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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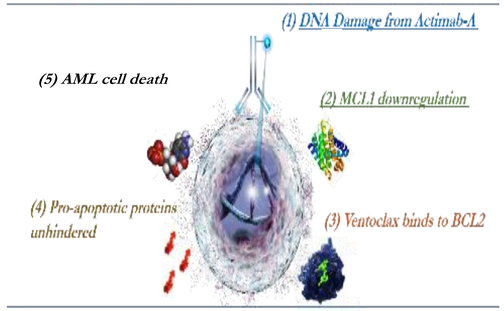
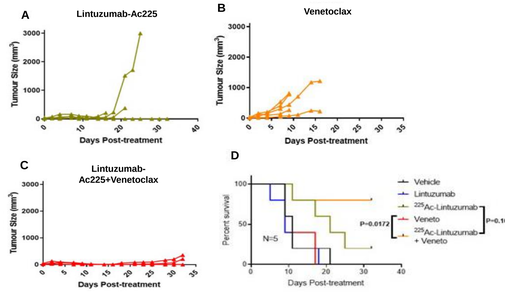
Background

Figure 1: Mechanism of Action



- Actinium 225 (Ac225) emits high-energy alpha particles which induces irreparable double stranded DNA damage enabling cell destruction.
- 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].
  - An overexpression of MCL-1, an anti-apoptotic protein, has been implicated in resistance to the BCL2 inhibitor, venetoclax, in leukemia.
  - Clinical data shows that many patients do not respond to initial therapy with venetoclax and most patients will eventually progress
  - By reducing MCL-1 levels by Lintuzumab-Ac225, it could dramatically prolong the response to venetoclax and re-sensitize resistant tumors to venetoclax therapy.

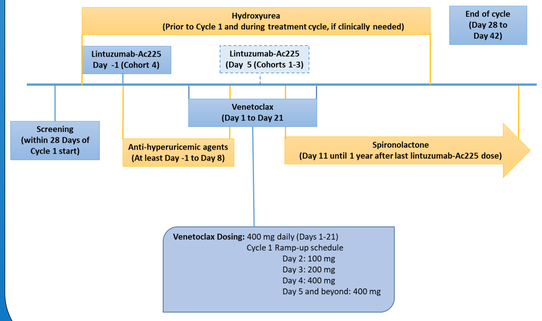
Figure 2: Lintuzumab-Ac225 enhanced tumor regression and increased survival in venetoclax-resistant AML Tumor model[2].



- Tumor-bearing mice were treated with 7.4 kBq Lintuzumab-Ac225 (0.2 µg) (A), venetoclax (200 mg/kg) (B), or combination of venetoclax and 7.4 kBq Lintuzumab-Ac225 (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



*Spironolactone is administered for kidney protection

- 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.
- The dose levels assessed for Lintuzumab-Ac225 are 0.5, 0.75, 1.0, 1.5, and 2.0 µCi/kg.

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 is administered as a single dose on Day 5 (Cohorts 1-3) and Day -1 (Cohort 4) of each cycle.
- Venetoclax: 400 mg/PO on Days 1 to 21 of each cycle. A dose ramp-up at Cycle 1 to reduce the risk of tumor lysis syndrome

Results

Table 1: Patient Characteristics (N= 17)

Cohort Dose Level	Cohort 1 (0.5 µCi/kg) N=3	Cohort 2B (0.75 µCi/kg) N=6	Cohort 2 (1.0 µCi/kg) N=3	Cohort 3 (1.5 µCi/kg) N=3	Cohort 4 (2.0 µCi/kg) N=2
Enrollment to Date	3	6	3	3	2
Age (Median)	54	66	72	50	78
Male (Female)	3 (0)	4 (2)	3 (0)	3 (0)	2 (0)
Refractory	3	2	1	1	0
Relapsed (1st and 2nd)	0	4	2	2	2
Prior Therapies					
HSCT	0	0	0	0	1
1 Induction Regimen	0	5	2	3	2
>2 Induction Regimen	3	1	1	1	0
Prior Therapies w/ Venetoclax	0	4	2	3	0
Risk Category (ELN)					
Favorable	0	0	0	1	0
Intermediate	0	1	1	1	1
Adverse	3	4	1	1	0
Unknown	0	1	1	0	1
ECOG Performance Status					
0	0	0	1	1	0
1	3	6	2	1	1
2	0	0	0	1	1

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)	Cohort 3 (1.5 µCi/kg)	Cohort 4* (2.0 µCi/kg)	Total
# of Evaluable Patients	N=3	N=6	N=3	N=3	N=2	N=17
Atrial Fibrillation	1 (33%)	0	0	0	0	1 (5.9%)
Heart Failure	1 (33%)	0	0	0	0	1 (5.9%)
Lung Infection	1 (33%)	0	0	0	0	1 (5.9%)
Anemia	1 (33%)	2 (33%)	0	0	2 (100%)	5 (29.4%)
Febrile Neutropenia	1 (33%)	4 (66%)	0	1 (33%)	0	6 (35.3%)
Neutrophil Count Decreased	0	2 (33%)	1 (33%)	1 (33%)	2 (100%)	6 (35.3%)
Platelet Count Decreased	1 (33%)	2 (33%)	1 (33%)	0	2 (100%)	6 (35.3%)
White Blood Cell Decreased	1 (33%)	0	1 (33%)	1 (33%)	1 (50%)	4 (23.5%)
Syncope	1 (33%)	2 (33%)	0	0	0	3 (17.5%)
Lymphocyte Count Decreased	0	0	1 (33%)	0	2 (100%)	3 (17.5%)
Hypertension	0	0	1 (33%)	0	0	1 (5.9%)
Failure to Thrive	0	0	1 (33%)	1 (33%)	0	2 (11.8%)
Sepsis	0	0	0	1 (33%)	0	1 (5.9%)
Nausea	0	0	0	1 (33%)	0	1 (5.9%)
Anorexia	0	0	0	1 (33%)	0	1 (5.9%)
Apnea	0	0	0	1 (33%)	0	1 (5.9%)
Hematuria	0	0	0	0	1 (50%)	1 (5.9%)

Data cut-off as of 07-Nov-2022. Data entry was not completed for all patients in Cohort 4 by date of data cut-off. Initial data; data collection is ongoing

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

Lintuzumab-Ac225-realted Grade 3/4 TEAEs	Cohort 1 (0.5 µCi/kg)	Cohort 2B (0.75 µCi/kg)	Cohort 2 (1.0 µCi/kg)	Cohort 3 (1.5 µCi/kg)	Cohort 4* (2.0 µCi/kg)	Total
# of Evaluable Patients	3	6	3	3	2	17
Anemia	1 (33%)	2 (33%)	0	1 (33%)	2 (100%)	6 (35.3%)
Neutrophil Count Decreased	0	1 (17%)	1 (33%)	1 (33%)	1 (50%)	4 (23.5%)
Platelet Count Decreased	0	2 (33%)	1 (33%)	0	1 (50%)	4 (23.5%)
White Blood Cell Decreased	0	1 (17%)	1 (33%)	1 (33%)	1 (50%)	4 (23.5%)
Febrile Neutropenia	0	1 (17%)	0	0	0	1 (5.9%)
Hyponatremia	0	1 (17%)	0	0	0	1 (5.9%)
Lymphocyte Count Decreased	0	0	1 (33%)	0	2 (100%)	3 (17.5%)

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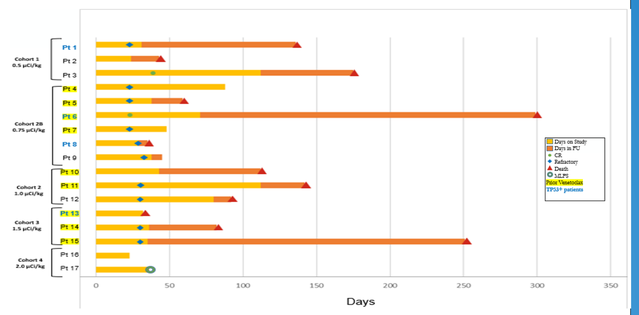
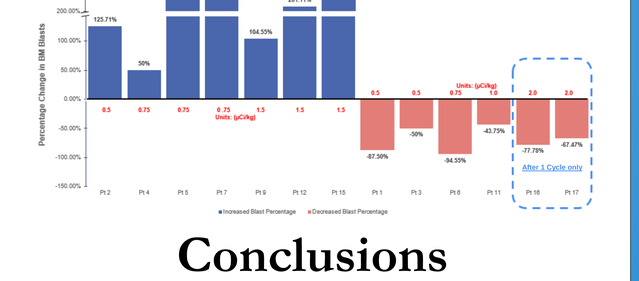
Figure 4A: Individual Patient Response and Survival



Patient IDs highlighted had relapsed/ refractory AML after prior Venetoclax + HMA treatment

Figure 4B: Percentage Change in BM Blasts in 13 Evaluable Patients



Conclusions

- Combining Lintuzumab-Ac225 dosing up to 1.5 µCi/kg (Cohort 1-3) 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 (Cohort 2B) experienced a DLT of prolonged thrombocytopenia
  - No DLTs were observed at 0.5 µCi/kg (Cohort 1), 1.0 µCi/kg (Cohort 2) and 1.5 µCi/kg (Cohort 3) of Lintuzumab-Ac225 in combination with venetoclax.
  - In Cohort 4 at 2.0 µCi/kg of Actimab-A plus venetoclax, two patients completed Cycle 1. No SAEs have been reported to date. The study enrollment and data collection are ongoing.
- The percentage of BM blasts was reduced in 6 of 13 evaluable patients, including 2 of 6 patients achieving CR/CRi/CRp and 1 of 6 achieving MLFS.
- The percentage of change in BM blasts of two patients in Cohort 4 (2.0 µCi/kg) with a modified dosing schedule was significantly reduced by more than 65%.
- **Future Direction:**
  To support the planned Phase 2 study; investigation to determine the MTD, efficacious dose of the new dosing schedule of Lintuzumab-Ac225 in combination with venetoclax in patients with R/R AML is ongoing.

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