Phase I Trial of Azacitidine, Venetoclax and Allogeneic NK Cells in Acute Myeloid Leukemia (ADVENT-AML): Results From Dose Escalation Phase

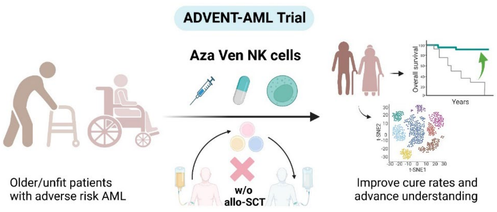
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Background

- Older/unfit pts with AML have limited treatment options and are usually ineligible for allogeneic stem cell transplant.
- We hypothesized that adding allogeneic NK cells to current standard of azacitidine-venetoclax (Aza-Ven) may work synergistically and improve long-term outcomes.
- We designed a phase I trial to evaluate the combination of allogeneic NK cells with Aza-Ven (NCT05834244).
- The dose escalation phase enrolled pts with R/R AML.



Objectives

Primary objective: to determine the safety of this combination.

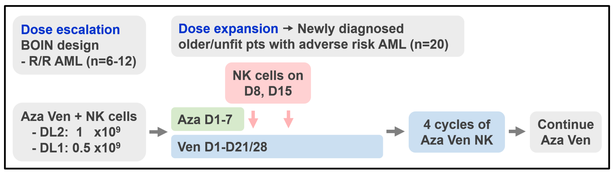
Secondary objectives: measures of efficacy ORR, CRc, OS, RFS

Exploratory objectives: persistence of NK cells, cytokine profiling and evaluation of immune microenvironment

Methods

Aza-Ven was administered as standard per USPI

Ex vivo expanded allogeneic NK cells CHM-201 were administered on days 8 and 15 of the first 4 cycles at flat doses of 0.5x10^9 (DL1) and 1 x10^9 (DL2) per dose.



Results

6 pts with R/R AML were enrolled across two dose levels. Baseline characteristics are shown in Table 1

Table 1. Baseline Characteristics	N=6
Age, yrs	64 (35-77)
ECOG PS 0-1	6 (100)
Bone marrow blasts, %	50 (20-59)
Cytogenomics	
Complex karyotype	4 (67)
MECOMr	1 (17)
Diploid	1 (17)
TP53	5 (83)
Prior lines of therapies	3 (2-4)
Intensive chemotherapy	6 (100)
Venetoclax	5 (83)
Hypomethylating agents	6 (100)
Stem cell transplantation	1 (17)
CAR-T	1 (17)

Safety: There were no DLTs, CRS/ICANS, or acute GVHD.

Most common treatment emergent adverse event of any grade were infusion reactions (8), pneumonia (5), and febrile neutropenia (4).

Table 2. Treatment-emergent adverse events (n)	Grade 1	2	3	4	5
Lung infection		1	3		1
Nervous system disorders[1]				1	
Febrile neutropenia			4		
Platelet count decreased	1	1	1		
Colitis		1	1		
Anemia			1		
Skin infection			1		
Skin and subcutaneous tissue disorders[2]	1	3			
Epistaxis	1	1			
Fall		1			
Gastric hemorrhage		1			
Infusion related reaction	8				
Nausea	5				
Constipation	4				
Diarrhea	4				
Abdominal distension	2				
Abdominal pain	2				
Dyspnea	2				
Edema limbs	2				
Fever	2				
Headache	2				
Postnasal drip	2				

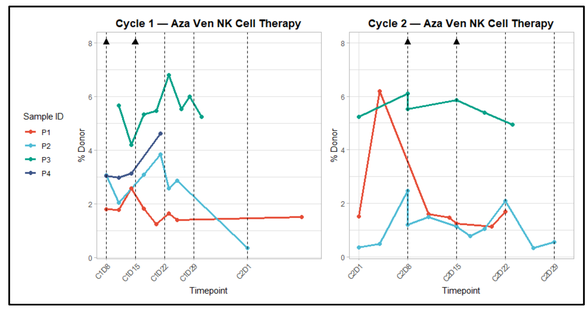
Treatment-emergent adverse events (n)	Grade 1	2	3	4	5
Anxiety	1				
Cough	1				
Dizziness	1				
Dysphagia	1				
Dysuria	1				
QTc prolonged	1				
Gastrointestinal disorders	1				
Hemorrhoids	1				
Infections and infestations	1				
Insomnia	1				
Mucositis oral	1				
Pain	1				
Paresthesia	1				
Pruritus	1				
Rhinorrhea	1				
Sinus bradycardia	1				
Urinary frequency	1				
Vomiting	1				
Weight loss	1				

1. Nervous system disorders included finding of finding intracranial leukemic chloromas or hemorrhagic metastases, 2. The skin and subcutaneous tissue disorders included wound at biopsy site (1), right forearm cellulitis (1), Generalized erythematic rash (1), Subcutaneous skin nodules (forearms, abdomen) (1), all unrelated to study regimen.

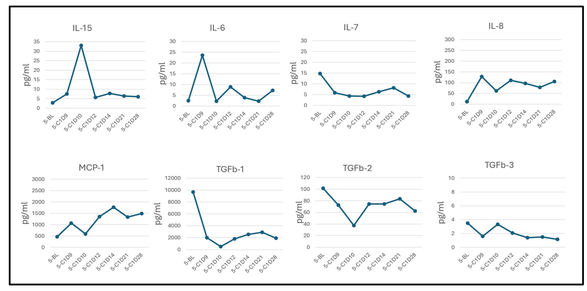
Results

Response: One out of 6 pts achieved CRi MRD positive.

Persistence: An NGS-based chimerism assay (sensitivity 0.1%) showed that infused NK cells could be measured for more than 2 weeks after repeat infusions (n=4).

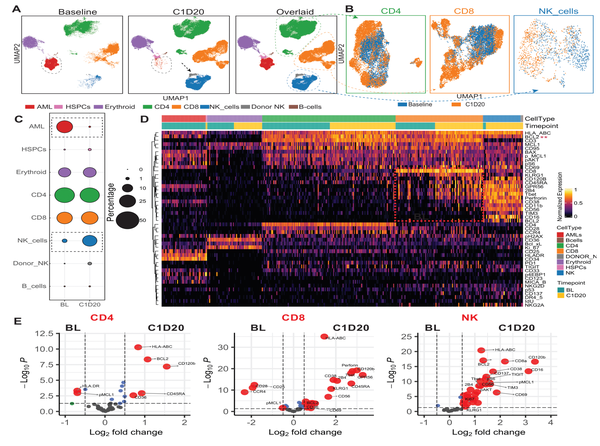


Cytokine profile: Serum cytokine assessment suggested increase in homeostatic cytokines, IL-6, -15, around day 9-10 and concurrent drop in TGFb-1 (n=2).



CyTOF single cell proteomics in the responding pt showed homing of infused NK cells to the BM on day 20, reduction in AML, and phenotypic changes in CD4/8 T cells.

- Expanded NK cells: elevated T-bet and perforin, markers of cytotoxic fitness
- AML cells: ↑ MICA/B, which could sensitize to NK cell killing
- ↑ HLA-ABC, BCL2 expression multiple immune subsets.



Conclusions

- Ex-vivo expanded allogeneic NK cells CHM-201 could be safely combined with Aza Ven in pts with R/R AML
- CHM-201 NK cells had significant persistence delivered without lymphodepletion and migration into BM.
- Dose expansion phase is currently enrolling older/unfit pts with newly diagnosed AML.

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