

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

ASCO 2017
Abstract TPS7070

Norbert Vey¹, Jan Kenneth Davidson-Moncada², Geoffrey L. Uy³, David Rizzieri⁴, Hanna Jean Khoury⁵, Matthew Charles Foster⁶,
John E. Godwin⁷, Max S. Topp⁸, Giovanni Martinelli⁹, Fabio Ciceri¹⁰, Matteo Giovanni Carrabba¹⁰, Gerwin A Huls¹¹,
Antje Wegener¹², Kathy Tran², Michele Shannon², Jichao Sun², Jon M. Wigginton², John F. DiPersio³



davidsonj@macrogenics.com

¹Institut Paoli Calmettes, Centre Régional de Lutte Contre le Cancer, Marseille, France; ²MacroGenics, Rockville, MD; ³Washington University School of Medicine, St Louis, MO; ⁴Duke University Medical Center, Durham, NC;
⁵Winship Cancer Institute, Emory University, Atlanta, GA; ⁶University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC; ⁷Providence Cancer Center, Portland, OR;
⁸Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Würzburg, Germany; ⁹AOU di Bologna Policlinico S. Orsola Malpighi, Bologna, Italy; ¹⁰Ospedale San Raffaele, Milan, Italy;
¹¹Universitair Medisch Centrum Groningen, Groningen, Netherlands; ¹²Institut de Recherches Internationales Servier, Suresnes, France

NCT02152956

Background

MGD006: Humanized CD123 x CD3 DART® Molecule

MGD006*

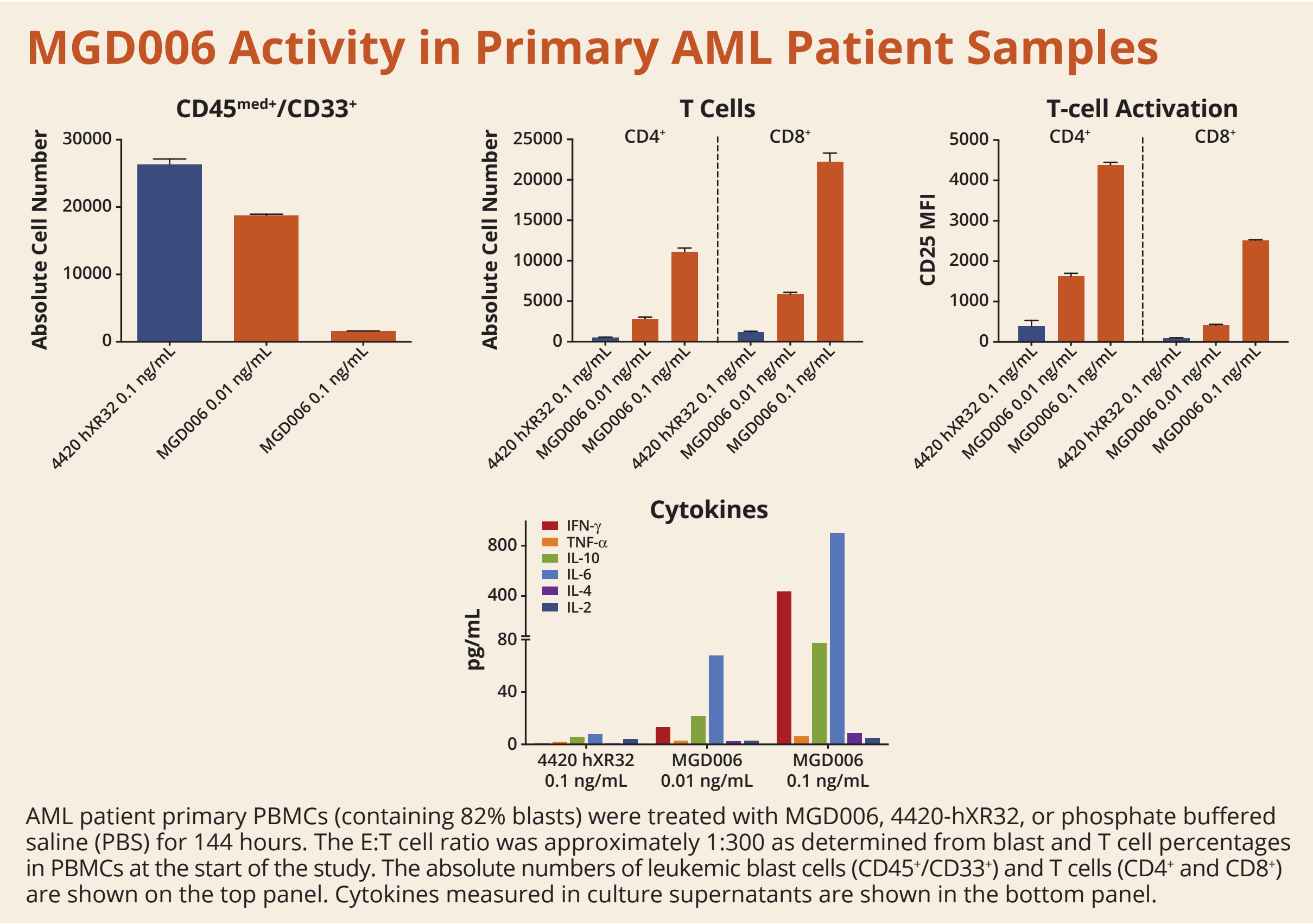
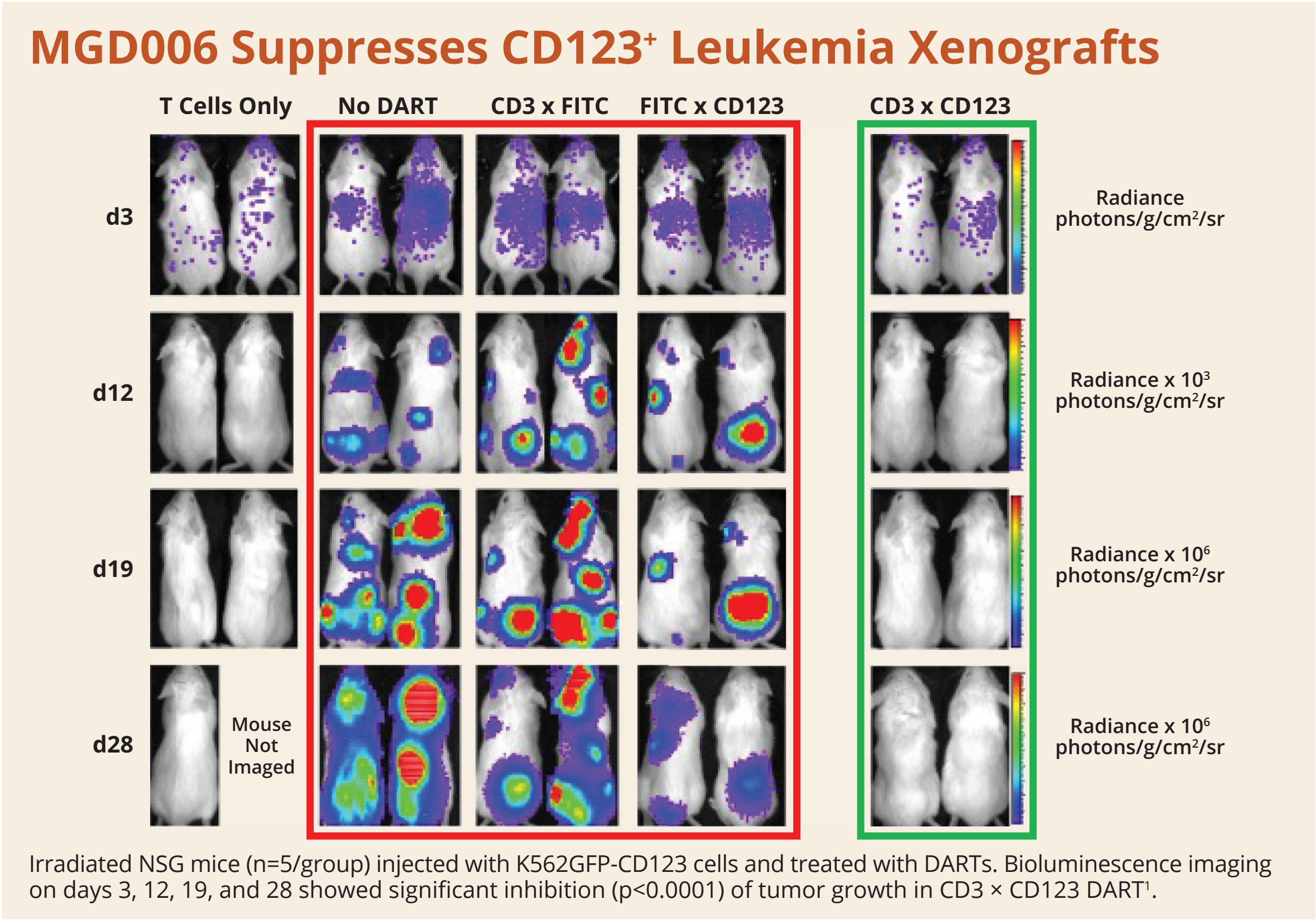
Anti-CD3 (hXR32)

Anti-CD123

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)

*Also known as S80880 and flotetuzumab



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 effector cells
- 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

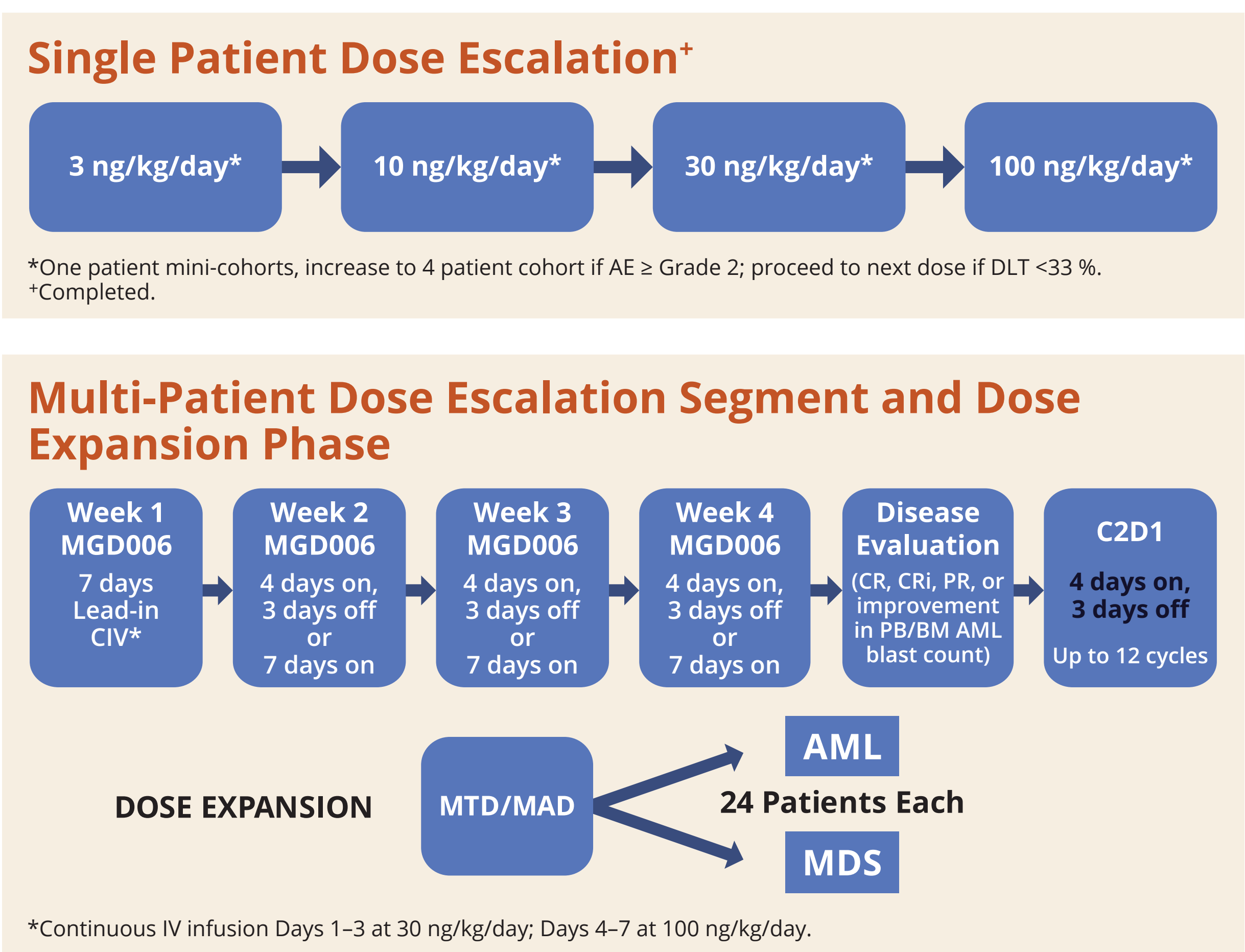
Key Study Objectives

- 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 (CIV) 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 MTDS or MAD is identified, two cohorts of 24 patients each, one in AML and one in MDS, will be enrolled

Study Schema



Entry Criteria

- 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 any 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 with 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 cytoreductive chemotherapy
 - History of or suspected current autoimmune disorders with certain exceptions
 - Second 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

Study Status

Enrollment ongoing in U.S. and Europe.

Location	Principal Investigator
Washington University	Geoffrey L. Uy
Duke University	David Rizzieri
Emory University	Hanna Jean Khoury
University of North Carolina	Mathew C. Foster
Providence Cancer Center	John Godwin
Institut Paoli-Calmettes	Norbert Vey
Universitätsklinikum Würzburg	Max S. Topp
Università di Bologna	Giovanni Martinelli
University Vita-Salute San Raffaele	Fabio Ciceri
University Medical Center Groningen	Geert Abraham (Gerwin) Huls
Erasmus University Medical Center	Bob Löwenberg

References

1. Al-Hussaini, et al. Blood 2016;127:122-31

Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from ASCO® and the author of this poster.