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The Pharmacokinetic and Pharmacodynamic Characterization of MGTA-117, an Anti-CD117-Amanitin Antibody-Drug Conjugate for Targeted Conditioning Prior to Transplant, in Nonhuman Primates

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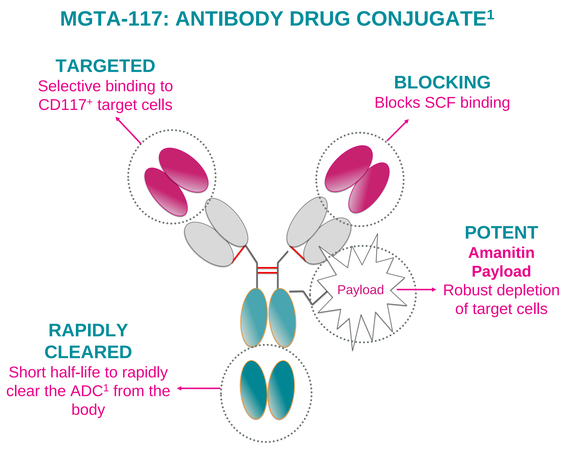
BACKGROUND

- Hematopoietic stem cell transplant is a highly effective and potentially curative treatment for malignant and nonmalignant blood disorders
- However, current preparative conditioning regimens are nonselective and result in significant mortality and morbidities, including organ toxicity, infertility, and secondary malignancies
- To reimagine conditioning, we have developed a potent, antibody-drug conjugate (ADC) targeting CD117 (c-kit) conjugated with a stable linker to an amanitin payload (**Figure 1**)
- Upon binding to CD117, the ADC is rapidly internalized, undergoing lysosomal degradation and intracellular release of the amanitin payload, leading to apoptosis of quiescent and cycling cells
- MGTA-117 is rapidly cleared from blood via selective binding and internalization of CD117
- In addition, the antibody component of the ADC is an antagonist of the natural ligand for CD117 (stem cell factor), providing a dual mechanism of target cell depletion
- We have demonstrated that MGTA-117 is highly effective at depleting human CD117^{+} stem cells and precursors in vitro and in humanized NSG mice
- In nonhuman primates (NHPs), we have determined a single administration of MGTA-117 resulted in significant depletion of stem and progenitor cells in the bone marrow and reductions in reticulocytes in peripheral blood reflecting the depletion of erythroid precursors

Figure 1. MGTA-117 ADC

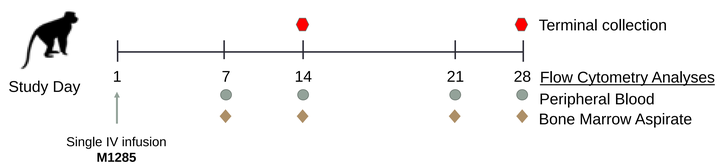


[1]Tsao et al., *Leuk Res.* 2004;28:373-8.
ADC, antibody-drug conjugate; SCF, stem cell factor.

METHODS

- Data presented are pooled across several individual studies with MGTA-117 in cynomolgus NHPs
- The objectives of these studies were to determine the dose and time relationship between dosing of MGTA-117 and the resulting depletion of bone marrow stem cells and peripheral reticulocytes utilizing an NHP model
- MGTA-117 was dosed at 0.05 to 3 mg/kg via intravenous infusion over 60 minutes in NHPs to determine the time course of pharmacokinetic (PK) and pharmacodynamic (PD) responses in stem cell and blood populations (**Figure 2**)
- Blood and bone marrow tissues were collected via standardized procedures during the study at the in-life testing facilities and occurred prior to treatment and then up to 28 days after dosing
- For analysis of stem cells counts, single cells in a heterogenous mixture were detected, counted, sorted, and profiled via single-file cell passage via flow cytometry
  - Cell composition was assessed using fluorescently conjugated antibodies against specific cell surface markers
  - Fluorescently conjugated antibodies are excited by a laser to emit light at specific wavelengths
  - Fluorescent emission is measured by an electronic detection apparatus as light scatter and fluorescence intensity
  - Specific cell populations within the heterogenous mixture were identified and quantified based on their emission profile
- For estimation of reticulocytes counts, standard hematology samples were collected and analyzed at the in-life testing facilities
- For PK analysis, an enzyme-linked immunosorbent assay (ELISA)-based assay was utilized for the estimation of ADC and therapeutic antibodies within each individual study
  - PK data presented reflect the mean (±SD) ADC concentrations collected within each animal receiving MGTA-117 after pooling the data at each relevant dose
  - The lower limit of quantification for MGTA-117 was consistent across each study

Figure 2. General Monkey Study Design

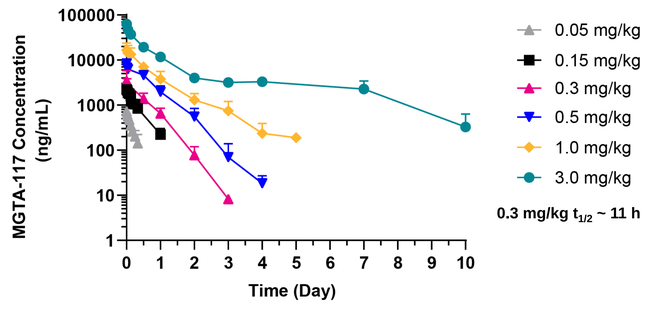


IV, intravenous.

RESULTS

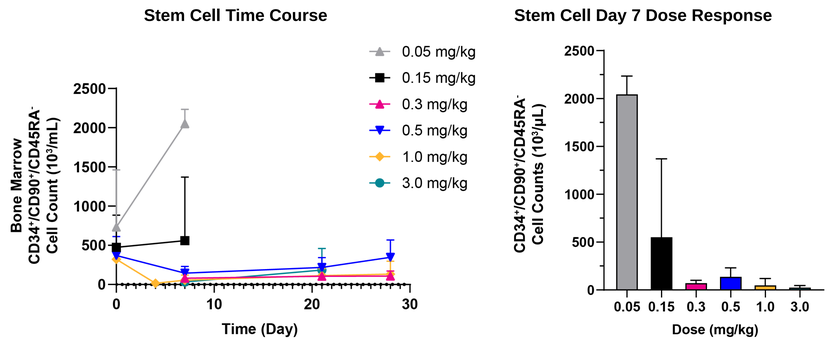
- Intravenous administration of MGTA-117 resulted in dose-dependent increases in exposures, with rapid rates of clearance at all dose levels (**Figure 3**)
- Nonlinear rates of clearance were apparent at the higher doses of MGTA-117; these observations are consistent with the expected target-mediated drug distribution profile, where nonlinear clearance is attributed to saturation of CD117 binding and internalization of the ADC
- Nonetheless, even at the highest doses tested, MGTA-117 was cleared quickly and was below the limit of quantification in blood 10 days after dosing

Figure 3. Plots of Mean (±SD) MGTA-117 Plasma Concentration in NHPs



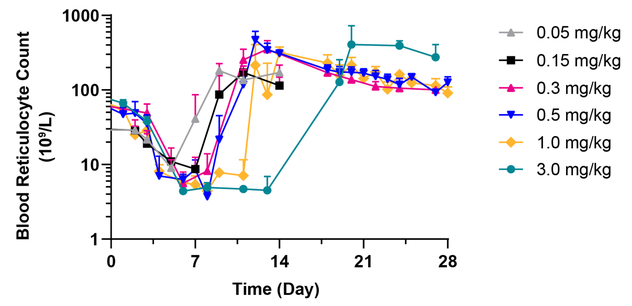
- In NHPs, >90% depletion of CD34^{+}/CD90^{+}/CD45RA^{-} stem cells within bone marrow were observed at MGTA-117 doses 0.3 mg/kg or higher (**Figure 4**)
- Lasting stem cell depletion was observed well after clearance of MGTA-117 from blood; the onset of stem cell depletion occurred as early as 7 days after dosing, with recovery delayed until at least 21 days after dosing in a dose-dependent manner

Figure 4. Plots of Mean (±SD) CD34^{+}/CD90^{+}/CD45RA^{-} Cell Counts Through 28 Days After Dosing (left), or Day 7 Only (right) in NHPs Receiving MGTA-117



- Robust depletion of blood reticulocyte counts were also observed, an indirect surrogate for the depletive effects of MGTA-117 on red blood cell progenitors in the bone marrow (**Figure 5**)
- While the onset of reticulocyte depletion is similar to stem cells, the time to recovery correlates directly with the clearance of MGTA-117 below active concentrations

Figure 5. Plots of Mean (±SD) Reticulocyte Cell Counts Through 28 Days After Dosing in NHPs Receiving MGTA-117



- Neutrophils and platelets were unaffected by any dose of MGTA-117 on Day 7 (data not shown)

CONCLUSIONS

- MGTA-117 demonstrated potent single-agent activity with predictable and consistent PK-PD across a wide range of doses in NHPs
- The rapid clearance of MGTA-117 from blood was consistent with CD117 binding and internalization
- At doses of 0.3 mg/kg and higher, the observed PD responses in stem cells confirm targeted depletion of CD117-expressing populations, with durable depletion extending beyond the actual clearance of ADC
- At all doses tested, depletion of blood reticulocyte populations were also observed, with the relative recovery correlated directly with the clearance of MGTA-117
- The significant and rapid reticulocyte depletion supported the hypothesis that reticulocytes are a blood biomarker for bone marrow depletion
- The dose dependency of PD responses suggests that effective doses of MGTA-117 may require maintenance of receptor occupancy to confer the targeted cytotoxic effects
- Mechanistic modeling of this predictable and potent profile in NHPs is supportive of predictions of biologic activity at low doses in humans
- Overall, the rapid PK clearance and prolonged stem cell depletive responses provide an attractive profile that supports MGTA-117 for clinical development as a conditioning agent prior to transplant
- MGTA-117 is being explored in an ongoing Phase 1/2 study (NCT05223699), initial results of which are being presented at ASH (abstract #874)

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