Lintuzumab-Ac225 in Combination with Intensive Chemotherapy Yields High Response Rate and MRD Negativity in R/R AML with Adverse Features

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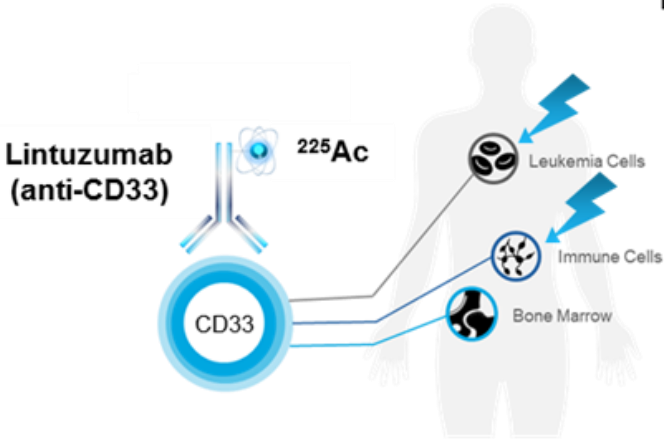
Background

- Lintuzumab-Ac225 represents a humanized anti-CD33 antibody Lintuzumab, linked to Actinium-225, a radioactive molecule that emits high-energy alpha particles over a micrometer range, resulting in dsDNA damage to only neighboring cells.
- Radioactive precautions are not required allowing administration in both inpatient and outpatient settings.

- As a single agent, higher doses of Lintuzumab-Ac225 yielded disease clearance both in the upfront and relapse setting. However, these doses also resulted in significant myelosuppression[1,2].

- **In this study, we hypothesized that Lintuzumab-Ac225 could eliminate residual/resistant AML by sequential administration after salvage chemotherapy, at lower doses that spare prolonged myelosuppression.**



1) Rosenblat et al. Clin Cancer Res. 2022; 13;28(10)
2) Atallah et al. JMIRS. 2019; 50(1), S37

Study Design and Treatment

Primary Objective

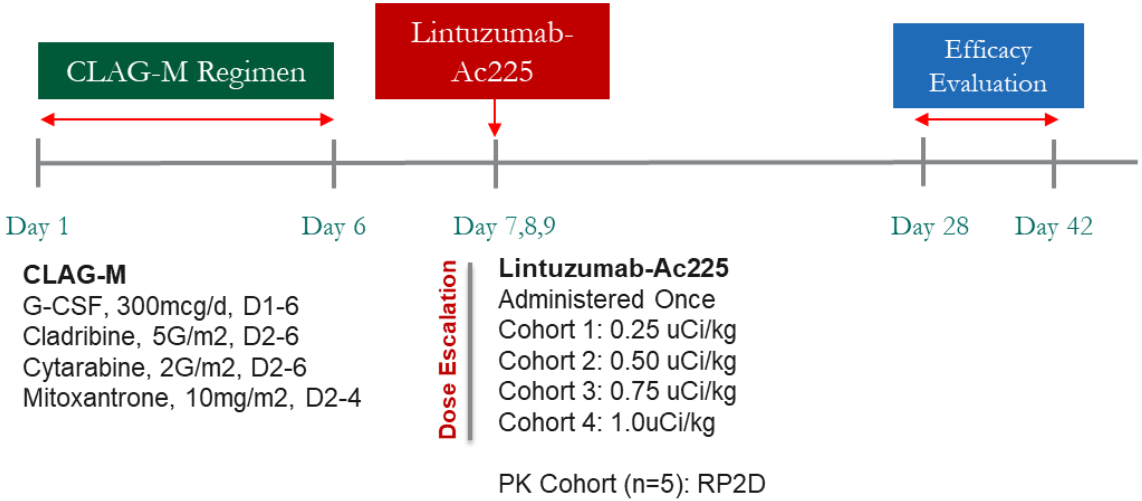
Determination of MTD and RP2D

Secondary Objectives

PK Profile of Lintuzumab Ac225
Response (CR, CRi, MLFS)
MRD(-) Response by MFC
Transplant eligible who proceed to HCT
Two-year OS

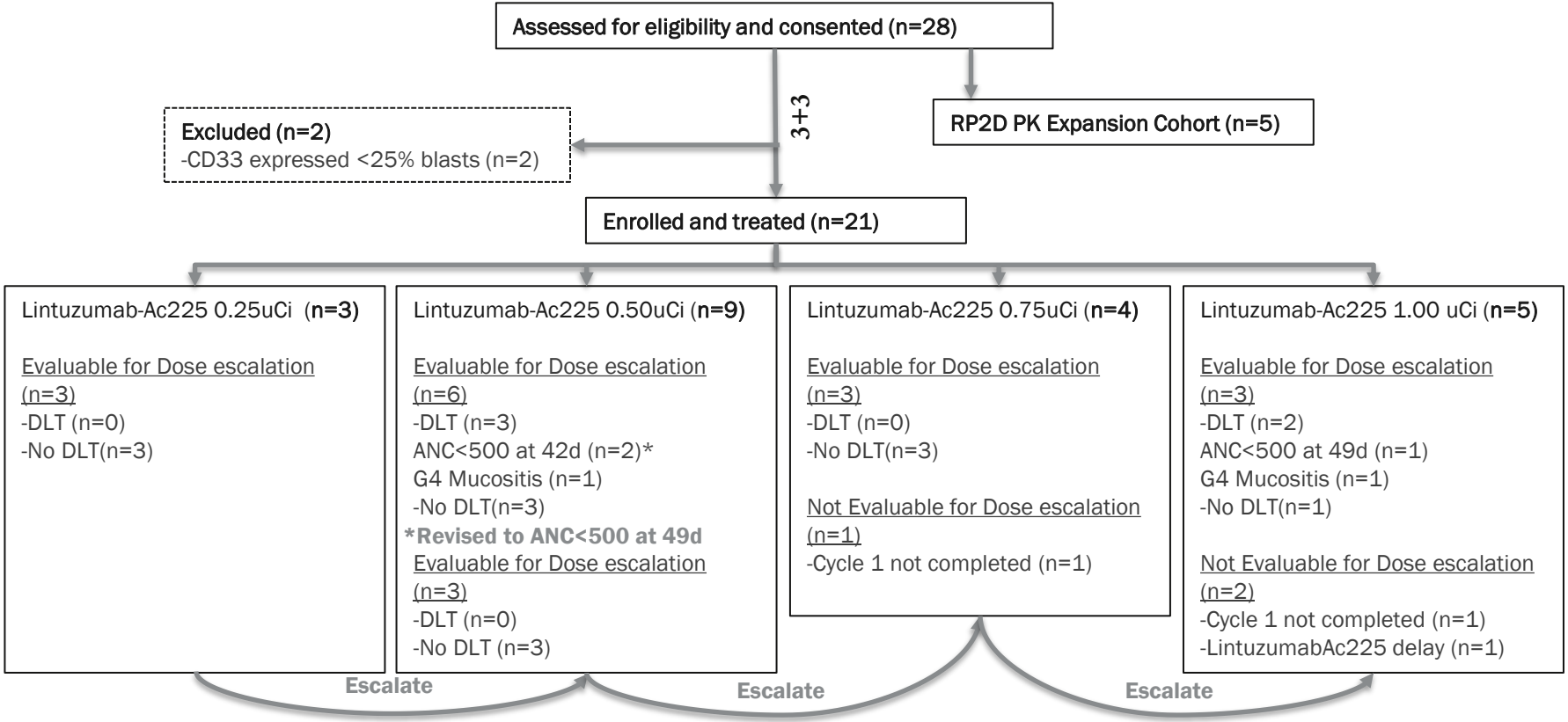
Key Eligibility Criteria

Adults (≥18 years) with R/R AML
ECOG PS 0-2
Adequate Organ Function
>25% of blasts must be CD33 positive by flow cytometry



MTD = Maximum tolerated dose. RP2D = Recommended Phase II Dose. PK = Pharmacokinetic.
CR = complete remission. CRi = CR with incomplete count recovery. MLFS = Morphologic leukemia free state
MRD = measurable residual disease. MFC = multiparametric flow cytometry
HCT = hematopoietic cell transplantation. OS = Overall Survival

Patient Enrollment



***Initial DLT criteria defined prolonged neutropenia as absolute neutrophil count (ANC)<500 lasting 42+ days, this was modified on FDA guidance to lasting 49+ days in the absence of AML**

Patient Characteristics

Characteristic	(n=23)
Age, median (range)	62 y (20-73y)
ECOG Score, n(%) 0-1 2	 17 (74%) 6 (26%)
Female, n(%)	10 (43%)
Relapsed, n(%)	5 (22%)
Refractory, n(%)	**18 (78%)**
2019 ELN Risk, n(%) Intermediate Adverse	 6 (26%) **17 (74%)**
Molecular Abnormalities TP53 mutation	 **12 (52%)**
Prior Therapies, median(range)	2 (1-5)
Prior Allogeneic Transplant, n(%)	13 (57%)
Prior Venetoclax Combination, n(%)	13 (57%)
%Blasts Expressing CD33, median(range)	82% (29-100%)
CD33 SNP, n(%)	13 (56%)

Mostly high-risk patients, including 74% with ELN 2019 adverse risk disease, and 52% with a TP53 mutation, were enrolled.

Mostly refractory patients enrolled. Prior to enrollment, 57% previously received a Venetoclax combination, and 57% were treated for recurrent disease after allogeneic HCT.

Treatment Emergent Adverse Events

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	All Patients (n=23)		0.75uCi/kg (n=8)	
	No.	%	No.	%
Any Adverse Event	23	100	8	100
Grade 3-4 Adverse Event	23	100	8	100
Dose Limiting Toxicity*	4	17	0	0

*Meeting final criteria, modified to allow for neutrophil recovery within 49 days.

Grade 3-4 Treatment Emergent Adverse Events Occurring in 2 or more patients

Adverse Event	All Patients (n=23)		0.75uCi/kg (n=8)	
	No.	%	No.	%
Anemia	5	22	2	25
Colitis	3	13	2	25
Febrile Neutropenia	19	83	7	88
Hypokalemia	2	9	-	-
Infection	8	35	2	25
Neutropenia	11	48	3	38
Rash - maculopapular	3	13	1	13
Thrombocytopenia	10	43	3	38

MTD and Recommended Phase II Dose

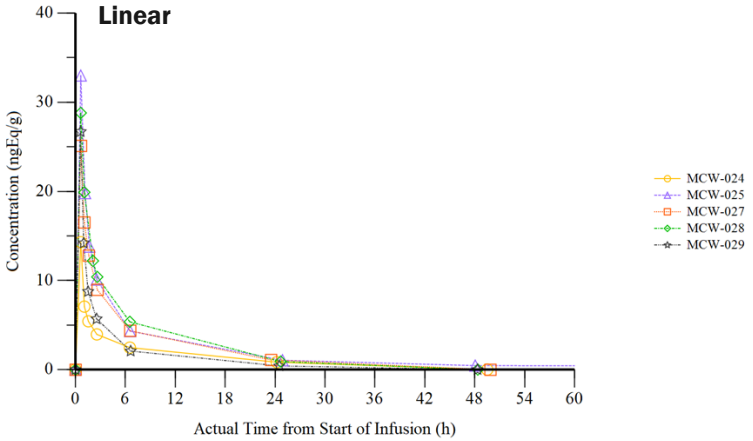
Dose (n)	# of Subject (s)	Dose Limiting Toxicity
Cohort 1 (0.25uCi/kg)	0/3	n/a
Cohort 2 (0.5uCi/kg)	3/6* 0/3	Prolonged Neutropenia (2)* Tumor Lysis Syndrome (1)*
Cohort 3 (0.75uCi/kg)	0/3	
Cohort 4 (1.0uCi/kg)	2/3	Prolonged Neutropenia (1) Mucositis (1)
Total (n=18)	4	

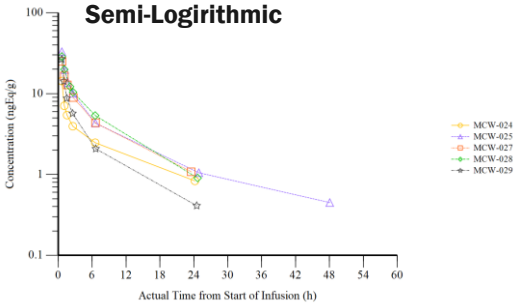
*DLT criteria were modified; and 3 additional patients were enrolled with FDA guidance

MTD: 1.0uCi/kg RP2D: 0.75uCi/kg

Pharmacokinetics

Ac225 Radioactivity after 0.75uCi/kg Dose	
$AUC_{0\text{-last}}$ (h*ngEq/g)	87.8 (39.4)
C_{max} (ngEq/g)	25.6 ngEq/g +/- 6.97
T_{max} (h)	0.6 +/- 0.01
$t_{½}$ (h)	8.6 +/- 2.8
CL (L/h)	3.15
t_{last} (h)	24.5h, range (23.5-48.1h)

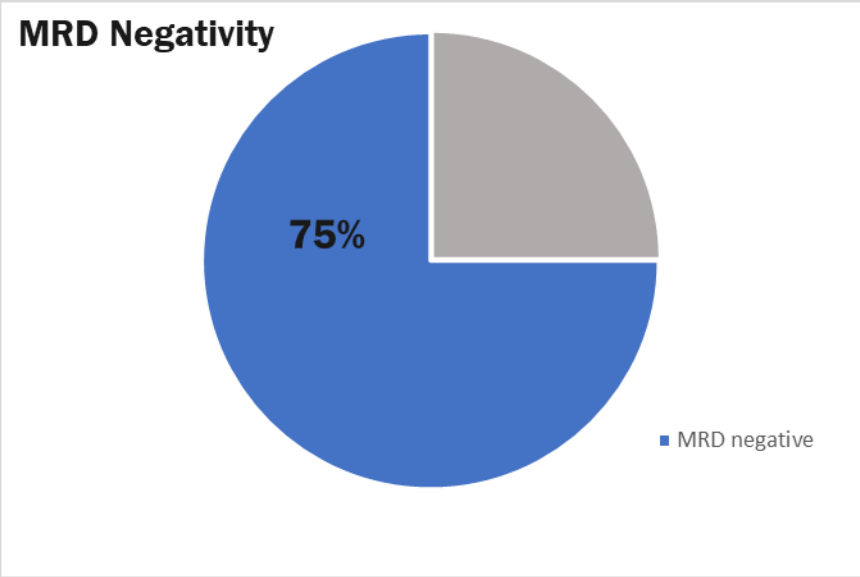




Response and MRD clearance

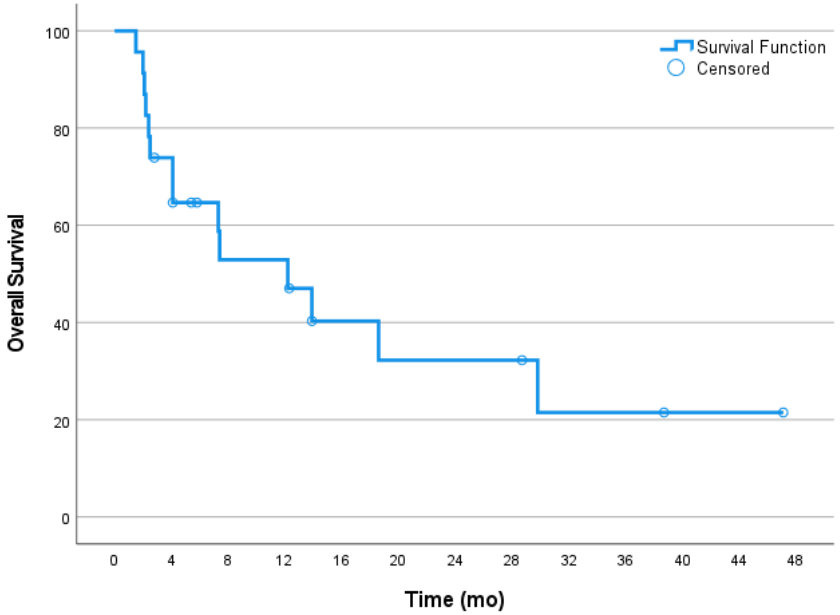
	All Patients n=23	RP2D (n=8)	Prior Ven (n=13)
CRc(CR+CRi)	**12 (52%)**	**5 (63%)**	**4 (31%)**
CR	5 (22%)	1 (13%)	2 (15%)
CRi	7 (30%)	4 (50%)	2 (15%)
MLFS	3 (13%)	1 (13%)	3 (23%)
Total Responses	**15 (65%)**	**6 (75%)**	**7 (54%)**
ANC>1000/uL, n(%)	13 (57%)	5 (63%)	5 (38%)
Days to ANC>1000/uL, median (range)	34d (25-61d)	34d (26-61d)	41d (30-61d)
Platelets>50k/uL, n(%)	7 (30%)	2 (25%)	3 (23%)
Days to Plt>50, median (range)	39d (25-56d)	49d (49-54d)	39d (33-56d)
HCT, if no prior HCT, %	64%	50%	75%

CRc = composite CR. CRi = CR with incomplete count recovery
HCT = Hematopoietic Cell Transplantation



MRD = measurable residual disease, assessed by multiparametric flow cytometry

Overall Survival



	Estimated Overall Survival	
	12-month %(SE)	24-month %(SE)
All (n=23)	53%(11)	32%(12)
1st/2nd Salvage (n=14)	61%(14)	49%(16)
CRc MRD neg (n=9)	89%(11)	48%(19)
TP53mut (n=13)	51%(15)	19%(16)
Prior Venetoclax (n=13)	59%(14)	32%(17)

Median Follow-up of survivors: 28 months

Conclusions

CLAG-M salvage chemotherapy and LintuzumabAc225 can safely be administered

- The recommended phase II dose for LintuzumabAc225 identified in this study is 0.75uCi/kg
- **Hematologic** toxicities observed on study were expected, we did not observe significant liver toxicities or VOD
- Responders had consistent neutrophil recovery, nearly half of responders achieved platelet stability

A single 30-minute infusion of LintuzumabAc225 at 0.75uCi/kg results in rapid radiation delivery and rapid clearance

- Peak radiation concentrations were detected in blood around 0.6hrs after administration
- Radioactivity was undetectable in blood largely by 24 hours.

Combination therapy yields a promising efficacy signal by eliminating residual leukemia cells

- Responses were observed in 65%, with high MRD negativity rate among patients in CRc at 75%
- Bridging to HCT was successful in 64% of eligible patients
- Over 50% of patients survived 1 year post therapy, including 51% patients with TP53mut and 59% receiving prior Ven
- Favorable survival was maintained at 2 years, at over 30%

Overall, this study supports further investigation of LintuzumabAc225 with CLAG-M in a large registration study and supports safety and potential efficacy in investigating LintuzumabAc225 in other combinations for AML

Acknowledgements

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