A Phase 2, Multicenter, Single-arm Study of Moxetumomab Pasudotox in Pediatric Subjects with Relapsed or Refractory Pediatric Acute Lymphoblastic Leukemia (pALL) or Lymphoblastic Lymphoma of B-cell Origin

Published: 07-10-2014
Last updated: 20-04-2024

The primary objective is:Assess the efficacy defined as Composite Complete Response (CRc)The secondary objectives of this study are:* Assess safety and tolerability* Assess immunogenicity and pharmacokinetics* Progression-free survival (PFS),...

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

Summary

ID

NL-OMON41557

Source
ToetsingOnline

Brief title
CD-ON-CAT8015-1036

Condition

- Leukaemias

Synonym
Pediatric Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma

Research involving

Human

Sponsors and support

Primary sponsor: MedImmune, LLC
Source(s) of monetary or material Support: MedImmune;LLC

Intervention

Keyword: LL of B-cell Origin, Moxetumomab Pasudotox, Pediatrics, Relapsed/Refractory ALL

Outcome measures

Primary outcome

The primary objective of this single-arm Phase 2 study is to evaluate the efficacy of moxetumomab pasudotox as measured by the CRc in the efficacy evaluable population. Evaluable subjects are those who receive any amount of moxetumomab pasudotox and complete a baseline disease assessment and at least one post-baseline disease assessment. The CRc includes confirmed CR, CRu, or CRi. Subjects with CR without platelet recovery (CRp) are included in the CRi response category. Confirmed responses are those that persist on repeat assessments >= 4 weeks after the initial documentation of response. The primary analysis of CRc rate and its 95% confidence interval (CI) will be based on response assessments obtained using independently reviewed data by the Data Monitoring Committee. The exact method will be used to calculate the 95% CI. A secondary analysis will be performed based on response assessments using investigator-determined data.

Secondary outcome

The secondary endpoints of antitumor activity include the MRD-negative (defined as < 0.01% leukemic cells) CRc rate, ORR, proportion of evaluable subjects who

become eligible for SCT and time to SCT, proportion of evaluable subjects who are neutropenic at study entry and who experience hematologic activity, DOCR, DOR, PFS, and OS. They will be performed based on response assessments using both investigator-determined data and independently reviewed data. Other secondary endpoints include safety, tolerability, and PK and IM assessments. Exploratory endpoints may include biomarkers that relate to treatment outcome. These will be analyzed using descriptive statistics.

Study description

Background summary

See Protocol Amendment dd 17Jun2014 - Section 1.1 Disease Background page 12 - 14

Study objective

The primary objective is:
Assess the efficacy defined as Composite Complete Response (CRc)

The secondary objectives of this study are:
* Assess safety and tolerability
* Assess immunogenicity and pharmacokinetics
* Progression-free survival (PFS), overall survival (OS), Duration of complete response (DOCR), Duration of overall response (DOR)
* Minimal residual disease negative CRc rate
* Number eligible for stem cell transplant
* Overall response rate (ORR)
* Hematologic activity

Study design

This is a global, multicenter, open-label, single-arm Phase 2 study to evaluate the efficacy and safety of moxetumomab pasudotox monotherapy in pediatric subjects with relapsed or refractory B-cell ALL or B-cell lymphoblastic lymphoma. Approximately 76 subjects will be enrolled at approximately 52 sites in North America, Europe, and Australia. Subjects will be treated with moxetumomab pasudotox at a dose of 40µg/kg.

This is an approximate 35-month study consisting of a 30-day screening period, 22-month enrollment period, and 12-month follow-up period from the last subject enrolled.
Subjects will receive treatment cycles of moxetumomab pasudotox every 21 days until progressive disease (PD), withdrawal of consent, death, initiation of alternative therapy, pregnancy, delay of cycle greater than specified in the protocol, Grade 3 or 4 allergic reactions related to investigational product despite pre-medication, or any significant drug-related toxicities or complications, which, in the opinion of the investigator, contraindicate further treatment with moxetumomab pasudotox.
There is a 30-day post-treatment follow-up period for safety. In addition, all subjects will be followed for disease evaluation every 3 months (± 2 weeks) after discontinuation of therapy until disease progression, initiation of alternate anti-cancer therapy, bone marrow transplant, death, withdrawal of consent, or end of study, and for survival every 3 months, until death, withdrawal of consent, or end of study.

Intervention

Subjects will receive a cycle of moxetumomab pasudotox every 21 days until PD or until they meet a study withdrawal criteria. Each cycle will consist of a total of 6 doses of moxetumomab pasudotox at 40µg/kg given every other day of a 21-day cycle. The first 6 doses of Cycle 1 must be administered in an inpatient setting. Moxetumomab pasudotox is administered intravenously over 30 minutes (+ 5 minutes).

Study burden and risks

An overview of the risks can be found in the informed consent, annex 2. Studyprocedures can be found in the informed consent, section 3 and also in the protocol under Study Procedures.

Contacts

Public
MedImmune, LLC

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US
Scientific
MedImmune, LLC

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Gaithersburg 20878
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Subjects must meet all of the following criteria:
1. Between the ages of >= 6 months and < 18 years of age at the time of screening
2. Written informed consent and written informed assent (if applicable) and any locally required authorization (eg, HIPAA in the USA, EU Data Privacy Directive in the EU) obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations
3. Must have histologically proven B-cell ALL or B-cell lymphoblastic lymphoma with marrow involvement according to the French-American-British classification. NOTE: Subjects with extramedullary involvement outside of the CNS will not be excluded provided they have marrow involvement.
4. All subjects (both ALL and subjects with lymphoblastic lymphoma) must have M2 or M3 bone marrow classification.
5. Disease status:
a. Subjects must have relapsed or refractory disease and have received at least one standard chemotherapy and either one salvage regimen or allogeneic stem cell transplant.
b. In the event of relapse after prior allogeneic HSCT, subjects must be at least 3 months post-transplant and have no evidence of active graft-vs-host disease, and must have been off immunosuppression for at least 4 weeks.
c. Must have resolution of the acute toxic effects to <= Grade 2 from prior chemotherapy before entry, in the opinion of the Principal Investigator or designee
6. For non-leukemic subjects (ie, subjects with lymphoma), an ANC > 1,000/µL and platelet count > 50,000/mm2 are required, unless cytopenias are judged by the Principal Investigator or designee to be due to underlying disease (ie, potentially reversible with antineoplastic therapy). NOTE: There will be no WBC count, ANC, hemoglobin (Hgb), or platelet count

requirement for enrollment of subjects with leukemia.
7. Performance status:
* For subjects >= 12 years of age, Eastern Cooperative Oncology Group (ECOG) score <= 2 (Appendix 2)
* For subjects < 12 years of age, Lansky scale >= 50% (Appendix 3)
* Subjects who are unable to walk, but who are upright in a wheel chair will be considered ambulatory (ECOG score >= 1 and <= 2, Lansky score >= 50% and <= 70%) for the purpose of calculating performance status (a conversion chart from ECOG, Karnofsky, and Lansky is located in Appendix 4).
8. Subjects with the following CNS status (CNS 1 or 2 as described below) are eligible only in the absence of neurologic symptoms, such as cranial nerve palsy, suggestive of CNS leukemia:
a. CNS 1, defined as absence of blasts in cerebral spinal fluid (CSF) on cytospin preparation, regardless of the number of WBCs
b. CNS 2, defined as presence of < 5/µL WBCs in CSF and cytospin positive for blasts, or > 5/µL WBCs but negative by the Steinherz/Bleyer algorithm:
i. CNS 2a: < 10/µL red blood cells (RBCs); < 5/µL WBCs and cytospin positive for blasts
ii. CNS 2b: >= 10/µL RBCs; < 5/µL WBCs and cytospin positive for blasts
iii. CNS 2c: >= 10/µL RBCs; >= 5/µL WBCs and cytospin positive for blasts, but negative by Steinherz/Bleyer algorithm (Appendix 1).
9. With permission from the parents/legal guardian, as required by local regulations, study staff will discuss with female subjects of childbearing potential and post-pubertal male subjects the use of an approved method of contraception for the study. Sexually active subjects must agree to use an approved method of contraception (see Table 4.2.1-1) or to abstain from vaginal sexual intercourse from screening through 90 days after the last dose of investigational product.;Table 4.2.1-1 Highly Effective Methods of Contraception
Barrier Methods:
Male condom plus spermicide
Copper T intrauterine device
Levonorgesterel-releasing intrauterine system
(eg. Mirena®)
This is also considered a hormonal method ;Hormonal Methods:
Implants
Hormone shot or injection
Combined pill
Mini pill
Patch

Exclusion criteria

Exclusion Criteria;1) Any condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results
2) Concurrent enrollment in another clinical study, for cancer treatment, unless the subject is in the follow-up period from a previous study

3) Employees of the study site directly involved with the conduct of the study at the site of proposed enrollment, or an immediate family member of any such individual
4) Isolated testicular or CNS ALL
5) Subjects with mixed-lineage leukemia (MLL) gene rearrangement
6) Inadequate Hepatic function
7) Inadequate Renal function
8) Radiologically-detected CNS lymphoma
9) Subjects with clear laboratory or clinical evidence of disseminated intravascular coagulation (DIC)
10) Hyperleukocytosis or rapidly progressive disease that would compromise ability to complete study therapy
11) QTcF interval (manually overread) of >= 481 milliseconds (ie, >= Grade 2) that is confirmed by 2 additional separate electrocardiograms (ECGs) within 28 days prior to starting study drug. The initial screening ECG need not be repeated for confirmation if the QTcF interval (manual
overread) is < 481 milliseconds.
12) Pregnant or breast-feeding females
13) Prior treatment with CAT-3888 (BL22), moxetumomab pasudotox, or any pseudomonas-exotoxin-containing compound
14) Prior treatment with any anticancer biologic therapy within 2 weeks prior to starting study drug, including but not limited to therapeutic monoclonal antibodies or antibody-drug conjugates
15) Systemic chemotherapy <= 2 weeks (6 weeks for nitrosoureas) and radiation therapy <= 3 weeks prior to starting study drug with exceptions per protocol.
16) Seropositivity for human immunodeficiency virus (HIV)
17) Seropositivity for hepatitis B (HBsAg) or hepatitis C (HCV antibody)
18) Clinically significant ophthalmologic findings (evidence of retinal damage or injury) during the screening
19) Uncontrolled, symptomatic, intercurrent illness including, but not limited to infection, congestive heart failure, cardiac arrhythmia, malaria infection or any other condition that would limit compliance with study requirements
20) Presence of a second invasive malignancy.
21)Any physical, social, or psychiatric condition, or any other condition which in the opinion of the Principal Investigator or designee would prevent effective cooperation or participation in the study
22) Uncontrolled pulmonary infection, presence of pulmonary edema
23) Inadequate Oxygen saturation
24) Serum albumin < 2 g/dL. Albumin infusions for correction of hypoalbuminemia are allowed, but cannot have been administered within 7 days prior to start of study drug.
25) Radioimmunotherapy within 2 years prior to start of study drug.
26) Subject with prior history of thrombotic microangiopathy or HUS.
27) T-cell ALL or T-cell lymphoblastic lymphoma
28) History of known congenital hypercoaguable condition
29) Previous life-threatening anaphylactic reactions to prior monoclonal antibody-based immunotherapy or any component of the moxetumomab pasudotox formulation
30) Subjects currently receiving high-dose estrogen therapy defined as >0.625mg/day of an estrogen compound or within 2 weeks prior to starting study drug.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2014
Enrollment:	4
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Moxetumomab pasudotox
Generic name:	-

Ethics review

Approved WMO Date:	07-10-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-05-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	23-07-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-08-2015
Application type:	Amendment
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	EUCTR2012-003101-10-NL
Other	IND 100372 en NTC0227108
CCMO	NL43470.078.14