Early Clinical Evaluation of Potential Synergy of Targeted Radiotherapy with Lintuzumab-Ac225 and Venetoclax in Relapsed/Refractory Acute Myeloid Leukemia (AML)

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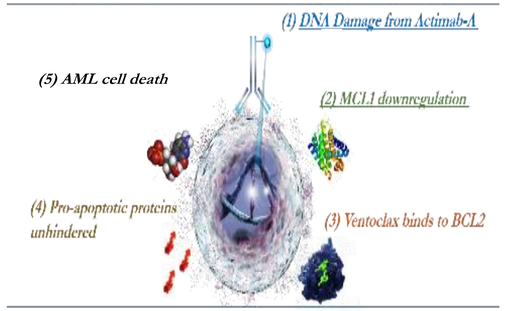
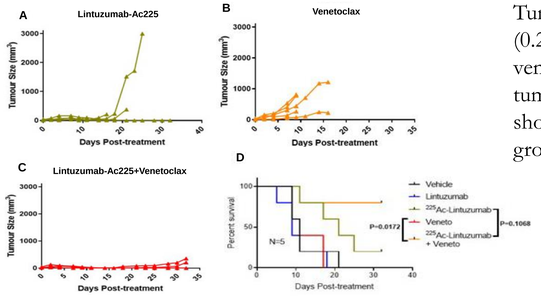
Background

Figure 1: Mechanism of Action



- Actinium 225 (Ac225) emits high-energy alpha particles that kill the cancer cell by causing irreparable damage, like shattering its DNA.
- Lintuzumab-Ac225 (Actimab-A): Actinium 225 (Ac225) conjugated to a humanized monoclonal antibody (HuM195 or lintuzumab) directed to CD33 antigens, which are highly expressed on leukemic cells of the myeloid lineage in humans.
- Lintuzumab-Ac225 depletes MCL-1 to increase cell sensitivity to venetoclax[1,2].
  - Clinical data shows that many patients do not respond to initial therapy with venetoclax and most patients will eventually progress.
  - An overexpression of MCL1, an anti-apoptotic protein, has been implicated in resistance to the BCL2 inhibitor, venetoclax, in leukemia.
  - By reducing MCL-1 levels by Lintuzumab-Ac225, it could dramatically prolong the response to venetoclax and re-sensitize resistant tumors to venetoclax therapy.

Figure 2: Lintuzumab-Ac225 enhanced tumor regression and increased survival in venetoclax-resistant AML Tumor model[2].



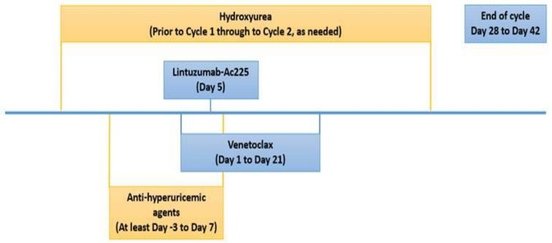
Tumor-bearing mice were treated with 7.4 kBq 225Ac-Lintuzumab (0.2 µg) (A), venetoclax (200 mg/kg) (B), or combination of venetoclax and 7.4 kBq 225Ac-Lintuzumab (C). Graph represents tumor volume of individual mice (N = 5). (D) Kaplan-Meier graph showing animal survival. Each curve represents five mice per group.

Results:

- Lintuzumab-Ac225 promotes MCL-1 degradation, resulting in cell sensitivity to venetoclax.
- Tumor regression and increased survival are observed in mice when given both venetoclax and lintuzumab-Ac225.

Study Design

Figure 3: Lintuzumab-Ac225 Treatment Schedule



Phase I portion of the study uses a 3+3 dose-escalation design to determine the maximum tolerated dose (MTD) of lintuzumab-Ac225 when given in combination with venetoclax.

Key Criteria for Study Entry

- Patients ≥18 years with relapsed or refractory AML (≥5% blasts)
- ≥25% CD33 positive leukemic blasts.
- ECOG performance status ≤ 2

Study Treatment

Lintuzumab-Ac225: - Dose levels are 0.5, 0.75, 1.0, and 1.5 µCi/kg.
- A single dose on Day 5 of each cycle and up to 4 cycles are allowed.

Venetoclax: - 400 mg/PO on Days 1 to 21 of each cycle.
- A dose ramp-up at Cycle 1 per PI

Results

Table 1: Patient Characteristics

Cohort reported as n (%)	Cohort 1 (0.5 µCi/kg)	Cohort 2B (0.75 µCi/kg)	Cohort 2 (1.0 µCi/kg)
Enrollment to Date	**3**	**6**	**3**
Age, median (range)	54	66	72
Male	3	4	3
Refractory	3	2	1
Relapsed (1st and 2nd)	0	4	2
Prior Therapies			
HSCT	0	0	0
1 Induction Regimen	0	5	2
≥2 Induction Regimens	3	1	1
Prior Therapies w/ Venetoclax	0	4	2
Risk Category (ELN)			
Favorable	0	0	0
Intermediate	0	1	1
Adverse	3	4	1
Unknown	0	1	1
ECOG Performance Status			
0	0	0	1
1	3	6	2
2	0	0	0

Table 2: Common Grade 3/4 Treatment-Emergent AEs

Common (in ≥ 20% of patients) Grade 3/4 TEAEs	Cohort 1 (0.5 µCi/kg)	Cohort 2B (0.75 µCi/kg)	Cohort 2 (1.0 µCi/kg)
# of Evaluable Patients	**3**	**6**	**3***
Atrial Fibrillation	1 (33%)	0	N/A
Heart Failure	1 (33%)	1 (17%)	N/A
Lung Infection	1 (33%)	0	N/A
Anemia	1 (33%)	2 (33%)	N/A
Febrile Neutropenia	1 (33%)	4 (66%)	N/A
Neutrophil count decreased	0	2 (33%)	N/A
Platelet count decreased	1 (33%)	2 (33%)	N/A
White blood cell decreased	1 (33%)	1 (17%)	N/A
Syncope	1 (33%)	2 (33%)	N/A
Generalized disorders and administrative site conditions- Other	0	1 (17%)	1 (33%)

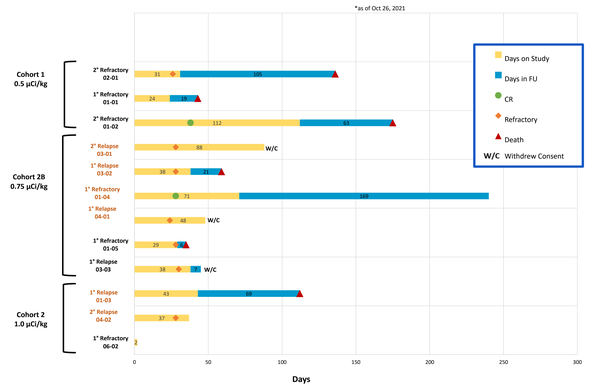
**Data cut-off as of 25-Oct-2021. Data entry was not completed for all patients in Cohort 2 by date of data cut-off.*

Table 3: Lintuzumab-Ac225 related Grade 3/4 AEs

Lintuzumab-Ac225-related Grade 3/4 TEAEs	Cohort 1 (0.5 µCi/kg)	Cohort 2B (0.75 µCi/kg)	Cohort 2 (1.0 µCi/kg)
# of Evaluable Patients	**3**	**6**	**3***
Anemia	1 (33%)	2 (33%)	N/A
Neutrophil count decreased	0	1 (17%)	N/A
Platelet count decreased	0	2 (33%)	N/A
White blood cell decreased	0	1 (17%)	N/A
Febrile Neutropenia	0	1 (17%)	N/A
Hyponatremia	0	1 (17%)	N/A

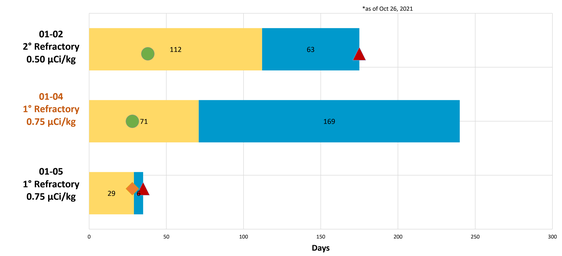
**Data cut-off as of 25-Oct-2021. Data entry was not completed for all patients in Cohort 2 by date of data cut-off.*

Figure 4A: Individual Patient Response and Survival



**Patient IDs coded in orange had relapsed/refractory AML after prior Venetoclax + HMA treatment*

Figure 4B: Response and Survival in TP53-mutant Patients



Conclusions

Combining Lintuzumab-Ac225 dosing up to 1.0 µCi/kg with venetoclax in patients with relapsed or refractory AML was well-tolerated, with a manageable adverse event profile.

- There were no early deaths observed (≤30 days)
- 1 of 6 patients received Lintuzumab-Ac225 at 0.75 µCi/kg experienced a DLT with prolonged thrombocytopenia

While sample size is limited, the clinical benefit ORR(CR/CRi) was observed in 2 of 11 (18%) patients, including 2 of 3 TP53-mutant R/R patients (67%). Early safety and limited clinical benefit data suggest potential synergy of this combination therapy.

Data-to-date support continued evaluation of combination in planned Phase 2 and will continue to evaluate the safety and efficacy of Lintuzumab-Ac225 in combination of venetoclax in TP53-mutant R/R AML population.

1. Garg R, Geoghegan E, Allen K, et al. 225Ac-CD33 Radioimmunotherapy Potently Increases the Sensitivity of Resistant Acute Myeloid Leukemia Lines to the Bcl-2 Inhibitor Venetoclax by Mediating a Reduction in Cellular Mcl-1 Levels. Cancer Res 2019; 79(13 Suppl) Abstract 3808
2. Garg R. et al. 225Ac-labeled CD33-targeting antibody reverses resistance to Bcl-2 inhibitor venetoclax in acute myeloid leukemia models Cancer Medicine 2020