A phase I, dose escalation study of S80880, a CD123 x CD3 *Dual Affinity Re-Targeting (DART)* bi-specific antibody-based molecule given as monotherapy in patients with acute leukaemias and other haematological malignancies expressing CD123

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON42264

Source
ToetsingOnline

Brief title
CL1-80880-001

Condition

- Leukaemias

Synonym
haematological maligancy; acute leukemias and myelodysplastic syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Institut de Recherches Internationales Servier I.R.I.S
Source(s) of monetary or material Support: IRIS (Institut de Recherches Internationales Servier)

Intervention

Keyword: AML, DART, dose escalation, S80880

Outcome measures

Primary outcome

The Primary endpoint is occurance of DLT (dose limiting toxicity) during cycle

1.

Secondary outcome

Secondary end points:

Safety profile of S80880 assessed by:

* All adverse events

* All serious adverse events

* Laboratory tests (haematology, blood biochemistry, coagulation, urinary

analysis, pregnancy test)

* Vital signs and performance status

* Clinical examination

* ECG parameters, cardiac function assessment

PK profile parameters of S80880 in serum

Response rate (any CR, PR or HI) as determined by investigator, using the

response criteria proposed by the International working Group for MDS, using

adapted criteria proposed by the International working Group for AML, B-ALL,

ALAL and BPDCN,

- Response duration,

- Event-free survival,

- Overall survival.

Study description

Background summary

Treatment outcome of adult acute myeloid leukaemia, has not improved in the past 20 years. Outcomes from standard therapy are disappointing. Given the current state of therapeutic options, novel therapeutic approaches are urgently needed. Recent studies have shown that CD123 - the alpha chain of the human IL-3 receptor - is highly expressed on leukaemia stem cells of patients with AMLand is correlated with tumour load and poor prognosis. S80880 also known as MGD006 or RES234 is a novel CD123 x CD3 DART protein (Dual Affinity Re-Targeting) and designed to target CD123-positive cells (including AML cells) for recognition and elimination by CD3-expressing T lymphocytes as effector cells. No clinical data are yet available with S80880. The first in human study started on 10 June 2014 in the VS.

Study objective

The primary objective of this study is to determine the maximum tolerated dose (MTD) for the administration of S80880.

Secondary objectives
To evaluate the safety profile of S80880.
To describe the pharmacokinetics (PK) profile of S80880 administered by continuous IV infusion.
To evaluate preliminary anti-leukaemic activity of S80880
To determine the recommended dose for phase II trials (RP2D)

Study design

This is an international, multicentre, single-arm, open-label phase I dose-escalation study.
Up to 48 patients will be enrolled in the dose escalation segment. The data of the FIH trial will be used to establish an acceptable starting dose for this

trial, which is expected to be 100 ng/kg/day. Patients will be included by cohort of 3. A minimum of 6 evaluable patients will be treated at the MTD.
Expansion cohorts: Up to 30 patients may be recruited at the MTD or at a lower dose level in 2 expansion cohorts in order to obtain more information about the safety profile, to provide additional PK data and anti-tumour activity data.
The dose scheme and/or schedule of S80880 administration may also be modified at the recommendation of the sponsor, the international coordinator and the investigators, and implemented accordingly after its approval by CA and EC.

Intervention

S80880 will be administered by continuous IV infusion from day 1 through day 4 of each week during the first 4-week cycle. Patients who then qualify for subsequent cycles will be given S80880 according to cycle 1 administration schedule.

Study burden and risks

The first in human study has just started with S80880 and this means no human data are available yet on S80880. Based on the results of the preclinical and animal studies with S80880, and based on other studies with similar type of drugs, the following events could happen: swelling around eyes and/or face, hypoalbuminemia, anemia, thrombocytopenia, serious allergic reaction or cytokine release syndrome (during the studydrug administration), tumor lysis syndrome, higher risk of infections, immune-related side effects and kidney toxicity.

Burden:The minimal duration of the study is 10 weeks, including screening/baseline period, the first cycle and the end of treatment visit. The patients must be hospitalised during the first cycle, to ensure optimal safety monitoring and management during the first study drug adminstration. This is longer than standard of care, although regular hospitalisation are frequent for acutely ill leukemic patients.
A central line will be placed for the adminstration of the study drug and an additional venous line for the adminstration of other drugs, eg in case treatment of infusion reactions.
The total amount of blood sampled during the study is acceptable (about 350 ml during baseline and first cycle).
Bone marrow biopsies and punctions can cause some discomfort, and are also commonly done during routine medical care of AML patients.
All necessary safety measures are taken, before, during and after the study drug administration.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- male or female > or <= 18 years
- Patients with cytologically confirmed and documented primary or secondary acute myeloid leukaemia (AML) without established therapeutic alternatives or when established therapeutic alternatives are ineffective, poorly tolerated or unacceptable for the patient:
- In newly diagnosed patients * 70 years not eligible for cytotoxic chemotherapy or
- in patients with relapsed or refractory disease who have failed conventional therapy after at least 1 line of treatment and who are not eligible for salvage therapy;
In following patients, in case established therapeutic alternatives are not available or when established therapeutic alternatives are ineffective, poorly tolerated or unacceptable for the patient:
- cytologically confirmed and documented relapsed/refractory B-cell acute lymphoid leukaemia (B-ALL),

- cytologically confirmed and documented relapsed/refractory Acute Leukaemia of Ambiguous Lineage (ALAL)
- patients with intermediate -2 of high risk myelodysplastic syndrome (MDS)
- cytologically and histologically confirmed relapsed/refractory blastic plasmacytoid dendritic cell neoplasm (BPDCN);- Circulating white blood cells * 20 000/mm3,
- Adequate hepatic and renal function
- life expectancy > or <= 4 weeks
- ECOG (Eastern Cooperative Oncology Group) performance status < or <= 2

Exclusion criteria

Diagnosis of myeloid sarcoma,
History of other malignancy within 3 years prior to start of protocol-specified therapy (exceptions: see protocol)
Patients who have not recovered from toxicity of previous antileukaemic therapy, including grade * 2 non-haematologic toxicity, prior to starting the test drug,
Patients previously treated by anti-CD123 therapy,
Any previous anticancer treatment for leukaemic disease within at least 2 weeks,
Previous radiotherapy or immunotherapy in the 4 weeks prior to first IMP intake,
Patients with previous history of allogeneic stem cell transplantation;
Any prior history of or suspected current autoimmune disorders (exceptions: see protocol),
Severe uncontrolled fungal, bacterial or viral infection,
Leukaemic central nervous system involvement,
Pregnant or breastfeeding women,
known hypersensitivity to murine or recombinant proteins, polysorbate 80, recombinant human serum albumin, benzyl alcohol or any excipient contained in the S80880 drug formulation, history of Quincke oedema,
Known infection with human immunodeficiency virus (HIV), infection with hepatitis B virus (HBsAg positive) or hepatitis C virus (anti-HCV positive),
Any other diseases (e.g. adrenal insufficiency, malabsorption syndromes, metabolic dysfunction, physical examination finding), or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patient at high risk for test drug complications.

Study design

Design

Study type: Interventional
Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	8
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	S80880
Generic name:	S80880

Ethics review

Approved WMO Date:	07-01-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-06-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2014-001396-31-NL
CCMO	NL49388.078.14