ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

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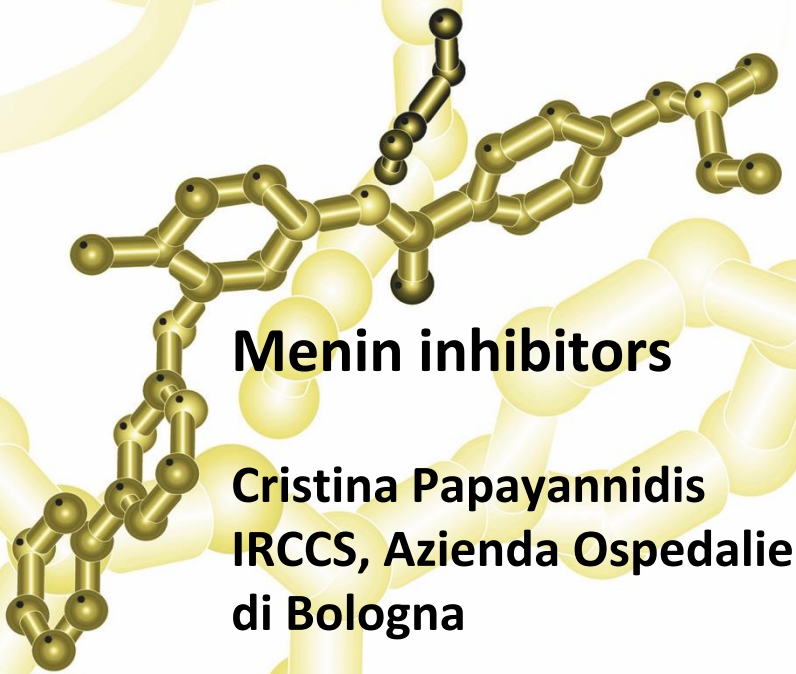

Menin inhibitors

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New Drugs in Hematology

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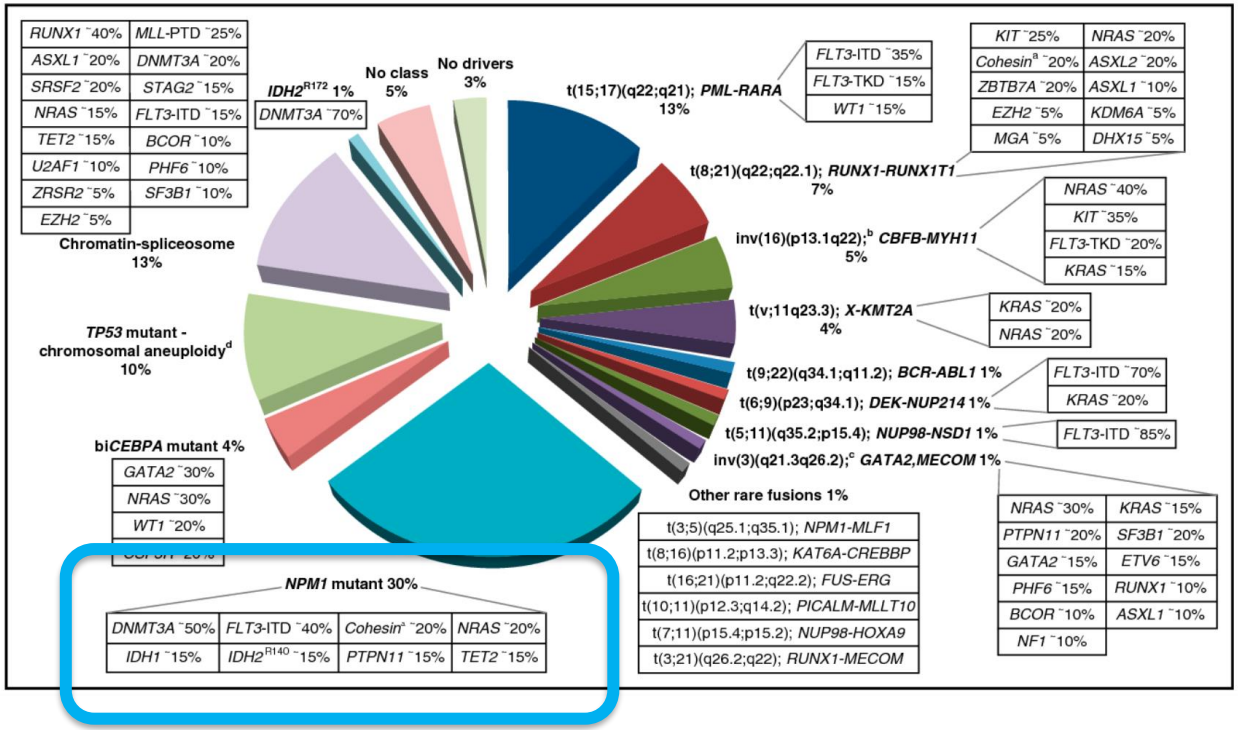
Disclosures of CRISTINA PAPAYANNIDIS

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie						X	X
Astellas						X	X
Servier							X
Menarini							X
BMS							X
Pfizer						X	X
Amgen							X
Janssen						X	
GSK						X	
Blueprint						X	
Incyte						X	X
Paladin Labs Inc							X
Jazz pharmaceuticals						X	
Novartis						X	
Delbert Laboratoires						X	

Menin inhibitors: for which patients?



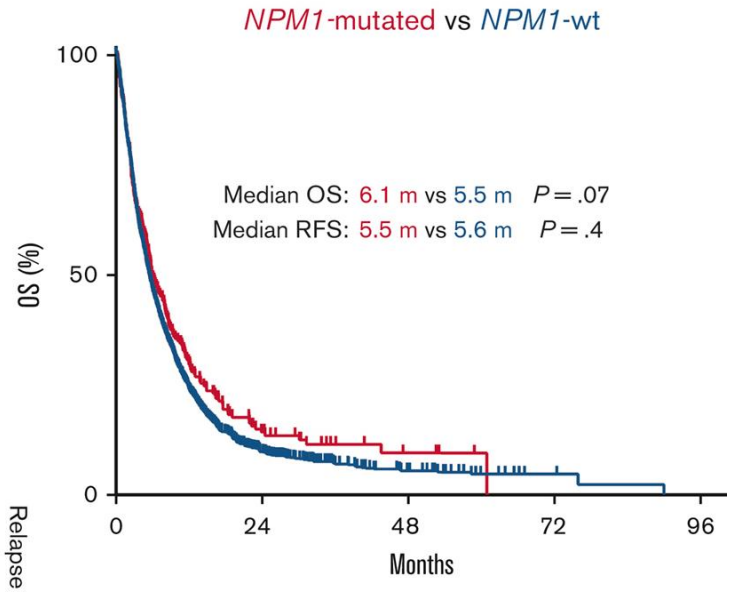
Dohner H et al., Blood 2017

Menin inhibitors: for which patients?

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]

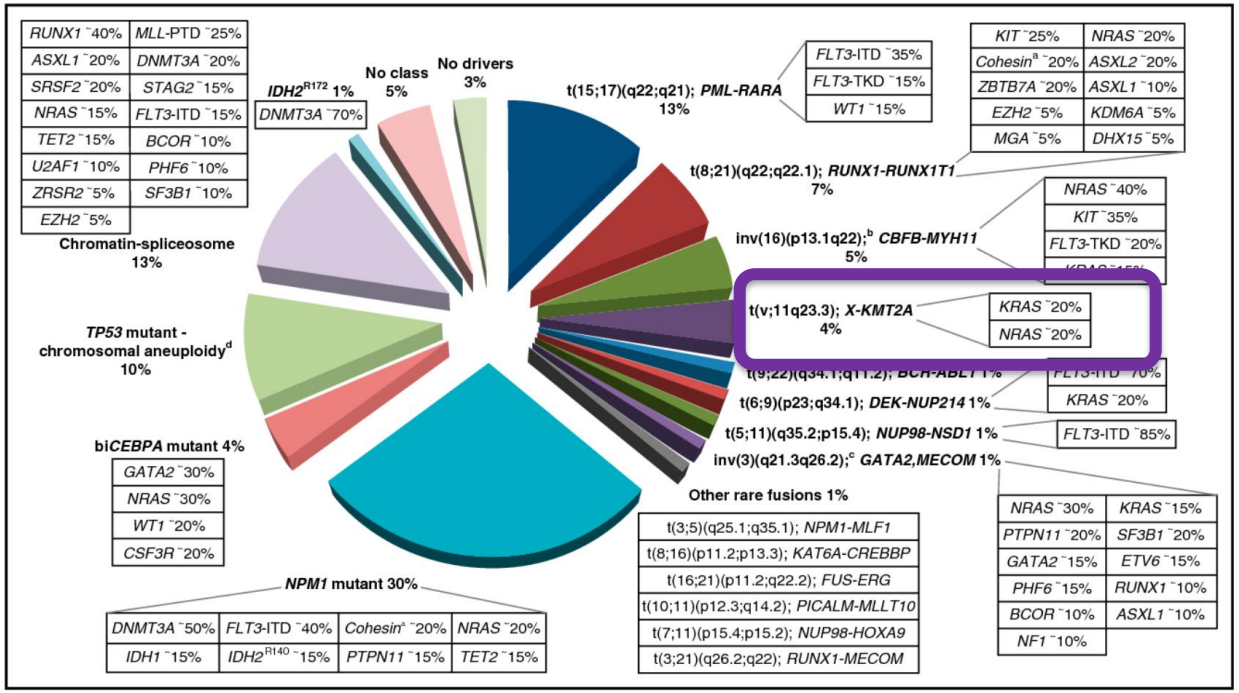
Dohner H et al., Blood 2022

R/R NPM1-mut OVERALL SURVIVAL



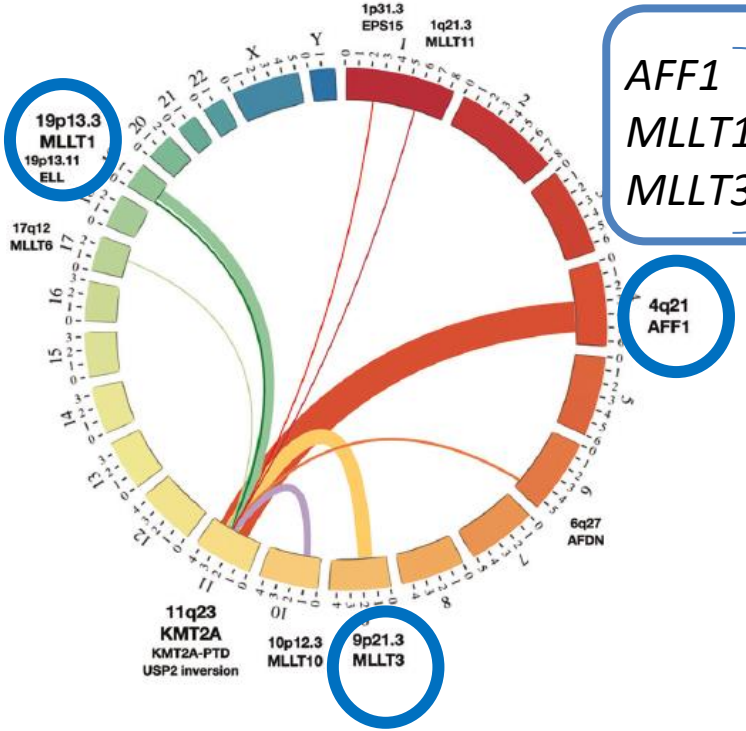
Issa GC et al., Blood Adv 2023

Menin inhibitors: for which patients?

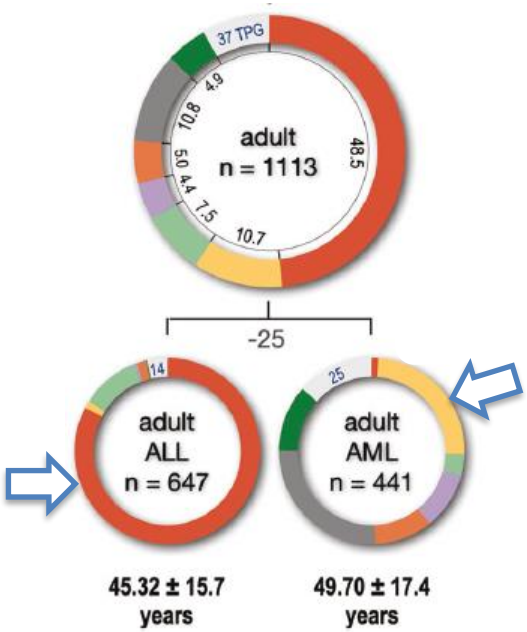


Dohner H et al., Blood 2017

Fusion partners genes vary according to age and phenotype

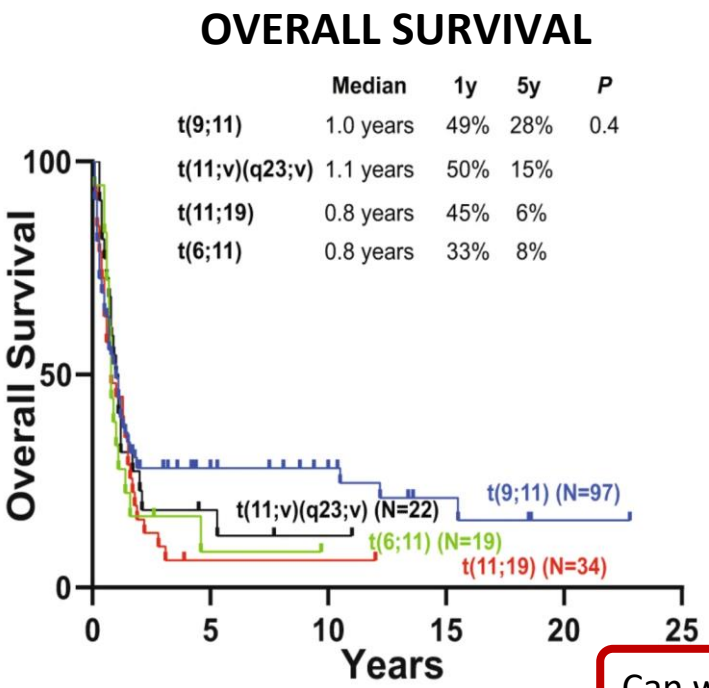


AFF1
MLLT1
MLLT3
87%
r-*KMT2A*
AL



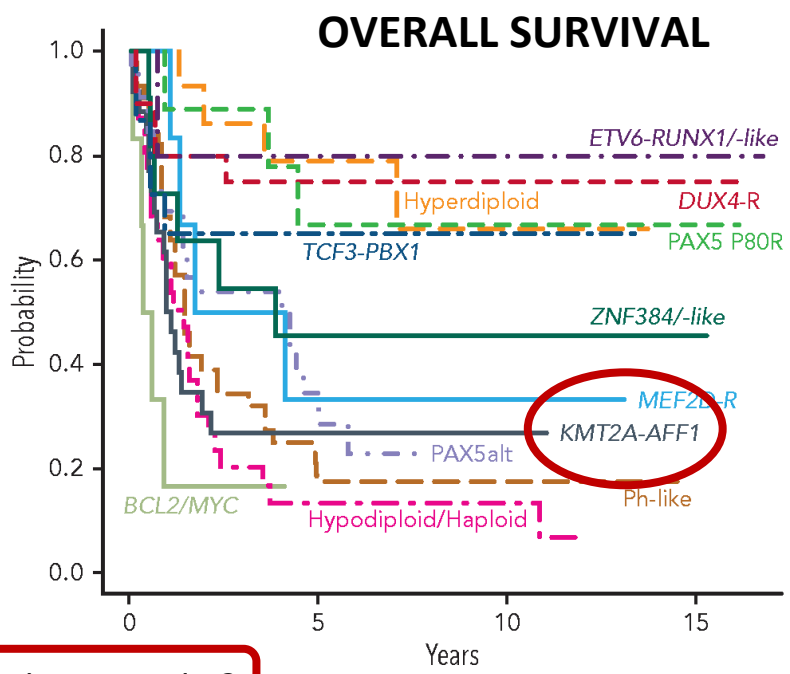
Meyer C et al, Leukemia 2023

r-*KMT2A* AML outcome



Issa G C et al, Blood Cancer Jour 2021

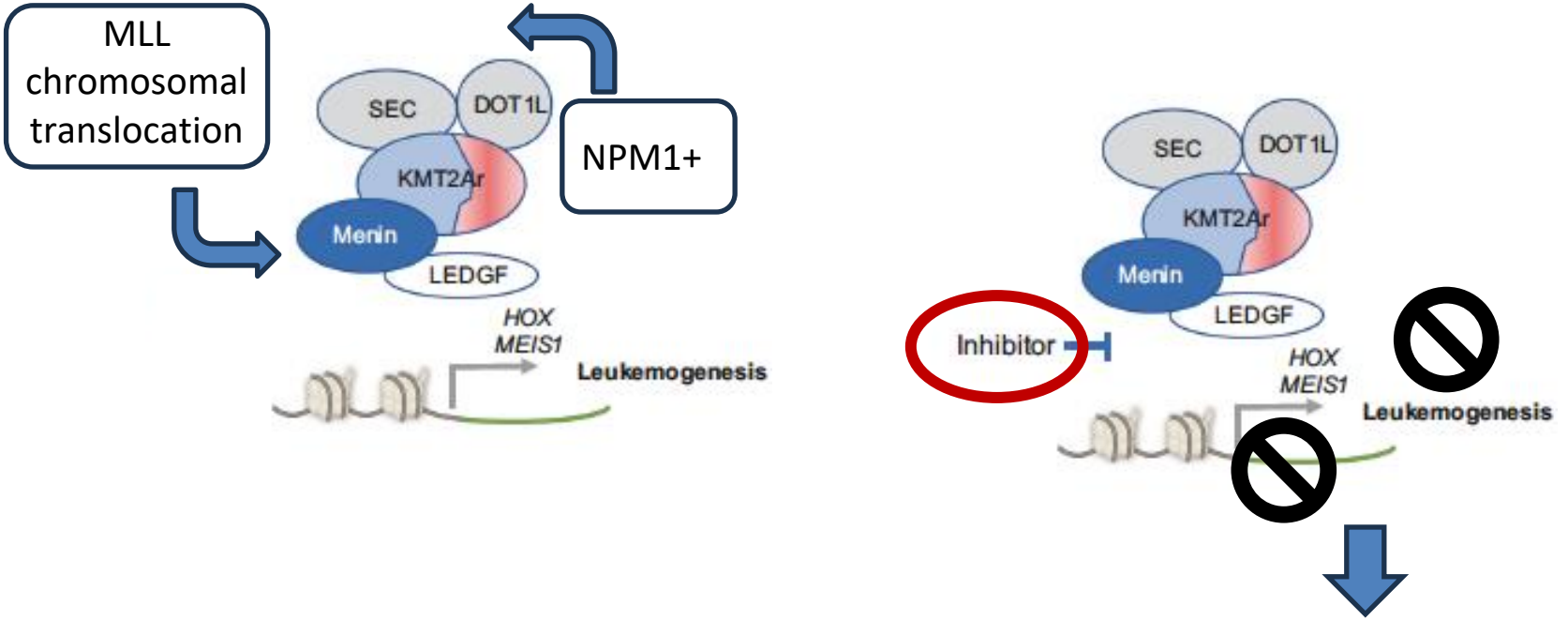
r-*KMT2A* ALL outcome



Paietta E et al, Blood 2021

Can we improve these results?

Menin is an essential oncogenic cofactor for leukemogenesis driven by NPM1 mut or r-*KMT2A*



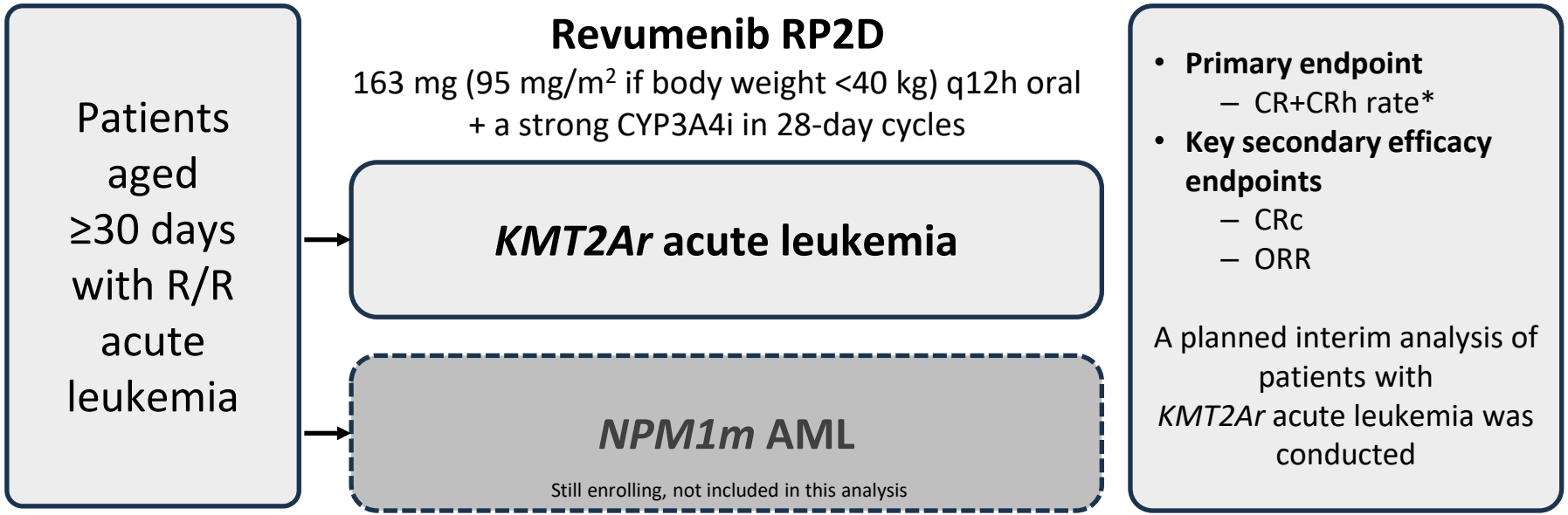
Modified from Issa GC et al, Leukemia 2021

Menin inhibitors in clinical trials

Clinical trial/status	Drug	Dosing	Min. age	Phase 2 expansion cohorts
AUGMENT-101 NCT04065399	SNDX-5613	PO BID	30 d	A. ALL or MPAL with *KMT2Ar* B. AML with *KMT2Ar* C. AML with *NPM1c*
KOMET-001 NCT04067336	KO-539	PO daily	18 yr	A. AML with *KMT2Ar* B. AML with *NPM1c*
NCT04752163	DS-1594	PO BID	18 yr	A. *KMTAr* leukemia: single agent B. AML with *NPM1c*: single agent C. AML with *KMT2Ar* or *NPM1c*: in combination with azacytidine and venetoclax D. ALL with *KMT2Ar*: in combination with mini-HCVD
NCT04811560	JNJ-75276617	PO daily	18 yr	–
	BMF-219	PO	–	–

Issa G C et al, Leukemia 2021

AUGMENT-101 Phase 2 Study Design



*CR+CRh rate >10% in adult evaluable population considered lower efficacy bound

AML, acute myeloid leukemia; CR, complete remission; CRc, CR composite (CR+CRh+CRp+CRi); CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; CYP3A4i, cytochrome P450 3A4 inhibitor; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearrangements; *NPM1m*, nucleophosmin 1–mutated; ORR, overall response rate; q12h, every 12 hours; RP2D, recommended phase 2 dose; R/R, relapsed/refractory.

Aldoss I et al, ASH 2023

Patient Demographics

Parameter	Efficacy population (n=57)	Safety population (n=94)[a]
Median age, y (range)	34.0 (1.3–75)	37.0 (1.3–75)
Age <18 y, n (%)	13 (23)	23 (25)
Age ≥18 y, n (%)	44 (77)	71 (76)
Sex, n (%)		
Female	33 (58)	56 (60)
Race, n (%)		
White	43 (75)	68 (72)
Non-White	10 (18)	14 (15)
Unknown	4 (7)	12 (13)

Data cutoff: July 24, 2023. [a]Defined as patients with *KMT2Ar* acute leukemia having received at least 1 dose of revumenib.

KMT2Ar, histone-lysine N-methyltransferase 2A rearrangements rearrangements.

Aldoss I et al, ASH 2023

Baseline characteristics

Parameter	Efficacy population (n=57)	Safety population (n=94)[a]
Leukemia type, n (%)		
AML	49 (86)	78 (83)
ALL	7 (12)	14 (15)
MPAL/Other	1 (2)	2 (2)
Co-mutations[b], n (%)		
FLT3	5 (9)	7 (7)
RAS	9 (16)	12 (13)
p53	4 (7)	5 (5)
Primary refractory, n (%)	14 (25)	18 (19)
Number of prior lines of therapy, median (range)	2 (1–11)	2 (1–11)
1, n (%)	17 (30)	25 (27)
2, n (%)	14 (25)	28 (30)
≥3, n (%)	26 (46)	41 (44)
Prior venetoclax, n (%)	41 (72)	61 (65)
Prior HSCT, n (%)	26 (46)	47 (50)

Data cutoff: July 24, 2023. [a]Defined as patients with *KMT2Ar* acute leukemia having received at least 1 dose of revumenib. [b]In patients that had co-mutation status reported.

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; *FLT3*, fms-related tyrosine kinase 3; HSCT, hematopoietic stem cell transplant; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearrangements; MPAL, mixed phenotype acute leukemia; *RAS*, rat sarcoma virus.

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 postbaseline disease assessment.

Aldoss I et al, ASH 2023

CR, complete remission; CRc, composite CR (CR+CRh+CRp+CRi); CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphological leukemia-free state; MRD, minimal residual disease; ORR, overall response rate (CRc+MLFS+PR); PD, progressive disease; PR, partial remission.

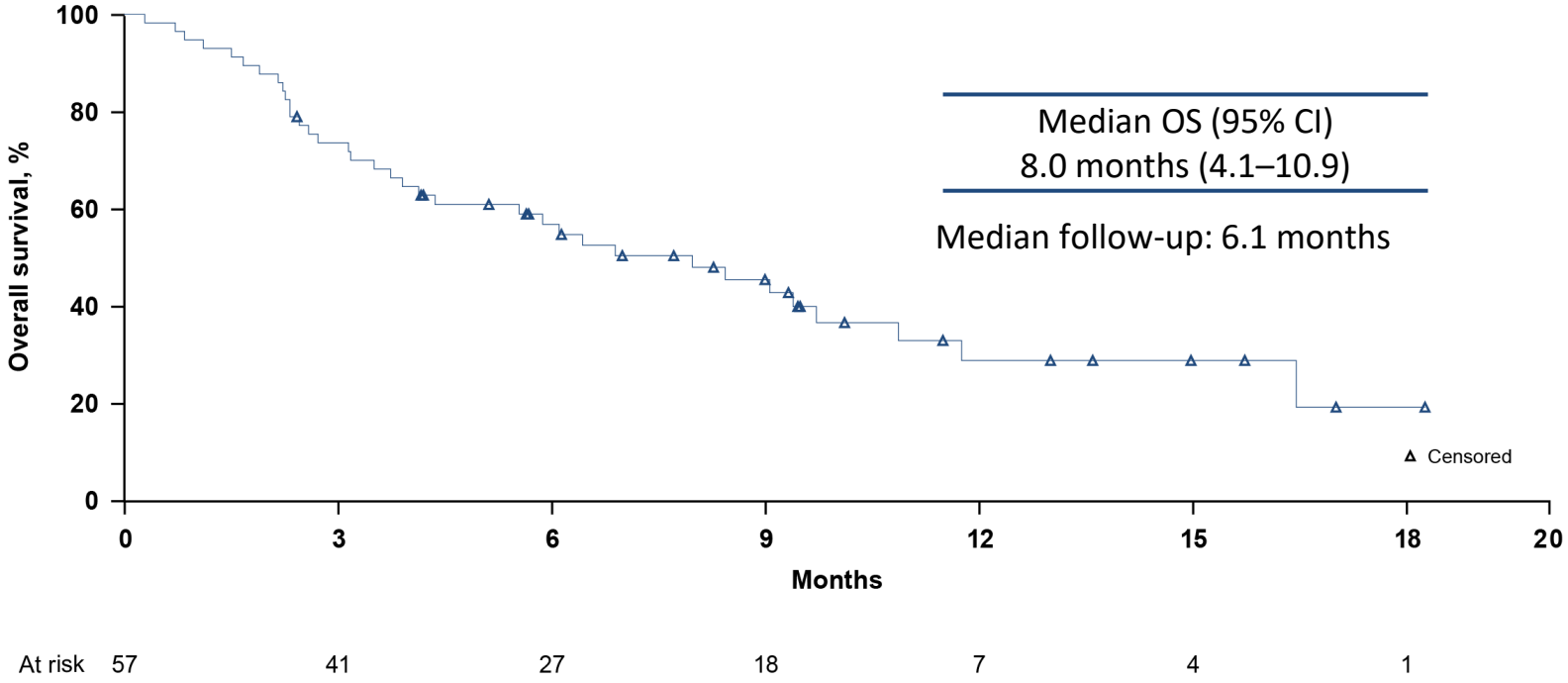
Responses observed across *KMT2A* rearrangements

KMT2A rearrangement/ translocation	Summary of ORR		Summary of CR+CRh rate	
	n/N	ORR (95% CI)	n/N	CR+CRh rate (95% CI)
9;11	10/11	91 (58.7–99.8)	2/11	18 (2.3–51.8)
11;19	7/13	54 (25.1–80.8)	2/13	15 (1.9–45.4)
10;11	5/7	71 (29.0–96.3)	2/7	29 (3.7–71.0)
6;11	5/7	71 (29.0–96.3)	2/7	29 (3.7–71.0)
4;11	2/2	100 (15.8–100.0)	0/2	0 (0.0–84.2)
1;11	0/2	0 (0.0–84.2)	0/2	0 (0.0–84.2)
11;16	1/1	100	0/1	0
11;22	1/1	100	1/1	100
Unknown *KMT2A* fusion partner	5/13	39 (13.9–68.4)	4/13	31 (9.1–61.4)

Aldoss I et al, ASH 2023

CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; *KMT2A*, histone-lysine N-methyltransferase 2A; ORR, overall response rate (CR+CRh+CRp+CRi+MLFS+PR); PR, partial remission.

Overall Survival



Aldoss I et al, ASH 2023

OS, overall survival.

Duration of response

Parameter	Patients achieving CR+CRh (n=13)
Median time to CR+CRh, mo (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)
Proceeded to HSCT in CR or CRh	6/14 (43)
Proceeded to HSCT in MLFS or CRp	8/14 (57)
Restarted revumenib post HSCT, n (%)	7/14 (50)*

Data cutoff: July 24, 2023
*3 additional patients remained eligible to initiate revumenib after HSCT at the time of data cutoff.

Aldoss I et al, ASH 2023

CR, complete remission; CRh, CR with partial hematologic recovery; CRp, CR with incomplete platelet recovery; HSCT, hematopoietic stem cell transplant; MLFS, morphological leukemia-free state; NR, not reached.

Revumenib safety profile (I)

All terms	Safety population (n=94)[a] TEAEs
Any grade, n (%)	93 (99)
≥Grade 3, n (%)	86 (92)
Serious AE, n (%)	72 (77)
AEs leading to:	
Dose reduction	9 (10)
Discontinuation	12 (13)
Death	14 (15)

Data cutoff: July 24, 2023. [a]Defined as patients with *KMT2Ar* acute leukemia having received at least 1 dose of revumenib.

R/R, relapsed/refractory; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Aldoss I et al, ASH 2023

Revumenib safety profile (II)

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)

Data cutoff: July 24, 2023. [a]Defined as patients with *KMT2Ar* acute leukemia having received at least 1 dose of revumenib.

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

KMT2Ar, histone-lysine N-methyltransferase 2A rearrangements; TEAE, treatment-emergent adverse event.

Menin inhibitors in clinical trials

Clinical trial/status	Drug	Dosing	Min. age	Phase 2 expansion cohorts
AUGMENT-101 NCT04065399	SNDX-5613	PO BID	30 d	A. ALL or MPAL with *KMT2Ar* B. AML with *KMT2Ar* C. AML with *NPM1c*
KOMET-001 NCT04067336	KO-539	PO daily	18 yr	A. AML with *KMT2Ar* B. AML with *NPM1c*
NCT04752163	DS-1594	PO BID	18 yr	A. *KMTAr* leukemia: single agent B. AML with *NPM1c*: single agent C. AML with *KMT2Ar* or *NPM1c*: in combination with azacytidine and venetoclax D. ALL with *KMT2Ar*: in combination with mini-HCVD
NCT04811560	JNJ-75276617	PO daily	18 yr	–
	BMF-219	PO	–	–

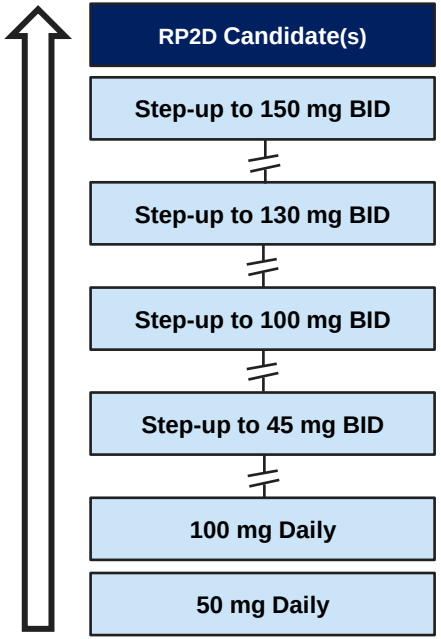
Issa G C et al, Leukemia 2021

JNJ-75276617
Ph1 Study design

Part 1: Dose Escalation (NCT04811560)
Ongoing; RP2D yet to be determined

Adult pts with R/R acute leukemia harboring *KMT2A* or *NPM1* alterations

- BOIN statistical design
- Pts receive JNJ-75276617 orally either daily or BID continuously
- Step-up dosing started early in dose escalation



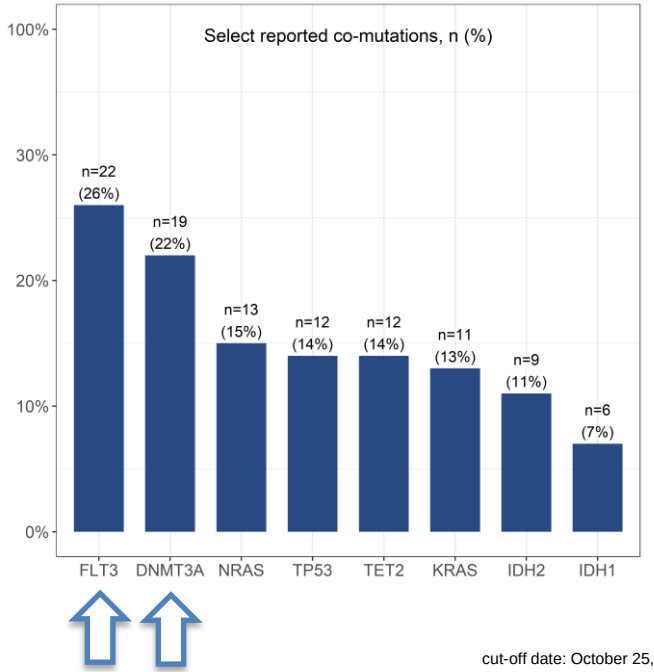
Primary objective:
Safety/RP2D

Secondary objectives:
Preliminary clinical activity, PK and PD

Jabbour E et al, ASH 2023

Demographics and Baseline characteristics

	All Treated (N=86)
Age, median (range), years	**59.5 (18-85)**
Female, n (%)	**49 (57)**
Male, n (%)	**37 (43)**
Diagnosis, n (%)	
AML	78 (91)
ALL	4 (4.5)
Other acute leukemia	4 (4.5)
Prior therapy	
Lines of prior therapy, median (range)	3.0 (1-7)
Prior HSCT, n (%)	20 (23)
Prior venetoclax therapy, n (%)	52 (61)
***KMT2A* alteration, n (%)**	**50 (58)**
Translocation	36 (72)
Amplification	5 (10)
Partial tandem duplication	5 (10)
Other/Unknown	4 (8)
***NPM1* alteration, n (%)**	**36 (42)**
Insertion/Frameshift	27 (75)
Translocation	6 (17)
Other/Unknown	3 (8)



cut-off date: October 25, 2023

Jabbour E et al, ASH 2023

Safety profile

TRAEs Observed in ≥5% of Pts (N=86)	All Grades	Grade ≥3
Total, n (%)	**45 (52)**	**26 (30)**
Differentiation syndrome (DS)	10 (12)	4 (5)
Neutropenia	10 (12)	9 (11)
Nausea	7 (8)	0 (0)
Thrombocytopenia	7 (8)	5 (6)
Anemia	6 (7)	4 (5)
Fatigue	5 (6)	0 (0)
Arthralgia	4 (5)	0 (0)

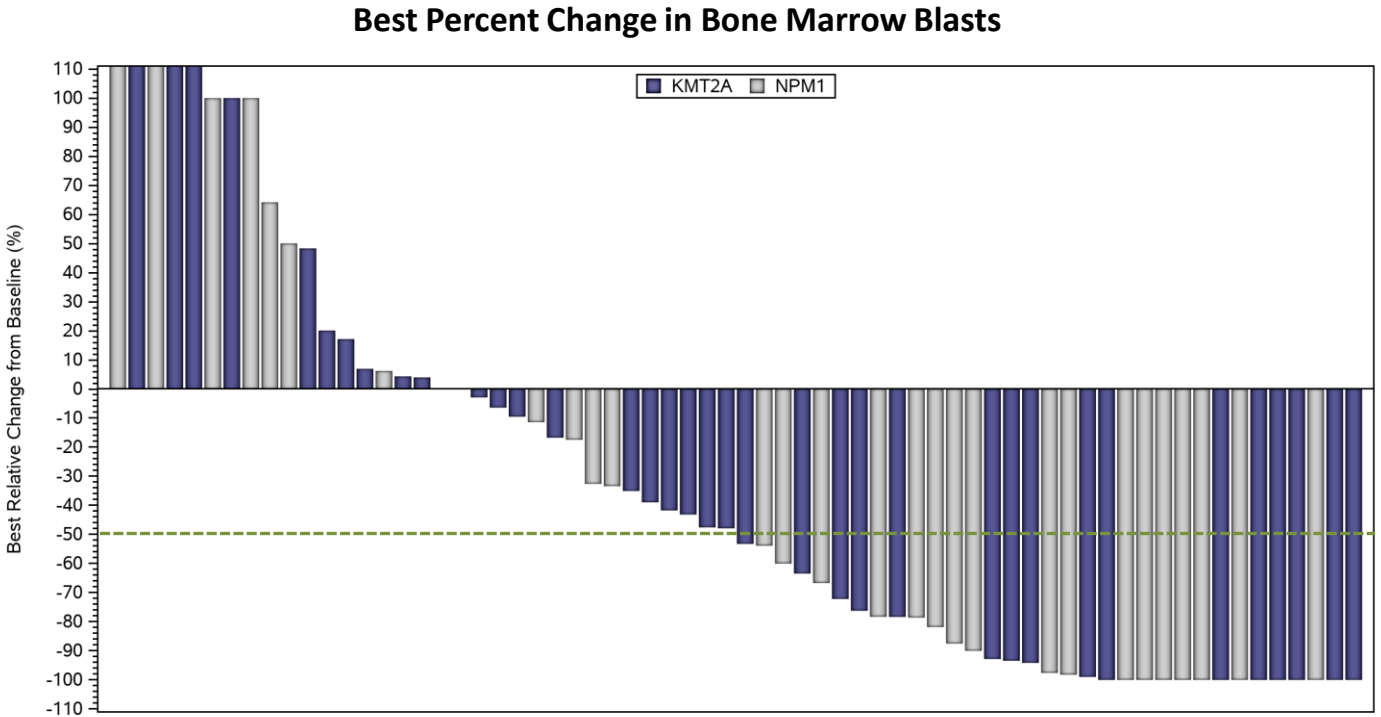
Symptoms of differentiation syndrome are not included in this summary; AEs were graded according to CTCAE v5.0

- **DS is only DLT observed in ≥2 pts**
  - 1 Gr 5 DS; BID and step-up dosing implemented
  - No dose dependent increase in incidence or severity
  - Median onset = Day 8 (2-19 days)
- **DLTs observed in 7 (8%) of pts**
  - One G3 QT prolongation AE observed
  - No other QT-related AEs observed on study

Data cut-off date: October 25, 2023

Jabbour E et al, ASH 2023

Change in leukemic burden



- **66 pts evaluable**
  - 37 *KMT2A*
  - 29 *NPM1*
- **47 (71%) pts with reduction in leukemic burden**
- **33 (50%) pts with ≥50% reduction**
- **Observed in both *KMT2A* and *NPM1***

20 Non-evaluable pts: Ongoing in Cycle 1, n=2; D/C for AE, n=13; D/C for PD, n=2; D/C subject refused, n=2; D/C physician discretion, n=1

Note: Bars are only presented for pts where a measurable change from baseline is found in the data; Each bar represents a unique pt; Five pts had best relative change from baseline of >100%.

Jabbour E et al, ASH 2023

Preliminary clinical activity

Efficacy subset	45-130 mg BID Cohorts (N=33, acute leukemia)	
ORR (≥PR), n (%)	**15 (46)**	
Ongoing responders	8 (53)	
Best response, n (%)		
CR/CRh/CRi	**9 (27)**	
CR/CRh	7 (21)	
CR	6 (18)	
MLFS/PR	**6 (18)**	
Median time to first response, mos	1.8 (0.9-3.3)	
Median duration of response, mos	6.5 (1.0-NE)	
	KMT2A (N=19)	**NPM1 (N=14)**
ORR, n (%)	8 (42)	7 (50)

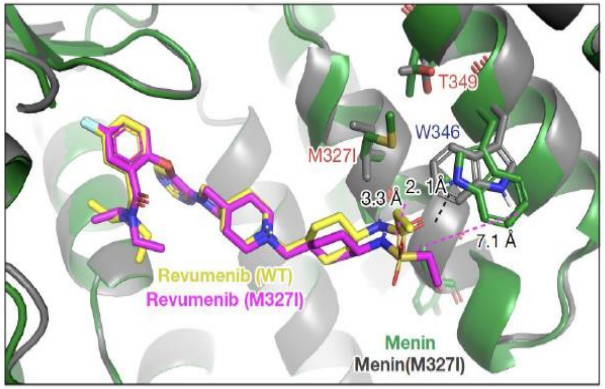
Responses were investigator-assessed per modified ELN 2017 recommendations (AML) or ESMO 2016 with NCCN 2020 modifications (ALL)

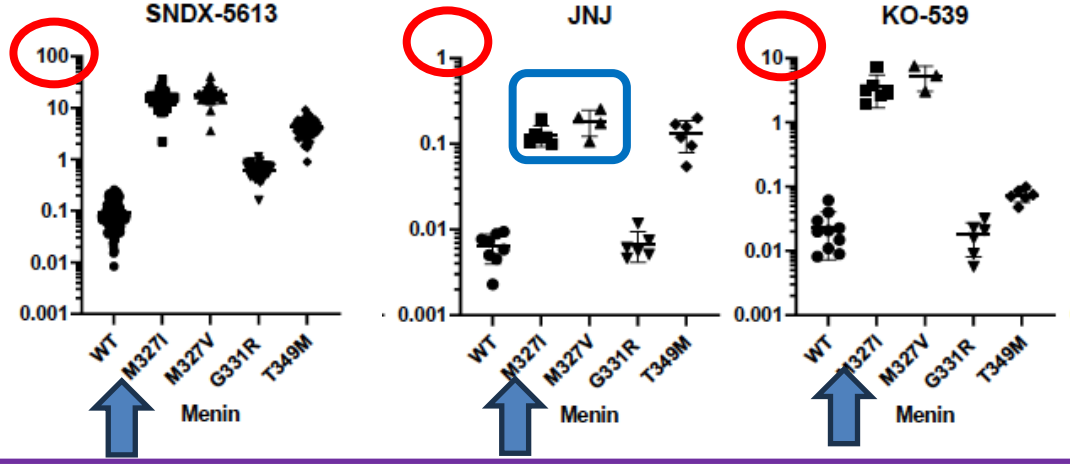
- 3/6 of CR were MRD negative
- 1 responder discontinued for HSCT
- 2 pts in ≥ Cycle 12
- Similar response rates observed in *KMT2A* and *NPM1*
- RP2D not yet determined

Data cut-off date: October 25, 2023

Jabbour E et al, ASH 2023

Why do patients relapse?
MEN1 mutations generate structural perturbations that impact small-molecule binding





Loss of hydrogen bond interactions between revumenib in the **M327I mutant** and the menin protein

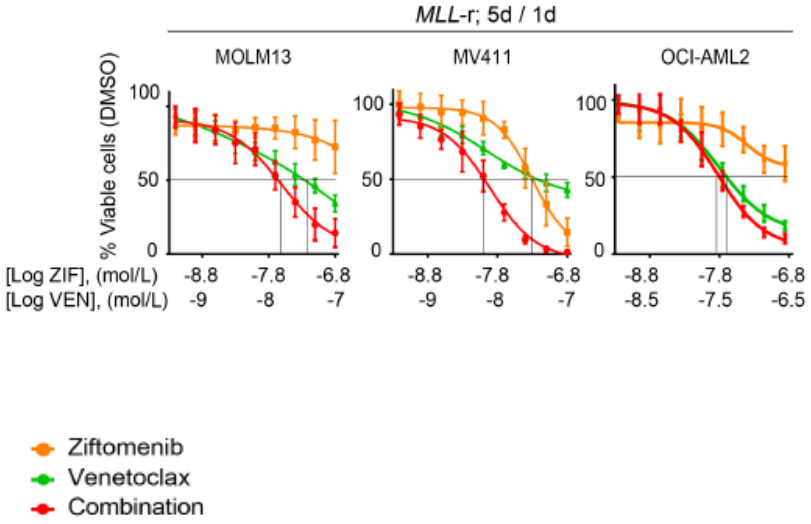
- Binding affinities of all compounds reduced by I/V mutations at M327
- T349M reduces binding for most chemotypes
- G331R change has variable effects across chemotypes

Perner F et al, Nature 2023

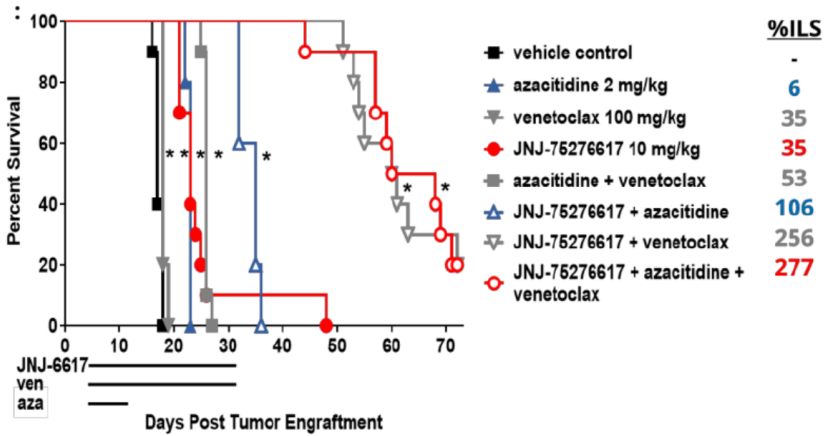
Perner F et al, AACR2023

Preclinical data support menin inhibitors combinations in r-*KMT2A* leukemia

Ziftomenib



JNJ-75276617



Rausch J et al, Haematologica 2023

Chul Kwon M et al, ASH 2023

Ongoing menin inhibitors combination clinical trials in ALL and AML

	Phase	Age	Schedule	Setting	Sites	NCT
Ziftomenib	I-II	Infants	Chemo+Blina+Ziftomenib	Frontline ALL	US	NCT05848687
	I	Adult	Chemo+Ziftomenib/Aza+Ven+Ziftomenib	Frontline AML	US	NCT05735184
	I	Adult	Chemo+Ziftomenib	R/R AML	US	NCT06001788
Revumenib	II	Children	Chemo+Revumenib	R/R ALL	US	NCT05761171
	I	Adult	Chemo+Revumenib	R/R ALL	US	NCT05326516
	I-II	Pediatric/AYA	Aza+Ven+Revumenib	R/R AML	US	NCT06177067
	I	Adult	Chemo+Revumenib	Frontline AML	TBD	NCT05886049
JNJ-75276617	I	Pediatric/AYA	Chemo+JNJ-75276617	R/R ALL R/R AML	EU+US	NCT05521087
	I	Adult	Chemo+JNJ-75276617/Aza+Ven+JNJ-75276617	Frontline AML	EU+US+AUSTRALIA	NCT05453903
DS-1594b	I-II	Adult	DS-1594b+mini-HCVD DS-1594b+Aza+Ven	R/R ALL R/R AML	US	NCT04752163

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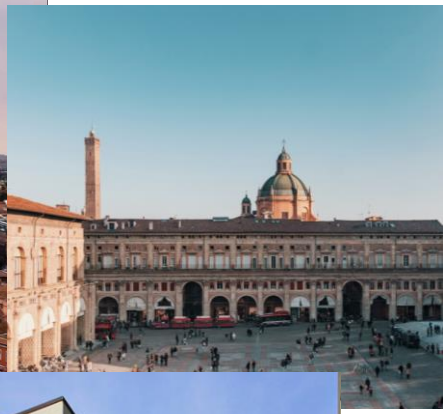
Take home messages

- Targeting menin leads to **complete remissions in both AML and ALL**
- Safety profile is manageable (DS may occur in a limited proportion of patients)
- Resistance to Menin inhibitors may be mediated by acquired ***MEN1*** **mutations,** but the identification of other mechanisms is ongoing
- **Combination studies** in both AML and ALL with menin inhibitors and standard chemotherapy/HMAs+Ven are ongoing

Thank you!



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