Navigating Relapsed/Refractory AML: Genetic Profiling, Targeted Therapies, and Optimized Outcomes

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Great Debates
Hematologic Malignancies
from Lymphoma • Leukemia & Myeloma Congress

Faculty Disclosures

- **Aaron D. Goldberg, MD, PhD:** Consultant—AbbVie, Astellas, Bristol Myers Squibb, Ikena Oncology, Molecular Partners, Remedy Plan Therapeutics, Syndax Pharmaceuticals; Advisory Board—AbbVie, Astellas, Bristol Myers Squibb, Molecular Partners, Syndax Pharmaceuticals; research funding—AbbVie, Aprea, Aptose, AROG, Kura, Pfizer Inc., Prelude Therapeutics; Data Safety Monitoring Board—Kura

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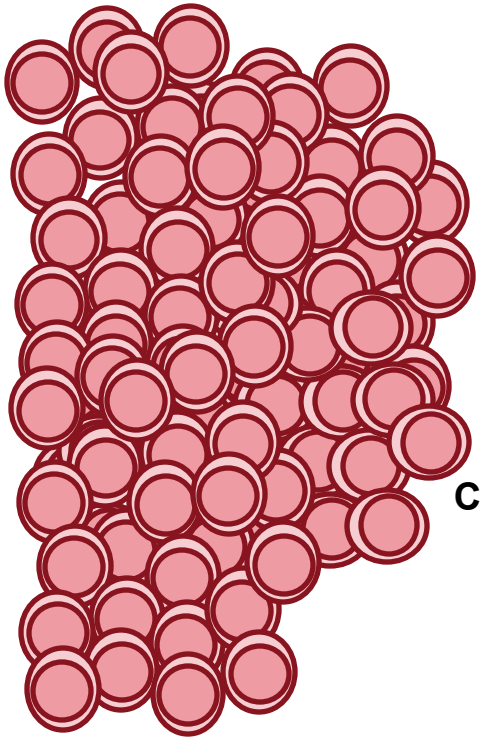
Learning Objectives

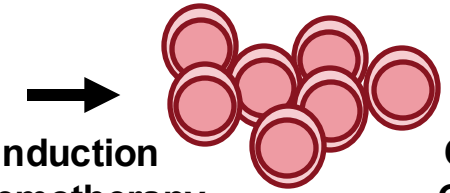
- Evaluate the utility of genetic profiling in AML to identify clonal evolution and acquired mutations in R/R disease to guide targeted therapies and improve outcomes
- Assess how key genetic mutations—such as *IDH*, *FLT3*, *NPM1*, *KMT2A*, and other actionable targets—influence prognosis and clinical decision-making
- Describe the mechanisms of action and key clinical data for available and emerging targeted therapies in R/R AML

AML = acute myeloid leukemia; R/R = relapsed/refractory.

Goal of Intensive or Non-Intensive Therapy in AML to Achieve Complete Remission



Goal of induction:
complete remission (CR) =
no AML detectable by
morphology (<5% blasts)
and count recovery



Induction Chemotherapy

Consolidation Chemotherapy

CURE

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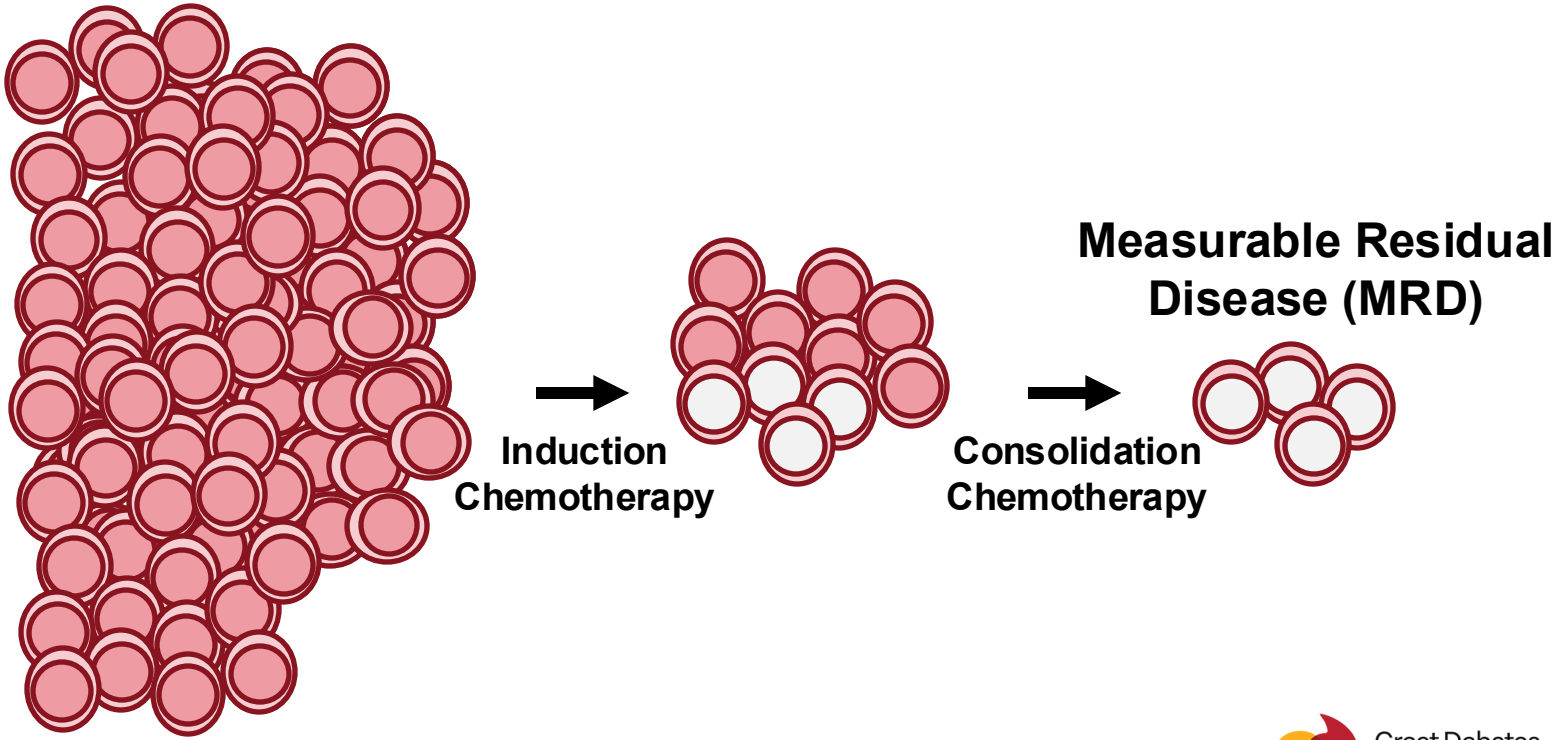
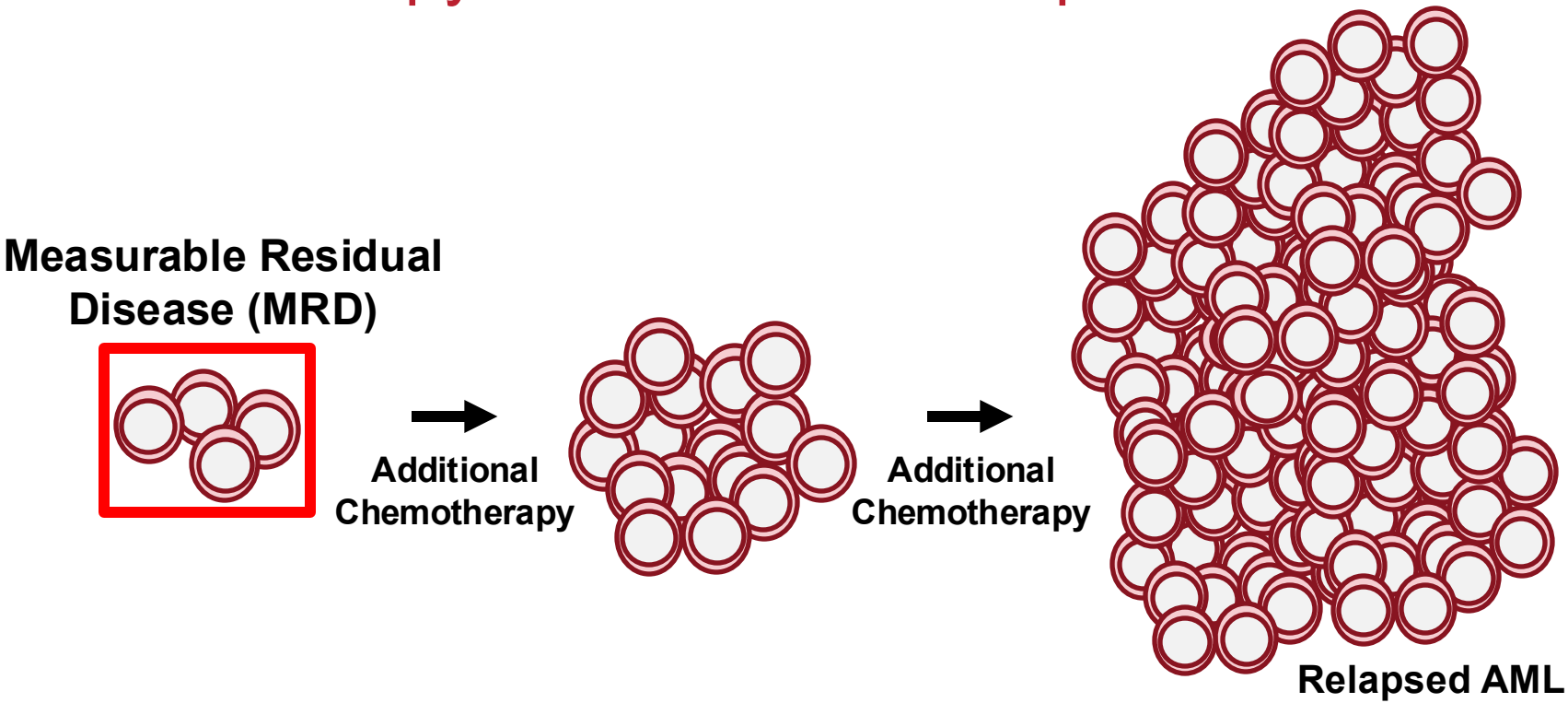
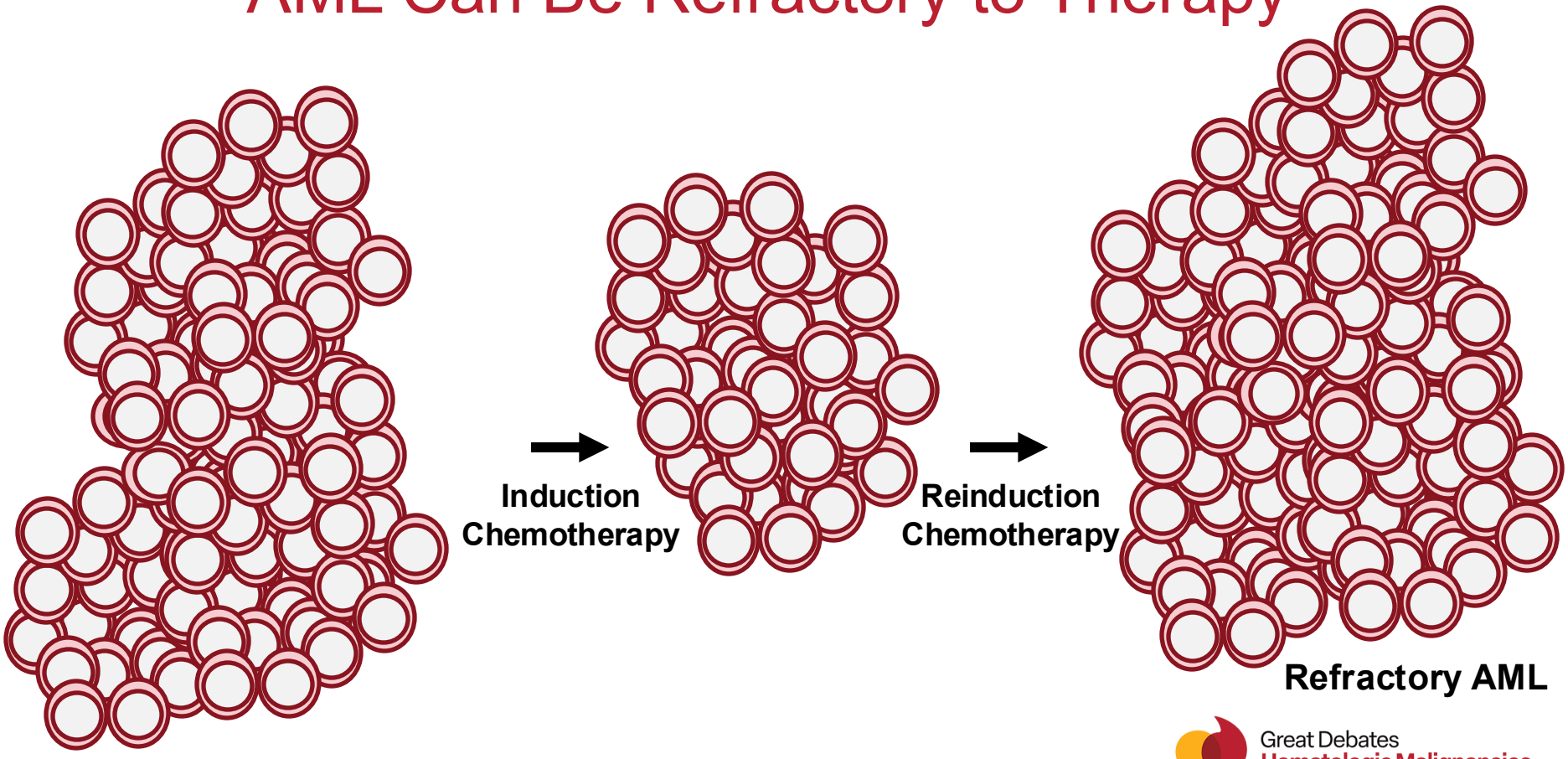
Chemotherapy May Fail to Eradicate Minimal/ Measurable Residual Disease (MRD)



MRD Is Often Resistant to Further Therapy and Leads to Relapsed AML



AML Can Be Refractory to Therapy



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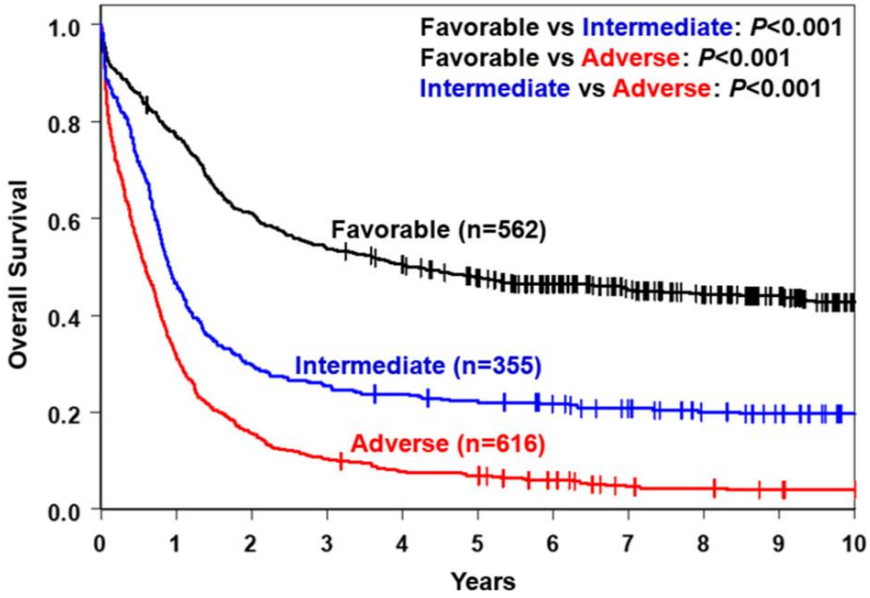
AML Prognosis after Intensive Chemotherapy Varies by Cytogenetic and Molecular Features

Risk category†	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*†,‡ • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*†,‡ • Mutated *NPM1*†,§ without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged# • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*, *MECOM*(*EVI1*) • t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype,** monosomal karyotype†† • Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and/or *ZRSR2*‡‡ • Mutated *TP53*[a]

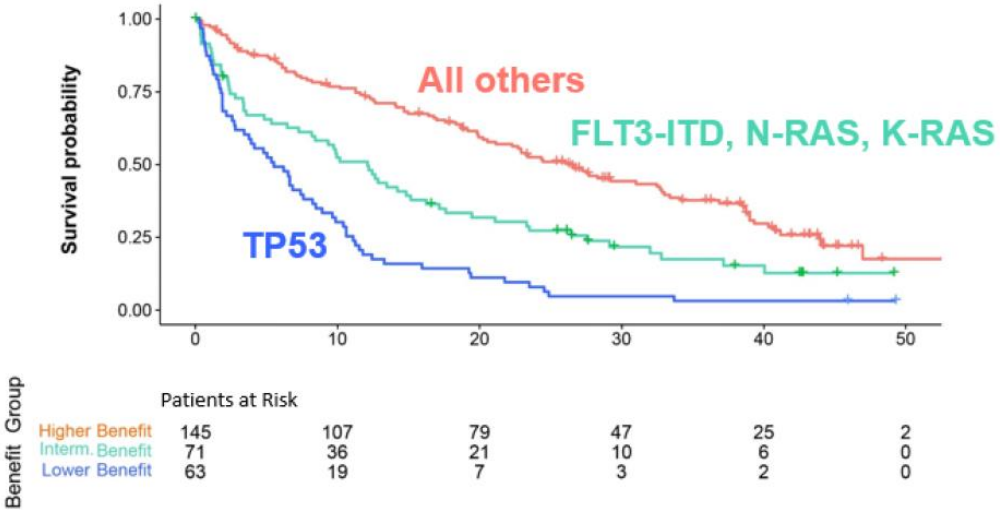


ITD = internal tandem duplication.

Döhner H, et al. *Blood*. 2022;140(12):1345-1377. Mrózek K, et al. *Leukemia*. 2023;37(4):788-798.

AML Prognosis after HMA/Venetoclax Varies by Molecular Features

- From diagnosis, four mutations categorize the likelihood of ven/aza survival benefit
  - Despite high remission rates (70% CR/CRi), *FLT3*-ITD predicts limited long-term benefit of venetoclax + azacitidine



Ven + Aza (N = 279)	n	Events	Median OS, months (95% CI)
Higher Benefit	145	96	26.51 (20.24, 32.69)
Intermediate Benefit	71	57	12.12 (7.26 – 15.15)
Lower Benefit	63	61	5.52 (2.79 – 7.59)

HMA = hypomethylating agents; CR = complete response/remission; CRi = complete remission with incomplete hematologic recovery; OS = overall survival.

Döhner H, et al. *Blood*. 2024;144(21):2211-2222. Döhner H, et al. *Blood*. 2022;140(Suppl 1):1441-1444. Konopleva M, et al. *Clin Cancer Res*. 2022;28(13):2744-2752.

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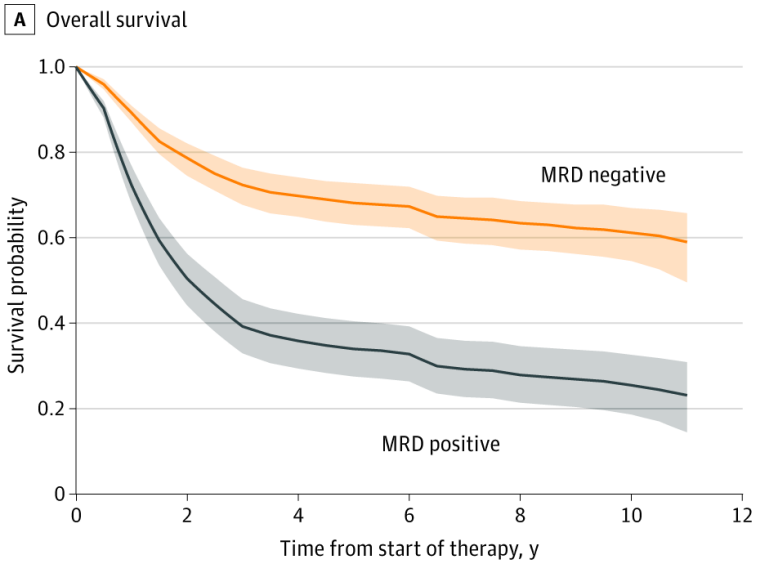
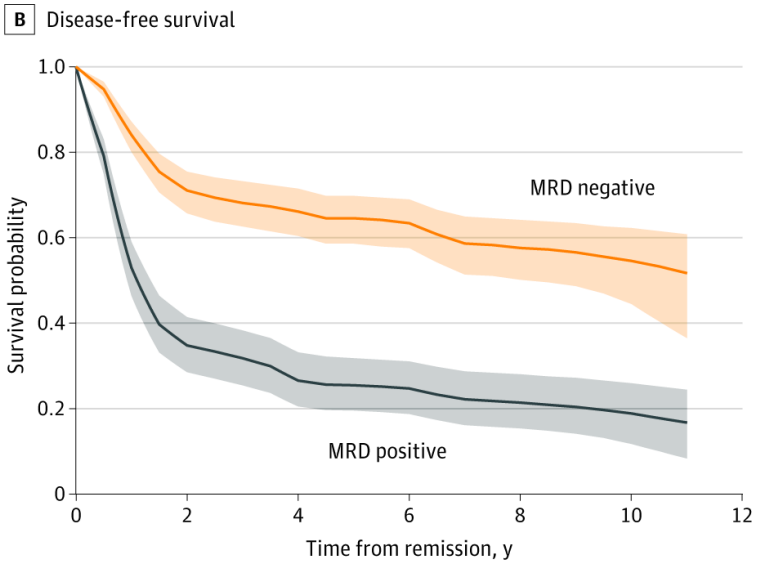
Prognostic Impact of MRD in AML



MRD-negative vs MRD-positive

- **5-year OS: 68% (95% CrI, 63%-73%) *vs* 34% (95% CrI, 28%-40%)**
- **Average HR: 0.36 (95% CrI, 0.33-0.39)**



MRD-negative vs MRD-positive

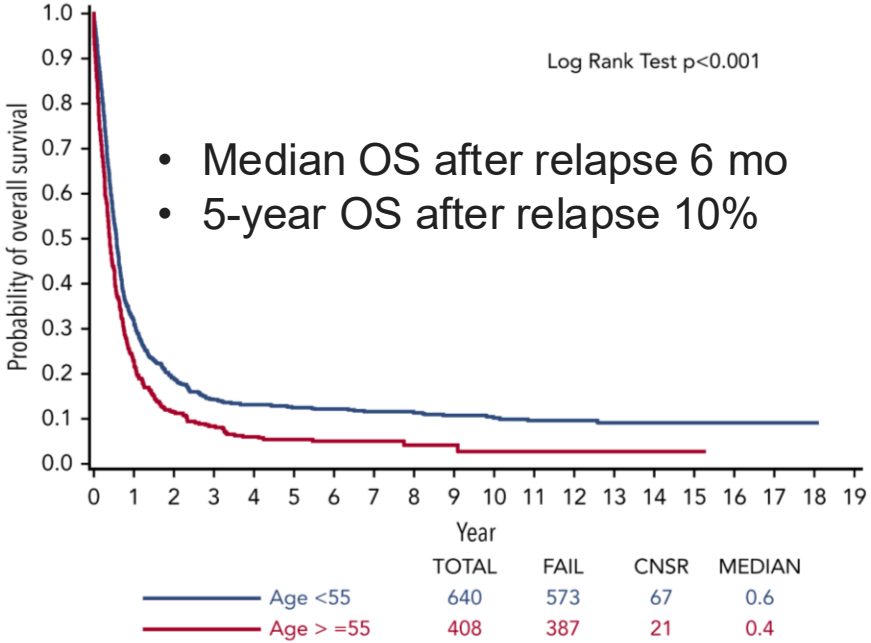
- **5-year DFS: 64% (95% CrI, 59%-70%) *vs* 25% (95% CrI, 20%-32%)**
- **Average HR: 0.37 (95% CrI, 0.34-0.40)**

DFS = disease-free survival.

Short NJ, et al. *JAMA Oncol*. 2020;6(12):1890-1899.

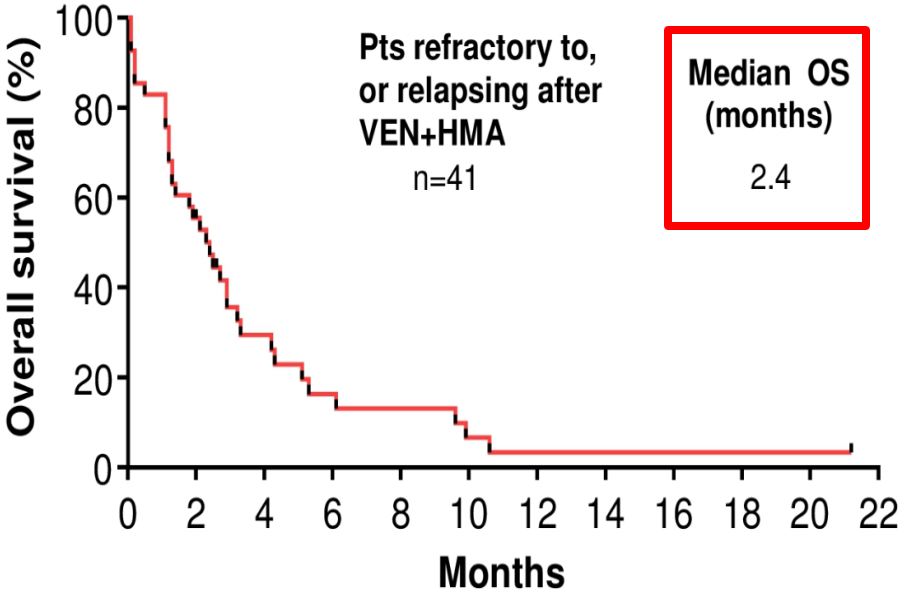
Patients with Relapsed and Refractory (R/R) AML Have a Poor Prognosis—Particularly after Venetoclax + HMA

R/R AML: All patients



- Median OS after relapse 6 mo
- 5-year OS after relapse 10%

R/R AML: after VEN+HMA



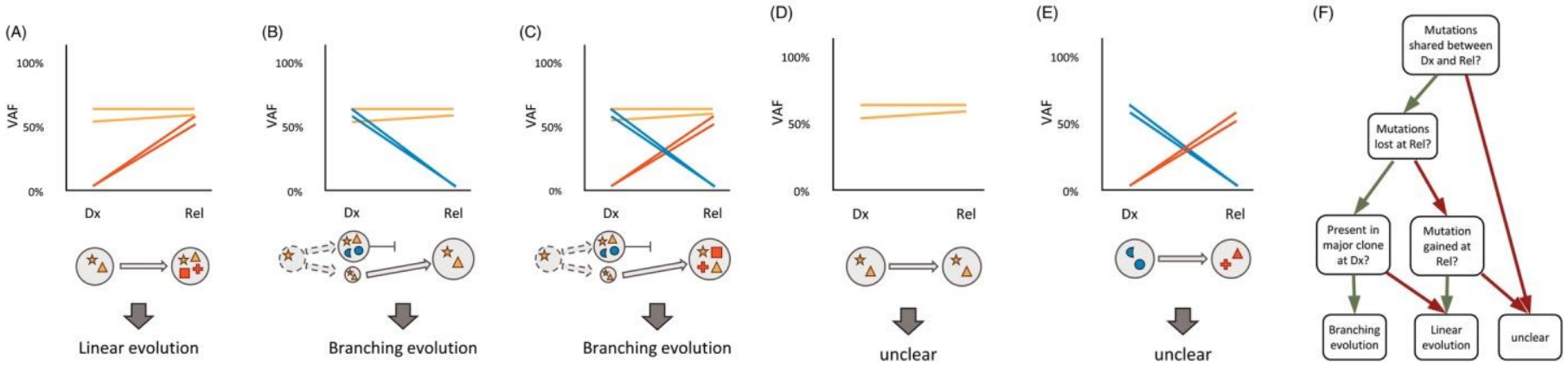
Ganzel C, et al. *Am J Hematol*. 2018;93(8):1074-1081. Reviewed in DeWolf S, Tallman MS. *Blood*. 2020;136(9):1023-1032. Maiti A, et al. *Haematologica*. 2021;106(3):894-898.

Overall Approach to R/R AML

- In R/R AML, allogeneic SCT is the only option for cure
- Consider goals of treatment (!)—is allogeneic SCT an option? Or are goals of treatment palliative?
- Consider age, fitness, comorbidities
- Consider prior therapy—intensive or non-intensive therapy, prior venetoclax or not, prior transplant; consider response to therapy
- Duration of CR1 remains important—poorest outcomes in relapse within 1 year
- Look for a clinical trial if available
- Critically important to **evaluate for targetable mutation**
  - *FLT3*-ITD, *FLT3*-TKD, *IDH1, IDH2, NPM1, KMT2A* rearrangement
- FDA-approved targeted therapy options in R/R AML: **gilteritinib, ivosidenib, olutasidenib, enasidenib, revumenib**
- Chemotherapy can still play a role in R/R AML—particularly in the absence of targetable mutation

SCT = stem cell transplantation; CR1 = first CR; FDA = US Food and Drug Administration.

Clonal Evolution and Acquired Mutations in R/R Disease



Critical mutations to evaluate at diagnosis and relapse

- *FLT3*-ITD, *FLT3*-TKD
- *IDH1, IDH2*
- *NPM1, KMT2A* rearrangement
  - Most mutations above can be identified on NGS panels
  - Evaluate for *KMT2A* rearrangement by FISH, karyotype, optical genome mapping, or targeted RNA-seq for fusions

Dx = diagnosis; rel = relapse; NGS = next-generation sequencing; FISH = fluorescence in situ hybridization; RNA-seq = RNA sequencing.

Vosberg S, Greif P. *Genes Chromosomes Cancer*. 2019;58(12):839-849.

Key Learning Points

- AML prognosis differs by molecular features
- Relapsed or refractory AML has a poor prognosis, particularly after venetoclax-based therapy
- In R/R AML, consider goals of treatment—consider possibility of bridge to allogeneic SCT
- Critically important to **evaluate for targetable mutations at diagnosis and again at the time point of relapsed or refractory disease**
  - *FLT3*-ITD, *FLT3*-TKD, *IDH1, IDH2, NPM1, KMT2A* rearrangement

Targeted Therapy in R/R AML

Mechanisms of Action, Key Clinical Trial Data

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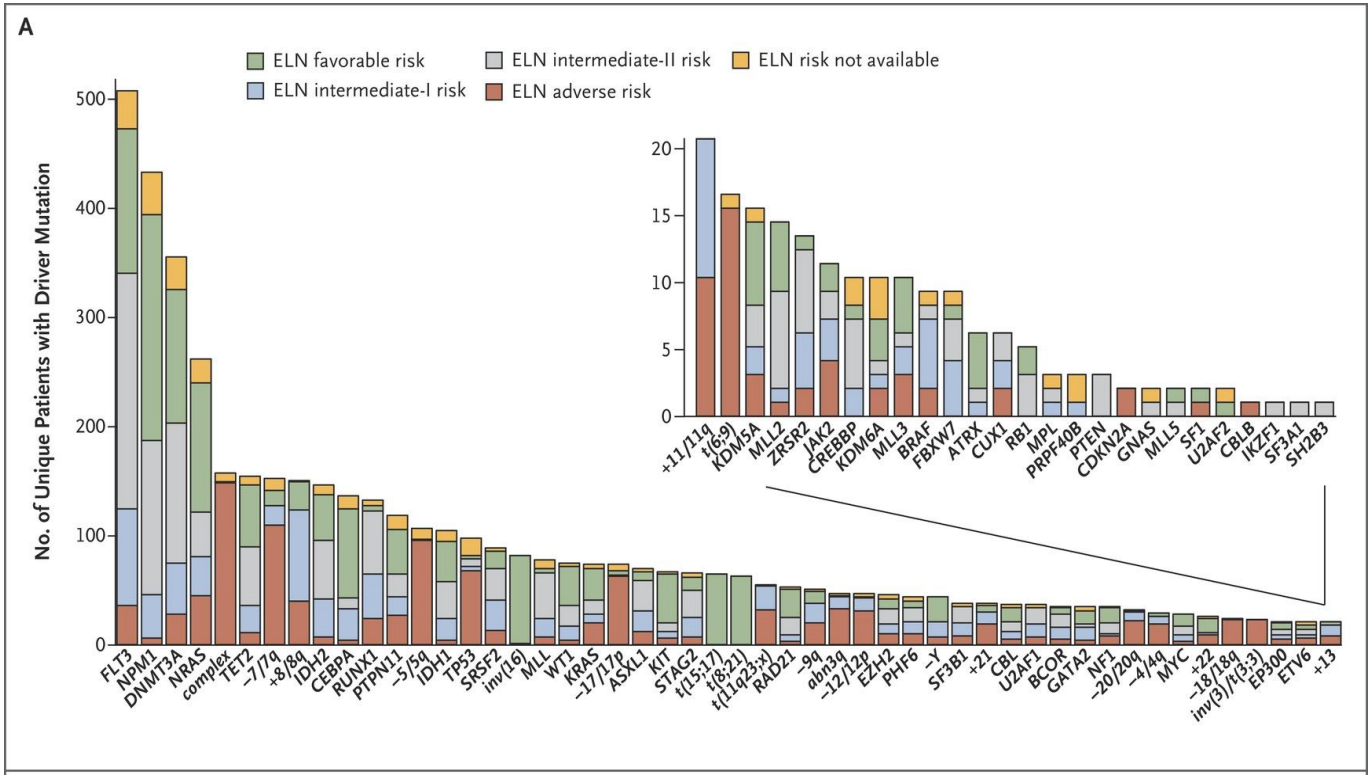
FLT3 Mutations and *FLT3* Inhibitors

FLT3: Most Frequently Mutated Driver Gene in NK AML

Found in 25-37% of patients



NK = natural killer; ELN = European LeukemiaNet.

Papaemmanuil E, et al. *N Engl J Med*. 2016;374(23):2209-2221.

FLT3: Most Frequently Mutated Driver Gene in NK AML

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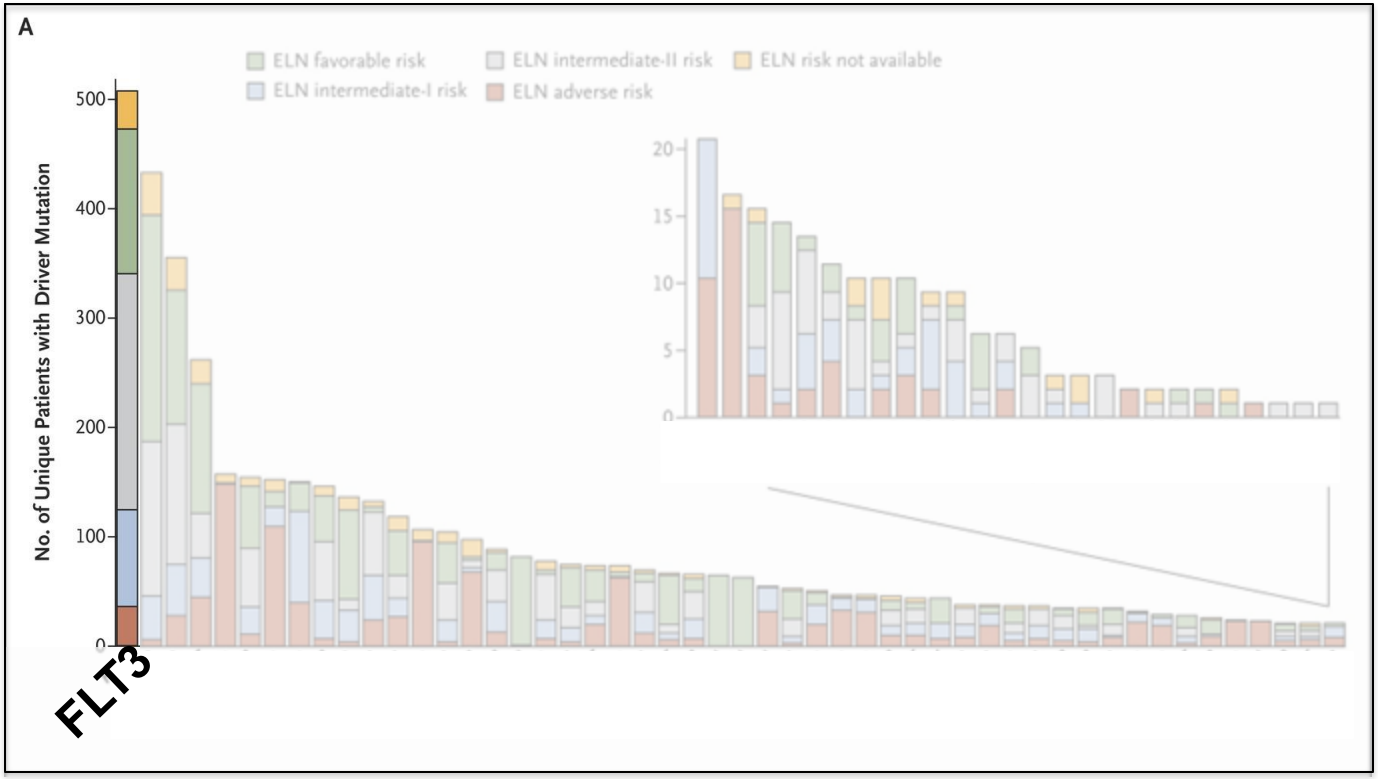

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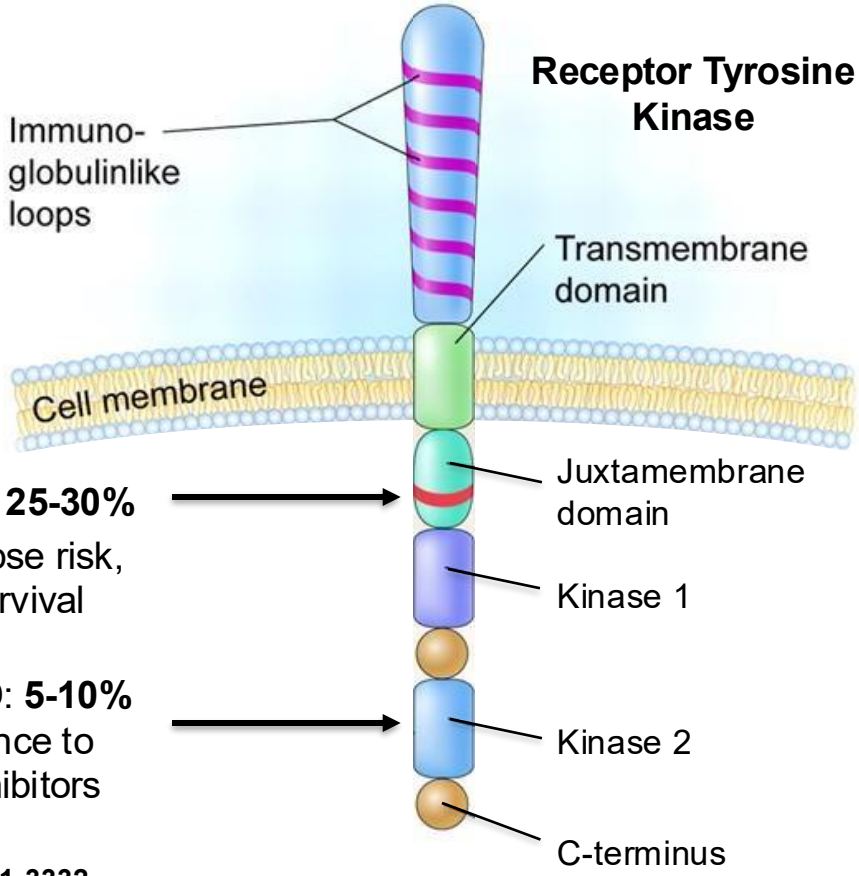
Papaemmanuil E, et al. *N Engl J Med*. 2016;374(23):2209-2221.

FLT3 Mutations in Acute Myeloid Leukemia

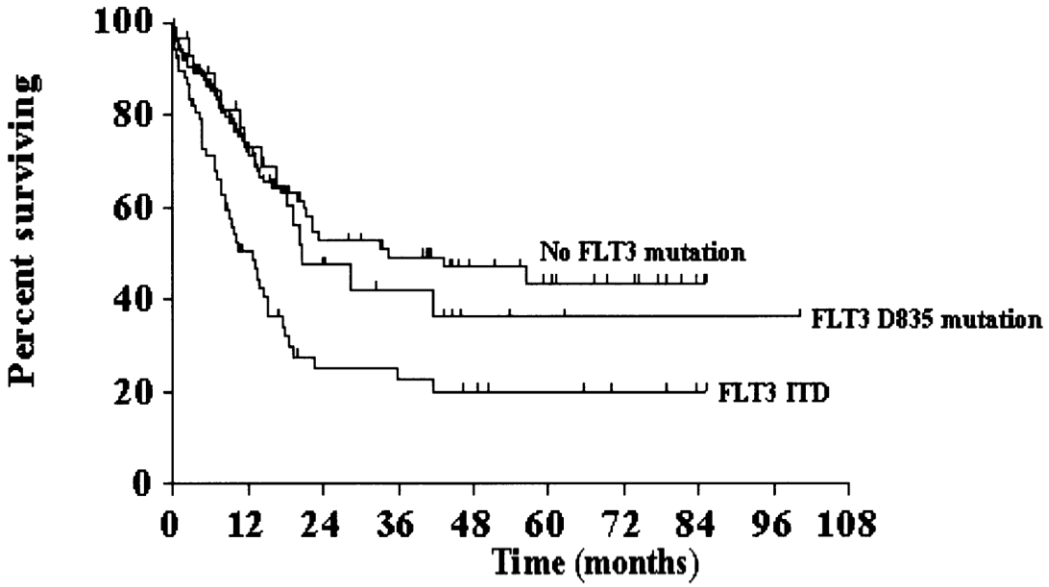


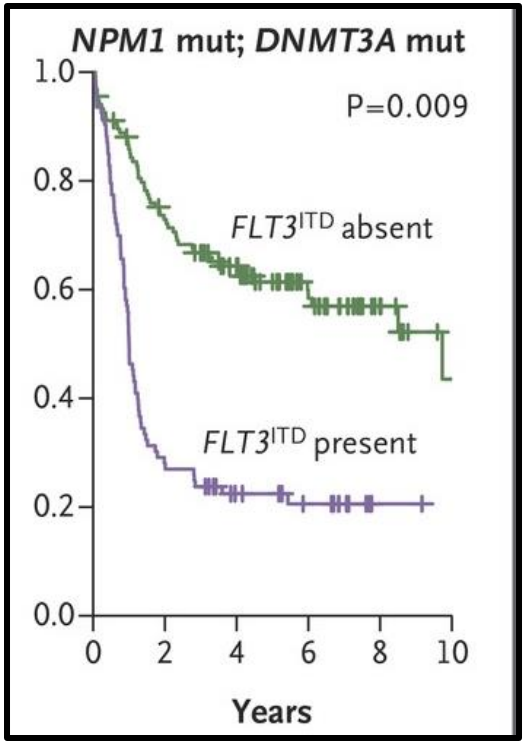
***FLT3*-ITD: 25-30%**
High relapse risk, poor survival

***FLT3*-TKD: 5-10%**
Resistance to FLT3 inhibitors

Litzow MR. *Blood*. 2005;106(10):3331-3332.

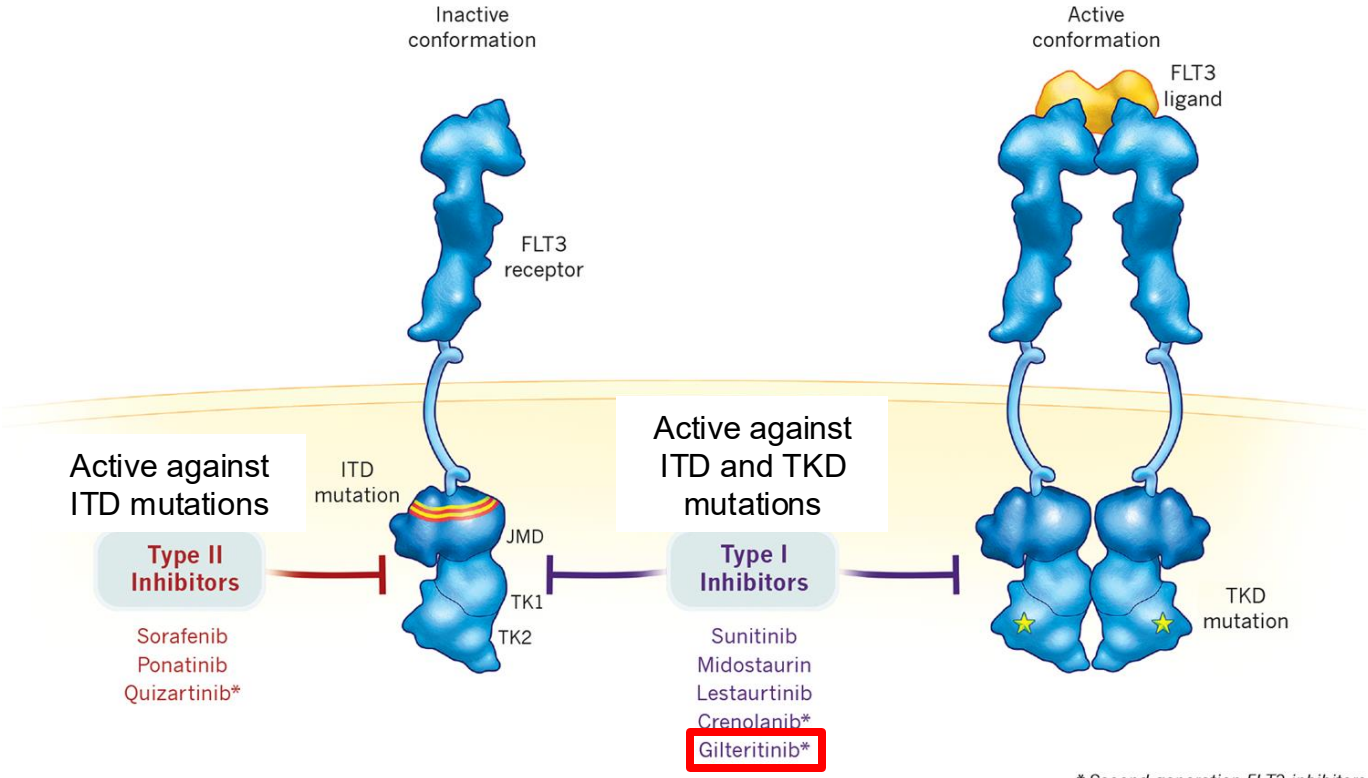
FLT3-ITD Mutations Are Poor Prognostic Markers in AML





Fröhling S, et al. *Blood*. 2002;100(13):4372-4380. Papaemmanuil E, et al. *N Engl J Med*. 2016;374(23):2209-2221.

FLT3 Inhibitors: Type II and Type I

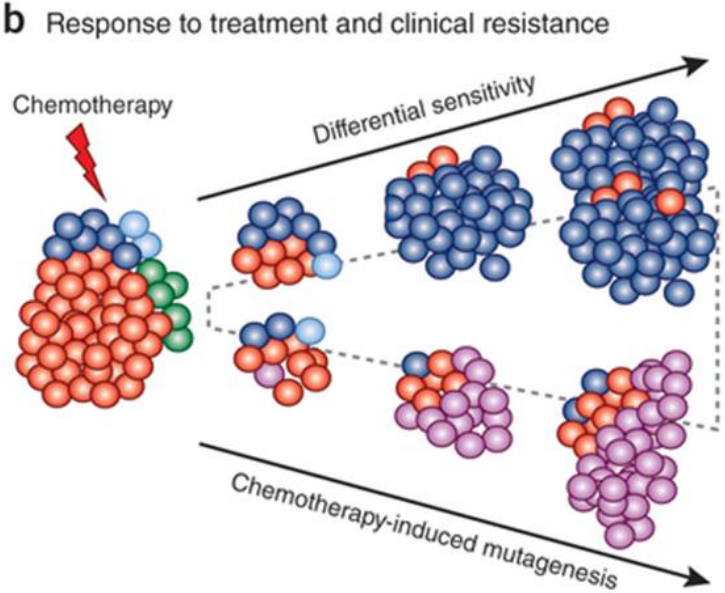


TKD = tyrosine kinase domain.

Daver N, et al. *Leukemia*. 2019;33(2):299-312.

FLT3 Mutations at Relapse

- *FLT3* mutational status unstable over the course of therapy
  - *FLT3*-wild type at diagnosis to *FLT3*-mutated at relapse ≈ 7-21%
  - *FLT3* mutations may also be lost at relapse (particularly when frontline *FLT3* inhibitor is used)

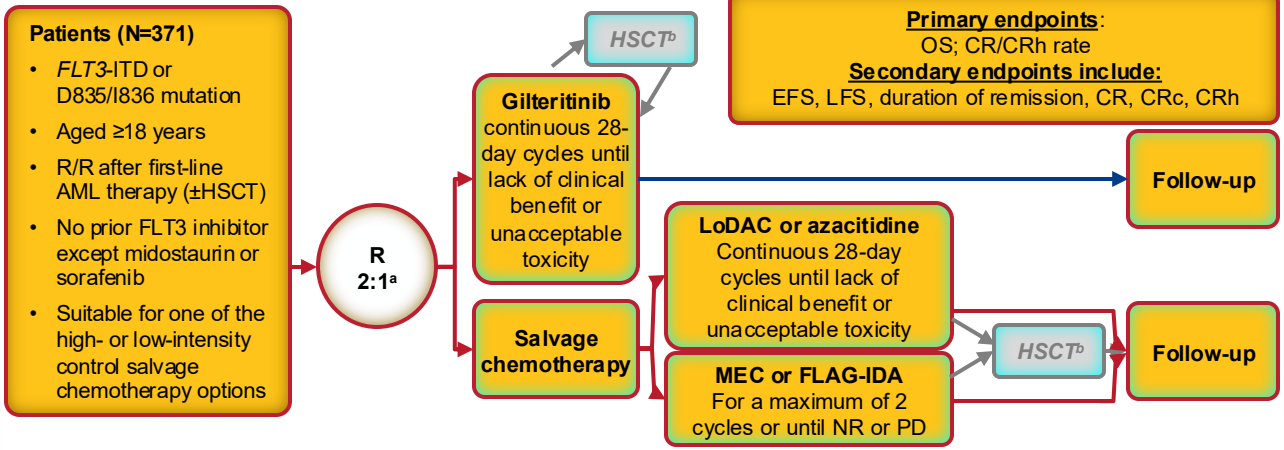


Repeat genomic analysis at relapse is imperative!

Kottaridis PD, et al. *Blood*. 2002;100(7):2393-2398. Nazha A, et al. *Haematologica*. 2012;97(8):1242-1245. Shih LY et al. *Blood*. 2002;100(7):2387-2392. Nakano Y, et al. *Br J Hematol*. 1999;104(4):659-664. Kleppe M, Levine RL. *Nat Med*. 2014;20(4):342-344.

Gilteritinib—Phase III ADMIRAL Study

Monotherapy vs salvage chemotherapy (ADMIRAL; NCT02421939)[1-3]



- ADMIRAL addresses gilteritinib efficacy in the R/R disease setting compared with salvage chemotherapy; the study includes patients who are and are not fit for high intensity chemotherapy
- Based on data from the ADMIRAL study, gilteritinib is approved in Japan and United States for treatment of adults with *FLT3*-mutated R/R AML

CRh = complete remission with partial hematologic recovery; CRc = composite complete remission; EFS = event-free survival; LFS = leukemia-free survival; HSCT = hematopoietic SCT; MEC = mitoxantrone, etoposide, cytarabine; FLAG-IDA = fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; PD = progressive disease.

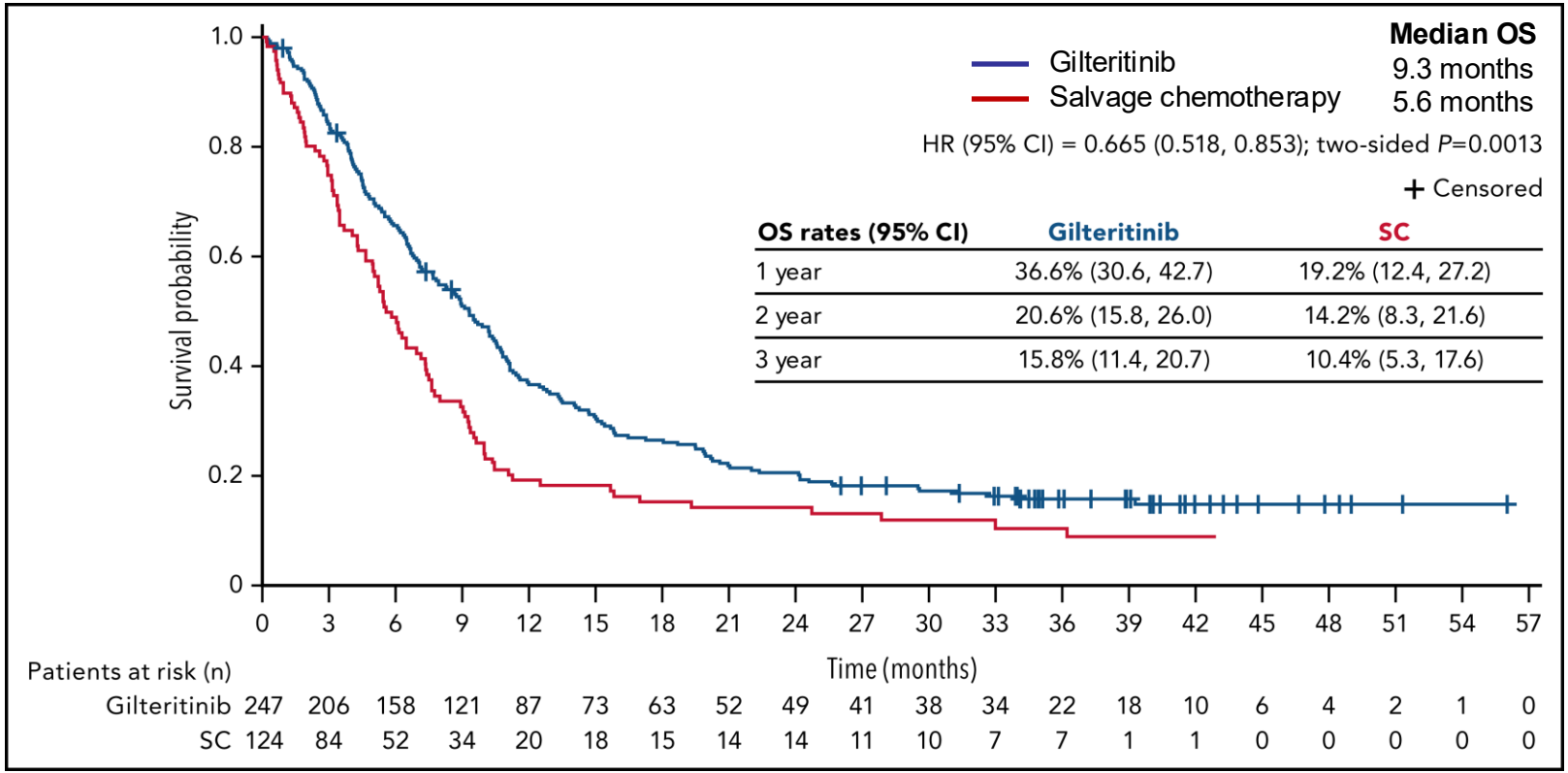
Perl AE, et al. *N Engl J Med*. 2019;381(18):1728-1740.

Response Outcomes (ITT Population: N=371)

Response Parameter*	Gilteritinib (n=247)	Salvage Chemotherapy (n=124)
CR, n (%)	**52 (21)**	**13 (11)**
CRh, n (%)	32 (13)	6 (5)
CRi, n (%)	63 (26)	14 (11)
CRp, n (%)	19 (8)	0 (0)
CRc, n (%)	**134 (54)**	**27 (22)**
CR/CRh, n (%)	**84 (34)**	**19 (15)**
PR, n (%)	33 (13)	5 (4)
ORR, n (%)	167 (68)	32 (26)
NR, n (%)	66 (27)	43 (35)
Mean time to achieve CRc (SD), months	2.3 (1.9)	1.3 (0.5)
Median DoR† (95% CI), months	11.0 (4.6, NE)	1.8 (NE, NE)
Allogeneic HSCT, n (%)	**63 (26)**	**19 (15)**

*Response was not evaluable in 14 patients (6%) in the gilteritinib arm and in 49 patients (40%) in the salvage chemotherapy arm. †Duration of remission includes duration of CRc, duration of CR/CRh, duration of CR, duration of CRp, and duration of response (CRc + PR).
CRp = complete remission with incomplete platelet recovery; DoR = duration of response/remission; ITT = intention-to-treat; ORR = overall/objective response rate.
Perl AE, et al. *N Engl J Med*. 2019;381(18):1728-1740.

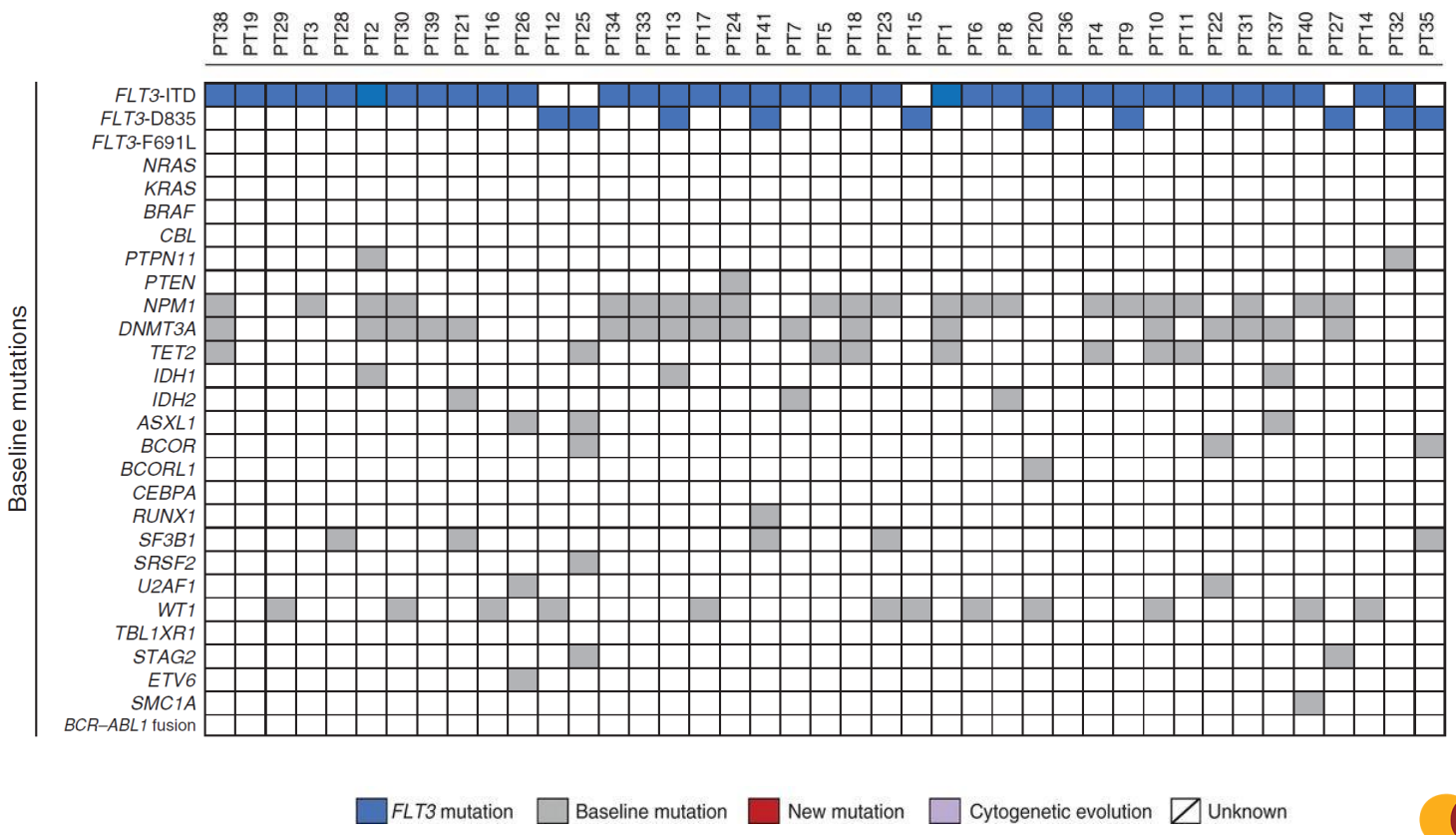
ADMIRAL: Overall Survival (ITT Population: N=371)



SC = salvage chemotherapy.

Perl AE, et al. *N Engl J Med*. 2019;381(18):1728-1740. Perl AE, et al. *Blood*. 2022;139(23):3366-3375.

Multiple Mechanisms of Gilteritinib Resistance

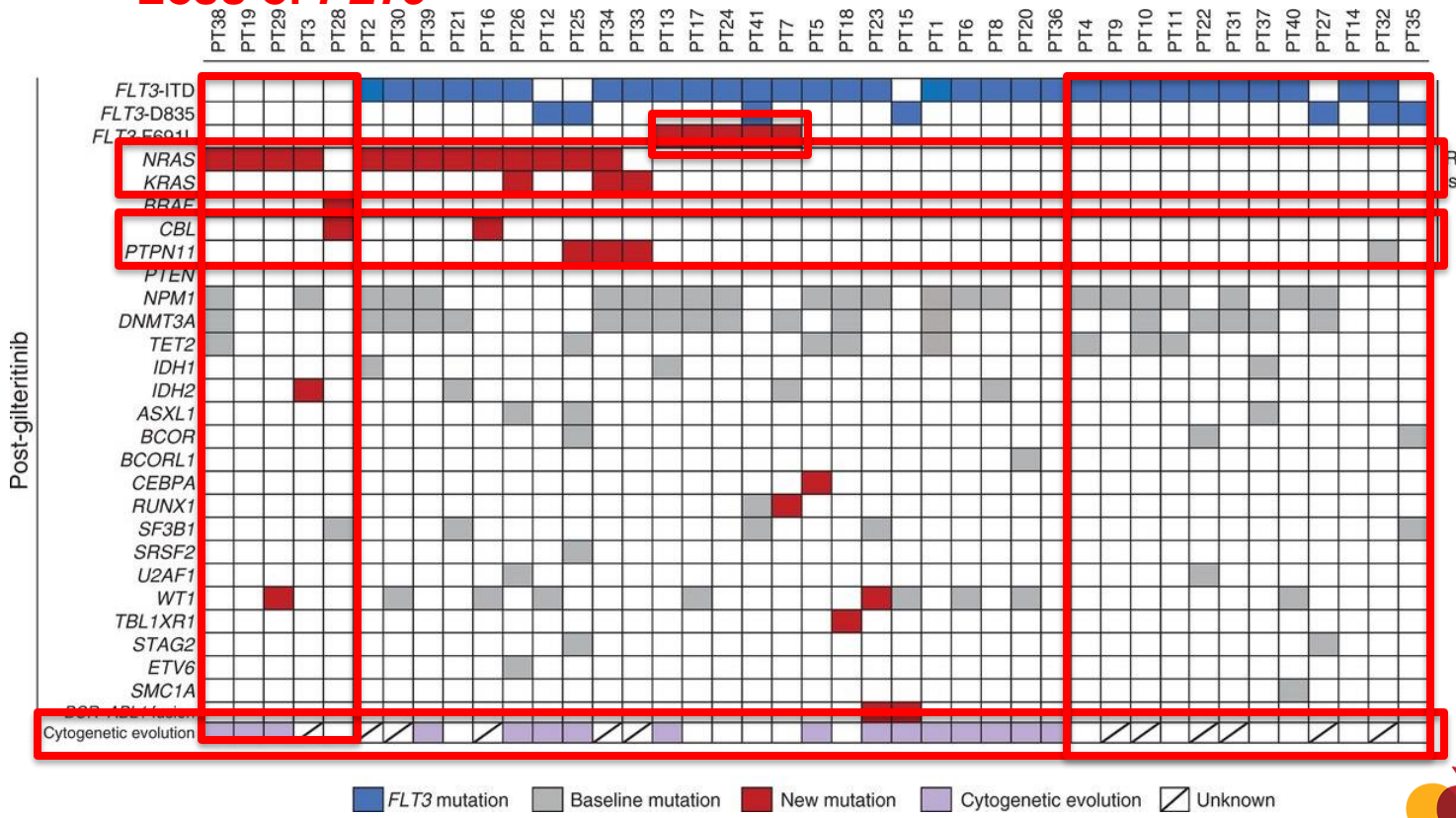


Cytogenetic evolution

McMahon CM, et al. *Cancer Discov*. 2019;9(8):1050-1063.

Multiple Mechanisms of Gilteritinib Resistance

Loss of *FLT3*



***FLT3* F691L**

Other RAS mechanisms

pathway

New mutations were acquired in 23/41 (56.1%) subjects at time of progression of gilteritinib

Cytogenetic evolution

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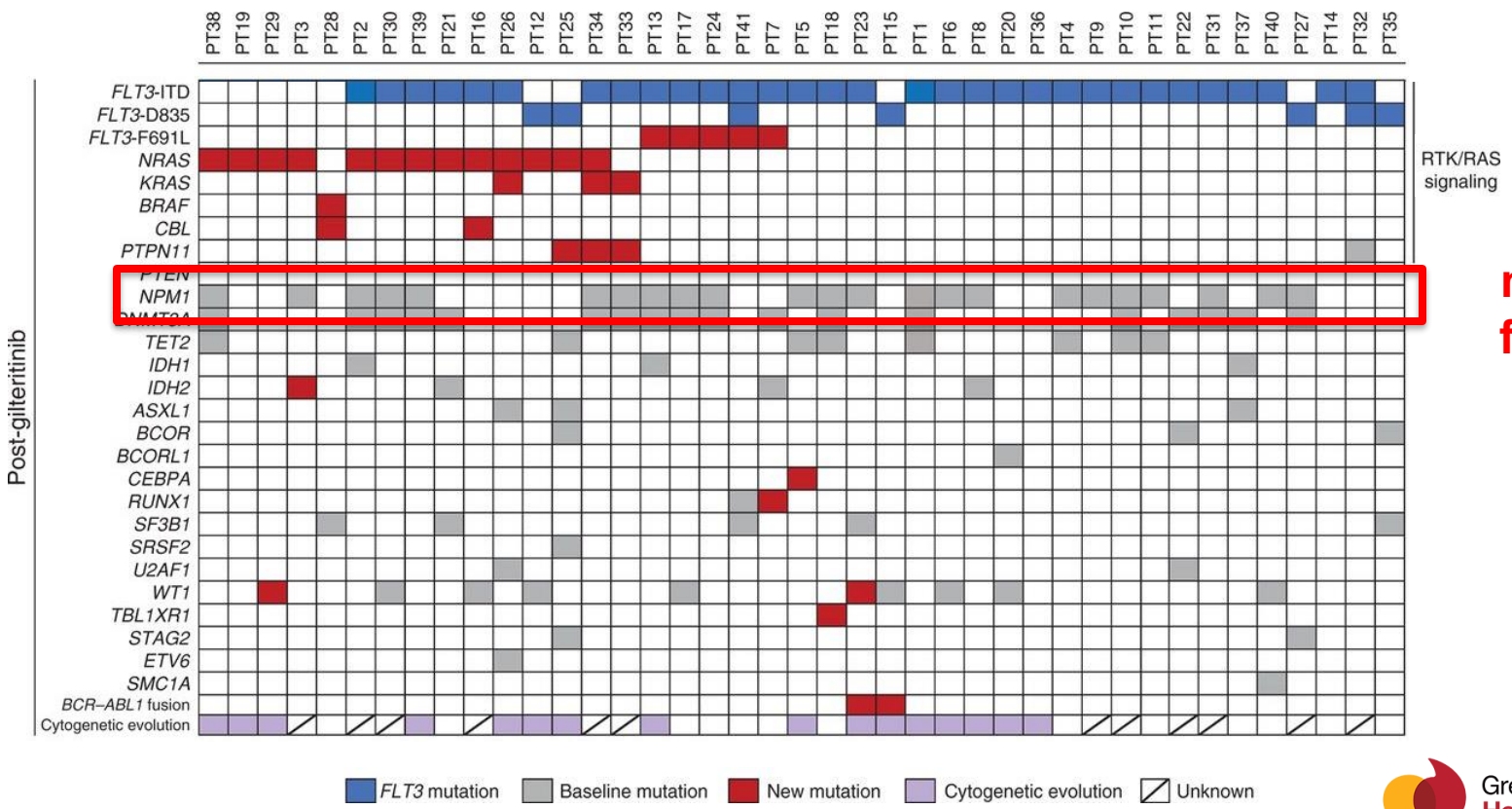
McMahon CM, et al. *Cancer Discov*. 2019;9(8):1050-1063.

Multiple Mechanisms of Gilteritinib Resistance



NPM1 **mutations frequently persist**

McMahon CM, et al. *Cancer Discov*. 2019;9(8):1050-1063.

*NPM1 M*utations and *KMT2A* Rearrangements: Menin Inhibitors

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Genomic Landscape of AML—*NPM1* and *KMT2A*

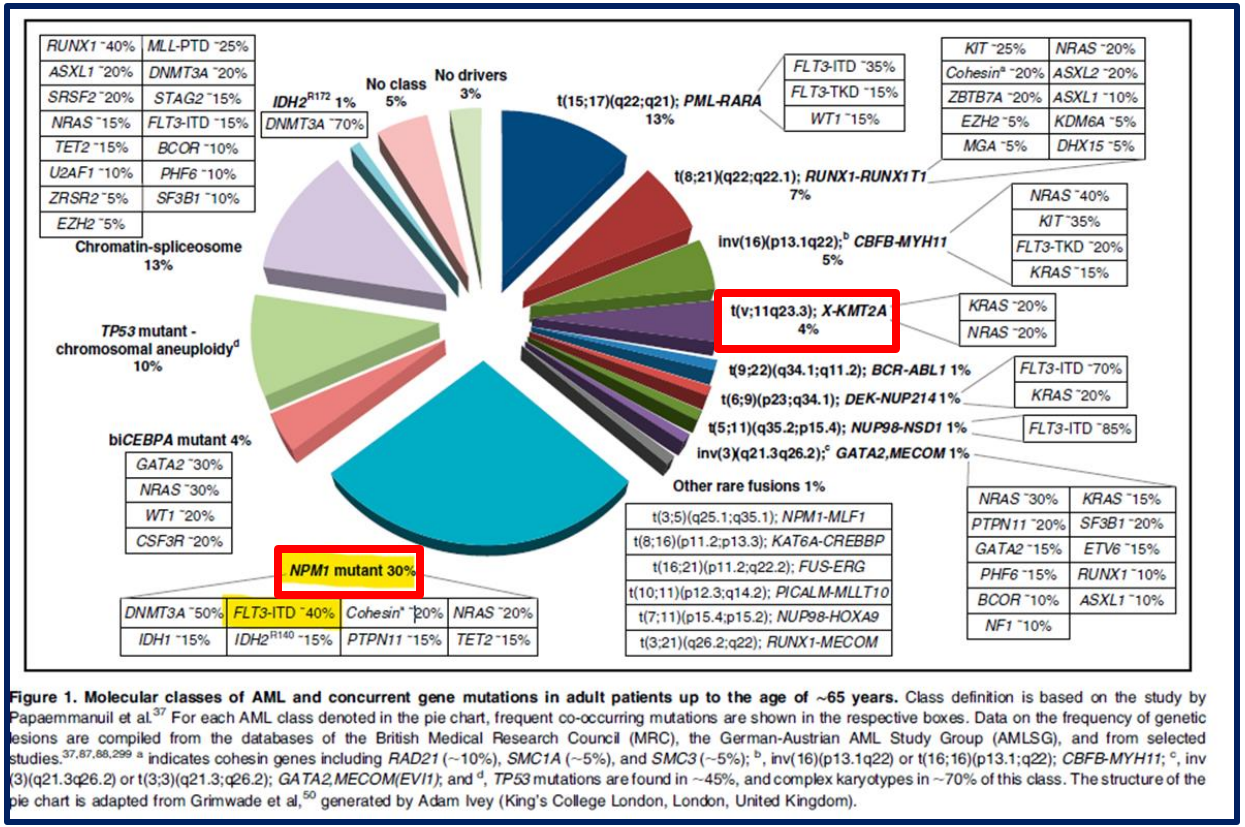

Figure 1. Molecular classes of AML and concurrent gene mutations in adult patients up to the age of ~65 years. Class definition is based on the study by Papaemmanuil et al.[37] For each AML class denoted in the pie chart, frequent co-occurring mutations are shown in the respective boxes. Data on the frequency of genetic lesions are compiled from the databases of the British Medical Research Council (MRC), the German-Austrian AML Study Group (AMLSG), and from selected studies.[37,87,88,299] [a] indicates cohesin genes including *RAD21* (~10%), *SMC1A* (~5%), and *SMC3* (~5%); [b], inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*; [c], inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*; and [d], *TP53* mutations are found in ~45%, and complex karyotypes in ~70% of this class. The structure of the pie chart is adapted from Grimwade et al,[50] generated by Adam Ivey (King's College London, London, United Kingdom).

Co-mutations are common

- *NPM1* mut: 30% of newly diagnosed AML, 50-60% of NK AML
- *FLT3*-ITD mut: co-mutation in 40% of *NPM1* AML
- *KMT2Ar*: 4-5% of new dx AML—enriched in R/R AML

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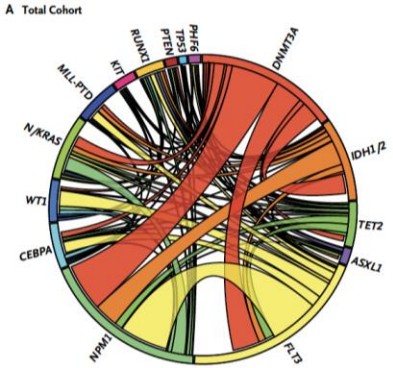
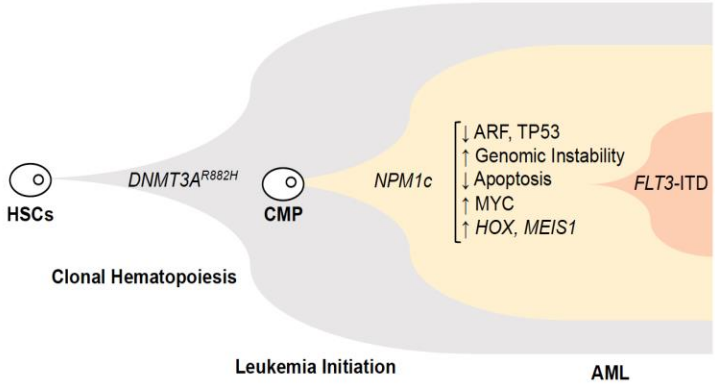
Döhner H, et al. *Blood*. 2017 ;129(4):424-447.

Actionable Target for Menin Inhibition in AML: *NPM1*



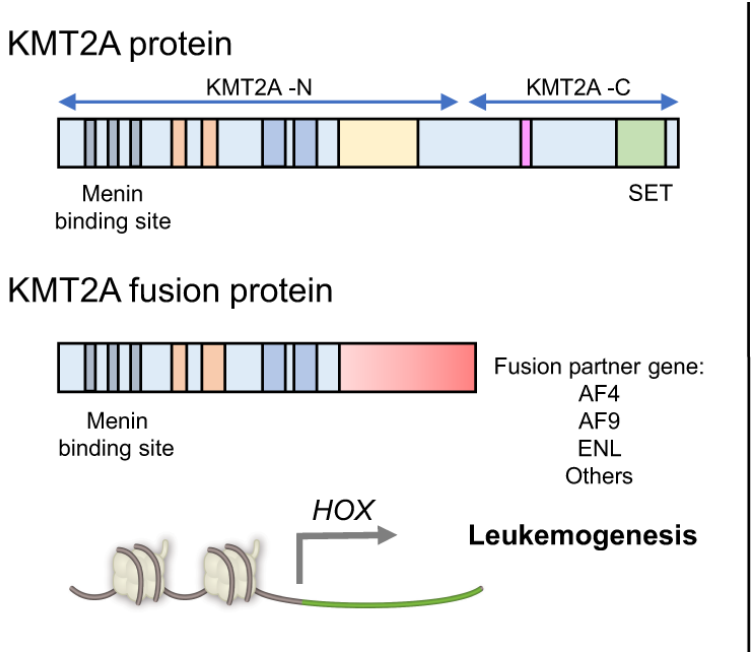
Gene	Overall Frequency (%)
FLT3 (ITD, TKD)	37 (30, 7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0



Risk category†	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*†,‡ • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*†,‡ • Mutated *NPM1*†,§ without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged# • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)* • t(3q26.2;v)/*MECOM(EVI1)*-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype,** monosomal karyotype†† • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2*‡‡ • Mutated *TP53*[a]

§AML with NPM1 mutation and adverse-risk cytogenetic abnormalities are categorized as adverse-risk. Patel JP, et al. *N Engl J Med*. 2012;366(12)1079-1089. Zarka J, et al. *Genes (Basel)*. 2020;11(6):649. Döhner H, et al. *Blood*. 2022;140(12):1345-1377. Pre-clinical studies: Loberg MA, et al. *Leukemia*. 2019;33(7):1635-1649. Sportoletti P, et al. *Leukemia*. 2015;29(2):269-278.

Actionable Target for Menin Inhibition in AML: *KMT2Ar*



Risk category†	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*†,‡ • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*†,‡ • Mutated *NPM1*†,§ without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged# • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)* • t(3q26.2;v)/*MECOM(EVI1)*-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype,** monosomal karyotype†† • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2*‡‡ • Mutated *TP53*[a]

†Mainly based on results observed in intensively treated patients. Initial risk assignment may change during the treatment course based on the results from analyses of measurable residual disease. ¶The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse risk gene mutations. #Excluding *KMT2A* partial tandem duplication (PTD).

Döhner H, et al. *Blood*. 2022;140(12):1345-1377. Issa GC, et al. *Leukemia*. 2021;35(9):2482-2495.

Other Potential Targets for Menin Inhibitors

Table 2 Genetic alterations with overexpression of *HOXA* genes predicted to potentially respond to menin inhibitors.

Alteration/mutation	Cytogenetics	Phenotype				References
KMT2Ar	11q23 rearrangements	AML, ALL, MPAL	✓	✓	✓	[26, 132, 133]
KMT2A-PTD	Normal karyotype	AML	✓	✓		[26, 134]
NPM1c	Normal karyotype	AML	✓	✓	✓	[26, 135]
NPM1-MLF1	t(3;5)(q25;q34)	MDS, AML	✓			[136, 137]
NUP98r	11p15 rearrangements	AML, T-ALL, MDS	✓	✓	✓	[122–124]
SET-NUP214	t(9;9)(q34;q34)	AML, T-ALL, AUL	✓		✓	[138]
RUNX1-EVI1	t(3;21)(q26;q22)	AML	✓		✓	[139]
MYST3-CREBBP	t(8;16)(p11;p13)	AML	✓			[140]
CDX2-ETV6	t(12;13)(p13;q12)	AML		✓		[141]
CALM-AF10	t(10;11)(p13;q14-21)	T-ALL, AML, MPAL	✓	✓	✓	[142–144]
MN1-ETV6	t(12;22)(p13;q12)	AML, MDS		✓	✓	[145]
EZH2	–	MDS, AML	✓			[146]
IDH1/IDH2	–	MNs			✓	[147, 148]
ASXL1	–	MNs		✓		[149]
CEBPA	–	AML			✓	[150]
	Trisomy 8	MNs	✓			[151]

Denotes direct examination of patient samples with the corresponding genotype showing upregulation of *HOXA* genes.

Denotes mouse models of the corresponding genotype leading to upregulation of *Hox* genes.

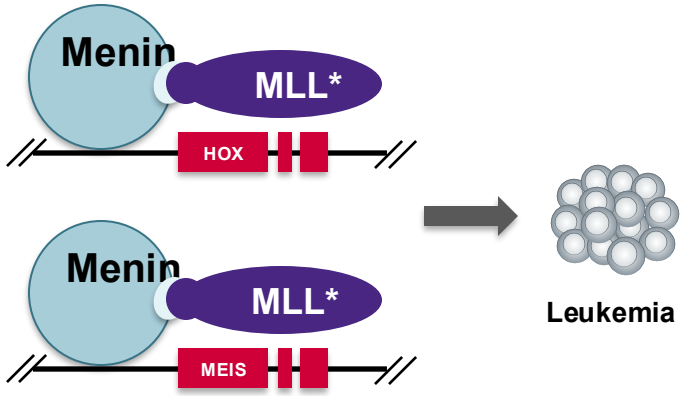
Denotes examination of cells lines or other in vitro investigations demonstration a role of *HOX* genes or menin inhibition in the corresponding genotype.

ALL = acute lymphoblastic leukemia; MPAL = mixed-phenotype acute leukemia; T-ALL = T-cell lymphoblastic leukemia; MDS = myelodysplastic syndrome; AUL = acute undifferentiated leukemia; MNs = myeloproliferative neoplasms.

Issa GC, et al. *Leukemia*. 2021;35(9):2482-2495.

Pathogenesis of *KMT2A*-Rearranged and *NPM1* Mutant Acute Leukemias

MLLr Acute Leukemias

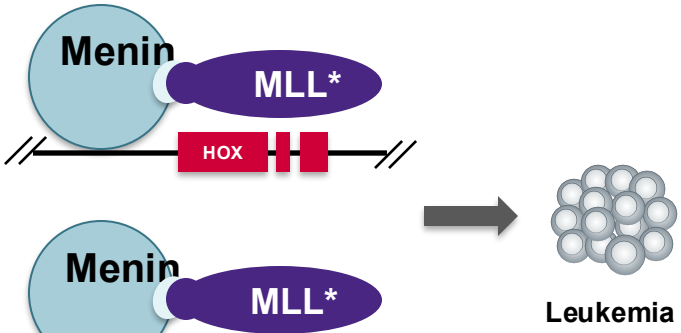


Gene transcription ON

MLL* = MLLr or MLL1 wildtype.
Adapted from: Uckelmann HJ, et al. *Blood*. 2018;132(Suppl 1):546.

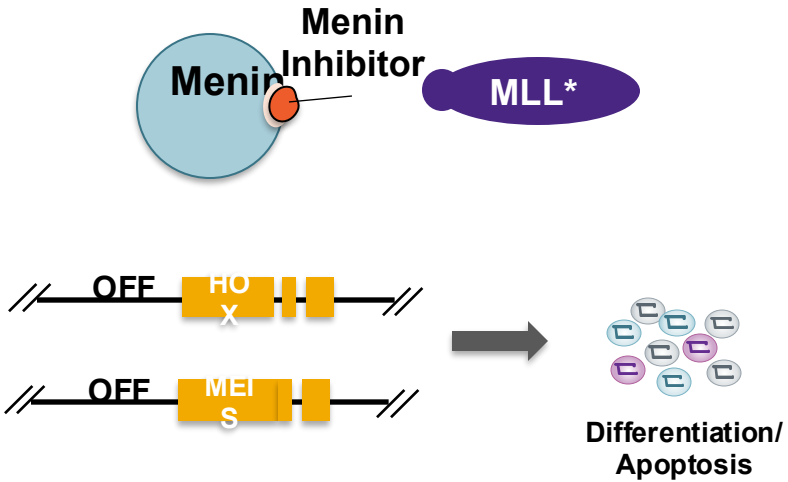
Revumenib Turns Off Leukemic Transcriptional Programs by Binding to Menin and Displacing MLL Complexes

MLLr Acute Leukemias



Gene transcription ON

Menin Inhibitor

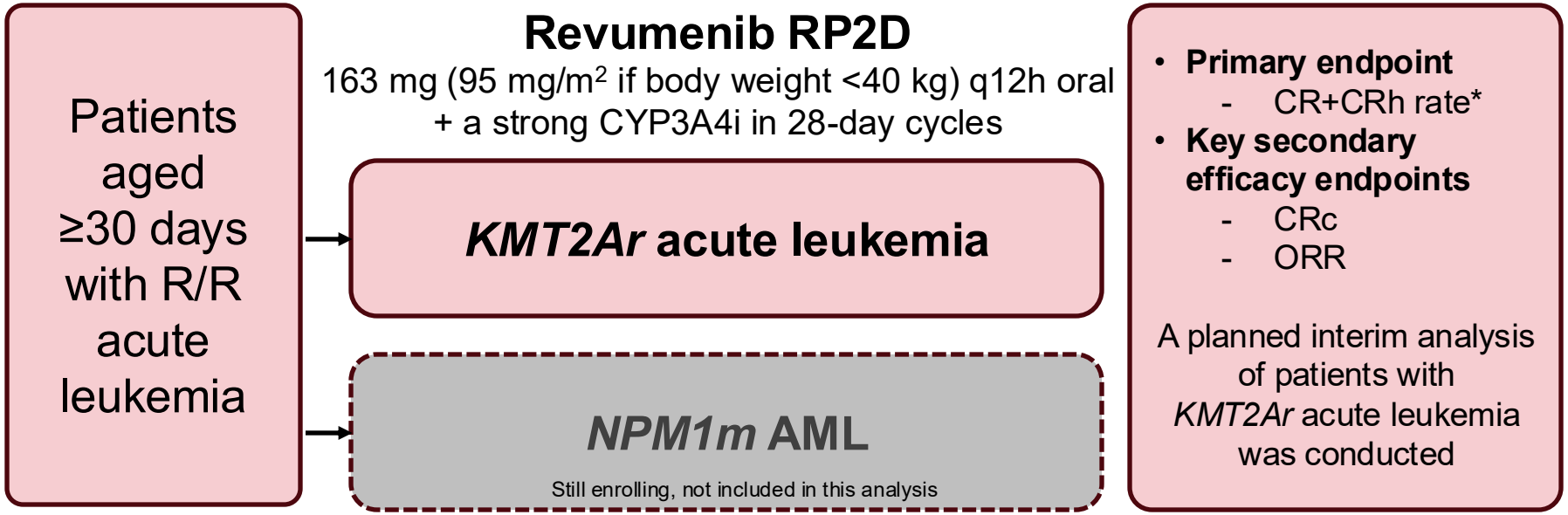


Gene transcription OFF

MLL* = MLLr or MLL1 wildtype.

Adapted from: Uckelmann HJ, et al. *Blood*. 2018;132(Suppl 1):546.

AUGMENT-101 Phase 2 Study Design



*CR+CRh rate >10% in adult evaluable population considered lower efficacy bound.
i = inhibitor; RP2D = recommended phase 2 dose.

Aldoss I, et al. Presented at: 65th American Society of Hematology (ASH) Annual Meeting; December 9-12, 2023; San Diego, California. Abstract LBA-5. Issa GC, et al. *J Clin Oncol*. 2025;43(1):75-84.

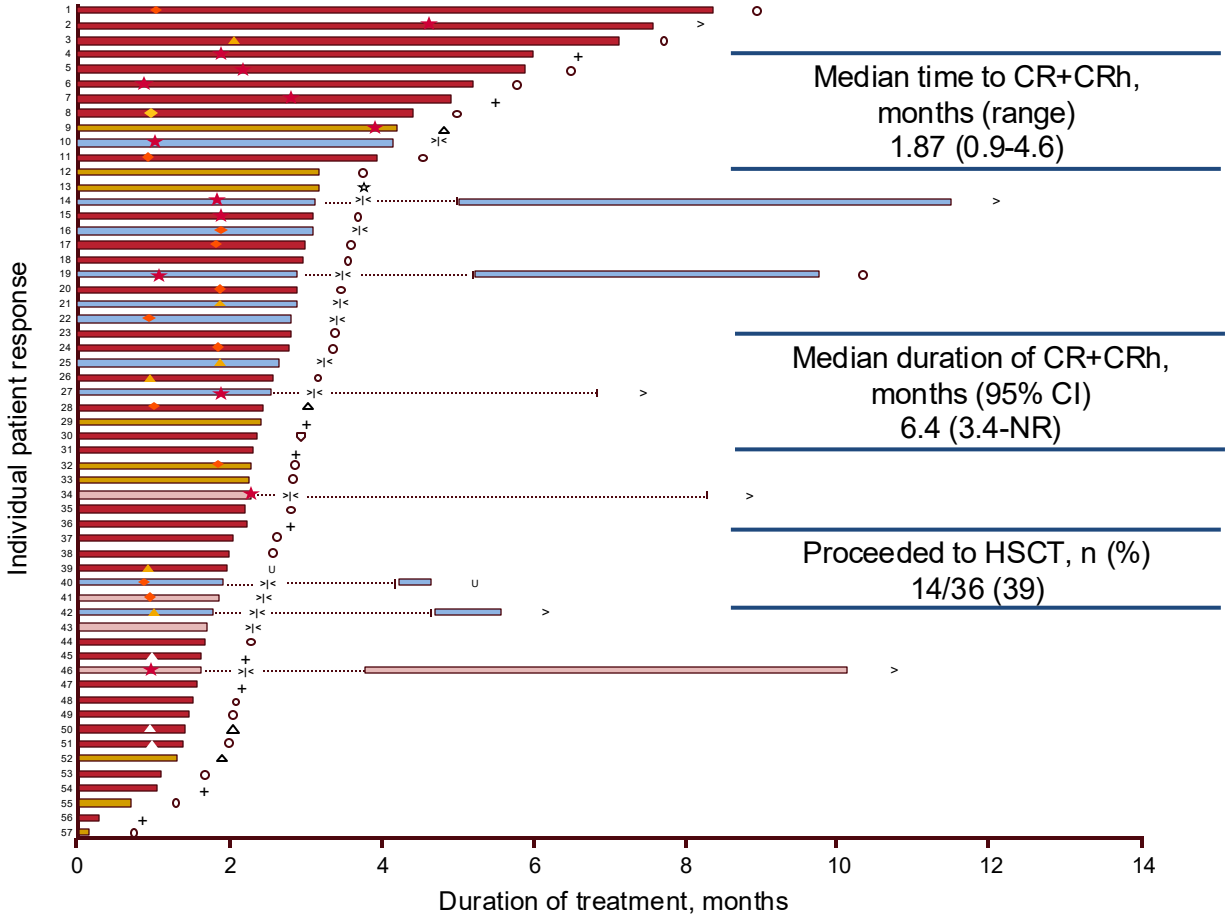
Response

Parameter	Efficacy population (n=57)
ORR, n (%)	**36 (63)**
CR+CRh rate, n (%)	13 (23)
95% CI	12.7-35.8
P value, 1-sided	0.0036
CRc	25 (44)
95% CI	30.7-57.6
Negative MRD status[a]	
CR+CRh	7/10 (70)
CRc	15/22 (68)

Parameter	Efficacy population (n=57)
Best response, n (%)	
CR	10 (18)
CRh	3 (5)
CRi	1 (1.8)
CRp	11 (19)
MLFS	10 (18)
PR	1 (1.8)
PD	4 (7)
No response	14 (25)
Other[b]	3 (5)

Data cutoff: July 24, 2023. [a]MRD done locally; not all patients had MRD status reported. [b]Includes patients without post-baseline disease assessment.
MLFS = morphological leukemia-free state; PR = partial response/remission.
Aldoss I, et al. Presented at: 65th ASH Annual Meeting; December 9-12, 2023; San Diego, California. Abstract LBA-5. Issa GC, et al. *J Clin Oncol*. 2025;43(1):75-84.

Time and Duration of Response



Median time to CR+CRh, months (range)
1.87 (0.9-4.6)

Median duration of CR+CRh, months (95% CI)
6.4 (3.4-NR)

Proceeded to HSCT, n (%)
14/36 (39)

- Adult
- Adult, underwent HSCT
- Pediatric
- Pediatric, underwent HSCT
- CR/CRh
- CRp/CRi
- MLFS
- Progressive disease
- Ongoing at data cutoff
- Adverse event
- Subject withdrew consent for treatment
- >|< HSCT
- Noncompliance
- Patient did not achieve at least a PR after 4 cycles
- U Prohibited concomitant medication

Aldoss I, et al. Presented at: 65th ASH Annual Meeting; December 9-12, 2023; San Diego, California. Abstract LBA-5.
Issa GC, et al. *J Clin Oncol*. 2025;43(1):75-84.

Revumenib Safety Profile

Any grade TEAEs that occurred in ≥25% patients

All terms, n (%)	Safety population (n=94)[a]
Nausea	42 (45)
Febrile neutropenia	36 (38)
Diarrhea	33 (35)
Vomiting	29 (31)
Differentiation syndrome	26 (28)
Hypokalemia	26 (28)
Epistaxis	25 (27)
QTc prolongation	24 (26)

Grade ≥3 TEAEs that occurred in ≥10% patients

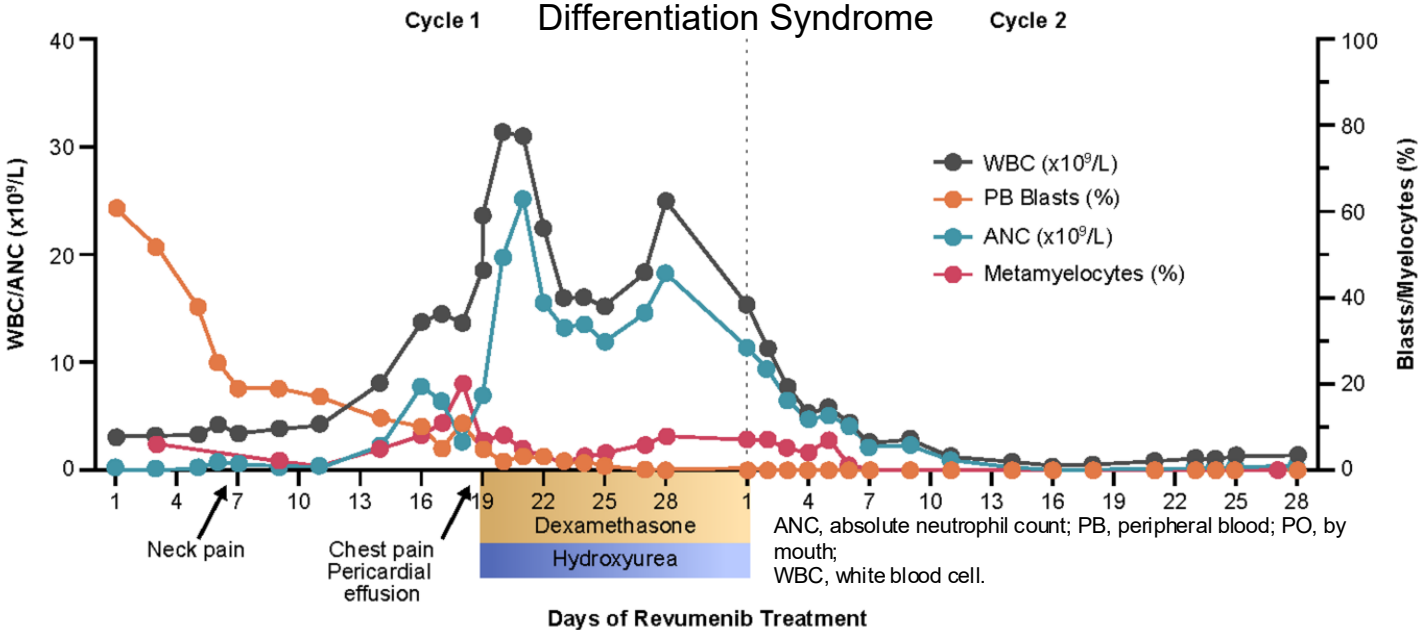
All terms, n (%)	Safety population (n=94)[a]
Febrile neutropenia	35 (37)
Decreased neutrophil count	15 (16)
Decreased white blood cell count	15 (16)
Decreased platelet count	14 (15)
Anemia	17 (18)
Differentiation syndrome	15 (16)
QTc prolongation	13 (14)
Sepsis	11 (12)
Hypokalemia	10 (11)

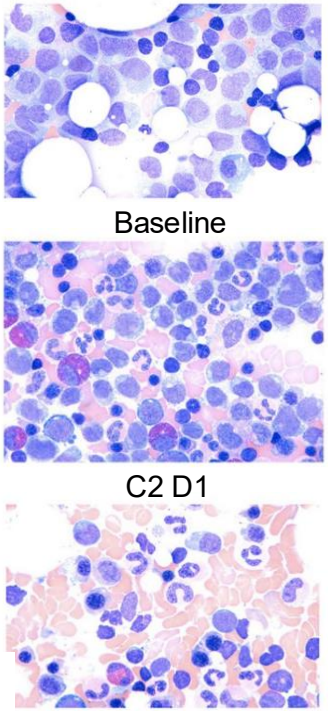
No patients discontinued due to differentiation syndrome, QTc prolongation, or cytopenias.

Data cutoff: July 24, 2023. [a]Defined as patients with KMT2Ar acute leukemia having received at least 1 dose of revumenib.
TEAE = treatment-emergent adverse event.
Aldoss I, et al. Presented at: 65th ASH Annual Meeting; December 9-12, 2023; San Diego, California. Abstract LBA-5. Issa GC, et al. *J Clin Oncol*. 2025;43(1):75-84.

DS Associated with Menin Inhibitors

Hallmarks of **differentiation** into normal hematopoietic cells





- 71-year-old with *KMT2Ar* AML relapsed after an allogeneic stem cell transplant
- Received revumenib at 339 mg PO q12h (arm A), and achieved CRh, MRD negativity

DS = differentiation syndrome.
Slide courtesy Issa G. Issa GC, et al. *Nature*. 2023;615(7954):920-924.

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Ziftomenib Demonstrates Meaningful Clinical Activity as Monotherapy

40% of *NPM1*-m patients achieved a CR during course of study

Best Overall Response	600 mg
NPM1-m Phase 1a + 1b	**(n=20)**
CR	**7 (35.0)**
CR/CRh	7 (35.0)
CRc	8 (40.0)
MRD negativity	4 (50.0)[1]
ORR	9 (45.0)
KMT2A-r Phase 1a + 1b	**(n=18)**
CR/CRh	2 (11.1)
CRc	3 (16.7)
MRD negativity	3 (100.0)
ORR	3 (16.7)

DIFFERENTIATED CR RATES VS. SOC IN HEAVILY PRETREATED PATIENTS

	MUTATION	CR %	mDOR	MEDIAN PRIORS
Ziftomenib 600mg QD	*NPM1*	**35%**	7.7 mo*	**3**
	FLT3	**33%**	-	
	IDH1/2	**50%**	-	
Gilteritinib	*FLT3*	14.2%	14.8 mo	1
Enasidenib	*IDH2*	19%	8.2 mo	2
Ivosidenib	*IDH1*	25%	10.1 mo	2

*Median DoR (Duration of Response) for CRc without censoring at HSCT
Source: USPI's

[1]MRD was assessed for 6/8 CRc patients; 4 of those 6 patients (67%) tested were MRD-negative. CRc includes CR, CRh, Cri, CRp; ORR includes CR, CRh, Cri, CRp, and MLFS.
SOC = standard of care; mDOR = median DOR;
Wang ES, et al. *Lancet Oncol.* 2024;25(10):1310-1324.

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Menin Inhibitor Monotherapy (R/R AML)

	Menin Inhibitor vs Standard	N	ORR	CR/CRh	Source
KMT2Ar					
Primary endpoint ✓	Revumenib (Ph 2)	57	63% (n=36)	23% (n=13)	Issa, JCO 2024
	Revumenib (Ph 1)	77	65% (n=50)	31% (n=24)	Aldoss, ASH 2023
	Ziftomenib (Ph 1)	18	17% (n=3)*	11% (n=2)	Wang, Lancet Onc 2024
	Bleximenib (Ph 1)	9	44% (n=4)*	33% (n=3)	Searle, ASH 2024
	Enzomenib (Ph 1)	23	65% (n=15)*	30% (n=7)	Zeidner, ASH 2024
	BN104 (Ph1)	23	91% (n=21)	61% (n=14)	Wu, ASH 2024
	BMF-219 (Ph 1)	6	0%	0%	Lancet, ASH 2023
	Standard therapies	217	9% (n=59)	5% (n=42)	Issa, Blood Cancer J 2021
NPM1mt					
Primary endpoint ✓	Revumenib (Ph 2)	64	47% (n=30)	23% (n=15)	Press release (11/12/24)
	Ziftomenib (Ph 1)	20	45% (n=9)*	35% (n=7)	Wang, Lancet Onc 2024
Primary endpoint ✓	Ziftomenib (Ph 2)	-	-	-	Press release (02/05/25)
	Bleximenib (Ph 1)	12	33% (n=4)*	33%? (n=4)*	Searle, ASH 2024
	Enzomenib (Ph 1)	17	59% (n=10)*	47% (n=8)	Zeidner, ASH 2024
	BN104 (Ph 1)	5	80% (n=4)	40% (n=2)	Wu, ASH 2024
	BMF-219 (Ph 1)	4	25% (n=1)	0	Lancet, ASH 2023
	Standard therapies	206	50% (n=102)	24%° (n=49)	Issa, Blood Adv 2023

***Results of ziftomenib shown for 600 mg only (the RP2D of monotherapy); of blexamenib at 90/100 mg BID (RP2D?); of enzomenib shown for active doses >140 mg BID.**
Slide courtesy Issa G. Unpublished (review in preparation: Issa, Cai, Bataller, Kantarjian, Stein).

Adverse Events with Menin Inhibitors

On-target (menin) effects

Reported in clinical trials

- Differentiation syndrome
- Myelosuppression

Off-target effects

- QT prolongation (revumenib, 10% Gr 3)
- DDI (CYP3A inhibitors or substrates)
- Pruritus (ziftomenib, 13% Gr 1-2)

Potential AEs (preclinical/animal studies)

- MEN1 syndrome
- Bone growth
- Neurologic
- Cardiac
- Embryo-fetal toxicity

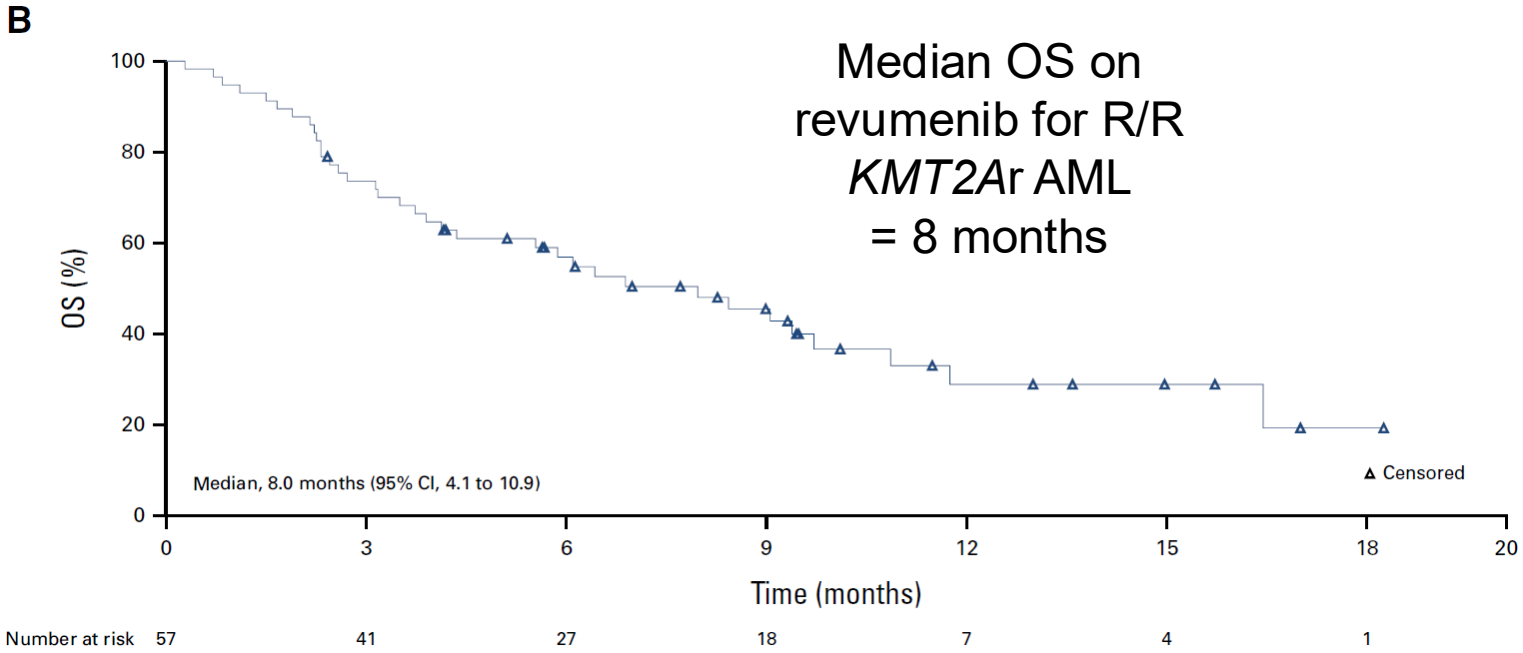
DDI = drug-drug interaction; MEN1 = type 1 multiple endocrine neoplasia.
Slide courtesy Issa G.

Rates of DS by Menin Inhibitor

Menin Inhibitor	DS (all grades)	Grade ≥3	Grade 5	Source
Revumenib (N=135)	39 (29%)	17 (13%)	1 (<1%)	USPI
Ziftomenib (N=83)	18 (22%)	10 (12%)	1 (<1%)	Wang, Lancet Onc 2024
Bleximenib (N=146)	14%	8%	Yes (%?)	Searle, ASH 2024
Enzomenib (N=84)	9 (11%)	?		Zeidner, ASH 2024
BN104 (N=40)	4 (10%)	?		Wu, ASH 2024

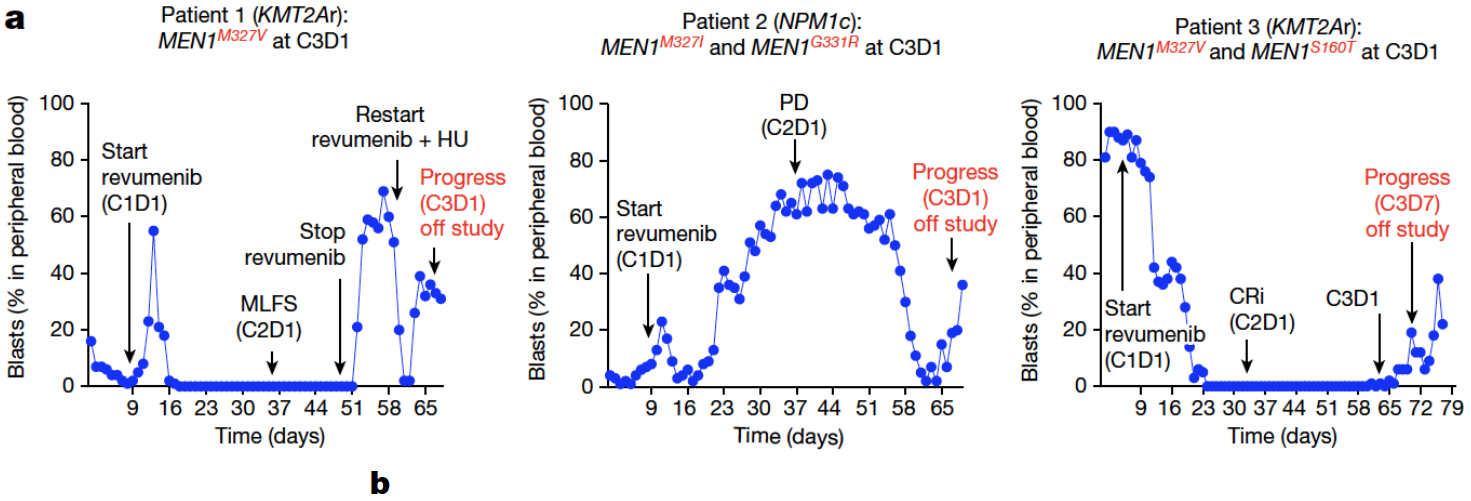
Slide courtesy Issa G.

Single-Agent Menin Inhibition Is Not Curative



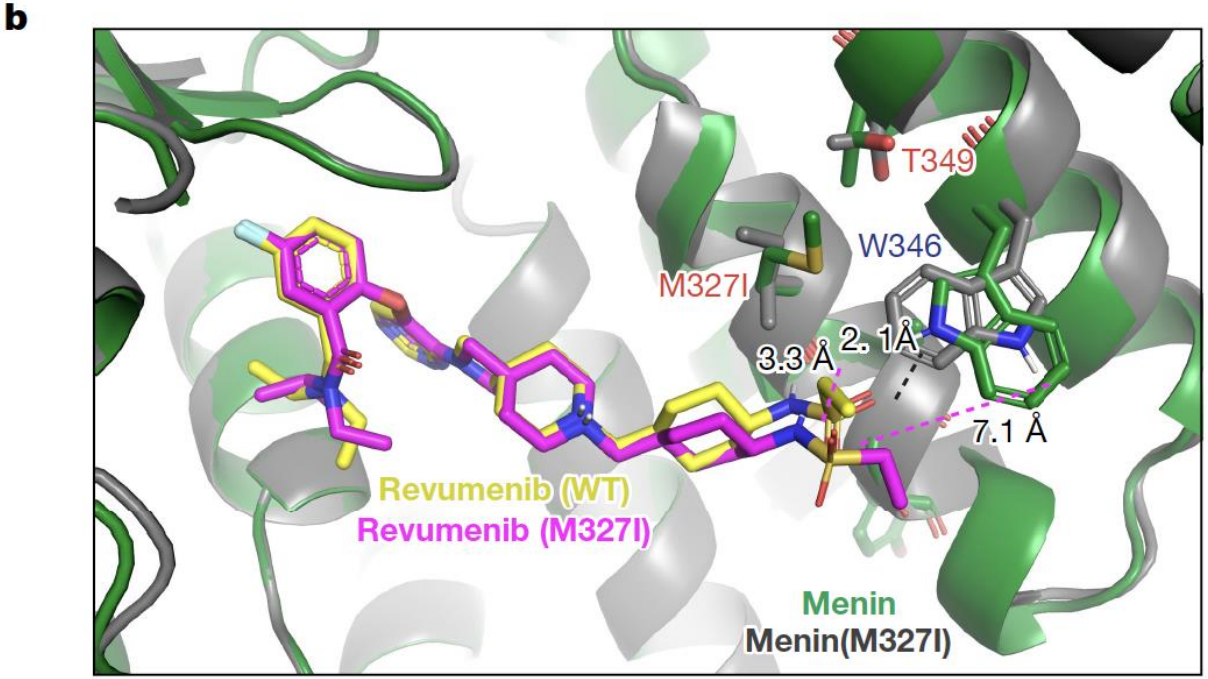
Issa GC, et al. *J Clin Oncol*. 2025;43(1):75-84.

Resistance to Menin Inhibition



Perner F, et al. *Nature*. 2023;615(7954):913-919.

Disrupted Revumenib Binding with Novel *MEN1* Mutations



Perner F, et al. *Nature*. 2023;615(7954):913-919.

IDH1 and *IDH2* Mutations: IDH1/2 Inhibitors

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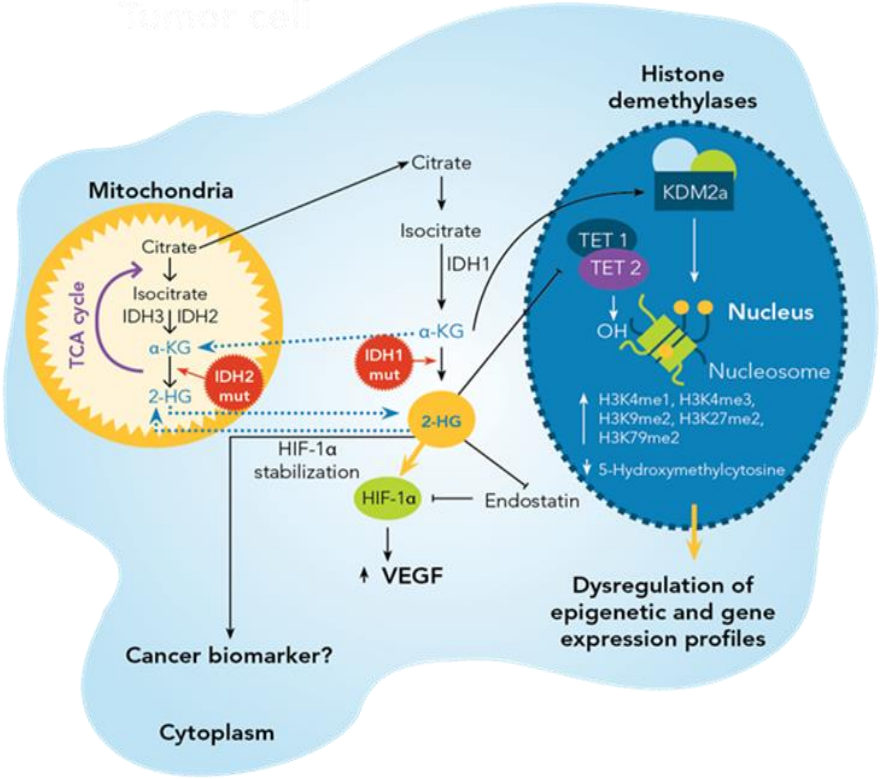
IDH Mutations in AML



- IDH: critical enzymes of the citric acid cycle
- *IDH* mutations produce 2-HG → alteration of DNA methylation and block of differentiation
- Incidence
  - 5-15% (*IDH1*)
  - 10-20% (*IDH2*)
- More common in older patients
- Approved agents
  - Ivosidenib, olutasidenib (*IDH1*)
  - Enasidenib (*IDH2*)

TCA = tricarboxylic acid; VEGF = vascular endothelial growth factor.
Prensner JR, Chinnaiyan AM. *Nat Med.* 2011;17(3):291-293.

Targeted IDH Inhibitors in the Clinic

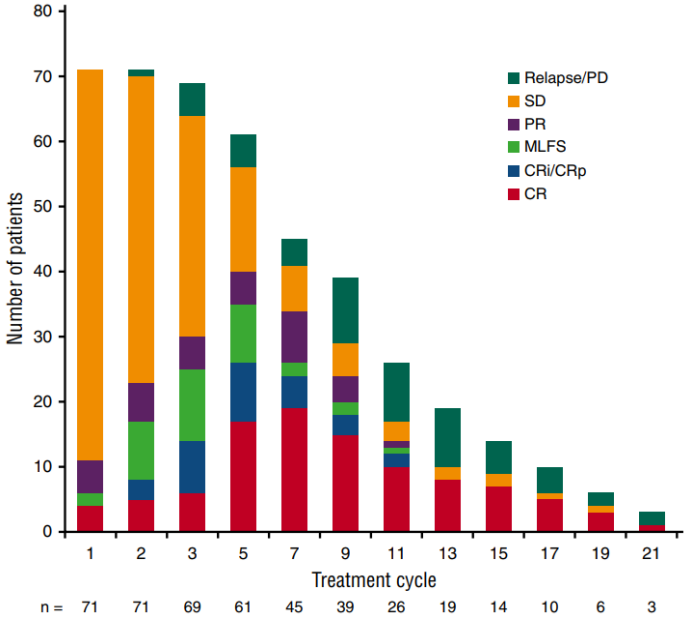
Targeted *IDH1/2* inhibitors: The class of "…sidenibs"

- **Enasidenib (AG-221):** First-in-class, oral, targeted inhibitor of *mIDH2* enzyme
- **Ivosidenib (AG-120):** First-in-class, oral, targeted inhibitor of *mIDH1* enzyme
- **Olutasidenib (FT-2102):** Second FDA-approved**,** oral, targeted inhibitor of *mIDH1* enzyme
- **Vorasidenib (AG-881):** Oral, potent, **brain-penetrant** targeted inhibitor of **both** *mIDH1* and *mIDH2*
  - Approved based on phase III INDIGO study of AG881 for residual/recurrent low-grade glioma post-surgery
- **LY3410738:** Novel covalent binding MOA, preclinical efficacy in ENA or IVO-resistant samples; under evaluation in *IDH1* or *IDH2*-mutated heme malignancies
- **HMPL-306:** Pan-*IDH1/2* inhibitor under evaluation in solid and malignant heme
- **IDH305, BAY19036, DS-1001b**: Oral, potent, targeted inhibitors of *mIDH1* enzyme, not currently under evaluation in heme malignancies

m = mutated; MOA = mechanism of action; ENA = enasidenib; IVO = ivosidenib.

Enasidenib for R/R *IDH2*-Mutated AML

- 176 patients with relapsed/refractory *IDH2*-mutated AML
- Enasidenib given at 50-650mg daily (expansion cohort: 100mg daily)
- ORR: 40%; CR rate: 19%
- Median OS: 9.3 months
- Grade ≥3 adverse events
  - Indirect hyperbilirubinemia (12%)
  - Differentiation syndrome (6%)



FDA-approved for R/R *IDH2*-mutated AML (2018)

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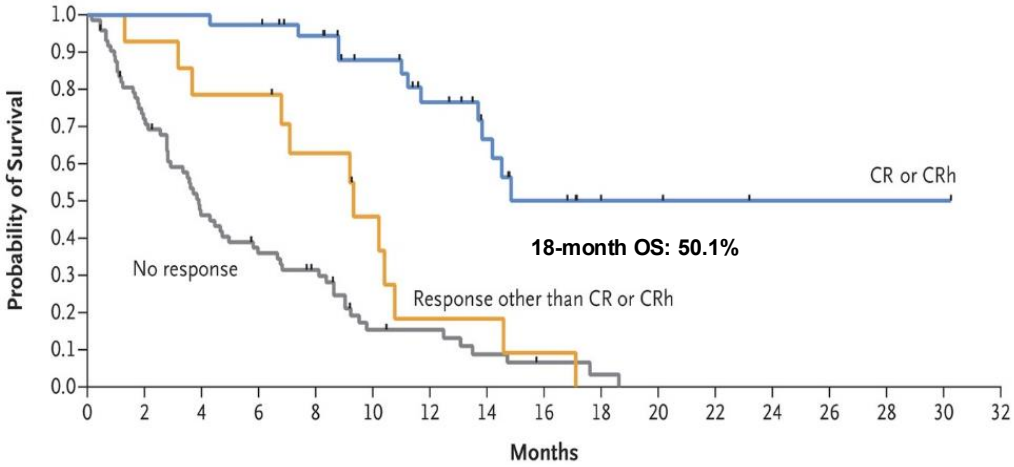
Stein EM, et al. *Blood*. 2017;130(6):722-731.

Ivosidenib for R/R *IDH1*-Mutated AML

- 179 patients with relapsed/refractory *IDH1* mutated AML
- Ivosidenib dose: 500 mg daily
- ORR: 42%; CR rate: 22%
- Median OS: 8.8 months
- Grade ≥3 adverse events
  - QTc prolongation (8%)
  - Differentiation syndrome (4%)



FDA-approved for

- **R/R *IDH1*-mutated AML**
- **Newly diagnosed *IDH1*-mutated AML in adults unsuitable for chemotherapy (alone or in combination with azacitidine)**

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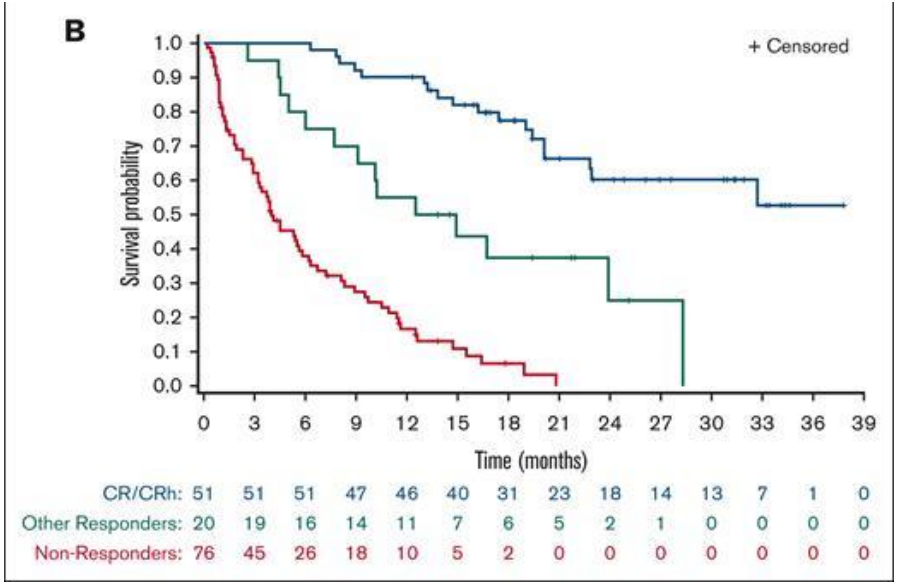
DiNardo CD, et al. *N Engl J Med*. 2018;378(25):2386-2398.

Olutasidenib for R/R *IDH1*-mutated AML

- 153 patients with relapsed/refractory *IDH1*-mutated AML
- Olutasidenib dose: 150 mg twice daily
- ORR: 48%; CR rate: 32%
- Median OS: 11.6 months
- Grade ≥3 adverse events
  - Hepatic toxicity (15%)
  - Differentiation syndrome (9%)



FDA-approved for R/R *IDH1*-mutated AML (2022)

de Botton S, et al. *Blood Adv*. 2023;7(13):3117-3127.

Olutasidenib in Post-Venetoclax AML with *IDH1*

- 18 patients with AML with *IDH1* who were either relapsed, refractory, or had incomplete hematologic recovery post-venetoclax
- CR 25%, CRh 6.3%
- Composite complete remission (CRc) 43.8%
- Median time to CRc: 1.9 months (range 1-2.8)
- Median duration of CRc not reached (range, 1.2-NR, ongoing at 30.4+ months)

Cortes J, et al. *Leuk Lymphoma*. 2024;65(8):1145-1152.

Comparing Toxicities of *IDH* Inhibitors

Treatment-Related TEAEs, Grade 3/4, n (%)	**Enasidenib** 100 mg/d (n=153)[1]		**Olutasidenib** 150 mg BID (n=153)[3]
Hyperbilirubinemia	**13 (8)**	NR	2 (1)
Prolonged QT interval	---	**14 (8)**	1 (<1)
***IDH* differentiation syndrome**	**11 (7)**	**7 (4)**	**12 (7)**
Anemia	10 (7)	4 (2)	7 (5)
Thrombocytopenia	8 (5)	3 (2)	6 (4)
Tumor lysis syndrome	5 (3)	---	3 (2)
Decreased appetite	3 (2)	---	---
Leukocytosis	2 (1)	3 (2)	7 (5)
Hepatic AESI (transaminitis)	---	----	**23 (15)**

Typical manifestations of differentiation syndrome

- Fever
- Dyspnea
- Pulmonary infiltrates
- Hypoxia
- Rash
- Edema

AESI = adverse event of special interest.

Stein EM, et al. *Blood*. 2017;130(6):722-731. DiNardo CD, et al. *N Engl J Med*. 2018;378(25):2386-2398. de Botton S, et al. *Blood Adv*. 2023;7(13):3117-3127.

Olutasidenib and Ivosidenib Data in R/R AML

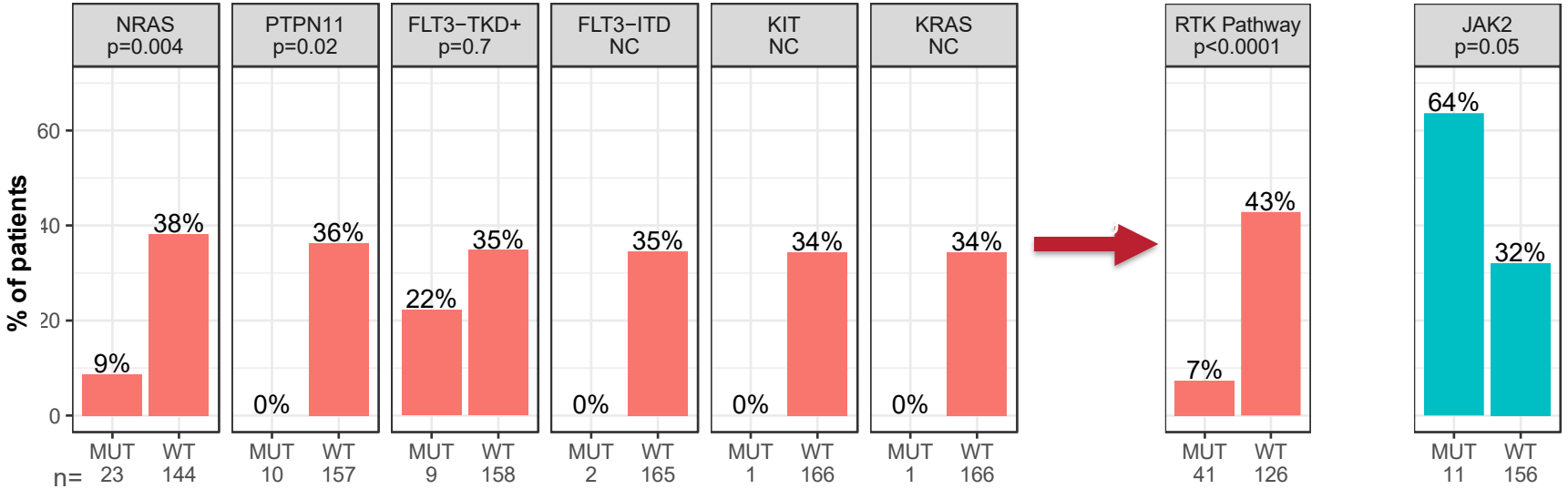
PARAMETERS	OLUTASIDENIB	IVOSIDENIB
Composite complete remission *(CR + CRh)*	**35%**	**33%**
Median duration of CR/CRh (95% CI)	**25.9 months (13.5, NR)**	**8.2 months (5.6, 12)**
Complete remission rate (CR)	**32%**	**25%**
Median duration of CR	**28.1 months**	**10.1 months**
Overall response rate *(CR + CRh + CRi + PR + MLFS)*	**48%**	**42%**
Median duration of overall response	**11.7 months**	**6.5 months**

Response rates are quite similar, but duration of remissions favor olutasidenib.

de Botton S, et al. *Blood Adv*. 2023;7(13):3117-3127. Ivosidenib prescribing information. DiNardo CD, et al. *N Engl J Med*. 2018;378(25):2386-2398. Drugs@FDA: FDA-Approved Drugs. Accessed June 26, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/211192s011lbl.pdf.

Baseline RTK Pathway Mutations Associated with Decreased Response to IDHi Monotherapy (IVO Data Shown)

- RTK pathway mutations associated with <10% CR/CRh response (>40% CR/CRh if NO RTK pathway!)



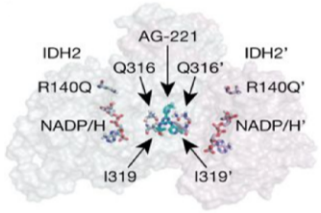
- 64% of patients with *JAK2* mutations achieved CR or CRh

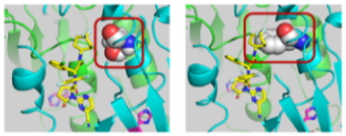
WT = wildtype.

Choe S, et al. *Blood Adv*. 2020;4(9):1894-1905.

Mechanisms of Relapse/Patterns of Clonal Selection

2HG Related

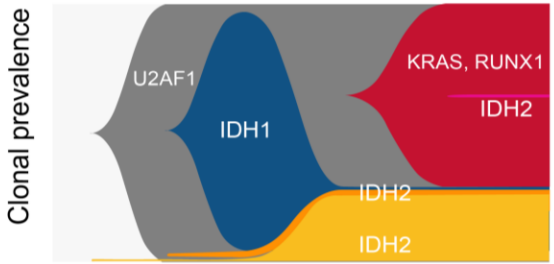




Entry	IDH1 mutant	Ivosidenib IC_{50}, μM
1	IDH1-R132C	0.019
2	IDH1-R132L	0.013
3	IDH1-R132C-S280F	>100
4	IDH1-R132C-R119P	0.15
5	IDH1-R132L-R119P	0.51

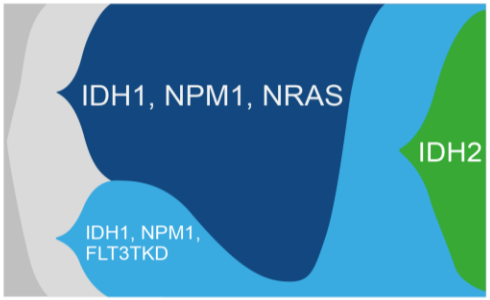
"Second Site Mutations"

Non-2HG Related

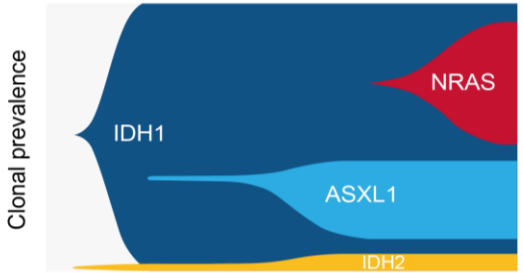


Reinstitution of Differentiation Block
(CEBPα, RUNX1, GATA2)

***IDH2* mutation acquired in *IDH1*-mutant clone with elevation of 2-HG at relapse (single-cell DNA-seq, individual patient)**



"Isoform Switching"

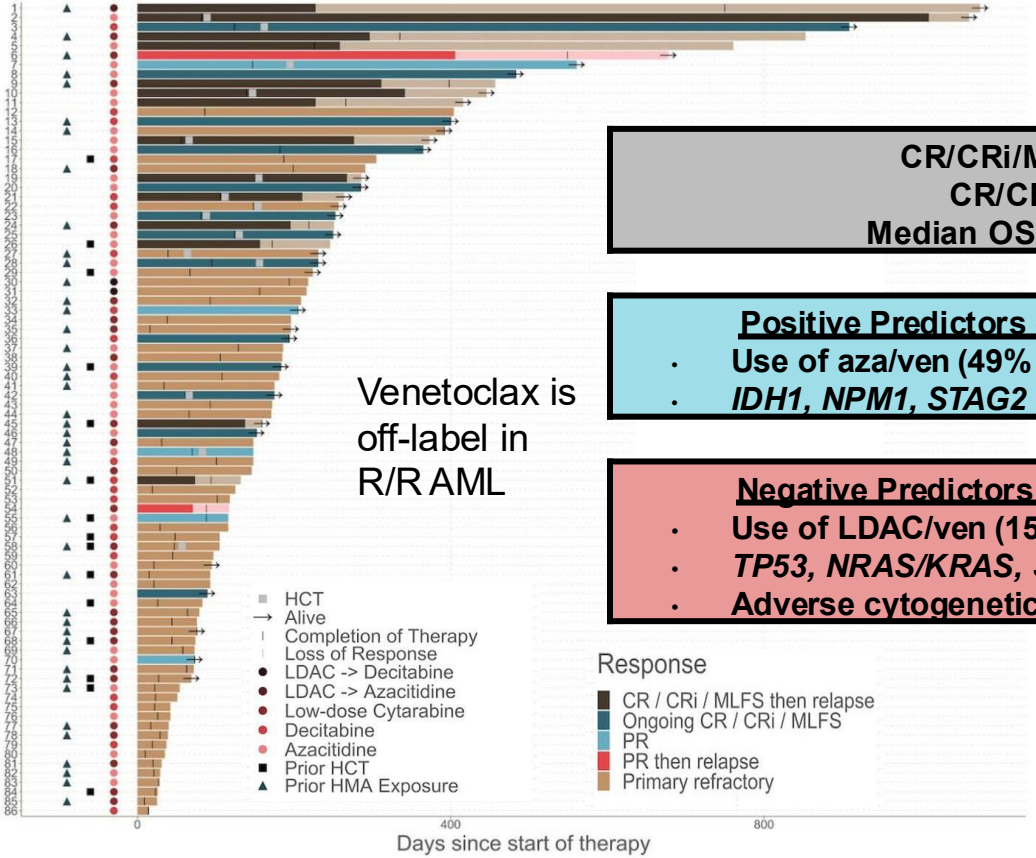


Activated Signaling / Proliferation Pathways
(FLT3-ITD, K/NRAS, PTPN11)

Quek L, et al. Nat Med. 2018;24(8):1167-1177. Intlekofer AM, et al. *Nature*. 2018;559(7712):125-129. Harding JJ, et al. *Cancer Discov*. 2018;8(12):1540-1547. Choe S, et al. *Blood Adv*. 2020;4(9):1894-1905.

Data for Off-Label Use of Venetoclax in R/R AML

Clinical and Molecular Predictors of Response and Survival following Venetoclax Therapy in R/R AML



Venetoclax is off-label in R/R AML

CR/CRi/MLFS = 31%
CR/CRi = 24%
Median OS = 6.1 months

Positive Predictors of Response/Survival:

- **Use of aza/ven (49% ORR) (ORR and OS)**
- ***IDH1, NPM1, STAG2* mutation**

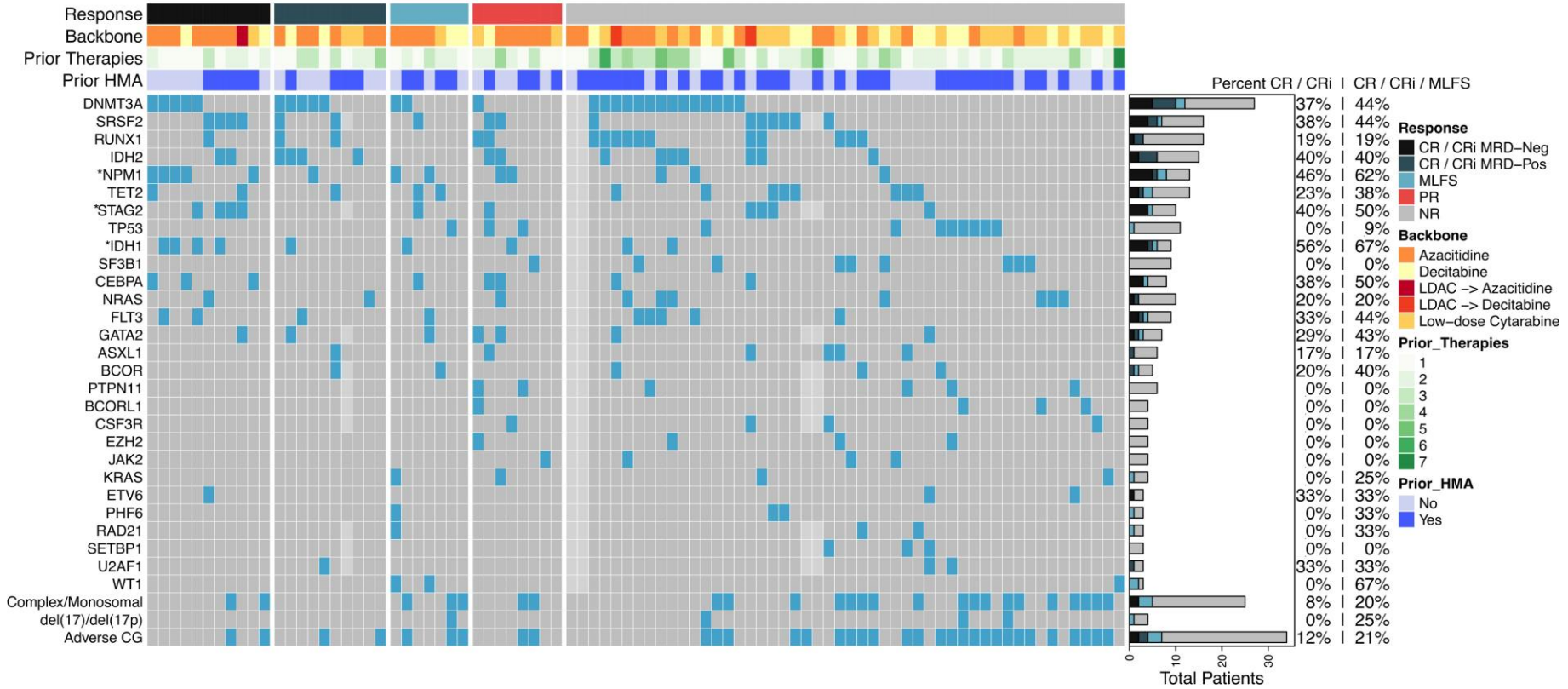
Negative Predictors of Response/Survival:

- **Use of LDAC/ven (15% ORR) (ORR and OS)**
- ***TP53, NRAS/KRAS, SF3B1, EZH2* mutation (OS)**
- **Adverse cytogenetics (ORR and OS)**

LDAC = low-dose cytarabine.
Stahl M, et al. *Blood Adv.* 2021;5(5):1552-1564.

Great Debates Hematologic Malignancies
from Lymphoma · Leukemia & Myeloma Congress

Oncoprint of Responses to Ven Combos in R/R AML



CG = cytogenetics.

Stahl M, et al. *Blood Adv.* 2021;5(5):1552-1564.

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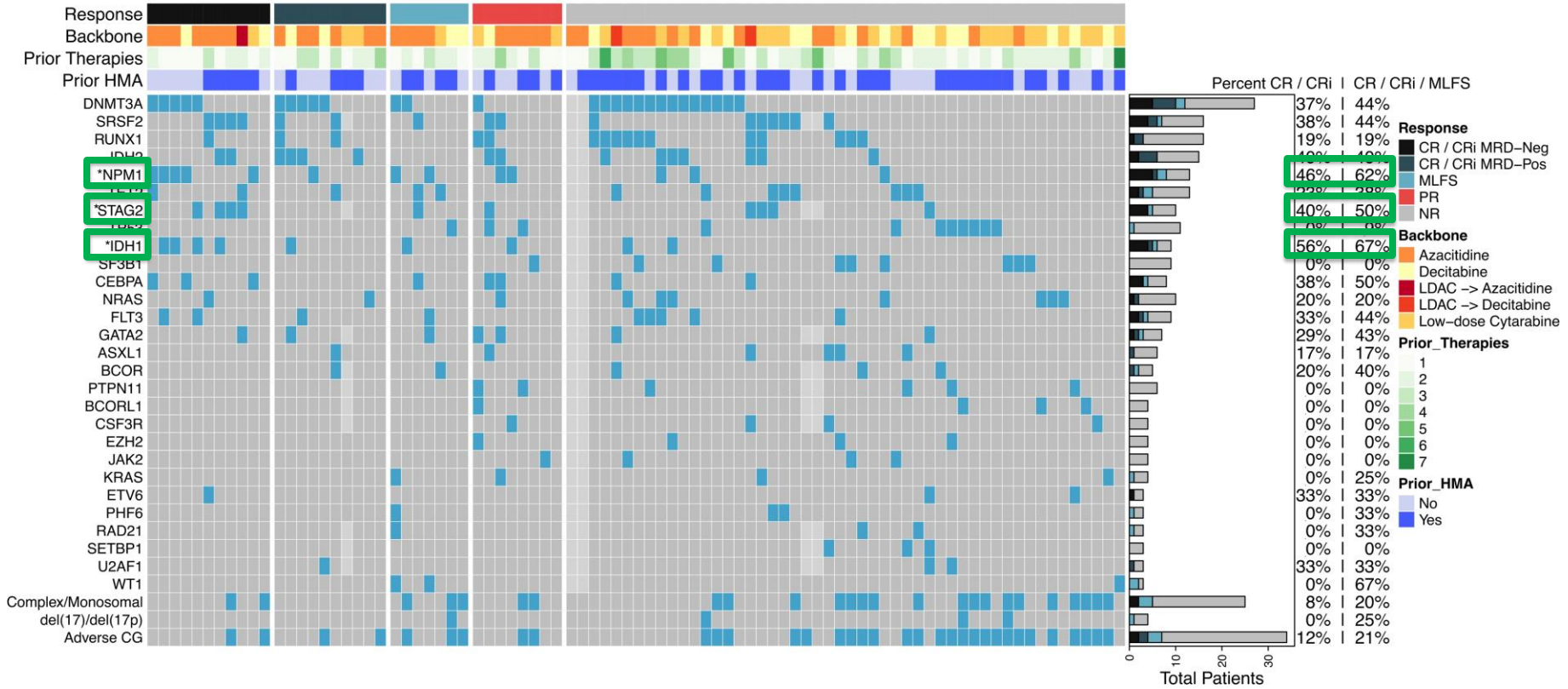
Oncoprint of Responses to Ven Combos in R/R AML



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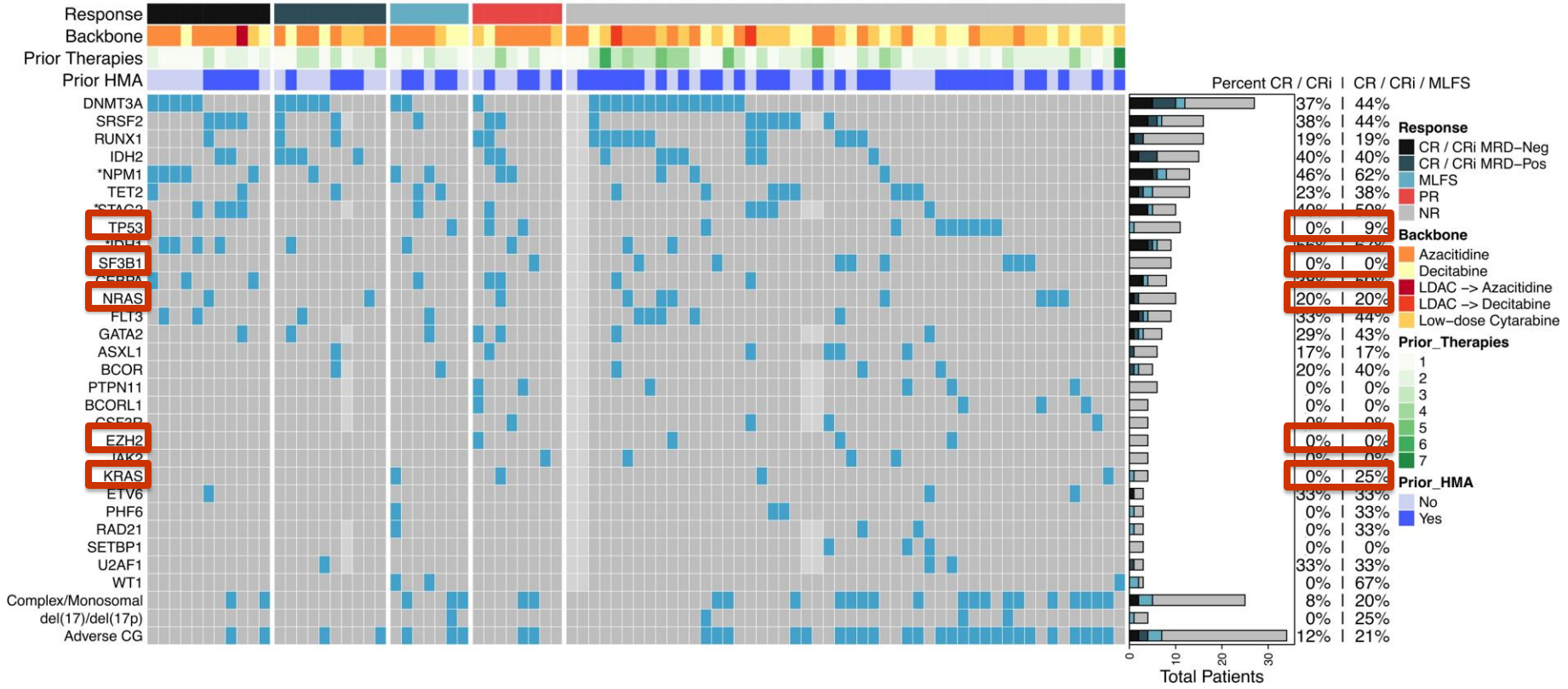
Stahl M, et al. *Blood Adv.* 2021;5(5):1552-1564.

Oncoprint of Responses to Ven Combos in R/R AML



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Stahl M, et al. *Blood Adv.* 2021;5(5):1552-1564.

Key Learning Points

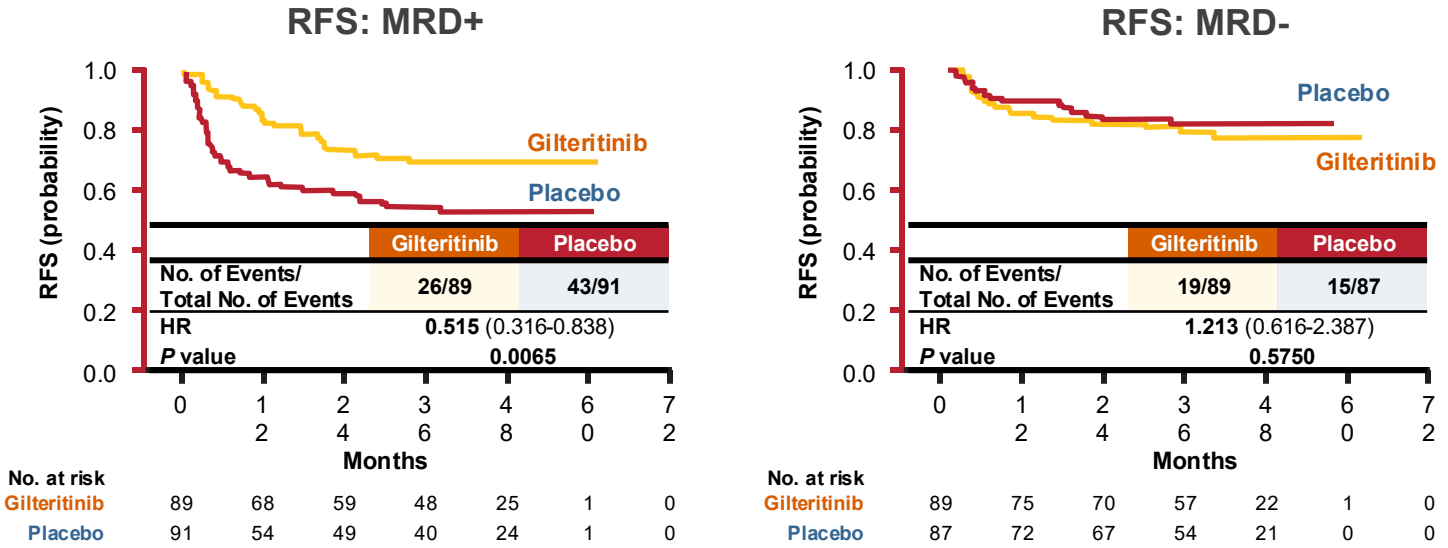
- *FLT3* inhibitor **gilteritinib** approved for R/R AML with *FLT3* mutations—OS benefit in randomized phase III trial against salvage chemotherapy
  - Other FLT3 inhibitors quizartinib and midostaurin currently approved in combination with chemo in new dx AML with *FLT3* mutations
  - *RAS* pathway mutations, loss of *FLT3*, multiple resistance mechanisms to *FLT3* inhibitors
- Menin inhibitor **revumenib** approved for R/R AML with *KMT2A* translocation
  - Other menin inhibitors promising including ziftomenib, bleximenib, enzomenib
  - Menin inhibitors also active against AML with *NPM1*, and other subtypes
  - Differentiation syndrome: expected side effect for menin inhibitors—manageable with early recognition and steroids; QT prolongation noted with revumenib
  - *MEN1* point mutations: resistance mechanisms to menin inhibition
- *IDH1* inhibitor **ivosidenib** and **olutasidenib** approved for R/R AML with *IDH1* mutation; *IDH2* inhibitor **enasidenib** approved in R/R AML with *IDH2* mutation
  - Olutasidenib has data for response post-venetoclax
  - RTK pathway mutations among resistance mechanisms to *IDH1/2* inhibition
- Consider off-label azacitidine + venetoclax in R/R AML if no prior veneotclax—responses vary significantly based on molecular features
- Targeted therapy not curative in R/R AML unless as bridge to allo
  - Multiple mechanisms of resistance to targeted therapy in R/R AML
- Branching patterns of clonal evolution on single-cell DNA sequencing may indicate greater clonal diversity and higher likelihood of therapeutic resistance
- IDH differentiation syndrome, an adverse event associated with olutasidenib, requires immediate intervention per clinical trial data
- Based on current guidelines and data, gilteritinib is the most appropriate agent to use for patients with R/R, FLT3-ITD mutated AML

RTK = receptor tyrosine kinase.

Future Directions in R/R AML

Targeting MRD to prevent R/R AML (*FLT3* inhibitors, menin inhib + ven)
Combination therapy (menin inhibitors + *FLT3* inhibitors)
Targeting novel therapeutic vulnerabilities (-7/del(7q))
Personalized cellular immunotherapy in splicing factor mutant AML

BMT-CTN 1506 (MORPHO): Gilteritinib Maintenance Improves Post-Transplant RFS Specifically for *FLT3*-ITD MRD+ Pre- or Post-Transplant



Gilteritinib shows a clear benefit for the 50% of patients with detectable MRD either before or after HCT, compared to those without detectable MRD.

RFS = relapse-free survival; HCT = hemopoietic cell transplantation.

Levis MJ, et al. *J Clin Oncol*. 2024;42(15):1766-1775.

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Clinical Trial to Eradicate MRD

A Multi-Site Break Through Cancer Trial: Phase II Study Investigating Dual Inhibition of BCL2 and Menin in AML MRD Using the Combination of Venetoclax and Revumenib (NCT06284486) *FDA/IRB approved* and *opening to accrual*

- AML MRD
- *KMT2Ar*, *NUP98r* or *NPM1mt*
- Age >12

→ Central MRD by Flow →

Phase I (up to 12 patients)
Revumenib PO Q12h (dose escalation)
+ Venetoclax 400 mg PO D1-D14
of each cycle; 1 cycle = 28 days

↓

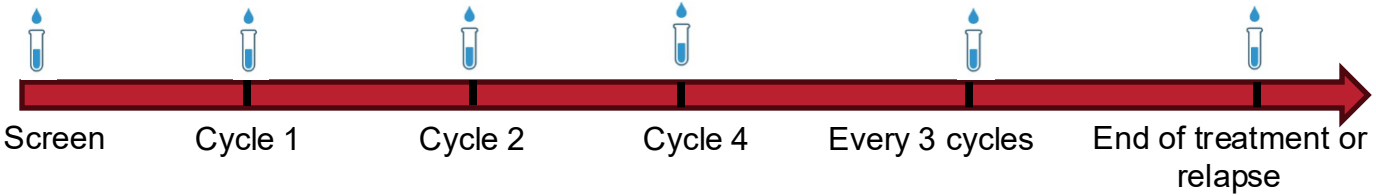
Phase II (up to 14 patients)
Revumenib PO Q12h (RP2D)
+ Venetoclax 400 mg PO D1-D14
of each cycle; 1 cycle = 28 days

→ Rate of MRD Clearance (Primary Endpoint) →

If response, therapy until progression, toxicity, or withdrawal of consent

If transplant, maintenance for up to 2 years

Sample collection to improve identification + understanding of MRD



IRB = institutional review board.
ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated June 12, 2025. https://clinicaltrials.gov/study/NCT06284486

Break Through Cancer
Ghayas Issa (MDACC) **Alex Ambinder (JHMI)**
Jacqueline Garcia (DFCI) **Aaron Goldberg (MSKCC)**

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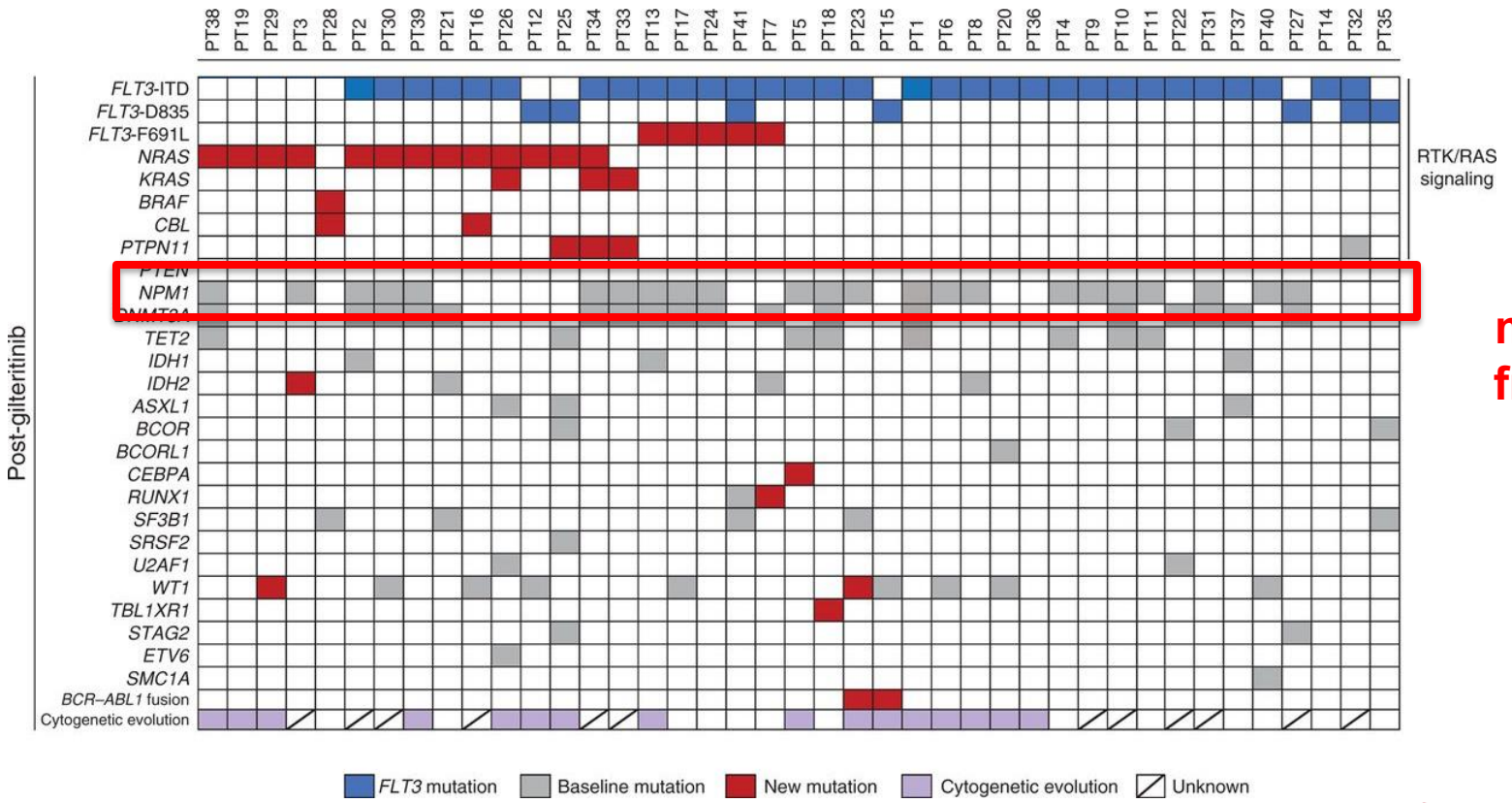
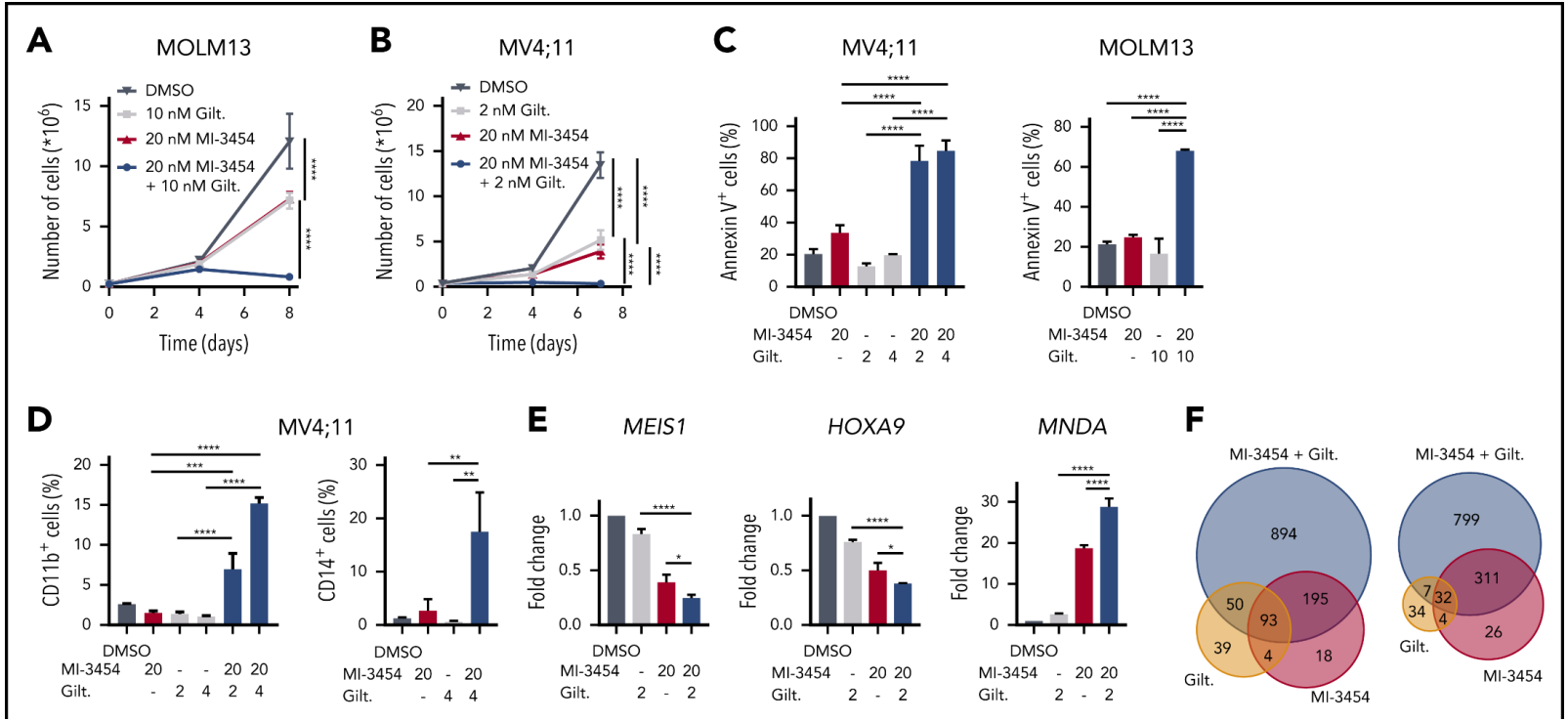
Multiple Mechanisms of Gilteritinib Resistance



NPM1 mutations frequently persist

McMahon CM, et al. *Cancer Discov*. 2019;9(8):1050-1063.

Combinatorial Treatment with Menin and *FLT3* Inhibitors Induces Complete Remission in AML Models with Activating *FLT3* Mutations



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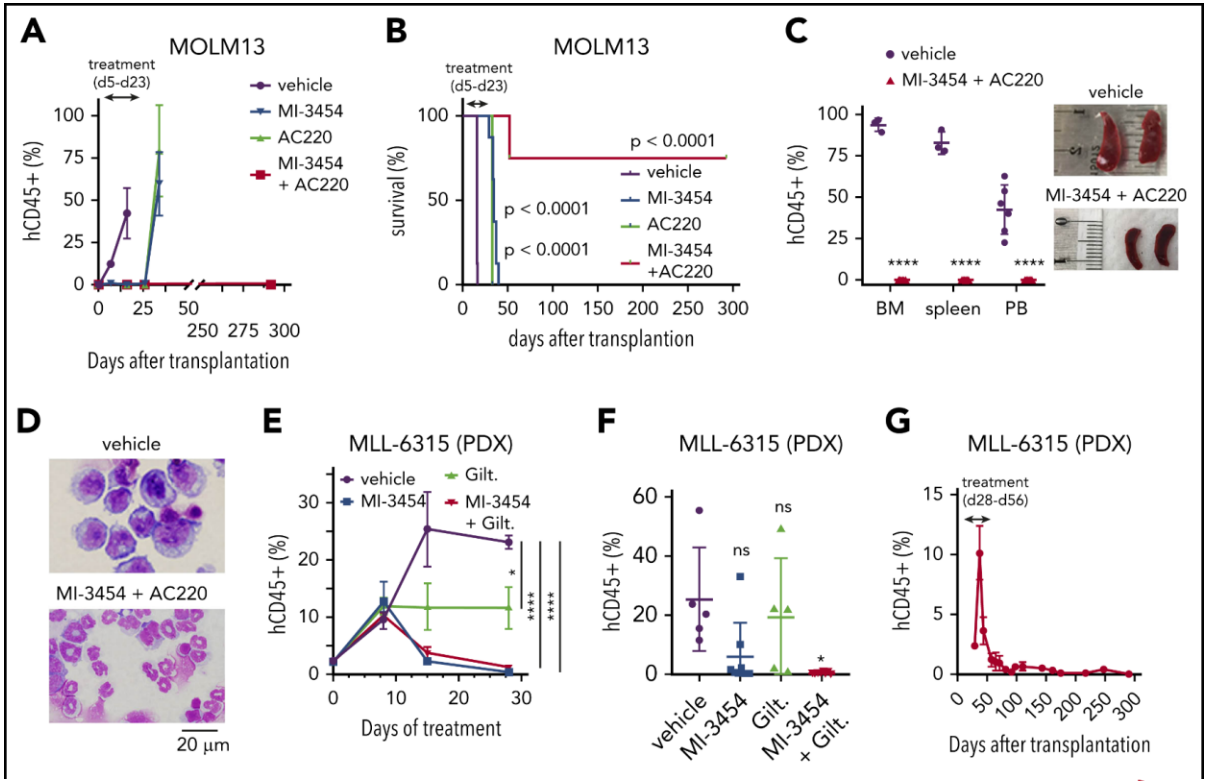
Miao H, et al. *Blood*. 2020;136(25):2958-2963.

Combinatorial Treatment with Menin and *FLT3* Inhibitors Induces Complete Remission in AML Models with Activating *FLT3* mutations



PDX = patient-derived xenograft.

Miao H, et al. *Blood*. 2020;136(25):2958-2963.

KOMET-008: A Phase 1 Study to Determine the Safety and Tolerability of Ziftomenib Combinations for the Treatment of *KMT2A*-Rearranged or *NPM1*-Mutant Relapsed/ Refractory Acute Myeloid Leukemia

Aaron D. Goldberg,[1] Daniel Corum,[2] Julie Ahsan,[2] Kun Nie,[2] Tom Kozlek,[2] Mollie Leoni,[2] and Stephen Dale[2]

[1]Memorial Sloan Kettering Cancer Center, New York City, NY; [2]Kura Oncology, Inc., Boston, MA.

Goldberg AD, et al. *Blood*. 2023;142(Suppl 1):1553.

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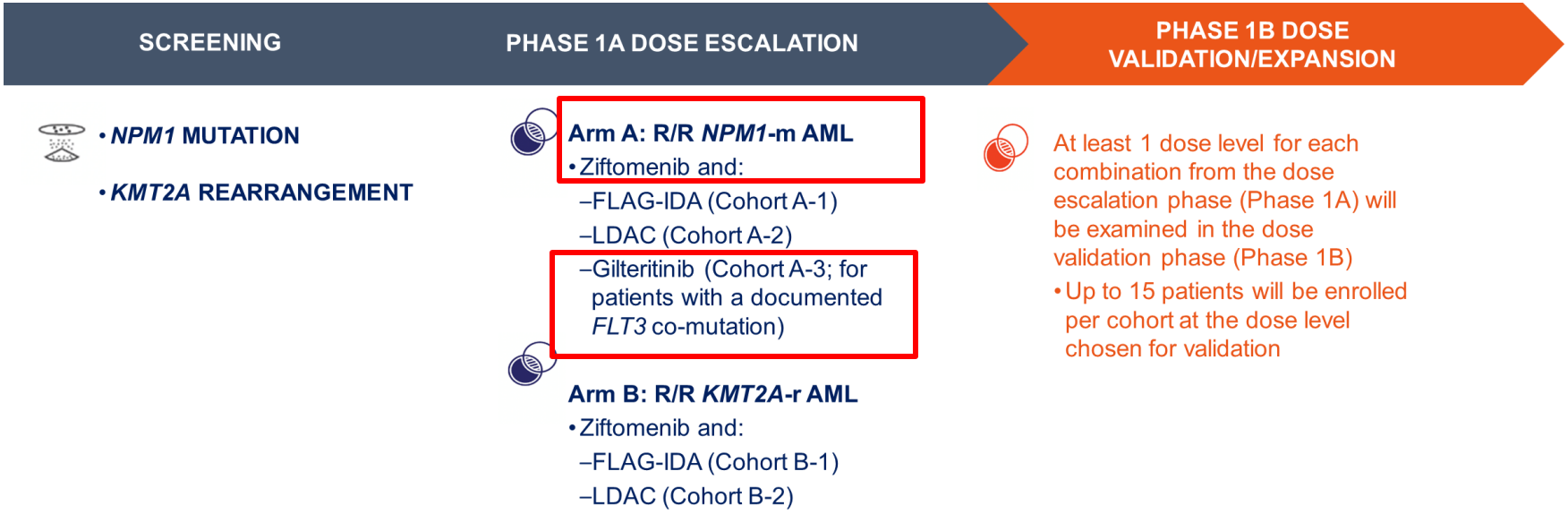
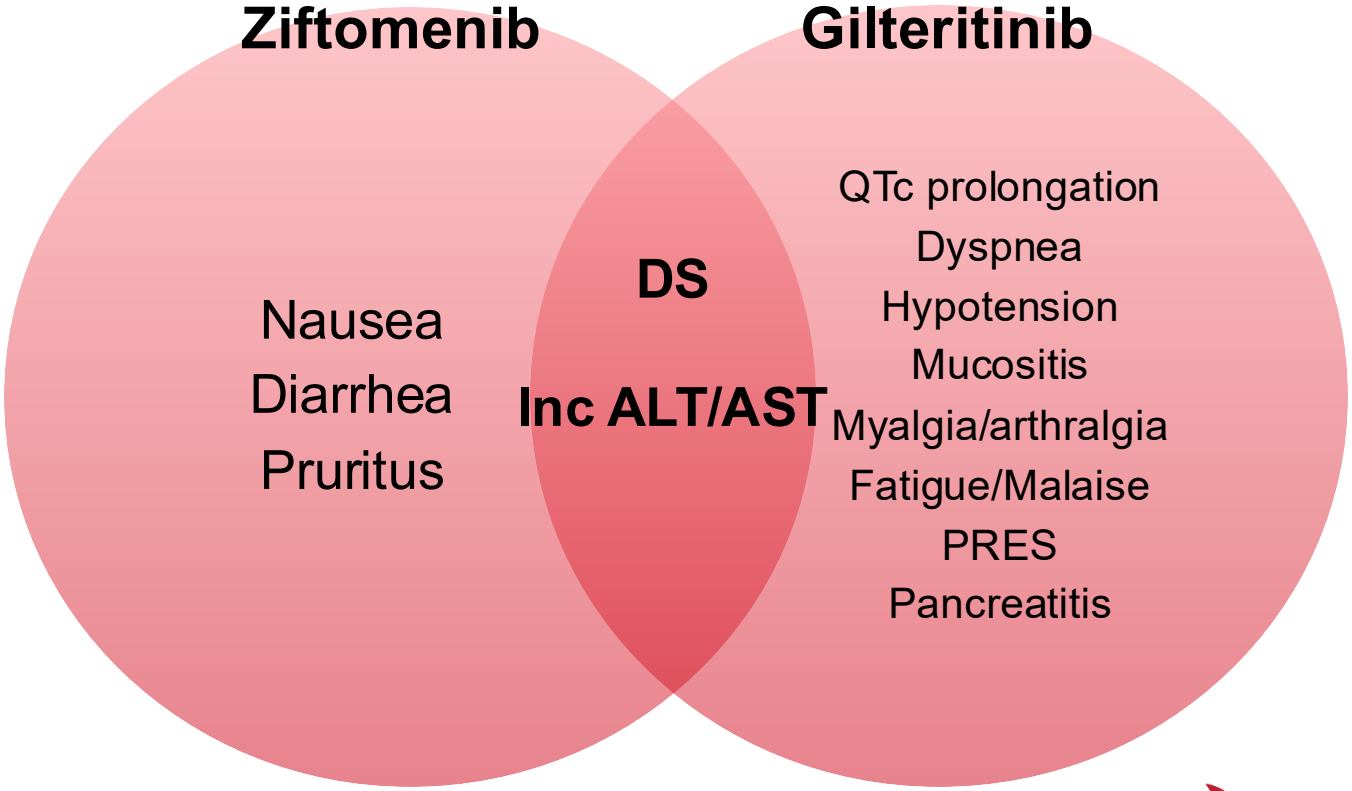
KOMET-008 Study Design



Goldberg AD, et al. *Blood*. 2023;142(Suppl 1):1553.

Toxicities of Ziftomenib and Gilteritinib



ALT = alanine transaminase; AST = aspartate transaminase; PRES = posterior reversible encephalopathy syndrome.

Summary of Menin Inhibitor Combinations

	Menin Inhibitor Combination	N#	ORR	CR/CRh	Source
R/R AML	SAVE (SNDX-5613+ASTX+ven)^	33	82% (n=27)	48% (n=16)	Issa, ASH 2024
	FA+revumenib#	27	52% (n=14)	22% (n=6)	Shukla, EHA 2024
	Aza+ven+bleximenib#	34	79% (n=27)	24% (n=8)	Wei, EHA 2024
	Aza+ven+ziftomenib*	39	56% (n=22)	31% (n=12)	Fathi, ASH 2024
	Ziftomenib + gilteritinib				Ongoing
Frontline AML	7+3+ziftomenib	46	91% (n=42)	91% (n=42)	Zeidan, ASH 2024
	7+3+bleximenib#	21	95% (n=20)	81% (n=17)	Recher, ASH 2024
	Beat AML (aza+ven+revumenib)	26	92% (n=24)~	77% (n=20)	Zeidner, EHA 2024

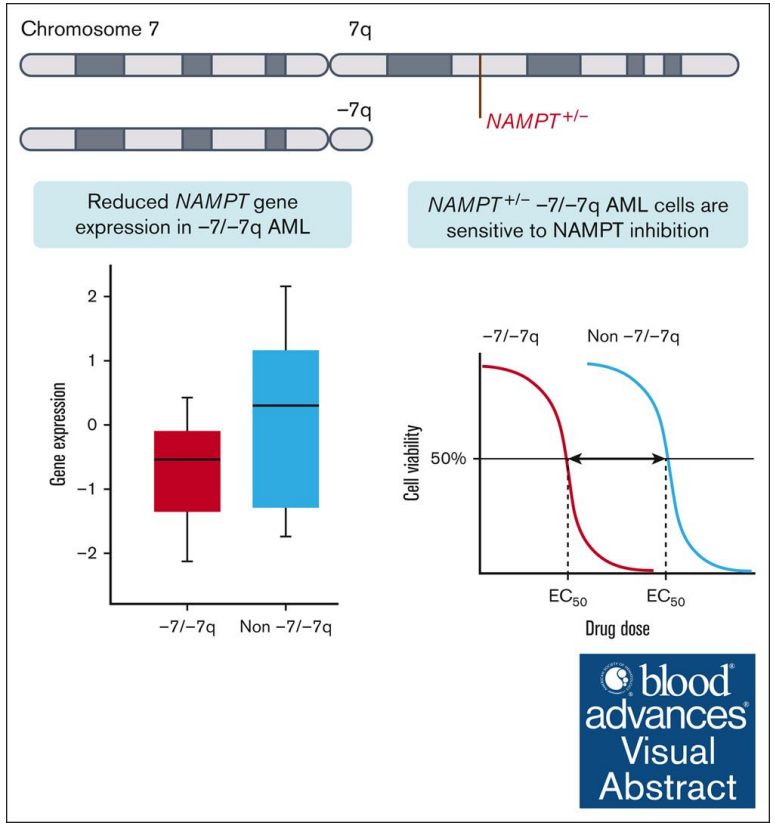
Revumenib (previously known as SNDX-5613)

#Relapsed or refractory acute leukemia, regardless of prior lines of therapy. SAVE and FA + revumenib include myeloid MPAL, allow EMD, KMT2Ar, NPM1mt or NUP98r. FA + revumenib allowed any acute leukemia. Ziftomenib and JNJ-75276617 included only AML, KMT2Ar or NPM1mt. SAVE age > 12; FA + revumenib age >30 days. ^On SAVE, all patients treated were considered efficacy-evaluable regardless of dose level. *Ziftomenib results for menin inhibitor-naïve. #Aza + Ven + JNJ-75276617: R/R 60 patients received combo (safety dataset); 34 patients were efficacy evaluable at dose levels ≥50 mg BID and completed cycle 1 (efficacy dataset). In newly diagnosed cohort, 28 pts dosed, 21 pts included in efficacy analysis (50 mg BID, and 1 disease evaluation). ~Beat AML: Analysis includes those who completed 1 cycle, 2 pts excluded from denominator of efficacy (24 pts not 26), 1 died of sepsis, and 1 went to hospice. 22 of 24 pts MRD neg.

ASTX = cedazuridine, decitabine

Slide courtesy Issa G. Unpublished (review in preparation: Issa, Cai, Bataller, Kantarjian, Stein)

Monosomy 7/del(7q) Causes Sensitivity to Inhibitors of Nicotinamide Phosphoribosyltransferase (NAMPT) in Acute Myeloid Leukemia

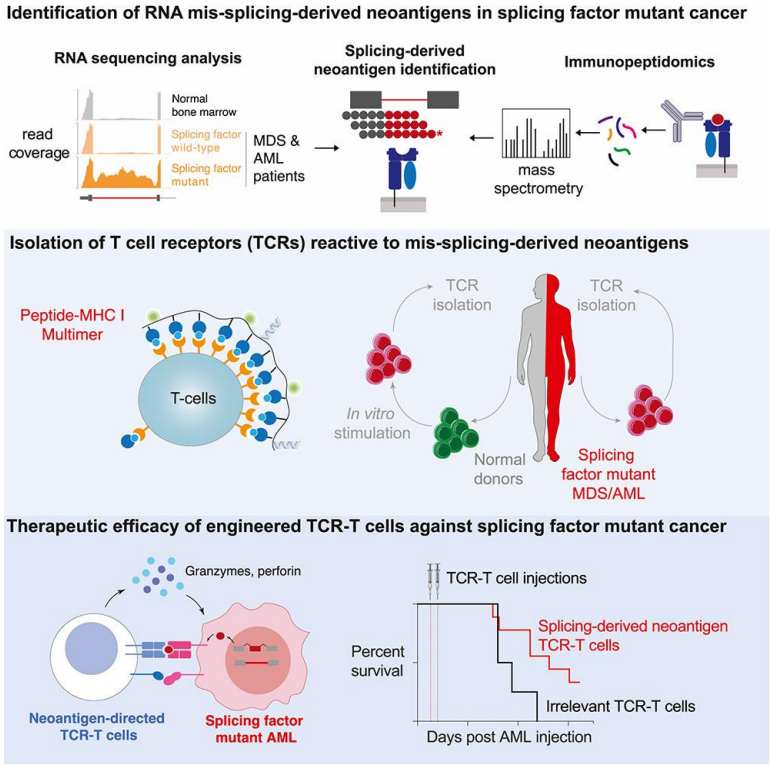


- NAMPT is the rate-limiting enzyme in the nicotinamide adenine dinucleotide (NAD) salvage pathway
- -7/-7q AML cells are highly sensitive to NAMPT inhibition; *NAMPT* gene is located at 7q22.3
- Deletion of 1 copy due to -7/-7q results in *NAMPT* haploinsufficiency, leading to reduced expression and targetable therapeutic vulnerability to NAMPT inhibition
- Hyperbolic NAMPT inhibitor RPT1G currently in healthy volunteer phase 1: plans for MDS/AML phase 1

Eldfors S, et al. *Blood*. 2024;8(7):1621-1633.

Engineered TCR T-Cell Therapy in Splicing Factor Mutant AML

- Oncogenic splicing factor mutations generate recurrent RNA-splicing-derived neoantigens
- T cells reactive to splicing-derived neoantigens are dysfunctional in leukemia patients
- Panels of TCRs targeting splicing-derived neoantigens can be generated
- Adoptive transfer of TCR-engineered T cells mediates specific tumor control *in vivo*



TCR = T cell receptor; MHC = major histocompatibility complex.

Kim WJ, et al. *Cell*. 2025 April 21:S0092-8674(25)00399-X [Epub ahead of print].

Key Learning Points

- Clinical trials are critical for progress in R/R AML
- Critically important to **evaluate for targetable mutations at diagnosis and again at the time point of relapsed or refractory disease**
  - *FLT3*-ITD, *FLT3*-TKD, *IDH1, IDH2, NPM1, KMT2A* rearrangement
- FDA-approved targeted therapy options in R/R AML: **gilteritinib, ivosidenib, olutasidenib, enasidenib, revumenib**
- Consider goals of treatment and potential role for allogeneic SCT—targeted monotherapy is not curative but can be a bridge to curative allogeneic SCT
- Targeting MRD may prevent AML relapse (gilteritinib post-transplant for MRD+)
- Combination therapies have significant rationale—targeting multiple mechanisms to overcome therapeutic resistance—phase 1 trials ongoing
  - Ziftomenib + gilteritinib for R/R AML with *NPM1/FLT3* mutations
  - Ziftomenib + FLAG-IDA for R/R AML with *NPM1* or *KMT2Ar*
  - Multiple other combination trials ongoing
- The 2025 SAVE Trial demonstrated that revumenib + decitabine/cedazuridine + venetoclax demonstrated an 82% overall response rate in patients with R/R AML harboring *NPM1mt*, *KMT2Ar*, and *NUP98r* genetic alterations
- Future: NAMPT inhibition represents a potential strategy to target -7/del(7q)
- Future: personalized TCR T cell therapy for AML with splicing factor mutations

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Susan DeWolf
Mark Geyer
Tamanna Haque
Prioty Islam
Michael Mauro
Varun Narendra
Jae Park
Lindsey Roeker
David Scheinberg
Rob Stanley
Meghan Thompson
Xiaodi Wu
Xin Wang
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MSKCC Leukemia

Break Through Cancer
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Naval Daver, MDACC
Farhad Ravandi, MDACC
Jacqueline Garcia, DFCI
Richard Stone, DFCI
Alex Ambinder, Johns Hopkins

Wenbin Xiao, Mikhail Roshal, Maria Arcila, Yanming Zhang, Filiz Sen, Ahmet Dogan
MSKCC Dept of Pathology

Andriy Derkach, Sean Devlin
Elli Papaemmanuil
Noushin Rahnamay Farnoud
MSKCC Biostatistics

Sergio Giralt, Miguel Perales, Roni Tamari
MSKCC BMT Service

AbbVie, Aprea, Aptose, AROG, Celularity, Daiichi-Sankyo, Kura, Pfizer, Prelude

Conquer Cancer Foundation

American Society of Hematology

Break Through Cancer

Memorial Sloan Kettering Cancer Center