A Single Dose of a Novel Anti-Human CD117-Amanitin Antibody Drug Conjugate (ADC) Engineered for a Short Half-Life Provides Dual Conditioning and Anti-Leukemia Activity and Extends Survival Compared to Standard of Care in Multiple Preclinical Models of Acute Myeloid Leukemia (AML)

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Background

- Hematopoietic stem cell transplant (HSCT) can be a highly effective, and often curative, treatment for patients with AML.
- Current conditioning regimens, such as myeloablative conditioning (MAC) and reduced-intensity conditioning (RIC) regimens, come with either high toxicity or higher chance of relapse, respectively.
- To address these issues, we have developed MGTA-117, an anti-human CD117(c-kit)-targeted antibody conjugated to amanitin, an RNA polymerase II inhibitor, and engineered for a short half-life to enable rapid ADC clearance prior to HSCT.
- MGTA-117 has previously been shown to elicit potent cytotoxicity on both primary human CD34+ cells and a CD117+ cell line *in vitro*, as well as selective depletion of human HSPCs at single doses in humanized NSG mice.
- To demonstrate anti-leukemic activity of MGTA-117, we studied its efficacy in multiple human leukemic xenograft murine models, including the CD117+ Kasumi-1 cell line derived model and two patient derived xenograft models representing high-risk populations in both untreated and relapsed refractory disease.

MGTA-117 robustly kills CD117+ cells *in vitro* and depletes human CD34+ BM cells *in vivo*

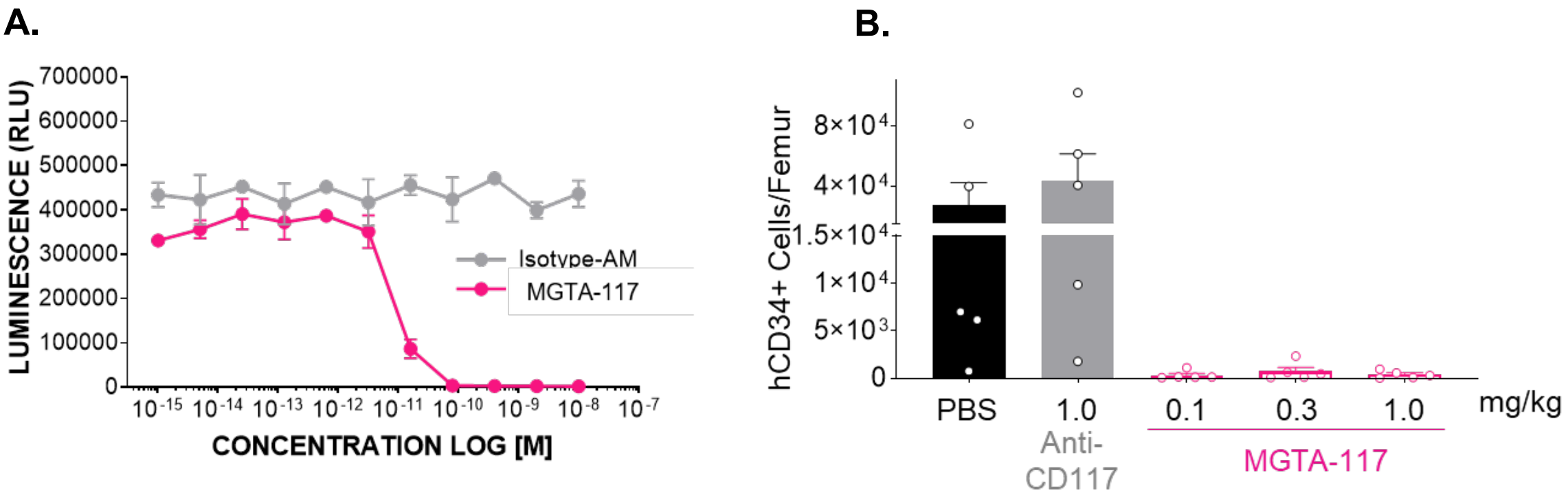
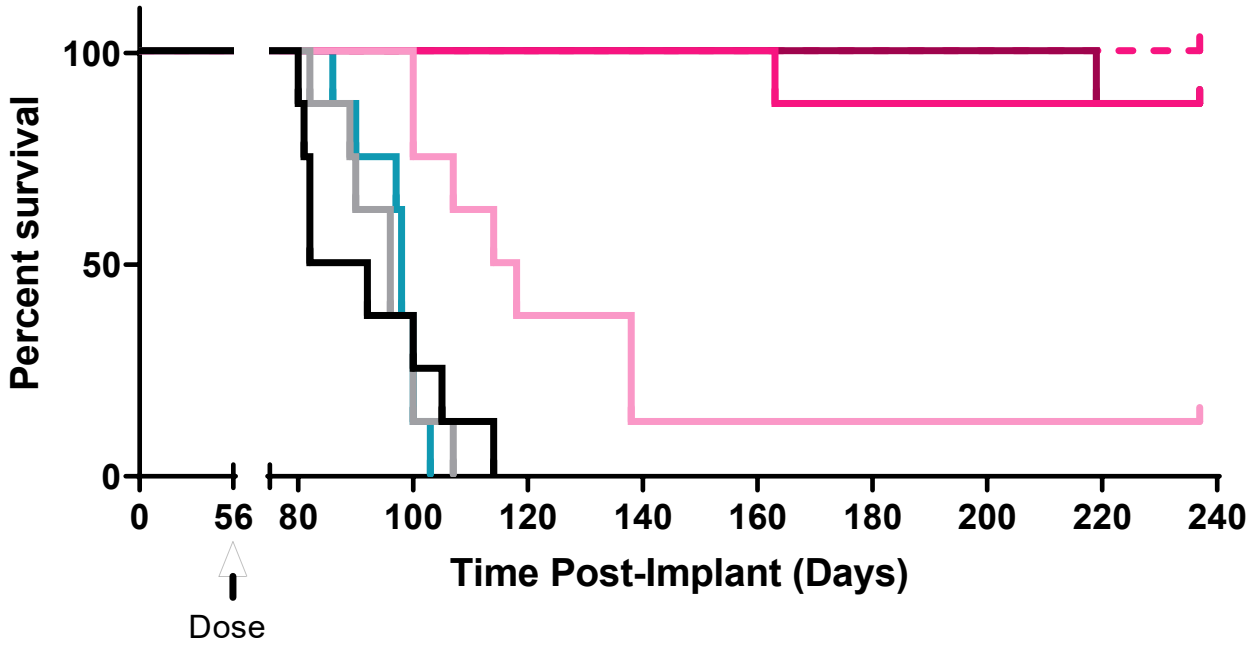


Figure 1: Single dose administration of MGTA-117 showed robust cytotoxicity to CD117+ Kasumi-1 cells *in vitro* and significant depletion of normal hCD34+ HSPCs *in vivo*. **(A)** Human Kasumi-1 cells were cultured for four days in the presence of 10 nM MGTA-117 or isotype-ADC, with 1:5 serial dilutions, after which viability was measured by Celtiter Glo. **(B)** Humanized NSG mice received a single IV injection of 0.1, 0.3 or 1 mg/kg MGTA-117, 1 mg/kg anti-hCD117 antibody or PBS vehicle. Bone marrow was extracted from treated mice and human CD34+ counts were determined by flow cytometry on day 21 post-dose.

MGTA-117 extends median survival in the Kasumi-1 AML cell line derived xenograft model



Treatment Groups		Median Survival (Days Post Implant)
PBS		87
10 mg/kg	Isotype-ADC	96
1 mg/kg	MGTA-117	116*‡
3 mg/kg		>237*‡
10 mg/kg		>237*‡
3 mg/kg QODx2		>237*‡
ARA-C 30 mg/kg QDx5		98

log-rank test p ≤ 0.01 compared to *PBS or Isotype ADC; ‡ compared to Ara-C

Figure 2: Treatment with MGTA-117 more than doubles the median survival compared to controls in the Kasumi-1 CDX AML model. A single dose (1, 3 and 10 mg/kg) or fractionated injection (3 mg/kg QODx2) of MGTA-117 administered 8 weeks post-implantation of Kasumi-1 cells resulted in a 2.1-2.7-fold increase in median survival compared to PBS, isotype-ADC or ARA-C treated controls.

MGTA-117 effectively depletes human leukemic cells in two patient derived AML models

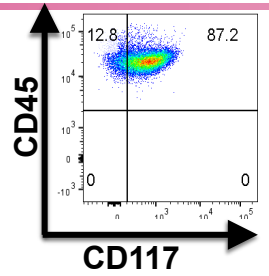
A.

PDX Model

Type
Previous treatment
Karyotype; Mutation

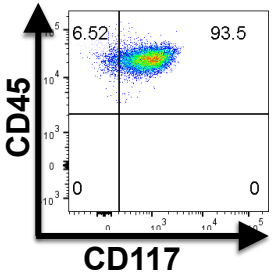
AML 1

AML, M4
No previous treatment
46, XY, FLT3+, NPM1+



AML 2

AML recurrent/Relapse
Allogeneic HSCT, Sorafenib, Hydroxyurea, Decitabine
Normal; FLT3+, NPM1+, DNMT3A+, IDH1+



B.

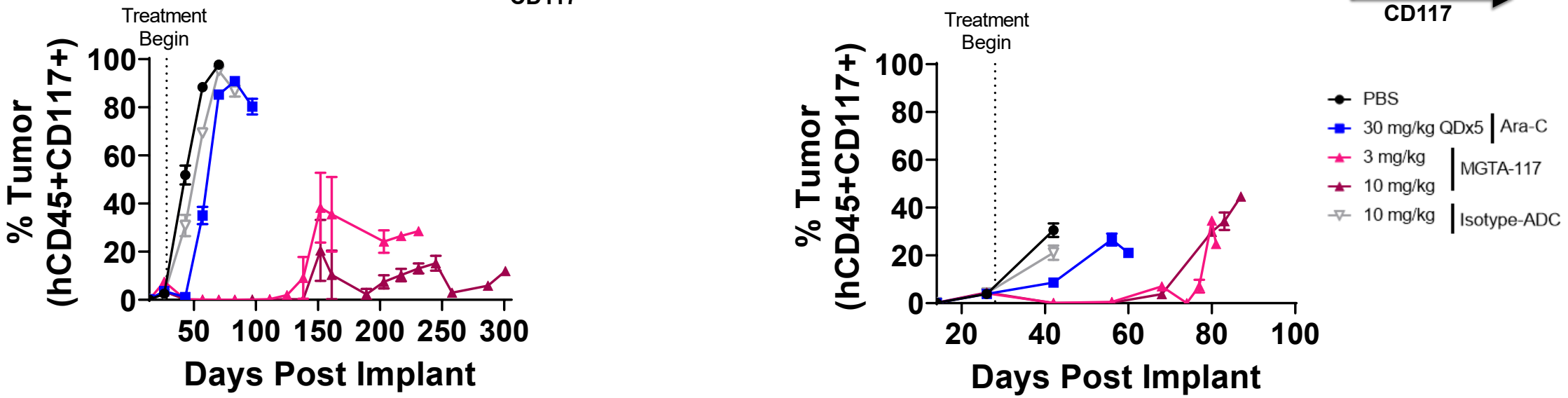
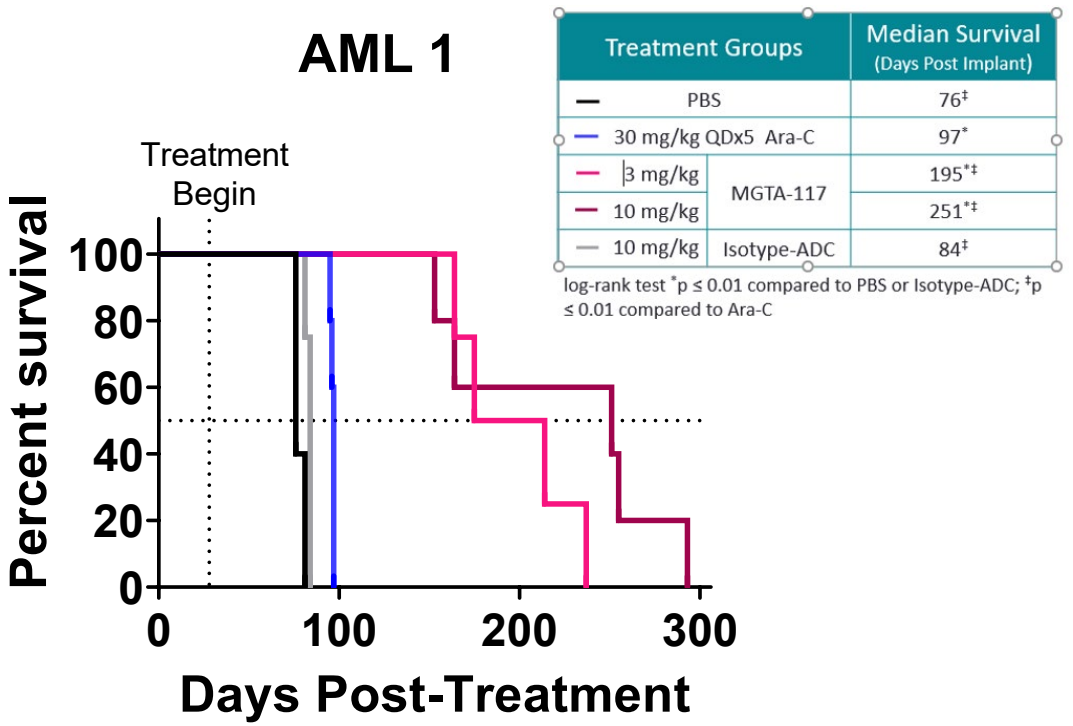


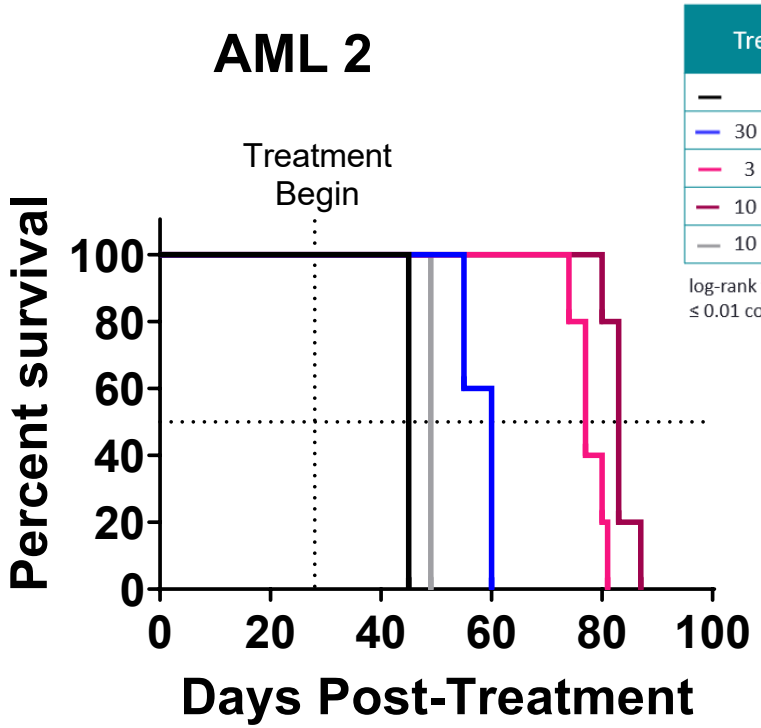
Figure 3: A single dose of MGTA-117 effectively decreases tumor burden of human myeloid leukemic cells across two patient derived xenograft models compared to PBS vehicle, isotype-ADC, or clinically validated standard of care ARA-C. **(A)** Disease characteristics of a treatment-naïve PDX model (AML 1) and highly pretreated relapsed refractory PDX model (AML 2). **(B)** Mice were treated with a single intravenous dose of 3 or 10 mg/kg MGTA-117, 10 mg/kg isotype-ADC or PBS vehicle. ARA-C was administered intravenously once daily for five consecutive days at a dose of 30 mg/kg. Mice were treated with ~5% blasts were detected in the periphery (n = 3-5 mice/group/model). MGTA-117 significantly delayed tumor burden (expressed as %hCD45) in the peripheral blood of treated mice compared to PBS, isotype-ADC and SOC controls.

MGTA-117 significantly extends survival in two patient derived high risk AML models



Treatment Groups		Median Survival (Days Post Implant)
PBS		76‡
30 mg/kg QDx5 Ara-C		97*
3 mg/kg	MGTA-117	195*‡
10 mg/kg	MGTA-117	251*‡
10 mg/kg	Isotype-ADC	84‡

log-rank test *p ≤ 0.01 compared to PBS or Isotype-ADC; ‡p ≤ 0.01 compared to Ara-C



Treatment Groups		Median Survival (Days Post Implant)
PBS		45‡
30 mg/kg QDx5 Ara-C		60*
3 mg/kg	MGTA-117	77*‡
10 mg/kg	MGTA-117	83*‡
10 mg/kg	Isotype-ADC	49*‡

log-rank test *p ≤ 0.01 compared to PBS or isotype-ADC; ‡ p ≤ 0.01 compared to Ara-C

Figure 4: A single dose of MGTA-117 increases median survival compared to PBS vehicle, isotype-ADC or clinically validated standard of care ARA-C. Survival curve of CD45+CD117+ (inset) PDX AML mice treated with a single intravenous dose of 3 or 10 mg/kg MGTA-117, 10 mg/kg isotype-ADC, or PBS vehicle. ARA-C was administered intravenously once daily for five consecutive days at a dose of 30 mg/kg. Treatment began when ~5% blasts were detected in the periphery (n = 3-5 mice/group/model). MGTA-117 treatment significantly increased median survival compared to PBS and isotype controls in both treatment naïve (2.3-3-fold) and relapsed-refractory (1.3-1.8-fold) models, compared to SOC ARA-C, which only increased median survival modestly (1.3-fold in both models).

Conclusions

- We have demonstrated that a single dose administration of MGTA-117 is well tolerated and capable of:
  - **Reducing tumor burden by targeting leukemia cells in both treatment naïve and relapsed refractory patient derived high risk AML xenograft models.**
  - **Significantly extending median survival in established leukemia xenograft models (cell line and patient derived) compared to controls and clinically validated standard of care**
- These results, combined with prior reports on MGTA-117's robust conditioning ability, demonstrate the dual potential of this agent to be a potent targeted conditioning agent that could improve HSCT outcomes in AML by reducing leukemic burden prior to transplant

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Conflict of interest statement: Leanne Lanieri is an employee and equity holder of Magenta Therapeutics.