A Phase 1/2, First-in-Human, Dose Escalation Study of MGD006, a CD123 x CD3 Dual Affinity Re-Targeting (DART) Bi-Specific Antibody-Based Molecule, in Patients with Relapsed or Refractory Acute Myeloid Leukemia or Intermediate-2/High Risk Myelodysplastic Syndrome

Published: 29-02-2016
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Primary Objective: To assess the anti-neoplastic activity of flotetuzumab in patients with PIF/ER AML, as determined by the proportion of patients who achieve CR/CRhSecondary Objectives:To describe response rate, duration of response, event-free...

Ethical review	Approved WMO
Status	Completed
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON55771

Source
ToetsingOnline

Brief title
CP-MGD006-01

Condition

- Leukaemias

Synonym
Acute Myeloid Leukemia; bloodcancer

Research involving
Human

Sponsors and support

Primary sponsor: MacroGenics Inc.
Source(s) of monetary or material Support: MacroGenics Inc.

Intervention

Keyword: Acute Myeloid Leukemia (AML), flotetuzumab, Myelodysplastic Syndrome (MDS), Phase 1/2

Outcome measures

Primary outcome

Efficacy based on CR/CRh rate:

Proportion of patients achieving a best response of CR (morphologic CR,

cytogenetic CR, molecular CR, or CRh per Interworking Group AML response

criteria.

Secondary outcome

Efficacy Endpoint:

response rate, duration of response, event-free survival, overall survival and

transplantation rate

Study description

Background summary

The Dual Affinity Re-Targeting (DART®) technology is a novel, bispecific antibody platform designed to eradicate AML (or other tumor) cells through co-engagement of a leukemia- or tumor-specific cell surface marker (e.g., CD123) and the T-cell receptor (TCR)/CD3 complex on T cells as effector cells.

Cell-association studies indicated that the DART protein architecture is well suited for maintaining cell-to-cell contact, apparently contributing to the high level of target cell killing. CD19 x TCR and CD19 x CD3 DART protein have demonstrated in vitro killing of B-cell lymphomas by human T cells or peripheral blood mononuclear cells (PBMCs) (14) that exceeds the killing associated with a similar bispecific antibody construct, BiTE. The CD19 x TCR DART protein has also been used in in vivo tumor models and has demonstrated inhibition of B-cell lymphoma in NOD/SCID mice when co-administered with human PBMCs.

Flotetuzumab, also known as S80880, is a novel CD123 x CD3 DART protein developed by MacroGenics, Inc. Flotetuzumab is designed to target CD123-positive cells (including AML cells) for recognition and elimination by CD3-expressing T lymphocytes as effector cells.

Flotetuzumab shows potent activity to redirect T cell killing against CD123-expressing cell lines and primary AML blasts in vitro. Flotetuzumab also demonstrated inhibition of growth of leukemic cell lines in mice and depletion of the CD123-positive pDC cells in the repeat-dose toxicology studies. The data from the nonclinical studies provide strong scientific rationale that an evaluation of the safety and potential activity of the CD123 x CD3 DART protein, Flotetuzumab, in patients with AML whose disease is not expected to benefit from additional cytotoxic chemotherapy (as specified below), is warranted.

Study objective

Primary Objective:
To assess the anti-neoplastic activity of flotetuzumab in patients with PIF/ER AML, as determined by the proportion of patients who achieve CR/CRh

Secondary Objectives:
To describe response rate, duration of response, event-free survival, overall survival and transplantation rate.

Study design

This is an open-label, multi-dose, single-arm, multi-center, Phase 1/2, dose-escalation and expansion study to define a MTDS; describe preliminarily safety; and assess the PK, immunogenicity, immunomodulatory activity, and potential anti-neoplastic activity of flotetuzumab in patients with AML and MDS whose disease is not expected to benefit from cytotoxic chemotherapy.

This study is designed in three segments: the Single Patient Dose Escalation Segment (completed), followed by the Multi-Patient Dose Escalation Segment (completed) and the MTDS Expansion Cohort Segment (ongoing). Two expansion

cohorts were planned, one in AML and one in MDS. As of amendment 7, the sponsor stopped enrolling patients with MDS into this study.

Intervention

See 'J: Aanvullende informatie'.

Study burden and risks

- Central line placement (for study drug infusions and drawing blood samples)

- Vital signs

- Electrocardiogram

- Physical examination

- Blood collection

- Urine collection

- Bone marrow aspirate/biopsies

- Treatment after Cycle 1 Day 8 may take place in the outpatient setting based on patient's tolerance of therapy. The patient may also be required to be in the hospital during the first 24 to 48 hours of Cycle 2 and any additional infusions depending on the dosing schedule.

Contacts

Public
MacroGenics Inc.

Medical Center Drive 9704
MD 20850 Rockville
US
Scientific
MacroGenics Inc.

Medical Center Drive 9704
MD 20850 Rockville
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Patients must have a confirmed diagnosis of primary or secondary AML (any subtype except acute promyelocytic leukemia [APL]) according to World Health Organization (WHO) classification.
2. Patients with AML must meet one of the following criteria:
a Primary Induction Failure (PIF) AML, defined as disease refractory to one of the following:
- An intensive induction attempt, per institution. Induction attempts include high dose and/or standard-dose cytarabine +/- an anthracyclines/anthracenedione +/- and anti-metabolite, with or without growth factor or targeted therapy containing regimes.
Examples include but are not limited to:
1. One cycle of high dose cytarabine (HiDAC) containing regimen
2. One cycle of liposomal cytarabine and daunorubicin
3. Two cycles of standard dose cytarabine containing regimen
- For adults who are age 75 years or older, who have comorbidities that preclude use of intensive induction chemotherapy; PIF is defined as AML refractory to one of the following less intensive regimes, 1 or 2:
1. >= 2 but <= 4 cycles of Bcl-2 inhibitors in combination with azacitidine, decitabine, or low dose cytarabine
2. >= 2 but <= 4 cycles of gemtuzumab ozogamicin monotherapy
b. Early Relapse (ER) AML, defined as AML in first relapse with initial CR 1 duration < 6 months.
3. Limit of 3 prior lines of therapy (excluding focal radiation therapy for palliative purposes): up to 2 induction (induction, re-induction) or 1 induction plus/minus 1 consolidation attempt, followed by a maximum of 1 salvage/re-induction attempt.
4. Eastern Cooperative Oncology Group (ECOG) performance status less-than or

equal to 2.
5. Life expectancy of at least 4 weeks.
6. Peripheral blast count less-than or equal to 20,000/mm3 at the time of first dose of study treatment (see related Exclusion Criterion 3).
7. Acceptable laboratory parameters and adequate organ reserve.
8. Adult: Eighteen (18) years of age or older.

Exclusion criteria

1. Prior history of allogeneic stem cell transplantation
2. Prior treatment with an anti-CD123-directed agent.
3. Need for concurrent other cytoreductive chemotherapy
4. Any active untreated autoimmune disorders (with the exception of vitiligo, resolved childhood atopic dermatitis, prior Grave's disease now euthyroid clinically and with stable supplementation)
5. Second primary malignancy that requires active therapy. Adjuvant hormonal therapy is allowed.
6. Antitumor therapy or investigational agent within 14 days or 5 half-lives of Cycle 1 Day 1.
7. Requirement, at the time of study entry, for concurrent steroids > 10 mg/day of oral prednisone or the equivalent, except steroid inhaler, otic preparations, nasal spray or ophthalmic solution
8. Use of immunosuppressant medications in the 2 weeks prior to study drug administration (Cycle 1 Day 1)
9. Use of granulocyte colony stimulating or granulocyte-macrophage colony stimulating factor in the 2 weeks prior to study drug administration (Cycle 1 Day 1)
10. Known central nervous system (CNS) leukemia.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	30-05-2017
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	flotetuzumab
Generic name:	nvt

Ethics review

Approved WMO Date:	29-02-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-11-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-12-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-12-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-07-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-07-2017
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-08-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-04-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-04-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-08-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-10-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-11-2019
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-02-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-03-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-06-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-07-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-11-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-02-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-07-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-11-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-03-2022
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-05-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-10-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-003813-11-NL
ClinicalTrials.gov	NCT02152956
CCMO	NL56485.042.16

Study results

Date completed:	05-07-2022
Results posted:	06-06-2023

First publication
17-03-2023