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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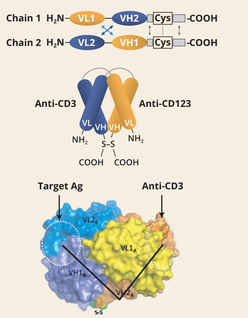
Background

- 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[1]
- 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

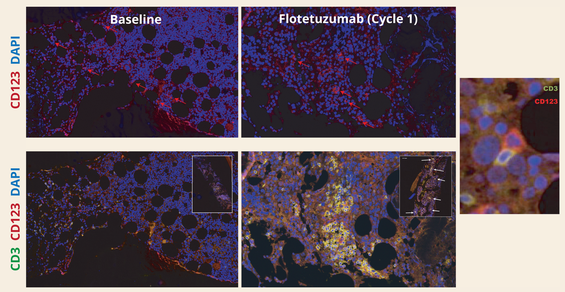
Flotetuzumab (MGD006): CD123 x CD3 Bispecific DART® Protein

- Flotetuzumab:
  - An investigational bispecific molecule that co-engages T cells (anti-CD3) with a tumor associated antigen (CD123)
  - Designed to:
    - Redirect T cells to kill tumor cells
    - Recognize tumors independent of TCR and MHC
  - Currently being tested in a Phase 1/2 study in AML
- CD123, the low-affinity IL-3 receptor (IL3Rα)
  - Normally expressed on plasmacytoid dendritic cells (pDCs), basophils, monocytes, and hematopoietic progenitor cells (HPCs)
  - Over-expressed on leukemic stem cells (LSCs) in AML and other hematologic malignancies

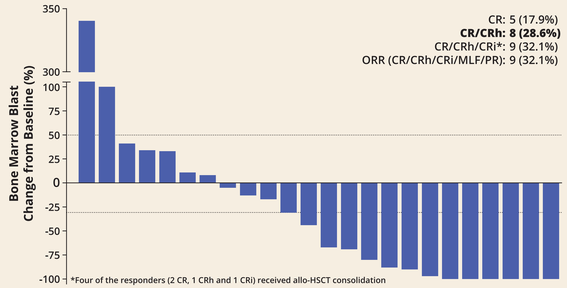


DART Crystal Structure[2]

T-cell Infiltration in the Bone Marrow of a Flotetuzumab-treated Patient[3]



Single-agent Flotetuzumab Has Shown Evidence of Clinical Activity in a Phase 1 Study of Refractory AML

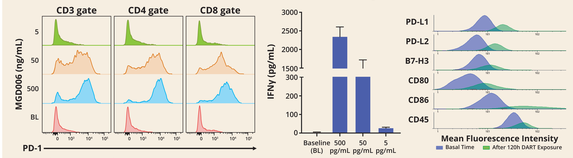


30 pts treated at RP2D: 28 response evaluable, 24 pts in waterfall plot, 4 PD on PB blasts, 2 non-evaluable pts (1 pt withdrew consent, 1 pt withdrawn due to non-TRAE).

CR: complete response; CRh: complete response with partial hematological recovery; CRi: complete response with incomplete hematological improvement. (CP-MGD006-01, NCT02152956). Data cut-off November 1, 2019.

In Vitro Upregulation of Checkpoint Molecules by Flotetuzumab

Upregulation of PD-1 on CD4 and CD8 T cells and of other checkpoint molecules on AML blasts upon co-incubation with flotetuzumab

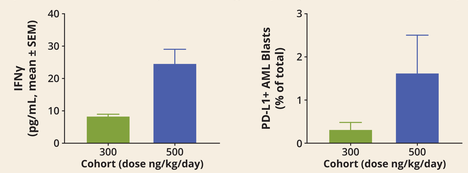


Top Panel: Donor PBMCs from an AML patient containing 24% CD123-positive cells and 14.2% CD3-positive T cells were cultured in a 96-well U-bottom tissue culture plate at 6 x 104 cells/well in the presence of 500 (blue shaded histograms), 50 (orange shaded histograms), or 5 (green shaded histograms) pg/mL of MGD006 for 2 days. PD-1 and PD-L1 expression was determined on non-T cells (CD3-negative cells) or on CD3-, 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 in non-T cells, the red dashed line was established based on the basal level of PD-L1 expression present within the untreated group and applied across all doses of MGD006.

Bottom Panel: Primary AML sample was incubated for 120 hours with 50 ng/ml of MGD006. Expression of check point inhibitors was measured at baseline and after incubation. Blue histograms represent basal levels and green post incubation.

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

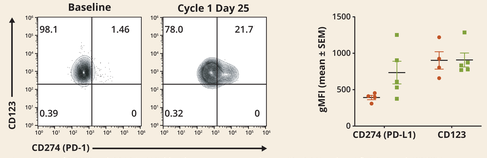
Dose-dependent detection of circulating IFNγ in flotetuzumab-treated patients



- Concurrent increase of PD-L1 expression on circulating AML blasts is noted associated with increased IFNγ in the circulation

Patient samples were evaluated for circulating IFNγ levels **(left panel)** and PD-L1 expression on circulating AML blasts at 2 dose levels: 300 ng/kg/day and 500 ng/kg/day.

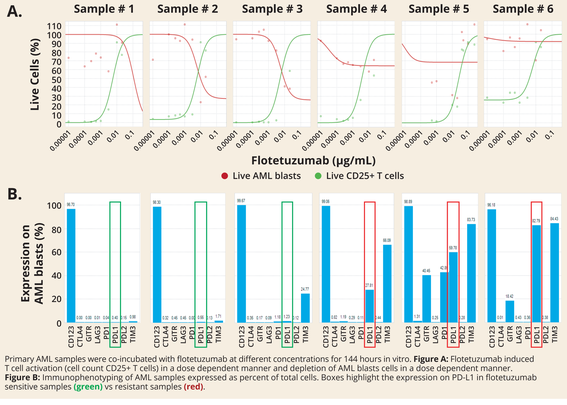
PD-L1 Upregulation in Residual Bone Marrow Blasts



Flow cytometry analysis of CD123 and PD-L1 in AML blast bone marrow samples pre (BL D-14) and post flotetuzumab (C1D25).

Flotetuzumab Activity and PD-L1 Expression

PD-L1 Expression Is Associated with Decreased Activity In Vitro and In Vivo

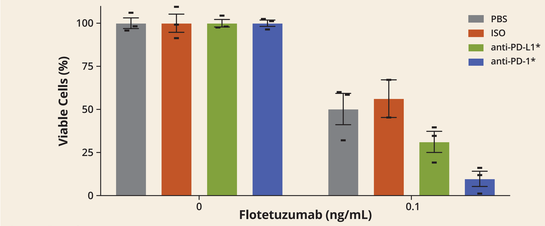


Primary AML samples were co-incubated with flotetuzumab at different concentrations for 144 hours in vitro. **Figure A:** Flotetuzumab induced T cell activation (cell count CD25+ T cells) in a dose dependent manner and depletion of AML blasts cells in a dose dependent manner. **Figure B:** Immunophenotyping of AML samples expressed as percent of total cells. Boxes highlight the expression on PD-L1 in flotetuzumab sensitive samples **(green)** vs resistant samples **(red)**.

Rationale

PD-1/PD-L1 Axis Blockade Enhances Flotetuzumab Anti-leukemic Activity In Vitro

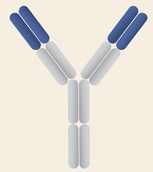
In vitro studies have shown synergistic T-cell mediated cytotoxicity of an AML cell line (KG1A) with flotetuzumab in the presence of PD-1/PD-L1 axis blockade compared to flotetuzumab alone



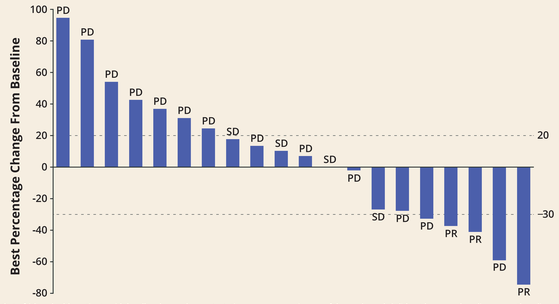
*statistically significant (p<0.05).
KG1A cells incubated with human T cells at E:T ratio 0.25:1 in the presence of flotetuzumab ± 10 μg/mL anti-checkpoint antibody.

MGA012*

Investigational anti-PD-1 antibody that has shown evidence of clinical activity in Phase 1 and 2 studies[6]



*Also known as INCMGA00012.

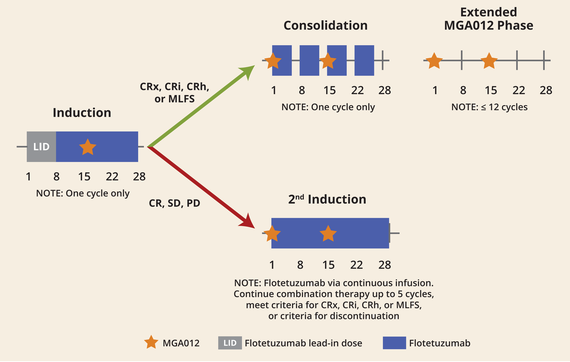


Out of 26 evaluable patients with locally advanced or metastatic squamous carcinoma of the anal canal, 6 did not have any baseline or postbaseline tumor assessments. Upper limit of dotted line indicates a criterion for PD (≥ 20% increase in sum of target lesion diameters) and lower limit indicates a criterion for PR (≥ -30% decrease in sum of target lesion diameters). PD, progressive disease; PR, partial response; SD, stable disease.

Flotetuzumab combination with CPI aims to obviate flotetuzumab-induced pathways of AML resistance and harness flotetuzumab-induced positive changes of immune modulation

- Flotetuzumab leads to T-cell activation, which in turn was associated with PD-1 induction on T lymphocytes, enhanced IFNγ secretion, and upregulation of PD-L1 expression by AML blasts[4,5]
- Residual bone marrow AML blasts show higher expression of PD-L1 positive compared to baseline
- Enhanced PD-L1 expression by AML blasts was associated with reduced flotetuzumab activity in vitro and in vivo
- In vitro studies have shown synergistic T-cell mediated cytotoxicity of an AML cell line (KG1A) with flotetuzumab in the presence of PD-1/PD-L1 axis blockade compared to flotetuzumab alone
- MGA012 is an anti-PD-1 antibody that has shown clinical activity in Phase 1 and Phase 2 studies[6,7]
- We hypothesize that combined checkpoint inhibition with MGA012 together with redirected T-cell killing of CD123+ cells with flotetuzumab may show enhanced activity over flotetuzumab alone

Study Design



Key Eligibility Criteria

Inclusion

- Confirmed diagnosis of primary or secondary AML (any subtype except acute promyelocytic leukemia) according to WHO classification
- Patients with AML must be unlikely to benefit from cytotoxic chemotherapy defined by any one of the following criteria:
  - 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
  - Leukemia in 2nd or higher relapse
- Prior treatment failure with at least 4 cycles of a hypomethylating agent
- Eastern Cooperative Oncology Group performance status of ≤ 2
- Life expectancy ≥ 4 weeks
- Peripheral blast count ≤ 20,000/mm^3 at the time of initiation of infusion on Cycle 1 Day 1
- Acceptable laboratory parameters and adequate organ reserve

Exclusion

- Prior treatment with an anti-CD123-directed agent, with the exception of patients who have failed or relapsed after treatment with monotherapy flotetuzumab on Protocol CP-MGD006-01 (NCT02152956)
- Need for concurrent other cytoreductive chemotherapy
- History of known or suspected autoimmune disease with the specific exceptions of vitiligo, resolved childhood atopic dermatitis, psoriasis not requiring systemic treatment (within the past 2 years), and patients with a history of Grave's disease that are now euthyroid clinically and by laboratory testing
- Previous treatment with radiotherapy, cytotoxic chemotherapy, immunotherapeutic agents, investigational agent, excluding prior flotetuzumab, in the 2 weeks prior to study drug administration; use of immunosuppressant agents in the 2 weeks prior to study drug administration
- Known central nervous system leukemia

References

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2. Root et al. *Antibodies*. 2016 5(1), 10.3390/antib5010006.
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