A Phase 1, First-in-Human Study of MGD006/S80880 (CD123 x CD3) in AML/MDS

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Background

MGD006: Humanized CD123 x CD3 DART® Molecule

![Diagram of MGD006 Molecule]

Proposed Function/Mechanism of Action
- Redirected T-cell killing against targeted leukemia cells
- Elimination of leukemic stem cells
- Capable of engaging any T cell without HLA-restriction
- Potent in vivo preclinical activity in preclinical models
- Extremely low clinical dosing (ng/kg)

Rationale

- CD123 is highly expressed in >90% of AML patients and at least 50% of MDS patients, making these diseases a reasonable target for T-cell-based immunotherapy
- MGD006 is a novel CD123 x CD3 DART molecule designed to target CD123-positive cells for recognition and elimination by CD3-expressing T lymphocytes as effectors
- MGD006 shows potent activity to redirect T cell killing against CD123-expressing cell lines and primary AML blasts in vitro, inhibition of the growth of leukemic cell lines in mice and depletion of CD123-positive plasmacytoid dendritic cells in cynomolgus macaques
- Large unmet need remains given toxicity and high rates of relapse with standard therapy

Key Study Objectives

Primary Objective:
- Characterize dose limiting toxicities (DLTs) and determine the maximum tolerated dose and schedule (MTDS) for MGD006 when given by continuous intravenous (IV) infusion over a broad dose range in two dosing schedules in patients with relapsed or refractory acute myeloid leukemia (AML) or intermediate-2/high risk myelodysplastic syndrome (MDS)

Secondary Objectives:
- Describe preliminary safety profile of MGD006 over a broad dose range in two dosing schedules
- Characterize pharmacokinetics (PK) and immunogenicity of MGD006 over a broad dose range in two dosing schedules
- Describe any evidence of anti-neoplastic activity in AML and MDS

Exploratory Objectives:
- Evaluate the utility of CD123 expression on blast cells in AML and MDS as a biomarker
- Evaluate cytokine production by immune effector cells
- Evaluate changes in T lymphocyte populations and activation markers
- Evaluate changes in leukemic and normal cells in PBMCs
- Evaluate changes in leukemic cells, leukemic stem cells and normal progenitor cells in bone marrow
- Evaluate molecular markers of minimal residual disease
- Examine changes in T lymphocyte repertoire
- Gain experience with the use of certain anti-cytokine agents in the prevention and/or treatment of cytokine release symptoms

Study Design

- Multi-center Phase 1, open-label 3+3 design dose escalation and cohort expansion study
- All patients start with a lead-in continuous IV infusion (IV) of 30 ng/kg/day for 3 days followed by 100 ng/kg/day for 4 days; dosing occurs in 28-day cycles. Subsequent weeks (2-4) are dosed in two different schedules. (See Study Schema)
- Beginning with second cycle, all patients receive MGD006 for 4 days on 3 days off at the maximal dose/cohort
- Treatment continues until 2 cycles after attainment of complete response, maximum of 12 cycles, DLT, or treatment failure
- CRS graded according to Lee criteria; response assessed by IWG (AML) or IPSS (MDS) criteria
- Once MDS or MAD is identified, two cohorts of 24 patients each, one in AML and one in MDS, will be enrolled

Key Inclusion Criteria

- Confirmed diagnosis of primary or secondary AML (any subtype except APL according to WHO classification) or MDS with an IPSS risk category of Int-2 or High Risk
- Refractory AML unlikely to benefit from cytotoxic chemotherapy as defined by one of the following criteria:
  - newly diagnosed leukemia refractory to ≥2 induction attempts,
  - leukemia in 1st relapse with initial CR duration ≤6 months,
  - leukemia in 1st relapse following ≥1 unsuccessful salvage attempts, or
  - leukemia in 2nd or higher relapse
- Patients with MDS must have experienced treatment failure with induction therapy or at least one cycle of hypomethylating therapy and have ≥10% marrow blasts
- Eastern Cooperative Oncology Group (ECOG) performance status ≤2
- Adequate hepatic and renal function and organ reserve
- Peripheral blast count ≤20,000/mm³ at the time of initiation of infusion on Cycle 1 Day 1

Key Exclusion Criteria

- Prior history of allogeneic stem cell transplantation
- Prior treatment with an anti-CD123-directed agent
- Need for concurrent other cytoktherapeutic chemotherapy
- History of or suspected current autoimmune disorders with certain exceptions
- Secondary primary malignancy that requires active therapy (adjuvant hormonal therapy allowed)
- Prior treatment with radiotherapy, immunotherapy, or other investigational agent within 4 weeks; use of immunosuppressant medications, granulocyte colony stimulating or granulocyte-macrophage colony stimulating factor within 2 weeks
- Known central nervous system leukemia

Entry Criteria

- Continuous IV infusion Days 1-3 at 30 ng/kg/day, Days 4-7 at 100 ng/kg/day.

References


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