A phase I, multicenter, open-label dose escalation and expansion study of LOP628, administered intravenously in adult patients with cKit-positive tumors and acute myeloid leukemia

Published: 03-11-2014
Last updated: 21-04-2024

Primary objective: To estimate the MTD/RDE of LOP628 in solid tumors and AML, respectively.Secondary objectivesL:- To characterize the safety and tolerability of LOP628- To characterize the pharmacokinetic profile of LOP628- To assess emergence of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON42287

Source
ToetsingOnline

Brief title
Phase I study with LOP628 in cKIT positive solid tumors and AML

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Acute Myeloide Leukemia, GIST, Small Cell Lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: AML, cKIT, LOP628, solid tumors

Outcome measures

Primary outcome

Incidence rate of dose limiting toxicities (DLTs)

Secondary outcome

- Incidence and severity of AEs and SAEs; including changes in laboratory

values; vital signs and ECGs

- Serum PK parameters (eg, AUC, Cmax, Tmax, half-life); Serum concentration vs.

time profiles

- Presence and/or concentration of anti-LOP628 antibodies

- GIST and SCLC: Overall response rate (ORR); Duration of response (DOR); PFS;

Disease Control Rate (DCR) at 4 months; best overall response (BOR)

- AML: percent of patients with CR, CRi, PR; BOR; duration of response (DOR);

and PFS

Study description

Background summary

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract. GISTs are malignant tumors most commonly resulting from activating mutations in the receptor tyrosine kinase cKit (CD117) or the platelet-derived growth factor receptors * (PDGFR*). More than 90% of GIST tumors are cKit positive. Presently, there are no standard

therapeutic options available for patients with GIST who have failed prior therapy with imatinib and sunitinib.

Small cell lung cancer (SCLC) is a very aggressive neoplasm accounting for about 14% of all lung cancers. Although SCLC is very responsive to initial treatment, most patients relapse with relatively resistant disease.

Activating mutations in cKit have been reported in acute myeloid leukemia (AML). The clinical and prognostic significance of cKit mutations in AML is unclear.

LOP628 is an anti-cKit humanized IgG1/* antibody conjugated to the MCC-DM1 linker payload, a maytansine payload and a non-cleavable linker, thus resulting in an antibody drug conjugate (ADC). The antibody component, LMJ729, specifically binds to cKit with high affinity. LOP628 exhibits potent single-agent anti-tumor activity in GIST, SCLC and AML xenograft models. Consequently, LOP628 activity is not dependent on blocking cKit activation or signaling, but is dependent on the DM1 payload.

This is the first use of LOP628 in humans; there is no prior clinical experience.

Study objective

Primary objective: To estimate the MTD/RDE of LOP628 in solid tumors and AML, respectively.
Secondary objectivesL:
- To characterize the safety and tolerability of LOP628
- To characterize the pharmacokinetic profile of LOP628
- To assess emergence of anti-LOP628 antibodies following one or more intravenous infusions of LOP628
- To assess the preliminary antitumor activity of LOP628 in patients with SCLC, GIST, and AML

Study design

A phase I, multi-center, open-label study to determine the MTD/RDE and safety of LOP628 administered intravenously once every 21 days in patients with cKit-positive advanced solid tumors and cKit-positive AML.
The study begins with a dose escalation part to determine the MTD/RDE in patients with cKit-positive advanced solid tumors. During the expansion part, LOP628 will be dosed at the MTD, or at a lower RDE. Upon determination of the MTD/RDE in patients with advanced solid tumors, dosing will commence in 2 dose expansion arms, one comprising patients with cKit-positive GIST and one comprising patients with cKit-positive SCLC.
A dose escalation arm comprising patients with cKit-positive AML will commence,

starting from at least one dose level below the MTD/RDE identified in solid tumors. Upon determination of the MTD/RDE in patients with cKit-positive AML, patients with AML are to be enrolled in an additional dose expansion arm at the recommended dose for expansion in that disease.
LOP628 will be administered until patient experiences unacceptable toxicity or progressive disease.
Approximately 105 patients may be enrolled in this study. Approximately 21 solid tumor patients and 12 AML patients are expected to be treated during the dose escalation parts.
Additional patients will be enrolled in the dose expansion part of the study to obtain approximately 30 patients each in GIST and SCLC, and approximately 20 patients in AML.
An adaptive BLRM with EWOC will guide the dose escalation to determine the MTD or RDE.

Intervention

The study treatment is LOP628. LOP628 will be administered via IV once every 3 weeks.
Starting dose: 0.3 mg/kg

Study burden and risks

Compared to regular treatment, more, and more often, tests and exams will take place. For the patient*s safety more ECGs will be made, additional eye examinations and more often blood will be drawn and the patient will have to visit the hospital more often. At the start of the study tumor biopsy or a bone marrow biopsy will be performed. To better assess the effect on the tumor, CT- or MRI-scans will be performed more often. Generally, the duration of the visits to the hospital will extend from 1 to 3 hours, because of the extra tests and exams done. The frequency of the several tests is further described in attachment B of the patient information.
Risks are possible side effects of the study medication, and those from the tests the patient is asked to do.
The potential side effects are based on information collected from laboratory and animal studies include:
* Reactions immediately after infusion. In animals symptoms would end about 1-4 hours after infusion.
* Decrease in blood counts (red blood cells, white blood cells and platelets.
* Increases in liver enzyme levels
* Eye toxicities (cornea) which may cause visual disturbances such as blurred vision. In laboratory studies, these findings were only seen at the highest dose tested of LOP628. Eye toxicity is rare and reversible.

The risks are further described in the patient information.

Contacts

Public
Novartis

Raapopseweg 1
Arnhem 6824 DP
NL
Scientific
Novartis

Raapopseweg 1
Arnhem 6824 DP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Main inclusion criteria (all patients)
*Documented cKit-positive neoplasms or AML
*ECOG Performance status of * 2;Inclusion criteria for patients with solid tumors
*Progressive disease as defined as either of the following:
o Patients with SCLC: have progressed after at least 1 prior therapy
o Patients with GIST: have relapsed or has refractory disease, and no further approved effective therapeutic option exists
o Patients with other cKit-positive solid tumors (dose escalation only): have progressed after at least one prior line of therapy and no further approved effective therapeutic option exists
*Measurable disease as per RECIST v1.1 criteria ;Inclusion criteria for patients with AML
*Progressive disease defined as relapsed or refractory non-PML AML following standard therapy or for whom no effective therapy exists.

*Blast count < 50,000/mm3.;For all inclusion criteria refer to protocol section 5.2.2 page 23-24

Exclusion criteria

Main Exclusion criteria for all patients
*Presence of other clinically significant hematologic, cardiac, respiratory, gastrointestinal, renal, hepatic or neurological conditions.
*History of serious allergic reactions, which may pose an increased risk of serious infusion reactions.
*Previously treated with cKit directed therapies ;Exclusion criteria for patients with solid tumors
*Central nervous system (CNS) metastatic involvement unless the CNS metastases have been previously treated and the patient is clinically stable and on a stable dose of corticosteroids for at least 4 weeks prior to enrollment. ;Exclusion criteria for patients with AML
*Prior allogeneic bone marrow transplant (BMT).;For all exclusion criteria refer to protocol section 5.2.3 page 2-25

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-12-2014
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	nog niet van toepassing
Generic name:	nog niet van toepassing

Ethics review

Approved WMO Date:	03-11-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-11-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	13-04-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2014-002262-76-NL
ClinicalTrials.gov	NCT02221505
CCMO	NL51140.058.14