MGTA-117, an Anti-CD117-Amanitin Antibody-Drug Conjugate, in Participants With Relapsed/Refractory Adult Acute Myeloid Leukemia (AML) and Myelodysplasia With Excess Blasts (MDS-EB): Safety, Pharmacokinetics, and Pharmacodynamics Initial Findings from a Phase 1/2 Study

Mark Juckett, MD[1]; Peter Westervelt, MD, PhD[2]; Partow Kebriaei, MD[3]; Andrew S. Artz, MD[4]; Onyee Chan, MD[5]; Philip L. McCarthy, MD[6]; Sherif S. Farag, MD, PhD[7]; Anurag K. Singh, MD[8]; Eytan Stein, MD[9]; Ji Hyun Lee, MD, MPH[10]; Alison Occhiuti, MS[10]; Jeanie Tang, BS[10]; David Santos, BS[10]; Kirk Bertelsen, PhD[10]; Balaji Mahender, BPharm, MS[10]; Megan Hoban, PhD[10], Nergis Kara, PhD[10]; Nicole Henry, BSN, RN[10]; Donald Pardy, MS[10]; June Li, PhD[10]; Christian Zdybowicz, MBA[10], Shawn Rose, MD, PhD[10]

[1]University of Minnesota, Minneapolis, MN, USA; [2]Washington University, St. Louis, MO, USA; [3]The University of Texas MD Anderson Cancer Center, TX, USA; [4]City of Hope, Duarte, CA, USA; [5]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [6]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [7]Indiana University Simon Cancer Center, Indianapolis, IN, USA; [8]University of Kansas Medical Center, Kansas City, KS, USA; [9]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [10]Magenta Therapeutics, Cambridge, MA, USA

BACKGROUND

MGTA-117 is a novel (c-KIT)-amanitin antibody-drug conjugate (ADC) targeting CD117 that is in development to enable hematopoietic stem cell transplantation (HSCT). Here, we report results from Cohorts 1-4 of a phase 1/2 clinical study in which MGTA-117 is administered IV as a single dose in adults with relapsed/refractory (R/R) acute myeloid leukemia (AML) or myelodysplastic syndrome with excess blasts (MDS-EB).

MGTA-117 (Anti-Human CD117-ADC) Properties

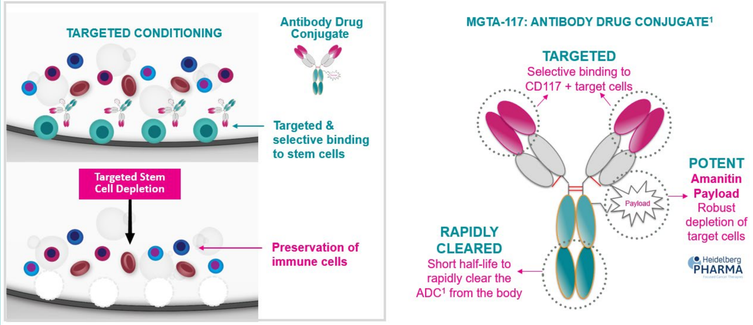
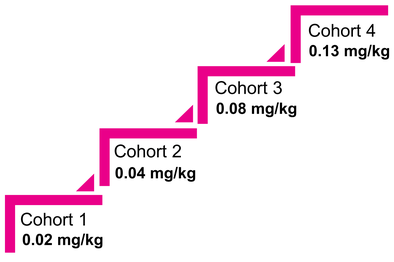


Figure 1: MGTA-117 is an ADC targeting CD117 that has been engineered to selectively deplete quiescent and actively dividing CD117-expressing cells.

STUDY DESIGN AND METHODS

A phase I/II study (NCT05223699) to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and potential antileukemic activity of MGTA-117



Study Design

- Multi-center, U.S. Study
- Open Label
- Single Ascending Dose(s)
- 3+3 Cohort Design
- Modified Fibonacci Sequence for Dosing

Key Objectives

- Target Engagement (RO)
- Robust Cell Depletion (PD)
- Rapid Clearance (PK)
- Tolerability/Safety

Figure 2: We report on 22 enrolled participants in an open label, 3+3 dose escalation Phase 1/2 trial of MGTA-117 administered as a single dose in R/R AML / MDS-EB

Key Eligibility Criteria

- Age 18-75 years old
- WHO-defined diagnosis of CD117+ R/R AML or MDS-EB with ≥5% marrow blasts
- Identified human stem cell donor
- ECOG performance status ≤2
- Adequate hepatic, renal, and cardiac function
- No evidence of APL or CNS leukemia, active GVHD, or active serious infection
- Washout of prior anti-leukemic therapies is required prior to MGTA-117 dosing

DEMOGRAPHICS AND DISEASE CHARACTERISTICS

Table 1: R/R AML and MDS-EB study population has a poor prognosis with a high burden of disease and multiple previous lines of therapy

Characteristics		Total (N=22)
Age, Year, Median (range)		64 (26-74)
Sex, Males/Female		11 / 11
Diagnosis, n, AML/MDS		17 / 5
ELN Risk Classification for AML		
Adverse		6
Intermediate		7
Unknown		4
Months Since Diagnosis,	Median (range)	9 (3-191)
Bone Marrow Blast % at BL,	Median (range)	21 (1-73)
Prior Line of Therapy,	Median (range)	2 (1-8)

SAFETY AND TOLERABILITY

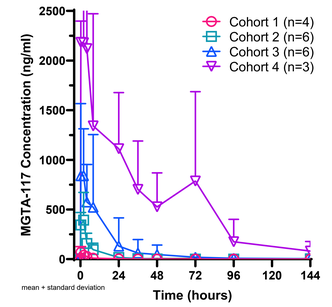
- Most treatment-emergent AEs were consistent with underlying disease
- Liver enzyme elevations in Cohorts 1-3 were expected, transient, low-grade, and resolved without any intervention
- 1 DLT (respiratory failure and cardiac arrest resulting in death) observed in Cohort 3
- Dosing suspended in Cohort 4 due to 3 DLTs (pneumonitis in one participant, pneumonitis and liver enzyme elevations in a second participant) occurring in 2 participants
- No treatment-related infusion reactions were observed in any Cohort

Table 2: Summary of Safety and Tolerability by Cohort

Category	Cohort 1 (N=4) n (%)	Cohort 2 (N=6) n (%)	Cohort 3 (N=9) n (%)	Cohort 4 (N=3) n (%)
Participants with Treatment-Emergent Adverse Events (TEAEs)				
TEAEs classified as dose-limiting toxicities	0	0	1 (11)	2 (67)
Serious AEs	1 (25)	4 (67)	3 (33)	2 (67)
Grade 3 or higher TEAEs	3 (75)	4 (67)	5 (38)	2 (67)
TEAEs resulting in death: AML disease progression, N=2; sepsis, N=1; respiratory failure, cardiac arrest, N=1	1 (25)	3 (33)	1 (11)	0 (0)
TEAEs in >20% of Participants Regardless of Causality				
Nausea (32%), Constipation (27%), Hypokalemia (27%)				
Participants with MGTA-117 Related TEAEs				
Grade 1 (liver enzyme elevations)	1 (25)	2 (33)	0	0
Grade 2 (fever, pleural effusion, haemoptysis)	0	1 (17)[1]	1 (11)	1 (33)
Grade 3 (leukopenia, worsening anemia)	0	0	2 (22)[2]	0
Grade 4 (leukopenia, pneumonitis)	0	0	1 (11)[3]	2 (67)[4,5]
Grade 5 (respiratory failure and cardiac arrest)	0	0	1 (11)[6]	0
Total	1 (25)	3 (50)	5 (56)	3 (100)

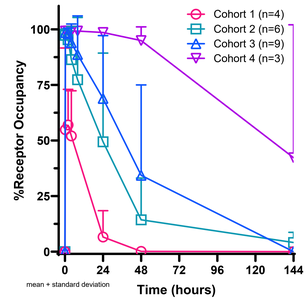
[1] One participant (Cohort 2) had a Grade 2 liver enzyme elevation not reflected in table
[2] Participant had severe neutropenia with Grade 2 leukopenia at baseline
[3] Participant had severe neutropenia with Grade 3 leukopenia at baseline
[4] Two participants had Grade 4 pneumonitis
[5] One participant with Grade 4 pneumonitis had Grade 4 liver enzyme elevation
[6] One participant with Grade 5 respiratory failure and cardiac arrest resulting in death
TEAEs observations are from independent participants
TEAEs: Treatment- Emergent Adverse Events; AEs: Adverse Events

Pharmacokinetics (N=19)



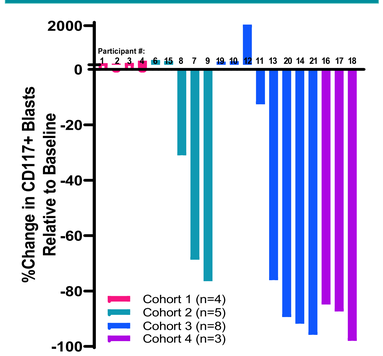
- Maximum concentrations of MGTA-117 reached in all participants within 2-4 hours of dosing
- As expected, there was rapid clearance in all Cohorts and non-linear clearance was observed in Cohort 4
- Confirmed *in vivo* stability of ADC: no free payload detectable at any timepoint after dosing (n=19)

Receptor Occupancy (N=21)



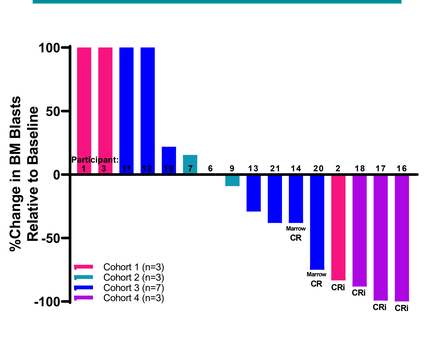
- Binding of CD117⁺ cells was observed in all participants within 15 minutes after dosing
- Greater levels and longer duration of RO was observed in higher dose cohorts
- >90% RO for 48 hours was observed in Cohort 4

Depletion in Blood (N=20)



- CD117⁺ blast cell depletion was observed in the blood in Cohorts 2, 3 and 4
- Increasing levels of depletion was observed with higher dose levels
- These findings were consistent with higher and longer receptor occupancy in the blood at higher dose levels

Depletion in Bone Marrow (N=16)



- Six clinically meaningful responses (4 CRi, 2 Marrow CR) were observed across dose levels
- 55% of bone marrow evaluable participants had a reduction in blasts across dose levels
- 100% of Cohort 4 participants (3/3) with R/R disease achieved morphologic and molecular remission in the bone marrow and are progressing to transplant

STUDY STATUS AND NEXT STEPS

- PK, RO, and PD (target cell depletion) data indicate that MGTA-117 is a potent myelodepletive agent with rapid clearance
- In this R/R transplant ineligible study population, treatment with MGTA-117 resulted in five AML or MDS-EB participants progressing to stem cell transplant
- Three participants experienced DLTs (2 in Cohort 4 and 1 in Cohort 3) in this trial
- The study has recently been terminated. The authors would like to thank the study participants and those who helped support the trial.