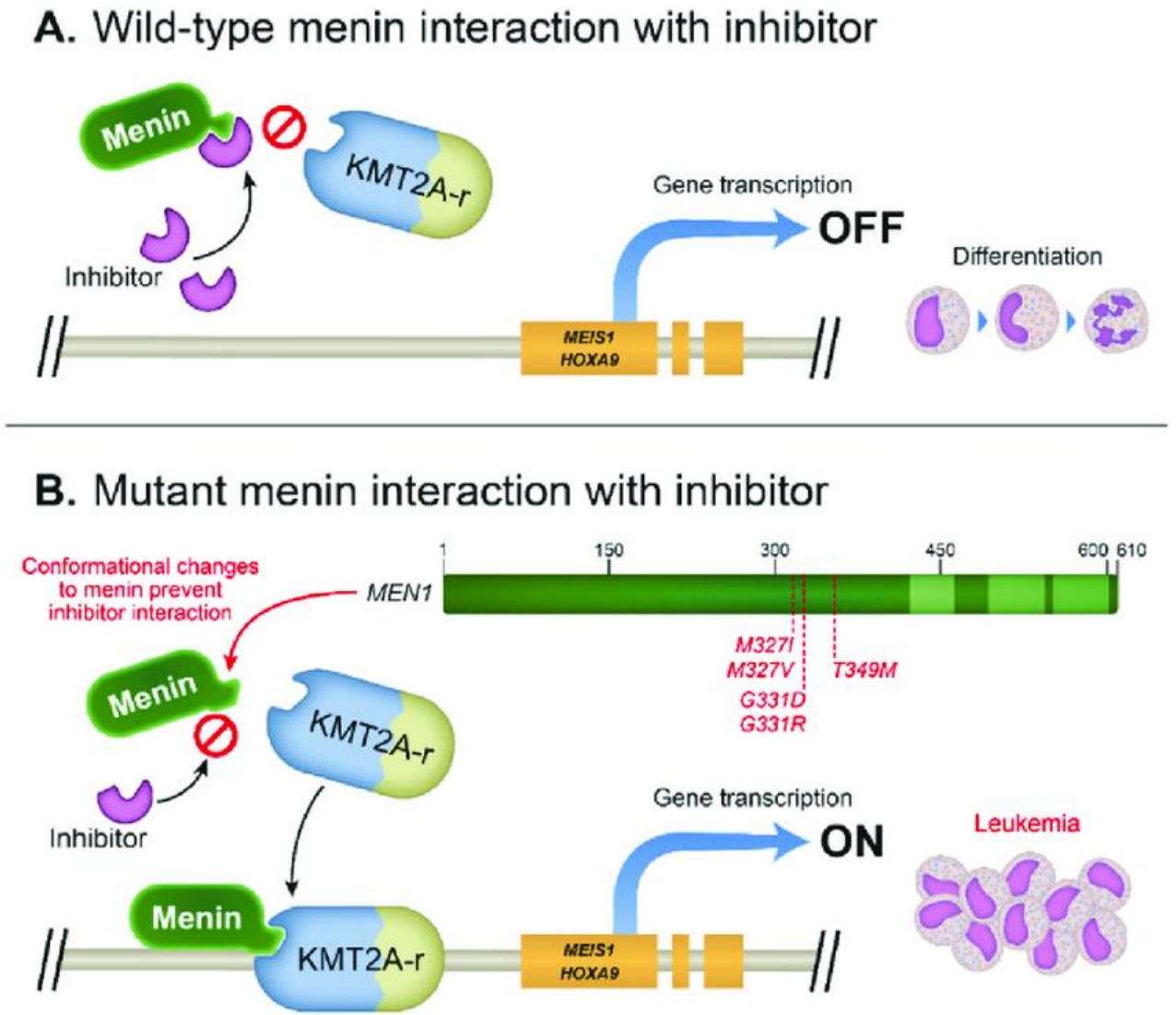
Stéphane de Botton,[1] Pau Montesinos,[2] Andre C. Schuh,[3] Cristina Papayannidis,[4] Paresh Vyas,[5] Andrew H. Wei,[6,7] Hans Ommen,[8] Sergey Semochkin,[9] Hee-Je Kim,[10] Richard A. Larson,[11] Jaime Koprivnikar,[12] Olga Frankfurt,[13] Felicitas Thol,[14] Jörg Chromik,[15] Jenny Byrne,[16] Arnaud Pigneux,[17] Xavier Thomas,[18] Olga Salamero,[19] Maria Belen Vidriales,[20] Vadim Doronin,[21] Hartmut Döhner,[22] Amir T. Fathi,[23,24] Eric Laille,[25] Xin Yu,[25] Maroof Hasan,[25] Patricia Martin-Regueira,[25] and Courtney D. DiNardo[26]

- Median age 72 years
- 77% had received 2 prior AML-directed therapies, including 73% received IC and 10% who had received prior HSCT
- Treatment options: azacitidine, intermediate-dose cytarabine (IDAC), low-dose cytarabine (LDAC), or best supportive care
- **No difference in OS**

	Enasidenib (n = 158)	CCR (n = 161)
ORR,* n/N (%)	64/158 (40.5)	16/161 (9.9)
Enasidenib vs CCR: OR (95% CI); *P* value	6.1 (3.3-11.1); *P* < .001	
Time to response, d, median (IQR)	92 (58-126)	59 (39-134)
Duration of response (mo), median (95% CI)	7.3 (5.6-11.1)	NE (2.5-NE)
CR rate, n (%)	37 (23.4)	6 (3.7)
Composite CR rate (CR+CRi+CRp), n (%)	47 (29.7)	10 (6.2)
CR+CRh rate, n (%)	40 (25.3)	8 (5.0)

Category Preferred term	Enasidenib (n = 157)	CCR (n = 141)
Any treatment-related adverse event, n (%)	121 (77.1)	86 (61.0)
Nausea	35 (22.3)	22 (15.6)
Blood bilirubin increased	31 (19.7)	1 (0.7)
Thrombocytopenia	24 (15.3)	15 (10.6)
Decreased appetite	23 (14.6)	5 (3.5)
Differentiation syndrome	22 (14.0)	0
Vomiting	20 (12.7)	8 (5.7)
Neutropenia	13 (8.3)	17 (12.1)
Febrile neutropenia	4 (2.5)	17 (12.1)

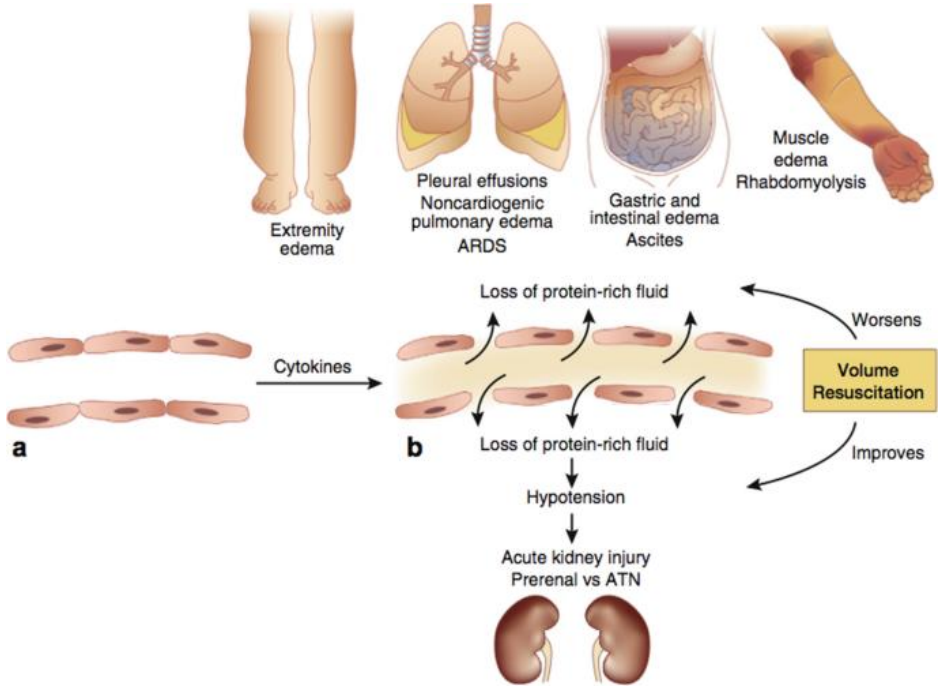
Menin Inhibitors



DOI:10.1038/s41375-024-02368-7

Differentiation Syndrome

- Dyspnea
- Fever
- Weight gain
- Hypotension
- Acute renal failure
- Pulmonary infiltrates or pleuropericardial effusion
- Multiple organ dysfuction



Menin inhibition with revumenib for *NPM1*-mutated relapsed or refractory acute myeloid leukemia: the AUGMENT-101 study

Martha L. Arellano,[1] Michael J. Thirman,[2] John F. DiPersio,[3] Maël Heiblig,[4] Eytan M. Stein,[5] Andre C. Schuh,[6] Andrius Žučenka,[7] Stephane de Botton,[8] Carolyn S. Grove,[9-11] Gabriel N. Mannis,[12] Cristina Papayannidis,[13] Alexander E. Perl,[14] Ghayas C. Issa,[15] Ibrahim Aldoss,[16] Ashish Bajel,[17,18] David S. Dickens,[19] Michael W. M. Kühn,[20] Ioannis Mantzaris,[21] Emmanuel Raffoux,[22] Elie Traer,[23] Irina Amitai,[24,25] Hartmut Döhner,[26] Corinna Greco,[27] Tibor Kovacsovics,[28] Christine M. McMahon,[29] Pau Montesinos,[30] Arnaud Pigneux,[31] Paul J. Shami,[32] Richard M. Stone,[33] Ofir Wolach,[25,34] John G. Harpel,[35] Yakov Chudnovsky,[36] Li Yu,[36] Rebecca G. Bagley,[36] Angela R. Smith,[36] and James S. Blachly[37]

Overall response rate, No. (%)[a]	36 (63.2)
95% CI	49.3 to 75.6
Time to first response, months, median (range)	0.95 (0.9-2.0)
Duration of response, months, median (range)	4.3 (1.9-NR)
CR + CRh rate, No. (%)	13 (22.8)
95% CI	12.7 to 35.8
P value, one-sided	0.0036
Time to first CR + CRh, months, median (range)	1.87 (0.9-4.6)
Duration of CR + CRh, months, median (95% CI)	6.4 (3.4 to NR)
CRc, No. (%)[b]	25 (43.9)
95% CI	30.7 to 57.6

Parameter	Adult efficacy-evaluable population (n = 64)
ORR, n (%)	30 (46.9)
95% CI	34.3-59.8
Time to first response, median (range), mo	1.84 (0.9-4.6)
Duration of first response, median (95% CI), mo	4.4 (1.2-5.6)
CR + CRh rate, n (%)	15 (23.4)
95% CI	13.8-35.7
P value, 1-sided	.0014
Time to first CR + CRh, median (range), mo	2.76 (1.8-8.8)
Duration of CR + CRh, median (95% CI), mo	4.7 (1.2-8.2)
CRc, n (%)	19 (29.7)
95% CI	18.9-42.4
Best response, n (%)	
CR	12 (18.8)
CRh	3 (4.7)
CRi*	2 (3.1)
CRp*	2 (3.1)
MLFS	9 (14.1)
PR	2 (3.1)
No response	19 (29.7)
Disease progression	5 (7.8)
Other†	10 (15.6)
No. of responders who proceeded to HSCT, n/N (%)	5/30 (16.7)
Resumed treatment after HSCT, n/N (%)	3/5 (60.0)

DS

- Interrupt study treatment
- Initiate high dose steroids
- Initiate treatment with hydrea/ other cytoreduction

Non-Fit Patients

- Non-curative intent
- Quality of life
- Try treatment for targetable mutations
- Remember differentiation syndrome with IDH1/2 inhibitors
- Consider Ven-aza “maintenance in low burden, non-proliferative disease

בהצלחה!!!

ד״ר בועז נחמיאס
שרות הלוקמיה, הדסה עין כרם
050-5172520
boazn@Hadassah.org.il