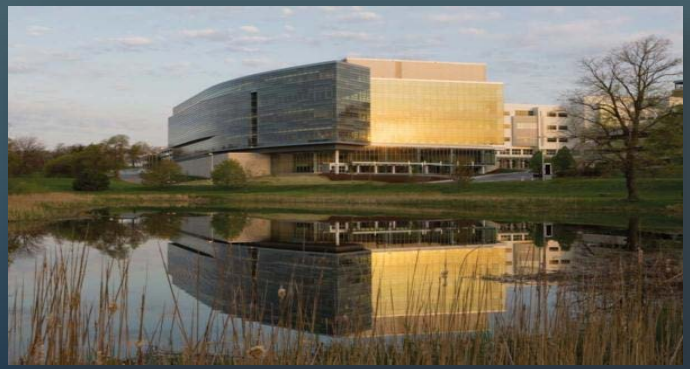
Updates in Relapsed/Refractory AML

Guru Subramanian Guru Murthy MD, MS
Associate Professor
Division of Hematology-Oncology



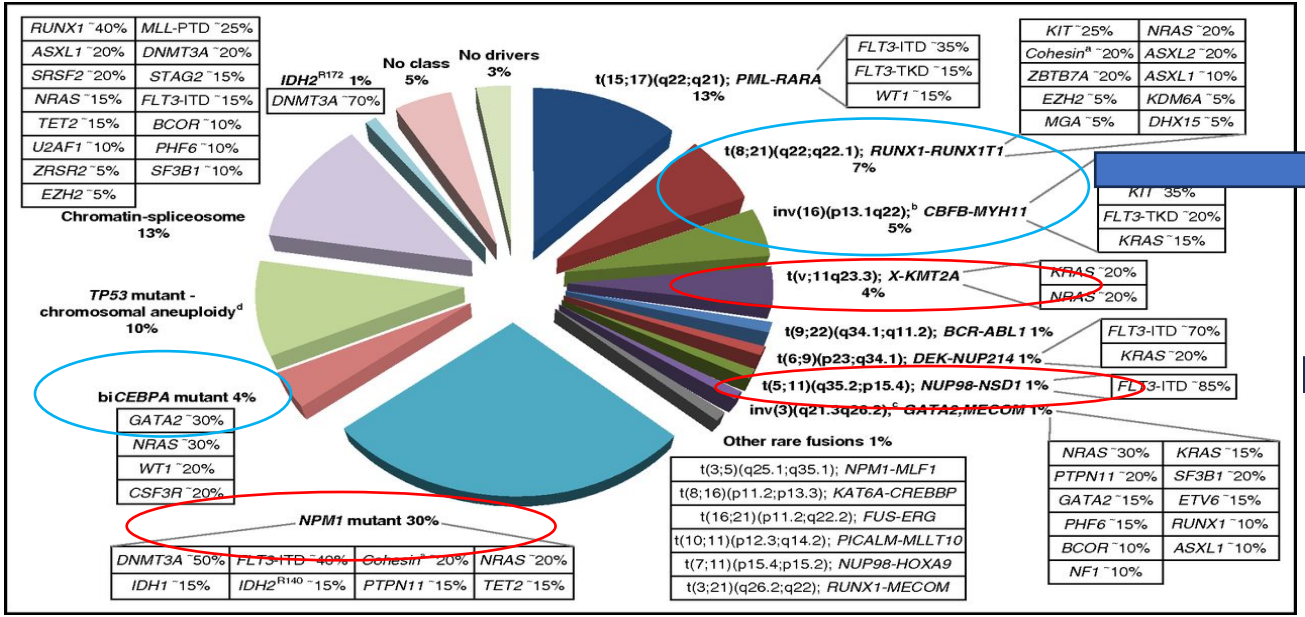
knowledge changing life

MEDICAL COLLEGE OF WISCONSIN

Disclosures

- Advisory board – Astra Zeneca, BMS, BeiGene, Pfizer, Daiichi Sankyo, Syndax, Gilead/Kite, Geron
- Speakers' bureau - Amgen

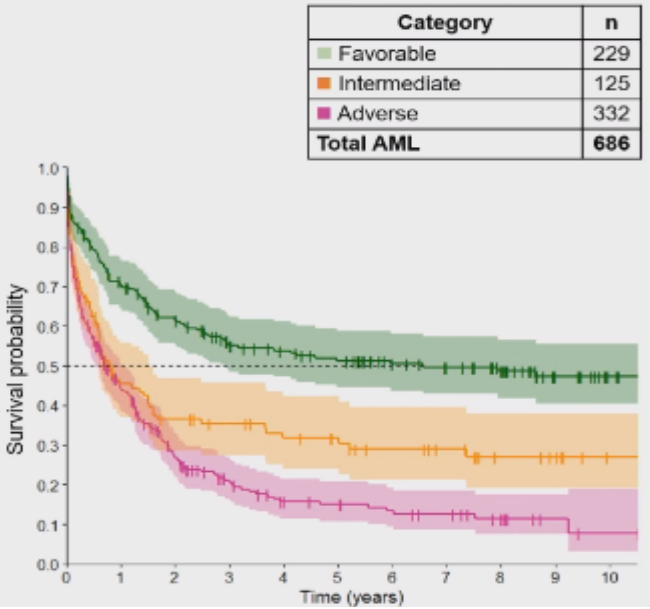
Genomic complexity in AML



Dohner H et al. Blood 2017

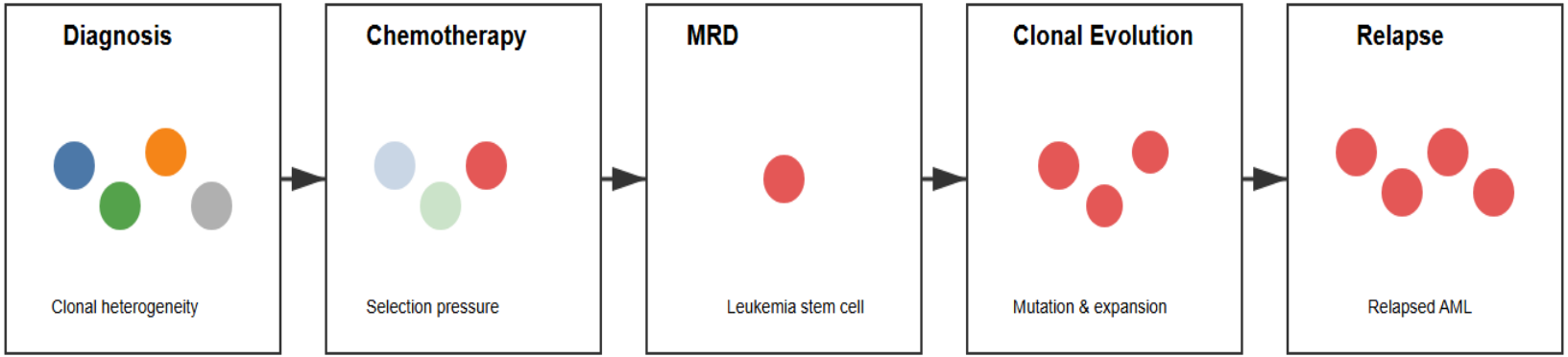
ELN 2022 Risk Stratification

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 • 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;p13)/*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/abnormalities (17p) • Complex karyotype, monosomal karyotype • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2* • Mutated *TP53*



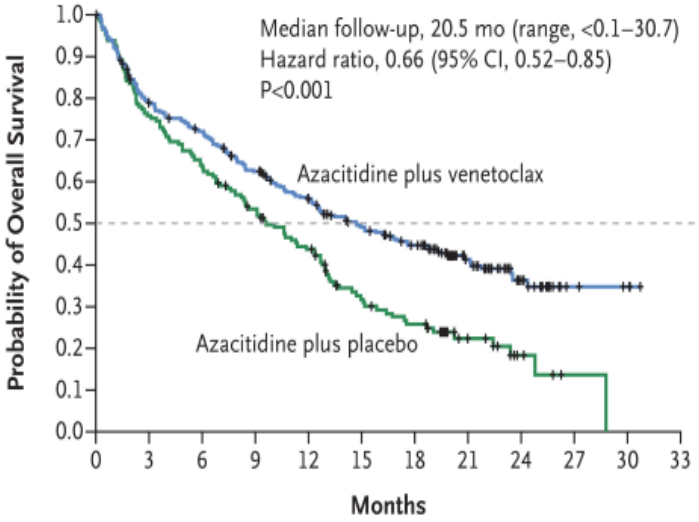
Dohner H et al. Blood 2022
Huber S et al. Leukemia 2023

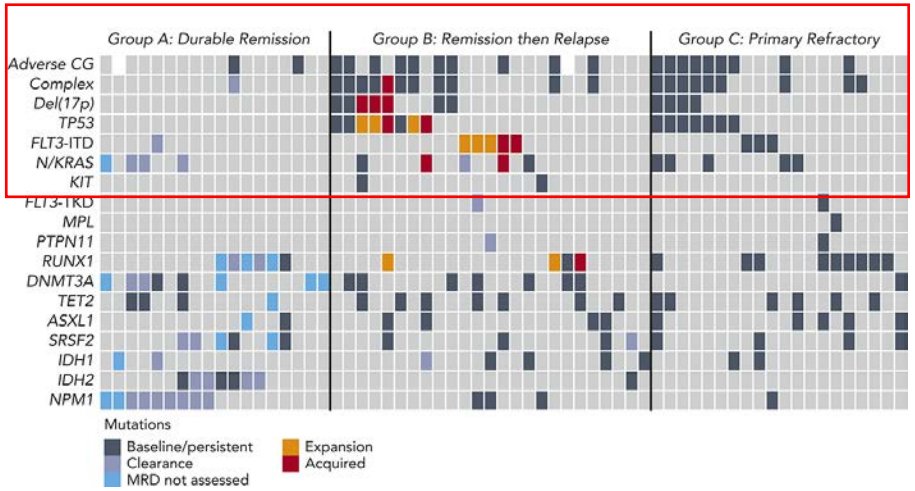
Mechanisms of Relapse in Acute Myeloid Leukemia



- Expansion of previous clones
- Emergence of RAS pathway mutations
- TP53 enrichment
- Loss of targetable clones

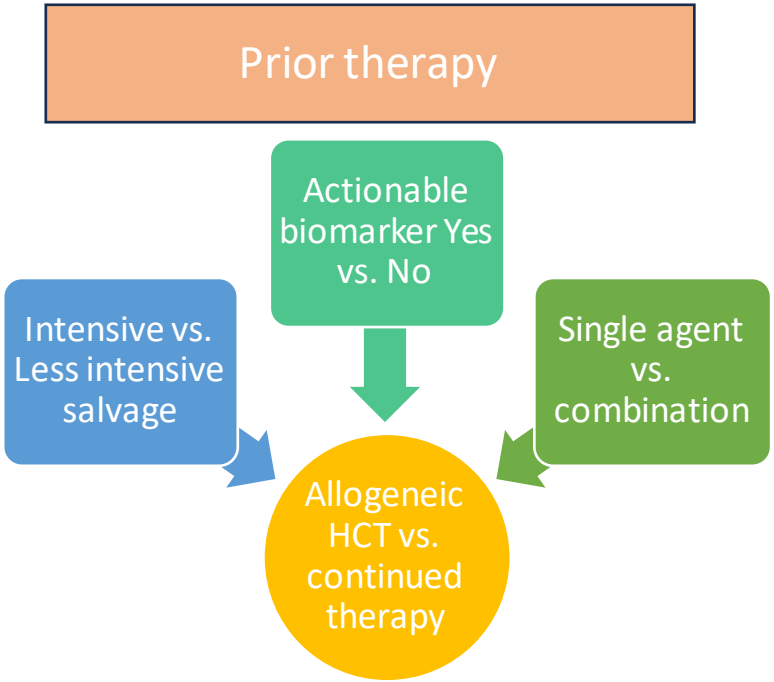
Resistance in the context of Bcl-2 inhibitor exposure





DiNardo CD et al. Blood 2020
DiNardo CD et al. NEJM 2020

Treatment approach



NCCN Guidelines Version 3.2026
Acute Myeloid Leukemia (Age ≥18 years)

THERAPY FOR RELAPSED/REFRACTORY DISEASE[i,yy]

Clinical trial[yy]

Targeted therapy[zz,aaa]:
- Therapy for AML with *FLT3*-ITD mutation
  - Gilteritinib (category 1)
  - HMAs (azacitidine or decitabine) + sorafenib
  - Quizartinib (category 2B)
- Therapy for AML with *FLT3*-TKD mutation
  - Gilteritinib (category 1)
- Therapy for AML with *IDH2* mutation
  - Enasidenib
- Therapy for AML with *IDH1* mutation
  - Ivosidenib
  - Olutasidenib
- Therapy for CD33-positive AML
  - Gemtuzumab ozogamicin
- Therapy for AML with lysine methyltransferase 2A gene (*KMT2A*) rearrangement
  - Revumenib
- Therapy for AML with *NPM1* mutation
  - Revumenib
  - Ziftomenib

Intensive therapy for appropriate patients[bbb,ccc]:
- Cladribine + cytarabine + G-CSF ± (mitoxantrone or idarubicin)
- Cytarabine ± (daunorubicin or idarubicin or mitoxantrone)
- Fludarabine + cytarabine + G-CSF ± idarubicin ± venetoclax[ddd]
- Etoposide + cytarabine ± mitoxantrone
- Clofarabine ± cytarabine ± idarubicin
- CLIA (cladribine + idarubicin + cytarabine) + venetoclax (category 2B)

Less intensive therapy:
- HMAs (azacitidine or decitabine)[t]
- LDAC (category 2B)
- (HMA or LDAC) + venetoclax[t,ddd]

Intensive salvage regimens

British Journal of Haematology, 1997, 99, 939–944

Fludarabine, cytarabine, G-CSF and idarubicin (FLAG-IDA) for the treatment of poor-risk myelodysplastic syndromes and acute myeloid leukaemia

J. E. Parker,[1] A. Pagliuca,[1] A. Mijovic,[1] J. O. Cullis,[1] B. Czepulkowski,[1] S. M. B. Rassam,[2] I. R. Samaratunga,[3] R. Grace,[4] P. A. Gover[4] and G. J. Mufti[1] [1]*Department of Haematological Medicine, King's College School of Medicine and Dentistry, London,* [2]*Queen Mary's Hospital, Sidcup,* [3]*Farnborough Hospital, and* [4]*Eastbourne Hospital*

European Journal of Haematology ISSN 0902-4441

ORIGINAL ARTICLE

Cladribine combined with high doses of arabinoside cytosine, mitoxantrone, and G-CSF (CLAG-M) is a highly effective salvage regimen in patients with refractory and relapsed acute myeloid leukemia of the poor risk: a final report of the Polish Adult Leukemia Group

Agnieszka Wierzbowska[1], Tadeusz Robak[1], Agnieszka Pluta[1], Ewa Wawrzyniak[1], Barbara Cebula[1], Jerzy Hołowiecki[2], Sławomira Kyrcz-Krzemień[2], Sebastian Grosicki[2], Sebastian Giebel[2], Aleksander B. Skotnicki[3], Beata Piątkowska-Jakubas[3], Kazimierz Kuliczkowski[4], Marek Kiełbiński[4], Krystyna Zawilska[5], Janusz Kłoczko[6], Agata Wrzesień-Kuś[1]

Wierzbowska A et al. Eur J Haematol 2008
Parker JE et al. Br J Haematol 1997

Venetoclax + Intensive salvage therapy options

FLAG-Ida-Venetoclax

- 59 patients
- CRc-66%
- OS-12 mon

CLAG-M-Venetoclax

- CR/CRi/MLFS was seen in 11/14 patients
- 3 proceeded to allo-HCT

CLAG-Venetoclax

- CRc- 75.6% (vs. 47.4% with CLAG)
- 1-year OS- 80% vs 57.4%

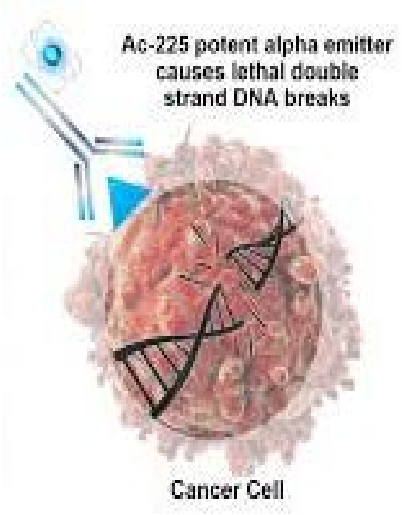
- Myelosupression and increased risk of infections
- Efficacy in prior venetoclax exposed patients is lesser

Raychaudhuri et al. ASH 2024
Yu G et al. ASH 2025
DiNardo CD et al. Leukemia 2025

CLAG-M Lintuzumab

- Lintuzumab-Ac225- Radioconjugate targeting CD33
- Phase I study – 26 patients with R/R AML
- 56.5% prior venetoclax exposed

Factor	Proportion
Response	CRc- 56.5% (62.5% at RP2D) 75% flow MRD negative
TP53 mutated	CRc 50%
Prior Venetoclax	CRc 38.5%
OS	All patients – 7 mon Bridged to allo-HCT – 24 mon



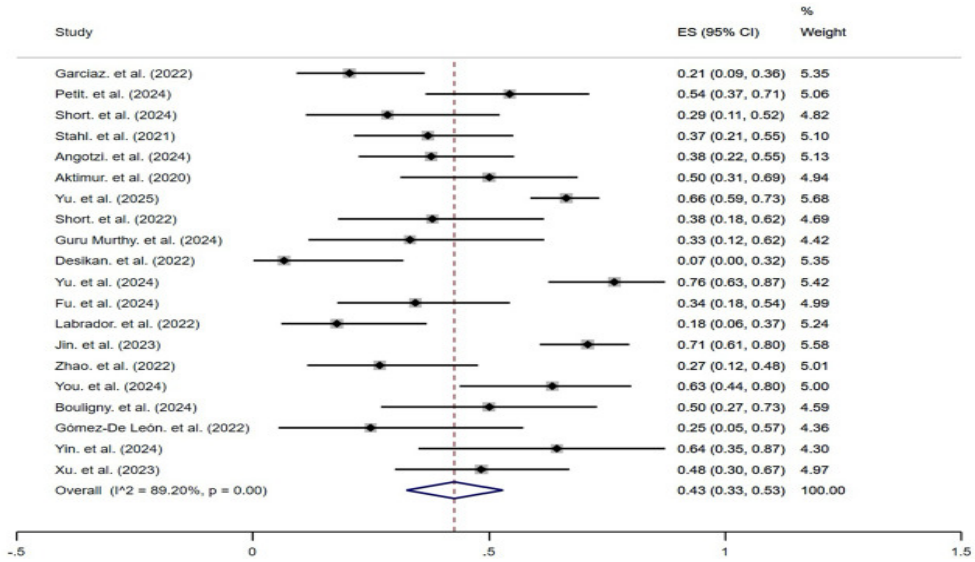
Abedin S, Guru Murthy GS, Atallah E et al. Leukemia 2025

Ideal candidates for intensive salvage therapy

- Age ≤ 75 years
- Good performance status (ECOG score 0, 1)
- No major organ related comorbidities
- Likely plan to bridge with allogeneic HCT when achieving response

Venetoclax-HMA in relapsed/refractory AML

- ORR 30–60%
- CR 20-50%
- No large prospective studies
- Higher response in IDH or NPM1 mutated AML



Cai Q et al. Ann Hematol 2025

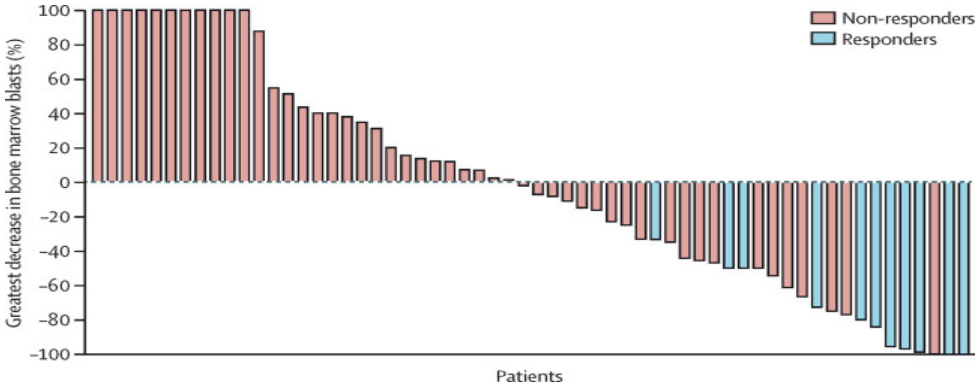
Novel agents in clinical trials

High unmet need for targeted treatment in those without actionable mutations

- ADC
- Bispecific

Pivekimab Sunirine

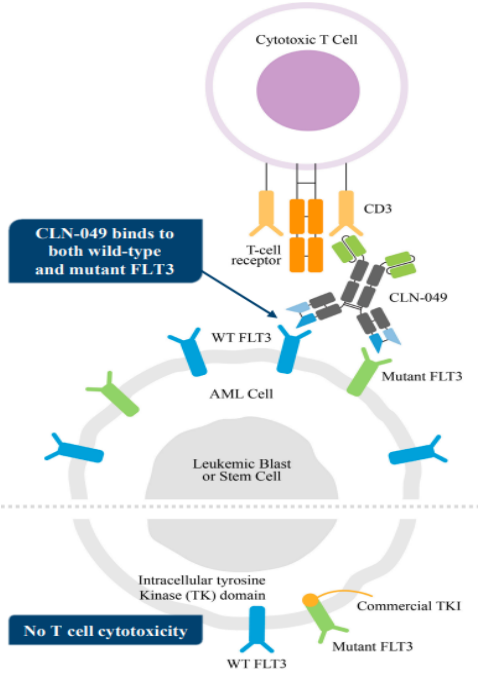
- ADC targeted against **CD123**
- Single arm study in 91 patients with relapsed/refractory AML
- **CRc 12%, 17% CRc at RP2D, MLFS 3%**



Daver N et al. Lancet Oncol 2024

Bispecific T-cell engager - CLN049

- Anti-FLT3 x anti-CD3 bispecific T-cell engager
- 34 patients with R/R AML, regardless of FLT3 mutation
- CR 9%, CRc rate of 30%, ORR of 57%
- Manageable CRS/ICANS profile
- Study ongoing



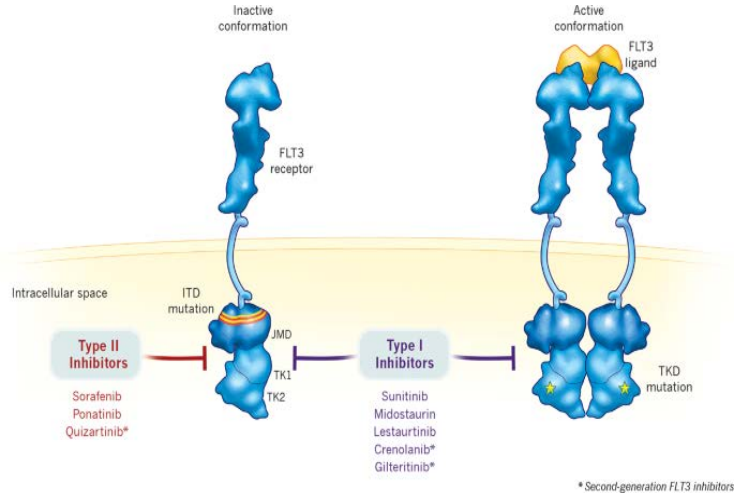
Abdul-Hay M et al. ASH 2025

Targetable Alterations in R/R AML

- FLT3
- IDH1
- IDH2
- NPM1
- KMT2A

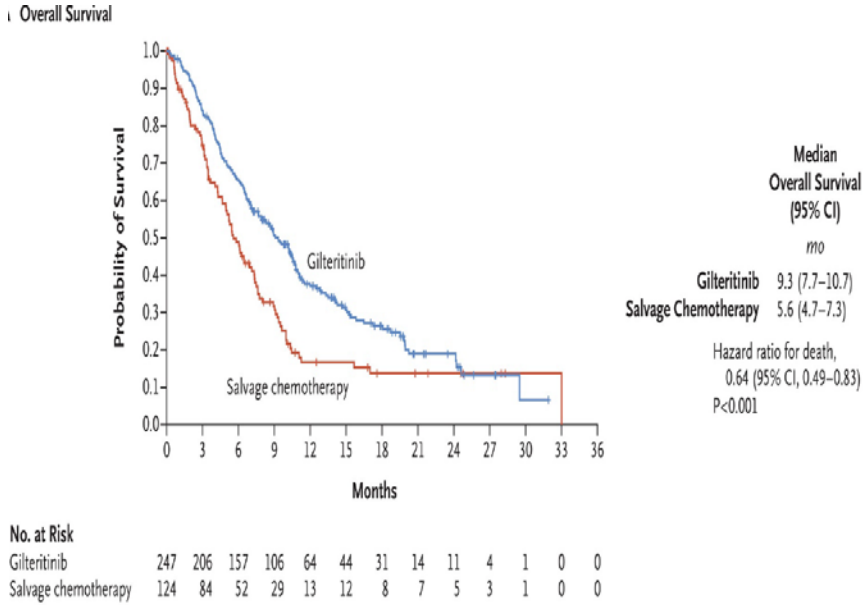
FLT3

- Upto 30% of AML
- Internal Tandem Duplication (ITD) or Tyrosine Kinase Domain (TKD)
- Co-mutation with NPM1 or IDH genes



Gilteritinib- FLT3 inhibitor

- Phase III: Gilteritinib vs Salvage Chemotherapy
- N=247
- Median OS: 9.3 vs 5.6 months
- CR/CRh: 34% vs. 15.3%
- 1-year OS: 37% vs 17%



Perl AE et al. NEJM 2019

Gilteritinib combinations

Gilteritinib-Venetoclax

Phase I study, n=61

- **mCRc -75%** (CR 18%; CRi 4%; CRp 18%, MLFS 36%)
- Median OS 10 mon

Aza-Ven-Gilteritinib

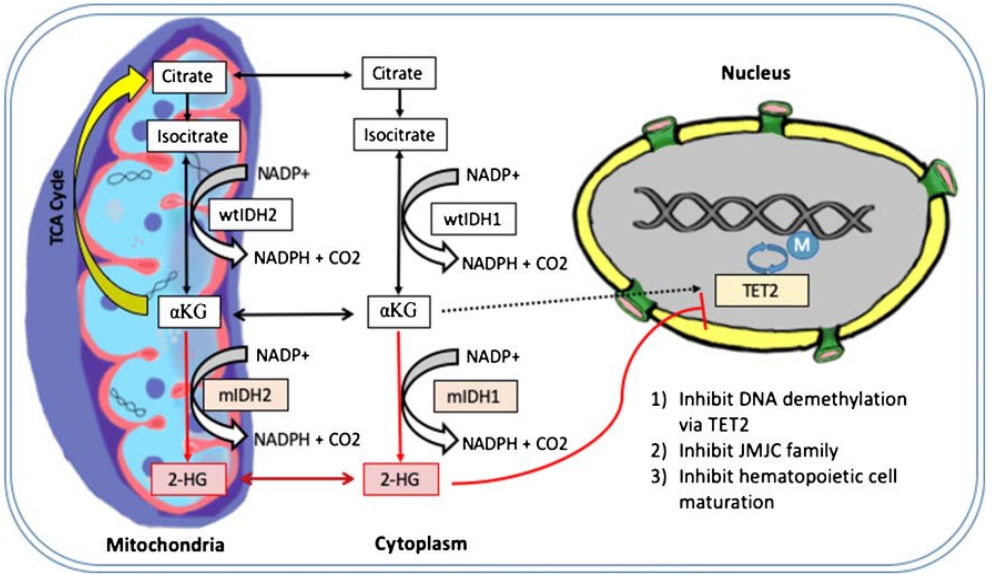
N=22, **ORR- 78%**, CR/CRi 27%; 41% MLFS

Median OS 5.8 mon (10.5 mon in HMA/Ven/Gilteritinib naïve patients)

Short NS et al. JCO 2024
Daver N et al. JCO 2022

IDH mutations in AML

- IDH1 or IDH2 mutation can be seen in upto 10% of AML



IDH1-Mutated Relapse

Ivosidenib – oral inhibitor of IDH1

- CR/CRh ≈30%, CR 21%
- Median OS 8.8 months
- Duration of response 8.2 mon

Olutasidenib – oral inhibitor of IDH1

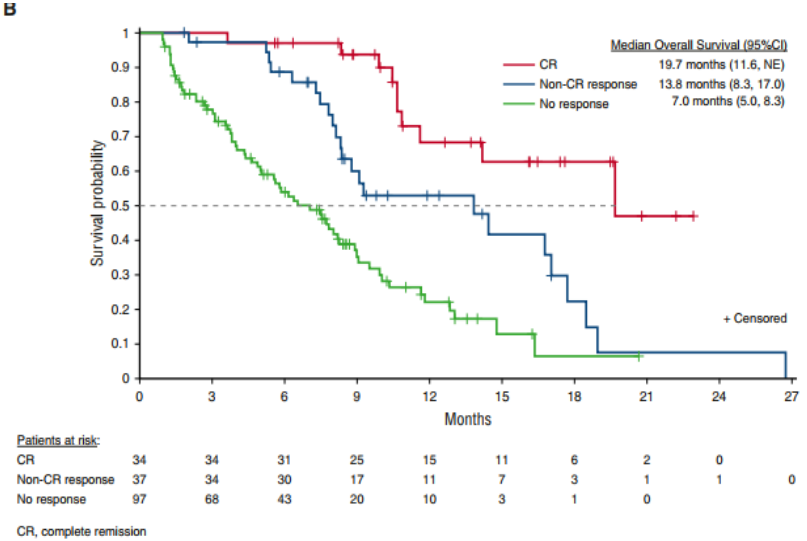
- CR/CRh- 35%
- Median OS 11.6 mon
- Duration of CR/CRh 25.9 months

DiNardo CD et al. NEJM 2018
DeBotton S et al. Blood Adv 2023

IDH2-Mutated Relapse

Enasidenib

- ORR ~40%
- CR ~19%
- Median OS 9.3 months



Stein EM et al. Blood 2017

IDH inhibitor combinations

Ivosidenib combination

- **Ivosidenib-venetoclax +/- azacitidine**
- CRc 63%, median OS 9 mon

Olutasidenib combination

- **Olutasidenib + azacitidine**
- 46% ORR, CR/CRh 31%, median OS 13 mon

Enasidenib combination

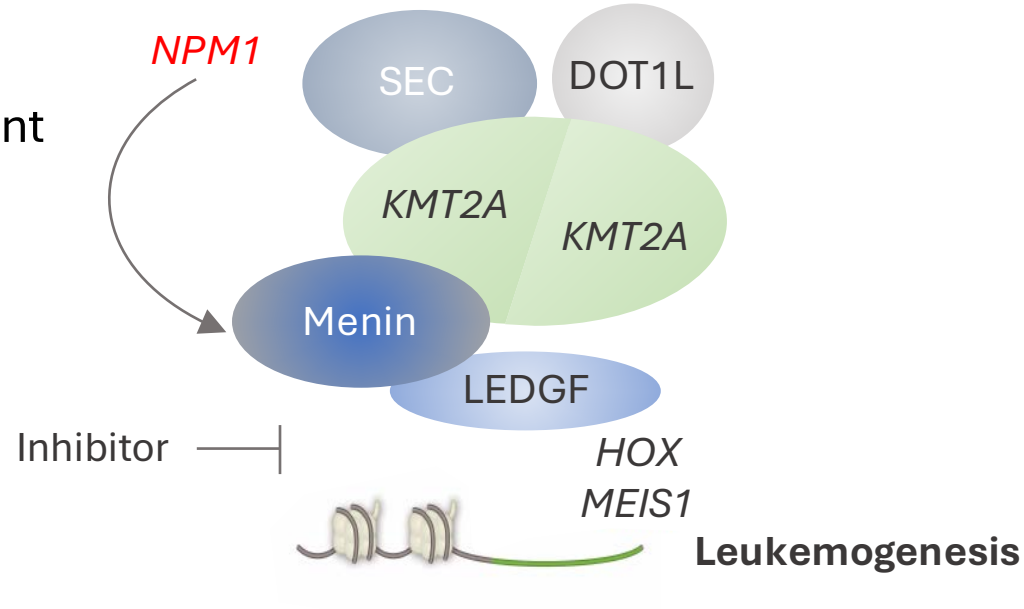
- **Enasidenib-Venetoclax** 62% ORR, 50% CR
- **Enasidenib-Azacitidine** CRc 58%, CR 26%, median OS 6 mon

Myelosupression needs dose modifications

Marvin-Peek J et al. ASH 2024
Lachowiez C et al. Blood Canc Discov 2023
Watts J et al. Lancet Haematol 2023
Cortes J et al. ASH 2024
Richard Carpentier G et al. Lancet Haematol 2025
Venugopal et al. Blood Cancer J 2022

Menin Pathway

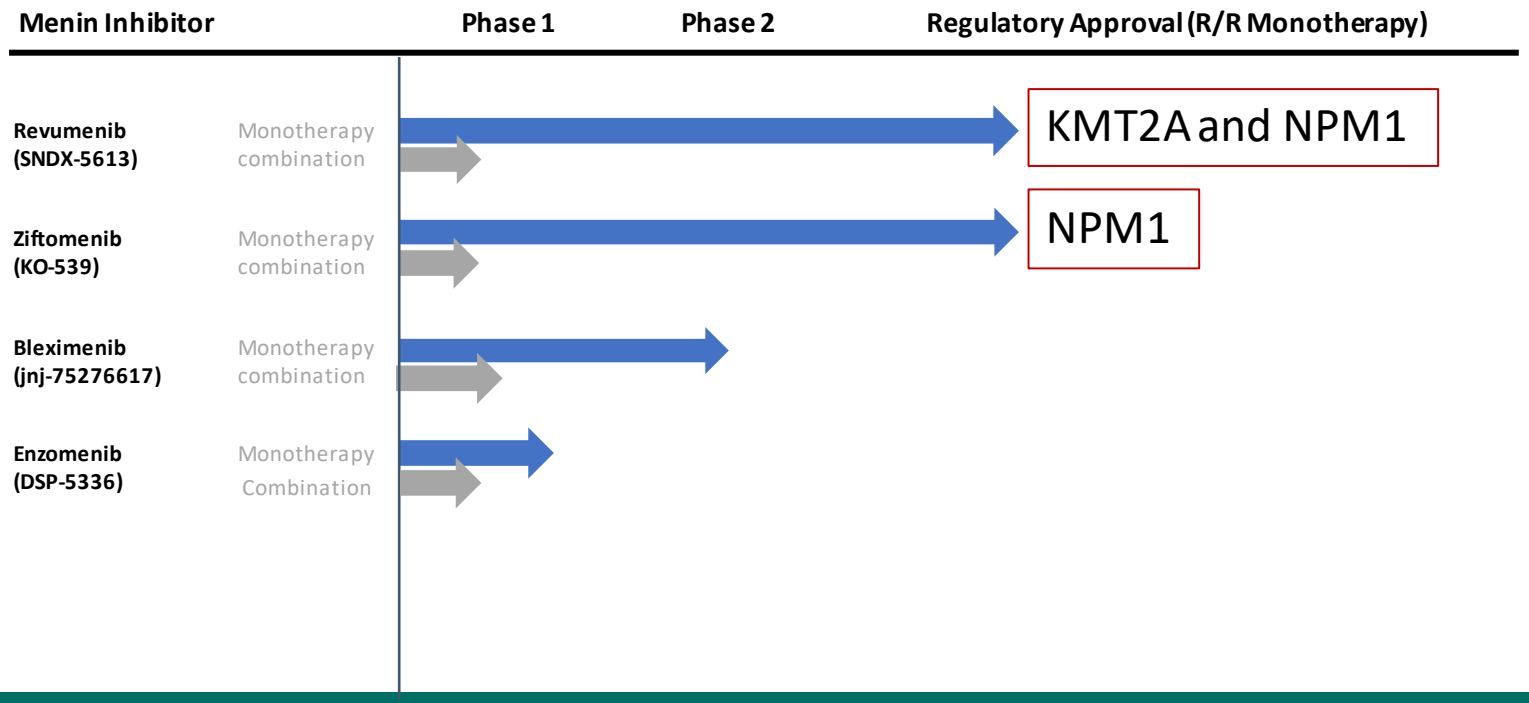
- HOX-MEIS1 overexpressed in AML with KMT2A rearrangement or NPM1 mutation
- Menin inhibitors block HOX-MEIS1 mediated leukemogenesis



Menin inhibition's role in other alterations

Alteration	Cytogenetics	Clinical activity	Mouse models	Cell lines
KMT2Ar	11q23 rearrangements	✓	✓	✓
NPM1c	Normal karyotype		✓	
NPM1-MLF1	t(3;5)(q25;q34)		✓	
NUP98r	11p15 rearrangements	✓	✓	✓
SET-NUP214	t(9;9)(q34;q34)	✓		
RUNX1-EVI1	t(3;21)(q26;q22)			✓
MYST3-CREBBP	t(8;16)(p11;p13)			✓
CDX2-ETV6	t(12;13)(p13;q12)			✓
CALM-AF10	t(10;11)(p13;q14-21)			✓
MN1-ETV6	t(12;22)(p13;q12)			✓
EZH2	–			✓
IDH1/IDH2	–			✓
ASXL1	–			✓
CEBPA	Trisomy 8			✓

Menin inhibitors in development



REVUMENIB – AUGMENT 101

Response	Efficacy population (*n* = 60)	*KMT2A*r (*n* = 46)	Mutated *NPM1* (*n* = 14)
Overall response	32 (53%)	27 (59%)	5 (36%)
CR/CRh	18 (30%)	15 (33%)	3 (21%)
MRD neg. rate within CR/CRh	14/18 (78%)	11/15 (73%)	3/3 (100%)

All terms, n (%)	Safety population (N=116)
Febrile neutropenia	45 (38.8)
Anemia	23 (19.8)
Decreased platelet count	19 (16.4)
Differentiation syndrome	17 (14.7)
Decreased neutrophil count	17 (14.7)
Decreased white blood cell count	17 (14.7)
Sepsis	16 (13.8)
QTc prolongation	15 (12.9)

Issa G et al. Nature 2023

ZIFTOMENIB – NPM1 mutated R/R AML

n (%)	Ziftomenib RP2D 600 mg QD Phase 2 (N = 92)	Ziftomenib RP2D 600 mg QD Pooled Phase 1b/2 (N = 112)
CR/CRh	**21 (23)**	**28 (25)**
Overall response	**30 (33)**	**39 (35)**
CR	13 (14)	20 (18)
CRh	8 (9)	8 (7)
CRi/CRp	3 (3)	4 (4)
MLFS	5 (5)	6 (5)
PR	1 (1)	1 (1)
Other[a]	62 (67)	73 (65)
Median duration of response, months (95% CI)		
CR/CRh	3.7 (1.9–NE)	3.7 (1.9–7.7)
CRc	4.6 (2.8–11.4)	5.1 (2.8–8.1)
ORR	4.6 (2.8–11.4)	4.6 (3.6–7.7)
Restricted mean duration of response[b], months (95% CI)		
CR/CRh	4.3 (3.1–5.6)	5.2 (3.6–6.7)
CRc	5.9 (4.0–7.7)	6.4 (4.6–8.1)
ORR	5.9 (4.4–7.5)	6.5 (4.9–8.1)
MRD negativity, n/N[c] (%)	**12/19 (63)**	**17/26 (65)**

Event, n (%)	Ziftomenib RP2D 600 mg QD Phase 2 (N = 92) Any Grade	Phase 2 (N = 92) Grade ≥ 3	Pooled Phase 1b/2 (N = 112) Any Grade	Pooled Phase 1b/2 (N = 112) Grade ≥ 3
Any ziftomenib-related AE	64 (70)	37 (40)	77 (69)	45 (40)
Hematologic AEs				
Anemia	5 (5)	5 (5)	6 (5)	6 (5)
Neutropenia	6 (7)	6 (7)	6 (5)	6 (5)
Nonhematologic AEs				
Differentiation syndrome	**22 (24)**	**14 (15)[a]**	**26 (23)**	**15 (13)[a]**
Pruritus	15 (16)	0	16 (14)	0
Nausea	8 (9)	0	13 (12)	0
Diarrhea	8 (9)	0	10 (9)	2 (2)
Alanine aminotransferase increased	6 (7)	2 (2)	7 (6)	2 (2)
Decreased appetite	5 (5)	0	6 (5)	0

Other menin inhibitors

Bleximenib

- Step-up dosing
- KMT2A and NPM1 mutated AML
- CRc around 40% in most recent update

Enzomenib

- Low lipophilicity, short half-life, BID
- Less interaction with azoles
- CR/CRh around 45% in recent update

Searle E et al. ASH 2024
Daver N et al. ASH 2025

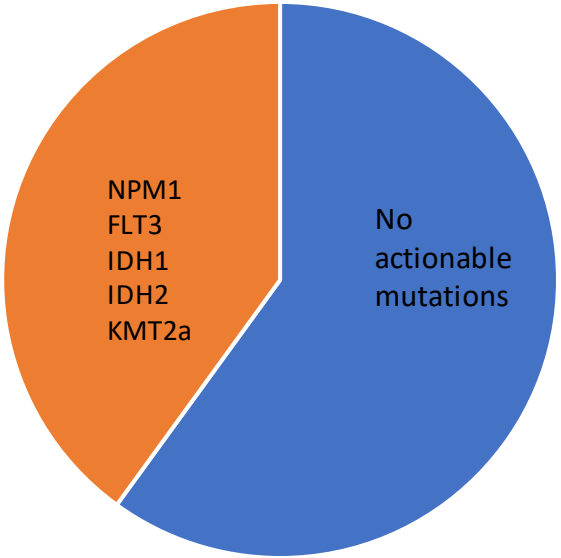
Combination data relapsed/refractory AML

Drug, N	Regimen	AEs	Responses
Rev - SAVE **N=33**	Oral decitabine, Venetoclax, **Revumenib**	DS: all Gr 6%, Gr 3 3% QTc: Gr 3+ 9%	**ORR 82%** **CR/CRh 48%**
KOMET-007 **N=70**	AZA/VEN + **Ziftomenib**	DS: all Gr 8%, Gr3 6% No QTc or DLT	NPM1 – **ORR 65%, CRc – 49%** KMT2Ar – **ORR 33%, CRc – 22%**
JNJ Ph1b **N=60**	AZA/VEN + **Bleximenib**	DS: all Gr 3% (1 Gr3 and 1 Gr5) No QTc prolongation	NPM1 - **CR/CRh 19%** KMT2A - **CR/CRh 31%**
Enzomenib **N=18**	AZA/VEN+ **enzomenib**	1 grade 2 DS No QTc prolongation	**ORR 83%, CRc 56%**

Wei A et al. EHA 2025, Issa G et al. ASH 2025, Issa G et al. ASH 2024, Watts J et al. ASH 2025

Management considerations in R/R AML

Targeted agent-based therapies



Novel agents
Conventional chemotherapy
Venetoclax-HMA

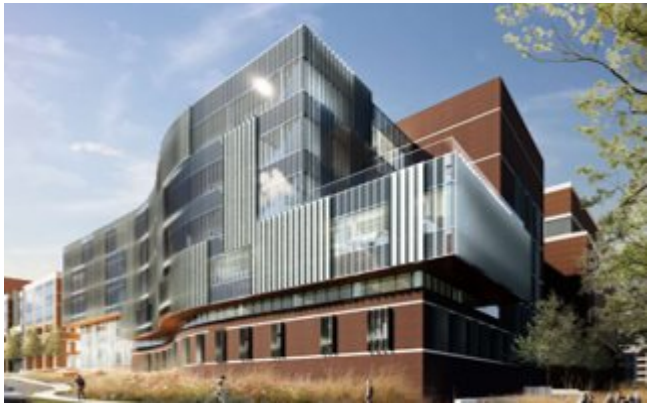
Unmet needs
TP53 mutation
Progression after current agents

Key Take-Home Points

- Relapsed AML is a genomically diverse disease
- Targeted therapies as single agent or as combination improves outcomes
- Transplant remains the only curative strategy
- Clinical trials should be prioritized

Acknowledgements

- Leukemia Physicians, APPs
- BMT Physicians, APPs
- Referring providers
- MCW Cancer Center Clinical Trials Office
- Patients and caregivers



THANK YOU

Email: gmurthy@mcw.edu