



2nd BOLOGNA WORKSHOP

on IMMUNOTHERAPY FOR ACUTE MYELOID LEUKEMIA

Bologna, Royal Hotel Carlton
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Menin inhibition: immunological effects and implications for future immunotherapies

Menin inhibitors

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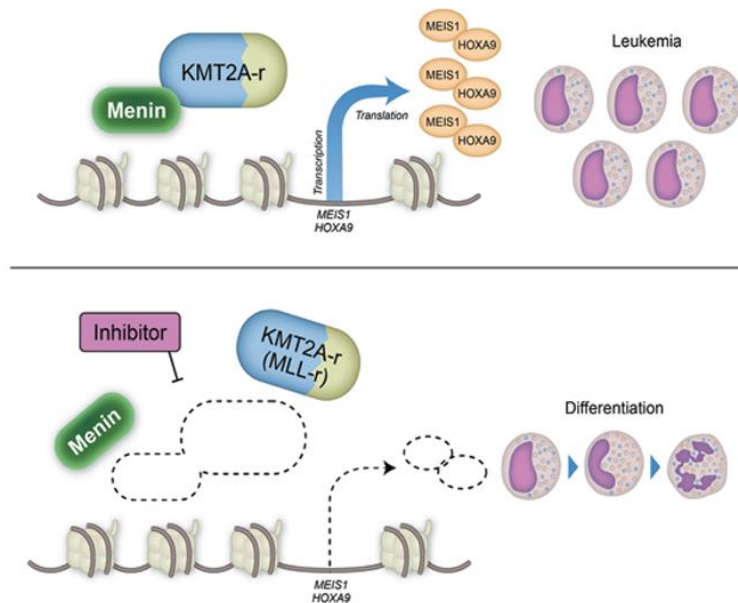
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Disclosures of CRISTINA PAPAYANNIDIS

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
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Astellas							X
Servier						X	X
Menarini							X
BMS							X
Pfizer							X
Amgen						X	X
Janssen						X	
GSK						X	
Blueprint							X
Incyte							X
Imcheck						X	
AZD						X	
Kura Oncology						X	
Jazz pharmaceuticals							X
MSD						X	
Otsuka						X	
Syndax						X	

The classical view of menin inhibition



- ✓ The menin–KMT2A complex sustains a transcriptional program involving HOXA and MEIS1 that maintains leukemic identity and self-renewal.
- ✓ Menin inhibitors disrupt this dependency.
- ✓ The result is transcriptional reprogramming, loss of the leukemic stem-like state, and induction of myeloid differentiation.
- ✓ But differentiation is not necessarily «immunologically neutral»

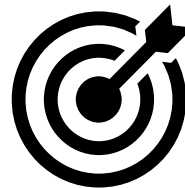
Menin inhibition in the clinic

	Revumenib	Ziftomenib	Bleximenib	Enzomenib
Dosing/Admin	270 mg BID (160 mg BID with CYP3A4 inhibitors)	600 mg DAILY (No PPI, H2A)	100 mg BID	300 mg BID
PK/PD properties	Half-life= 3-10h	Long half-life=61-93h	Not reported	Short half-life=2-10h
CR/CRI	21.2% (KMT2Ar); 23.1% (NPM1m)	21.4% (NPM1m)	33% (KMT2Ar); 33% (NPM1)	40% (KMT2Ar); 43% (NPM1m)
Overall survival	8.0 mos (KMT2Ar); 4.0 mos (NPM1m)	6.0 mos (NPM1m)	CR/CRI: 6.4 mos; OS not reported	11.8 mos (KMT2Ar); 8.5 mos (NPM1m)
Major toxicities	QTC (Any: 36%; G3: 17%) DS (Any: 18-33%, G3: 12%) Cytopenia (21-38%)	DS (Any:26%, G3:13%) QTC (Any:12%, G3 8%) Pruritis (Any:13%)	DS (Any: 14%; G3 8%) Cytopenias (26-31%) QTC (1 patient)	DS (Any:13%, Gr3 8%) QTc (Any:9.5%; G3 3%) Cytopenia (20-30%)
MEN1 resistance mutations	M327, S160, G331, T349	<i>M327, G331 (in vitro)</i>	? M327, T349 (in vitro)	<i>S160, M327, T349 (in vitro for all)</i>
Approval Status	R/R KMT2Ar & NPM1m acute leukemia (USA)	R/R NPM1m AML (USA)	Not approved	Not approved

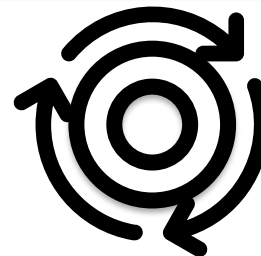
Revumenib PI; Ziftomenib PI; Searle ASH 2024; Daver ASH 2025

Does menin inhibition make leukemia more visible?

TARGET THE LEUKEMIA

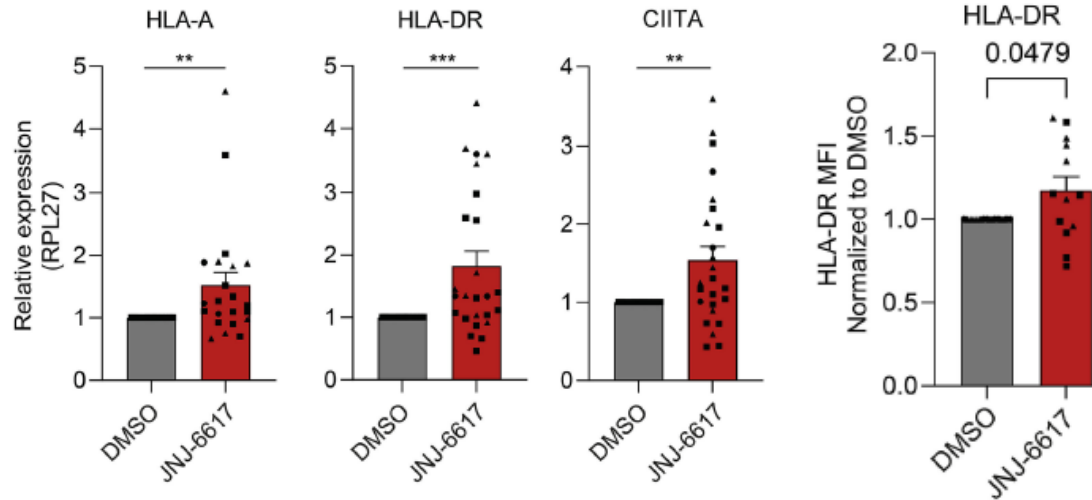


REMODEL THE LEUKEMIA



Can menin inhibition create an immune-accessible leukemia?
...The first evidence comes from antigen presentation

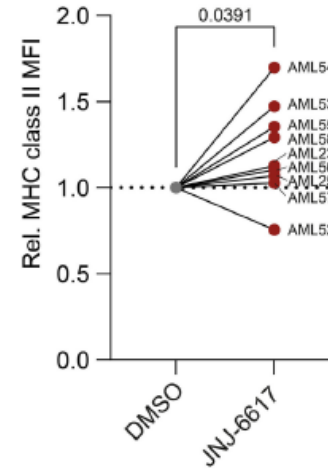
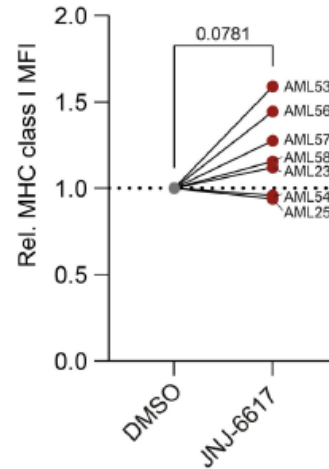
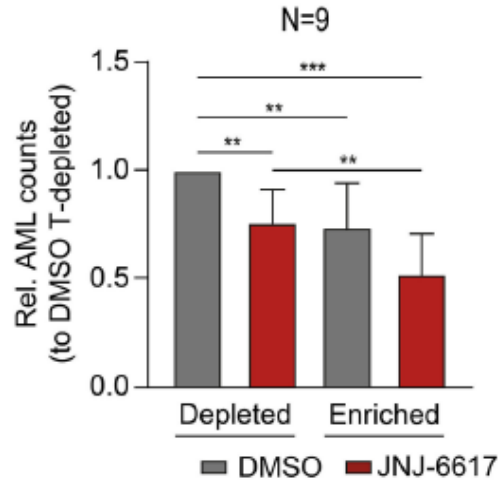
Menin inhibition reactivates antigen presentation



- ✓ With bleximenib, inhibition of the menin–KMT2A interaction resulted in epigenetic activation of HLA loci.
- ✓ Both MHC class I and class II increased.
- ✓ MHC class II induction was associated with activation of CIITA and was not simply explained by loss of MEIS1.

Menin inhibition appears to do something more than induce differentiation
...The leukemia is becoming more visible

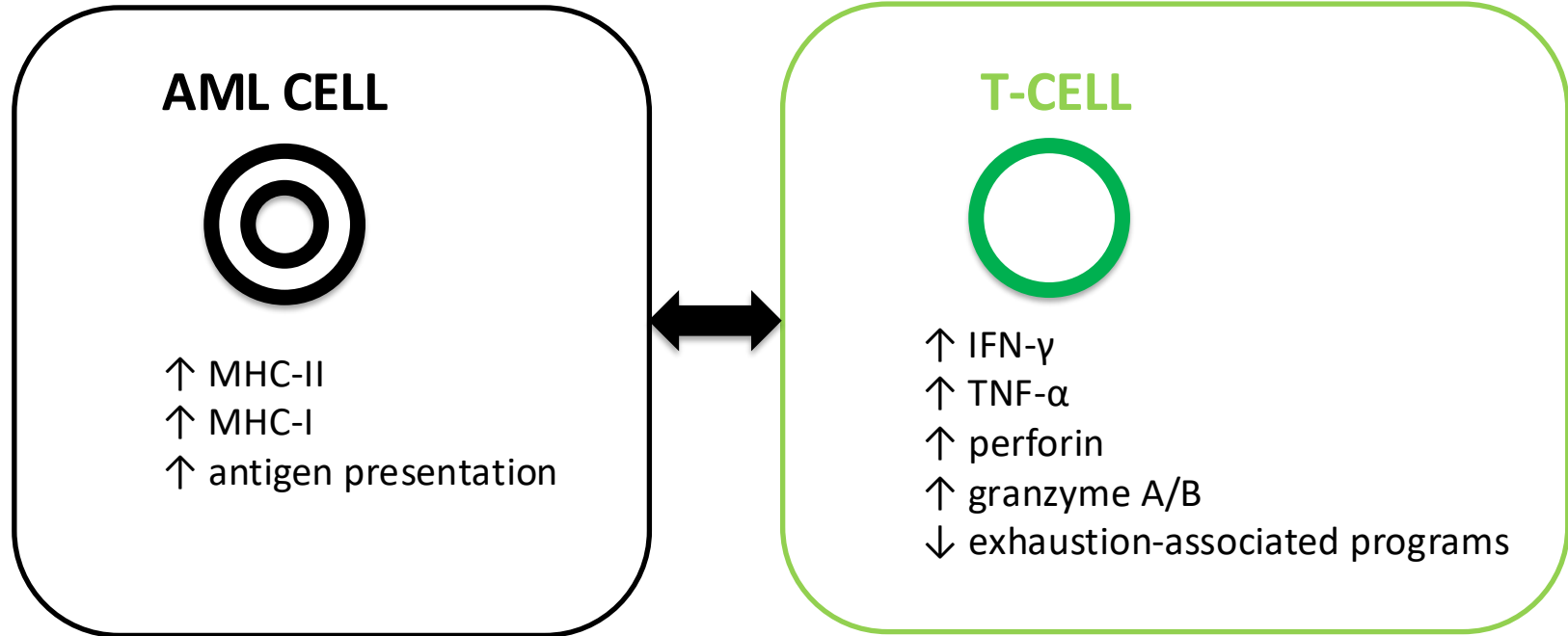
More antigen presentation translates into greater T-cell sensitivity



✓ Menin inhibition increased the susceptibility of AML cells to T-cell-mediated cytotoxicity.

First immunological message:
menin inhibition can make AML more visible to T cells

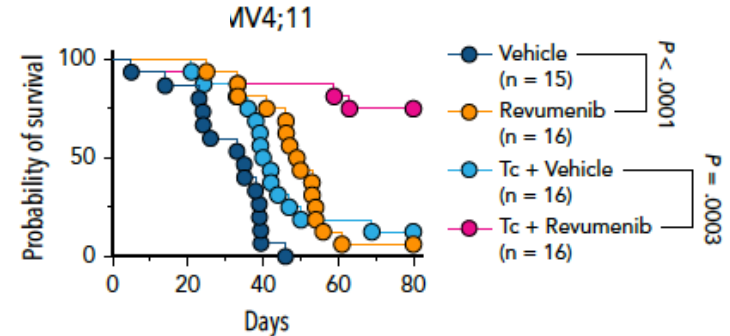
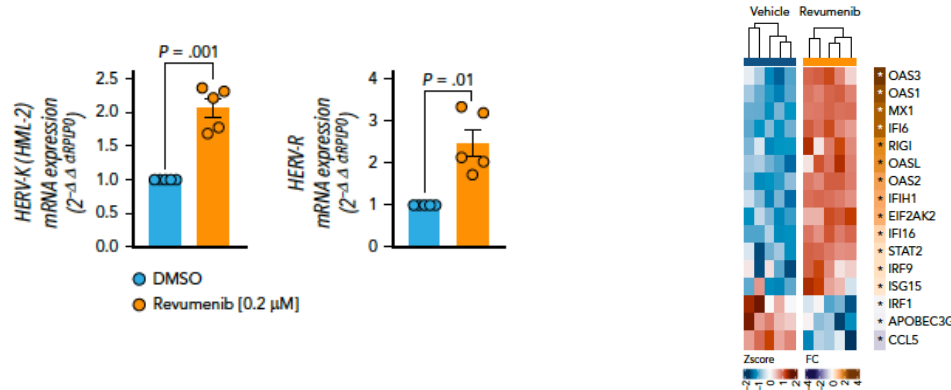
Menin inhibition does not only change the leukemia cell



A TWO-SIDED IMMUNE REMODELING PROCESS

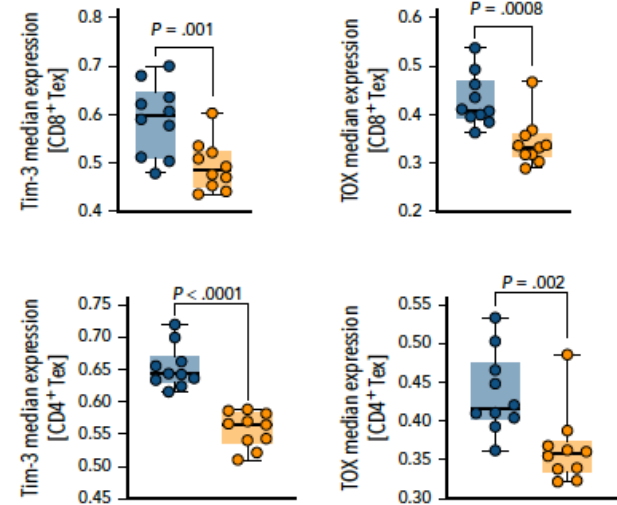
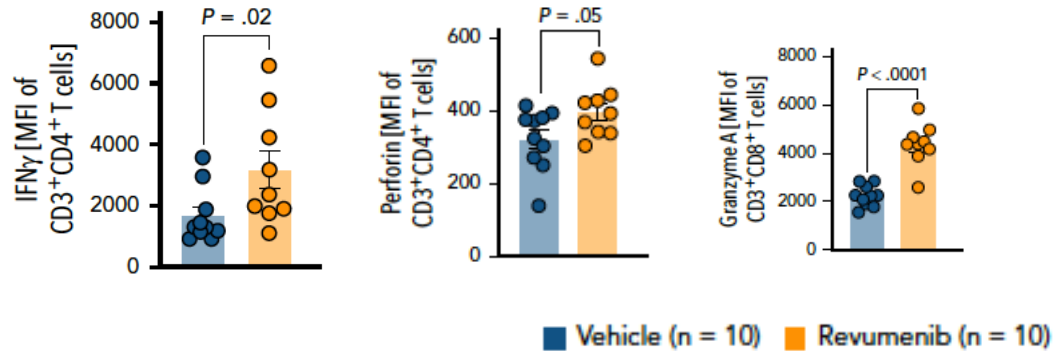
Menin inhibition enhances graft-versus-leukemia

↑ HERV expression $\Rightarrow$ ↑ Interferon-stimulated genes $\Rightarrow$ ↑ MHC class II expression induction



→ Functionally, this enhanced T-cell-mediated elimination of AML after transplantation in preclinical models

Donor T-cells showed increased production of TNF-alpha, IFN-gamma, perforin and granzymes



Second immunological message:
**menin inhibition appears to create a more immunogenic leukemia and
a more effective antileukemic T-cell response**

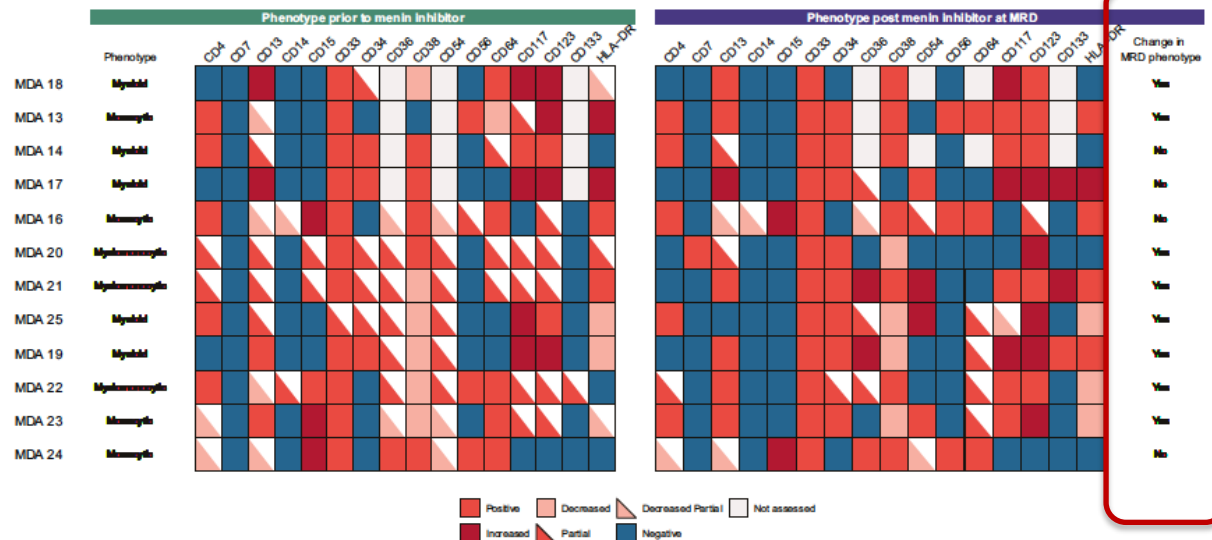
Menin inhibition creates an immune-permissive state

- ✓ Menin inhibition is not an immunotherapy, but **it may act as an immune-enabling therapy**
- ✓ It remodels the leukemia, increases antigen presentation and interferon-related programs, and may simultaneously improve the functional state of T cells.
- ✓ The therapeutic opportunity is therefore to ask whether menin inhibition can **prime leukemia for immunotherapy**

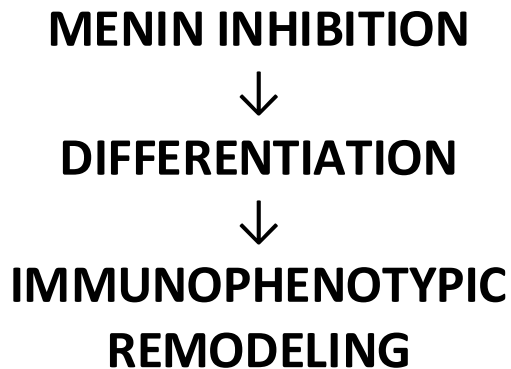
The immunophenotype is dynamic

- ✓ The leukemia we target after menin inhibition may not be the same leukemia we started with
- ✓ Leukemia could move between more stem-like or myeloid phenotypes and more monocytic or myelomonocytic phenotypes, with substantial changes in antigen expression

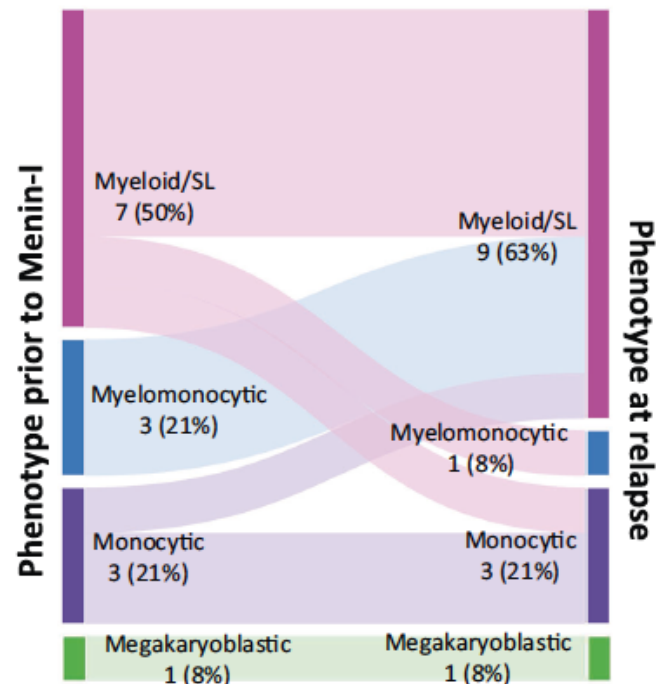
MENIN INHIBITION
 ↓
DIFFERENTIATION
 ↓
IMMUNOPHENOTYPIC REMODELING



The immunophenotype is dynamic also at relapse



This matters for immunotherapy.
If menin inhibition changes the phenotype of the leukemia, then the optimal immune target may also change over time



Menin inhibition may create an actionable immune target: CLEC12A

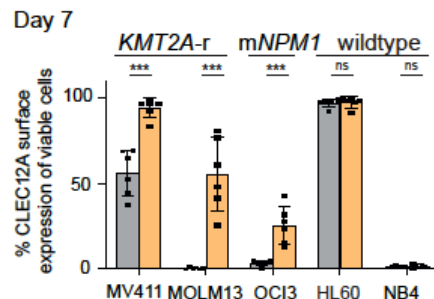
**Differentiation /
immune remodeling**



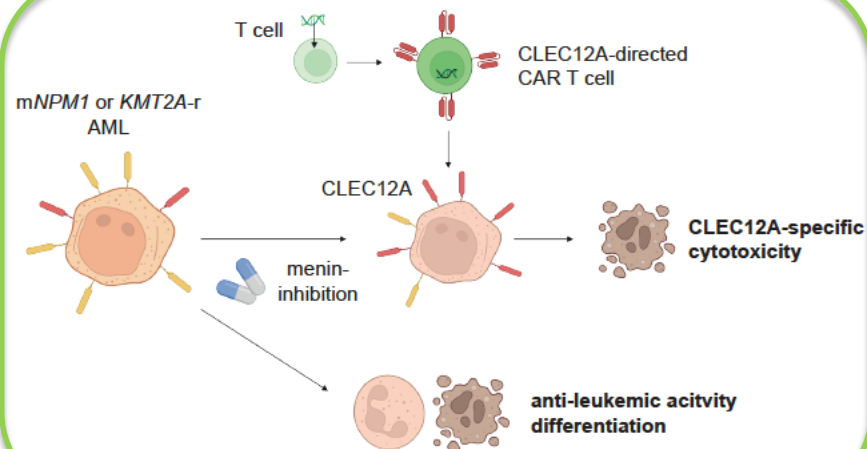
↑ CLEC12A / CLL-1



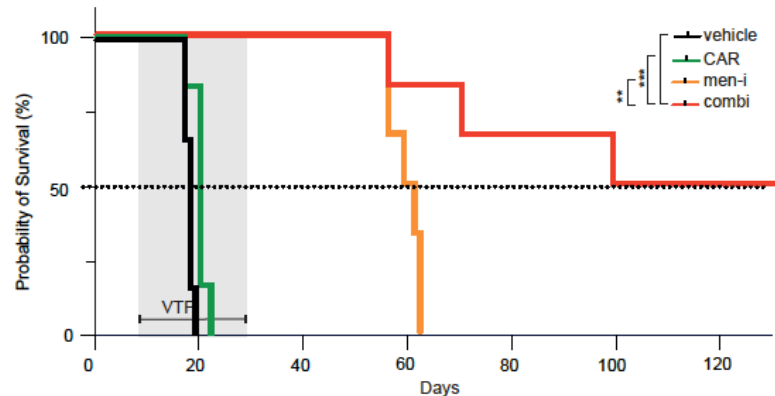
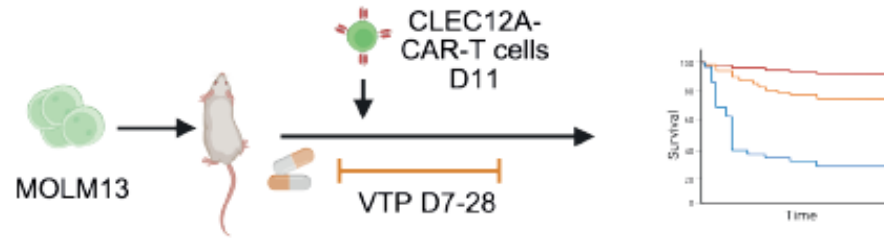
**CLEC12A-directed
CAR-T / CAR-NK**



Menin inhibition increases
CLEC12A surface
expression in
 $NPM1^{mut}$ AML cells *in vivo*



Potential clinical implications



- Combining CLEC12A-directed CAR T-cell therapy with menin-inhibition significantly prolongs the survival of mice in a KMT2A-r AML xenograft model
- Menin inhibition may create the target that a cellular therapy needs**

Menin inhibition could be an immune-priming platform

Menin-induced change	Potential immune strategy
↑ MHC-I / MHC-II	T-cell-based therapies
↑ HERV / IFN signaling	T-cell recognition
↑ CLEC12A	CAR-T / CAR-NK
↑ differentiation	Antigen-targeted strategies
↑ GVL	allo-HCT / maintenance 

Third immunological message:

Menin inhibition may be a “priming” therapy rather than the final immune therapy

Revumenib as maintenance after HSCT

Table 1. Baseline Characteristics

Characteristic	All Patients (N = 24)	Adult (N = 13)	Pediatric (N = 11)
Median age, years	22 [1 – 74]	58 [21 – 74]	13 [1 – 17]
Female	14 (58)	10 (77)	4 (36)
Genotype			
<i>NPM1mt</i>	6 (25)	6 (46)	0 (0)
<i>KMT2Ar</i>	17 (71)	7 (54)	10 (91)
<i>NUP98r</i>	1 (4)	0 (0)	1 (9)
Prior HSCT	13 (54)	5 (38)	8 (73)
Lines of Therapy	3 [1 – 11]	3 [1 – 11]	3 [1 – 6]
CR Status at HSCT			
CR1	6 (25)	5 (38)	1 (9)
CR2+	18 (75)	8 (62)	10 (91)
Regimen Pre-HSCT			
Revumenib monotherapy*	10 (42)	4 (31)	6 (55)
SAVE†	14 (58)	9 (69)	5 (45)

* All relapsed/refractory

† Frontline n = 6, relapsed/refractory n = 8

Revumenib as maintenance after HSCT

Table 2. Transplant Characteristics

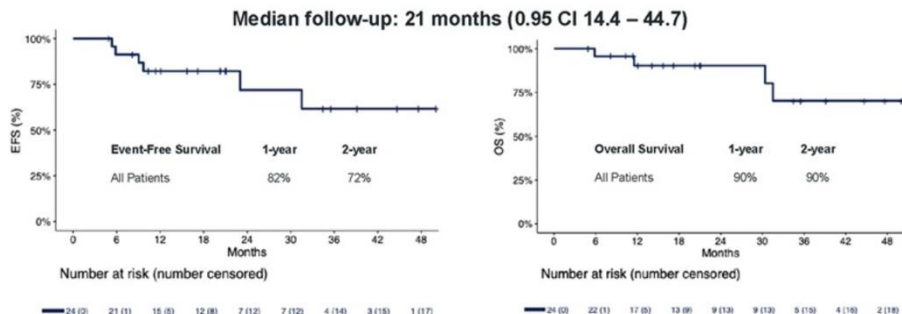
Characteristic	All Patients (N = 24)	Adult (N = 13)	Pediatric (N = 11)
Type of HSCT			
MUD	9 (38)	8 (62)	1 (9)
Haplo	5 (21)	2 (15)	3 (27)
MSD	4 (17)	2 (15)	2 (18)
Cord	4 (17)	0 (0)	4 (36)
MMUD	2 (8)	1 (8)	1 (9)
Conditioning			
Reduced Intensity	9 (38)	8 (62)	1 (9)
Myeloablative	15 (63)	5 (39)	0 (0)
			10 (91)
GVHD Prophylaxis			
Tacrolimus	21 (88)	10 (77)	11 (100)
PTCy	13 (54)	9 (69)	5 (46)
Time to Revumenib Maintenance (days)	82 [42 – 174]	62 [42 – 133]	116 [57 – 174]
Pre-Maintenance Labs			
WBC ($\times 10^9/L$)	5 [2 – 14]	6 [2 – 10]	5 [3 – 14]
Hgb (g/dL)	11 [8 – 14]	11 [8 – 14]	12 [9 – 14]
Plt ($\times 10^9/L$)	171 [73 – 411]	146 [73 – 302]	186 [114 – 411]

Revumenib as maintenance after HSCT

Table 3. Treatment Emergent Adverse Events (TEAE)

TEAEs	All Grades	≥Grade 3	AE with Dose Interruption/Reduction	AE with Discontinuation
Thrombocytopenia	20 (83)	11 (46)	11 (46)	3 (13)
Neutropenia	5 (21)	1 (4)	1 (4)	1 (4)
Infection	4 (17)	2 (8)	2 (8)	1 (4)
GVHD	3 (13)	1 (4)	0 (0)	0 (0)
Nausea/vomiting	2 (8)	0 (0)	1 (4)	0 (0)
Elevated LFTs	1 (4)	0 (0)	0 (0)	0 (0)
Diarrhea	1 (4)	1 (4)	0 (0)	0 (0)
Prolonged QTc	0 (0)	0 (0)	0 (0)	0 (0)
Differentiation syndrome	0 (0)	0 (0)	0 (0)	0 (0)

Figure 1. Survival of Entire Cohort



- Revumenib as maintenance post-HSCT was feasible with no unexpected safety signals
- Thrombocytopenia was common, occurring in 83% of patients (grade ≥ 3 46%), **however this was manageable with dose modifications**
- In our **heavily pre-treated cohort** (CR2+ 74%, prior HSCT>50%), **survival outcomes appear encouraging** relative to historical expectations with 2-year overall survival and event-free survival rates of 90% and 72%, respectively
- Limitations include the small, single-arm design with heterogeneity in disease biology
- These findings **support further prospective evaluation of menin inhibition as maintenance therapy post-HSCT**

Comment > Cancer Cell. 2026 Aug 10;44(8):1544-1546. doi: 10.1016/j.ccell.2026.06.012.

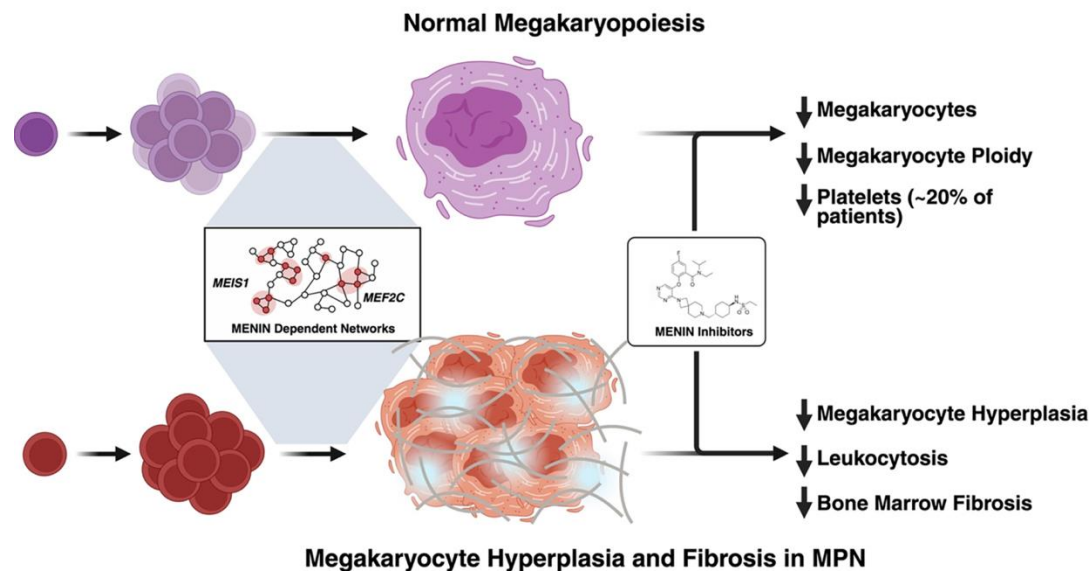
Epub 2026 Jul 9.

Menin in normal and malignant megakaryopoiesis

Justin C Wheat¹, Sheng F Cai²

Affiliations + expand

PMID: 42425077 DOI: [10.1016/j.ccell.2026.06.012](https://doi.org/10.1016/j.ccell.2026.06.012)



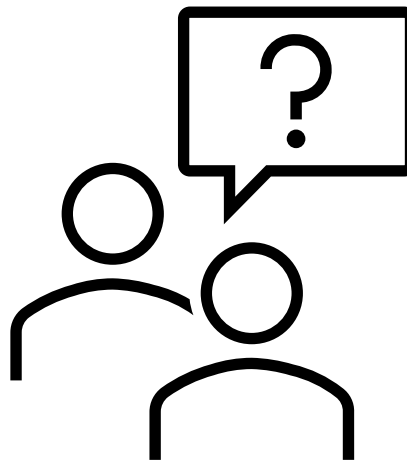
- Menin-dependent transcriptional programs, including MEIS1 and MEF2C, support megakaryocyte progenitor proliferation and maturation.
- Therefore, **when we inhibit menin, megakaryopoiesis is reduced**, which can explain the thrombocytopenia observed in some patients.
- Interestingly, this same biology could potentially be exploited therapeutically in myeloproliferative neoplasms

What about immune checkpoint blockade?

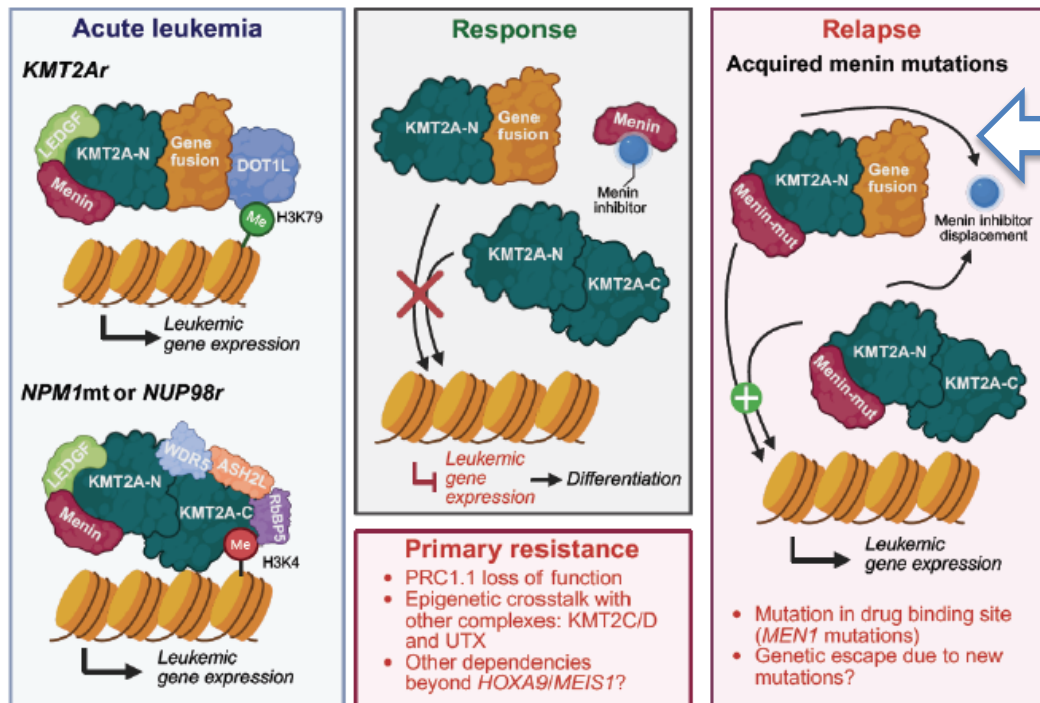
If we increase antigen presentation and interferon signaling, **perhaps checkpoint inhibition could further amplify the immune response.**

The strongest evidence we currently have is for antigen presentation, T-cell cytotoxicity and graft-versus-leukemia effects

A menin inhibitor plus checkpoint blockade remains a **hypothesis**, not a clinically established strategy.



What happens when leukemia escapes menin inhibition?

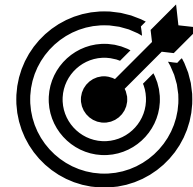


MEN1 mutations generate structural perturbations that impact small-molecule binding

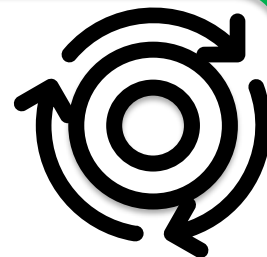
- How do we overcome resistance to menin inhibition?
- How can we exploit the phenotype created by menin inhibition?

Can we exploit the remodeled leukemia after menin inhibition?

TARGET THE LEUKEMIA



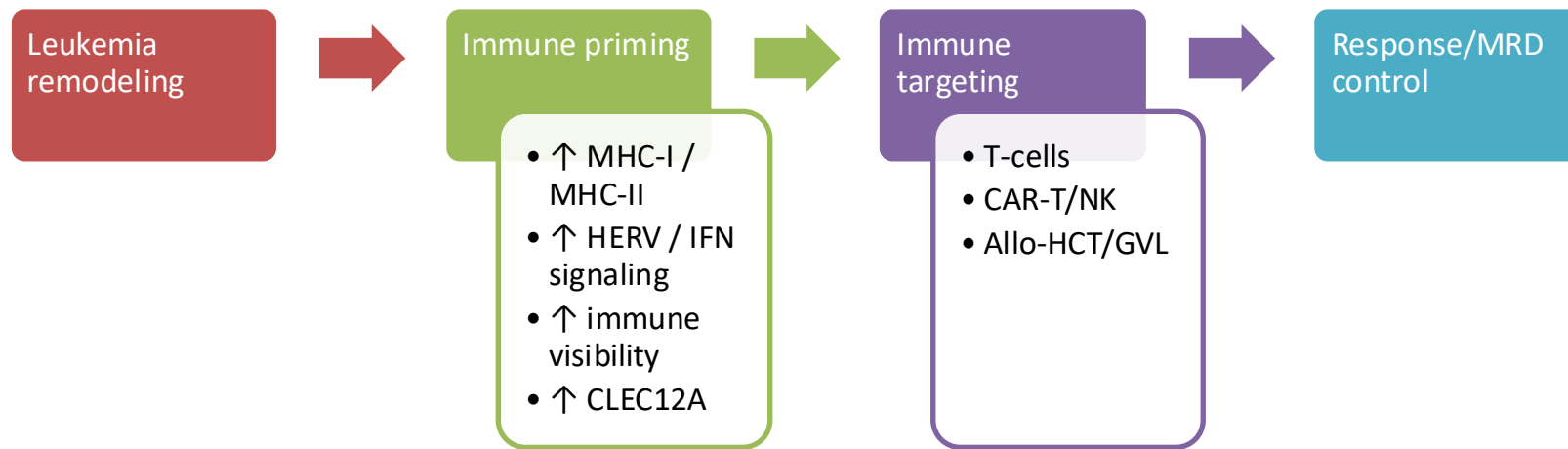
REMODEL THE LEUKEMIA



EXPLOIT THE REMODELED LEUKEMIA



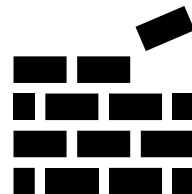
A potential therapeutic sequence



This is a therapeutic hypothesis, not an established treatment sequence.

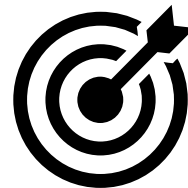
The optimal sequence may depend on antigen kinetics, disease burden and immune fitness.

What do we need now?



- Who is most likely to be immune-primed by menin inhibition?
- How early does immune remodeling occur?
- Which antigen should we target after menin inhibition?
- What is the optimal sequence and how integrate different approaches?
- Can immune targeting prevent or overcome menin-inhibitor resistance?

Take home messages



- Menin inhibition remodels AML beyond differentiation.
- It can increase leukemia visibility and T-cell vulnerability.
- This creates a rationale for sequential or combinatorial immunotherapy.

From targeting leukemia → to remodeling leukemia → to exploiting the immune system

Thank you!



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