Lintuzumab-Ac225 in Combination with CLAG-M Yields High MRD (-) Responses in R/R AML with Adverse Features: Interim Results of a Phase I Study

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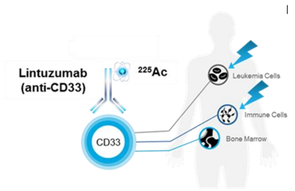
BACKGROUND

The development of novel salvage regimens in AML remains an area of great need as most AML patients still develop refractory or relapsed disease. Multiple studies have shown that the addition of CD33 directed ADCs to multi-agent chemotherapy may improve remission rates and depth (MRD negativity)[1-3]

- **Lintuzumab-Ac225 is a novel CD33 directed antibody-radiotherapy conjugate. Ac225, which is conjugated to the humanized anti-CD33 antibody Lintuzumab, emits high-energy alpha particles at a limited range, resulting in DNA damage and cell death**
- **Unlike gemtuzumab ozogamicin, veno-occlusive disorder (VOD) is not a known toxicity with Lintuzumab-Ac225**
- **Furthermore, Lintuzumab-Ac225 does not require internalization, and is not subject to resistance through multidrug resistance P-glycoprotein efflux pumps.**



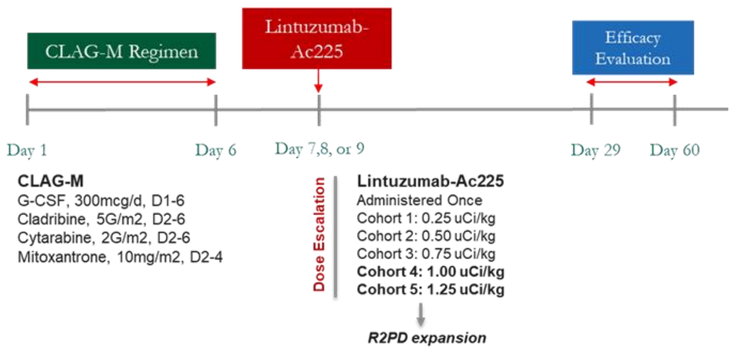
HYPOTHESIS

We hypothesized that lintuzumab-Ac225 (Actimab-A), added to salvage chemotherapy (CLAG-M) is safe, and will improve remission rates and remission depth in patients with relapsed/refractory Acute myeloid leukemia.

Eligibility and Design

Key Eligibility:

- **Adults (≥18 years) with R/R AML, including relapse post HCT.**
- **ECOG PS 0-2**
- **Fit, with adequate organ function**
- **>25% of blasts must be CD33 positive by flow cytometry**



RESULTS

Table 1: Demographics

Cohort	Cohort 1 (0.25uCi/kg) n=3	Cohort 2 (0.50uCi/kg) n=9	Cohort 3 (0.75uCi/kg) n=3	Cohort 4 (1.0uCi/kg) n=3
Age, median (range)	55 y (51-59y)	62 y (53-73y)	65 y(20-69 y)	50 y (44-68y)
Female, n(%)	1 (33%)	4 (44%)	2 (67%)	1 (33%)
Relapsed, n(%)	1 (33%)	2 (22%)	1 (33%)	0
Refractory, n(%)	**2 (67%)**	**7 (78%)**	**2 (67%)**	**3 (100%)**
Cytogenetics, n(%) Intermediate Adverse	 1 (33%) **2 (67%)**	 3 (33%) **6 (67%)**	 1 (33%) **2 (67%)**	 1 (33%) **2 (67%)**
Prior Therapies, median(range)	2 (1-4)	3 (1-5)	2 (1-2)	2 (2-3)
Prior Venetoclax Combination, n(%)	1 (33%)	5 (56%)	1 (33%)	3 (100%)

Figure 1: Grade 3+ TEAEs

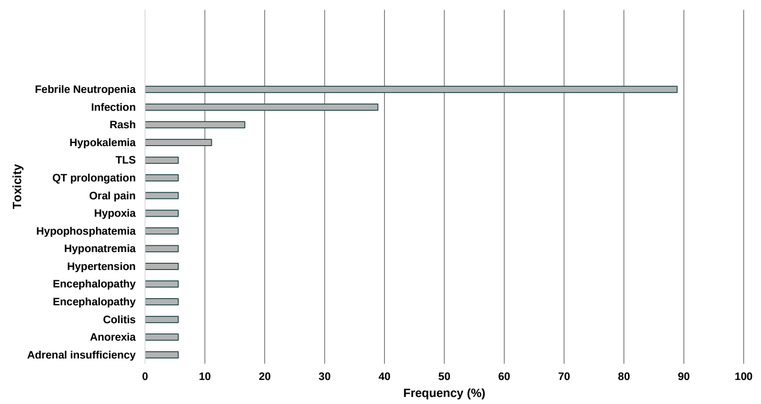


Table 2: Responses

	All (n=18)	Cohort 1 (n=3)	Cohort 2 (n=9)	Cohort 3 (n=3)	Cohort 4 (n=3)	Prior Ven (n=10)
Response, n(%)						
CR	5 (28%)	1	3	1	0	2 (20%)
CRp	5 (28%)	0	2	2	1	2 (20%)
MLFS	2 (6%)	0	1	0	1	2 (20%)
Total	**12 (67%)**	**1 (33%)**	**6 (67%)**	**3 (100%)**	**2 (67%)**	**6 (60%)**
30-day mortality	0	0	0	0	0	0
Median time to best response	40 days	40 days	42 days	47 days	49 days	41 days
HCT, if no prior, %	75%	100%	67%	100%	100%	75%

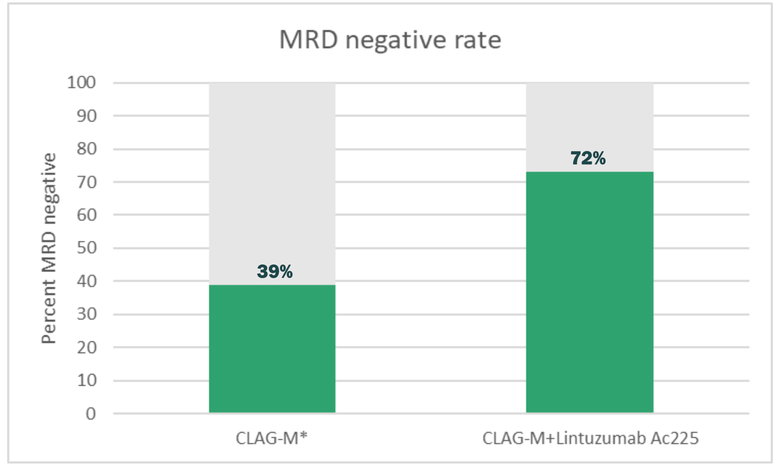
Table 3: Dose Limiting Toxicities

Dose (n)	# of Subject (s)	DLT Term
Cohort 1 (0.25uCi/kg)	0/3	n/a
Cohort 2 (0.5uCi/kg)	2/9*	Prolonged Neutropenia (1) Mucositis (1)
Cohort 3 (0.75uCi/kg)	0/3	
Cohort 4 (1.0uCi/kg)	2/3	Prolonged Neutropenia (1) Mucositis (1)
Total (n=18)	4	

*Initial DLT criteria defined prolonged neutropenia as ANC<500 lasting 42+ days, this was modified to lasting 49+ days

***Recommended Phase II Dose: 0.75uCi/kg**

Figure 2: Responses achieving MRD negativity



*** Historical in-house response.** Mushtaq et al. Leukemia & Lymphoma 2020

Conclusion

MTD is determined at 1.0 uCi/kg. RP2D is 0.75uCi/kg

Combination is safe, with expected toxicities

- As expected, neutropenic fever and infection is common, along with prolonged thrombocytopenia
- No cases of VOD were observed on study and in patients who went onto Allo-HCT

Promising efficacy in mostly adverse risk patients

- CRc: 67%, with high MRD negativity rate, 72% among responders
- Efficacy was similar among patients who previously failed Venetoclax
- 75% of eligible patients bridged to HCT

- **Phase II study is under planning**

References:
1) Lambert et al. Oncotarget. 2014; 5(15)
2) Lambert et al. Haematologica 2019; 104(1)
3) Kapp-Schwoerer et al. Blood 2020; 136(26)