A Novel Short Half-life Anti-Human CD117-Amanitin ADC Exhibits Dual HSCT Conditioning and Anti-Leukemia Activity and Extends Survival in Multiple Preclinical Models of AML

Leanne Lanieri, Tahirih Lamothe, Oliver Mikse, Sean M McDonough, Prashant Bhattarai, Kellie Latimer, Junia Dushime, Nidhi Jain, Rahul Palchaudhuri, John C Davis, Lisa M Olson, Jennifer L Proctor
Magenta Therapeutics, Cambridge, MA

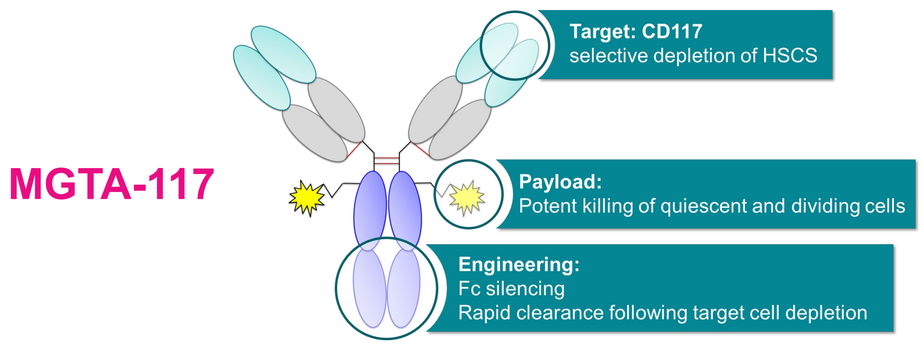
INTRODUCTION

Hematopoietic stem cell transplant (HSCT) can often be a curative treatment for patients with AML. Present conditioning regimens, such as myeloablative conditioning (MAC) and reduced-intensity conditioning (RIC), are associated with severe toxicities or higher post-transplant relapse and graft failure, respectively. Thus, the need for safe and effective targeted conditioning agents for a broader use in transplant in both malignant as well as non-malignant settings is critical.

METHODS

MGTA-117 is an antibody drug conjugate (ADC), using an anti-human CD117-targeted antibody (Ab) conjugated to amanitin, an RNA polymerase II inhibitor. The ADC was engineered to have a short-half life (t1/2) to enable ADC clearance prior to HSCT. The antibody component binds CD117, which is expressed on hematopoietic stem and progenitor cells (HSPC) and in ~80% of AML and MDS cells (Gao, PLOS One. 2015). This targeted and optimized approach not only has a broad therapeutic window across preclinical models but could also provide the dual benefit of effective conditioning for HSCT and reduction of target-expressing tumor cells. We therefore tested MGTA-117 for its ability to deplete CD117+ Kasumi-1 cells in vitro (Fig. 1A) and its ability to deplete hCD34+ HSPCs in vivo (Fig. 1B) following a single dose. MGTA-117 was then tested in a Kasumi-1 cell line derived AML model (Fig. 2) as well as in two patient derived AML models to determine the ability to deplete leukemic cells and extend survival (Fig. 3).

CD117-Targeted Conditioning for Stem Cell Gene Therapy and Hematologic Malignancies with antibody drug conjugate



RESULTS

MGTA-117 Robustly Kills CD117+ cells In Vitro and Depletes Human CD34+ BM Cells In Vivo

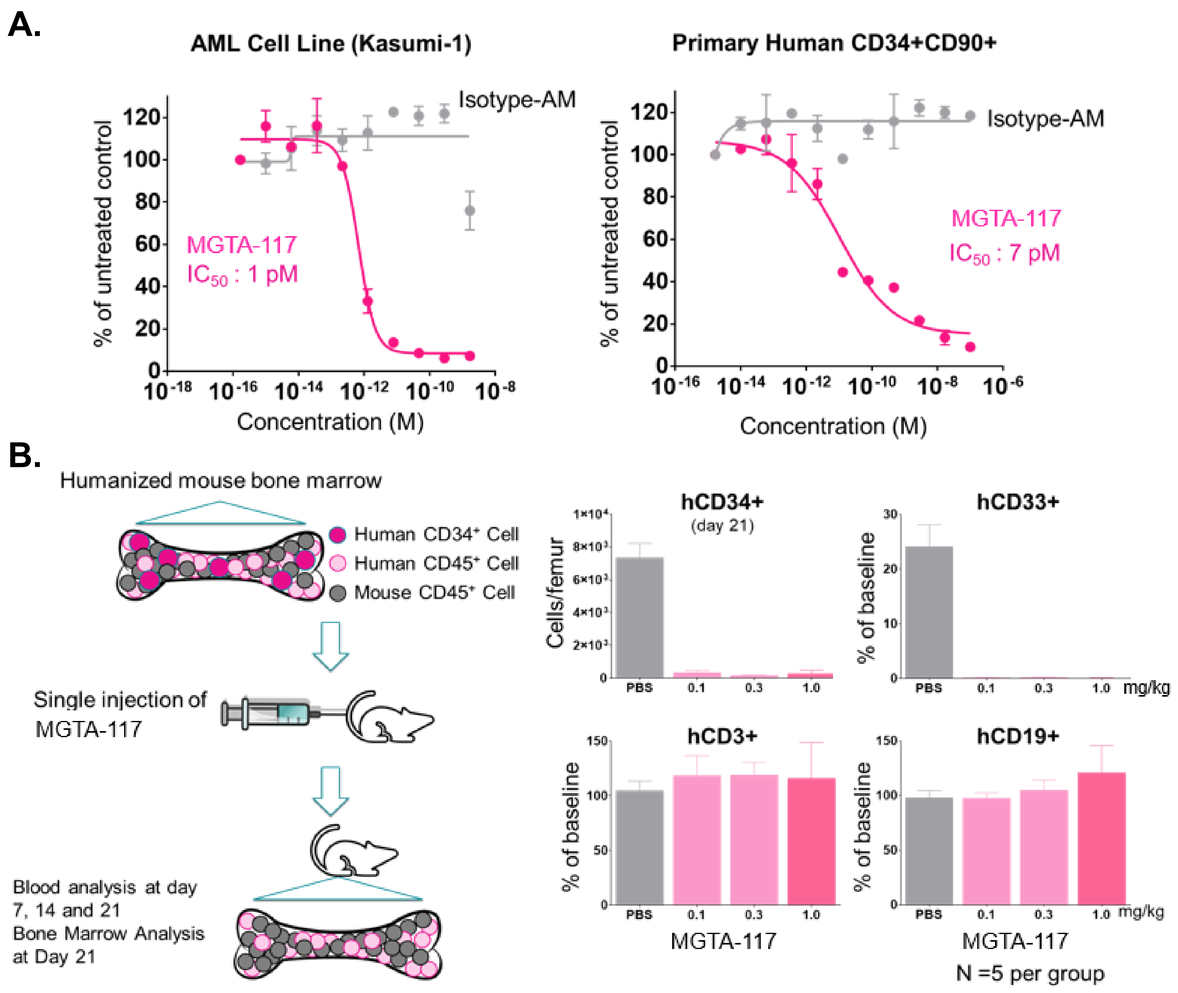
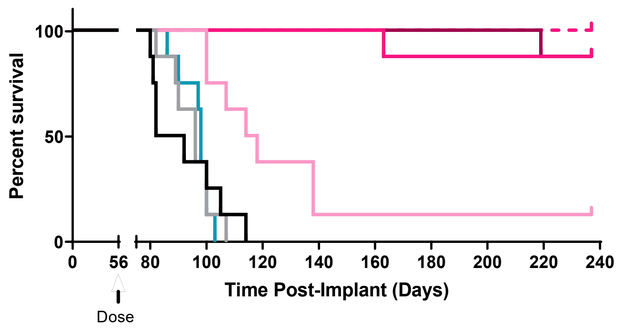


Figure 1: MGTA-117 showed robust cytotoxicity to CD117+ Kasumi-1 cells in vitro and significant depletion of normal hCD34+ HSPCs in vivo following a single dose. (A) Human Kasumi-1 cells (left) or primary human CD34+CD90+ cells (right) were cultured for four days in the presence of 10 nM MGTA-117 or isotype-ADC, with 1:5 serial dilutions, after which viability was measured by Celltiter 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

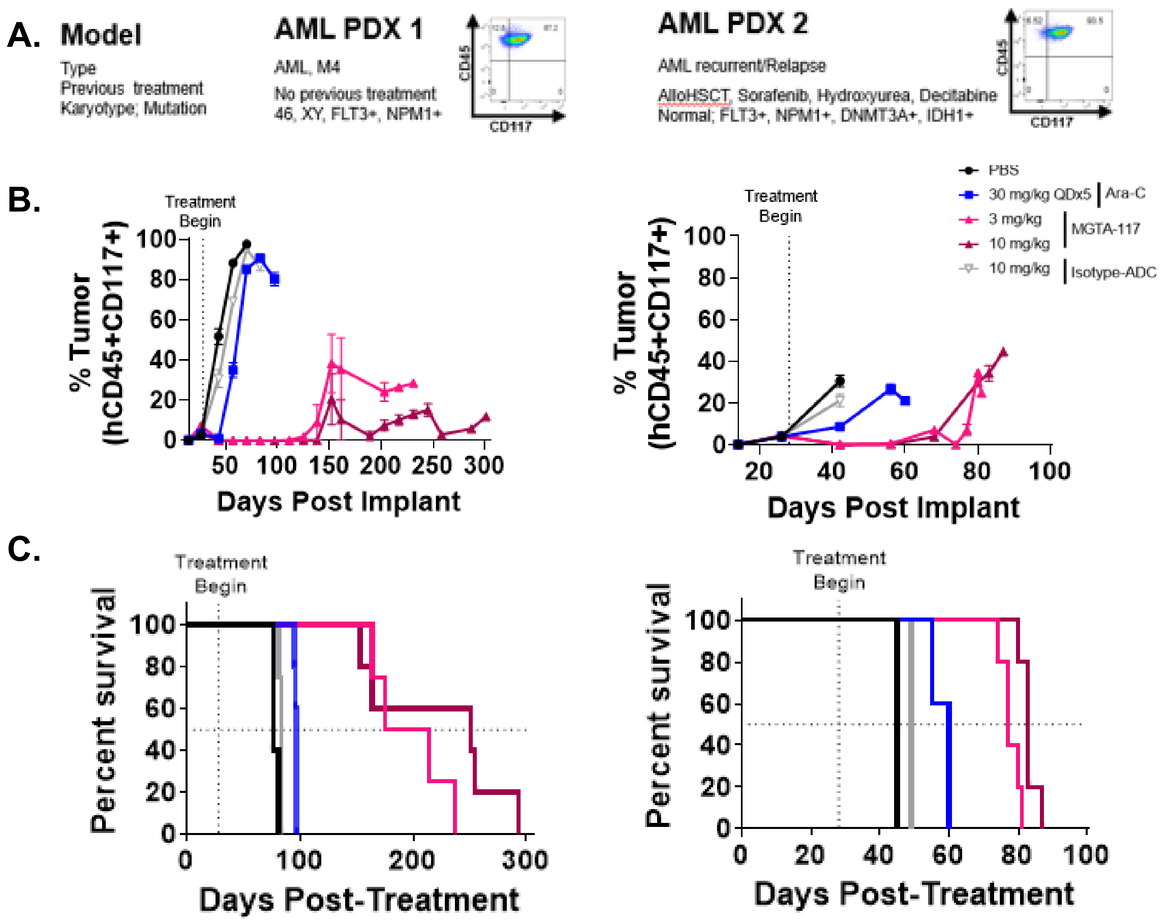


Treatment Groups		Median Survival (Days Post Implant)
PBS		87
10 mg/kg	Isotype-ADC	96
1 mg/kg	MGTA-117	116*‡
3 mg/kg	MGTA-117	>237*‡
10 mg/kg	MGTA-117	>237*‡
3 mg/kg QODx2	MGTA-117	>237*‡
ARA-C 30 mg/kg QDx5		98

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 and Significantly Extends Survival in Two Patient Derived AML Models



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

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

Figure 3: MGTA-117 Effectively Depletes Human Leukemic Cells and Significantly Extends Survival in Two Patient Derived AML Models. Humanized NSG mice bearing J00106134 (AML PDX 1) or J000106132 (AML PDX 2) cells. (A). AML PDX model characterization. CD117 and CD45 cell surface expression on splenocytes from diseased mice was evaluated by flow cytometry. Mice were administered a single dose unless otherwise noted with MGTA-117, Isotype-AM ADC, PBS or cytarabine (ARA-c) when peripheral tumor burden reached 2-5% (4-5 mice/group/AML-PDX model). (B) Leukemic tumor burden assessment over a time course in the peripheral blood of PDX AML mice (C) Survival was significantly increased in recipients of anti-CD117-AM as compared to vehicle controls.

CONCLUSIONS

We have demonstrated that a single dose administration of MGTA-117 is well tolerated and capable of:

- **Reducing tumor burden by potently 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