A Phase 1 Study of Flotetuzumab, a CD123 x CD3 DART® Protein, Combined with MGA012, an Anti-PD-1 Antibody, in Patients with Relapsed or Refractory Acute Myeloid Leukemia

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Key Eligibility Criteria

- **Inclusion**
  - Patients with AML with relapsed or refractory disease.
  - Patients with AML with high-risk cytogenetics.
  - Patients with AML who have failed or relapsed after treatment with conventional chemotherapy.
  - Patients with AML who have received prior immunotherapy.

- **Exclusion**
  - Patients with central nervous system leukemia.
  - Patients with known hypersensitivity to flotetuzumab or MGA012.
  - Patients with known co-morbidities that would make them ineligible for the study.

**Rationale**

- Flotetuzumab is a CD123 x CD3 DART® protein that is currently being tested in a Phase 1/2 study in AML.
- Flotetuzumab co-engages T cells (anti-CD3) with a tumor antigen (anti-CD123) in a dose-dependent manner.
- Flotetuzumab leads to T-cell activation, which in turn was associated with PD-1/PD-L1 changes of immune modulation.

**Background**

- Acute myeloid leukemia (AML) blasts and leukemic stem and progenitor cells typically express higher levels of CD123 than their normal hematopoietic stem cell counterparts, making CD123 an attractive target.
- Leukemic CD123 expression is associated with poor prognosis, high-risk disease, and increased risk of induction failure.
- Single-agent flotetuzumab, an investigational CD123 x CD3 bispecific DART® protein, has shown evidence of clinical activity in a Phase 1 study of relapsed/refractory (R/R) AML.

**Flotetuzumab (MGD006): CD123 x CD3 Bispecific DART® Protein**

- Flotetuzumab is a bispecific monoclonal antibody that co-engages T cells (anti-CD3) with a tumor antigen (anti-CD123).
- Normal CD3- or CD4- or CD8-gated T cells using flow cytometry. Untreated PBMCs (red shaded histograms) from this AML-patient were used to establish a baseline control for PD-1 and PD-L1 expression. In order to better visualize the dose response of MGD006 in upregulating PD-L1 expression, CD3-, CD4-, or CD8-gated-T cells were used.

**In Vitro Uptregulation of Checkpoint Molecules by Flotetuzumab**

- Flotetuzumab upregulates PD-1 and PD-L1 in AML blasts and CD8 T cells in a dose-dependent manner.
- Flotetuzumab treatment leads to enhanced IFNγ production and PD-L1 expression on AML blasts.

**Induction of IFNγ and PD-L1 In Flotetuzumab-treated Patients**

- Patients received Flotetuzumab (Cycle 1) and MGA012 (Cycle 1) in a Phase 1 study.
- Flotetuzumab treatment led to enhanced IFNγ production and PD-L1 expression on AML blasts.

**PD-L1 Uptregulation in Residual Bone Marrow Blasts**

- Residual bone marrow AML blasts show higher expression of PD-L1 positive blasts compared to baseline.
- Enhanced PD-L1 expression was associated with reduced Flotetuzumab activity in vitro and in vivo.

**Flotetuzumab Activity and PD-1 Expression**

- Flotetuzumab combination with CPIs to obviate Flotetuzumab-induced pathways of AML resistance and harness Flotetuzumab-induced positive changes of immune modulation.
- Patients with AML who have failed or relapsed after treatment with monotherapy Flotetuzumab.

**References**


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