A Randomized, Open-label, Controlled Phase 3 Trial to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab as Consolidation Therapy Versus Conventional Consolidation Chemotherapy in Pediatric Subjects with High-risk First Relapse B-precursor Acute Lymphoblastic Leukemia (ALL)

Published: 12-08-2015
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Primary Objective:• To evaluate event-free survival (EFS) after blinatumomab when compared to standard ofcare (SOC) chemotherapySecondary Objective(s):• To evaluate the effect of blinatumomab on overall survival (OS) when compared to SOCchemotherapy...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON53052

Source
ToetsingOnline

Brief title
20120215

Condition

- Leukaemias

Synonym
acute lymphoblastic leukemia (ALL), leukemia

Research involving
Human

Sponsors and support

Primary sponsor: Amgen
Source(s) of monetary or material Support: Amgen

Intervention

Keyword: acute lymphoblastic leukemia, blinatumomab, pediatric/adolescent patients, phase 3

Outcome measures

Primary outcome

Primary Endpoint:

• EFS

Secondary outcome

Secondary Endpoints:

• OS

• MRD response, defined as MRD level < 10-4 at the end of treatment with

investigational

product(s)

• Incidence of adverse events (both serious and non-serious), treatment-related

adverse

events, adverse events of interest, clinically significant changes in

laboratory values

• Survival status at 100 days following alloHSCT

• Incidence of anti-blinatumomab antibody formation (blinatumomab arm only)

• population pharmacokinetic (PK) analysis

Study description

Background summary

Blinatumomab is a bispecific, single-chain antibody construct designed to link CD19 expressing B cells, and T cells together, causing T cell activation and a cytotoxic T cell response against the CD19 expressing cells. In vitro data indicate that CD19+ lymphoma and leukemia cell lines are extremely sensitive to blinatumomab-mediated cytotoxicity.

Study objective

Primary Objective:

• To evaluate event-free survival (EFS) after blinatumomab when compared to standard of
care (SOC) chemotherapy

Secondary Objective(s):

• To evaluate the effect of blinatumomab on overall survival (OS) when compared to SOC
chemotherapy
• To evaluate reduction in minimal residual disease (MRD) after blinatumomab when
compared to SOC chemotherapy
• To evaluate the safety of blinatumomab when compared to SOC chemotherapy
• To evaluate the safety of allogeneic hematopoietic stem cell transplantation (alloHSCT)
after blinatumomab when compared to alloHSCT after SOC chemotherapy

Study design

After induction therapy and 2 cycles of high-risk consolidation 1 and 2 (HC1 and HC2) chemotherapy, subjects will be randomized in a 1:1 ratio to receive a third consolidation course consisting of either blinatumomab (Arm 1A) or standard high-risk consolidation 3 (HC3) chemotherapy (Arm 2A). Most subjects who are in or achieve cytomorphological CR2 (M1 marrow) after completing

consolidation therapy will undergo alloHSCT. Following alloHSCT, subjects will be followed for disease and survival status for a maximum of 36 months.

Intervention

Amgen Investigational Product Dosage and Administration:

Blinatumomab is administered as a continuous intravenous infusion (CIVI). One cycle of blinatumomab treatment includes 4 weeks of CIVI of blinatumomab. AlloHSCT can be conducted any time after completion of the blinatumomab infusion. If in case of adaptation 3 cycles are administered, one cycle is defined by a 4- week CIVI of blinatumomab and a 2-week treatment-free interval. Subjects randomized to the blinatumomab arm will be dosed at 15 µg/m2/day.

Non-Amgen Investigational Product Dosage and Administration:

HC3 is the standard intensive consolidation chemotherapy course based on modifications to the ALL (Associazone Italiana Ematologica Oncologia Pediatrica-Berlin-Franklin-Munster) AIEOP-BFM HR2 course. HC3 will be considered non-Amgen investigational product.
HC1 is the standard intensive consolidation chemotherapy course based on modifications to the ALL AIEOP-BFM HR1 course.
HC2 is the standard intensive consolidation chemotherapy course based on modifications to the ALL AIEOP-BFM HR3 course. In case of study design adaptation, HC1 and HC2 will also be considered non-Amgen investigational product.

Study burden and risks

Survival for first relapse of B-precursor acute lymphoblastic leukemia (B-ALL) is suboptimal. Blinatumomab is a promising novel agent for the treatment of B-lineagelymphoid malignancies. In a Phase 2 trial of adult B-ALL, patients with MRD persistence or relapse after induction and consolidation therapy received blinatumomab as a 4-week CIVI at a dose of 15 µg/m2/day. Of 21 treated patients, 16 patients became MRD negative as assessed by quantitative PCR for either rearrangements of immunoglobulin or T cell receptor genes, or specific genetic aberrations. Among the 16 responders, 12 patients had been molecularly refractory to previous chemotherapy. Probability for relapse-free survival was 78% at a median follow-up of 405 days (Topp et al, 2011; Topp et al, 2012a; Topp et al, 2012b). Blinatumomab was similarly effective and well tolerated in an anecdotal report of a small series of pediatric cases (Handgretinger et al, 2011; Schlegel et al, 2014).
Blinatumomab is presently being evaluated in children with R/R ALL in an Amgen-sponsored Phase 1/2 study (MT103-205) being conducted in collaboration

with the Children*s Oncology Group (COG) and the I-BFM European childhood leukemia cooperative group with promising early results. As of September 2013, 34 patients have been treated in the Phase 1 portion. Across all dose levels, 11 (32%) patients had CR
(Gore et al, 2013; Stackelberg et al, 2013). The Phase 2 portion of the study is being conducted at 13 COG and 14 European institutions and closed accrual in May 2014. The level of single agent activity seen with blinatumomab has not been seen in recent Phase 2 ALL studies outside the use of tyrosine kinase inhibitors (TKI) in patients with Ph+ ALL, thus supporting a Phase 3 randomized clinical trial with EFS endpoints. This
study uses an approach to test whether incorporating blinatumomab into treatment of high-risk first relapse B-ALL will reduce rates of second relapse and improve EFS. Additionally, success in relapsed B-ALL will provide additional rationale to test blinatumomab in newly diagnosed B-ALL patients in order to reduce rates of first relapse.
As experience with blinatumomab remains relatively limited, this study will include close early stopping rules for medically important adverse events, such as relevant neurologic events, in subjects receiving blinatumomab. In addition, the potential for adverse effects from long term depletion of CD19+ normal lymphocytes with decrease in immune globulins following blinatumomab treatment is unknown and so monitoring for immuneglobulin recovery and for potential adverse effects related to delayed recovery are included.
Neurologic events have been described with blinatumomab mainly in adult patients but still will be closely monitored on this study. One potential concern regards the safety of combining blinatumomab with intrathecal chemotherapy. In the current Phase 1/2 pediatric study cited above, intrathecal MTX or intrathecal triples are included prior to Cycle 1, at Day 15 of Cycle 1 and at Day 29 of each cycle. No unusual or
increased CNS side effects have been seen in this setting (Gore et al, 2013; Stackelberg et al, 2013).
CRS has also been described. This is more prevalent in patients with higher leukemia burden. Pre-medication with dexamethasone immediately before treatment start, in order to mitigate first dose effects, is mandated in the protocol. An anti-IL6 monoclonal
antibody (i.e. tocilizumab) was shown to be effective in one patient in reverting overt and life-threatening CRS (Teachey et al, 2013). Other common transient adverse events associated with cytokine release are pyrexia, headache, and elevation in liver enzymes,
which have not led to treatment discontinuation. Thus the potential benefit reported to date for blinatumomab outweighs the potential risk.

Contacts

Public

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)

Inclusion criteria

* Subjects with Philadelphia (Ph-) chromosome negative high-risk (HR) first relapse B-precursor ALL (as defined by I-BFM SG/IntReALL criteria), * Subjects with M1 or M2 marrow at the time of randomization , * Age > 28 days and <18 years at the time of informed consent/assent, * Subject*s legally acceptable representative has provided informed consent when the subject is legally too young to provide informed consent and the subject has provided written assent based on local regulations and/or guidelines prior to any study-specific activities/procedures being initiated
* Availability of the following material from relapse diagnosis for central analysis of MRD by PCR: clone-specific primers and reference DNA, as well as primer sequences and analyzed sequences of clonal rearrangements (cases with isolated extramedullary relapse or cases with technical and/or logistic hurdles to obtain and process bone marrow material are exempt from providing this material. In these cases, central MRD analysis only by Flow is permitted).)

Exclusion criteria

* Clinically relevant CNS pathology requiring treatment (eg, unstable epilepsy) Evidence of current CNS (CNS 2, CNS 3) involvement by ALL. Subjects with CNS relapse at the time of relapse are eligible if CNS is successfully treated prior to enrollment., * Abnormal renal or hepatic function prior to start of treatment (day 1) as defined below:
a. Serum creatinine levels above upper limit of normal, based on the normal ranges for age and gender of the local laboratories
b. Total bilirubin > 3.0 mg/dL prior to start of treatment (unless related to Gilbert*s or Meulengracht disease)
* Peripheral neutrophils < 500/µl prior to start of treatment,
* Peripheral platelets < 50,000/µl prior to start of treatment,
* Currently receiving treatment in another investigational device or drug study, or less than 4 weeks since ending treatment on another investigational device or drug study(s). Other investigational procedures while participating in this study are excluded. Procedures required by IntReALL HR guidelines are allowed.,
* Chemotherapy related toxicities that have not resolved to <= grade 2 ,
* Symptoms and/or clinical signs and/or radiological and/or sonographic signs that indicate an acute or uncontrolled chronic infection, any other concurrent disease or medical condition that could be exacerbated by the treatment or would seriously complicate compliance with the protocol,
* documented infection with HIV,
* Known hypersensitivity to immunoglobulins or any of the products or components to be administered during dosing (excluding asparaginase),
* Post-menarchal subject who is pregnant or breastfeeding, or is planning to become pregnant or breastfeed while receiving protocol-required therapy and for at least 48 hours after the last dose of blinatumomab, or 12 months after the last dose of chemotherapy
* Post-menarchal female subject who is not willing to practice true abstinence or use a highly effective form of contraception while receiving protocol-required therapy and for at least 48 hours after the last dose of blinatumomab, or 12 months after the last dose of chemotherapy
* Sexually mature male subject who is not willing to practice true abstinence or use a condom while receiving protocol-required therapy and for at least 48 hours thereafter ,
* Sexually mature male subject who is not willing to abstain from sperm donation while receiving protocol-required therapy and for at least 48 hours thereafter

Refer to section 4.2 of the protocol.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-02-2017
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bite Antibody Blinatumomab
Generic name:	NAP

Ethics review

Approved WMO Date:	12-08-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-09-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	09-12-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-01-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-07-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-07-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-04-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-05-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-07-2017

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-12-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	18-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-06-2019
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-06-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-10-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-10-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-03-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-03-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-06-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	26-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-03-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-04-2022
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	EUCTR2014-002476-92-NL
ClinicalTrials.gov	NCT02393859
CCMO	NL52375.078.15

Study results

Results posted:	30-05-2023

First publication
01-01-1900