Actimab-A, a CD33-Targeted Actinium-225 Radioconjugate, Drives Mutation-Agnostic Anti-Leukemic Activity and Synergizes with Standard Therapies in AML Through Transcriptional Reprogramming

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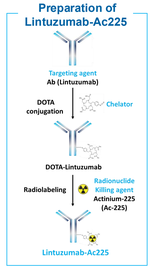
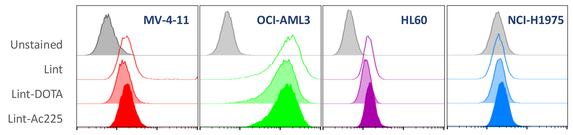
Background

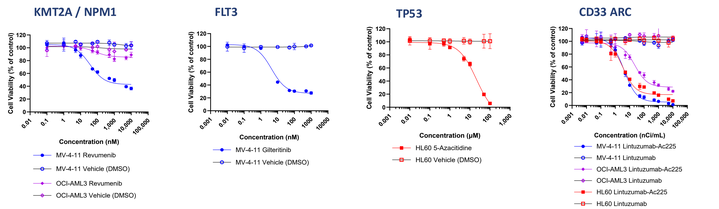
- Acute myeloid leukemia (AML) is a genetically heterogeneous and aggressive malignancy with limited durable treatment options.
- Actimab-A (Lintuzumab-Ac225, Lint-Ac225), a CD33-targeted antibody radioconjugate, delivers the alpha emitter actinium-225 (Ac-225) to AML cells, inducing potent, localized DNA damage.
- Clinical studies have shown encouraging responses when combined with CLAG-M chemotherapy in relapsed/refractory AML, including in patients with TP53 mutations or venetoclax resistance.
- Lintuzumab-Ac225 has shown potent anti-leukemic activity in AML cells regardless of mutations (FLT3, TP53, NPM1, and KMT2A) in both in vitro and in vivo AML models.
- Here, we demonstrated in primary AML patient samples that lintuzumab-Ac225 has strong translational therapeutic potential both as monotherapy and in combination with standard of care (SOC) therapies.
- We also defined the transcriptional profiles of AML cells treated with lintuzumab-Ac225 combination therapies to understand the underlying molecular mechanisms of anti-leukemic activity of these combination treatments.

Lintuzumab-Ac225 has Potent Binding and Robust Cytotoxicity in AML Cell Line Panel with Different Mutations





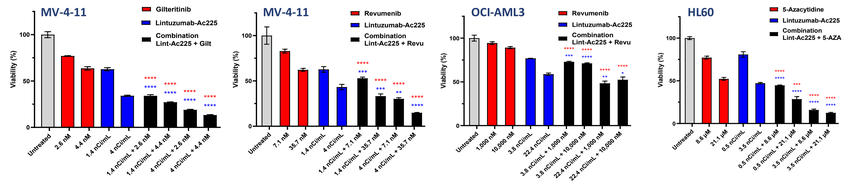
AML Cell Line Panel					
Cell Line	KMT2A	FLT3	NPM1	TP53	CD33
MV-4-11	MLL-AFF1	ITD		WT	Positive
OCI-AML3			NPM1	WT	Positive
HL60				Deletion	Positive
NCI-H1975					Negative



AML Cell Line	Menin Inhibitors		FLT3 Inhibitors		Targeting CD33	
	Revumenib (nM)		Gilteritinib (nM)		Lintuzumab-Ac225 (nCi/mL)	
	IC25	IC50	IC25	IC50	IC25	IC50
MV-4-11	7.1	35.7	2.6	4.4	1.4	4
OCI-AML3	~1,000	~10,000			3.8	22.4

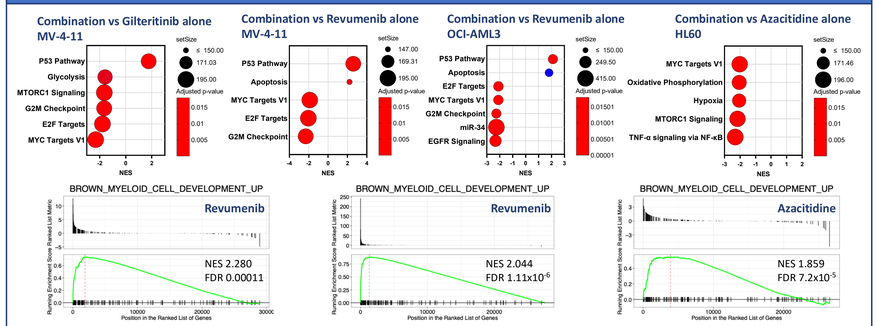
AML Cell Line	Chemo Agent		Targeting CD33	
	5-Azacitidine (μM)		Lintuzumab-Ac225 (nCi/mL)	
	IC25	IC50	IC25	IC50
HL60	8.6	21.1	0.5	3.5

Lintuzumab-Ac225 Combination with SOC Enhances AML Cytotoxicity



- Combining lintuzumab-Ac225 with targeted agents significantly increased cytotoxicity compared with monotherapy, demonstrating broad, mutation-independent potentiation of anti-leukemic activity.

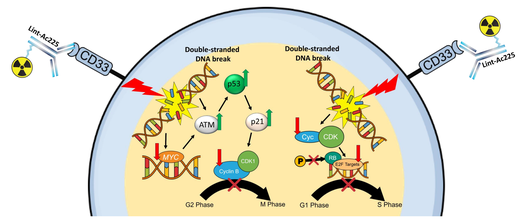
Transcriptional Profiling Shows Combination Treatment caused p53 Pathway Activation, Apoptosis, and Myeloid Differentiation Signatures



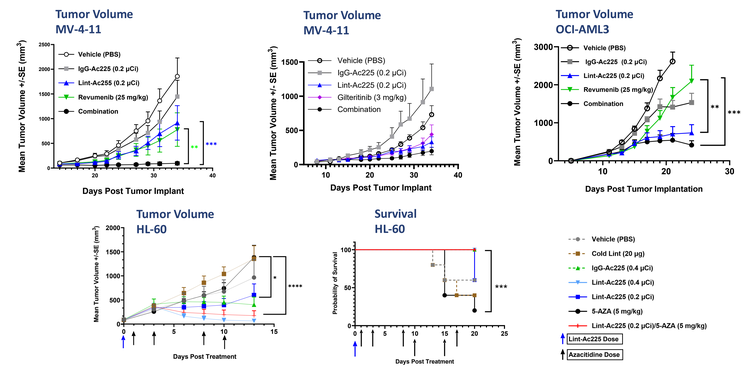
- Combination treatment produced consistent pathway-level changes compared with monotherapy. Gene set enrichment analyses (GSEA) showed enhanced myeloid differentiation signatures with the addition of lintuzumab-Ac225 to revumenib, gilteritinib, and azacitidine.
- Across models, combinations were associated with downregulation of proliferative programs, including MYC target genes, E2F targets, and G2/M checkpoint signatures, together with enrichment of p53-associated stress response and apoptosis pathways.

Mechanism of Action: Lintuzumab-Ac225 Combination with SOC

- Combination therapies with lintuzumab-Ac225 induce double-stranded DNA damage, which causes *Myc* to be downregulated and p53 to be upregulated in AML models.
- Cyclin B-CDK1 complex degradation leads to G2-M arrest and prevents retinoblastoma protein phosphorylation and downregulates E2F target genes.

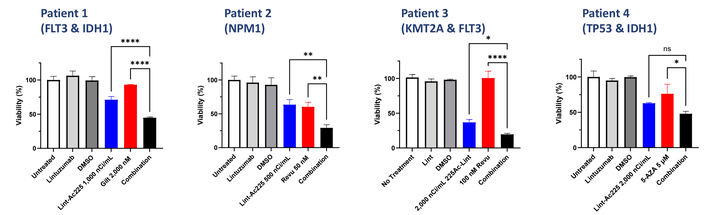


Combination of Lintuzumab-Ac225 with SOC Inhibitors Potentiates In Vivo AML Cell Death Independent of Mutations



- Lintuzumab-Ac225 potentiates cell death in tumor-bearing mouse models of AML when combined with revumenib, gilteritinib, and azacitidine.

Lintuzumab-Ac225 Combination with SOC Enhances Cytotoxicity in Primary AML Patient Samples



- Lintuzumab-Ac225 showed a robust cytotoxicity in primary AML patient samples, irrespective of FLT3, KMT2A, NPM1, IDH1 or TP53 status.
- Combining SOC therapies with lintuzumab-Ac225 enhanced efficacy.

Conclusions

- Actimab-A (lintuzumab-Ac225) shows broad mutation-independent anti-leukemic activity in AML cell lines and primary AML patient samples.
- When combined with standard therapies, Actimab-A drives complementary transcriptional programs that enhance depth and durability of response.
- These findings support the clinical evaluation of Actimab-A combinations as a strategy to overcome resistance and enhance therapeutic efficacy in AML.

Actinium Pharmaceuticals posters are available at the following QR code:

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