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

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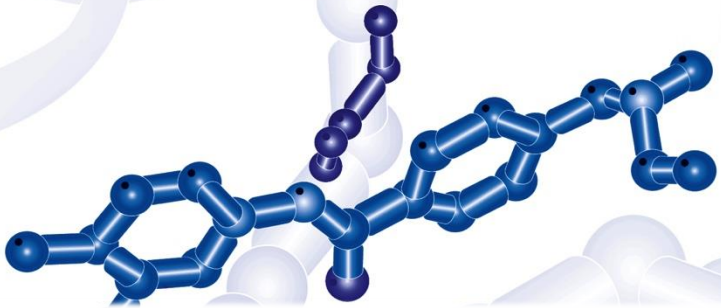

New Drugs in Hematology

Menin inhibitors in AML and ALL

Cristina Papayannidis, MD, PhD
IRCCS Azienda Ospedaliero Universitaria di Bologna

President: Pier Luigi Zinzani

Bologna,
Royal Hotel Carlton
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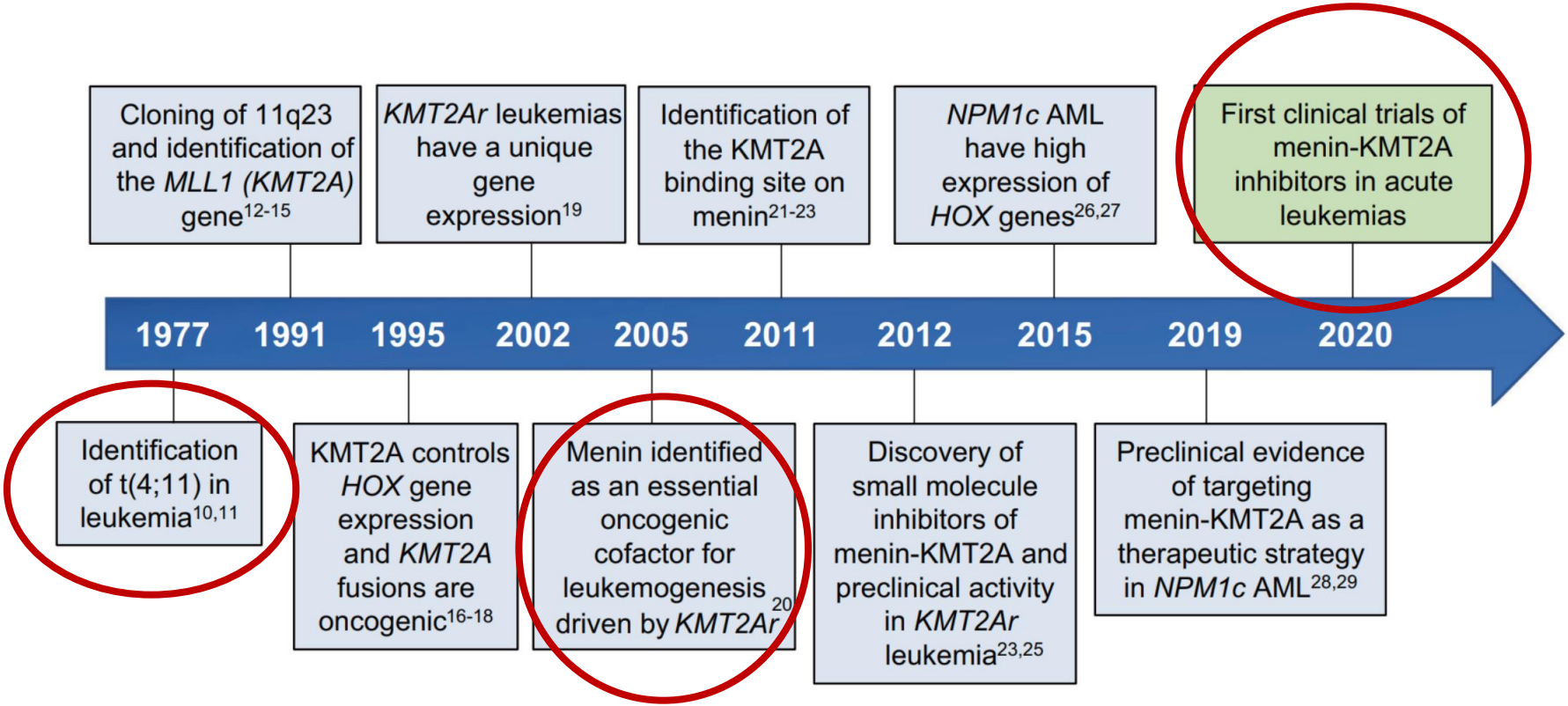
Disclosures of Cristina Papayannidis

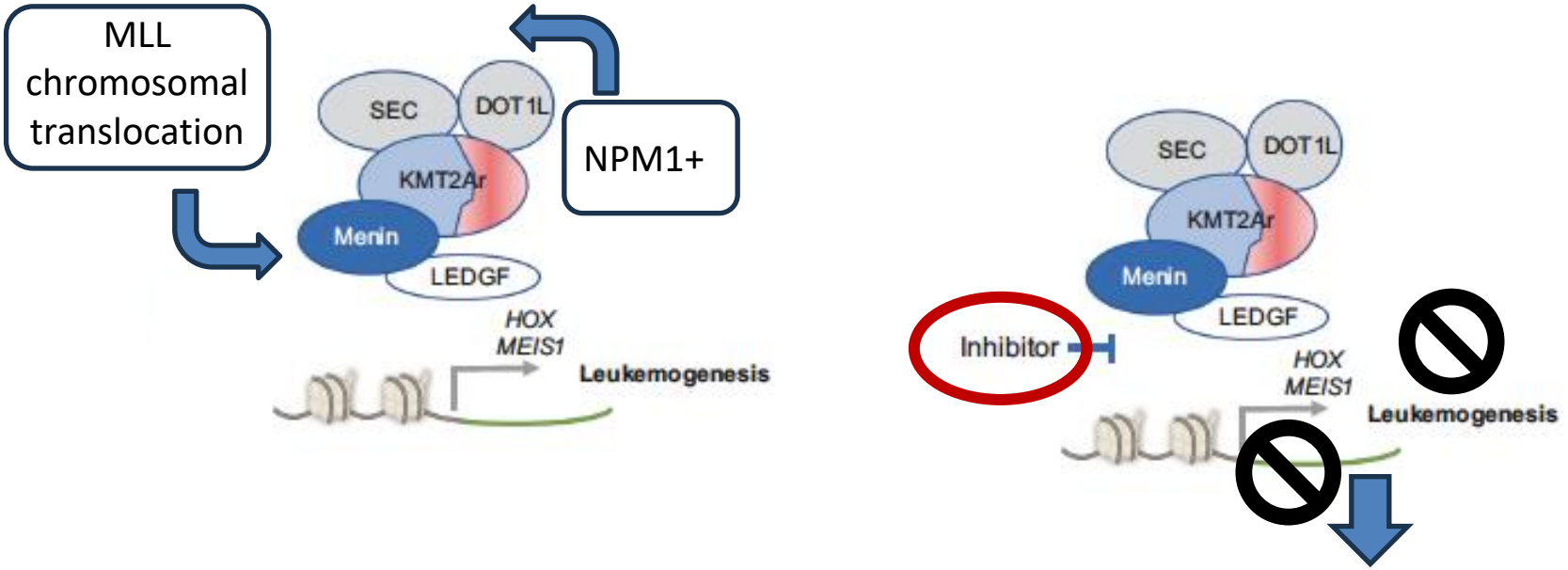
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Pfizer					x	x	
Amgen						x	
Astellas					x		
Abbvie					x		
Menarini Stemline						x	
Servier					x		
Incyte					x		
Janssen						x	
Syndax						x	
Blueprint					x	x	
GSK						x	
Istituto Gentili					x	x	
Jazz Pharmaceuticals					x	x	

Menin inhibitors: timeline



Issa GC et al, Leukemia 2021

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



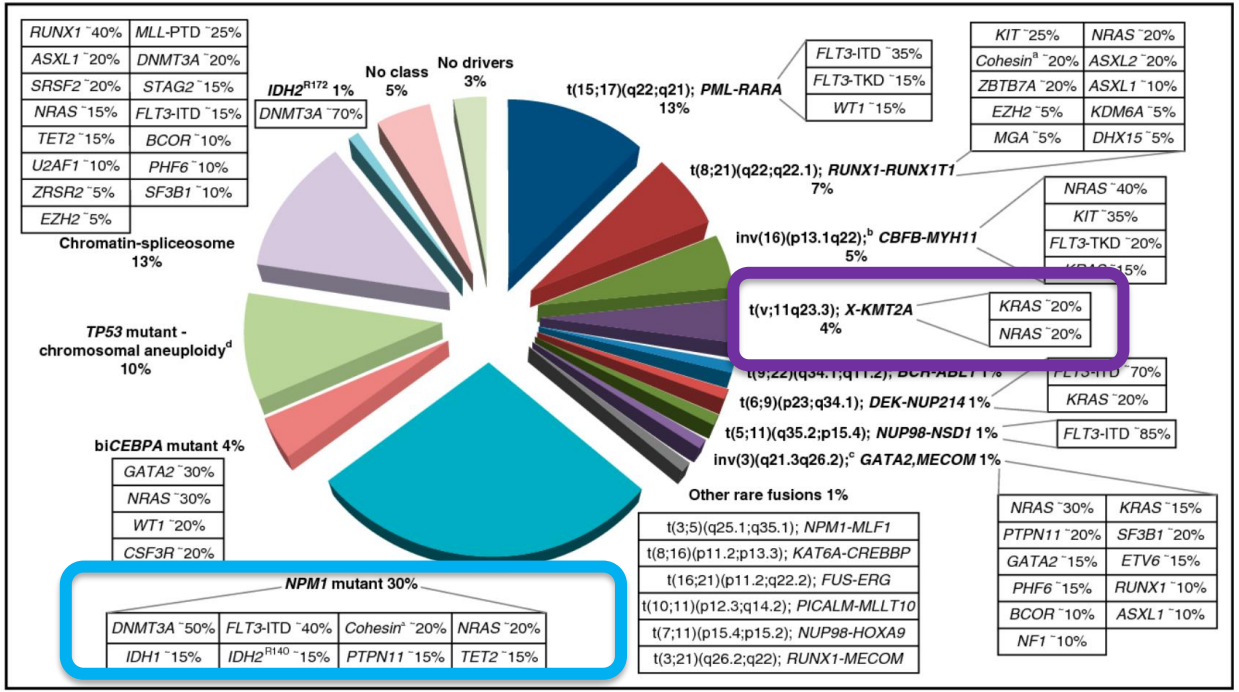
Modified from Issa GC et al, Leukemia 2021

Agenda

- For which patients today?
- How many menin inhibitors do we have today?
- What about safety with menin inhibitors as single agents?
- Which results can we achieve with menin inhibitors?

  -R/R single agents
- What about resistance?
- How can we overcome these mechanisms?
- For which patients, tomorrow?

Background (I)



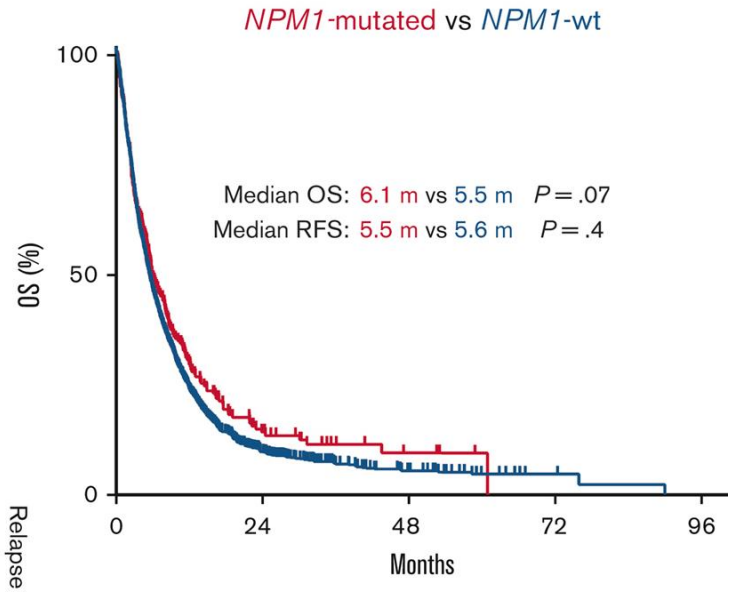
Dohner H et al., Blood 2017

Background (II)

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]

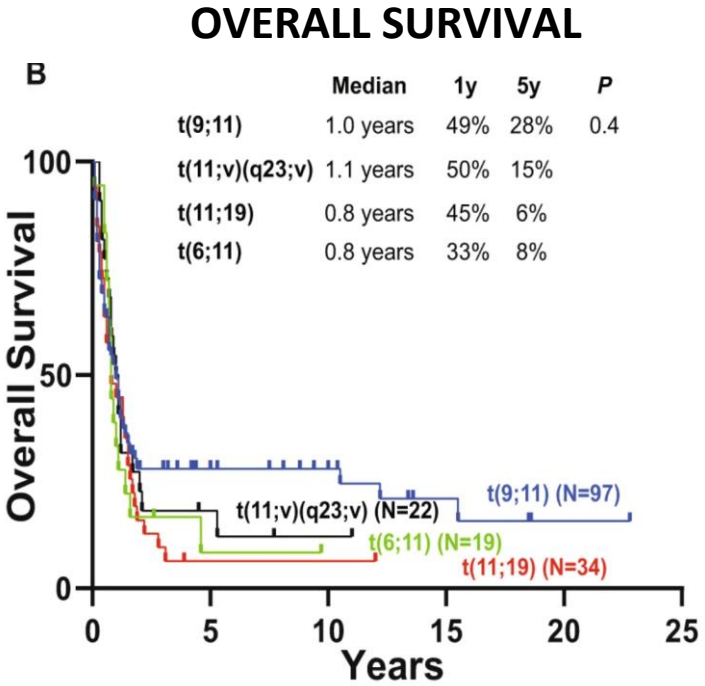
Dohner H et al., Blood 2022

R/R NPM1-mut OVERALL SURVIVAL



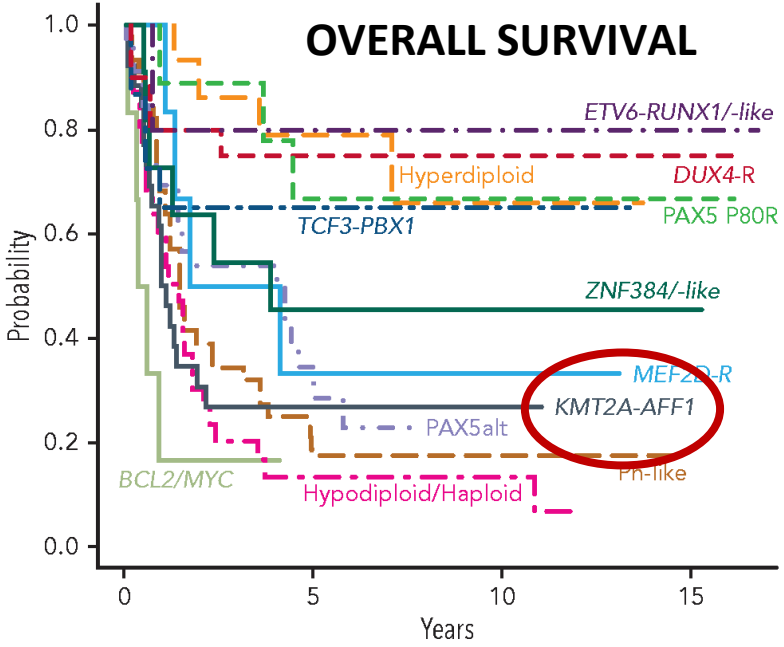
Issa GC et al., Blood Adv 2023

r-*KMT2A* AML outcome



Issa G C et al, Blood Cancer Jour 2021

r-*KMT2A* ALL outcome



Paietta E et al, Blood 2021

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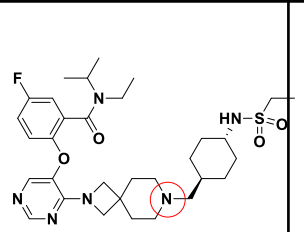
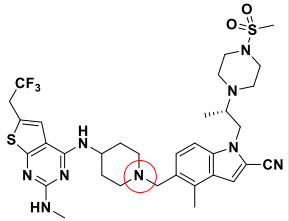
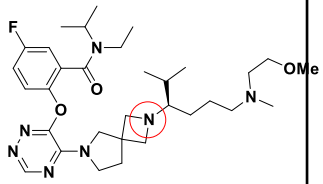
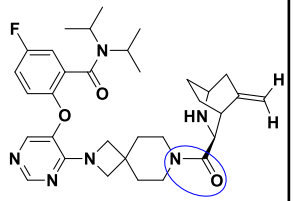
Menin inhibitors in clinical development

Trial name (NCT)	Agent (route)	Phase 1/ 2 expansion cohorts For relapsed/refractory disease	Phase /# pts	Current status
AUGMENT-101 (NCT04065399)	**Revumenib** (SNDX-5613) PO BID	(a) ALL or MPAL with *KMT2Ar* (b) AML with *KMT2Ar; (c) NPM1*	Phase 1 /2 (n=186)	**NPM1^{mut} r-KMT2A FDA approval Nov 15, 2024**
KOMET-001 (NCT04067336)	**Ziftomenib** (KO-539) PO QD	(a) AML with KMT2Ar (b) AML with NPM1c	Phase 1 /2 (n=199)	**NPM1 mut FDA approved in 2025**
NCT04811560	**Bleximenib** (JNJ-75276617) PO QD	(a) AML/ALL with *KMT2Ar* (b) AML with *NPM1c*	Phase 1 (n=110)	**Phase 1 (EHA 2024) Recruiting in combination with chemo**
NCT04988555	**Enzomenib** (DSP-5336) PO QD	RR-AML/RR-ALL Ph2:*NPM1/KMT2Ar*	Phase 1/2 (n=70)	**Phase 1 (EHA 2024) Recruiting**
COVALENT-101 (NCT05153330)	BMF-219 PO	(a) AML/ ALL (KMT2Ar, *NPM1*) (b)DLBCL; (c) MM; (d) CLL/SLL	Phase 1 (n=177)	Multiple cohorts Actively enrolling

www.clinicaltrials.gov

Menin inhibitors are not the same with differencies in chemical structure and physiochemical properties

	Revumenib	Ziftomenib	Bleximenib	Enzomenib
Structure*				
	Tertiary amine bond	Tertiary amine bond	Tertiary amine bond	**Amide bond**

*National Center for Biotechnology Information (2024). PubChem Compound Summary for CID 132212657, 138497449, 156498110, 146430058

- Each menin inhibitor has a different chemical structure and different physiochemical properties such as polar surface area, lipophilicity, and basicity that may impact safety and efficacy[1,2]

Chemical Property*	Polar Surface Area[1,2,3]	Lipophilicity[1,2]	Basicity[1,2]
Target Value	PSA > 75	ClogP <3.0	Pka <7.4
Enzomenib	**89.8**	**2.9**	**6.68**
Revumenib	106.9	3.13	9.27
Bleximenib	85.6	3.63	9.48
Ziftomenib	119.7	5.88	8.85

Daver N et al, ASH 2025

**Numeric values derived from ChemDraw based on NIH CID*

Hughes, J., et. Al (2008) Biorg Med. Chem. Lett., 18, 17, 4872-48Yukawa T., Naven R. (2020) ACS Med. Chem.Lett., 11, 203-209

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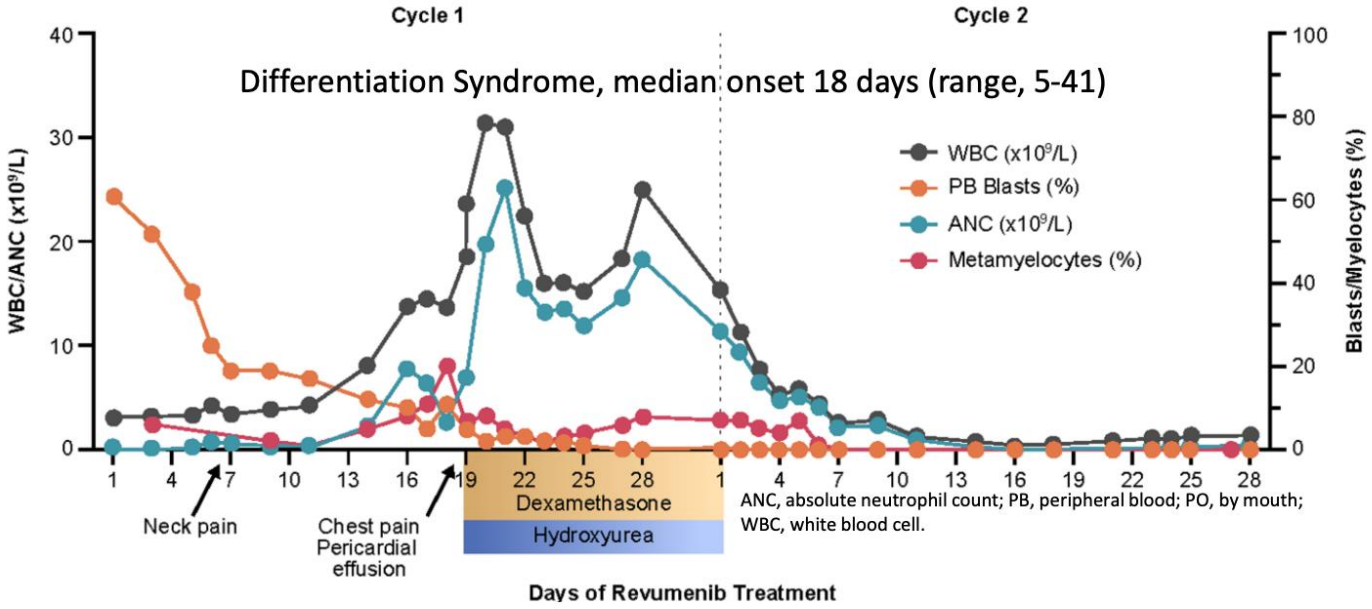
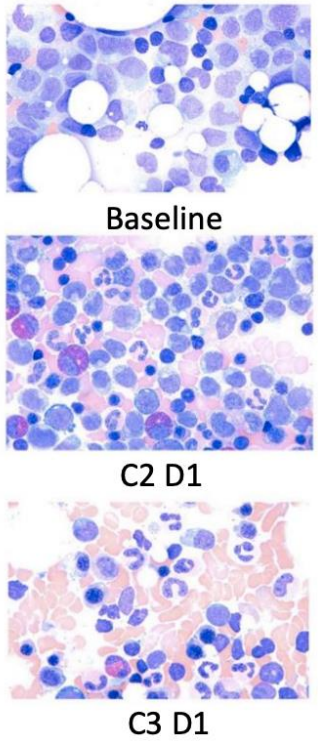
Safety profile

Agent (# pts)	Revumenib (n=199)	Ziftomenib (n=112)	Bleximenib (n=146)	Enzomenib (n=84)
Trial	Phase 2	Phase 1b/2	Phase 1	Phase 1
DLT (Y/N)	Yes	Yes	Yes	No
DLT	QTC prolongation	DS	DS	Not reported
DS (all)	KMT2Ar:27.7%; NPM1:19%	24%	14.4% all doses	10.7%
DS (≥Gr3)	13-16%	13%	6.8%	None reported
Febr Np (≥Gr3)	34.5-38.3%	22%	19.2%	23.8%
Neutrop (≥Gr3)	29.8%	Not reported	28%	17.9%
Thromb (≥Gr3)	16.7-23.4%	20%	36%	23.8%
QTc PR (any)	25.5%-42.9%	3%	0%	1%
QTc PR (≥Gr3)	13.8-22.6%	2%	0%	1%

Issa GC et al JCO 2025; Wang ES et al JCO 2025; Searle E et al Blood 2024; Zeidner J et al Blood 2024

Differentiation Syndrome

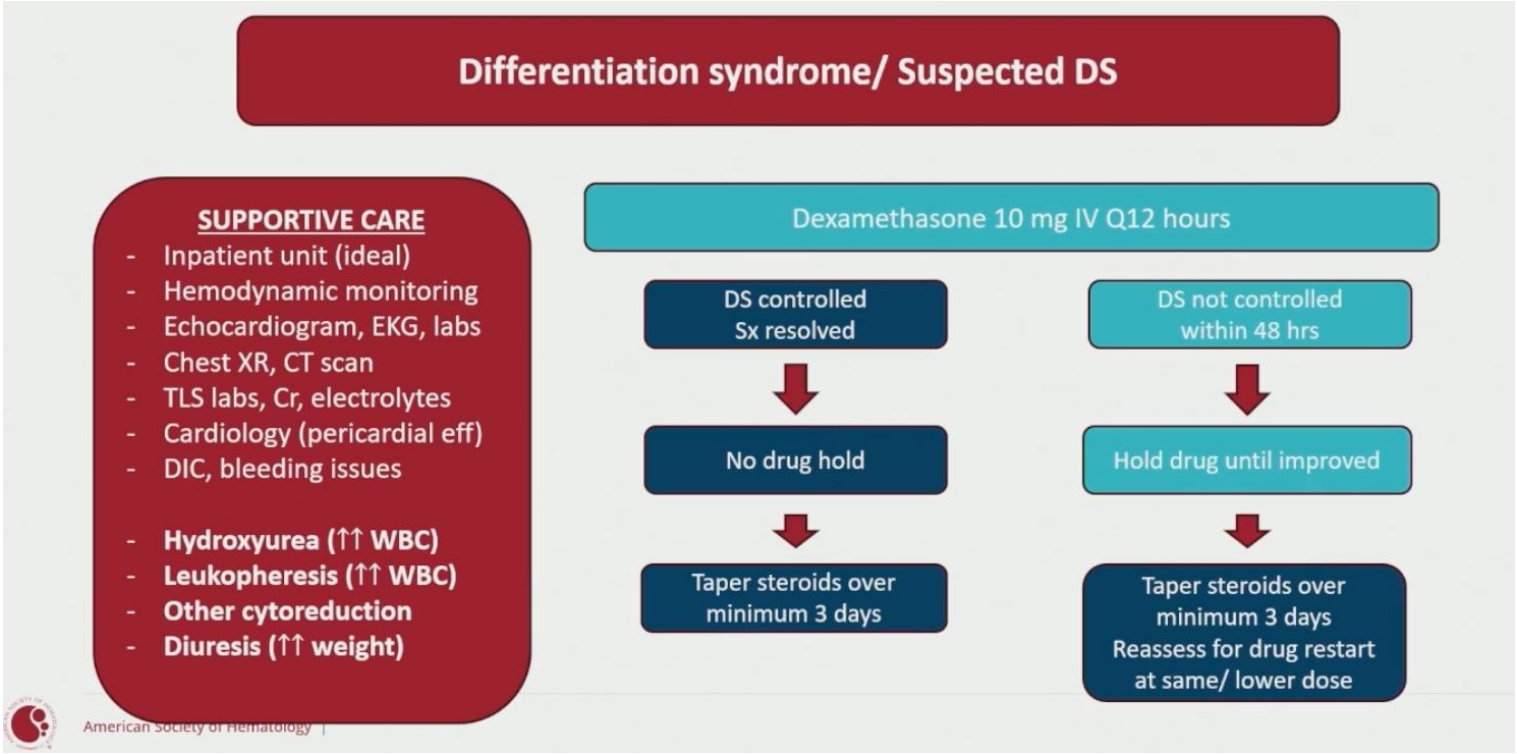




- 71-year-old with *KMT2Ar* AML relapsed after an allogeneic stem cell transplant
- Received revumenib at 339 mg PO q12h (Arm A), and achieved CRh, MRD negative

Issa GC et al, Nature 2023

How to manage Differentiation Syndrome



Wang E, ASH 2025

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Issa GC et al JCO 2025; Wang ES et al JCO 2025; Searle E et al Blood 2024; Zeidner J et al Blood 2024

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Menin inhibitors in R/R setting (single agents)

Menin inhibitor	Revumenib	Ziftomenib	Bleximenib	Enzomenib
Phase Trial	Ph 2	Ph 1b/2	Ph 1	Ph 1
Dose/frequency	163 mg bid	600 mg qd	90-100 mg bid	200-300 mg bid
KMT2Ar (n)	97	None	15	23
NPM1m (n)	83	93	14	17
CR	KMT: 15.5%; NPM1: 18.8%	NPM1: 18%	N/A	N/A
CR/CRh	KMT: 22.7%; NPM1m: 23.4%	NPM1: 35%	38%	37.5%
ORR (CRc+PR + MLFS)	KMT: 63.9%; NPM 46.9%	NPM1: 35%	47%	62.5%
MRD-neg CR/CRh	KMT: 61%; NPM: 64%	NPM1: 65%	N/A	N/A
Median DOR CR/CRh	KMT: 6.4; NPM1: 4.7 mo	NPM1: 3.7 mo	6 mo	KMT: NR; NPM1 7.0mo
Median OS (mo)	KMT: 8.0; NPM1: 4.0 mo	NPM1: 6.1 mo	N/A	N/A

Aldoss I et al EHA abstract 2025; Arellano et al EHA abstract 2025; Wang E et al JCO Nov 2025; Zeidner J et al ASH abstract 2025

Enzomenib response rates

KMT2Ar AL (n = 39)

- Optimal RP2D as monotherapy is 300 mg po bid (n=15)
- At RP2D
  - Overall Response rate (CR/CRh/CRi/MLFS) 73.3%
  - Composite CR rate (CR/CRh/CRi) 60%
  - CR + CRh rate 40%

NPM1m AML (n = 25)

- Dose optimization is ongoing at 200, 300 and 400 mg po bid and initial activity is similar across dose levels

Response Category* * Pts who achieved CRh and CRi or MLFS were counted as CRh	NPM1m 200 mg BID (n = 10)	300 mg BID (n = 7)	400 mg BID (n = 8)
Overall Response rate (CR/CRh/CRi/MLFS)	60% (6/10)	57.1% (4/7)	37.5% (3/8)
Composite CR rate (CR/CRh/CRi)	50% (5/10)	42.9% (3/7)	37.5% (3/8)
CR/CRh rate	50% (5/10)	42.9% (3/7)	37.5% (3/8)

Daver N et al, ASH 2025

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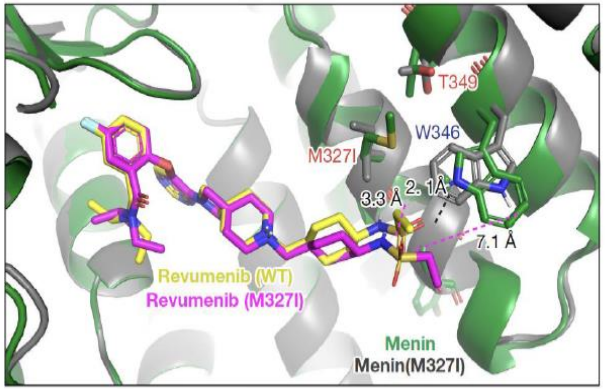
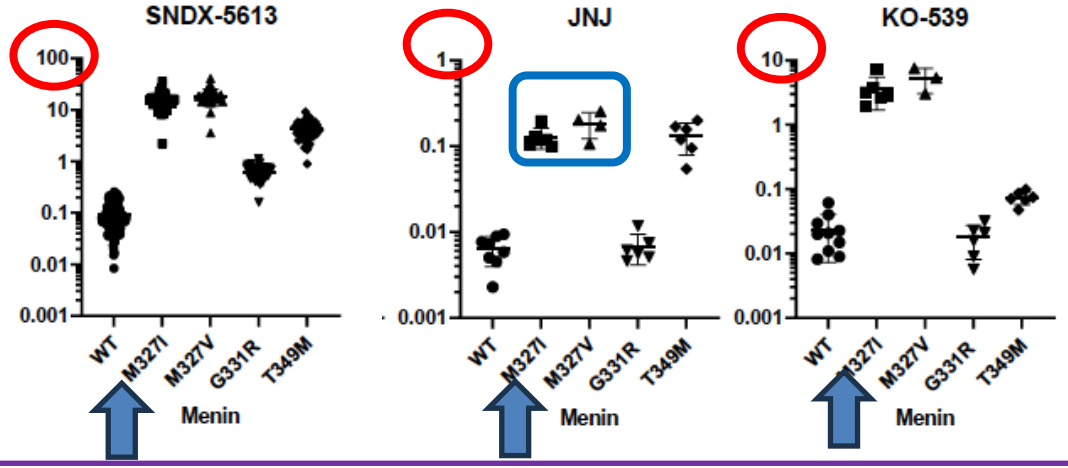
MEN1 mutations generate structural perturbations that impact small-molecule binding





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

Other resistance mechanisms

Resistance mechanism	Genetic/epigenetic alterations	Consequences	Frequency/ detection method	Therapeutic strategey
Mutations in menin-binding domain	**MEN1 mutations (e.g. M3271, T349M, G331R, E368K)**	Reduced menin inhibitor binding	39-40% after revumenib by RNA sequencing	**Alternative menin inhibitors; combination therapy**
Alternative proliferation pathways	**RAS pathway mutations (NRAS, KRAS, PTPN11)**	Leukemic proliferation indept of menin inhibition	Common acquired pathways by DNA/RNA NGS	**Combination therapy with MAPK, FLT3, or other inhibitors**
Apoptotic and differentiation resistance	**TP53 mutations, MCL-1 upregulation, BCL-xL**	Reduced apoptosis and differentiation response	Frequently co-occurring in high-risk AML	**Combine with MCL-1 inhibitors or or BCL-2 inhibitors**
Epigenetic reprogramming and MYC activation	**Loss of PRC1.1, MYC upregulation**	Blocked differentiation, altered epigenetics	Identified by chromatin & transcriptome assays	**Combine with epigenetic modifiers**

Thakur R and Wang ES. ASH Education Bk 2025

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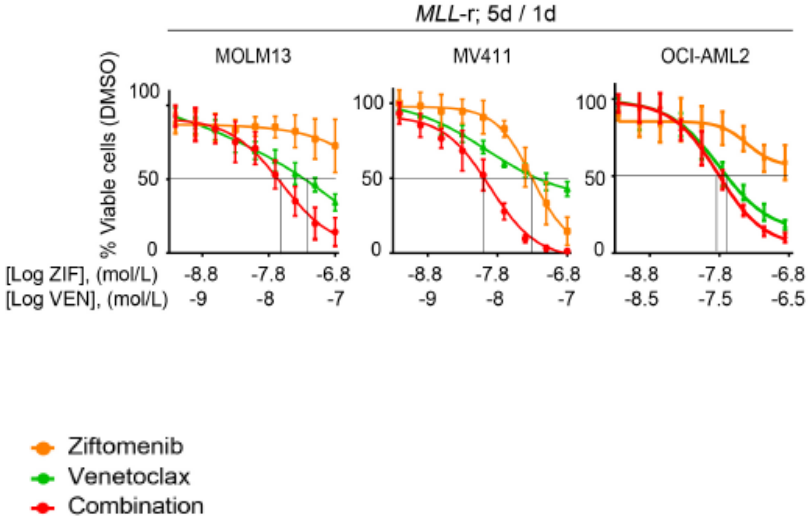
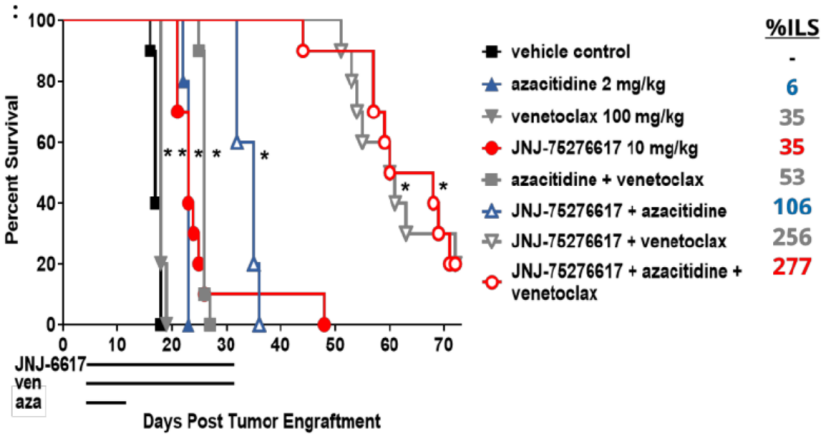
Preclinical data support menin inhibitors combinations in r-*KMT2A* leukemia

Ziftomenib



Rausch J et al, Haematologica 2023

JNJ-75276617



Chul Kwon M et al, ASH 2023

Menin inhibitors partners

Conventional or approved agents

- Standard high or low intensity chemotherapy regimens
- Hypomethylating agents[1]
- BCL2 inhibitors[1,2]
- FLT3 inhibitors[3,4,5]
- IDH inhibitors[6]
- Blinatumomab (CD3;CD19)
- Inotuzumab (ADC: CD22)
- Gemtuzumab (ADC: CD33)

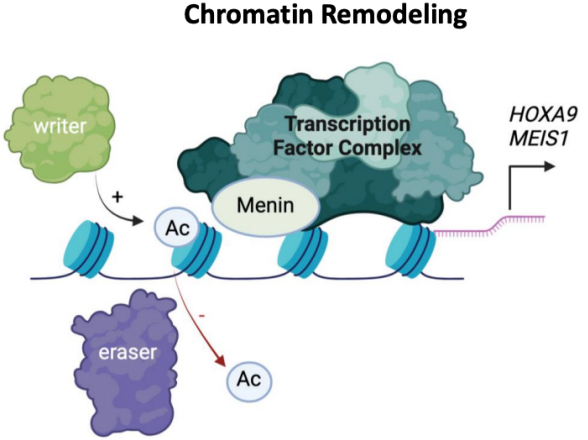
- Revlimid[7]
- […]

Investigational agents/targets

Writers
- DOT1L[8,9]
- CBP/p300[10]
- KAT6
- HBO1

Readers
- BRD4[10]
- ENL YEATS
- LEDGF
- SGF29

Erasers
- HDAC[11]
- LSD1
- CDK4/6[12]
- CDK9
- SWI/SNF
- XPO1[13,14,15]
- […]



References indicate preclinical evidence of combination with menin inhibition

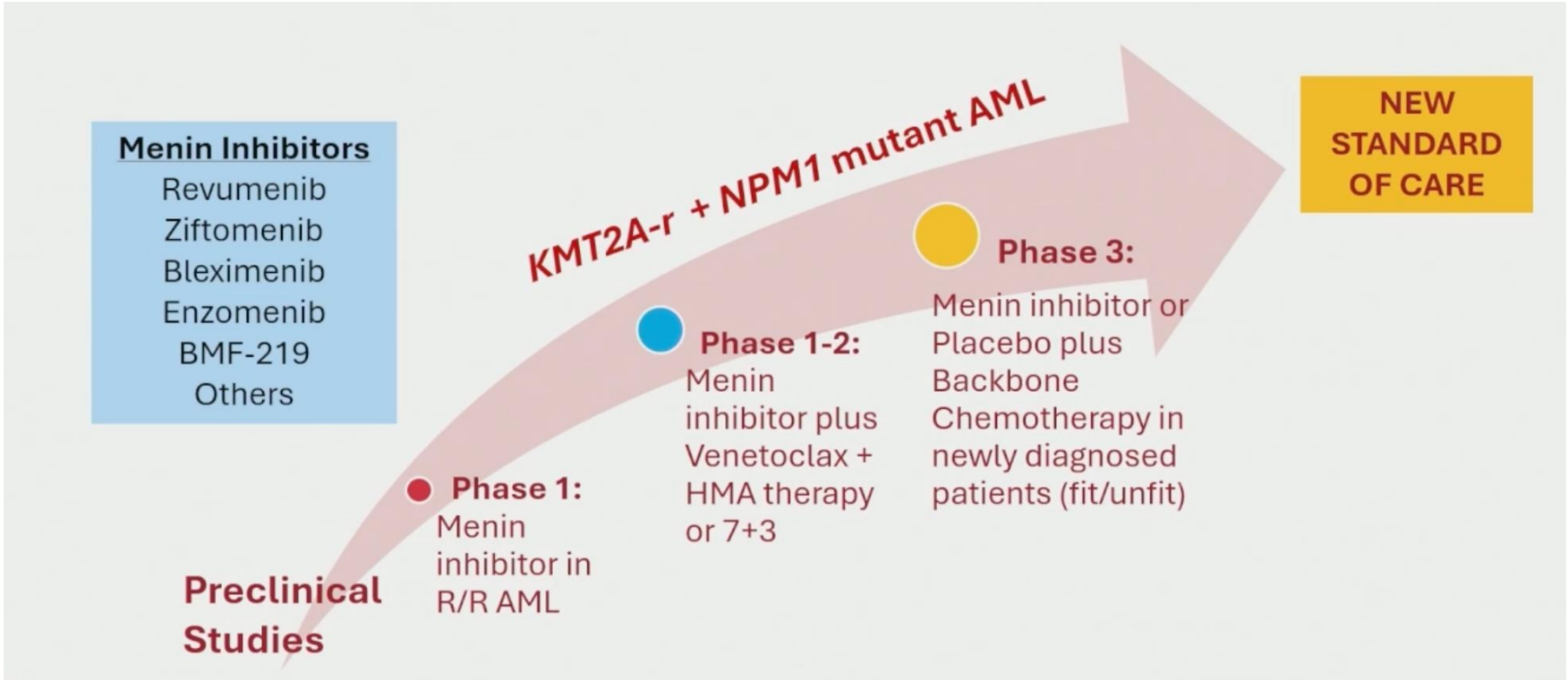
[1]Carter B. et al. Blood (2021) 138 (17): 1637–1641;2; [2]Fiskus W et al. Blood Cancer J. 2022 Jan 11;12(1):5; [3]Dzama MM et al. Blood. 2020;136(21):2442-56. [4]Miao H et al. Blood. 2020;136(25):2958-63. [5]Carter B et al. Haematologica. 2023 Feb 2. [6]Yoon JJ et al. Blood (2022) 140 (Supplement 1): 5946. [7]Aubrey BJ et al. Nat Cancer. 2022 May;3(5):595-613. [8]Kühn MW et al. Cancer Discov. 2016 Oct;6(10):1166-1181. [9]Dafflon C et al. Leukemia. 2017;31:1269–77. [10]Fiskus, W. Et al. Blood Cancer J. 13, 53 (2023). [11]Mill CP et al. Leukemia. 2023 Mar 28. [12]Soto-Feliciano et al Cancer Discov 1 January 2023; 13 (1): 146–169 [13]Brunetti L et at. Cancer Cell. 2018 Sep 10;34(3):499-512.e9. [14]Uckelmann et al. Cancer Discov 1 March 2023; 13 (3): 724–745. [15]Wang XQD et al. Cancer Discov 1 March 2023; 13 (3): 746–765.

Menin inhibitors in triplets for R/R AML patients

Agent (# pts)	Bleximenib + Ven/Aza	Revumenib + Ven/Aza (SAVE)	Ziftomenib + Ven/Aza (KOMET-007)	Enzomenib + Ven/Aza
Trial	Phase 1	Phase 1	Phase 1	Phase 1
Number Pts	N=125	N =33	N=83	N=22
Start Menin Inhib	C1 D4	C1 D1	C1 D8	C1 D1
DS	6% (5 Gr3)	9% ((1 Gr3)	1%	10% (no Gr3)
QTc prolongation	4%	64%; 9% ≥Gr3	0%	10% (no Gr 3)
CR	Not reported	39%	27%/6%	Not reported
CR/CRh	40.9%	48%	NPM 40%/KMT 22%	Not reported
CRc (CR/CRh/CRi)	59.1%	60%	NPM 48%/KMT 28%	50%
ORR	81.8%	82%	NPM 65%/KMT 41%	77%

Wei et al EHA 2025; Issa et al ASH 2024; Issa G et al ASH 2025; Watts J et al ASH 2025

Let's move Menin inhibitors to the first line

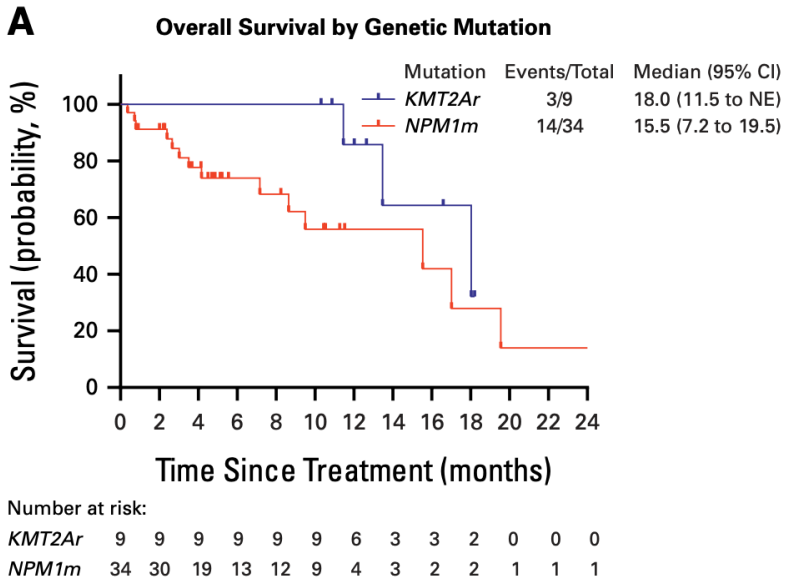


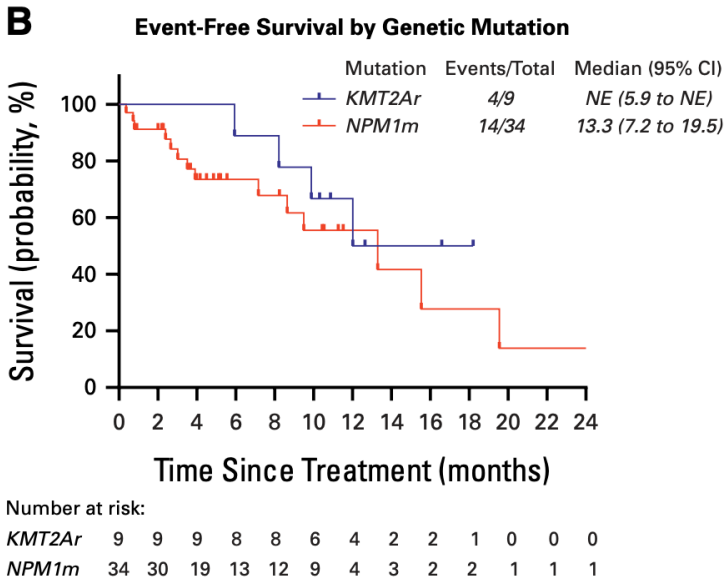
Menin inhibitors in triplets for ND unfit AML patients

Agent (# pts)	Bleximenib + Ven/Aza	Revumenib + Ven/Aza (SAVE)	Ziftomenib + Ven/Aza (KOMET-007)
Trial	Phase 1	Phase 1	Phase 1
Number Pts	N=125	N =21	N=40
Start Menin Inhib	C1 D4	C1 D1	C1 D8
DS	6% (5 Gr3)	19% (10% Gr 3)	3% (no Gr3)
QTc prolongation	4%	43% (No ≥Gr3)	3% (1 Gr 3)
CR	Not reported	76%	73%
CR/CRh	65%	81%	78%
CRc (CR/CRh/CRi)	75%	86%	86%
ORR	90%	86%	89%

Wei A et al EHA 2025; Jen W et al ASH 2025; Roboz G et al ASH 2025

Acacitidine+Venetoclax+Revumenib: Survival





SCT 23%

Zeidner J et al, JCO 2025

Menin inhibitors in clinical development in 1L AML fit patients

	Revumenib		Ziftomenib	Bleximenib
Trial	Ph 3 REVEAL-ND NPM1 NCT07211958	*Ph 2 RAVEN ISS* *(planned in H2'26)*	Ph 3 KOMET-017 NCT07007312	Ph 3 HOVON-181 NCT07223814
Mutation	mNPM1	*KMT2Ar*	mNPM1, KMT2Ar (one arm)	mNPM1, KMT2Ar (one arm)
Regimen	REV + **'7+3'**	*REV + **VEN/AZA***	ZIF + **'7+3'**	BLE + **'7+3'**
Enrolment	468	*n/a*	1300	875

www.clinicaltrials.gov

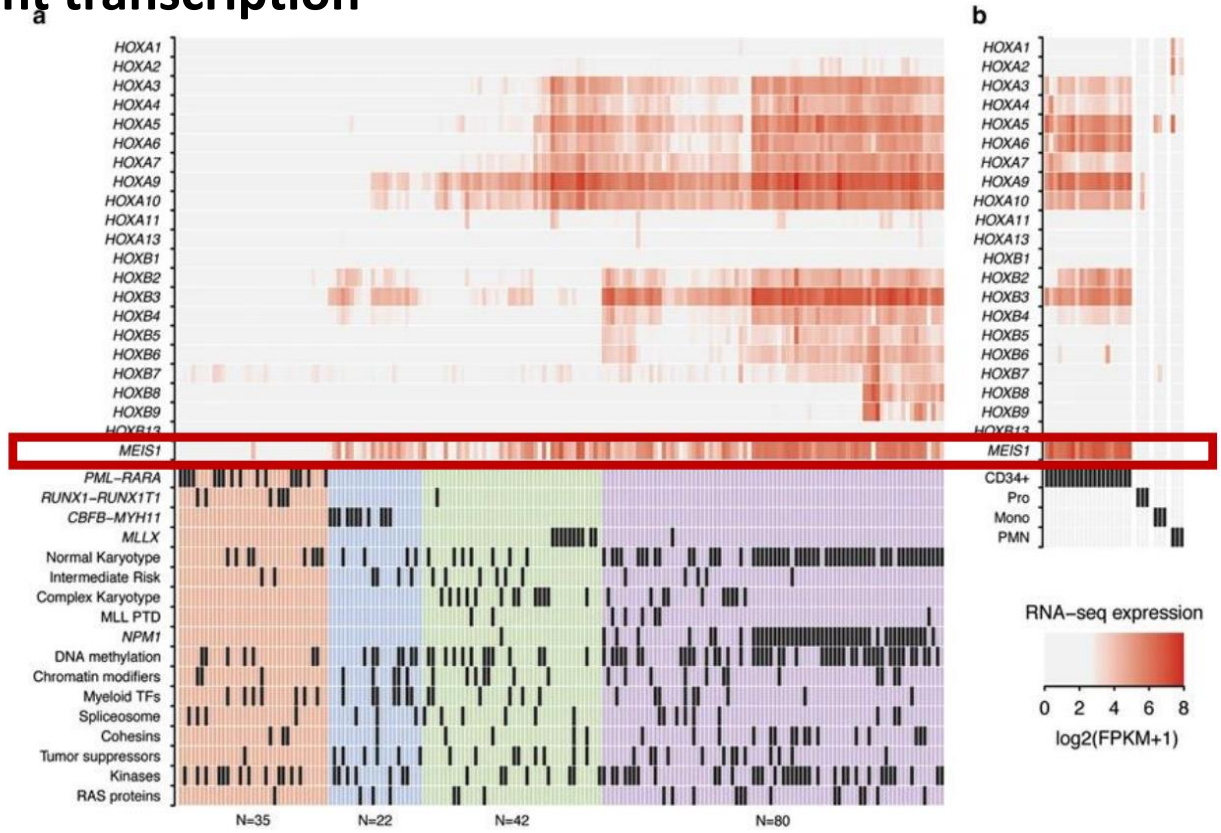
Agenda

- For which patients today?
- How many menin inhibitors do we have today?
- What about safety with menin inhibitors as single agents?
- Which results can we achieve with menin inhibitors?

  -R/R single agents
- What about resistance?
- How can we overcome these mechanisms?
- For which patients, tomorrow?

Targeting menin-dependent transcription

~ 60% of AML with upregulation of *HOX/MEIS* *(associated with other genotypes in addition to KMT2Ar and mNPM1)*



Spencer DH et al, Leukemia 2015

Targeting menin-dependent transcription

Table 2 Genetic alterations with overexpression of *HOXA* genes predicted to potentially respond to menin inhibitors.[1]

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.

One patient with AML (*SETD2*, *RUNX1*) attained CR, MRD+ with ziftomenib 100 mg.[2]

Issa GC et al, Leukemia 2021; Wang E et al, Blood 2020; Barajas JM et al, Blood 2024

Menin inhibitors: take home messages (I)

- **At least 4 agents in development, 2 FDA approved (Revumenib, Ziftomenib)**
- Clinical activity as single agent in R/R AML with NPM1mut and r-KMT2A:

✓ 30-60% ORR

✓ Duration of response: 5-7 months

✓ Overall survival: 6-8 months

- On target drug effect: **Differentiation syndrome**

- Are there **differencies between agents**? Yes, due to:

✓ Drug: Half-lives, tissue penetration, azole interactions, QTc prolongation

Menin inhibitors: take home messages (II)

- **Triplets** are promising
- Reduced DS compared to monotherapy
- R/R: **60-80% ORR**
- ND: **80-90% ORR**

- Phase 3 randomized trials ongoing (Ava-Ven/3+7)
- Combination with other targeted agents?
- Efficacy in **other leukemia subtypes**?
- Sequential menin inhibitors treatment? Role of MRD?

Thank you!

PL Zinzani

Antonio Curti
Giovanni Martinelli
Chiara Sartor
Jacopo Nanni
Stefania Paolini
Sarah Parisi
Caterina Azzimondi
Raffaele Ciruolo
Giulia Masala
Benedetta Pagano

Francesca Bonifazi
Enrico Maffini
Sadia Falcioni

Simona Soverini
Emanuela Ottaviani
Carolina Terragna
Cecilia Monaldi
Sara de Santis
Valentina Robustelli
Marina Martello
Claudia Venturi
Manuela Mancini
Lorenza Bandini
Carmen Baldazzi
Gabriella Chirumbolo
Dorian Forte
Martina Barone
Francesco Ingletto
Gaia Chinnici

cristina.papayannidis@unibo.it